Drug Misuse

Opiate detoxification for drug misuse

National Clinical Practice Guideline Number X

**National Collaborating Centre for Mental Health
Commissioned by the
National Institute for Health and Clinical
Excellence**

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1 Executive summary

(Summary recommendations [NICE guideline] to be inserted after consultation.)

2 Introduction

This guideline has been developed to advise on the opiate 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.

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.

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 people with these disorders and situations. However, there will always be some people and situations for which clinical guideline recommendations are not readily applicable. This guideline does not, therefore, override the individual responsibility of healthcare professionals to make appropriate decisions in the circumstances of the individual, 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 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 unit (College Research and Training Unit – CRTU) and the British Psychological Society's equivalent unit (Centre for Outcomes Research and Effectiveness – CORE).

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 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 (PCTs), trusts responsible for mental health and social care and Health Authorities have implemented these guidelines.

2.2 The national opiate detoxification for drug misuse guideline

2.2.1 Who has developed this guideline?

The Guideline Development Group (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, prison service, National Treatment Agency for Substance Misuse 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 Adviser 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 advisers 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 opiate detoxification for drug misuse. Specifically, it aims to:

- evaluate the role of opiate detoxification in the treatment of drug misuse
- evaluate the role of specific psychosocial interventions in combination with opiate 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 and a general introduction to guidelines and to the methods used to develop them. The fourth chapter provides an introduction to the drug misuse topic. 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. 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 chapter. Full details about the included studies can be found in Appendix 10. Where meta-analyses were conducted, the data are presented using forest plots in Appendix 11 (see Text Box 1 for details).

Text Box 1: Appendices supplied as separate files

Content	Appendix
Included/ excluded studies	Appendix 10
Forest plots	Appendix 11
GRADE evidence profiles (available with final draft)	Appendix 12

3 Methods used to develop this guideline

3.1 Overview

The development of this guideline drew upon methods outlined by NICE (*The Guidelines Manual*[1][NICE, 2006]). A team of health 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 opiate 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.

3.2 The scope

Guideline topics are selected by the Department of Health 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*

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

Overview for Stakeholders, the Public and the NHS (second edition)[2]). The remit for this guideline was translated into a scope document by staff at the NCCMH.

The purpose of the scope was to:

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

- 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 NCC and the remit from the Department of Health/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 can be carried out within an 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 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.

3.3   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.

3.3.1   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

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[2] National Institute for Health and Clinical Excellence (September 2006) *The Guideline Development Process – An Overview for Stakeholders, the Public and the NHS (second edition)*. London: National Institute for Health and Clinical Excellence. Available from: www.nice.org.uk

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.

3.3.2 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 health care professionals). Topic groups refined the clinical questions, refined 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.

3.3.3 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.

3.3.4 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 2 lists those who agreed to act as special advisors.

3.3.5 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 5 lists researchers who were contacted.

3.4   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 necessary, sub-questions were generated. The final list of clinical questions can be found in Appendix 6.

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?

Questions relating to diagnosis do not involve an intervention designed to treat a particular condition, therefore the PICO framework was not used. 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 Department of Health (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; 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 (e.g. 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

3.5   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 3.5.6) and the need for future research was specified.

3.5.1 Methodology

A stepwise, 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] 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

- New Zealand Guideline Group

- NHS Centre for Reviews and Dissemination

- Oxford Centre for Evidence-Based Medicine

- Scottish Intercollegiate Guidelines Network (SIGN)

- United States Agency for Health Research and Quality

- Oxford Systematic Review Development Programme

- Grading of Recommendations: Assessment, Development, and Evaluation (GRADE) Working Group.

3.5.2 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 under-lying 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

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[3] National Institute for Health and Clinical Excellence (April 2006) *The Guidelines Manual*. London: National Institute for Health and Clinical Excellence. Available from: www.nice.org.uk

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 randomised controlled trials (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.

Where the evidence base was large, recent high-quality English-language systematic reviews were used primarily as a source of RCTs (see Appendix 9 for quality criteria used to assess systematic reviews). However, in some circumstances existing data sets 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 3.5.6). 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 5), 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; 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 3.5.6).

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 (Appendix 7).

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 reviews and primary-level studies were critically appraised for methodological quality (see Appendix 9 and Appendix 10 [the characteristics of included studies table]). 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)

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

- 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 they should modify their 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.

3.5.3 Data extraction and synthesising the evidence

Outcome data were extracted from all eligible studies, which 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 10). 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 data set. 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, 2001).

3.5.4 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 Error! Reference source not found. 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 9 for the quality checklists and Appendix 10 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 bupronorphrine vs.adrenergic agonists (not all outcomes are shown)

No of studies	Design	Limitations	Consistency	Directness	Other considerations	Bupronorphine	Adrenergic adgonists	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
				Quality assessment		**No of patients**		**Effect**			
								Summary of findings			
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	⊕⊕⊕⊕	9

									(-0.86 to -0.36)	High	

Footnotes:
1. 1 study
2. I-squared > 50%
3. RR > 2

Forest plots

Forest plots were used to present the results of the meta-analyses to the GDG (see Appendix 11). Each forest plot displayed the effect size and confidence interval (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 (RR) 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.

Figure 1. Example of a forest plot displaying dichotomous data

Review: NCCMH clinical guideline review (Example)
Comparison: 01 Intervention A compared to a control group
Outcome: 01 Number of people who did not show remission

Study or sub-category	Intervention A n/N	Control n/N	RR (fixed) 95% CI	Weight %	RR (fixed) 95% CI
01 Intervention A vs. control					
Griffiths1994	13/23	27/28		38.79	0.59 [0.41, 0.84]
Lee1986	11/15	14/15		22.30	0.79 [0.56, 1.10]
Treasure1994	21/28	24/27		38.92	0.84 [0.66, 1.09]
Subtotal (95% CI)	45/66	65/70		100.00	0.73 [0.61, 0.88]

Test for heterogeneity: Chi² = 2.83, df = 2 (P = 0.24), I² = 29.3%
Test for overall effect: Z = 3.37 (P = 0.0007)

0.2   0.5   1   2   5
Favours intervention   Favours control

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.

Figure 2. Example of a forest plot displaying continuous data

Review:	NCCMH clinical guideline review (Example)
Comparison:	01 Intervention A compared to a control group
Outcome:	03 Mean frequency (endpoint)

Study or sub-category	Intervention A N	Mean (SD)	Control N	Mean (SD)	SMD (fixed) 95% CI	Weight %	SMD (fixed) 95% CI
01 Intervention A vs. control							
Freeman1988	32	1.30(3.40)	20	3.70(3.60)		25.91	-0.68 [-1.25, -0.10]
Griffiths1994	20	1.25(1.45)	22	4.14(2.21)		17.83	-1.50 [-2.20, -0.81]
Lee1986	14	3.70(4.00)	14	10.10(17.50)		15.08	-0.49 [-1.24, 0.26]
Treasure1994	28	44.23(27.04)	24	61.40(24.97)		27.28	-0.65 [-1.21, -0.09]
Wolf1992	15	5.30(5.10)	11	7.10(4.60)		13.90	-0.36 [-1.14, 0.43]
Subtotal (95% CI)	109		91			100.00	-0.74 [-1.04, -0.45]

Test for heterogeneity: Chi² = 6.13, df = 4 (P = 0.19), I² = 34.8%
Test for overall effect: Z = 4.98 (P < 0.00001)

-4   -2   0   2   4

Favours intervention   Favours control

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 follow 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 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 to 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).

3.5.5   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).

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

In the absence of level I 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 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 done.

5. At this time, subject possibly to further reviews of the evidence, a series of statements that directly addressed the clinical question were developed.

6. Following this, on occasions and as deemed appropriate by the development group, 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.

3.6 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 health care 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

- Department of Health 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 attended a briefing meeting held by NICE

- Contributing possible clinical questions and lists of evidence to the GDG

- Commenting on the first and second drafts of the guideline.

3.7   Validation of this guideline

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

Following the final 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.

4 Introduction to drug misuse

4.1 Drug misuse and opiate dependence

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

Opiates refer to a class of psychoactive substances derived from the poppy plant, including opium, morphine and codeine, as well as semi-synthetic forms including heroin (WHO, 2006). In this guideline, the term 'opiate' is used more broadly to incorporate synthetic compounds (including methadone and buprenorphine) with similar properties, also commonly known as opioids (WHO, 2006). Illicit use of opiates generally involves injection, or inhalation of the fumes produced by heating the drug.

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 (Department of Health, 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).

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 World Health Organization (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). Following WHO, this guideline defines dependence 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).

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 people who misuse drugs who return to drug doses at a level to which they had previously developed tolerance. This can lead to accidental overdoses and, in the case of opiate misuse, could lead to respiratory depression and death.

Withdrawal syndromes have clearly been identified after cessation or reduction of opiate 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 (American Psychiatric Association, 1994).

Opiates also produce intoxication, that is, disturbances in psychophysiological functions and responses, including consciousness, cognition and behaviour, following administration of a psychoactive substance (WHO, 2006). These are described in greater detail in section 4.5.

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

- physical health problems (for example, thrombosis, abscesses, overdose, hepatitis B and C, 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 opiates also misuse a range of other substances concurrently and regularly (known as polydrug misuse). The use of opiates 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) suggested that 22% of participants drank alcohol frequently, 17% drank extremely heavily and 8% drank an excessive amount on a daily basis (Gossop *et al.*, 2000a). People who misuse opiates in particular may often take a cocktail of substances, including alcohol, cannabis and prescribed drugs such as benzodiazepines, which can have particularly dangerous effects in comparison with those of each drug taken by itself.

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 amongst known offenders in the UK than amongst comparable age cohorts 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 opiates. 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: between 41 and 54% of remand and sentenced prisoners were reported to be opiate, 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 cconsequence, the prison and the broader criminal justice system is an increasingly significant referral source and venue for the provision of drug treatment.

4.2   Epidemiology of drug misuse

According to the national British Crime Survey (Roe & Man, 2006), 34.9% of 16–59 year olds have used one or more illicit drugs in their lifetime, 10.5% in the last year and 6.3% in the last month. These figures are much lower for opiate use, with 0.1% of the population having used opiates (including heroin and methadone) in the last 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 thousand of the population aged 15–64 years (360,811), of whom 3.2 per thousand (123,498) are injecting dug 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 opiate misuse (National Treatment Agency, 2005b). Males comprise over 70% of new presentations to treatment, and the majority of those requiring treatment are opiate dependent (typically using illicit heroin). Similar figures have emerged from Frischer and colleagues (2001), who estimated that 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 opiates and/or crack cocaine) in the UK, with 280,000 of these opiate users (Hay *et al.*, 2006).

Drug misuse is commoner in certain vulnerable groups. For example, Ward and colleagues (2003) found that amongst 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 past month.

4.3   Aetiology and maintenance of drug misuse

Drug misuse is increasingly portrayed in the field as a medical disorder, in part due to advances in our understanding of the neurobiology underlying dependence (Volkow & Li, 2005). This is known as the 'disease model' of drug misuse. 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.

A defining characteristic of drug dependence is that drug use initiates 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 opiates, 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, opiates, glutamates and cannabinoids) are implicated in the misuse of specific drugs.

Studies of twins, families, and people who have been adopted show that vulnerability to drug misuse may have a genetic component (Prescott *et al.*, 2006), but it is not clear whether for a given individual repeated use is primarily determined by genetic predisposition or whether socioeconomic and psychological factors lead an individual to try and then later to use opiates compulsively. Family relationships play a part and experiences such as childhood neglect, homelessness or abuse increase the likelihood that the individual will develop problems with drugs later in life (Kumpfer & Bluth, 2004). Risk factors for heavy, dependent drug use are much more significant when they occur together rather than individually.

Initiation into drug use does not lead inevitably to regular and problematic use for many people. 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. However, it is clear that when use begins, it often escalates to misuse and then to dependence (tolerance, withdrawal symptoms and compulsive drug-taking). Once dependence is established, particularly with opiates, there may be repeated cycles of cessation and relapse extending over decades (NCDPEMTOA, 1998).

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 argues 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).

4.4   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). Of those attending for treatment (predominantly opiate users), most individuals develop dependence in their late teens or early twenties, several years after their first use of heroin, and continue use over the next 10–20 years. In a long-term outcome study (up to 24 years) of 581 male opiate users in the US, 29% were abstinent, 23% had positive urine tests for opiates, 18% were in prison and 28% were dead (Hser *et al.*, 1993). Longitudinal data from the US also showed that the average time from first to last opiate use was 9.9 years, with 40% addicted 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 opiate 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, conventionality in a social role (such as a job, mortgage or marriage), a social context not favourable to using drugs (for example, employment), and good health are not associated with long-term use. Peer influences are a major influence on experimental use and are also likely to influence the move towards regular use. The level of drug use is also a predictor of continued use; the more used, the more likelihood there is of continued problematic use. Once an individual is dependent, drug use is generally a chronic condition, interspersed with periods of relapse and remission. Repeated interaction with the criminal justice system, long-term unemployment and increasing social isolation serve to further entrench drug use.

4.5   The pharmacological effects of the misuse of opiates

Opiate drugs have many effects on the brain, mediated through specific receptors (μ, κ, or δ). The key opiate receptor subtype is μ, which mediates euphoria as well as respiratory depression and is the main target for opiates (Lingford-Hughes & Nutt, 2003). 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 agonists.

Soon after injection (or inhalation), heroin metabolises into morphine and binds to opiate receptors. This is subjectively experienced as a euphoric rush, normally accompanied by warm flush, dry mouth, and sometimes nausea, vomiting and severe itching. As the rush wears off, drowsiness, slowing of cardiac function and breathing (sometimes to the point of death in an overdose) persist for several hours (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.

The most obvious consequence of long-term opiate use is the development of opiate dependence itself, and the associated harms. Repeated injection will also 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).

4.6   The public health impact of drug misuse

The harms associated with illicit heroin use 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 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 times (Oppenheimer *et al.*, 1994) and 22 times (Frischer *et al.*, 1997) that of the general population. In England and Wales, there were between 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 of intentional self-poisoning. Opiates (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 opiate. This is supported by research that shows those whose deaths were attributed to overdose have opiate 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).

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, with 5.6% of all UK diagnoses attributed to injecting drug use by the end of 2005 (Health Protection Agency, 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, 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, 2005).

Psychiatric comorbidity, particularly anxiety and depression, is common in drug misuse populations, with antisocial and other personality disorders common 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 patients with schizophrenia compared with 16% in the general population, and 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 patients 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. 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 opiates 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).

4.7   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 patients who use drugs. Many drug users do not present to drug treatment services, with perhaps 50% of drug misusers not seeking treatment, although this represents a significant improvement on the position in the UK in the early 1990s when perhaps only 20% of drug misusers 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, 2006).

Routine screening for drug misuse is largely restricted in the UK to criminal justice settings, including police custody and prisons (Matrix Research and Consultancy & 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 patients admitted to hospital had undergone screening for drug misuse (Barnaby *et al.*, 2003). The updated National Treatment Agency's 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 on Drug misuse: psychosocial management of drug misuse (NICE, in press).

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 substance 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 blood-borne viruses, medical history, forensics and previous contact with treatment services. The assessment of a patient is a continuous process carried out at every contact with the individual and their healthcare professional/counsellor/social worker and can be carried out 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 the monitoring 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/liaise appropriately (that is, 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, HIV and immunisation against hepatitis should take place.

4.7.1 Clinical practice recommendations

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

4.7.1.2   Healthcare professionals should involve service users, and where appropriate their families and carers, in collaborative decision making about their treatment and subsequent care.

4.7.1.3   People who are opiate dependent should be treated with the same care, respect and privacy as any other individual.

4.7.1.4   In order to obtain informed consent, healthcare professionals should provide accurate and detailed information about the components of detoxification and the associated risks and benefits, including:

- the physical and psychological aspects of opiate withdrawal symptoms, including the length and intensity of symptoms, and how these may be managed
- the use of non-pharmacological approaches, where appropriate, to manage or cope with opiate withdrawal symptoms
- the potential medical risks inherent in detoxification
- the loss of opiate tolerance that follows detoxification and the ensuing risks, including overdose, because there is a potential risk of an increase in illicit drug and/or alcohol use as a response to opiate withdrawal symptoms
- the importance of continued psychosocial interventions and support, and appropriate pharmacological treatments, to maintain abstinence, and where necessary to treat comorbid mental health problems.

4.8   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 key-working 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 to the wider 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 opiate dependent, through the prescription of opiate substitutes (methadone or buprenorphine). This therapy aims to reduce or end their illicit drug use and the consequential harms of such.

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 overdose death in the event of relapse after a period of abstinence during which time drug tolerance is lost (Verger, 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 opiate drugs are eliminated from dependent opiate users in a safe and effective manner, such that withdrawal symptoms are minimised (WHO, 2006). With opiates, this process may be carried out by using the same drug or another opiate in decreasing doses, and can be assisted by the prescription of adjunct medications to reduce withdrawal symptoms (DH, 1999). .It is often the first stage in the process 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 involves the gradual reduction in dose to zero of the opiate and the use of adjunctive medication if necessary to help with withdrawal symptoms. Detoxification from opiates takes place in a variety of settings, including the community, inpatient units, residential units and prisons and at a variety of rates.

Care planning When developing any treatment or management plan, the content of such a plan should include:

- type and pattern of use

- level of dependence

- comorbid mental and physical health problems

- setting

- age and gender

- patient 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 mandated drug treatment have been reviewed recently elsewhere (NICE, 2007). For most people in long-term treatment, that is those with opiate 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.

Key-working forms the core part of treatment for most service users with long-term drug misuse problems (NTA, 2005). Typically, this involves the following:

- conducting an assessment of need (and 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 client in treatment and to support the treatment plan (for example, use of drug diaries and motivational skills) in the absence of delivering a complete episode of formal psychological therapy.

4.8.1 Clinical practice recommendations

4.8.1.1 Healthcare professionals should give appropriate advice to service users, and, where appropriate, facilitate referrals to relevant specialists (for example, dieticians), on aspects of lifestyle to which service users should pay particular attention during opiate detoxification. These include:
- a balanced diet
- adequate hydration
- sleep hygiene
- regular physical exercise.

4.8.1.2 Healthcare professionals who are responsible for the delivery and monitoring of an agreed care plan should ensure that:

- an appropriate therapeutic relationship is established and sustained
- the service user is helped to identify situations or states where he or she is vulnerable to drug use and to consider alternative coping strategies
- full access to a wide range of appropriate healthcare services is available to all service users
- maintaining engagement with services remains a major focus of the care plan
- effective liaison and collaboration with other care providers is maintained.

4.9 The development of detoxification services

As stated above, opiate 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). Opiate withdrawal includes a variety of symptoms: anxiety, tremors, nightmares, insomnia, weight loss, nausea, vomiting, seizures, 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 opiates 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 opiate 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 opiate users (Dole, 1989; Gerstein & Harwood, 1990). The aim of using methadone to detoxify heroin users is to suppress withdrawal symptoms through the provision of an opiate-based substitute medication. Service users are initially provided with a dose of methadone equivalent to their illicit opiate (heroin) use, and doses are gradually lowered until they are opiate-free. The most rapid regimes take 7 to 21 days, whilst '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 heroin

effects wear off in 2 to 3 hours, the effects of oral methadone continue for 12 to 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 opiate that acts as a substitute for heroin. It was licensed for use for opiate dependence treatment in the UK in 1999, and thus it is not as well established as other detoxification treatments (Lintzeris, 2002). Buprenorphine is a partial opiate 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 to 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 opiate withdrawal symptoms (those associated with the noradrenaline system; including sweating, shivering, runny nose and eyes). Clonidine, originally developed as an anti-hypertensive drug, had received widespread use as one of the first non-opiate-based options for managing opiate 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 opiate detoxification. Whilst alpha$_2$ adrenergic agonists allow for detoxification to be attained over a shorter length of time (typically ranging from 5 to 7 days) compared to buprenorphine, they do not address other (non-noradrenergic) withdrawal symptoms, and therefore must be supplemented by additional medications.

Problems commonly associated with detoxification treatment 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 opiate antagonist, first approved for use in 1984 as a maintenance treatment to block the effects of opiates after detoxification (Tai & Blaine, 1997). When used in the context of opiate detoxification, it displaces any opiates 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 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.

4.10 Current care and treatment in the NHS

The UK 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 patients who were addicted, 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 British 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 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.

The emergence of HIV/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 Department of Health and the National Treatment Agency as its key partners, introduced the Drug

Interventions Programme, 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 mandated treatment, whereby the person who misuses drugs is mandated 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 diversion away from the judicial process, usually following arrest and charge for drug-related and other offences. Despite recent policy shifts of diversion 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 (Department of Health, 2006c). Whilst 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 opiate substitution therapy and psychosocial interventions.

Current practice in detoxification

Much of the current treatment of drug misuse in the NHS services (those directly provided or purchased by the NHS) focuses on the treatment of opiate misuse. In large part, this is reactive to the drug problems that service users present, which 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 general practitioners (GPs) were seeing people who misused opiates compared with in 1989 (Strang *et al.*, 2005). GPs are now a large part of the substance misuse work force. 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.

Only a minority of people starting treatment choose abstinence initially; this is perhaps around 10% in secondary care services, but higher in primary care (perhaps over 20%). Enforced abstinence appears ineffective; in the region of 30,000 detoxifications are carried out each year and the majority are in the community. 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 attending either a GP or to a community drug team are assessed initially and their plans for treatment elicited. One of the dilemmas of drug treatment is that most service users want to become drug free so usually ask for detoxification. This is often unrealistic as the individual may have many risk factors which make abstinence unlikely to be possible for them at that time. These risk factors would include drug-related ones such as polysubstance use and social ones such as homelessness. 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 opiate (either methadone or buprenorphine). The stabilisation results in the cessation of illicit drug use with the individual feeling comfortable on the dose of substitute opiates they are 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 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, whilst buprenorphine reductions are typically carried out over 14 days to a few weeks. Detoxification using lofexidine is much faster than both, typically lasting 5 to 7 days, up to a maximum of 10 days.

Many service users in the community start detoxification programmes that ultimately fail because they start to use illicit drugs when their substitute opiate dose is reduced. The programme can then be changed to a maintenance one 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 programmes are not really detoxifications but gradual dose reductions. 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 environment can take place over a shorter time 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 opiate and then gradual dose reduction. In an inpatient environment reduction typically takes place over a shorter time; 14 to 21 days for methadone and 7 to 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 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 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.

4.11 The experience of drug misuse – personal perspectives

4.11.1 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 which had been 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, mushrooms, to dextromoramide, secobarbital, diazepam, dipipanone and methaqualone.

I was about sixteen 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 of 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 had suffered depression 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. At one point my father disowned me and my sister thought I was just a waste of time. I moved away from my hometown to London in 1982 in an attempt to give up heroin. Since then I 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. 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'. Being an addict, I lied a lot about where I was going and what I was doing.

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 key worker 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 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 lofexedine 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 two days later started taking subutex, 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 turned 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: subutex, 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 subutex I really don't have any craving for heroin. I am now thinking about stopping taking subutex.

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.

4.11.2 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 out of school. Eventually, I was expelled from school for selling drugs, non-attendance and disruption. I wasn't actually caught with any drugs when I was in school, but someone to whom I'd sold LSD got caught taking it by their parents, who then informed the school, who called the police. 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 peoples. Most people with whom I took drugs, for example amphetamine, 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 off 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, so 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 ten years. People would come to the house demanding money; one time I was even kidnapped, and my mother had to bail me out. I have 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 opiates, 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 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 whilst inside prison in November 2003. To gain entry into the programme, I had to agree to go on to 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 drug treatment and testing order (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 upon 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 never had I 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 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 key worker in probation agreed that I should be maintained on subutex 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 CBT techniques. I went through opiate 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 key worker 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.

4.12 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. For example, 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. Additionally, the NTA user satisfaction survey found that 25% of respondents felt that staff did not offer families and carers enough support (Best *et al.*, 2006).

There has also been a growth in carer organisations, most notably Adfam and Families Anonymous (FA), 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 (FA) 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 NICE, 2007). 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 (2002) report identified a number of needs for families of people who misuse drugs and alcohol. One of the major needs reported by families was the need to cope 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, 2002), but even where these services were available, many families were either not aware of them or knew 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 user and the workers.

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 support both 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).

4.12.1 Clinical practice recommendations

4.12.1.1 Healthcare professionals should explore with people who present for detoxification whether to involve their families and carers in their treatment, ensuring that the service user's right to confidentiality is respected.

4.12.1.2 Healthcare professionals should enquire about and discuss concerns regarding the impact of drug use on families (including children) and carers. They should also:

- consider offering the family member/carer an assessment of their personal, social and mental health needs
- provide verbal and written information and advice on the impact of drug use on service users, families (including children) and carers
- provide specific information about detoxification and the settings in which it may take place

- provide information about self-help and support groups for families and carers.

4.13 Economic impact of drug misuse

Drug misuse is a growing public health and health economics concern. It is often associated with health and social costs as a result of transmission of infectious disease, crime and violence (Petry *et al.*, 2004). In a study of 1,127 AIDS cases reported in Philadelphia (USA), 40% were attributable to drug use by injection (Davis *et al.*, 2005). It has been estimated that problematic drug use accounts for annual economic and social costs in England and Wales of approximately £13,750 million, or £35,455 per user, per year (Godfrey *et al.*, 2002. In addition to the costs of crime, chronic health problems comprise a significant element of the health and social care costs of drug misuse. For example, the prevalence of HIV among new injecting drug users is 4.2% (Judd *et al.*, 2005). The costs associated with HIV may have very little, if any, lag time following the initial infection. Godfrey and colleagues (2002) estimated the median per person annual cost of combination therapy at £13,381 for asymptomatic, £14,222 for symptomatic and £24,314 for patients 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% amongst 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 in 2002 was 53,975 (median estimate). An annual cost of £143 per year assumes a lifetime cost of £4,300 to treat patients 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 from the user, the NHS costs relating to drug misuse as it affected neonates 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. The same authors estimated the median number of HIV positive injectors in England and Wales at the time of 2002 to comprise 931 asymptomatic, 1,756 symptomatic and 1,007 with AIDS. Thus the health and cost burden due to drug-related diseases is considerable.

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 costs £ 1,000 per user, per year (Godfrey *et al.*, 2002).

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 opiate 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 opiate 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 opiates, additional to any prescribed medication. Often they may also misuse and be dependent on benzodiazepines and/or alcohol, or stimulants such as cocaine or amphetamines.

It is important that any opiate 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 healthcare professional conducting a clinical assessment that their degree of opiate 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 opiate drugs at all. This can lead to the prescription of dangerously high doses of opiates. Adequate assessment of a service user's opiate dependence status is therefore crucial prior to undertaking opiate detoxification.

Opiate 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 opiate 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 (for example, the Severity of Dependence Scale; Gossop *et al*, 1995) may sometimes be employed as an aid to the assessment of dependence. The use of biological testing is important to confirm the reported use of specific drugs, including prescribed and illicit opiates and other non-opiate 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 opiate 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 opiate 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 opiate 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 opiate 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 on deciding whether to detoxify from benzodiazepines concurrently or separately from opiates.

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 by a practitioner 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 again may be useful in that they aid standardisation, but they are not a substitute for appropriate clinical assessment. Regular review is crucial as 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   For people presenting for opiate detoxification, an assessment should be conducted to determine opiate dependence, as well as the misuse of and/or dependence on other substances including stimulants, alcohol and benzodiazepines. The assessment should include:

- urinalysis to aid the identification of the use of opiates and other substances; consideration may also be given to alternative/additional methods such as oral fluid and/or breath testing
- clinical assessment of opiate withdrawal symptoms where present (the use of formal rating scales may be considered as an adjunct to but not as a substitute for clinical assessment)
- previous history of drug and alcohol misuse, and current or previous treatment for these problems
- current and previous physical health problems and comorbid mental health problems, and current or previous treatment for these problems
- risk factors including risk of self-harm, potential increase in illicit drug or alcohol use as a response to opiate withdrawal symptoms, and loss of tolerance
- social and personal circumstances including employment and financial status, living arrangements, social support, criminal activity and the presence of any dependants.

5.2.3.2   For women who are opiate dependent during pregnancy, detoxification should only be undertaken with caution, and referral for specialist advice should be considered.

5.2.3.3   For people who are opiate dependent and have comorbid mental and/or physical health problems, such problems should be managed and treated, alongside the opiate dependence, in line with relevant NICE guidance (see section 6 of the NICE guideline).

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

5.2.3.4 For people presenting for opiate detoxification who also misuse alcohol, healthcare professionals should consider the following.

- If the service user is not alcohol dependent, attempts should be made to address their alcohol misuse. Healthcare professionals should be aware that service users may increase their alcohol misuse as a response to withdrawal symptoms associated with opiate detoxification, or substitute alcohol for their previous opiate misuse.

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

5.2.3.5 Healthcare professionals should consider benzodiazepine detoxification for people presenting for opiate detoxification who are also benzodiazepine dependent. Healthcare professionals should take into account the service user's informed choice and the severity of dependence for both substances when deciding on benzodiazepine detoxification, and whether it should be carried out concurrently with or separately from opiate detoxification.

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, opiate 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, whilst hair and blood testing are utilised to a lesser extent (Wolff, in press). 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 opiate 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, opiates, 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 (Wolff, 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 (Wolff, in press).

Whilst new technologies based on techniques such as Fourier transform infrared (FTIR) spectroscopy and nanotechnology are under active development and techniques using liquid chromatography in combination with tandem mass spectroscopy (LC-MS[n]) 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; Wolff, in press). 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 (Wolff, in press). 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 (Wolff, in press). A further advantage of this testing method is that it can detect drug use during the previous few days. Most opiates can be detected between 2 and 3 days after use, methadone up to 9 days and cannabis use 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, including various 'detox teas' (Wolff, in press). 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 opiates (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 opiates, 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.

Similarly, George and Braithwaite's (2002) review of near-patient testing for misused drugs suggested limited or variable sensitivity in detecting drug use. Moreover, Wolff (in press) argues that such devices may be useful for the detection of short-term usage of drugs but not suitable for widespread routine use.

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, whilst maintaining an acceptable balance between service-user dignity and sample integrity (Wolff, in press). On the other hand, many opiate users will have a dry mouth on presentation for detoxification and may have genuine difficulty in providing a suitable sample (Wolff, in press). 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 (Wolff, in press).

There is sparse evidence for the sensitivity and specificity of oral-fluid testing products (Wolff, 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 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 including if the sample was taken some time after drug ingestion, adulteration of 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 terminated rapidly with non-specialised staff or equipment.

The majority of the cases presenting for detoxification will involve opiates detectable by near-patient testing. However some opiates, 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 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 of a high standard, with appropriately trained staff who all participate in programmes of continuing professional education, where there are appropriate established standard operating and safety procedures in place, and where there is participation in quality assurance schemes which 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, 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; Wolff, in press). 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 opiates 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 in the safe management of service users undergoing opiate 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 opiate 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 very clear of the confirmation of clinical dependence or organise a setting with adequate observation and dose titration.

Training is important for all clinicians and 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 need for confirmatory testing and ensuring clinical governance and quality assurance to this aspect of care.

5.3.5   Clinical practice recommendations

5.3.5.1   Healthcare professionals should, in addition to near-patient testing, normally use confirmatory laboratory tests (analyses of biological samples, for example, urine or oral fluid) to test for the

presence of certain target drugs, when opiate dependence or tolerance is uncertain, including:

- when a young person first presents for opiate detoxification
- when a near-patient test result is inconsistent with clinical assessment.

5.3.5.2 Near-patient and confirmatory testing should be conducted by appropriately trained staff according to established standard operating and safety procedures.

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

- appropriate monitoring of medication compliance
- means of limiting the possibility of diversion where necessary, including the use of supervised consumption

5.4 Psychometric assessment tools

5.4.1 Introduction

The importance of a clinical assessment of opiate (and other drug or alcohol) dependence and monitoring withdrawal before and during detoxification has been discussed above (see section 8.2). This section is concerned with the use of psychometric instruments as adjuncts to clinical assessment and monitoring.

Crome and colleagues (2006) argue there are a number of advantages for the use of assessment tools these include: recording is standardised, a checklist of domains ensures that important issues are covered, and that multidisciplinary professionals have a common shared understanding of what has been assessed. Furthermore, if tools are implemented over time this 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 will be discussed below.

5.4.2 Assessment of dependence

Identification (simple assessment) tools have most recently been reviewed by NICE (2007). 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 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

Leeds Dependence Questionnaire (LDQ; Raistrick *et al*, 1994) is a 10 item self-report scale designed to measure dependence upon 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 SODQ for opiate users, 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%).

Severity of Dependence Scale (SDS; Gossop *et al,* 1995) is a short (five item) self report scale designed to measure the degree of dependence for a variety of drugs. The SDS was related to behavioural patterns of drug taking such as heroin dose (r =0.24), frequency of heroin use (r=0.43), and duration of heroin use (r=0.27). In addition, it has good concurrent validity, with treatment-seeking participants reporting higher mean scores (t=10.00, p<.001) than non-treatment seeking controls (Gossop *et al*, 1995). The scale was also found to have a high level of internal consistency (Cronbach alpha 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 (99%) the most highly out of all the assessment scales they reviewed. However, another reviewer expressed major concerns for 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, psychiatric. This assessment tool has been investigated extensively. Makela (2004) in a review of 37 studies on the psychometric properties of the ASI concluded 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).

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.

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, 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, both Sperling and colleagues (2003) and Scottish Executive reviews raised caution about 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.

Christo Inventory for Substance-misuse Services (CISS; Christo *et al*, 2000) is a 10 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 ICC of 0.82. Both Sperling and colleagues (2003) and Scottish Executive (2003) reviews 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 their dose. This is primarily monitored by clinical assessment but the use of psychometric measures can be an aid in 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: Clinical Opiate Withdrawal Scale (COWS; Wesson & Ling, 2003) Opiate Withdrawal Scale (OWS; Bradley et al 1987), Short Opiate Withdrawal Scale (SOWS; Gossop, 1990), Subjective and Objective Withdrawal Scale (SOWS/OOWS; Handelsman *et al.*, 1987).

The self-reported Opiate Withdrawal Scale 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. A rise in distress was reported as methadone dose was reduced 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 opiate withdrawal scale and nurse observation of withdrawal. Although correlations between nurse observation and the opiate withdrawal scale 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 Opiate Withdrawal Scale (32 items). A very high correlation (r = 0.97) was found between these measures suggesting the usefulness of the shorter version.

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

6.1 Introduction

The aim of detoxification for a dependent opiate user is to eliminate the effects of opiate 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 opiate dependence

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

Opiate agonists

All opiates, including heroin and methadone, are agonists which stimulate opiate receptors. A range of opiate 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 opiate 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).

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), buprenorphine will displace the full agonist to occupy all the receptors but only partially stimulating the receptors, with the difference resulting in the individual experiencing withdrawal. This can be seen when a person converts 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 opiate agonist, it behaves like an antagonist. Buprenorphine is 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; it is a low potency μ agonist but may also have partial agonist properties. 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 opiate 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 will stop this stimulation, resulting in abrupt withdrawal.

Tolerance

If opiates 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 opiates is not clearly defined in the literature, but it is likely that it involves changes in opiate receptor availability and function through changes within the cell or effects on other neurotransmitter systems, for example noradrenaline (Maldonado, 1997). In a dependent opiate user, changes in the brain's circuitry (involving reward, learning, impulse control) also occur. The brain's opiate system is thought to play a significant role in mediating reward to other drugs of abuse including alcohol and cocaine (Herz, 1997; Van Ree *et al.*, 2000). Tolerance can also vary depending on the context or environment in which the opiate is being taken and can lead to a dose of opiates 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. Minimising these symptoms, which emerge within 6 to 12 hours from short-acting opiates such as heroin and about 24 to 36 hours after the last dose of methadone or buprenorphine depending on the dose, is the main aim in any opiate 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 antagonist, such as naloxone or naltrexone for opiates, is taken; this is called precipitated or abrupt withdrawal. While the withdrawal syndrome for opiates is rarely life-threatening (unlike for alcohol due to the potential for seizures and delirium tremens), the discomfort for some people makes it hard to withstand.

Opiate 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 opiate 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 opiate system directly producing withdrawal symptoms are less clear, although increased receptor availability has been shown (Williams, 2007, in press). Gradual reductions of opiate 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 opiates 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 opiate users when they cannot obtain heroin.

6.2 Pharmacological interventions in detoxification

6.2.1 Introduction

Opiate agonists and partial agonists

The most straightforward pharmacological approach to detoxify a dependent opiate user is by the reduction over a period of time of an opiate 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 to 21 days, whilst '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 from heroin (indeed any opiate 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 opiate substitute prior to starting detoxification.

Opiate antagonists

Opiate 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 opiate antagonist to remove all agonists and fully occupy the opiate receptors. If given at the start of detoxification, this will lead to abrupt withdrawal for a dependent user with opiates in their 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 opiate antagonists in this way is often referred to as ultra-rapid or rapid detoxification and covered in detail in section 6.3.

Alternatively to minimise discomfort, naloxone or naltrexone are started after a few days of detoxification and not at full dose, thus avoiding requiring sedation or general anaesthesia. This approach is covered in greater detail in section 6.1.8.

Adjunctive medications

Adjunctive medications are used to ameliorate symptoms of opiate 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 opiate 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 medication is often used during detoxification. This is particularly important when conducting a detoxification with non-opiate 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 sedation, is also not uncommon during a detoxification using opiate 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 in to consideration. This is especially important when comparing opiates (methadone or buprenorphine) against noradrenergic alpha$_2$ adrenergic agonists (clonidine or lofexidine).

Current practice

In the UK, only methadone and buprenorphine are licensed as substitute opiates for the management of opiate dependence. In addition, lofexidine is licensed for symptomatic relief during opiate detoxification. These medications are currently used in the vast majority of opiate 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 opiate 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 opiate 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 9.

6.2.2   Treatment outcomes

Abstinence

This refers to evidence for the absence of drug use at a particular time point (for example, at end of treatment or 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 re-establishment 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 opiates, many signs and symptoms can become evident. These can be categorized broadly as due to opiate 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 opiate use may have reduced their 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 amongst 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.*, 1997).

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 opiate agonist, methadone can result in respiratory depression. Therefore initiation should be undertaken with care (NICE, in press). 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 opiate 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, in press). The additive or synergistic effects of

such depressant drugs, particularly alcohol or benzodiazepines, may play a contributory role to deaths involving either methadone, buprenorphine or other opiate 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 which 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, whilst 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 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	Opiate dependent
Interventions	Methadone, buprenorphine, other opiate agonists, alpha$_2$ adrenergic agonists, opiate 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 for observational studies was undertaken to assess the safety of pharmacological detoxification.

The following treatments were included in this review:
- Methadone
- Buprenorphine
- Dihydrocodeine
- Clonidine
- Lofexidine
- Naltrexone
- Naloxone
- Benzodiazepines
- Carbamazepine

6.2.6   Opiate agonists

Methadone

For comparisons of methadone against other opiate 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.

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

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[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).

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

	Methadone versus other opiate 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
Diagnosis	Opiate dependence	Opiate dependence	Opiate dependence Polydrug use: illicit benzodiazepines 67.6%, crack cocaine 35.2%, cocaine powder 22.1% (HOWELLS2002); benzodiazepines 43% (BEARN1996)
Mean years of opiate use	7.8 to 9.1 (TENNANT 1975), 13.6 to 16 (TENNANT1978)	2 to 6 (GERRA2000), 8.8 to 9.5 (HOWELLS 2002)	Heroin: 10.5 (BEARN1996)
Mean daily opiate use	Not reported	Street heroin: 1.5 to 2.0 (GERRA2000)	Heroin (g): 0.46 (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	10-20 days 10 days: HOWELLS2002 20 days: BEARN1996
Length of follow-up	Up to 18 months	None	None
Age	28 to 37 years	24 to 40 years	31 to 32 years

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

	Methadone versus other opiate 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
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) *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 = 54 *Lowest*: SMD -0.03 (-0.53 to 0.47) K = 1, N = 54 *Overall*: SMD -0.12 (-0.62 to 0.37) K = 1, N = 54

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 opiate detoxification

Study ID or reference	Primary detoxification regimen	Adjunct medications	Symptoms of withdrawal, medication side effects and adverse events (AEs)
Methadone versus other opiate agonists (RCTs)			
SALEHI2006	**Methadone** versus **tramadol**	Both groups given 0.3mg/day clonidine and 10 to 30mg/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 groups at end of active medication period, but methadone group had significantly more drowsiness and sweating – at end of 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 opiate 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** (24mg) versus **propoxyphene napsylate** (800mg)	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 to methadone patients (16.7%).
TENNANT1978	**Methadone** (15mg) versus **methadone** (25mg) **+ propoxyphene napsylate** (600mg)	Not mentioned.	Many side effects listed including numbness, 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 60mg twice daily for 2 days, baclofen 10mg three times daily, ketoprofene IV 400mg daily	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
		Did not report administration of adjuncts to remaining groups.	Methadone group: presented anxiety, tachycardia, insomnia, rhinorrhoea, mydriasis, aching muscles and irritability. Also showed a consistent level of dysphoria.
JIANG1993	**Clonidine** versus **methadone**	Not mentioned.	List of 21 symptoms, includes: 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** (20mg) vs **clonidine** (0.3 up to 1.0mg, depending on withdrawal severity and effect on BP)	'The only additional medication permitted during the study was choral hydrate, 0.5 to 1g, for insomnia' However: 'A "blind" physician… gave recommendations as to the need for ancillary medication *such as* [emphasis added] for 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.	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: 10 methadone and 7 clonidine due to 'rated as experiencing unacceptably high withdrawal symptoms'; 1 methadone and 7 clonidine due to 'rated as experiencing unacceptable side effects' Side effects in 2 cases (both clonidine) were severe: 1 persistent vomiting, 1 complained of impaired breathing and 'throat swelling' Comment: Hypotension was not a prominent side effect.
SAN1990	*Clonidine (max 1.05mg; CLON) versus guanfacine (max 3.58mg; GFN) versus methadone (max 37.3mg; MTD)*	'Exceptionally prescribed benzodiazepines.'	'More frequently observed side effects during detoxification' were: MTD group – hot flashes, asthenia, salivation, mental clouding, thirst CLON and GFN groups – asthenia, dry mouth, flushing, mental clouding (in that order, and CLON > GFN) Recorded hypotension with CLON and GFN Comment: No description of adverse events.
UMBRICHT2003	**Buprenorphine** versus **clonidine** versus **methadone** All participants were HIV positive.	*Used morphine to control withdrawal symptoms whilst waiting for enrolment, and also for pain relief during detoxification – data only available for 53 patients, and 50% had morphine.*	*Clonidine group – 2 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.

WASHTON1980	**Methadone** vs **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** (~60mg)	*If on benzodiazepines given some diazepam, otherwise not mentioned.*	*Two patients (female) experienced dizziness, so lofexidine dose reduced.*
HOWELLS2002	**Lofexidine** (0.6 up to 2.0mg, then tapered to 0) vs **methadone** (30mg)	'Only a very small amount' – 4/32 (12.5%) in lofexidine group and 7/36 (19.4%) in methadone group: 2 in each group received diazepam for entire duration of study for their benzodiazepine dependence 1 in each group taking medication for pre-existing conditions (epilepsy and hereditary angioedema) 2 in lofexidine group received medication for insomnia, 1 in methadone group for nausea and vomiting	Few occurrences of transient hypotension (sitting systolic BP < 90mmHg) 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).

Table 4 and Table 5 show studies comparing methadone against 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 to other opiate agonists (propoxyphene napsylate, LAAM, tramadol). These are neither licensed nor routinely used in the UK for the treatment of opiate dependence.

Buprenorphine

For comparisons of buprenorphine against 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. Whilst 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 with one study conducted on adolescents (MARSCH2005). In addition, one cluster-randomised trial (PONIZOVSKY2006) compared buprenorphine against methadone. All were published in peer-reviewed journals, with additional unpublished data for one trial provided by the authors (RAISTRICK2005).

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

Table 6: Study information table for trials of buprenorphine for opiate 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	Opiate dependence Other substance dependence: 33 to 42% (cocaine; PETITJEAN2002) Other substance misuse: alcohol (50%), cocaine (46%), benzodiazepines (62%) (SEIFERT2002)	Opiate dependence Other substance dependence: alcohol 5.2 to 12%, cocaine 17.3 to 22.1%, benzodiazepines 0.9 to 4.4% (LING2005), alcohol 17 to 18%, cocaine 3 to 17%, cannabis 12 to 22% (MARSCH2005)	Opiate dependence Other substance use: 37%, including cannabis (16%), cocaine (15%), benzodiazepines (6%) and alcohol (6%)
Mean years of opiate use	Months of present addiction: buprenorphine 19.8 (14.0), methadone 38.1 (49.4) to 40.9 (55.9) (JOHNSON1992) Years opiate misuse: 8.6 (6.8)-10.5 (7.5) (SEIFERT2002), 4.6-4.7 (PETITJEAN2002)	10.7 to 12.6 (CHESKIN1994), 7 to 9 (LING2005), 7.5 (3.6) (JANIRI1994), 4-5 (NIGAM1993), 7.7 to 8.9 (O'CONNOR1997)	
Mean daily opiate 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) Polysubstance use: weekly cocaine 0.38 to 0.96g, weekly alcohol 3.3 to 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) vs 4 days (lofexidine)
Length of follow-up	None	Up to 1 month	1 month
Age	32 to 40 years	17 years: MARSCH2005 21 to 45 years: all other studies	28 years

Table 7: Summary evidence table for trials of buprenorphine for opiate 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
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 *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	*1 month follow-up*: 35% versus 25%, RR 1.37 (0.90 to 2.09) K = 1, N = 210
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) N = 3, K = 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)			
JOHNSON1992	**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.
PETITJEAN2002	**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 900mg).	'No severe side effects occurred during treatment in either group.'
UMBRICHT2003			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* *For first 3 days, mean peak and area-under-curve diastolic and systolic BP 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 BP and heart rate.*
LING2005	**Buprenorphine-naloxone** versus **clonidine**	Use of ancillary medication was the same in inpatient study for buprenorphine-naloxone & clonidine. Mean ~ 2.7 doses. Also no difference for completers. 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.	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 vs 1.1 Serious AEs: Inpatient – 2 deaths: respiratory failure in buprenorphine-naloxone, bacterial endocarditis in clonidine group. Neither was due to study medication. In addition: buprenorphine-naloxone – 2 had suicidal behaviour, 1 had severe vomiting Clonidine – vomiting, road traffic accident, cellulitis Outpatient sites – 14 cases in buprenorphine-naloxone (10 continued substance misuse/overdose, 2 depression, 1 severe vomiting, spine surgery?), 4 in clonidine group (1 of each of following: substance misuse, nausea/vomiting, pneumonia, kidney stones). No deaths. Comment: No description of timeframe of AEs.

LINTZERIS2002	**Buprenorphine** (10mg) vs **clonidine** (0.9mg) in dependent heroin users (had not been undergoing MMT)	Clonidine group - metoclopramide (mean 17.7mg, frequency unknown), diazepam (14mg) to temazepam, quinine (380mg), hyoscine (34mg), ibuprofen (940mg) Does not appear that buprenorphine group were offered any adjuncts.	Similar reports in both groups. Buprenorphine group – 1 patient had precipitated withdrawal when given buprenorphine, so 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** vs **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 used, timing, amount and type of use not reported* Existing medications at intake or during study were tracked to ensure they were not contraindicated with study medications.	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.
O'CONNOR1997	**Buprenorphine** versus **clonidine** versus **clonidine with naltrexone**	Clonidine was prescribed to *all* groups, 0.1 to 0.2mg every 4 hours as needed, to control withdrawal symptoms Following adjunct medications also available to all participants as needed: oxazepam (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 (15mg nocte). Aspirin and imodium also given to a 'few'	*Clonidine: greater hypotension (3 patients left study as a result), c/o also of giddiness, dry mouth, constipation*

PONIZOVSKY 2006 (cluster-randomised trial)	**Buprenorphine** (median 10mg) vs **clonidine** (0.15mg x 4)	Clonidine group – promethazine 150mg/day, dipyrone 1,500mg/day, trazodone 100mg/Nocte, phenobarbital 200mg/Nocte, antiemetics Does not appear that buprenorphine group gets these medications.	Significantly lower level of side effects for buprenorphine compared to clonidine *No mention of hypotension* Comment: Does discuss overlap between withdrawal symptoms and side effects.
UMBRICHT2003		See Table 5 [Methadone]	
Buprenorphine versus lofexidine (RCTs)			
RAISTRICK2005	**Buprenorphine** versus **lofexidine**	Buprenorphine group: vast majority received no adjuncts, however 5 participants received chlordiazepoxide on Day 1 or Day 2. Lofexidine group: Published lofexidine protocol began with 1600mg on Day 1, "allowed for clinical judgment but in practice the regimens were rarely subject to significant variation". *Majority of participants began with lofexidine 800mg and chlordiazepoxide 70mg*. Cophrenotrope, hyoscine butylbromide or chlorpromazine listed in published lofexidine regimen, but not to have been used by any participant in either group.	'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 have been logged as an adverse event, rather misjudged [detoxification] management."

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 to 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-analyses and is thus summarised here. Opiate dependent participants were randomised to receive 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 to 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 opiate agonist licensed in the UK for pain relief. It has also seen some use in a range of UK settings as a substitute medication for opiate dependence both in maintenance and detoxification (Day et al., 2005; Strang et al., 2005; Wright et al., 2007).

Two RCTs (WRIGHT2007A, WRIGHT2007B) comparing dihydrocodeine against buprenorphine met the eligibility criteria, providing data on 150 participants. One (WRIGHT2007A) was published in a peer-reviewed journal, with unpublished data for both trials provided by the authors.

Table 9: Evidence table for trials of dihydrocodeine for opiate detoxification

	Buprenorphine versus dihydrocodeine
Total no. of trials (total no. of participants)	2 RCTs (N = 150)
Study ID	WRIGHT2007A WRIGHT2007B (unpublished)
Diagnosis	Opiate dependence
Mean years opiate use	7.8 (WRIGHT2007A), 9.3 (WRIGHT2007B)
Mean daily opiate use	Illicit opiates: £15.60 to £23.20 (WRIGHT2007A), £41.05 to £45.56 (WRIGHT2007B)
Treatment length	12 days (dihydrocodeine) versus 9 days (buprenorphine)
Length of follow-up	6 months
Mean age	29 to 31 years
Overall quality of evidence	High
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, 2.86) *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) N = 2, K = 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 (AEs)
Buprenorphine versus dihydrocodeine (RCTs)			
WRIGHT2007A	**Buprenorphine** versus **dihydrocodeine** Dosages at the discretion of prescribing doctor but within standard regimens.	None reported.	'*No serious adverse events were reported*'
WRIGHT2007B (unpublished)	**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   Alpha2 adrenergic agonists

Alpha$_2$ adrenergic agonists act to reduce the noradrenergic hyperactivity seen in opiate withdrawal. They are therefore a type of adjunctive medication. They can be either used alone or alongside a rapid reduction in opiate 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 in to 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.

Table 11: Study information and summary of evidence table for trials of alpha$_2$ adrenergic agonists in opiate 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	Opiate dependence: all Heroin: 100% (LIN1997) MMT: 64.8% (CARNWATH1998) IDU: 56.4% (CARNWATH1998), 88% (LIN1997) Polydrug use: 35.7% (KAHN1997), 17.5% (methamphetamine; LIN1997)	Opiate dependence: all Heroin: 100% (SAN1994) MMT: 100% (GHODSE1994) HIV positive: 52% (SAN1994)
Mean years of opiate use	6.9 (CARNWATH1998), 3 to 6 (GERRA2001)	Not reported
Mean daily opiate use	Heroin (g): 1.5 to 2.0 (GERRA2001), 1.05 (LIN1997)	Heroin (g): 0.66 (SAN1994) Methadone dose at entry (mg): 35.1 (GHODSE1994)
Treatment length	3 days: GERRA2001 6 days: LIN1997 12 days: CARNWATH1998 18 days: KAHN1997	14 days: GHODSE1994 18 days: SAN1994
Length of follow-up	Up to 3 months	None
Age	20 to 32 years	25 to 27 years
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 0.96 (0.63 to 1.46) 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 to 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 alpha₂ adrenergic agonists in opiate 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 (<40mg) or using heroin – stopped abruptly at start of detoxification. 0.2mg versus 0.1mg – upto 8 capsules	Clonazepam 0.5mg four times daily, nitrazepam 10mg, hyoscine 20mg 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 SOWS between lofexidine and clonidine No further description *Comment: Patients were asked if symptoms were side effects of drug or due to withdrawal.* Some went back onto methadone at end –what was the aim of detoxification?
GERRA2001	**Lofexidine** (1.2 to 1.6mg) versus **clonidine**	Oral oxazepam 60mg twice daily, oral baclofen 10mg three times daily (for muscle relaxation), ketoprofene IV 400mg (non-steroidal analgesic). All participants received naloxone IV (0.04mg) and naltrexone (5mg) on second day.	Measured blood pressure – systolic BP 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'

KAHN1997	**Lofexidine** (0.4mg) versus **clonidine** (0.2-1.8mg) for patients previously undergoing MMT (stopped on day 3)	Clonidine group – 8 patients received regular psychoactive medication: 3 nitrazepam, 4 temazepam, 1 temazepam + thioridazine (against protocol) Lofexidine group – 5 patients: 1 nitrazepam, 4 temazepam No doses or frequency mentioned For acute anxiety or agitation additional medication – lorazepam – was available. Used by 10 patients in each group: on 71 occasions in lofexidine group (126mg total), 72 in clonidine group (148.5mg 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: 4 patients, all clonidine; no further description Comment: *What were adverse events and what were withdrawal symptoms?*
LIN1997	**Lofexidine** (0.2mg) versus **clonidine** (0.075mg, four to eight times daily) for dependent heroin users	Lorazepam (1-2mg four times daily) Flunitrazepam (4-8mg 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: *Measured hypotension and withdrawal symptoms – on which was withholding of medications based?*
Methadone with alpha₂ adrenergic agonists versus methadone alone (RCTs)			
GHODSE1994	**Clonidine** (0.2-1.2mg) versus **methadone** (~60mg)	Not mentioned.	10 patients – 9 were in clonidine group (of 42) left study due to hypotension Comment: No difference in side effect profile.

| SAN1994 | **Methadone** (MTD group) versus **methadone + guanfacine -** GFN-1 group: 3mg; GFN-2 group: 4mg

Methadone dosages were individually titrated at start to body weight and amount of heroin used, but by Day 8 MTD 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 19.0mg for MTD; 20.3mg for GFN-1, 16.3mg for GFN-2

No frequency or duration of administration reported. | Similar decreases in blood pressure in MTD and GFN-1 groups

Greater reduction in GFN-2 groups (d13 when 4mg reduced to 2mg)

No pre-post difference in heart rate in MTD or GFN-1, but bradycardia in GFN-2.

Comment: Asthenia – either side effect of guanfacine or withdrawal symptom

'Low' doses of MTD: 38mg |
|---|---|---|---|

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 a full description was lacking of which medication was used, nor was it possible to take this fully in to 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

Opiate antagonists

In conscious, non-sedated patients, opiate antagonists such as naloxone or naltrexone have been used to accelerate detoxification in combination with clonidine or lofexidine or buprenorphine. In addition this approach may help establish service users on naltrexone for relapse prevention.

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 335 participants.

In this approach, unlike more accelerated detoxification regimens using opiate antagonists (ultra-rapid, rapid, see section 6.3) detoxification had already commenced (BESWICK2003A, GERRA1995) and/or a low dose of the opiate 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 (12.5mg) is different to the so-called 'Asturian method' where 50mg of naltrexone is given at the start with a greater range and higher doses of medication to treat opiate withdrawal symptoms (Carreno *et al.*, 2002; see section 6.3.5).

Table 13: Evidence table for trials of opiate antagonists as adjuncts in opiate detoxification

	Rapid detoxification with opiate antagonists as adjuncts versus no opiate antagonists
Total no. of trials (total no. of participants)	5 RCTs (N = 399)
Study ID	Naloxone with lofexidine: BESWICK2003ANaltrexone with clonidine: GERRA1995 GERRA2000 O'CONNOR1997 Naltrexone with buprenorphine: UMBRICHT1999
Diagnosis	Opiate dependence: all Heroin: 100% (GERRA1995) IDU: 30% (UMBRICHT1999)
Mean years of opiate use	Heroin: 2 to 4 (GERRA1995), 2 to 6 (GERRA2000), 6.5 to 8.3 (UMBRICHT1999), 7.7 to 8.9 (O'CONNOR1997)
Mean daily opiate use	Heroin: 0.5g (GERRA1995), 0.55g (BESWICK2003), 1.5 to 2.0 (street heroin; GERRA2000) Bags of heroin in past 30 days: 3.8 to 4.0 (O'CONNOR1997) Days of heroin use in past 30 days: 29 (UMBRICHT1999Methadone dose at entry (mg/day): 41.9 (BESWICK2003)
Treatment length	4 days: GERRA1995 6 days: BESWICK2003A 8 days: O'CONNOR1997, UMBRICHT1999
Length of follow-up	Up to 6 months
Age	18 to 56 years
Overall quality of evidence	Moderate
Benefits	
Abstinence	*Maintained abstinence throughout at 9-month follow-up*: 20% versus 9%, RR 2.30 (0.76 to 6.94) *Abstinent in past month at 9-month follow-up:* 36% versus 26%, RR 1.36 (0.73 to 2.55) K = 1, N = 91
Drug use	*Relapsed by 6-month follow-up*: 47% versus 56%, RR 0.83 (0.52 to 1.35) K = 1, N = 64
Completion of treatment	78% versus 77%, RR 1.01 (0.86 to 1.17) K = 4, N = 335
Started naltrexone maintenance	RR 1.41 (0.96 to 2.07) K = 1, N = 64
Self-rated withdrawal severity	*Peak*: SMD 0.51 (-0.58 to 1.60) K = 2, N = 162 *Overall*: SMD -0.13 (-0.51 to 0.24) K = 1, N = 109*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 14: Adjunct medications, symptoms and adverse events for opiate antagonists in opiate detoxification

Study ID or reference	Primary detoxification regimen	Adjunct medications	Symptoms of withdrawal, medication side effects and adverse events (AEs)
Rapid detoxification with opiate antagonists as adjuncts versus no opiate antagonists (RCTs)			
BESWICK2003A	**Lofexidine** (1.8mg) **with naloxone** (0.8mg) versus **lofexidine with placebo**	Prochlorperazine (5mg) given at start to alleviate nausea Diazepam available as required evening before first dose of study medication (5mg) and daily (max 15 to 20mg) thereafter to reduce anxiety and restlessness. Additional lofexidine (up to 0.4mg/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 day 3 one hour after the injection, and then at times on days 5, 6, 7 & 8. More diazepam was used in the 'naloxone' group on day 3 & 4 but not on other days.
GERRA1995	**Clonidine with naltrexone** versus **clonidine with placebo**	Not mentioned.	*List of 9 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]		

UMBRICHT1999	**Buprenorphine with naltrexone** versus **buprenorphine with placebo**	A range of medications according to 'standard indications' for withdrawal symptoms, initiated when OOWS is 5 or greater	Measured withdrawal using Objective Opiate Withdrawal Scale (OOWS)
		Included: clonidine (83% of participants), hydroxyzine (77%), diazepam (25%), ibuprofen (50%), acetaminophen (78%), dicyclomine (43%), diphenoxilate (35%). 16% in each group required no adjuncts	Among dropouts, 4 participants in naltrexone group gave withdrawal as reason (including 1 abdominal pain), 1 from placebo group experienced severe buprenorphine-induced withdrawal, and acknowledged having used methadone just before admission
		Mean and dose ranges given; significantly more participants in naltrexone group received hydroxyzine, and significantly higher doses of ibuprofen also used in this group.	Regarding physiological measures including pupil size, heart rate, BP: *"It cannot be excluded that adjunct medication used for withdrawal management on day 2 and day 8 may have blunted differences between groups"*

In summary, adding an opiate antagonist to a clonidine, lofexidine or buprenorphine detoxification had no effect on completion of detoxification, but showed a trend for increased withdrawal severity, as might be expected from precipitating withdrawal. There was also a trend for increased abstinence at follow-up, but it is unclear whether this may be attributed to the use of naltrexone or naloxone during detoxification itself, or an increase in uptake of naltrexone maintenance subsequent to detoxification.

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 opiate agonist for opiate detoxification has been studied. One study (DRUMMOND1989) has 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. The meta-analysis failed to find a difference between the use of benzodiazepines and opiate agonists for completion of detoxification treatment (see Table 15).

Table 15: Evidence table for trials of benzodiazepines for opiate detoxification

	Opiate 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	Opiate dependence
Mean years of opiate use	4.7 (DRUMMOND1989), 10.1 (SCHNEIDER2000)
Mean daily opiate use	Heroin (g): 0.8 (DRUMMOND1989)
Treatment length	13 days: DRUMMOND1989 21 days: SCHNEIDER2000
Length of follow-up	None
Age	24 to 31 years
Overall quality of evidence	Low
Benefits	
Completion of treatment	57% versus 48%, RR 1.19 (0.71 to 1.98) N = 2, K = 50

RR > 1 favours opiate agonists.

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 against 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 proportion (RR = 6.50; 95% CI: 0.90 to 47.19) of the diazepam group (5 of 10) completed detoxification in comparison with the doxepin group (1 of 13), who also presented a greater proportion of opiate-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, Bigelow and Liebson (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 20mg/day, or clonidine 0.2mg/day) and placebo capsules, in a random order. Participants then received either capsule of their choice. All participants were tapered from 50mg 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 *et al.*, 2003) as well as being used for a variety of neuropsychiatric conditions. Therefore, the rationale of using it as an adjunct in opiate detoxification is to see if carbamazepine improved outcome in polydrug users. Two studies have given carbamazepine to all patients when comparing methadone and buprenorphine detoxification (SEIFERT2002) and 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

Table 16: 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	Opiate dependent
Interventions	Pharmacological medication: Methadone, buprenorphine, other opiate agonists, alpha$_2$ adrenergic agonists, opiate antagonists, sedatives (including benzodiazepines and Z-drugs) Dosage of medication: low, moderate, high starting dose Duration of detoxification: short, moderate, long duration of 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

The efficacy of substitute (for example, methadone or buprenorphine) and adjunctive medications (for example alpha$_2$ adrenergic agonists) have 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 17 summarises study information and evidence from studies comparing high and moderate starting doses. Both studies were on methadone and may be considered as slow taper regimens, consisting of a six 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.

Table 17: Study information and summary of 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	Opiate dependence
Mean opiate use	No data (BANYS1994) 25.3 times in last 30 days (STRAIN1999)
Treatment length	70 days: STRAIN1999 79 days: BANYS1994
Length of follow-up	None
Age	18 to 65
Overall quality of evidence	Moderate
Benefits	
Abstinence	*Proportion opiate 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 = 1, N = 142

RR > 1 and negative SMD favours high dose.

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 60mg methadone over 70 days (n = 13), or from 30mg 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 Opiate Withdrawal Scale 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, 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 to be 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 (χ^2 = 4.49, $p < 0.05$), and in a significantly shorter timeframe (t = 1.97, $p < 0.05$). However urinalysis suggested no significant difference between groups in illicit opiate use (12.5% for self-regulated, 53.3% for fixed) 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%, χ^2 = 32.12, $p < 0.01$), 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 & 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 Opiate Withdrawal Scale during the acute phase of withdrawal (F = 4.34, $p < 0.05$).

Duration of buprenorphine detoxification

The typical duration of detoxification using buprenorphine is between 4 to 8 days. There is one RCT (Assadi *et al.,* 2004) that compared regimens using a high dose buprenorphine in the first 24 hours only, with a more typical regimen reducing buprenorphine over 5 days. Buprenorphine was given intramuscularly; the high dose (12mg; 6 x 1.5mg doses) was equivalent to 21.3 mg sublingual and reducing regimen started at 1.5mg bd of intramuscular buprenorphine. No significant differences in treatment retention, successful

detoxification (negative naloxone challenge test) or severity of withdrawal were reported. Adjunctive medications (trazodone, indomethacin) were used more by the high dose group than when buprenorphine was reduced with equal amounts of the others (diazepam, chlorpromazine, hyoscine).

Clinical summary

For methadone, a high starting dose (80-100mg/day) appeared to be superior to a standard starting dose (40-50mg/day) in abstinence (opiate 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 opiates. Improved completion rates could be the result of participants being better stabilised at the outset on a higher dose.

Regarding the duration of detoxification, a long methadone taper (up to 70 days) or a fairly short programme (14 days) were no better than a standard 21-day taper. Also keeping service users fully informed about different aspects of detoxification appears to have some effect in minimising reported withdrawal severity.

6.3   Overall summary

Opiate agonists - Methadone and buprenorphine both appeared to be effective in comparison with other detoxification treatments such alpha$_2$ adrenergic agonists and other opiate 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 were 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 opiate withdrawal and often were non-specific.

6.4 Clinical practice recommendations

6.4.1 The use of opiate agonists

6.4.1.1 Buprenorphine or methadone should be considered the first-line treatments in opiate detoxification. When deciding between these medications, healthcare professionals should take into account the following factors:

- if the service user is currently maintained on methadone or buprenorphine, opiate detoxification should normally be started on the same medication
- the informed preference of the service user.

6.4.1.2 Dihydrocodeine should not be routinely used in opiate detoxification.

6.4.2 Use of adjunctive medications in opiate detoxification

6.4.2.1 Lofexidine may be considered for:

- people who have made an informed and appropriate decision not to use methadone or buprenorphine for detoxification
- people who have made an informed and appropriate decision to detoxify within a short period – usually less than 7 days
- mild or uncertain dependence, including in young people.

6.4.2.2 Clonidine should not be used for opiate detoxification.

6.4.2.3 Naltrexone and naloxone should not be routinely used to precipitate opiate withdrawal at the start of detoxification.

6.4.2.4 When prescribing adjunctive medication during detoxification, healthcare professionals should:

- be alert to the interactions between the adjunctive medications prescribed, as well as the interactions of the adjunctive medications with the opiate agonist
- limit use to the minimum dose required to address identified withdrawal symptoms or symptoms that have been experienced in previous detoxifications, including agitation, nausea, insomnia or pain.

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 detoxification, healthcare professionals, in discussion with the service user, should consider:

- the severity of dependence (particular caution should be exercised where there is uncertainty about dependence)

- the stability of the service user (including polydrug and alcohol use, and psychiatric comorbidity)
- the pharmacology of the chosen detoxification medication and any adjunctive medication
- the setting in which detoxification is conducted.

6.4.3.2 The duration of opiate detoxification should normally be within 4 weeks for an inpatient/residential setting and within 12 weeks for a community setting.

6.4.4 Research recommendation - adjunctive medication during detoxification

6.4.4.1 For people who are opiate dependent and require adjunctive medication during detoxification in addition to their opiate 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

Studies assessing the use of adjunctive medication for detoxification, particularly when alpha$_2$ adrenergic agonists were used, have indicated the use of a large variety of adjunctive medications for the management of withdrawal symptoms. The variety and quantity of such medications suggests the need for research to guide decisions on how best to manage withdrawal symptoms with minimal risk of harm to the service user.

6.5 Rapid and ultra-rapid detoxification under sedation and/or general anaesthesia

6.5.1 Introduction

Ultra-rapid and rapid detoxifications are approaches for detoxifying opiate-dependent patients using opiate antagonists, such as naloxone, naltrexone or nalmefene under general anaesthesia or heavy sedation. The aim is to flood the brain with an opiate antagonist to remove all agonists whilst 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. In ultra-rapid detoxification, patients are admitted to the 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 opiate withdrawal. In rapid detoxification, instead of anaesthesia, sedation with a benzodiazepine (most commonly, midazolam) is used but otherwise the medications used are broadly similar.

Others however (O'Connor & Kosten, 1998) have also referred to ultra-rapid detoxification when anaesthesia or heavy sedation is used, and rapid detoxification when an opiate antagonist is used to precipitate withdrawal in awake patients.

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. It therefore may be suited to or most appealing to those individuals that fear withdrawal symptoms. 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 potential high degree of risk, including fatalities. This is particularly striking given that opiate withdrawal alone rarely results in death. Furthermore, the associated costs required to give the appropriate medical support are much greater than other methods of detoxification. There has been much debate over its effectiveness with limited long-term outcome data available.

Current practice

In the UK such approaches 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, Netherlands), and Australia (Mattick *et al*, 2001). Definitions of levels of 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 patient 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 previous section 6.2).

Moderate sedation

A higher level of sedation, moderate sedation occurs where patients appear obviously sedated , but importantly they are able to independently maintain a patent airway and respond to stimuli purposefully (such as verbal questioning).

Deep sedation

An even higher level of sedation, the patient is clearly sedated, 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). A patient may experience partial or complete loss of protective reflexes including the ability to independently and continuously maintain a patent airway. Patients may therefore require assistance in maintaining a patent airway, and spontaneous ventilation may be inadequate. Cardiovascular function is usually maintained.

Whilst this state 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 patient requires a level of care identical to that needed for general anaesthesia.

General anaesthesia

Under general anaesthesia, a patient is unconscious and unresponsive, even in the face of significant stimuli. The ability to independently maintain ventilatory function is often impaired. Patients often require assistance in maintaining a patent 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.

6.5.2   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 18.

Table 18: 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 to January 2007
Study design	RCT
Patient population	Opiate dependent
Interventions	Rapid detoxification under moderate sedation, ultra-rapid detoxification under general anaesthesia or deep sedation
Outcomes	Abstinence, treatment completion, safety/adverse events, severity of withdrawal

6.5.3   Studies considered[6]

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

6.5.4   Rapid detoxification under moderate sedation

Asturian method

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

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[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).

Furthermore, this method of detoxification is unlikely to be supported in the UK. Recently a practitioner has been erased from the Medical Register by the General Medical Council, following the death of a service user as the result of a detoxification regimen at home similar to that described above (General Medical Council, 2006).

6.5.5   Ultra-rapid detoxification under general anaesthesia or deep sedation

 For comparisons of ultra-rapid detoxification against detoxification under minimal or no sedation, 5 RCTs (COLLINS2005, DE JONG2005, FAVRAT2006, MCGREGOR2002, SEOANE1997) met the eligibility criteria, providing data on 815 participants. In addition, one RCT (HENSEL2000) one quasi-experimental study (Hoffman *et al.*, 1998), four case series (Armstrong *et al.*, 2003; Cucchia, 1998 *et al.*, 2001; Elman *et al.,* 2001; Hamilton *et al.*, 2002) and three case reports (Cook & Collins, 1998; Roozen *et al.,* 2002; Sheeram *et al.*, 2001) provided data on adverse events in ultra-rapid detoxification. All studies were published in peer-reviewed journals.

Table 19: Evidence table for trials of ultra-rapid opiate detoxification

	Ultra-rapid detoxification under general anaesthesia versus detoxification under light or minimal sedation
Total no. of trials (total no. of participants)	5 RCTs (N = 815)
Study ID	Propofol anaesthesia (versus no general anaesthesia): COLLINS2005 DE JONG2005 FAVRAT2006 MCGREGOR2002 Propofol with midazolam (versus light sedation with same agents): SEAONE1997
Diagnosis	Opiate dependence
Years of opiate use (mean or range)	Heroin: 9.9 (MCGREGOR2002), 12.0 (DE JONG2005) Lifetime heroin use disorder: 7.5 (COLLINS2005)
Daily opiate use (mean or range)	Heroin (mg): 741.3 (SEAONE1997) 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: SEAONE1997 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 to 36 years
Overall quality of evidence	Moderate
Benefits	
Abstinence	*1-month follow-up*: 63% versus 60%, RR 1.05 (0.87 to 1.26) K = 1, N = 272 *3-month follow-up*: 23% versus 14%, RR 1.58 (0.77 to 3.25) K = 2, N = 142 *6-month follow-up:* 22% versus 8%, RR 2.70 (0.92 to 7.91) *12-month follow-up*: 20% versus 14%, RR 1.40 (0.58 to 3.39) K = 1, N = 101
Completion of treatment	82% versus 57%, RR = 1.49 (0.73 to 3.04) K = 3, N = 243
Started naltrexone maintenance	RR = 1.11 (0.81 to 1.51) K = 4, N = 515
Harms	
Adverse events	*Serious adverse events:* RR 3.62 (1.36, 9.61) K = 3, N = 644

For abstinence, completion and starting naltrexone maintenance, RR > 1 favours ultra-rapid detoxification. For adverse events, RR < 1 favours ultra-rapid.

Table 20: Adjunct medications, symptoms and adverse events for 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** 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 keotacidosis 2 days after discharge - 'had concealed' previous such history. *Comments: 'had concealed'*
DE JONG2005	**Rapid detoxification with (RD-GA) versus without (RD) general anaesthesia:** naltrexone, clonidine (to reduce hypertension; 0.3mg), diclofenac, ondansetron, diazepam (10mg), nicotine patch, octreotide, butylscopolamine, haloperidol (1-3mg iprn), midazolam General anaesthesia: propofol, gallamine, octreotide		RD group – no AEs RD-GA group – 5 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?); Previous psychiatric history – treated for agitation with propofol sedation (?delirium psychotic episode due to detox + anaesthesia); Hypoxia – had history of COPD & pneumonia; Fever, cause unknown; Anaesthesia associated aspiration – pneumonia.

FAVRAT2006	**Rapid under anaesthesia** (propofol) – naltrexone, lidocaine (to deepen anaesthesia), clonidine (to control withdrawal), octreotide (anti-diarrhoeal), ketorolac (NSAID), droperidol (if delirious), neostigmine		No description of AEs
			'No patients died or had severe complications'
	Clonidine group – 0.6mg in divided doses; loperamide (4mg for diarrhoea), tolperisone (150mg for muscular aches), ondansetron (4mg for nausea), zolpidem (10mg for insomnia), olanzapine (5mg for agitation), paracetamol (500mg for headaches)		*quotes Hamilton et al. (2002) - pulmonary oedema, aspiration, respiratory depression, psychosis, arrhythmias / increased risk of psychiatric decompensation, overdose, suicide – but is this due to rapid protocol?*
			One patient 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 antidepressant, also had gastrointestinal bleeding.
HENSEL2000	**Rapid under anaesthesia –** propofol (induction at 1.5-3mg, maintained with 0.1-0.35mg/kg), clonidine (2mcg/kg/hour), naltrexone		Stated that there were no anaesthetic complications, but then 'negligible side effects – depended on dose of propofol', which were was significantly lower when EEG monitoring was used.
	Aim was to study using EEG to measure withdrawal		8 patients had bradycardia, required treatment
			1 patient: first degree heart AV block, required treatment.
			6 patients: mild but persistent hypotension (SBP: 80-90 mmHg) – required treatment.
MCGREGOR2002	**Anaesthesia** versus **inpatient +** **naltrexone:** propofol (intubated), clonidine, octreotide	Inpatient – symptomatic medications: clonidine, diazepam, orphenadrine, paracetamol, temazepam, naproxen, metoclopramide, buscopan, vitamins.	In Discussion – no serious AEs.
	Inpatient 'normal clinic practice'		

| SEOANE1997 | Ultra-rapid detoxification with **light** versus **deep sedation**

Light – propofol, midazolam

Deep – as above at higher doses | Clonidine, metoclopramide, naloxone/naltexone. | 97.3% discharged from hospital after 24 hrs; 2.3% (7 patients) within 48 hrs due to vomiting, diarrhoea, fever; 1 within 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, 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 emergency department following detoxification,. Common symptoms were vomiting, diarrhoea, abdominal pain, agitation requiring sedation, excessive drowsiness

Most symptoms were managed with simple supportive care. |
| **Cook & Collins (1998)**

Case report | Underwent rapid detoxification under anaesthesia (RODA) | | 38 year old injecting heroin user for over 20 years. On reducing use, experienced shakiness, stomach cramps, cold sweats, visual hallucinations, formication (tactile hallucination)

Detoxification resulted in mild hypertension, tachycardia and goosebumps. Also progressive fall in blood pressure, heart rate and temperature during procedure

Only temperature was out of normal range, and was treated with a warming blanket

On waking patient was easily weaned off assisted ventilation and extubated. Patient reported feeling 'fantastic' and remained opiate free for 11 months whilst receiving professional counselling. |

Cucchia (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 $\pm$ 53mg, versus 178 $\pm$ 89mg), 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 serious suicide attempt with antidepressants given by clinician on previous day.
Elman *et al.* (2001) *Case series*	**Ultra-rapid detoxification under general anaesthesia** 6 participants had been maintained on methadone, 1 had been using transdermal fentanyl patches.		During anaesthesia phase, plasma ACTH and cortisol levels were markedly increased During post-anaesthesia phase, marked withdrawal and rapid breathing occurred in all patients. Respiratory distress in one patient, 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.

Hamilton *et al.* (2002) Case series	**Ultra-rapid detoxification under general anaesthesia**, with subcutaneous naltrexone pellets.	*Case 1:* Patient had acute dyspnea (shortness of breath). Agitated, yawning, had diarrhoea; diagnosed with acute pulmonary edema (fluid in lungs). Pellet removed, withdrawal symptoms resolved after 12 hours. *Case 2:* 27 year old patient experienced 5 days of vomiting, diarrhoea, dry mouth, weakness, fatigue, poor urine output and hyperalgesia (lowered threshold to pain) – all symptoms started immediately after detoxification. Pellet removed on patient's request. *Case 3:* During entire post-detoxification period, complained of intractable nausea and vomiting, which did not respond to antiemetics. 2 weeks after detoxification, presented at emergency department still complaining of persistent nausea, vomiting, weakness, dry mouth, and poor urine output. Had weight loss of 15-20 pounds, chills, sneezing, coughing, anorexia, abdominal pain. Pellet was removed, after which patient received treatment for dehydration and withdrawal symptoms. Within 24-hours patient was tolerating an oral diet and discharged. *Case 4:* 6 hours after detoxification, found unresponsive in bed with vomit around mouth. Admitted to emergency and treated with 'variety of drugs'. 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. 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**		URD participants (n = 20) compared to 5 control patients showed elevated BP and lower heart rates under baseline conditions. URD was associated with increases in respiratory rates and minute ventilation. These reached peak levels approximately 3 hours after the start of naltrexone treatment and remain elevated at end of the treatment Rapid breathing was seen for up to 24 hours after URD.
Roozen *et al* (2002) *Case report*	**Rapid naltrexone-accelerated detoxification under sedation –** *level of sedation unclear from report*.	Clonidine (0.15mg qid), lorazepam (2mg tid), midazolam (15mg/day), dexamethasone (6mg, day 1 only), ondansetron (8mg tid)	37 year old male, opiate dependent for 20 years and currently maintained on methadone (40mg/day) Adjunct medications failed to ameliorate diarrhoea and vomiting – admitted to intensive care after 36 hours of detoxification. On arrival, patient was drowsy, skin was cold, extremities cyanotic. Appeared severely dehydrated and tests indicated acute renal insufficiency After admission, patient was rehydrated rapidly. Diarrhoea lasted for several days, full recovery after 2 weeks.

Shreeram *et al.* **(2001)** *Case report*	**Ultra-rapid detoxification**	45 year old woman taking 100mg/day methadone and 4mg/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 patient was agitated despite being fully orientated. After detoxification, ingested pills not provided by clinicians – alprazolam 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.*

6.5.6 Clinical summary

Rapid detoxification under moderate sedation – There is no established evidence base to support this as a safe and effective method of detoxification.

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 opiate detoxification under minimal sedation. Although the evidence suggests ultra-rapid detoxification may have better abstinence outcomes at follow-up, these benefits are out-weighed by the considerable risks.

6.6 Clinical practice recommendations

6.6.1 Rapid and ultra-rapid detoxification

6.6.1.1   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.

6.6.1.2   Opiate detoxification may be undertaken under light or moderate sedation where the service user is able to respond to appropriate verbal stimulation and can maintain a patent airway. It should only be undertaken where adequate medical and nursing support is available, regular monitoring of the service user's level of sedation and vital signs is carried out, and staff have the competence to support airways.

6.6.2 Physical and complementary interventions during detoxification

It is acknowledged that many complementary interventions are offered to individuals with opiate dependence as well as for alcohol or other drug misuse. In this review, we focused on their use specifically during or for detoxification and did not investigate their role in other stages of dependency or treatment such as initiation or maintenance of substitute medication.

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 (Zeng *et al*, 2005), of acupuncture as an adjunct to tapered methadone, 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 to 2006. No other suitable/appropriate studies for review were found on any other physical or complementary intervention.

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), thereby treating and preventing disease. The review concluded that despite there being some evidence potentially supporting the use of acupuncture in opiate 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 opiate dependence (Jordan, 2006).

Further trials, in addition to Jordan's review were also identified. Zeng and colleagues (2006) 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 to 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.

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 a safe and effective method of detoxification.

7 Psychosocial interventions in opiate detoxification

7.1 Introduction

Although detoxification from opiates 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 (SCAN, 2006) and in the USA (CSAT, 2006) suggests that attempts to treat opiate 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 addiction. If treatment outcomes can be enhanced through the quality of the therapeutic environment, the availability of adjunctive psychosocial interventions and consequently the 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 their drug misuse. This process should begin even as the service user is being medically stabilized (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).

This underlying assumption that psychosocial interventions are an important element of detoxification programmes is based on several assumptions (Wanigaratne et al 2005; NTA Models of Care for Substance Misusers, 2006; CSAT, 2006). These 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; addressing the psychological, social and relationship problems that may have initiated or be maintaining drug use.

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 opiate 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 7.5). There is more evidence for the efficacy of these psychosocial interventions alone and in combination with opiate agonist maintenance treatment for the treatment of drug misuse (NICE, in press). One of the interventions assessed by NICE (in press), the abstinence-oriented 12-steps and related self-help approaches, may have an important role in supporting those undergoing opiate detoxification and pursuing abstinence.

7.1.1 Clinical practice recommendation

7.1.1.1   For service users considering opiate detoxification, healthcare professionals should provide information about self-help groups (such as 12-Step groups) and service user support groups (such as The Alliance) and, where appropriate, facilitate engagement with such services.

7.2 Current practice

Currently a range of formal psychosocial interventions are available in NHS programmes and include: motivational enhancement; cognitive behaviour therapy, 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: assessment of need (and risk assessment); establishing and sustaining a therapeutic relationship; identification of treatment goals; implementation and evaluation of a treatment plan; liaison and collaboration with other care providers; and efforts to engage and retain the client in treatment and to support the treatment plan (e.g. use of drug diaries, motivational interviewing skills) in the absence of delivering a complete episode of formal psychological therapy. Contacts between service users vary

but for those in maintenance treatment typically this would be fortnightly. In contrast in the United States, standard care at least as described in most of the US studies on detoxification, (often referred to as 'drug counselling') will involve a more frequent level of contact with formal psychological treatments much more frequently provided.

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 2006).   Interventions that aim to address a substance misuser's co-existing mental health difficulties 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 to £10) for performing the target behaviour, for example, 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. An example of clinic privileges is take-home methadone doses (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 the draws say 'Good job!' The other half result in the earning of a prize, which may range in value from £1 to £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

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

The assessment of individual's needs, provision of information and referral to services to meet these needs (including psychosocial interventions, methadone, residential rehabilitation). No attempt is made to engage in any specific form of psychological intervention. Sessions are normally weekly and last 15-20 minutes (Rawson *et al*, 1983).

Interpersonal therapy

Interpersonal therapy is a discrete, time limited, structured psychological intervention, originally developed for the treatment of depression, 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).

Standard cognitive behavioural therapy

Standard cognitive behavioural therapy 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 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).

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 to 30 sessions (Leichsenring *et al,* 2004).

7.4   Outcomes

The main two 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 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 21.

Table 21: 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 to January 2007
Study design	RCT
Patient population	Opiate Dependent
Interventions	Detoxification treatments: Methadone, Buprenorphine, Adrenergic Agonists, Psychosocial treatments: Relapse prevention cognitive behavioural therapy, Standard cognitive behavioural therapy, Contingency Management (CM), Community reinforcement approach, Family interventions, social network interventions, Interpersonal therapy, short term psychodynamic interventions, individual drug counselling
Outcomes	Abstinence, Treatment Completion, Severity of Withdrawal

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.

In the review of contingency management in combination with detoxification six trials (BICKEL1995, 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.

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[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).

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 (BICKEL1995, 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 10).

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 22: Study information and summary of evidence table for trials of opiate detoxification plus psychosocial interventions

	Detoxification plus CM 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-randomized (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	Opiate dependence	Opiate dependence	Opiate dependence	Opiate dependence
Detoxification regimen and treatment length	**Buprenorphine:** 4 days detoxification (+7days clonidine patch post-detox) CM: $100 voucher for completion of detoxification (KATZ2004)	**Methadone:** dose reduced by 5mg every 2 weeks until zero dose Family interventions: up to 16 sessions, initially every two weeks then less	**Buprenorphine:** 5 weeks stabilisation, 13 weeks detoxification Social network interventions: 36 sessions for 30 minutes, 18 weeks	**Methadone:** 3 weeks detoxification Individual drug counselling: 3 sessions for 15-20 minutes, 3 weeks (RAWSON1983)

		frequently (YANDOLI2002)	(GALANTER2004)	
	1 week stabilisation + additional 7-72 days of stabilisation depending on starting dose/70kg + detoxification for the remainder of 26 weeks			
	CM: 23 weeks (week 1 and weeks 25-26 did not receive CM), vouchers increase in value with continuous periods of abstinence from illicit drugs (BICKEL1997)			
	Methadone:			
	16 days detoxification			
	CM: 5 vouchers (between $4-10) can be earned during detoxification for abstinence from illicit drugs and $15 on completion of detoxification (HALL1979)			
	3 weeks stabilisation, 10 weeks detoxification			
	CM: week 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			
	CM: 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
Overall quality of evidence	Moderate	Moderate	Moderate	Low
Abstinence	End of treatment: 31.1% versus 16.6%, RR 1.73 (1.12, 2.68) 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 1.59 (1.07, 2.36) 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

7.8 Clinical summary

Table 22 summarises the study information and evidence from the included studies. Most studies assessing the efficacy of adjunctive psychosocial interventions were focused on contingency management. 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 (four 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, two weeks) and those of longer duration (for example, six months). NICE (in press) have assessed the use of contingency management to maintain abstinence, including for people who were opiate dependent, finding similar benefits as summarised above suggesting the use of this intervention after, as well as during, opiate detoxification.

The trial of family interventions consisted of 16 sessions over an indefinite period of time beginning once every two 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 to 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 three week detoxification and 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 Clinical practice recommendations

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

7.9.1.2 Contingency management during and after detoxification should adhere to the following principles.
- The scheme should provide incentives (usually privileges or vouchers) contingent on each presentation of a drug-negative screen (for example, free from non-prescribed opiates or cocaine).
- 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 once weekly thereafter until stability is achieved.
- If vouchers are used they should have monetary values in the region of £5 which increase in value with each additional, continuous period of abstinence.
- Urinalysis is the preferred method of testing but consideration may be given to the use of oral fluids.

7.9.1.3 When delivering contingency management programmes, healthcare professionals should ensure that:
- the target goal is agreed in collaboration with the service user
- the service user fully understands the relationship between the desired behaviour change and the incentive schedule
- incentives are individualized, with choice available so that the incentive is perceived as such by the service user (not just the healthcare professional) and supports a healthy/drug-free lifestyle.

8 Settings for opiate detoxification

8.1 Introduction

Detoxification from opiates 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 opiate detoxifications take place in the community with only a very small number being treated as inpatients. The National Drug Treatment Monitoring System (NDTMS) 2003-04 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 opiate cases (NTA, 2005). 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 (DRRs; formerly drug treatment and testing orders), and under voluntary conditions as the Drug Interventions Programme (DIP).

Inpatient detoxification is expensive to provide and this has lead to a reduction in its availability so that in some areas of England and Wales provision is almost non-existent despite recommendations that it should be available (NTA, 2002, 2006). 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 as to which service users are likely to do well in what setting. 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 community counterparts.

Treatment settings in England and Wales

Detoxification in community settings have traditionally divided into specialist and primary care based services. Specialist services, often known as community drug teams, are multi-disciplinary 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, 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 Drug Interventions Programme (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 in-patient or residential settings.
As noted above in-patient 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 with 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 opiate 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 opiate users 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 accompany the provision of the pharmacological treatments for 28 days after reception into prison (Home Office Drug Strategy Directorate, 2006). Prisoners who are opiate 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, short period of remand and for those in police custody. In such situations 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 supports that are provided within a community setting, for

example: how much individual contact does the service user spend 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 opiate dependence following a long period of maintenance treatment. Accident and emergency departments are often the first point of contact with health services for many drug users (Gossop *et al.*, 1995). Drug users primarily attend for treatment of accidental overdose. 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 opiate users who want to become abstinent are offered community detoxification as the first-line treatment. In some areas of the country, opiate users currently have a choice over treatments offered by the local community drug service or from 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 in-patient 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 or residential treatment (Day *et al.,* 2005).

8.1.1 Clinical practice recommendation

8.1.1.1 Opiate detoxification should not be routinely offered to:
- people with a medical condition that requires urgent treatment
- people in police custody, or on a short prison sentence or a short period of remand

- people presenting to an acute or emergency setting. The primary emergency problem should be addressed, and opiate withdrawal symptoms appropriately 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

Table 23: 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 to January 2007
Study design	RCT Observational studies
Patient population	Opiate dependent
Interventions	Detoxification in the following settings: inpatient, community, residential
Outcomes	Abstinence, treatment completion

8.2.2   Studies considered[8]

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 were published in peer-reviewed journals (GOSSOP1986; WILSON1975) 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.

In addition, two studies were excluded from the analysis. The most common reason for exclusion was lack of adequate comparison groups (further

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[8] 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).

information about both included and excluded studies can be found in Appendix 10).

8.2.3 Inpatient detoxification versus community-based detoxification

Three trials were identified that compared inpatient and community-based detoxification. The two RCTs (Day, 2006; Wilson, 1975) were meta-analysed and summarised below (see Table 24). The third trial, which did not provide separate data for patient preference and randomised samples, was reported separately.

Table 24: Summary evidence table for inpatient detoxification compared with community-based detoxifcation

	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
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

Table 24 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 (Day, 2006) in comparison with Wilson and colleagues' (1975) an earlier US trial (RR =1.91; 95% CI: 1.03 to 3.55). A number of additional problems with Wilson and colleagues (1975) 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 detoxification. Sixty participants, who were opiate 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 to the other RCTs (Day, 2006; Wilson *et al*, 1975). In total 81% of the inpatient group, were successfully detoxified from opiates 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 (Wilson et al, 1975; 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 opiate dependence receiving detoxification in a specialist drug dependency unit (DDU) with those on a general psychiatric ward (GEN). A total of 186 participants were randomised to the waiting list for treatment on either DDU (n = 115) or GEN (n = 71). However, only 69 in the DDU group and 30 participants in the GEN group remained after the waiting list period to enter inpatient treatment. A total of 75% completed detoxification in the DDU compared with 43% in the GEN (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 DDU group compared to the GEN 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 DDU (methadone) and GEN (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 GEN 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 from Australia (Gibson *et al*, 2003) 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 on 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 opiate 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 of cost effectiveness between primary and secondary care settings.

8.2.6 Predictors of outcome in inpatient settings

Table 25: 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 to January 2007
Study design	RCT Observational studies
Patient population	Opiate 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 & Hendrinks, 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 et al (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 1070 patients admitted for inpatient detoxification and found that outcomes were better in service users already on MMT (50.4% completed) compared with those (35.9%) who were primarily heroin injectors (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 (χ^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<.001) of a treatment programme (Franken and 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 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 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 inputs in those settings. Some participants may have poor prognostic factors, as compared to other participant groups, but still benefited more from inpatient treatment than they would have done in the community.

8.2.7 Clinical practice recommendations

Community detoxification

8.2.7.1 Healthcare professionals should normally consider community detoxification in preference to inpatient or residential detoxification as the first-line treatment for people who have made an informed and appropriate decision to undergo opiate detoxification.

8.2.7.2 Community detoxification should normally include:
- prior stabilisation of opiate drug use through appropriate pharmacological treatment
- effective co-ordination of care competent primary or specialist practitioners
- the provision of psychosocial interventions, where appropriate, during the stabilisation and maintenance phases.

Inpatient and residential detoxification

8.2.7.3 Inpatient and medically managed residential detoxification should be conducted with 24-hour medical and nursing support commensurate with the complexity of the service user's drug misuse and physical and psychiatric problems. Both pharmacological and psychosocial interventions to support the effective treatment of both the drug misuse and other significant psychological and physical comorbidities should be available.

8.2.7.4 Inpatient detoxification should be considered for people who have had at least one previous unsuccessful detoxification attempt within a community setting and who:
- require a high level of medical and nursing support because of significant comorbid physical and/or psychiatric problems **or**
- are polydrug users and require concurrent detoxification from alcohol.

8.2.7.5 Residential detoxification that is medically managed should be considered for people who have had at least one previous unsuccessful detoxification attempt within a community setting and/or who may be experiencing considerable social chaos and who:
- have comorbid physical and/or psychiatric problems **and**
- are polydrug users and require concurrent detoxification from opiates and benzodiazepines, or sequential detoxification from opiates and alcohol

      or

- have less severe levels of opiate dependence, for example if early in their drug-using career.

8.2.7.6   Residential detoxification that is not medically managed should be considered for people who have had at least one previous unsuccessful detoxification attempt within a community setting and/or who may be experiencing considerable social chaos and who:

- have less severe levels of opiate dependence, particularly if early in their drug-using career **and**
- would significantly benefit from a residential rehabilitation programme throughout and after detoxification.

8.2.8   Research recommendation - predictors of benefit from inpatient/residential detoxification

8.2.8.1   For people who are receiving inpatient/residential opiate detoxification, what participant characteristics are associated with greater levels of abstinence and completion of treatment, and lower levels of relapse?

Why this is important

There are relatively few studies comparing inpatient/residential and community detoxification. However, the studies that have been conducted do not strongly indicate the efficacy of inpatient/residential detoxification for all people. Therefore it is important to assess if there are particular subgroups more likely to benefit.

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 opiates 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 for this section of the guideline can be found in

Table 26.

Table 26: 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 to January 2007
Study design	Observational studies Non-comparative studies
Patient population	Opiate dependent
Interventions	Unassisted detoxification
Outcomes	Abstinence, treatment completion

8.3.2 Studies considered[9]

The review team conducted a new systematic search for observational and non-comparative studies that assessed the efficacy of unassisted detoxification.

Four interview-based studies (GOSSOP1991; ISON2006; NOBLE2002; SCHERBAUM2005) documented service users' experiences on 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

Whilst it is common practice for drug users 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; Noble *et al*, 2002; Scherbaum *et al*, 2005; Ison *et al*, 2006). 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 opiate users, attempts to self-detoxify involved either abrupt cessation of drugs or detoxification with self-administered drugs including benzodiazepines and opiates. 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 one year or more. There were no differences in outcomes for

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[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).

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%), cannabis (22%), methadone (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 one 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 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 opiate 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 opiate dependent users, the most common reason for not accessing medically assisted detoxification was 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 via attention directed 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 a reduction in 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 opiate dependent and considering self-detoxification should be encouraged to seek detoxification within a structured treatment programme.

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 and management of individuals with opiate 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 their drug treatment capacity so there is an increasing opportunity to offer detoxification programme to opiate misusers.

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 27.

Table 27: 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 to January 2007
Study design	RCT Observational studies
Patient population	Opiate dependent
Interventions	Prison-based detoxification
Outcomes	Abstinence, treatment completion

8.4.2 Studies considered[10]

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

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[10] 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).

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. They point 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 opiate toxicity at the outset of treatment is therefore ever present.

Detoxification resulting in abstinence from opiates 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 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 immediate past drug use most centres 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   For people in prison who have made an informed and appropriate decision to undergo opiate detoxification, the same treatment options for detoxification that are available in the community should be offered. Healthcare professionals should take into account additional considerations specific to the prison setting, including:

- limitations in the assessment of dependence, with the associated risk of opiate toxicity in the early period of treatment
- length of sentence or remand, and the possibility of unplanned release
- risks of self-harm, suicide and post-release overdose.

9 Appendices

Supplied as separate files:

Appendix 1: Scope for the development of the clinical guideline

Final versions

28th September 2005

Guideline title

Drug misuse: opiate detoxification of drug misusers in the community hospital and prison[11].

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 detoxification of drug misusers in the community, hospital and prison settings[12] 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). 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. 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

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[11] The guideline title changed during the development process to *Drug Misuse: Opiate Detoxification for Drug Misuse*

[12] The term *drug misusers* has been replaced with *people who misuse drugs* throughout the guideline with the exception of the scope

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 is 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, buprenorphien, 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 describes how organisations can become involved in the development of a guideline. Guideline Development Methods – Information for National Collaborating Centres and guideline developers 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). 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.

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.)

Naltrexone to prevent relapse in drug misuse. NICE Technology Appraisal. (Publication expected March 2007.)

Drug Misuse: psychosocial management of drug misuse. NICE Clinical Guideline (Publication expected July 2007.)

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.

Further information

Information on the guideline development process is provided in:

- The Guideline Development Process – An overview for stakeholders, the public and the NHS
- Guideline Development Methods – Information for National Collaborating Centres and guideline developers

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 drug misuser

Appendix 2: 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 3: Stakeholders who responded to early requests for evidence

Britannia Pharmaceuticals
Buckinghamshire Mental Health Trust
Derbyshire Mental Health Services
Oxfordshire Mental Health Trust
Pfizer
Rethink
Royal College of Nursing
Royal College of Psychiatrists
Rosemont Pharmaceuticals
Sheffield Teaching Hospitals NHS Trust

Appendix 4: Stakeholders and experts who responded to the consultation draft of the guideline

Stakeholders

Experts

Appendix 5: Researchers contacted to request information about unpublished or soon-to-be published studies

Robert Ali
Seyed M Assadi
Jenny Bearn
James Bell
David Best
Eric D Collins
Jon Currie
Shane Darke
Cor A J De Jong
Detox 5
Michael Farrell
Bernard Favrat
Gilberto Gerra
Mark S Gold
Michael Gossop
Paul Griffiths
Nick Heather
Paul Krabbe
Fergus Law
Walter Ling
Nicholas Lintzeris
Lisa Marsch
John Marsden
Catherine McGregor
Kenzie Preston
Duncan Raistrick
Alison Ritter
Roy Robertson
John B Saunders
Udo Schneider
Juergen Seifert
Dwayne Simpson
Nora D. Volkow
Jason White

Appendix 6: Clinical questions

Topic Group 1: Pharmacological and Physical Interventions

1) For people who are opiate 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 opiate 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 opiate dependent, are there particular groups that are more likely to benefit from detoxification?

3) For people who are opiate 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 opiate 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 opiate dependent, are there particular groups that respond better/worse to particular treatment settings?

5) For people who are opiate 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 opiate 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 opiate dependence is suspected, are oral fluid and urine testing reliable methods, e.g. in terms of sensitivity and specificity, for identifying, confirming, quantifying and monitoring drug use?

7) In the context of opiate detoxification, what is good clinical practice in the assessment of dependence and monitoring of withdrawal?

> 7.1) In the context of opiate detoxification, are there reliable and valid rating scales for the assessment of dependence and monitoring of withdrawal?

Appendix 7: Search strategies for the identification of clinical studies

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. Randomised Controlled Trial 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 8: Clinical study data extraction form

Information about each study was entered into an Access database using specially designed forms (see below for an example).

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

Lower Mean Upper   Length of Followup (text)
Duration (days) 1   7
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
Diagnosis Tool   100
DSM-IV

Record: I◄ ◄   1 ► ►I ►* 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	Setting	Mean dose
Symptomatic	Inpatient	

Intervention Details
During anaesthesia, octreotide.
After anaesthesia, during recovery phase: 30mg keterolac IV, glycopyrrolate if needed and 5mg droperidol for delirium if needed

For this group's other interventions, move to the next record below
Record: I◄ ◄   2 ► ►I ►* of 5
For the next group's interventions move to the next record below
Record: I◄ ◄   2 ► ►I ►* of 2

Outcomes

OutcomeID	Usable	Reason
Abstinence: 3 months	☑	

Record: I◄ ◄   1 ► ►I ►* 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 9: Quality checklists for clinical studies and reviews

The methodological quality of each study was evaluated using dimensions adapted from SIGN (Scottish Intercollegiate Guidelines Network, 2001). SIGN originally adapted their 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 Not addressed Adequately addressed Not reported Poorly addressed Not applicable
1.2	A description of the methodology used is included.	Well covered Not addressed Adequately addressed Not reported Poorly addressed Not applicable
1.3	The literature search is sufficiently rigorous to identify all the relevant studies.	Well covered Not addressed Adequately addressed Not reported Poorly addressed Not applicable
1.4	Study quality is assessed and taken into account.	Well covered Not addressed Adequately addressed Not reported Poorly addressed Not applicable
1.5	There are enough similarities between the studies selected to make combining them reasonable.	Well covered Not addressed Adequately addressed Not reported Poorly addressed 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 as 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.

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 Not addressed Adequately addressed Not reported Poorly addressed Not applicable
1.2	The assignment of subjects to treatment groups is randomised.	Well covered Not addressed Adequately addressed Not reported Poorly addressed Not applicable
1.3	An adequate concealment method is used.	Well covered Not addressed Adequately addressed Not reported Poorly addressed Not applicable
1.4	Subjects and investigators are kept 'blind' about treatment allocation.	Well covered Not addressed Adequately addressed Not reported Poorly addressed Not applicable
1.5	The treatment and control groups are similar at the start of the trial.	Well covered Not addressed Adequately addressed Not reported Poorly addressed Not applicable
1.6	The only difference between groups is the treatment under investigation.	Well covered Not addressed Adequately addressed Not reported Poorly addressed Not applicable
1.7	All relevant outcomes are measured in a standard, valid and reliable way.	Well covered Not addressed Adequately addressed Not reported Poorly addressed 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 Not addressed Adequately addressed Not reported Poorly addressed Not applicable
1.10	Where the study is carried out at more than one site, results are comparable for all sites.	Well covered Not addressed Adequately addressed Not reported Poorly addressed 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: randomised controlled trials

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, 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.	

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 Not addressed Adequately addressed Not reported Poorly addressed 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 Not addressed Adequately addressed Not reported Poorly addressed 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 Not addressed Adequately addressed Not reported Poorly addressed 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 Not addressed Adequately addressed Not reported Poorly addressed 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 Not addressed Adequately addressed Not reported Poorly addressed Not applicable
ASSESSMENT	
1.7 The outcomes are clearly defined.	Well covered Not addressed Adequately addressed Not reported Poorly addressed Not applicable
1.8 The assessment of outcome is made blind to exposure status.	Well covered Not addressed Adequately addressed Not reported Poorly addressed 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 Not addressed Adequately addressed Not reported Poorly addressed Not applicable
1.10 The measure of assessment of exposure is reliable.	Well covered Not addressed Adequately addressed Not reported Poorly addressed 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 confidence in study quality.

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.

Appendices 10 and 11 are supplied as separate files on the website; appendix 12 will be included with the final draft

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11 Abbreviations

AA	Alcoholics Anonymous
A&E	accident and emergency
AGREE	Appraisal of Guidelines for Research and Evaluation Instrument
AMED	A bibliographic database produced by the Health Care Information Service of the British Library
ASI	Addiction Severity Index
ASPD	antisocial personality disorder
AUDIT	Alcohol Use Disorders Identification Test
BBV	blood-borne virus
BCT	behavioural couples therapy
BNF	British National Formulary
CA	Cocaine Anonymous
CBT	cognitive behavioural therapy (S: standard; RP: relapse prevention)
CENTRAL	Cochrane Central Register of Controlled Trials
CI	confidence interval
CINAHL	Cumulative Index to Nursing and Allied Health Literature
CM	contingency management
CPN	community psychiatric nurse
CRA	community reinforcement approach
CUAD	Chemical Use Abuse and Dependency scale
CVD	cardiovascular disease
CXR	chest x-ray
DALI	Dartmouth Assessment of Lifestyle Instrument
DARE	Database of Abstracts of Reviews of Effects
DARP	Drug Abuse Reporting Programme
DAST-10	Drug Abuse Screening Test
DATOS	Drug Abuse Treatment Outcome Study
DDA	Drug Dependents Anonymous
DH	Department of Health
DSM	Diagnostic and Statistical Manual of Mental Disorders (versions III-R and IV-TR)
DUDIT	Drug Use Disorders Identification Test
EMBASE	Excerpta Medica database
EMCDDA	European Monitoring Centre for Drugs and Drug Addiction

FA	Families Anonymous
FSO	family members and significant others
GDG	Guideline Development Group
GMC	General Medical Council
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
HRQoL	health-related quality of life
HTA	Health Technology Assessment
ICD	International Classification of Diseases (10th edition)
ICER	incremental cost-effectiveness ratio
IDU	injecting drug user
IPT	interpersonal therapy
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
MRC	Medical Research Council
NA	Narcotics Anonymous
NACRO	National Association for the Care and Rehabilitation of Offenders
NCCMH	National Collaborating Centre for Mental Health
NDUDA	National Drug Users Development Agency
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
NPV	negative predictive value
NSC	National Screening Committee
NSE	needle and syringe exchange
NSF	National Service Framework

NTA	National Treatment Agency for Substance Misuse
NTORS	National Treatment Outcomes Research Study
OECD	Organistion for Economic Co-operation and Development
OHE HEED	Office of Health Economics, Health Economics Evaluation Database
OTI	Opiate Treatment Index
PAIS International	Database containing references to a wide range of indexed research material from over 120 countries
PCT	Primary Care Trust
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
POSIT	Problem-Oriented Screening Instrument for Teenagers
PPD	purified protein derivative
PPV	positive predictive value
PsycINFO	An abstract (not full text) database of psychological literature from the 1800s to the present
QALY	quality adjusted life years
QoL	quality of life
RBT	reinforcement-based therapy
RCT	randomised controlled trial
RP	relapse prevention
RR	relative risk
RRP	residential rehabilitation programme
SAS-SR	Social Adjustment Scale — Self-Report
SD	standard deviation
SHG	self-help group
SIGLE	System for Information on Grey Literature in Europe database
SIGN	Scottish Intercollegiate Guidelines Network
SMD	standardised mean difference
SMI	serious mental illness
SR	systematic review
SSCI	Social Sciences Citation Index
STPT	short-term psychodynamic therapy

TAU	treatment as usual
TB	tuberculosis
TC	therapeutic community
TOPS	Treatment Outcome Prospective Study
WHO	World Health Organization
WMD	weighted mean difference

12 Glossary

12-step self-help 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. Opiate drugs, for example heroin and **methadone**, are agonists that produce responses such as 'liking', analgesia and respiratory depression.

Alcoholics Anonymous (AA)
Alcoholics Anonymous is an informal fellowship of people who, through shared experiences and support for one another, aim to achieve abstinence and help others to recover from alcoholism. The only requirement for membership is a desire to stop misusing alcohol. An international organisation, AA was founded in the US in 1935 and established in the UK in 1947. It was from AA that the **12-step** treatment model originated.

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.

Behavioural couples therapy
Behavioural couples therapy usually involves (a) the person who misuses drugs stating his or her intention not to use drugs each day and his or her partner expressing support for the former's efforts to stay abstinent; (b) teaching more effective communication skills, such as active listening and expressing feelings directly; and (c) helping to increase positive behavioural exchanges between partners by encouraging them to acknowledge pleasing behaviours and engage in shared recreational activities (Fals-Stewart *et al.*, 2002).

Brief intervention
Brief interventions are those with a maximum duration of two sessions, lasting up to an hour each. The main principles include expressing empathy with the service user, not opposing resistance and offering feedback in order to increase the motivation of the service user to make changes to his or her drug use.

Buprenorphine
An analgesic **opiate** 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.

Case management
Case management is a method of co-ordinating care for people who misuse drugs. An individual worker, the case manager, is responsible for the co-ordination and, where necessary, provision of this care. Contact with the case manager is usually expected to be on a regular ongoing basis.

Coerced/legally mandated treatment
Coerced, or legally mandated, treatment 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.

Cognitive behavioural therapy
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**.

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

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 two 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, and prize-based, whereby participants receive prize-draw entries upon presentation of a negative biological sample.

Dependence

Dependence is defined by the World Health Organization 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 Advisory Council on the Misuse of Drugs 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).

Extended outpatient treatment

Treatment occurs in regularly scheduled sessions, usually totalling fewer than 9 contact hours per week. Examples include weekly or twice-weekly individual therapy, weekly group therapy or a combination of the two in association with participation in self-help groups.

Family-based intervention

Family-based interventions work jointly with the person who misuses drugs and his or her family members, partner or others from a wider social network (for example, a close friend) to seek reduced drug use or abstinence based on cognitive-behavioural principles.

Harm reduction
Harm reduction describes 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.

Interpersonal therapy
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.

Last observation carried forward (LOCF)
A type of data analysis used in clinical trials, often when data is lacking, in which the last results before a subject drops out of the trial are counted as if they occurred at the end of the trial.

Maintenance
Maintenance-oriented treatment in the UK context refers primarily to the pharmacological maintenance of people who are opiate dependent; that is, prescription of opiate substitutes (**methadone** or **buprenorphine**). This aims to reduce illicit drug use and its consequent harms.

Meta-analysis
The use of statistical techniques in a **systematic review** to integrate the results of several independent studies.

Methadone
A synthetic, psychoactive **opiate** substitute used in **maintenance**-oriented treatment, particularly heroin dependence. Methadone has **agonist** properties.

Naltrexone
An **antagonist** that blocks the effects of **opiate** drugs on receptors in the brain, naltrexone is used in **maintenance** treatment.

Narcotics Anonymous (NA)
Narcotics Anonymous is a non-profit fellowship of men and women for whom drug misuse has become a severe problem. Members meet regularly with the aim of helping each other to remain abstinent. The only requirement for membership is a desire to stop misusing drugs. Originating in the US in 1953, the first UK NA meeting was held in 1980. At the core of the NA programme is the **12-step** treatment model, adapted from **Alcoholics Anonymous**.

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: public health, health technologies and clinical practice.

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
Near-patient testing 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 (e.g. opiates, 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 (NSE)
NSE services aim 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.

Opiate
Opiates refer to 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 'opiate' is used more broadly to incorporate synthetic compounds (including **methadone**) with similar properties, also commonly known as opioids.

Outreach
Outreach involves targeting high risk and local priority groups. The general aims of outreach work are to: identify and contact hidden populations, refer members of these populations to existing care services, initiate activities aimed at prevention and at demand reduction, and to promote safer sex and safer drug use (European Monitoring Centre for Drugs and Drug Addiction, 1999).

Point abstinence
Point abstinence refers to evidence for the absence of drug use at a particular point in time (for example, at the end of treatment or at 12-month follow-up).

Psychoeducation
Psychoeducation is a programme designed for individuals or groups of people who misuse drugs that combines education about blood-borne viruses with skills training to improve communication, assertiveness and safe sexual and injection risk behaviour. It also provides people with an opportunity to ask questions and receive relevant feedback.

Psychosocial intervention
Psychosocial interventions are 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.

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
Screening is 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
Psychological interventions, derived from a psychodynamic/psychoanalytic model in which: a) therapist and patient 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.

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
Standard cognitive behavioural therapy 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).

Standard deviation (SD)
A statistical measure of variability in a population of individuals or in a set of data. Whilst 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**, an SMD is 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
Stimulants refer broadly to 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 (SR)
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.

Therapeutic community
The primary goal of therapeutic communities is abstinence from illicit and prescribed drugs, with the residential 'community' acting as the key agent for change. Peer influence is used to help individuals acquire social skills and

learn social norms, and so take on an increased level of personal and social responsibility within the unit (Smith *et al.,* 2006).

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.