Review of the evidence on the effectiveness of antagonists in managing opioid dependence

Richard P. Mattick, James Bell,
Lynn C. Daws, Jason M. White,
Susannah O'Brien & Simon J. Harris

NDARC Monograph No. 34

REVIEW OF THE EVIDENCE ON THE EFFECTIVENESS OF ANTAGONISTS IN MANAGING OPIOID DEPENDENCE

Richard P. Mattick, James Bell, Lynn C. Daws, Jason M. White, Susannah O'Brien & Simon J. Harris

National Drug and Alcohol Research Centre
University of New South Wales

Monograph No. 34
ISBN: 0 947 229 83 3
NDARC 1998

 The work herein was commissioned by the Department of Health and Family Services and partly supported by a grant to R.P. Mattick at the National Drug and Alcohol Research Centre (NDARC), University of New South Wales, Sydney, NSW, 2052, Australia, and also supported by the National Drug and Alcohol Research Centre.

The authors contributed to the final document in the following ways: RPM wrote the Executive Summary and Recommendations and sections 1, 2.3, 3, 4, and 5. LCD and JMW wrote section 2.1; JB and SO'B wrote section 2.2 and SO'B completed Table 1; SH wrote section 2.4 and Table 2. RPM and SO'B edited the document and wrote most of the Summaries. Linda Gowing provided detailed feedback on the Draft Report and the workshop, and assisted by providing text included in section 5 and in the Executive Summary and Recommendations. The workshop participants all contributed to the final document through their involvement and feedback. We also gratefully acknowledge the assistance of Eva Congreve in retrieving research papers, and Elizabeth Hill for editorial assistance with the penultimate draft.

Table of Contents

Page

Executive Summary and Recommendations

Induction onto naltrexone maintenance

The procedure of rapid opioid detoxification using naltrexone is linked to naltrexone maintenance and it is recommended that any measure of effectiveness of rapid detoxification must primarily take account of the long-term outcomes of patients in naltrexone maintenance. Naltrexone maintenance will prove beneficial for *some* patients wishing to cease opioid use. The objective of any research conducted in this area should be to trial the efficacy, safety and cost-effectiveness of *naltrexone maintenance and the ability of different methods of inducting patients onto naltrexone maintenance to achieve long-term abstinence successfully*.

Approaches to induction onto naltrexone maintenance

There are a number of methods for commencing naltrexone maintenance, including:

i accelerated induction using naltrexone in conscious patients without sedation / anaesthesia delivered as an in-patient or day-patient and transfer to naltrexone maintenance;

ii accelerated induction with anaesthesia using naltrexone and transfer to naltrexone maintenance;

iii transfer from heroin / methadone to buprenorphine and then to naltrexone maintenance;

iv standard in-patient or out-patient detoxification with clonidine and other medications for symptomatic relief and transfer to naltrexone maintenance.

It is possible that the induction process may influence the outcomes of naltrexone maintenance treatment, and this needs to be investigated. However, anaesthesia may not be required or beneficial, and there is a need to trial non-anaesthesia methods of induction onto naltrexone maintenance. The most parsimonious position at this time is that of Dr Colin Brewer, a long-standing practitioner of anaesthesia-based detoxification, who states that it cannot be claimed that patients having precipitated withdrawal with opioid antagonists show better long-term results than comparable patients who complete conventional inpatient withdrawal programmes (Brewer, 1997b), as there is no evidence to date for or against the claim that anaesthesia improves long-term outcomes. It is recommended that the ability of any procedure inducting patients onto naltrexone to successfully lead to long-term abstinence from opioids be tested carefully.

Planned trials

A number of planned or mooted trials are thought to be important. These include a randomised clinical trial assessing the value of using buprenorphine to transfer stable methadone patients to naltrexone maintenance, a randomised clinical trial of accelerated induction onto naltrexone maintenance treatment, and a randomised clinical trial of anaesthesia assisted accelerated induction onto naltrexone maintenance treatment. As we do not have good knowledge about the effect of antagonists on opiate receptor activity, in any research it will be valuable to examine the functional effect of these medications and their ability to reduce craving and their potential to increase overdose deaths.

Standard of the research

It is recommended that the guidelines for Good Clinical Research Practice (GCRP) in Australia or a similar standard for the research should be adopted in randomised trials, provided that adequate funding is provided. These guidelines have the objective of safeguarding the interests of subjects, investigators, sponsors and society in ensuring that only adequately planned and conducted clinical studies are performed. Unless the entire procedure, including the analysis of data, is adequately conducted, there is a risk of failure and hence an unethical waste of human and financial resources.

Combining data from different trials in Australia

There are likely to be a number of trials mounted of induction onto naltrexone maintenance. Research results from different trials should be combined to allow quasi-experimental comparisons. The other advantage of pooling data is that the individual trials are unlikely to be able to address the question of which patients fare best with each procedure, and a large sample of patients undergoing different procedures will allow the development of an

understanding of patient-treatment matching. This will assist to guide policy and practice. The core data set to be collected, and the most appropriate mechanism to support the combination of results from the different research projects, requires further consideration to ensure that the different research groups agree on the data to be collected, its analysis and dissemination.

Serious adverse events associated with induction onto naltrexone maintenance

Deaths associated with rapid induction onto naltrexone maintenance under anaesthesia are relatively unlikely in well-supported intensive care units or similarly supported medical wards. There is a lack of clear information concerning symptoms during and soon after accelerated detoxification prior to the induction onto naltrexone. There are sufficient comments in the literature about patients suffering under accelerated detoxification procedures using naltrexone, for extreme caution to be exercised in any trial. One area of concern regarding naltrexone maintenance treatment is that it (like other procedures which lead to abstinence from opioids) may increase the risk of overdose for patients who cease naltrexone treatment and relapse to either occasional or regular opioid use. Another concern is the potential for induction onto naltrexone to destabilise patients who were functioning well in methadone maintenance therapy. It is important to inform patients of the potential risks of destabilisation, and to provide safeguards for these patients, including ensuring entry into methadone maintenance therapy should the patient fare poorly.

Media scrutiny and rational policy development

The level of media attention given to rapid detoxification using naltrexone to date, and the subsequent public perception that this procedure provides a "cure" for opioid dependence remains an issue. Any study of induction onto naltrexone maintenance will receive substantial media attention, and reports of even small groups of "successfully" treated patients could result in considerable pressure for the procedure to be implemented more widely. Any pre-post evaluation of rapid opioid detoxification runs the risk that methods of induction onto naltrexone maintenance will not be subject to the standards of evidence required of other interventions for serious disorders in Australia. Methods to deal with this problem need to be considered.

Key outstanding issues

There are three remaining issues:

i An analysis of current and proposed research projects should be undertaken to ensure that there are no substantial gaps in assessment of the different mechanisms of induction onto naltrexone maintenance.

ii A mechanism for centralised, coordinated, national analysis of the outcomes of the various trials needs to be agreed and established in a fashion that protects each groups rights and responsibilities with regard to the data they collect.

iii A strategy for managing the media attention and public perceptions regarding unique effectiveness of rapid opioid detoxification should be developed and nationally agreed.

Summary of Review Conclusions

Support for rapid opioid detoxification with anaesthesia/sedation (RODA) as an approach to the treatment of opioid dependence comes from arguments: that it is an intervention which can "cure" heroin dependent individuals; that it is humane to provide such treatment to the small proportion of patients who require it (as is done, for example, with dental phobics); that existing treatments for opioid dependence are unsatisfactory; and that there is a well-understood and accepted mechanism of action to explain why RODA will provide improved outcomes beyond alternative methods of either accelerated detoxification or more conventional methods of withdrawal management. 2

Arguments against rapid opioid detoxification with anaesthesia (RODA) include the views: that detoxification is not a cure for dependence; that there is no basic research to support the belief that anaesthesia will improve outcomes beyond those achieved with awake patients undergoing similar treatment, nor does the available clinical research support such a view; that the recent "marketing" campaign of RODA in Australia is biased against obtaining valid evidence about its likely efficacy; that there are unacceptable risks associated with the procedures, compared with the likely benefits; that RODA is not relevant to the management of the vast majority of opioid dependent patients; that the use of ICU beds is expensive and unlikely to become routinely available for this indication in the public hospitals in Australia; and that the proponents of the procedure have failed to provide any reasonable data on efficacy or cost-effectiveness. 3

Opioid antagonists produce: (1) increased sensitivity to opioid agonists; (2) increased sensitivity to opioid antagonists; (3) increased opioid receptor numbers in some brain regions. Yet, it is still not clear whether the changes in opioid receptor number per se, is the critical adaptation which occurs in response to chronic treatment with opioids. Moreover, experiments to date have not adequately addressed the time course of the effectiveness of opioid antagonists in the treatment of abstinent opioid users. Finally, the experiments providing the evidence in support of points (1)-(3) above, have been carried out in opioid naive animals. There is no body of literature that describes the effects of naltrexone in animals with a history of opioid dependence. It is possible that naltrexone and other antagonists may assist to "reset" the endogenous opiate system in chronic dependent users of opioids, but currently there is no body of empirical research data in animals or humans to support such a view. As such, claims that antagonists can return the endogenous opiate system to "baseline functioning" should be viewed as unsupported. 8

The studies on the value of rapid opioid detoxification without anaesthesia (ROD) typically involve administering incremental doses of antagonist medication. The literature on ROD consists primarily of a series of reports and controlled trials and to a lesser extent double-blind, placebo controlled studies. Overall, the detoxification results achieved to date with ROD are encouraging, indicating that the majority of patients (83%) entering non-sedated/anaesthetised treatment can be successfully detoxified, and then transferred to full doses of naltrexone. There is, however, an overall lack of follow-up, and when follow-up data are presented they have not been confirmed with urinalysis. The nature of any psychosocial support provided during and/or following withdrawal requires greater clarification, as does patient selection. Seemingly outstanding detoxification and relapse prevention results were achieved in the randomised controlled trial of ROD published by Gerra et al., (1995). This study needs to be replicated. 15

The RODA research literature consists primarily of a small number of short research reports and clinical reports. In general, these reports are not single or double-blind controlled trials and they are mostly based on relatively small patient numbers (n = 12, 6, 18, 7, 11, 1, and 83). A more recent study (Seoane et al., 1997) using a large sample (n=300) has recorded some impressive results. However, patient motivation appears an important prognostic factor with only "highly motivated" patients included in this study. Additionally, the issue of whether anaesthesia is required has not been addressed. The efficacy of RODA for longer term relapse prevention is also unknown. The impact of other variables, such as psychosocial support provided, patient motivation and familial support need to be considered in any evaluation of RODA efficacy. Presently, the lack of scientific studies makes it difficult to comment on the efficacy of RODA for either detoxification or relapse prevention. Nothing has been published on the cost-effectiveness of these procedures. 20

The ability of antagonists to affect the endogenous opiate system has been studied in non-dependent animals. The impact of antagonists is not well-understood in opioid dependent animals or in dependent patients. Large doses of opioid antagonist produce rapid displacement of agonist binding. The rate of change of this process is presumably the major determinant of withdrawal severity, with spontaneous withdrawal being less severe and withdrawal by a large bolus of antagonist being most severe, as all receptors change simultaneously. Smaller doses produce less rapid displacement of receptor binding, and thus a less severe

precipitated withdrawal. Factors other than the pharmacology are important in influencing the severity of withdrawal symptoms in opioid dependent patients. 22

One argument in favour of RODA is that the symptoms suffered are either non-existent or very mild. However, there are no systematic data to support the proposition that the withdrawal is symptom-free, and some of the descriptions of what patients go through during accelerated detoxification indicate that the procedure is not always without severe withdrawal symptoms. 23

Rapid detoxification with and without anaesthesia does have risks associated with it. There have been a number of deaths associated with RODA. Naloxone reversal of opioid overdose has been associated with serious adverse events. However, the probable prevalence of serious adverse events in ROD or RODA is difficult to estimate. 23

Detoxification from heroin can be achieved safely and effectively, and fairly rapidly, either on an outpatient or inpatient basis without opioid antagonists, although completion is greater on an inpatient basis. Accelerated detoxification offers two potential advantages - cost (reduced due to the brevity of the procedure, requiring shorter hospitalisation) and improved rates of induction onto naltrexone. The ability of RODA to improve rates of entry into, and more importantly retention in, naltrexone maintenance is unclear. The value of ROD and RODA for heroin users is unclear. 24

One rationale for accelerated detoxification as a way of coming off methadone has been the prolonged nature of methadone abstinence syndrome. While acute withdrawal can clearly be achieved, there is as yet no evidence that accelerated detoxification can shorten the protracted abstinence from methadone. The other rationale for rapid detoxification is to allow patients with minimal symptomatic distress to switch from methadone to naltrexone. The availability of naltrexone maintenance broadens the treatment repertoire. However, the promotion of accelerated detoxification techniques runs a real risk that encouraging patients to leave methadone maintenance will destabilise them and compromise any benefits of treatment. 26

On average, the uptake of antagonist maintenance therapy among opioid dependent patients is very poor. The likelihood of entry into and completion of maintenance therapy is poorest among street users. Methadone maintenance patients are more likely to enter and complete antagonist maintenance therapy, but they are deterred by prolonged withdrawal processes prior to medication commencement. The best results are obtained in well-motivated individuals who are opioid-free. The results of the research on uptake rates are consistent with the view that shortening the duration of detoxification, and lessening the severity of withdrawal symptoms may increase uptake. 38

Naloxone maintenance trials have provided equivocal results. The poor results combined with the short half-life of the medication, requiring oral doses as high as 2-3 gm to provide 24-hour blockade, make it costly to use. It is not a suitable medication for antagonist maintenance, especially in the light of naltrexone's longer duration of action at lower doses. 39

Naltrexone maintenance trials have provided evidence of benefit for highly motivated patients who have external pressures to become and stay opioid free. Heroin users tend to fare poorly, as do most methadone patients. Motivated patients with good social supports and strong incentives to remain drug free are most likely to benefit. Ancillary services are associated with better retention in naltrexone maintenance. 41

Both pharmacologically and clinically, -2 adrenergic agonists have shown their usefulness in suppressing the adverse effects experienced by patients undergoing withdrawal from chronic self-administration of opioids. Clonidine is limited by its hypotensive and sedative effects, while lofexidine is expensive. Further, certain side-effects exist, and all of the symptoms associated with opioid withdrawal are not inhibited by these drugs. The use of these drugs may, however, provide encouragement and incentive for some patients contemplating detoxification from opioids. 45

In terms of research directions for Australia, pre-post (observational) research will not be of value in developing an understanding of the efficacy of different withdrawal approaches. Problems associated with patient selection bias, motivational differences and other obvious limitations on inferences make such research unhelpful, and even detrimental to developing knowledge in this area. We argue that any research on ROD or RODA should be in the form of a randomised trial. As set out in a recent NIDA report (Herman & Czechowicz, 1996), there are too few well-controlled studies to allow a rigorous scientific opinion on the value, safety and costs of these procedures. We suggest that the appropriate design to evaluate RODA is a comparison of the outcome of patients who go through the detoxification with clonidine and other medications to reduce symptoms in an awake state. Additionally, research on the value of naltrexone and buprenorphine has been commenced and should be pursued examining the value of these procedures for stabilised methadone patients. The value of buprenorphine in the management of withdrawal of heroin users will be pursued. 54

Research undertaken in Australia in this area should be conducted in accordance with appropriate national and international standards. The Guidelines for Good Clinical Research Practice should be adhered to in the design and conduct of any trials. 55

Future research in Australia in this area should use common measures. The Opiate Treatment Index is suggested as a core instrument, along with measures of retention and urinalysis. Additionally, investigators may wish to develop or include other measures. 55

The research studies should provide data that can be pooled for analysis of the outcomes of patients from the different procedures, even if those trials are distinct randomised clinical trials. This approach will allow for some direct comparisons of different research study results, albeit of a quasi-experimental nature. We suggest that researchers agree to pool data, and that funding bodies foster collaborative arrangements. Funding for pooling data and for the analysis of those data should be made available from governments. 56

What is the place of RODA in the management of opioid dependence? It does not seem likely that it will be an appropriate first line of treatment for heroin users. This group would probably be better offered maintenance therapy to allow them to stabilise their lifestyles and stop opioid use. To do otherwise would expose street heroin users to ongoing risks associated with injecting given the high likelihood of relapse. Similar comments pertain to many methadone patients, who are not likely to benefit from attempts at withdrawal. Yet, it is most likely to be the stable, drug-free, employed, and motivated methadone patient who may benefit most from attempts at detoxification. Even so, this group will not all require anaesthesia, as many will detoxify using more conventional methods. Thus, we are left with a small group who are so sensitive to withdrawal symptoms that they are unwilling to attempt withdrawal. 57

Other withdrawal strategies should be considered including the value of lofexidine as a suitable pharmacotherapy for management of opioid withdrawal. Naltrexone may be used in suitably selected methadone patients who have been transferred to, and stabilised on, buprenorphine. Psychological adjuncts in the form of simple accurate information about the withdrawal process and about antagonist maintenance should be developed. 58

Research priorities include that RODA be assessed in a randomised trial against ROD. The value of transferring stable methadone patients to buprenorphine and then naltrexone will be assessed. ROD in outpatient detoxification for heroin dependent patients compared with conventional outpatient detoxification and/or with buprenorphine, followed by naltrexone maintenance should be assessed. 59

1. Introduction

1.1. The controversy

> "Heroin addiction is … a central nervous system disorder that is reversible. … [It] can be healed — without methadone, without psychological counselling and without being locked away in rehabilitation centres." (p.83). (Barnao, 1997).

> "CITA … [and] Megama … report that 12-18 months after initial treatment, almost 60 per cent of patients are living opiate-free lifestyles" (p.22) (McKey, 1997).

> "I do not think it can be claimed that patients having precipitated withdrawal [with opioid antagonists] show, in general, better long-term results than comparable patients who complete conventional inpatient withdrawal programmes" (p.299) (Brewer, 1997b).

> "Based upon the available information, it is the opinion of selected experts in the U.S. who are prominent in the opiate addiction field, that the [ultra-rapid opiate detoxification] … anaesthesia method is currently without ethical, medical, scientific or financial justification as a clinical detoxification treatment" (p.1) (Herman & Czechowicz, 1996).

Recently, in Australia, the attention of the general community, politicians, health care policy makers and providers, and researchers has been focused on the ability of opioid antagonists to assist in the detoxification from opioids of either illicit opioid users or patients in methadone maintenance treatment. As the above quotations indicate, the various views in this area have been at odds with each other. Specifically, the ability of naltrexone (or naloxone) administered under sedation or anaesthesia to speed up detoxification (followed by months of naltrexone maintenance), to restore or "reset" the endogenous opiate system to baseline functioning, and to bring about long-term abstinence, has been debated. Claims of "cures", and of the broad effectiveness of naltrexone administered under sedation, published in popular press have been extravagant (Barnao, 1997). The likely accuracy of these claims has been questioned by some in Australia (Hall & Mattick, 1997; Hall, Mattick, Saunders & Wodak, in press), and doubts about immoderate assertions have been expressed by others internationally who have either researched the procedure (Gossop & Strang, 1997), have provided it (Brewer, 1997b), or have reviewed the evidence for it (Herman & Czechowicz, 1996). Others have pointed to the way in which the reported effectiveness of accelerated detoxification has been used recently in arguments against the harm minimisation approach (Caplehorn, 1997).

This Report reviews what is known about the likely impact of accelerated detoxification either under sedation or anaesthesia (rapid opioid detoxification under anaesthesia: RODA), or in the awake patient with symptomatic relief with medications such as clonidine (rapid opioid detoxification: ROD). The review commences with a consideration of the current state of knowledge of the regulation of receptors by opioid antagonists. This is followed by a review of the literature on the impact of ROD and RODA on patient outcomes, and a consideration of the research literature on maintenance with opioid antagonists. Finally, an overview of the literature on the basis for and effects of therapy with -2 adrenergic agonists is presented, with a focus on lofexidine as it is an important withdrawal management medication which is not available for use in Australia. Implications for future research are also discussed.

1.2. Rationale for antagonist precipitated detoxification

Proponents of accelerated detoxification under sedation or anaesthesia argue on several grounds that the procedure has unique value, significantly above and beyond the value of existing forms of detoxification. Some of these arguments in favour of accelerated detoxification are set out below.

> Arguing from a humane perspective, some point to research literature showing that severe withdrawal symptoms prevent many users from withdrawing from opioid use, and that 25% of patients in inpatient withdrawal and 80% of patients in outpatient withdrawal will not successfully complete the regime. Comparisons are made with individuals suffering fear of dental treatment who may be offered sedation or general anaesthesia, allowing successful dental fillings or extractions (Brewer, 1997a; Brewer, 1997b). Consistent with this view, there is a problem of detoxification fear or phobia affecting up to one-third of those dependent on opioids in some studies (Brewer, 1997b), and indeed there is research literature on this fear (Milby et al., 1987; Raczynski, Wiebe, Milby & Gurwitch, 1988).

Risk of death or other serious adverse events "especially in a predominantly young and fit population — are now extremely low. ... [as] developments in intensive care" allow prolonged anaesthesia with safety (Brewer, 1997a).

There have been criticisms of existing treatments for opioid dependence. Waismann has stated "I am . . . tired of seeing heroin addicts . . . fed government supplied drugs [methadone] to keep them under control" (p.83) (Barnao, 1997).

From a pharmacological perspective it is asserted that repeated exposure to opioid agonists results in down-regulation of opiate receptor sites in the central nervous system, and that antagonist maintenance results in up-regulation of the receptors, thus "resetting" the endogenous opiate system towards baseline functioning (Brewer, 1997b).

Summary.

Support for rapid opioid detoxification with anaesthesia/sedation (RODA) as an approach to the treatment of opioid dependence comes from arguments: that it is an intervention which can "cure" heroin dependent individuals; that it is humane to provide such treatment to the small proportion of patients who require it (as is done, for example, with dental phobics); that existing treatments for opioid dependence are unsatisfactory; and that there is a well-understood and accepted mechanism of action to explain why RODA will provide improved outcomes beyond alternative methods of either accelerated detoxification or more conventional methods of withdrawal management.

1.3. Concerns about antagonist precipitated detoxification

A number of concerns have been expressed about the repeated claims that accelerated detoxification with or without anaesthesia will provide a "cure" for opioid dependence.

Detoxification from drugs, at whatever speed or rate it is achieved, is not a treatment for opioid dependence, as most patients completing detoxification will relapse unless given further treatment (Mattick & Hall, 1996).

There is no reason to believe that the use of naltrexone under anaesthesia or sedation will improve outcomes beyond what would be achieved by the use of naltrexone and clonidine (or lofexidine), with concomitant doses of benzodiazepines and other medications to reduce unpleasant symptoms, in awake patients (Hall & Mattick, 1997).

Accurate information may be useful in assisting to alleviate detoxification fear and anxiety, as demonstrated in some research (Green & Gossop, 1988).

The "marketing campaign" surrounding RODA recently observed in Australia has put its evaluation outside normal processes of peer-reviewed assessment of appropriately randomised controlled research studies (Caplehorn, 1997; Hall & Mattick, 1997). This campaign has led to the media responding to public desperation for a "heroin cure", and a relaxation of the standards which would properly be demanded in support of therapeutic claims for new treatments of AIDS, cancer or heart disease.

Opioid withdrawal is not life-threatening, but there have been deaths associated with rapid opioid detoxification under anaesthesia (RODA), and these may increase if RODA is provided in an unregulated fashion (Herman & Czechowicz, 1996).

RODA is expensive because it requires an intensive care unit (ICU) bed, specialist ICU nursing staff, and an anaesthetist for the duration of the procedure to supervise the anaesthesia. The costs of the ICU procedure need to also take into account 12 months of naltrexone maintenance at approximately $5.00 per day for the medication, and further costs associated with prescribing and dispensing (Hall & Mattick, 1997). Of course, the requirement that an ICU bed be used raises the issue of community and political acceptance of users occupying these beds, especially in an environment where health care resources for expensive medical beds are limited.

The proponents of RODA have not provided evidence from controlled trials that it is more effective and more cost-effective than existing forms of opioid detoxification and maintenance therapy (Gossop & Strang, 1997).

Summary.

Arguments against rapid opioid detoxification with anaesthesia (RODA) include the views: that detoxification is not a cure for dependence; that there is no basic research to support the belief that anaesthesia will improve outcomes beyond those achieved with awake patients undergoing similar treatment, nor does the available clinical research support such a view; that the recent "marketing" campaign of RODA in Australia is biased against obtaining valid evidence about its likely efficacy; that there are unacceptable risks associated with the procedures, compared with the likely benefits; that RODA is not relevant to the management of the vast majority of opioid dependent patients; that the use of ICU beds is expensive and unlikely to become routinely available for this indication in the public hospitals in Australia; and that the proponents of the procedure have failed to provide any reasonable data on efficacy or cost-effectiveness.

2. Review of Research

2.1. Pharmacology of rapid opioid detoxification:
Regulation of opioid receptors by opioid antagonists

2.1.1. Introductory comments.

Opioid receptor antagonists can effectively reverse both acute and chronic actions of opioids and have been used in the diagnosis of opioid dependence and in the treatment of opioid addiction. As noted above, their use in rapid opioid detoxification has, however, generated considerable controversy both ethically and scientifically. Consequently, the mechanism of action of opioid antagonists has come under intense scrutiny in recent years. The present paper aims to describe our current understanding of the pharmacology of opioid antagonists in relation to their clinical efficacy. This review will focus on naltrexone, an opioid antagonist which has been successfully used as a maintenance agent in the treatment of opioid addiction (Gonzalez & Brogden, 1988) and more recently has been trialed in rapid opioid detoxification programmes (Simon, 1997). Other opioid antagonists, such as the shorter acting naloxone, can be expected to have similar properties.

2.1.2. Adaptation to opioid agonists and antagonists.

Repeated administration of a wide range of drugs induces adaptational changes in the receptor and second messenger systems responsible for mediating their effects. The results of such adaptation include the development of tolerance and physical dependence. Tolerance is characterised by a decrease in the effect of the drug following repeated administration of the drug, while physical dependence is manifested as a withdrawal syndrome following cessation of drug administration. Such withdrawal reactions are thought to be a consequence of the lag in re-adaptation of these systems (Johnson & Flemming, 1989).

Long-term treatment with either opioid agonists or antagonists is well known to change the potency of morphine and other opioid agonists. For example, chronic administration of morphine often leads to tolerance to its analgesic actions. By way of contrast, chronic treatment with an opioid antagonist, such as naltrexone, can lead to the development of supersensitivity to the analgesic and other actions of opioid agonists. These findings have led to the implication that an opioid antagonist such as naltrexone could reduce tolerance in that it may induce up-regulation of opioid receptors. Thus, the use of opioid antagonists in the treatment of abstinent opioid users may result in a more rapid "re-setting" of the endogenous opioid systems. One consequence of this may be that the lag time for re-adaptation following cessation of opioid agonist administration is reduced. The functional consequence will be a shorter acute, rather than protracted, withdrawal phase. However, controversy exists with regard to the underlying mechanisms responsible for these sensitivity changes. It is the aim of this review to integrate and discuss the present state of the literature describing the mechanism of action of opioid antagonists and how this relates to their clinical use.

2.1.3. Receptor regulation by opioid antagonists.

Up-regulation of brain opioid receptor binding after treatment with naltrexone has been well documented (Bardo, Bhatnagar & Gebhart, 1983; De Vries, Tjon Tien Ril, Van der Laan, Mulder & Schoffelmeer, 1993; Millan, Morris & Herz, 1988; Morris, Millan & Herz, 1988; Tempel, Gardner & Zukin, 1985). Up-regulation has consistently been reported to be due to an increased number of receptors and not a change in the affinity of the opioid receptors (Marley et al., 1995; Yoburn, Shah, Chan, Duttaroy & Davis, 1995). Of the putative brain opioid receptors, long term administration of naltrexone has been reported to increase the number of μ, and receptors (Tempel, Zukin & Gardner, 1982). For example, treatment with naltrexone for one week produces a twofold increase in the number of μ and opioid receptors in rat brain as measured by radioligand binding (Cote, Izenwasser & Weems, 1993; Danks et al., 1988; Tempel et al., 1985; Unterwald et al., 1995). Antagonist-induced opioid receptor up-regulation is, however, dependent upon brain region. For example, naltrexone does not appear to affect μ and receptors in the cortex, whereas these receptors are up-regulated in both midbrain and hindbrain (Marley et al., 1995).

Changes in sensitivity to opioids and increased opioid receptor number are also dependent on the frequency of antagonist administration. The time course of naltrexone-induced μ-receptor up-regulation has been established in rats after both continuous (i.e. continuous infusion) and intermittent (e.g. one dose/week over two months) administration. After continuous infusion of naltrexone a significant increase in binding is apparent as early as two days and binding continues to increase until day eight, at which time the increase in receptor number reaches a plateau. Upon cessation of treatment, both binding and behavioural indices of supersensitivity decline to control levels within a few days (Bardo et al., 1983; Bardo, Miller & Risner, 1984; Yoburn & Inturrisi, 1988).

By contrast, when naltrexone is administered intermittently, μ-receptors are up-regulated in hindbrain and paradoxically down-regulated in midbrain (Marley et al., 1995). Moreover, in brain regions where receptor up-regulation is observed, the magnitude of the increase in receptor number is significantly less than when naltrexone is continuously infused. In the case of continuous infusion, increases in receptor number of more than 50% are generally reported (Bardo et al., 1983; Tempel et al., 1985), while increases after intermittent administration are always less than 50% (Marley et al., 1995). Interestingly, although increases in opioid receptor number are not as great after intermittent naltrexone administration, receptor numbers remain elevated for a longer period after cessation of treatment. For example, when opioid antagonists are continuously infused, receptor number generally returns to normal within a few days after cessation of infusion (Tempel et al., 1985). When naltrexone is given intermittently, opioid receptors remain elevated for up to 7 days after the treatment has ceased (Marley et al., 1995).

These results are of particular relevance as, in clinical settings, both continuous infusion and intermittent administration of opioid antagonists are used. We must be careful then, to consider the dosing regime used when extrapolating from data derived from animal studies. Continuous antagonist infusion results in a more dramatic but short lived increase in receptor number compared to intermittent administration. It may be that the enhanced sensitivity following continuous infusion of opioid antagonists represents a different phenomenon to that induced by intermittent dosing, a conclusion supported by several studies (Marley et al., 1995; Schindler, Wu, Su, Goldberg & Katz, 1990).

2.1.4. Mechanism of action of antagonist-induced changes in receptor number.

The mechanism underlying opioid antagonist-induced receptor up-regulation remains unresolved. Changes in receptor number of other systems (e.g., adrenergic) have been shown to be associated with a change in the levels of receptor mRNA. Recent cloning of a rat μ-opioid receptor has enabled investigation of receptor regulation at the level of gene expression. However, such studies have provided evidence that opioid antagonist-induced up-regulation of μ-opioid receptors is not a consequence of increases in mRNA turnover. Rather, chronic treatment with naltrexone appears to produce a region-specific down-regulation of μ-opioid mRNA which may be secondary to naltrexone-induced increases in μ-receptor number (Unterwald et al., 1995). Indeed, the decrease in μ-opioid mRNA appears to be most robust in areas where μ-opioid receptor increases are greatest (e.g., thalamus, hypothalamus and brainstem).

Brodsky and co-workers (Brodsky, Elliott, Hynansky & Inturrisi, 1995) proposed that the 21-28% decrease in μ-opioid mRNA levels detected after eight days of naltrexone treatment may be secondary to the naltrexone-induced increase in μ-opioid receptors. This may represent a negative feedback system. Such a feedback mechanism could account for the lack of further increase in μ-opioid receptor binding beyond day 8 and for a relatively fast return of μ-opioid receptor binding to control levels upon cessation of treatment with naloxone.

Based on the above finding, it appears that alterations in opioid receptor number are due to mechanisms beyond the level of gene expression. Clearly, mechanisms including differential G-protein occupancy of different receptors, inhibition of receptor down-regulation by endogenous opioid peptides, processing of latent or precursor receptors, differential compartmentalisation of receptor molecules, and inhibition of receptor degradation are among some of the possibilities requiring further investigation.

2.1.5. Functional correlates.

In addition to the enhanced response to opioid agonist administration, chronic exposure of rodents to opioid antagonists such as naltrexone has also been reported to result in enhanced sensitivity to the behavioural and physiological effects of the antagonist itself (Marley et al., 1995; Millan et al, 1988; Schindler, Goldberg & Katz, 1993; Schindler, Marley & Goldberg, 1992; Schindler et al., 1990; Tempel et al., 1985). For example, when rats are treated chronically with naltrexone, the degree of salivation induced by subsequent, same dose, naltrexone treatments is significantly increased. This enhanced sensitivity to naltrexone is observed as early as a few days after treatment is initiated and continues to increase as treatment progresses (Marley et al., 1995). Similarly, rats display enhanced sensitivity in operant responding tasks during the second or third cumulative dosing with an opioid antagonist. This opioid antagonist-induced supersensitivity in operant responding reaches a peak after around six weeks of treatment and is long lasting (Gewiss, Marley, Thorndike, Goldberg & Schindler, 1994; Schindler et al., 1993; Schindler et al., 1990).

In spite of the numerous studies which have attempted to determine whether changes in the number of opioid binding sites are responsible for functional alterations observed after chronic treatment with opioid antagonists there is still no consensus. Evidence exists that the behavioural supersensitivity observed after chronic treatment with naltrexone may not be mediated by mechanism(s) involving the μ-opioid receptor itself. For example, chronically administered morphine, a μ-opioid receptor agonist, or naloxone, a μ-opioid receptor antagonist, failed to alter the tail-flick response of rats even though both drugs produced significant changes (in opposite directions) in μ-opioid receptor number (Paronis & Holtzman, 1992). Another example of apparent discordance between receptors and functional end-points is provided by a study where rats were

treated with naltrexone (10 mg/kg) for eight days. The resulting increase in striatal μ-opioid receptors was not associated with changes in the functional properties of μ-opioid receptors mediating inhibition of cAMP production or noradrenaline release (De Vries et al., 1993).

2.1.6. Naltrexone pharmacokinetics and receptor binding.

In order to understand the action of naltrexone it is important to consider the duration of occupancy of opioid receptors by naltrexone. The binding of a radiolabelled narcotic, [11C]carfentanil, was measured in the brain of five normal volunteers with a positron radiation detection system before, and 1,48,72,120 and 168 hours after a single, oral dose of naltrexone (50 mg) (Lee et al., 1988). Based on these results the estimated effective half-time for return to baseline opioid receptor occupancy is 72-108 hours. This half-time is much longer than the first or second component of the plasma clearance for naltrexone and its major active metabolite, -naltrexol, which range from 1 to 10 hours, and from 8 to 19 hours respectively (Meyer, Straughn, Lo, Schary & Whitney, 1984; Verebey, Volavka, Mulé & Resnick, 1976; Wall, Brine & Perez-Reyes, 1981). It appears then, that plasma clearance half-times can be misleading when used to estimate the duration of drug action at a receptor site.

Verebey (Verebey et al., 1976) reported that in addition to the two initial components of naltrexone clearance there is a third, terminal phase, with an estimated plasma clearance half-time of 96 hours. This group also found that the inhibition of the physiologic and subjective effects of heroin in human volunteers persists for 72 hours after 100 mg of oral naltrexone (Verebey et al., 1976). Thus, the duration of receptor occupancy by naltrexone measured with [11C]carfentanil correlates well with both the duration of the pharmacologic effects of naltrexone as measured by heroin challenge and with the long half-time of the terminal phase of the plasma clearance of naltrexone (96 hours).

There is evidence to suggest that for opioid withdrawal symptoms to completely subside, all opioid receptors must be blocked (Kleber, Topazian, Gaspari, Riordan & Kosten, 1987; Vining, Kosten & Kleber, 1988). Currently the standard "blocking" dose of naltrexone given in opioid detoxification is 50 mg/kg p.o. This dose (whether given as a bolus in rapid detoxification or attained over several days) has generally been very effective in reducing or eliminating the withdrawal syndrome (Simon, 1997). Based on the receptor occupancy study by Lee and co-workers (Lee et al., 1988) this dose results in plasma levels of naltrexone and -naltrexol much greater than that needed to fully occupy opioid receptors.

Given the above pharmacodynamics and pharmacokinetics of naltrexone it would appear that its effectiveness in rapid detoxification is its ability to rapidly displace opioid agonists from the opioid receptors and occupy these receptors for relatively long periods.

2.1.7. Conclusion.

Administration of opioid antagonists such as naltrexone produces several outcomes: (1) an increase in sensitivity to opioid agonists; (2) an increase in sensitivity to opioid antagonists; (3) an increase in opioid receptor numbers in at least some brain regions. The time course of these effects depends on the dosing regime as well as the kinetic properties of naltrexone itself.

It has been claimed that administration of an opioid antagonist to an opioid dependent person may, in addition to precipitation of withdrawal, rapidly normalise opioid activity. Such claims are based on (1) and (3) above. However, several important issues regarding the utility of opioid antagonists in opioid detoxification remain unresolved.

First, it is still not clear whether the changes in opioid receptor number *per se*, is the critical adaptation which occurs in response to chronic treatment with opioids. This is highlighted by the failure of experiments to demonstrate any functional significance of changes in receptor number. Moreover, there is a considerable body of literature which suggests that the result of chronic administration of an opioid agonist is the uncoupling of opioid receptors from second messenger systems (Self & Nestler, 1995). Thus, alterations in second messenger systems may be more important in reducing sensitivity to subsequent opioid stimulation than decreases in receptor number.

Second, experiments to date have not adequately addressed the time course of the effectiveness of opioid antagonists in the treatment of abstinent opioid users. It remains unclear whether significant effects are observed when opioid antagonist administration is ceased, particularly after short-term antagonist administration. Thirdly, the experiments providing the evidence in support of points (1)-(3) above, have been carried out in opioid naive animals. There is no body of literature that describes the effects of naltrexone on opioid receptors and opioid function in animals with a history of opioid dependence. Thus, any use of the research findings described above in support of rapid opioid detoxification requires considerable extrapolation. Finally, the implication that an opioid antagonist can enhance functional responses raises the concerns of increased use of opioid narcotics (e.g. due to an enhanced "high") and the possibility of overdose after cessation of antagonist administration.

Summary.
Opioid antagonists produce: (1) increased sensitivity to opioid agonists; (2) increased sensitivity to opioid antagonists; (3) increased opioid receptor numbers in some brain regions. Yet, it is still not clear whether the changes in opioid receptor number per se, is the critical adaptation which occurs in response to chronic treatment with opioids. Moreover, experiments to date have not adequately addressed the time course of the effectiveness of opioid antagonists in the treatment of abstinent opioid users. Finally, the experiments providing the evidence in support of points (1)-(3) above, have been carried out in opioid naive animals. There is no body of literature that describes the effects of naltrexone in animals with a history of opioid dependence. It is possible that naltrexone and other antagonists may assist to "reset" the endogenous opiate system in chronic dependent users of opioids, but currently there is no body of empirical research data in animals or humans to support such a view. As such, claims that antagonists can return the endogenous opiate system to "baseline functioning" should be viewed as unsupported.

2.2. Review of rapid opioid detoxification

2.2.1. Opiate Withdrawal Syndrome.

The opiate withdrawal syndrome is characterised by a variety of signs and symptoms, including lacrimation, rhinorrhoea, yawning, sweating occurring 8-12 hours after the last dose of heroin or morphine, followed by increasing restlessness, dilated pupils, piloerection, tremor, irritability, anorexia, bone and joint pain and stomach cramps. As symptoms peak at 48-72 hours, the dependent user will experience an intensification of symptoms: insomnia, more marked lack of appetite, violent yawning and sneezing, severe lacrimation, profuse nasal discharge and inflammation of the nasal mucous membrane. The symptoms largely disappear within 7 to 10 days, although this does not imply that there is a restoration of physiological equilibrium associated with opioid dependence. There appears to be a longer- term "secondary" or "protracted" abstinence syndrome comprised of general malaise, fatigue, decreased well-being, poor tolerance of stress and a craving for opiates which may last some months, during which time opioid dependent persons have a high rate of relapse to regular opiate use. The extent to which this secondary syndrome is in fact a result of drug withdrawal, rather than the user experiencing a "normal" state is unclear, and controlled studies of the occurrence of withdrawal symptoms appear necessary.

Unlike the alcohol withdrawal syndrome, the opiate withdrawal syndrome is very rarely life-threatening. It has been described as "immiserating", and as being like a bout of bad influenza that lasts about a week. Nonetheless, it is sufficiently aversive for many opiate dependent persons, to be an obstacle to abstinence that needs to be removed humanely and effectively for those who wish to cease all opioid use.

2.2.2. Rapid opioid detoxification regimes (ROD).

“Rapid opioid detoxification” has been the usual label applied to a range of approaches which have in common the use of opioid antagonists to shorten the duration of the abstinence syndrome during withdrawal. However, “rapid” is a relative concept. In the United Kingdom, the standard approach to detoxification has been a 21 day tapering methadone assisted withdrawal, while in Australia heroin withdrawal is often completed (without the use of narcotic antagonists) in 4-5 days. In this review, the label “accelerated detoxification” is used to include techniques that use opioid antagonists to shorten the duration of the opioid abstinence syndrome, with rapid opioid detoxification (ROD) referring to detoxification with antagonists but no deep sedation/anaesthesia, and RODA referring to the procedure under anaesthesia. The plan of this part of the review is to summarise: (1) ROD and RODA detoxification regimes as detailed in the research literature, or from other sources; (2) the issues for use of the procedures raised in clinical reports; (3) the safety of accelerated detoxification; and (4) the benefits and costs of accelerated detoxification.

2.2.2.1. Riordan and Kleber (1980). Kleber is the pioneer of rapid opioid detoxification (ROD). As detailed in Table 1, in his 1980 report he described the use of repeated injections of naloxone to achieve withdrawal during a three night hospital admission (Riordan & Kleber, 1980). On day one, clonidine 6µg/kg is administered in three divided doses. On day two, clonidine 11µg/kg in three divided doses, with naloxone 0.4mg IMI given every two hours, commenced ½ hour after the first dose of clonidine. On day three, clonidine 0.6 g/kg given in two doses, and naloxone 0.8mg IMI q2h. On day four, patients received 1.2mg naloxone and if this is tolerated is considered ready for naltrexone treatment. This is a report on four inpatients, three using heroin and one in methadone treatment, all of whom were "successfully detoxified" (100%). The report suggests inpatient treatment using this technique may be more desirable, as three other patients treated as day patients failed to return after going home in the evening. The report also notes that withdrawal scores were maximal after the first two naloxone injections, dropping quickly thereafter.

2.2.2.2. Charney, Riordan, Kleber et al. (1982). In 1982, the Kleber group reported on ROD using graduated doses of naltrexone (Charney et al., 1982). Eleven patients wishing to withdraw from methadone were treated. Each patient received a final methadone dose at 9am on day zero. On day one they were hospitalised and received clonidine 5 g/kg for three doses, six hours apart. After that, clonidine was titrated against symptoms. On day two, naltrexone 1mg was administered, and increased by 1mg increments at four hourly intervals. On day three, naltrexone was increased by 2mg increments if withdrawal rating was <5. On day four, naltrexone 10mg was given at 9am, 1pm, and 5pm. Four patients were given 10mg at 9pm, and six were given 15mg. Next day all patients received 50mg of naltrexone at 9am. From day four, clonidine was only given as needed. Symptoms were maximal on day two, and by days five-six symptoms were declining towards baseline levels. However, there was persistent muscle aching, insomnia, restlessness and anorexia, although at lower levels than the peak of withdrawal. Ten of eleven patients successfully withdrew (91%). No follow-up data were provided.

2.2.2.3. Charney, Heninger and Kleber (1986). In an attempt to confirm and extend their 1982 findings with a larger patient sample, this group reported on 40 methadone patients withdrawn as inpatients in 4-5 days (38 or 95% of the patients completed the procedure) (Charney, Heninger & Kleber, 1986). The mean daily methadone dose was 32mg (10-65mg/day).

The withdrawal procedure and medications used are shown in Table 1. Subjects received their usual methadone dose on day one. On day two, 14 subjects (group A) received clonidine 5 g/kg at 9am, with two further doses at 3pm and 9pm, the later doses titrated against side effects and withdrawal severity. On days three and four, subjects received naltrexone, fourth hourly doses starting at 1mg and increased in 1mg increments on day one and 2mg increments on day two. No dose increases were made after 5pm to allow patients to sleep. On day five, naltrexone 10mg tds was given, and on day six, the majority of patients received naltrexone 50mg at 9am. A second schedule, used in 26 patients (group B), omitted day two (the clonidine only day). Two patients dropped out after their first dose of naltrexone. One such patient, who was on 60mg methadone, had a very severe withdrawal reaction, experiencing psychotic phenomena and bizarre behaviour. The symptoms abated within 90 minutes of being given 25mg of methadone.

Features of this study are: (1) it employed high doses of clonidine (300-400 gq4h), which were rapidly tapered after the first 2 days; (2) 1mg naltrexone induced withdrawal symptoms in 32 of the 38 patients, with marked variability (every subject got up to 2mg by next morning); (3) during the second naltrexone day, naltrexone did not intensify withdrawal phenomena (withdrawal scores peaked on the first naltrexone day, were slightly lower next day, and persisted to day five); and (4) the authors noted that signs and symptoms were not related to methadone dose. They comment, however, that in their experience rapid detoxification is suitable for patients on doses less that 60mg of methadone. As noted above 95% of patients completed the procedure. No follow-up data were provided.

2.2.2.4. Kleber, Topazian, Gaspari, Riordan and Kosten (1987). Using similar techniques on an outpatient basis, Kleber et al. treated 14 heroin dependent patients over a five day period (Kleber et al., 1987). As detailed in Table 1, patients were administered the naloxone challenge test and initial clonidine doses were determined based on the ensuing withdrawal symptoms. On day two, an initial dose of 1mg of naltrexone was given, incrementing gradually to a total dose of 40mg on day three, 50mg on day four and 150mg on day five.

The regime enabled 12 of 14 (86%) patients to completely withdraw from opioids in 5 days while simultaneously initiating naltrexone maintenance. For all patients the most persistent symptoms were restlessness, anxiety, muscular aching, craving, insomnia and hot and cold flashes, although overall, patient ratings indicated the process "was relatively comfortable for the majority of patients"

(p.6). These results are comparable to the groups previous experience with methadone maintained inpatients (Charney et al., 1982, Charney, 1986 #179). However, the authors point out that comparison with the 1982 study, which employed identical rating scales, generally reveals a lesser occurrence of withdrawal symptoms in the current study while using smaller total daily doses of clonidine, leading the group to suggest that methadone withdrawal may be more difficult than heroin withdrawal (p.11).

At one month follow-up, 5 of the 12 patients were still taking naltrexone, 3 patients were using opioids regularly again and 3 claimed to be abstinent, although this was not substantiated by urine analysis. The remaining patient returned to naltrexone maintenance two months after detoxification having used heroin intermittently in the interim.

2.2.2.5. Brewer, Rezae and Bailey (1988). Encouraged by the findings of Charney et al. (Charney et al., 1986), Brewer et al. describes 60 episodes of accelerated detoxification involving 56 heroin and other opioid dependent inpatients using similar techniques (Brewer, Rezae & Bailey, 1988). As detailed in Table 1, two treatment schedules were followed, both involving graduated doses of naltrexone, but one using significantly higher doses, administered sooner in an attempt to shorten the duration of inpatient treatment. Impressive results were achieved in this study with 55 out of 56 patients (98%) considered successfully detoxified as defined by being able to accept 50mg naltrexone in a 24 hour period and feeling "well enough to return home" (p.341). Brewer et al. report that by administering significantly higher doses of naltrexone and clonidine on the first day withdrawal time was significantly reduced.

Typical of the majority of studies reviewed so far, no follow-up data are presented. Also, little detail is provided regarding the symptomatic state of the patients during and after detoxification with Brewer et al. reporting the response to naltrexone was "variable" with some patients having few symptoms, while others experienced significant discomfort requiring maximal doses of clonidine and diazepam (p.341). Another concern regarding this study is the very high doses of diazepam used without either intubation or an intensive care setting. The safety of this approach has been questioned (Simon, 1997).

2.2.2.6. Vining, Kosten and Kleber (1988). Like Brewer et al. (1988), the Kleber group also examined the effect of administering naltrexone sooner on withdrawal duration (Vining et al., 1988). In contrast to Brewer et al., however, single daily doses of naltrexone were used in tablet form and detoxification was conducted on an outpatient basis.

The withdrawal procedure is detailed in Table 1. Seventeen heroin dependent patients received clonidine 600 g daily, and naltrexone in ascending daily doses of 12.5, 25, 50, and 100mg, completing detoxification in either four or five days depending on the treatment schedule. Encouraging results were achieved with 14 of 17 (82%) patients detoxified and the authors claiming “the treatment regimen effectively suppressed signs and symptoms of withdrawal” (p.570). The authors commented that the rates of successful detoxification for detoxification using clonidine alone is 31- 40%, based on the extant research at that time.

Vining et al. speculated that a single larger dose of naltrexone kept opioid receptors blocked and actually reduced withdrawal symptoms compared to repeated small doses used in other studies which may repeatedly precipitate withdrawal. The authors also note that an "interesting effect of the addition of larger doses of naltrexone to the detoxification has been the decrease in the amount of clonidine required”. At 1 month follow-up the authors state 9 out of the 14 patients detoxified were still taking naltrexone. Unfortunately, no further data were presented to substantiate these claimed results.

2.2.2.7. Senft (1991). In another study also using the naltrexone tablet, Senft replicated the method of Vining, initiating treatment with 12.5mg of naltrexone (given as ¼ tablet) (Senft, 1991). Fifty-five episodes of detoxification, involving 52 opioid dependent inpatients are described in the report, with 49 patients successfully detoxified (94%).

The withdrawal procedure is detailed in Table 1. Senft reports that symptoms occurred mostly in the first 12 hours, and that by the morning of the second day, most patients "felt much improved" (p.258). Withdrawal symptoms ranged in severity from no significant symptoms to "significant" symptoms of anxiety, restlessness, abdominal cramps, diarrhoea (the occurrence of which was "frequent"), and transient vomiting (which occurred in one third of the patients). Ancillary medications prescribed were dicyclomine for abdominal cramps, Kaopectate for diarrhoea, hydroxyzine for nausea and vomiting, and chlordiazepoxide for anxiety and insomnia. Major adverse events were 2 episodes of delirium, each of which resolved after 4-6 hours. One patient was placed in restraints, the other received a single intramuscular dose of droperidol. Senft states that after discharge on day 3, the "usual" residual symptoms were insomnia, chills and fatigue. It should be noted, that although all completers were placed on naltrexone maintenance at discharge, few continued with the treatment "unless coerced by court or employer" (p.258). No other follow-up data is presented.

2.2.2.8. Azatian, Papiasvilli and Joseph (1994). In contrast to the encouraging detoxification results achieved by others with the naltrexone-clonidine method, Azatian et al. report that all but 3 of the 44 heroin dependent patients they treated using this technique left treatment against medical advice due to intolerable withdrawal symptoms (Azatian, Papiasvilli & Joseph, 1994). As detailed in Table 1, these researchers had difficultly stabilising patients on higher doses of naltrexone with doses of 50mg only reached on the sixth day. In fact, only 2 patients were able to tolerate 75mg by the 9th day of treatment. The authors postulate Russian users may experience a more severe withdrawal syndrome than their American counterparts due to higher opioid purity and warn the use of antagonists "to treat opioid addicts either in maintenance or detoxification should be approached with extreme caution especially in populations where the social and psychological supports are, at best, fragile and where illegal opioids are used without contaminants" (p.52).

2.2.2.9. Unpublished comments (1994). Variations of the naltrexone-clonidine technique continue to be used overseas. We are aware of a description of the technique as utilised in one hospital in Europe. Although unpublished, this edited description is valuable in conveying something of what may occur during accelerated detoxification.

> *Patients are nursed on a mattress on the floor to avoid falls. Vomiting and diarrhoea are expected. Premedication of cimetidine 800mg, clonidine 400 g, lorazepam 5-10mg, chlorpromazine, 100-500mg is given. After 45 minutes, by which time the patient is asleep, 0.5mg naltrexone is administered orally. Thereafter, naltrexone 0.5mg is given every hour up to a total of 3mg. This induces diarrhoea, vomiting, sweating, cramps, and intense distress. A classical delirium occasionally occurs. On day 2, naltrexone is continued, and usually by about 10pm on day 2 is up to 12.5 mg (and a total dose of 50mg). By the third day "patients usually feel pretty shattered". They are discharged this day after taking 50mg of naltrexone. Their discharge medications are naltrexone, clonidine, Rohypnol (up to 4 nightly), thioridazine, and Buscopan. Over the next 5-10 days they will experience insomnia, chills, aching joints, cramps, lethargy (for which dexedrine may be prescribed), emotional lability. This post-detoxification drug support usually lasts not more than 1 month. Naltrexone symptoms usually resolve within a week.*

The above description of severely symptomatic rapid detoxification, requiring enormous doses of sedation accompanied by prolonged post-detoxification symptoms, is remarkably at odds with some other accounts of rapid opioid detoxification.

2.2.2.10. Gerra, Marcato, Caccavari et al. (1995). More recently, Italian researchers reported on a double blind, placebo controlled, randomised trial in which 152 patients were treated in a day hospital setting (Gerra et al., 1995). As detailed in Table 1, patients underwent therapy with an intravenous cannula, receiving infusions for 7 hours each day for 4 days. Group A received 4 days of IV clonidine (150 g tds), and oral placebo for 3 months. Group B received IV clonidine plus naltrexone 12.5mg on day 2, then 50mg daily for 3 months. Group C received clonidine, plus naloxone 0.2mg iv on day two, 0.4mg bd for next two days, oral placebo days 2-4, and naltrexone 50mg daily for 3 months thereafter. Group D received saline and placebo. The number of patients randomly assigned to each condition was, respectively, with one week drop-outs in brackets: Group A = 33 (2 dropouts), Group B = 42 (2 dropouts), Group C = 58 (1 dropout), and Group D = 19 (5 dropouts).

At 24 hours, the clonidine only group had fewest symptoms, the placebo group most, and the naltrexone and naloxone group similar severity of withdrawal symptoms (slightly more with naloxone group). By 48 hours, the placebo group had significantly more symptoms, the two antagonists had high but comparable symptoms. At 72 hours withdrawal was over in the 3 groups receiving clonidine, but still severe in the placebo group. Groups A and D showed more positive urine tests for morphine, and the naltrexone group showed fewer positive morphine samples than the naloxone group. At 3 and 6 months, groups B and C (both on NTX) had lower rates of positive urines (statistically significant). Dropout rates were low and comparable in all groups (only 2 subjects per group, rising to 4 and 6 at 3 months, in the antagonist groups).

This seems like a remarkable study – highly successful detoxification, using only clonidine for symptomatic relief, and commencing with 12.5 mg – a dose much higher than initial doses utilised by Charney and Brewer, yet seemingly associated with less severe withdrawal. The report indicates that all subjects had used heroin up to 12 hours prior to initiation of treatment (confirmed by urine testing). Furthermore, this was a randomised trial, and patients undergoing spontaneous withdrawal had more severe symptoms (and worse outcomes) than those undergoing rapid withdrawal with clonidine. Thus, the seemingly mild withdrawal in the naltrexone and naloxone treated groups cannot satisfactorily be attributed to patient selection or low levels of neuroadaptation. Finally, the remarkable results achieved in the next 3 months are well beyond expectations based on previous published studies. Drop-out rates were remarkably low, even in the placebo treated group. Results of naltrexone maintenance were astoundingly good (80% abstinent from opioids at 6 months).

This raises three questions, not fully addressed in the paper. Was there selection bias towards better prognosis patients? What was the method of randomisation resulting in groups of unequal numbers? What was the ancillary treatment given? Regarding the latter concern, although precise details are not provided, all four groups received intense psychosocial support throughout the trial. The impressive naltrexone maintenance results reported in this study suggest the importance of psychosocial support to long-term outcome.

2.2.2.11. Merrill and Marshall (1997). Finally, at the opposite end of the spectrum to the very intensive treatment offered in rapid detoxification with anaesthesia, a very simple study from the UK indicates that rapid detoxification from methadone can be accomplished by a single injection of naloxone administered daily (Merrill & Marshall, 1997). Using the technique outlined in Table 1, the authors claim that withdrawal from methadone was accomplished in 6 days for 75% of patients, a considerable shortening of the normal duration of withdrawal. However, the end-point used in this study - ability to tolerate a bolus dose of naloxone, 0.4mg, may be a valid measure of acute withdrawal, but tells little about the symptomatic state of the

patients. It should also be keep in mind when interpreting these results that patients taking more than 100mg of methadone daily and those dependent on benzodiazepines or alcohol were excluded from the study. The authors also refer to a daily "educational and psycho-therapeutic programme" following each injection, the nature of which is not specified.

2.2.2.12. *O'Connor, Carroll, Shi, Schottenfeld, Kosten and Rounsaville (1997)*. In a very recently published account, US researchers report on a randomised, double-blind trial comparing the efficacy of the naltrexone-clonidine technique to clonidine only and buprenorphine (O'Connor et al., 1997). One hundred and sixty-two heroin dependent patients were treated on an outpatient basis, with successful detoxification considered achieved when patients received 50mg naltrexone. The withdrawal procedures are detailed in Table 1. All patients attended a clinic daily where medication was dispensed to manage withdrawal symptoms until the next visit. Patients in the clonidine protocol (n=55) received .1-.2mg clondine every 4 hours "as needed" from days 1-7 and detoxified patients were given 50mg naltrexone on day 8. In the combined clonidine and naltrexone protocol (n=54), patients received clondine on a similar schedule and ascending daily doses of naltrexone (12.5mg on day 1, 25mg on day 2, and 50mg on day 3) . Patients in the buprenorphine protocol (n=53) received 3mg of buprenorphine sublingually on days 1-3 and then clonidine as outlined above plus 25mg naltrexone on day four and 50mg on day 5. In all three treatment groups, on an as needed basis, oxazepam was used for insomnia and cramps, ibuprofen or ketorolac for muscle cramps and prochlorperazine for nausea.

The successful detoxification rates using these procedures were as follows: 65% for the clonidine only group; 81% for the combined clonidine and naltrexone group; and 81% for the buprenorphine group. Those assigned to the combined clonidine and naltrexone group had the most severe withdrawal symptoms early in detoxification, followed by the clondine only group, with those in the buprenorphine group recording a significantly lower mean overall withdrawal symptom score than either group. The authors point out that retention after eight days did not differ across the groups, with those receiving clonidine alone somewhat more likely to have retention than those receiving combined clonidine and naltrexone.

That buprenorphine was as effective as combined clonidine and naltrexone for detoxification and resulted in fewer withdrawal symptoms lead the authors to suggest that buprenorphine may provide a more "comfortable detoxification for patients" (p.529), while combined drugs may be useful for those highly motivated patients who want to complete detoxification rapidly and begin maintenance with naltrexone or return to work quickly.

In terms of the generalisability of these results, it should be noted that patients who did not have "sufficient" social support for outpatient detoxification (such as safe transportation and a residence) were excluded from this study. Another concern is the absence of any follow-up data.

2.2.2.13. *Comment.* One interesting aspect of the foregoing is that the successful withdrawal rates using antagonists to precipitate and accelerate the process of detoxification from opioids in these 11 reports are, on average, quite high, with the exception of the Russian study. Specifically, the completion rates are as follows: 4/4, 10/11, 38/40, 12/14, 55/56, 14/17, 49/52, 3/44 (the Russian study), not provided, 97/100, 15/20 and 44/54. Averaging these rates yields a successful completion rate of 83%, increasing to 92% when the Russian study is excluded. It may be that the participants in these studies are a selected sample with a good prognosis, but the results stand in stark contrast with those cited earlier for completion of inpatient or outpatient withdrawal. Of course, those entering detoxification services generally do so for many reasons, and not necessarily because they wish to complete withdrawal, but also for shelter, accommodation and respite. However, the good completion rates still need to be considered in the light of the fact that detoxification is but the

first step of a process, and that the more critical component of the process of cessation of opioid use is the management of the post-detoxification period.

Summary.
The studies on the value of rapid opioid detoxification without anaesthesia (ROD) typically involve administering incremental doses of antagonist medication. The literature on ROD consists primarily of a series of reports and controlled trials and to a lesser extent double-blind, placebo controlled studies. Overall, the detoxification results achieved to date with ROD are encouraging, indicating that the majority of patients (83%) entering non-sedated/anaesthetised treatment can be successfully detoxified, and then transferred to full doses of naltrexone. There is, however, an overall lack of follow-up, and when follow-up data are presented they have not been confirmed with urinalysis. The nature of any psychosocial support provided during and/or following withdrawal requires greater clarification, as does patient selection. Seemingly outstanding detoxification and relapse prevention results were achieved in the randomised controlled trial of ROD published by Gerra et al., (1995). This study needs to be replicated. Nothing has been published on the cost-effectiveness of these procedures.

2.2.3. Rapid opioid detoxification under anaesthesia (RODA).

The alternate approach to administering incremental doses of antagonist (i.e., rapid opioid detoxification) is through the use of a bolus dose, usually administered under anaesthesia. This technique was pioneered in Austria by the Loimer group, however, more recently it has been used in Spain and Israel, where is has been referred to as "ultrarapid" detoxification, and to a lesser extent in the USA.

2.2.3.1. Loimer, Schmid, Presslich and Lenz (1988). The first published descriptions of opioid withdrawal precipitated and accelerated by opioid antagonists under anaesthesia come from the Loimer group in Vienna. In a journal letter these researchers describe the detoxification of 12 opioid addicts given a single iv dose of naloxone (10mg) during 30-60 minutes of general anaesthesia (Loimer, Schmid, Presslich & Lenz, 1988). Upon awakening, patients showed only mild signs of withdrawal. The bolus was followed by an infusion at 0.8mg/hour of naloxone for 24 hours. After 24 hours, 6 of the patients were treated with intermittent doses of naloxone for another 24 hours. The remaining 6 patients continued on a naloxone infusion until their urines were no longer opioid positive (about 72-96 hours after initiation of treatment). In the group receiving intermittent naloxone withdrawal signs were seen while urines remained positive for opioids. The second group had no withdrawal signs. All patients completed the withdrawal successfully, but no long-term outcome data were provided.

This brief reports gives little detail about the patients' condition, or about the type of anaesthesia employed. A later study by these researchers describing the detoxification of six opioid addicts using similar techniques, gives greater detail but is limited by small patient numbers, single group design and no follow-up (Loimer, Schmid, Presslich & Lenz, 1989) (see Table 1).

2.2.3.2. Loimer, Schmid, Lenz, Presslich and Grunberger (1990). This subsequent research by Loimer et al. represents one of the only two randomised controlled trials of accelerated detoxification with anaesthesia to be found in the research literature (Loimer, Schmid, Lenz, Presslich & Grünberger, 1990). In 18 opioid dependent patients, these authors examined the contribution of naloxone versus placebo in combination with methohexitone anaesthesia in achieving detoxification. The withdrawal procedure is outlined in detail in Table 1. Basically, all patients were sedated with methohexitone, intubated and ventilated and kept sedated with further methohexitone before being randomly assigned to one of two groups. In Group A a naloxone bolus dose was given immediately following anaesthesia, compared to a placebo bolus dose to Group B. After approximately 40 minutes, all patients were then given a 2mg naloxone provocation test. In the event of severe withdrawal, indicating the patients were given placebo, further methohexitone was administered, followed by a naloxone bolus dose of 10mg. The study then continued in an open design with all patients given a naloxone infusion for the

following 48 hours. All patients completed the withdrawal successfully, but again no long-term outcome data were provided.

The authors claim all of the patients were successfully detoxified with only minimal withdrawal symptoms. However, as pointed out by Herman and Czechowicz (1996), the results are somewhat difficult to interpret as no side by side comparison of numerical data for the two groups has been presented. Tentatively, it is suggested that both barbiturates and high doses of naloxone induce short-term decreases in opioid withdrawal.

2.2.3.3. Loimer, Lenz, Schmid and Presslich, (1991). In a later publication, this group reported on 7 patients acutely detoxified from methadone (Loimer, Lenz, Schmid & Presslich, 1991). The methadone doses ranged from 40-120mg/day (mean 72mg). As detailed in Table 1, 24 hours after their last methadone dose, patients received a bolus dose of 30mg midazolam. Within 10 minutes, a naloxone infusion was commenced (4mg in 200ml saline), and sedation was maintained with repeated doses of midazolam (50-75mg). When the 4mg of naloxone had been infused, sedation was reversed with flumazenil (a highly specific benzodiazepine antagonist), and the patients commenced on oral naltrexone 50mg/day. Two of the seven patients elected to remain on naltrexone.

The authors report that midazolam completely suppressed withdrawal, and that on awakening, and after naltrexone 50mg, there was no evidence of withdrawal. Wang scores rated at 9am daily were unchanged from before detoxification. However, the authors note that 2 subjects reported diaphoresis, lasting 4-6 hours, about 48 hours after the procedure. This report appears to confirm that large doses of opioid antagonists can allow complete withdrawal from methadone very rapidly.

2.2.3.4. Legarda and Gossop (1994). Legarda and Gossop reported on the detoxification of 11 patients using on average ¼ gram of heroin daily (Legarda & Gossop, 1994). As shown in Table 1, patients presented at 9am and were initially treated with repeated doses of guanfacine (1-2mg hourly) until BP<90 systolic and pulse less than 55bpm (guanfacine is an -2 adrenergic agonist, with similar actions to clonidine). The patients were then transferred to ICU and given naltrexone 50mg, loperamide 4mg, and ondansetron 8mg. Sedation was achieved with midazolam 0.5-0.7mg/kg, and maintained with an adjusted infusion. The depth of sedation is not specified, but it appears that patients were not intubated. When piloerection, sneezing and motor agitation were no longer apparent, (4 hours after induction of "sleep"), a test dose of 0.8mg naloxone was administered. On awakening, (again, after an unspecified period) further doses of guanfacine were administered. The patients were discharged the next day and instructed to take naltrexone 50mg/day for 3 months, preferably under the supervision of a close friend or relative. The authors claim at 1 month follow-up all patients were still taking naltrexone, however, this claim is not substantiated by urinalysis or other data, and no long-term outcome data are provided.

This report again gives little detail about the patient selection, duration and depth of sedation, and severity of patients' reactions. Herman and Czechowicz (1996) recommend the study be replicated using a two group double-blind design with both groups undergoing identical medication regimen but varying naltrexone/placebo, with more participants and better outcome measures, if a scientific interpretation of the methodology is to be generated.

2.2.3.5. Bartter & Gooberman (1996). A report of rapid detoxification under anaesthesia, with intubation, is given by Bartter & Gooberman (Bartter & Gooberman, 1996). However, this report relates several different techniques "ranging from intramuscular and oral sedation to intravenous sedation, paralysis, and intubation". Thus it is not

possible to assess any given method reported by these authors. Gooberman, in a conference presentation, reported that many patients on awakening from anaesthesia, had residual symptoms (reported in Simon, 1997).

2.2.3.6. Demaria, Rodgers and Braccia (1997). Demaria and colleagues report a single case of accelerated detoxification using propofol anaesthesia (Demaria, Rodgers & Braccia, 1997). The patient used daily. The withdrawal procedure is shown in Table 1. On admission, the patient was prescribed clonidine and oxazepam for symptomatic treatment. The following morning, clonidine, nizatidine, and metoclopramide were administered. Three hours later the patient was taken to a postanaesthesia care unit, and given midazolam 2mg, ondansetron 8mg, and 1mg/kg propofol. Five minutes later the bolus of propofol was repeated, and a propofol infusion at 200ug/kg/min was established. An intravenous bolus of naloxone, 10mg, was given, leading to the immediate onset of mydriasis, piloerection, and restlessness. After 20 minutes, the propofol infusion rate was halved, and then ceased after another 10 minutes. Thirty minutes later the patient was awake, oriented, and reporting very mild withdrawal symptoms (abdominal cramping and a cold feeling). Two milligrams of naloxone produced no change in symptoms. Seventy minutes after the initial propofol dose, he was given 200mg naltrexone, and discharged (and, incidentally, lost to follow-up).

2.2.3.7. Rabinowitz, Cohen, Tarrasch and Kotler (1997). The above description by Demaria et al. is of interest as it presumably resembles the commercially used techniques which have aroused interest worldwide. These employ propofol anaesthesia, clonidine, and naltrexone administered by nasogastric tube (Rabinowitz, Cohen, Tarrasch & Kotler, 1997). The procedure, detailed in Table 1, lasts 6-8 hours. Patients are intubated. Post extubation, supplementary medication (including clonidine, a benzodiazepine, and loperamide) are given "as needed".

Rabinowitz et al. (1997) comment that the day following the procedure, patients are given 50mg naltrexone, and if withdrawal is mild, the patient is discharged. In "less than about 10%" of patients, a further night of hospitalisation is needed due to "uncontrolled severe diarrhoea or vomiting, anxiety, aggressiveness or exhaustion". The Rabinowitz paper contains no further detail about patients' condition post-procedure, although it is clear that some patients are ill.

One and a half years on average after detoxification, Rabinowitz et al. report that they contacted 83 of the 113 randomly selected patients who did not live overseas, and found that 36 (43%) had relapsed but 57% had not, a good result for naltrexone maintenance. However, the results were gathered by telephone interview, and while there was corroboration from a significant other, urinalysis data would make an impressive result more convincing. It is also unclear whether these patients can be taken as typical of unselected patients samples in other countries, as they had good prognostic signs. Consistent with the broader literature on naltrexone maintenance, motivation was a good prognostic factor. In one study of naltrexone maintenance, for instance, those who completed treatment (whether in naltrexone or placebo) were more likely to: have graduated from high school; have steady employment; have completed compulsory military service; have had fewer criminal charges; and be married (Lerner et al., 1992). In the Rabinowitz et al. (1997) paper, approximately half of the sample was working prior to detoxification, had completed army service or reserve duty, had never been imprisoned, and were married or living together in a *de facto* relationship.

2.2.3.8. Brewer , Laban, Schmulian et al. (1996). Using similar techniques, Brewer et al. describe their experience with 510 patients having undergone RODA at clinics in London (80 cases), Merchantville, New Jersey (355 cases), Athens (25 cases) and Cairo (50 cases) (Brewer et al., 1996). The majority of patients were heroin dependent, with the exception of the London patients of whom 30% were detoxified from methadone.

All patients had assisted ventilation, and to reduce the total amount of propofol anaesthesia required, the muscle relaxant atracurum was usually given. Premedication included antiemetics, usually droperidol or ondansetron, and a benzodiazepine. H_2 blockers or proton pump inhibitors were administered to reduce acid secretion in case of aspiration and all centres used clonidine. Propofol was used in the majority of cases for anaesthesia, although in some instances isoflurane or

thiopentone was used. The duration of anaesthesia was 4 hours in New Jersey and 4-6 hours at the other clinics. According to Brewer et al., profuse liquid diarrhoea is common in precipitated withdrawal and all centres initially used pre-treatment laxatives and/or enemas for this condition. Subsequently, the growth-hormone analogue octreotide was found to be more effective and doses of 50-100mcg 12-hourly were used instead. Further doses of antiemetics and octreotide were given for nausea and diarrhoea, if required, upon emerging from anaesthesia, as was clonidine. Naloxone 1.6-2mg was given initially, followed by naltrexone in doses ranging from 12.5-25mg via the nasogastric tube 20 minutes later. Further doses of naltrexone were given 2-3 hour after the above to a total of 50-200mg.

Following naltrexone administration, there were usually "few signs of withdrawal" with most patients fit to be discharged within 24 hours. However, Brewer et al. assert that claims patients experience no withdrawal symptoms are "manifestly untrue", with a small minority having persistent, if largely subjective symptoms, which can be very distressing. Apart from naltrexone and clonidine or lofexidine, hypnotics were the most widely prescribed class of drug following withdrawal, with Brewer et al. stating sleep patterns can take several weeks to normalise

Follow-up data are presented for the Cairo patients only as the other centres' data were "incomplete". For the first 30 patients, abstinence rates as high as 76% were achieved at four months follow-up (assuming five "lost" cases had relapsed). However, Brewer et al. acknowledge this high rate probably reflects both the rigorous selection of well-motivated patients and the suitability of the Egyptian family to treatment involving family-supervised naltrexone.

Brewer et al. claim that these results confirm that RODA is an effective and acceptably safe method of opioid withdrawal, with patients successfully withdrawn from as much as 200mg of methadone daily. However, it needs to be stressed that based on their experience the authors also believe RODA patients "probably don't have better long-term results than comparable patients who complete conventional in-patient withdrawal programmes" (p.4). In their opinion, RODA is neither appropriate nor necessary for all opioid addicts but attractive to those patients who find conventional withdrawal difficult and/or unpleasant. According to Brewer et al., it appears likely that "a significant proportion of these patients who would fail (or have repeatedly failed) to complete conventional withdrawal will succeed with the help of anaesthesia or sedation" (Brewer, 1997b).

2.2.3.9. Seoane, Carrasco, Cabre et al. (1997). In a recently published randomised controlled trial of accelerated detoxification with anaesthesia, the researchers specifically recruited subjects who had a history of several unsuccessful detoxification episodes (Seoane et al., 1997). As outlined in Table 1, 300 heroin dependent inpatients were randomly assigned to receive intravenous detoxification treatment under either light or deep intravenous sedation.

Sedation was induced in both groups with propofol in bolus at a dose of .3mg/kg, combined with bolus of midazolam at a dose of .04mg/kg. Whereas the Light Sedation Group (LSG) group had a very long induction lasting approximately 60 minutes, induction in the Deep Sedation Group (DSG) lasted only the time necessary to put the patient to sleep (usually 2-4 minutes). After induction, maintenance sedation was started in both groups with a continuous infusion of propofol 3mg/kg/h combined with midazolam .10mg/kg/h for 6-8 hours. The second major difference between the groups concerns the method of monitoring. The sedation level in the LSG was monitored with the Glasgow Coma Score scale with the objective being to maintain values of between 8-9 out of 15, together with appropriate spontaneous breathing and the presence of aerial protection reflexes. In the DSG group, however, the Glasgow Coma Score scale was not used, rather the therapeutic goal was to achieve unintelligible language and assurance that the patients could not be easily awakened with verbal or nociceptive stimuli.

Following sedation, both groups received 3mg/kg of clonidine every four hours and .7mg/kg metoclopramide. Detoxification was then carried out with .06-.08 mg/kg naloxone given through intravenous infusion for 5-10 minutes, followed by the administration of 50mg of naltrexone via a nasal-gastric probe.

Using the above techniques, Seoane et al. claim all 300 patients were successfully detoxified with 292 of the patients discharged after 24 hours of hospitalisation. Of the remaining eight patients, seven were discharged within 48 hours because of minor complications (vomiting, diarrhoea or fever) and in the only case of severe complication, one patient was discharged on the fifth day after developing nosocomial aspirative pneumonia. The most frequent complication was respiratory depression as a result of excessive sedation occurring in six patients, with those in the DSG requiring twice as many intubations as those in the LSG. The most frequently observed signs were polypnoea (37%), diarrhoea (18%), vomiting (12%), diaphoresis (29%) and piloerection (23%). The frequency of these signs was similar in both groups .

These results are impressive, particularly considering a relapse rate of only 7% at one month follow-up is reported based on self-report and negative urine tests. Patient motivation, once again, appears an excellent prognostic factor with all potential participants who were not "highly motivated" excluded from the trial after an interview with a psychologist. Quite possibly, the high abstinence rate at one month follow-up was influenced by the psychosocial support provided to patients in the month following treatment. Indeed, for the first two weeks following detoxification, patients were visited daily by a physician and a psychologist, reducing to twice weekly visits in the remaining two weeks. Clearly, longer-term follow up is required.

Summary.
The RODA research literature consists primarily of a small number of short research reports and clinical reports. In general, these reports are not single or double-blind controlled trials and they are mostly based on relatively small patient numbers (n = 12, 6, 18, 7, 11, 1, and 83). A more recent study (Seoane et al., 1997) using a large sample (n=300) has recorded some impressive results. However, patient motivation appears an important prognostic factor with only "highly motivated" patients included in this study. Additionally, the issue of whether anaesthesia is required has not been addressed. The efficacy of RODA for longer term relapse prevention is also unknown. The impact of other variables, such as psychosocial support provided, patient motivation and familial support need to be considered in any evaluation of RODA efficacy. Presently, the lack of scientific studies makes it difficult to comment on the efficacy of RODA for either detoxification or relapse prevention. Nothing has been published on the cost-effectiveness of these procedures.

2.2.4. Mechanisms of withdrawal

The animal literature on the effects of antagonists on the endogenous opiate system was reviewed earlier. The clinical studies in humans raise some further issues. Loimer and colleagues postulated that withdrawal depends on the presence of persisting small concentrations of opioids which are able to produce withdrawal symptoms if receptors are not blocked (Loimer et al., 1988, Loimer, 1989 #1472). This explains why in their study, after a bolus dose of naloxone under anaesthesia, subjects receiving continuous naloxone had no withdrawal symptoms, while those receiving intermittent injections continued to have withdrawal symptoms.

This hypothesis would explain the observation that duration of withdrawal is prolonged after use of long half-life drugs (as persisting low concentrations contribute to withdrawal symptoms). It is consistent with the observation from Brewer that accelerated withdrawal and induction onto naltrexone equalised the duration of withdrawal from heroin and methadone (Brewer et al., 1988). Others make the same observation (Kleber et al., 1987). This makes sense if the end point is induction onto full dose naltrexone, as the low persisting levels of opioid which contribute to longer withdrawal from long acting drugs would be antagonised.

If the presence of persisting low levels of opioids contributes to withdrawal symptoms, this could explain the observation of Vining and colleagues that higher initial doses of naltrexone (12.5mg) actually produce milder withdrawal than initiating treatment with very low doses, as blockade of opioid receptors prevents persisting withdrawal symptoms (Vining et al., 1988). A dose of 12.5mg of naltrexone may be assumed to produce a fairly considerable blockade of opioid receptors. Martin demonstrated that 15mg of oral naltrexone produced blockade of morphine 30mg sc, an effect lasting 24 hours (Martin, Jasinski & Mansky, 1973).

Naltrexone and naloxone are reversibly bound, competitive inhibitors of μ-opioid receptor pure agonists. Large doses produce rapid displacement of agonist binding. The rate of change of this process is presumably the major determinant of withdrawal severity, with spontaneous withdrawal being less severe and withdrawal by a large bolus of antagonist being most severe, as all receptors change simultaneously. Smaller doses produce less rapid

displacement of receptor binding, and thus a less severe precipitated withdrawal. However, if persisting low quantities of opioids continue to stimulate some receptors, low doses of antagonist may paradoxically contribute to more severe or more persistent symptoms.

However, there needs to be caution in interpreting the results of a small number of studies. Factors other than pharmacology are important in influencing the severity of withdrawal symptoms. The studies of Gerra *et al*. (1995) and Vining *et al*. (1988) both employ a fixed protocol, using only clonidine for symptomatic relief. It is possible that the absence of alternative medication, coupled with reliance on supportive care rather than medication to deal with symptoms, may produce better symptom relief than those clinical approaches in which multiple medications are given on an "as needed" basis. This is consistent with the finding that "giving patients clear information about the course of opioid withdrawal is important, and has been associated with significantly increased completion rates and decreased subjective withdrawal distress" (Mattick & Hall, 1996). Furthermore, the very large doses of diazepam prescribed in the Brewer (1988) study would be sufficient to induce a degree of delirium in many non-tolerant patients, and, particularly in people undergoing a stressful detoxification, may paradoxically exacerbate withdrawal symptoms (O'Reilly & Smith, 1991). In comparing opioid withdrawal regimens, the non-pharmacological treatment (provision of information and structured protocols for nursing and other supportive care) as well as medication protocols need to be clearly defined, as these are important (Green & Gossop, 1988). Such trials of accelerated detoxification have not been performed.

Summary.
The ability of antagonists to affect the endogenous opiate system has been studied in non-dependent animals. The impact of antagonists is not well-understood in opioid dependent animals or in dependent patients. Large doses of opioid antagonist produce rapid displacement of agonist binding. The rate of change of this process is presumably the major determinant of withdrawal severity, with spontaneous withdrawal being less severe and withdrawal by a large bolus of antagonist being most severe, as all receptors change simultaneously. Smaller doses produce less rapid displacement of receptor binding, and thus a less severe precipitated withdrawal. Factors other than the pharmacology are important in influencing the severity of withdrawal symptoms in opioid dependent patients.

2.2.5. How debilitating is rapid detoxification?

It has been suggested that the primary goal of detoxification programmes is "to achieve a safe and humane withdrawal from a drug of dependence" (Mattick & Hall, 1996). Protagonists of rapid detoxification have argued that the advantage of detoxification under anaesthesia is that patients have no unpleasant experience of withdrawal, and this reduces the likelihood of post-detoxification relapse (Legarda & Gossop, 1994) (although memory of severe withdrawal may also reduce propensity to future use). Rapid-detoxification is promoted as a solution to patients who suffer from "detoxification phobia". These claims are important, as they probably contribute to the consumer appeal of rapid detoxification.

However, there are no systematic data to support the proposition that the withdrawal is symptom-free, and some of the descriptions of what patients go through during accelerated detoxification raise questions as to whether this is a humane procedure. Although the case study from Demaria et al. (1997) suggests that withdrawal under anaesthesia can be basically asymptomatic, the comments of Rabinowitz et al. (1997) suggest that at least a proportion of patients experience quite severe post-detoxification symptoms. McLellan (personal communication) suggests that many patients who have undergone detoxification under anaesthesia in the USA are discharged on high doses of medication for symptomatic relief. Brewer states that claims that patients undergoing anaesthesia assisted rapid opioid detoxification experience no withdrawal symptoms are manifestly untrue (Brewer et al., 1996). Currently, there is a lack of systematic information on the condition of patients after all forms of accelerated detoxification, including RODA.

It is difficult to estimate the severity of symptoms experienced by patients undergoing accelerated detoxification without anaesthesia. There is no way of comparing the severity of withdrawal across the different studies. Some reports utilised Wang withdrawal scores, but the way in which these have been reported makes comparisons difficult. The most satisfactory account comes from Gerra et al. (1995). In their randomised trial, patients undergoing accelerated detoxification experienced milder withdrawal than patients undergoing unmedicated spontaneous withdrawal.

Summary.
One argument in favour of RODA is that the symptoms suffered are either non-existent or very mild. However, there are no systematic data to support the proposition that the withdrawal is symptom-free, and some of the descriptions of what patients go through during accelerated detoxification indicate that the procedure is not always without severe withdrawal symptoms.

2.2.6. The risks of accelerated detoxification.

There are published case studies of risks associated with rapid detoxification, and numerous anecdotal reports of risks associated with this treatment. San *et al.* reported a patient who developed vomiting and respiratory distress with marked desaturation occurring during rapid detoxification (San, Puig, Bulbena & Farre, 1995). The vomiting occurred despite pretreatment with ondansetron. The authors attributed desaturation to naloxone-induced pulmonary oedema (a curious diagnosis given that there was no evidence of pulmonary oedema). There are case reports that naloxone can cause pulmonary oedema (Taff, 1983, Partridge, 1986 #1503), a problem common to all opioid type drugs (Gould, 1995).
Mayor discusses a death due to convulsions followed by asystole in a patient undergoing rapid detoxification in a private clinic in London (Mayor, 1997). The patient was said to have been prescribed 15 medications during the procedure. Brewer reports awareness of four deaths related to RODA (Brewer, 1997a), although none of these occurred while the patient was anaesthetised. Nonetheless, the recommendation from Brewer is for monitoring patients in an ICU setting for at least 12 hours after extubation. Mayor cites specialist medical opinion, consistent with Brewer's own view, that "'[g]iving an anaesthetic over several hours requires detailed monitoring, particularly in a patient undergoing opiate withdrawal'. . . . [T]his should be carried out by anaesthetists with extensive experience, supported by suitably trained nursing staff in an environment where the patient can be monitored continuously" (p.1365).

Deep sedation without intubation exposes patients to the risk of aspiration. Since detoxification increases the risk of vomiting, RODA is presumably safer when the patient's airway is protected through intubation (Simon, 1997). While documentation of risks of rapid opioid detoxification is poor, some measure of the potential hazards can be gained from data on the use of comparatively small bolus doses of naloxone to reverse opioid-induced coma. Osterwalder (1996) surveyed complications associated with intravenous bolus doses of naloxone given to reverse acute opioid overdose (Osterwalder, 1996). Six of 453 intoxicated subjects (1.3%; 95% confidence interval 0.4%-3%) suffered severe adverse effects within ten minutes after naloxone administration (one asystole; three generalised convulsions; one pulmonary oedema; and one violent behaviour). After the ten minute period, no further complications were observed. While this is very different to accelerated detoxification, under anaesthesia or under clonidine cover, it still demonstrates the potential for major problems due to rapid reversal of opioid dependence.

Summary.
Rapid detoxification with and without anaesthesia does have risks associated with it. There have been a number of deaths associated with RODA. Naloxone reversal of opioid overdose has been associated with serious adverse events. However, the probable prevalence of serious adverse events in ROD or RODA is difficult to estimate as the published literature is scant on the details.

2.2.7. Benefits and costs of accelerated detoxification from heroin.

Detoxification from heroin can be achieved safely and effectively, and fairly rapidly, either on an outpatient or inpatient basis. Accelerated detoxification offers two potential advantages - cost (reduced due to the brevity of the procedure, requiring shorter hospitalisation) and improved rates of induction onto naltrexone. Set against these potential benefits are the risks of a more invasive procedure. *Prima facie*, a more invasive procedure must have clearly demonstrated benefits over a less invasive one if it is to be adopted. This is particularly the case in opioid detoxification, which is a palliative procedure rather than a curative one.

In terms of cost, outpatient detoxification with clonidine can be accomplished cheaply. There are scant systematic data on completion rates. Figures quoted tend to be low, such as the study showing 40% of patients completing outpatient detoxification with clonidine (Rounsaville, Kosten & Kleber, 1985). One recent report indicated that 98% of opioid users completed home-based detoxification using lofexidine (Everleigh, 1997).
In-patient treatment is more expensive, but hospitalisation is seldom indicated on medical grounds. However, hospitalisation increases completion rates, to around 80% (see, for example, (Gossop, Johns & Green, 1986)).

The end-point of most studies of accelerated detoxification, and implicitly the rationale for this procedure, is induction onto naltrexone maintenance. Although controlled trials are not available, it is claimed that accelerated detoxification increases the likelihood of induction into naltrexone maintenance. This is *prima facie* credible, particularly for detoxification under anaesthesia. However, only the paper from Gerra et al. (1995) provides any evidence that accelerated detoxification increases the likelihood of medium term abstinence for detoxified heroin users. In that

study ongoing treatment with naltrexone maintenance was clearly identified as one factor contributing to medium-term abstinence. However, this promising result is sharply at odds with previous reports on naltrexone maintenance, which has not been shown to alter the course of opioid dependence (Jaffe, 1995). The study needs to be replicated, with detailed information on patient selection and the nature of ancillary treatment provided.

It is worth noting that in the case series reported by Senft (1991), using similar methods to Gerra *et al.* (1995), "All patients were offered naltrexone maintenance, but few continued unless coerced by court or employer". It seems that there is more to successful detoxification and induction onto naltrexone than simply a medication regimen.

Summary.
Detoxification from heroin can be achieved safely and effectively, and fairly rapidly, either on an outpatient or inpatient basis without opioid antagonists, although completion is greater on an inpatient basis. Accelerated detoxification offers two potential advantages - cost (reduced due to the brevity of the procedure, requiring shorter hospitalisation) and improved rates of induction onto naltrexone. The ability of RODA to improve rates of entry into, and more importantly retention in, naltrexone maintenance is unclear. The value of ROD and RODA for heroin users is unclear. There is no evidence on cost-effectiveness.

2.2.8. Benefits and costs of accelerated detoxification from methadone.

One rationale for accelerated detoxification as a way of coming off methadone has been the prolonged nature of methadone abstinence syndrome (which may be symptomatic for up to 6 weeks). The assumption is that accelerated detoxification can shorten the period of symptomatic distress after stopping methadone. However, this has not been documented. Rather, studies have used as an end point the fact that patients can tolerate a 50mg dose of naltrexone. The prolonged methadone abstinence syndrome is subtle and subjective, and there is to date no evidence that patients are symptomatically more comfortable after accelerated withdrawal than after (or during) spontaneous withdrawal. No sort of comparisons, let alone placebo controlled trials, have been performed. Therefore, while acute withdrawal can be achieved, there is no evidence that accelerated detoxification can shorten the protracted abstinence from methadone.

The other rationale for rapid detoxification is to allow patients with minimal symptomatic distress to switch from methadone to naltrexone. The availability of naltrexone maintenance broadens the treatment repertoire, and provides many individuals with an alternative to methadone maintenance. However, this is also a potential problem. Many patients in methadone treatment are deeply ambivalent about methadone. The promotion of accelerated detoxification techniques may contribute to worse treatment outcomes for many such patients. Rather than addressing ambivalence, discussion of rapid detoxification focuses on alternatives and ignores the fact that methadone maintenance has documented efficacy (Ward, Mattick & Hall, 1997), which is lacking for naltrexone (Jaffe, 1995), except as a relapse prevention method in motivated patients (see later).

There is a real risk that encouraging patients to leave methadone maintenance will only destabilise them and compromise any benefits of treatment. Methadone maintenance is a maintenance intervention, and there is no evidence that the benefits of treatment extend beyond the period of treatment (Ward, Mattick & Hall, 1992; Ward et al., 1997). Thus, in order to be able to provide patients and families with appropriate advice, it is essential that studies be undertaken to determine whether accelerated detoxification and naltrexone maintenance actually contribute to improved outcomes for selected patients who wish to leave methadone treatment.

Not only is the technique novel, and therefore attractive, it is very "biomedical" - the patient undergoes a procedure and emerges "cured". There is a great appeal in this passive "patient" role, in which the efficacy of the treatment becomes the determinant of outcome. However, this is a doubtful model of treatment for any chronic medical condition, and is particularly unsatisfactory for the treatment of drug dependence. There is a risk that focussing on biomedical techniques will undermine efforts to promote patients' autonomy and social reintegration.

Finally, for the individuals involved, and for the treatment system as a whole, there are potential benefits and risks which remain to be properly evaluated. There will be a demand for accelerated detoxification, as part of the continual pressure to promote abstinence as a goal of addiction treatment. Many administrators are keen to see long-term patients come off methadone. As summarised by Latowsky in a recent review, "In spite of the well-documented benefits of MMT, patients continue to detoxify from methadone for a variety of reasons both overt and covert. Variable outcomes and generally poor long-term abstinence rates results. At present uncertainty still exists

surrounding who should attempt detoxification, when or how this should be done, or whether in fact detoxification should be attempted at all" (Latowsky, 1996).

Summary.
One rationale for accelerated detoxification as a way of coming off methadone has been the prolonged nature of methadone abstinence syndrome. While acute withdrawal can clearly be achieved, there is as yet no evidence that accelerated detoxification can shorten the protracted abstinence from methadone. The other rationale for rapid detoxification is to allow patients with minimal symptomatic distress to switch from methadone to naltrexone. The availability of naltrexone maintenance broadens the treatment repertoire. However, the promotion of accelerated detoxification techniques runs a real risk that encouraging patients to leave methadone maintenance will destabilise them and compromise any benefits of treatment.

TABLE 1: Summary of trials, research reports and clinical reports of Rapid Opioid Detoxification (ROD) and Rapid Opioid Detoxification under Anaesthesia (RODA).

Study Year	Study type, design and sample	Duration	Pre-withdrawal preparation/ medication#	Withdrawal medication#	Post-withdrawal preparation/ medication	Status at Completion	After care	Comments
Riordan and Kleber, 1980 "Clonidine and repeated injections of naloxone"	ROD Single group n=4 3 daily heroin users and 1 methadone patient (daily dose 25mg).	4 days hospitalisation.	Day 1: Patients pretreated with clonidine 6 g /kg in 3 doses 6-8 hours apart. 1st dose usually .1 g to assess patients' reaction.	Day 2: Clonidine 11 g /kg given in 3 doses; Naloxone (NLX) .4mg im given every 2 hours for total of six doses beginning 30 minutes after the 1st clonidine dose. Day 3: Clonidine .6 g /kg given in 2 doses at about 8am and 2pm; NLX .8mg im given every 2 hours starting 30 minutes after the 1st dose. Day 4: NLX im 1.2mg given at 8pm after last dose of clonidine. If no withdrawal symptoms to this dose, considered detoxified and ready for NTX treatment.	NTX maintenance alluded to but not specified.	"we have successfully detoxified four patients on an inpatient service" (p.1079). Withdrawal scores were highest after the first 2 NLX injections and none of the patients reacted to the 1.2mg NLX dose on day 4.	None specified. No follow-up data supplied.	-small numbers, patient details scant; -report suggests technique more desirable on an inpatient basis as 3 patients treated so far on an outpatient basis failed to return to the programme despite having few objective with-drawal symptoms.
Charney et al., 1986 (paper includes data from 1982 study by Charney et al.) "Naltrexone-clonidine to withdraw methadone inpatients"	ROD Controlled trial, double-blind design n=40 **methadone maintained** patients (mean daily dose of 32mg, range 10-65mg).	5-6 days hospitalisation. (N.B. The length of admission varied as patients discharged when they felt mild or no withdrawal symptoms)	Day 1: Patients received methadone dose at 9am.	24 hours after last methadone dose: Group A (n=14): Day 2: Clonidine 5 g /kg at 9am with two further doses at 3pm and 9pm titrated accordingly. Day 3 & 4: Naltrexone (NTX) oral treatment began, administered every 4 hours starting at 1mg and increased by 1mg increments on 1st day and 2mg on 2nd day (no increases given after 5pm). Day 5: NTX given 4 times; majority of patients receiving 10mg 3 times and 15mg 1 time. Day 6: NTX 50mg given at 9am each day until discharge to majority of patients. Group B (n=26): Same as above without Day 2 (the clonidine only day). Flurazepam used for night time sedation.	Naltrexone was provided as specified until discharge.	NB: results for Group A and B combined as efficacy and side effects essentially identical. 38 of 40 patients were "successfully withdrawn from long-term metha-done therapy within 4-5 days after its abrupt discontin-uation" (p.835). No follow-up data supplied.	None specified and no follow-up data given but authors state this treatment would enable patients to directly begin a NTX mainten-ance program after with-drawal.	Two patients dropped out after 1st NTX dose in light of substernal chest pain and hallucinations/ bizarre behaviour respectively; -patients' signs and symptoms did not appear to be related to meth-adone dose or duration of use and authors state their "experience suggests" patients on doses up to 50mg/day would be appropriate for this treatment (p.836).

Study Year	Study type, design and sample	Duration	Pre-withdrawal preparation/ medication#	Withdrawal medication	Post-withdrawal preparation/ medication	Status at Completion	After care	Comments
Kleber et al. 1987 "Naltrexone-clonidine to withdraw heroin outpatients"	ROD Single group n=16 heroin dependent patients.	5 days in outpatient setting.	Day1: NLX challenge test of .8mg im. NB. 2 subjects had negative naltrexone (NLX) challenge tests and were excluded from the study.	Day 1: Following NLX challenge test, clonidine .1-.3mg given three times daily as needed (patients also given .1-.2mg clonidine to use as needed at home). Day 2: In addition to clonidine, initial dose of NTX 1mg given (total day 1 dose 8mg), increasing gradually to 50mg by day 4 and 150mg by day 5; clonidine reduced to .2mg by day 5. Chloral hydrate 1g or flurazepam 30mg given for sleep disturbances.	NTX maintenance.	12 of 14 (86%) successfully withdrew from opioids over 5 days and simultaneously initiated NTX maintenance.	NTX maintenance: At 1 month follow-up 5 of 12 still taking NTX and 3 drug-free.	- drop-outs possibly prevented if treated on inpatient basis; -suggested that programme most successful for well-motivated and relatively stable patients.
Brewer et al., 1988 "Modification of the naltrexone-clonidine technique to reduce inpatient treatment duration"	ROD Observational study of two withdrawal schedules, consecutive sample. n=56 opioid dependent patients (60 withdrawals as 4 patients, 2 in each group, detoxified twice).	3-4 days hospitalisation: - 3.3 days on average withdrawal for Group A; - 2.3 days on average withdrawal for Group B.	Group A (n=35): Day 1: After physical exam., test dose of clonidine .1mg given and again 2 hours later. Further clonidine .2-.3mg given 4-hourly as needed. Diazepam given if above inadequate. Group B(n=21): Day 1: ASAP after admission, test dose of clonidine .2mg given. After 1 hour further clonidine .1mg given.	Group A (n=17*): On day 2 or afternoon of day 1 if patient admitted in the morning, initial NTX dose of 1mg given and repeated 4-hourly, increasing to 2mg if symptoms well controlled. Average doses on day 1 day 2: NTX 3.3mg (1-7) 15mg (2-50) Clonidine .64mg (.3-1.2) .84mg (.3-.9) Diazepam 65mg (30-130) 68mg(35-140) Group B (n=21): On day 1 45 minutes after clonidine dose, NTX 1mg given and repeated every 90 minutes with each dose progressively increased to 2mg and then 5mg if well tolerated. If symptoms distressing, NTX withheld until controlled with clonidine and if necessary, diazepam. Average doses on day 1 day 2: NTX 21mg(5-50) 47mg (14-50) Clonidine 1.2mg(.8-1.6) .7mg (.2-1.3) Diazepam 75mg (40-180) 39mg(10-110) Hyoscine used for abdominal cramping and nausea. Nitrazepam or flurazepam given at night if required. (*18 patients' records incomplete)	None specified.	55 out of 56 successfully completed programme as defined by patient being able to receive 50mg NTX in a 24 hour period and feeling well enough to go home. Giving significantly higher doses of NTX and clonidine on day 1 significantly reduced average withdrawal time, despite lower clonidine dosage and significantly lower diazepam dosage administered to Group B on day 2 and the fact this group had a higher average daily use of heroin.	None specified. No follow-up data supplied.	-the safety of using very high doses of diazepam without intubation or ICU setting questioned (Simon, 1997); - no reason given for the 1 drop out from Group A; - little detail given about the symptomatic state of patients during and after detoxification.

Study Year	Study type, design and sample	Duration	Pre-withdrawal preparation/ medication#	Withdrawal medication	Post-withdrawal preparation/ medication	Status at Completion	After care	Comments
Vining et al. 1988 "Modification of the naltrexone-clonidine technique using NTX tablet on an outpatient basis"	ROD Observational study of two treatment schedules, consecutive sample. n=18 heroin dependent outpatients.	4-5 days in outpatient setting: - 5 days withdrawal for Group A; - 4 days withdrawal for Group B.	NLX challenge test of .8mg im prior to 1st dose of clonidine. NB. 1 subject had a negative NLX challenge test and was dropped from the study.	In day setting following NLX test: Group A (n=9) <u>5-day detoxification:</u> Clonidine therapy given 3 times a day. NTX oral treatment began **next day** with clonidine treatment. Group B (n=8) <u>4-day detoxification:</u> Clonidine therapy administered 3 times a day and 1st dose NTX given afternoon of same day. (Single <u>daily</u> doses of NTX given in ascending doses of, 12.5, 25, 50 and 100mg. Further clonidine(.3mg) given as needed following each NTX dose on days 1,2 and 3). Chloral hydrate, flurazepam or diazepam for insomnia.	N/A	14 of 17 (82%) patients were withdrawn from opioids within a 4-5 day period and began NTX maintenance. Starting NTX sooner shortened withdrawal syndrome without increasing symptomatology and patients less likely to use opioids in early stages of detoxification.	NTX maintenance: 10 of 14 patients were maintained on NTX after detoxification. 1 month f/u showed 9 out of 14 still taking NTX.	-suggested that single larger dose of NTX kept opioid receptors blocked and reduced symptoms compared to small repeated doses which may repeatedly precipitate withdrawal; -NTX tablets available to any opioid treatment facility; - larger doses of NTX resulted in a decrease in clonidine used.
Senft, 1991 "Naltrexone-clonidine technique using NTX tablet on an inpatient basis"	ROD Single group n=52 opiate dependent patients (55 withdrawals).	3 days in intermediate-level medical detoxification facility. (NB. length of admission varied with some patients discharged on morning of day 2 to be followed as outpatients)	<u>Day 1:</u> Patients admitted at 8am and vital signs monitored.	In detoxification facility: <u>Day 1:</u> Clonidine .3mg given 3 times 6-hourly with dosage modified depending on symptoms and vital signs (eg. sys BP); NTX oral 12.5mg given at 10:30am. Dicyclomine for abdominal cramps. Kaopectate used for diarrhoea. Hydroxyzine for nausea and vomiting. Chlordiazepoxide for agitation, insomnia. <u>Day 2:</u> Clonidine .2mg given 3 times 6-hourly with decreases or increases made based on 1st day's response; NTX 25mg given at 10:30am. <u>Day 3:</u> Clonidine .2mg at 9am; NTX 50mg at 9am; Patients discharged with an evening clonidine dose recommended.	Evening dose of clonidine .2mg recommended on day of discharge. NB. originally clonidine to be tapered over 4 days after discharge but many patients discontinued treatment "because of fatigue" (p.259).	All but 3 patients completed detoxification. Insomnia, chilliness, and fatigue were the usual residual symptoms immediately after discharge.	All patients placed on NTX maintenance at discharge but despite low or no cost " **few continued long unless coerced by court or employer"** (p.258)	-during detoxification "symptomatology varied considerably" from "no significant symptoms" to vomiting in a third of patients on day 1, diarrhoea also "frequent"; -2 patients developed delirium, resolving in 4-6 hours; -several cases of transient hypotension or bradycardia reported, which resolved upon clonidine moderation.

Study Year	Study type, design and sample	Duration	Pre-withdrawal preparation/ medication	Withdrawal medication	Post-withdrawal preparation/ medication	Status at Completion	After care	Comments
Azatian et al. 1994	ROD Single group n=68 opiate-dependent volunteers in Moscow of whom 44 entered withdrawal phase.	Up to 14 days hospitalisation. (NB. a 4 day or less detoxification period was planed but the schedule had to be extended due to the severity and persistence of withdrawal symptoms)	None specified.	<u>Withdrawal phase:</u> Clonidine given 3-4 times per day. Average day 1 dose .62mg decreasing to .5mg on day 8. NTX oral 12.5mg (average dose) given 20 minutes after clonidine with 1st day of administration set by opioid use (eg. subjects with low levels of use given NTX 48 hours after last opioid intake and those with high levels given NTX on 3rd or 4th day). Diazepam, nitrazepam and amitriptyline given to majority. Antipsychotics for aggressive behaviour.	NTX maintenance: only 3 patients continued with NTX maintenance after 10-14 days of detoxification treatment.	"Within a period of 14 days, all but 3 of the 44 patients... left treatment against medical advice"(p.47).	NTX mainten-ance. (NB. all 3 patients discon-tinued within 5 days)	- physical and psychological discomfort was a major factor for drop-out; -Russian addicts may have more severe withdrawal than US users due to higher purity.
Gerra et al. 1995	ROD RCT n=152 heroin "abusers" (met criteria for drug abuse disorder as defined by DSM III-R).	-4 day detoxification period in outpatient recovery centre; -3 month outpatient after care.	Patients began detoxification 12 hours after last iv heroin use.	In outpatient recovery centre; For 4 days patients underwent therapy with indwelling cannula for 7 hours; The 4 treatments groups included; A) Clonidine iv (.15mg in 250ml saline/3 times a day) for detoxification and placebo for Relapse Prevention* (RP) from day 2. (n=33) B) Clonidine and NTX iv (clonidine dose as above, NTX 12.5mg on day 2, then 50mg daily) for detoxification and NTX 50mg/day for RP. (n=42) C) Clonidine and NLX iv (clonidine dose as above, NLX .2mg on day 2 and at .4mg two times/day for next 2 days, oral placebo given on days 2-4) for detoxification and NTX 50mg daily for RP thereafter. (n=58) D) Placebo iv for detoxification and placebo for RP from day 2. (n=19)	*Relapse prevention medication provided for 3 month period after detoxification-ification as specified. Psychosocial support provided to all 4 groups to same degree (ie. psycho-therapy once per week and supervision by a counsellor).	At 72 hours all three clonidine groups (either with or without NLX or NTX showed virtually no with-drawal symptoms compared with significant with-drawal symptoms displayed in the placebo group. At 6 months the % of "dirty" urines: 74% in placebo group, 59% in Clonidine group and 20% in the clonidine/ opioid antagonist groups (clonidine/ NTX slightly lower %).	As specified. At 3 months, drop-out rates low, even in placebo group. At 6 months 60% of the antag-onist groups still attending meetings (clonidine / NTX higher %).	-results show efficacy of clonidine in treating with-drawal symptoms and that addition of antagonist de-creased length of symptoms to 2 days increasing their expression on 2nd day (Herman & Czechowicz, 1996); -data indicate the efficacy of NTX in decreasing relapse when **combined with psychosocial support** (Herman & Czechowicz, 1996).

Study Year	Study type, design and sample	Duration	Pre-withdrawal preparation/ medication#	Withdrawal medication	Post-withdrawal preparation/ medication	Status at Completion	After care	Comments
Merrill and Marshall 1997 "Withdrawal using single daily naloxone injections"	ROD Single group n=20 opioid users voluntarily electing NLX detoxification. (19 methadone maintained, mean dose 46mg)	- six day inpatient detoxification; - inpatient care after detoxification available; (NB. mean duration of inpatient admission was 21 days for those completing treatment)	On admission: patients commenced on clonidine .2mg given 4 times daily based on diastolic blood pressure.	24-48 hours after last opioid intake: NLX iv .8mg given and then same single dose repeated im once daily until physical withdrawal symptoms ceased; up to 50mg diazepam daily for symptom relief; clonidine and diazepam gradually reduced and ceased within 5 days. Thioridazine 25-50mg used for night sedation if required. Daily educational and psychotherapeutic programme followed each injection.	-inpatient care available but details not specified; -5 patients began NTX treatment after last NLX dose.	15 patients (75%) completed detoxification. "typically the fifth NLX injection produced no subjective or objective withdrawal reaction"(p.5)...even though the patients were not receiving any clonidine or diazepam by then.	NTX maintenance: 5 patients began NTX after detoxification. No follow-up data supplied.	-technique unique in administering only 1 dose of NLX daily requiring minimal medical and nursing supervision; -4 of 5 drop-outs discharged for suspected or proven illicit drug use.
O'Connor et al. 1997	ROD Double-blind, RCT of clonidine, combined clonidine and NTX and buprenorphine n=162 heroin dependent patients.	3-8 days in outpatient setting depending on treatment group; NB. Detoxification considered successful when patient received 50mg NTX.	None specified.	Days 1-8: *all patients* attend clinic daily. Patients randomly assigned to one of 3 treatment groups: A) Clonidine group (n=55): .1-.2mg clonidine taken every 4 hours as needed to control withdrawal symptoms from days 1-7. Patients given NTX 50mg on day 8. B) Combined clonidine and NTX group (n=54): Clonidine taken as above, with ascending daily doses of NTX of 12.5, 25 and then 50mg on day 3. C) Buprenorphine group (n=53): Buprenorphine 3mg given sublingually on days 1-3 and then clonidine as described above plus 25mg of NTX on day 4 and 50mg on day 5. Oxazepam given for insomnia and cramps, ibuprofen[14] or ketorolac[14] for muscle cramps and prochlorperazine[10] for nausea, to all 3 groups as needed.	All patients who completed detoxification were referred for NTX maintenance.	65% of patients receiving clonidine, 81% receiving combined clonidine and NTX and 81% who received buprenorphine were successfully detoxified. Retention similar across all groups after 8 days. Patients receiving buprenorphine had a significantly lower mean overall withdrawal symp-tom score than both other groups.	NTX maintenance. No follow-up data supplied.	-patients who did not have sufficient social support (eg. safe transportation and residence) for outpatient detoxification excluded; -authors state that combined clonidine and NTX may be useful for highly motivated patients who want to complete detoxification rapidly, however, these patients require closer observation; -no longer term follow-up.

Study Year	Study type, design and sample	Duration	Pre-withdrawal preparation/ medication#	Withdrawal medication	Post-withdrawal preparation/ medication	Status at Completion	After care	Comments
Loimer et al. 1989 "The original technique with NLX bolus followed by infusion"	RODA Single group n=6 opiate dependent patients as defined by DSM III-R criteria.	Approx. 7 days hospitalisation: - 3 days maintained on morphine; - detoxification on day 4 with barbiturate anaesthetic (30-50min duration); - inpatient care up to day 7 (Brewer, 1997).	Day 1-3: Patients stabilised on morphine 270mg/ day for 3 days.	Day 4 onwards: Methohexitone iv 500-1000mg for sedation; Intubate and ventilate; NLX 10mg iv given within 10 minutes of above and treatment continued with infusion of .4mg/h NLX for following 72 hours.	None/not specified.	"When patients awoke, little or no evidence of with-drawal was observed. As long as NLX was administered to the patients (up to 72 hours) withdrawal signs never reappeared and NLX treatment could be discontinued without any reactions" (p.84).	None. No follow-up data supplied.	-small single group and no follow-up.

Loimer et al. 1990 "The original technique"	RODA RCT of NLX versus placebo n=18 opiate dependent patients as defined by DSM III-R criteria.	Approx. 7 days hospitalisation: - patients admitted to hospital 1 day before treatment; - 2 days maintained on morphine; - detoxification began on day 3 with barbit-urate anaesthetic (30-40 minutes duration); - inpatient care encouraged up to day 7 (Brewer, 1997).	<u>Day 1 and 2:</u> Patients stabilised on oral morphine 100-300mg/day for 2 days.	12 hours after last morphine intake: *To all patients* Methohexitone iv 100mg for sedation; Intubate and ventilate; Methohexitone iv 400mg to maintain anaesthesia. **Random assignment** <u>Group A (n=9):</u> NLX iv bolus 10mg given immediately after anaesthesia. <u>Group B (n=9):</u> Placebo iv bolus given immediately after anaesthesia. *All patients* given NLX iv 2mg as provocation test about 40 minutes later. <u>Group B:</u> Methohexitone iv 250mg in total given in the event of severe withdrawals (indicating patient received placebo) followed by NLX iv bolus10mg. **<u>Study continued in open design</u>** *All patients* given NLX iv .8mg/h for following 48 hours.	Observation and evaluation until day 7 and discharge, however, authors state "in our experience, patients do not require any special care after the acute detoxification procedure, and....might be discharged after 2-4 days"(p.751)	"All of the patients were discharged.. after seven days of admission with only minimal levels of observable subjective or objective physical withdrawal symptoms"(p.751)	None No follow-up data supplied.	-double-blind placebo-controlled study; -results difficult to interpret as no side by side comparison of numerical data for 2 groups; -results tentatively suggest that both barbiturates and high doses of NLX induce short-term decreases in opiate withdrawal (Herman & Czechowicz, 1996).
Study Year	Study type, design and sample	Duration	Pre-withdrawal preparation/ medication	Withdrawal medication	Post-withdrawal preparation/ medication	Status at Completion	After care	Comments

Loimer et al. 1991 "Sedation with iv midazolam, naloxone, reversal of sedation with flumazenil, transfer to naltrexone after 2-3 hours"	RODA Single group n=7 **methadone maintained** patients from outpatient clinic (mean daily dose 73mg, range 40-120mg /day)	Approximately 5 days hospitalisation: - 2-3 hours sedation.	None. Patients began detoxification-ification 24 hours after last methadone dose.	24 hours after last dose of methadone: Midazolam iv bolus 30mg for sedation; NLX 4mg in 200ml .9% saline iv infusion administered within 10 minutes of above; Midazolam iv 50-75mg administered in repeated doses as necessary to maintain sedation.	Shortly after NLX infusion completed: Flumazenil 2-6 mg given in repeated doses until patient fully awake. NTX oral 50mg/ day given for approximately 5 days until no opiates detected in urine samples.	"all 7 patients successfully completed detoxification as verified by negative results on urine tests and pretreat-ment levels of withdrawal distress" (p.934).	2 patients chose to continue NTX maint-enance at end of study. No follow-up data supplied.	-2 patients had mild perspiration (lasting 4-6 hours) 48 hours after detoxification initiated; -Simon (1997) claims great risk for vomiting and aspiration of vomitus into lungs and states the methods used in the study run "contrary to the principles of safe anaesthetic man-agement"(p.108).
p)SM (all)in).	2-3 days hospitalisation: - 2 hours acute detoxification; - in-patient care for following 2 days.	None. Patients began detoxification 12 hours after last heroin intake.	12 hours after last heroin intake: Midazolam oral 60mg for sedation; Clonidine oral .3mg and Ondansetron oral 5mg given simultaneously; NTX oral 50mg given 10 minutes after above; Withdrawal precipitated by NLX **nasal** spray 4mg 15 minutes later; Ondansetron administered every 12 hours as required.	NTX oral 50mg/ day continued for next 2 days before discharge.	"All patients were successfully transferred to NTX" (p.839).	None specified and no follow-up data supplied.	-technique modified for use in 3rd World Countries minim-ising the need for syringes, iv infus-ions, anaesthesia and skilled personnel.	
ıe, nd	Duration	Pre-withdrawal preparation/ medication	Withdrawal medication#	Post-withdrawal preparation/ medication	Status at Completion	After care	Comments	

ndent efined R abuse e on g. o- nd	24 hours hospitalisation: - 3 hours preparation; - 4 hours sedation/ detoxification; - remaining time spent as inpatient.	After admission at 9am: Repeated doses of guanfacine[11] 1-2mg/hour given until B/P <90-60 (systolic) and pulse rate <55 bpm.	Patients to ICU at 12am: NTX oral 50mg; Loperamide oral 4mg and Ondansetron oral 8mg administered; Midazolam iv .5-.7mg/kg given immediately after above, followed by adjusted infusion to maintain sedation.	When patient no longer showing signs of opiate withdrawal (approximately 4 hours after sleep induction) NLX test performed; iv .8mg. Guanfacine administered in decreasing doses on awakening.	"Withdrawal symptoms were observed only under sedation and no physical signs or symptoms were reported upon waking when Opiate Withdrawal Scale scores were at normal baseline levels" (p92). "all patients discharged without withdrawal symptoms"(p.91).	-50m NTX at disch and patie told t take over 3 mo minir -out- patie t'mer 1/wk next week
ndent	2 days hospitalisation: - 1 day preparation; - 1 hour sedation/ detoxification; - remaining time spent as inpatient.	<u>On admission:</u> Clonidine and Oxazepam given "as needed" to suppress withdrawal symptoms. <u>Next morning:</u> Patients given Clonidine .3mg Nizatidine[12] 150mg and Metoclo-pramide[10] 10mg.	Patient to post-anaesthesia care unit 3 hours later: Midazolam iv 2mg; Ondansetron 8mg; Propofol[13] iv 1mg/kg; Propofol bolus dose repeated 5 minutes later to deepen sedation and maintained with infusion of 200 g/kg/min; NLX iv bolus 10mg given (resulting in mydriasis, piloerection, increase in pulse and BP); Propofol infusion halved after 20 minutes and stopped after another 10 minutes; NLX 1mg challenge dose administered.	Patient awake 30 minutes after propofol stopped: NLX iv 2mg challenge given; Dicyclomine oral 40mg given for abdominal cramps; NTX oral 200mg given (about 70 minutes since initial propofol dose) . Patient returned to hospital room and discharged next day.	Upon awaking, on a scale of 0-10 patient gave his withdrawal symp-toms a severity rating of 1. On day of discharge patient reported "feeling weak with lingering opiate withdrawal symptoms" he rated as ranging from 1-4 (p.291).	None spec Patie lost t follov
e, nd	Duration	Pre-withdrawal preparation/ medication	Withdrawal medication#	Post-withdrawal preparation/ medication	Status at Completion	Af ca

ve nts er ents ts f 20 ere 1.5 er n).	6-8 hours detoxification.	Patients admitted to hospital on morning or evening before detoxification. In ICU: Patients given enema and administered fluids iv based on hydration requirements.	In ICU; Intubate; Midazolam and Propofol iv given to induce anaesthesia; NTX and clonidine regimen administered via gastric tube. NLX challenge test given - if test fails to elicit withdrawal symptom treatment terminated, anaesthesia stopped and trachea extubated.	As patients recover from anaesthesia, clonidine, benzodiazepine and loperamide given "as needed" (p.80). Day after detoxification, patients given NTX and if withdrawal mild, discharged.	"In less than about 10% of cases patients are kept in the hospital an additional night after detoxification to treat uncon-trolled severe diarrhoea or vomiting, anxiety, aggressiveness or exhaustion"(p.81). No other details of patients' condition after detoxification provided.	Patie starte 9 mo daily NTX main ance 50mg plus sess of ps socia coun ing.
e, nd e	Duration	Pre-withdrawal preparation/ medication	Withdrawal medication#	Post-withdrawal preparation/ medication	Status at Completion	Af ca

iv us ion ıent roin	24 hours hospitalisation.	Admitted to ICU at 10am; -patients' vitals monitored; -random assignment to one of 2 sedation groups	Following monitoring, patients sedated: <u>Light sedation group (n=150):</u> Very long sedation induction with propofol bolus .3mg/kg combined with midazolam bolus .04mg/kg (lasting about 60 minutes); Maintenance with continuous infusion of propofol 3mg/kg /h combined with midazolam .10mg/kg /h for 6-8 hours; Sedation level monitored with Glasgow Coma Score scale with aim of main-taining a score of 8-9/15 points together with spontaneous breathing and presence of protection reflexes. <u>Deep sedation group (n=150):</u> Propofol bolus .3mg/kg combined with midazolam bolus .04mg/kg given for **2-4 minutes only**; Immediately after, sedation maintained with infusion of propofol 3mg/kg/h and midazolam .10mg/kg/h for 6-8 hours; Aim to achieve sedation level where patient cannot be easily awakened with verbal or nociceptive stimuli and producing unintelligible language. Following sedation, *all patients* given clonidine 3mg/kg every 4 hours and metoclopramide .7mg/kg; NLX .06-.08mg/kg iv infusion given for 5-10 minutes and afterwards NTX 50mg administered via nasal-gastric probe.	When values higher than 10 maintained on the Glasgow Coma Score scale, patients transferred out of ICU and dis-charged after completing 24 hours of hospitalisation. Patients went home under the supervision of a relative.	All patients were successfully detoxified and 93% remained abstinent 1 month later. "The scores of withdrawal severity induced by NLX allow the assertion that both sedation methods managed to suppress withdrawal signs almost completely" (p.344).	NTX main tenar NTX 50mg day g for 1 and c epan 30mg acco to symp mato Patie visite daily phys and p cholc for fir week reduc to twi week visits next week

# = all medications are listed in order of administration;
ROD = Rapid Opioid Detoxification;
RODA = Rapid Opioid Detoxification with Anaesthesia;
NTX = Naltrexone;
NLX = Naloxone;

1 = hyoscine, dicyclomine - antispasmodic agents
2 = Kaopectate, loperamide - antidiarrhoeal agents (loperamide is an opioid and ineffective when antagonists are used.)
3 = hydroxyzine - mild sedative and minor tranquilliser
4 = chlordiazepoxide - antianxiety agent
5 = amitriptyline - antidepressant agent with mild tranquillising properties
6 = thioridazine - antipsychotic agent
7 = methohexitone - barbiturate anaesthetic agent for the induction of anaesthesia
8 = midazolam - short acting benzodiazepine for the induction of sedation
9 = flumazenil - detoxifying agent for the reversal of the central sedative effects of benzodiazepines
10 = ondansetron, metoclopramide - antinauseant, antiemetic
11 = guanfacine - $_2$-adrenergic agonist agent similar to clonidine
12 = nizatidine - competitive, reversible inhibitor of histamine at the histamine H_2-receptors used to inhibits gastric acid secretions
13 = propofol - short acting iv anaesthetic agent
14 = ibuprofen, ketorolac - anti-inflammatory agent

2.3. Antagonist Maintenance

2.3.1. Rationale for antagonist maintenance.

As set out elsewhere (Mattick, Oliphant, Hall & Ward, 1997; Tucker & Ritter, 1997; Ward et al., 1997), the suitability of opioid antagonists such as naloxone and naltrexone as maintenance drugs for treatment of the opioid dependence has been examined over the past two decades in a large number of studies. These will not all be reviewed herein. The rationale for the use of antagonists in maintenance treatment is that a patient maintained on an opioid antagonist will not experience any opioid agonist effects after using heroin or other opioids. It was proposed that this lack of effect from injecting opioids in the presence of pre-treatment with an antagonist might result in a decline in use of opioids.

2.3.2. Uptake rates.

The available research shows that the uptake rates of offers of entry into antagonist maintenance vary widely, but they tend to be poor, especially for users who are not in treatment. Between half and virtually all of the patients offered treatment have failed to enter it (Singleton, Sherman & Bigelow, 1984). Reasons for the failure to do so include detoxification fear, prompt relapse post-detoxification prior to commencing antagonist maintenance, concerns about the possible aversiveness of the drug, lack of interest in cessation of opioid use, and the lack of any opioid effect from the antagonist. The issue of prompt relapse prior to commencing antagonist therapy is of interest in the current context, especially if either shortening the withdrawal period or immediately commencing antagonist therapy assists in retaining patients in antagonist therapy.

In one patient series, 735 were selected as eligible to enter a placebo controlled study of naltrexone treatment, 543 of whom dropped out prior to commencing the study medication. Of the 192 patients commencing treatment with naltrexone or placebo, 13 completed the nine month study period. None of the completers was from the 254 street addicts, three were from the 276 methadone patients, and 10 were from the 205 "post-addict" group. This last group was better motivated and opioid-free (post incarceration or after drug-free treatment) prior to commencing treatment. In the authors' opinion, factors contributing to attrition were the long period of medication, and the slow schedules of detoxification from methadone (21-28 days). This latter comment is certainly consistent with the view that shortening detoxification duration is important prior to commencing naltrexone treatment. (Report of the National Research Council Committee on Clinical Evaluation of Narcotic Antagonists, 1978).

In another large series, 738 were offered naltrexone. Of these, 133 expressed some interest, 47 agreed to commence therapy, but only 22 were actually dosed (Lewis, Mayer, Hersch & Black, 1978). Tucker and Ritter (1997) have reviewed other studies with similar results.

Summary.

On average, the uptake of antagonist maintenance therapy among opioid dependent patients is very poor. The likelihood of entry into and completion of maintenance therapy is poorest among street users. Methadone maintenance patients are more likely to enter and complete antagonist maintenance therapy, but they are deterred by prolonged withdrawal processes prior to medication commencement. The best results are obtained in well-motivated individuals who are opioid-free. The results of the available research on uptake rates are consistent with the view that shortening the duration of detoxification, and lessening the severity of withdrawal symptoms may increase uptake.

2.3.3. Naloxone maintenance.

Naloxone was thought suitable as an opioid replacement therapy as it does not produce dependence and does not have serious side-effects (Kurland, McCabe & Hanlon, 1975). However, it has the disadvantages that oral doses as high as 2-3 gm were necessary to provide 24-hour blockade, making it costly to use. The alternative of parenteral route of administration by injection was not thought appropriate for obvious reasons.

Some early trials of naloxone maintenance were carried out by Kurland and his colleagues (Kurland & Hanlon, 1974; Kurland et al., 1975) with a group of parolees who were required to attend a clinic, to provide daily urines, and to receive weekly psychotherapy sessions after they had been discharged from U.S. correctional institutions. Pilot studies established that an oral regimen of naloxone was feasible and that there were no serious side-effects or toxicity associated with long-term administration. Subsequent controlled trials were carried out to assess the effectiveness or otherwise of naloxone maintenance.

In the first controlled trial, 119 parolees were randomly assigned to one of three groups: a no-treatment control condition in which no medication was prescribed; a group which received naloxone; and a group which received a

placebo in place of naloxone (Kurland & Hanlon, 1974). All participants had to provide regular urine samples and attend a weekly psychotherapy group. Outcome was measured by opioid use and retention in treatment over the nine months of the study. The results failed to show any difference between the placebo and naloxone on retention in treatment or opioid use.

Subsequently these investigators examined the effects on treatment retention and opioid use of administering increasing doses of naloxone when either opioid use was detected or suspected (Kurland et al., 1975). This contingent administration of naloxone was proposed as a way of reducing the high cost of providing large quantities of naloxone on a daily basis. These trials found no advantage to the use of contingent naloxone administration. The authors identified lack of compliance with naloxone ingestion as being a major impediment to success with naloxone. While naloxone adequately blocked the effects of opioids, lack of motivation to ingest the medication was the main reason identified for high rates of relapse to heroin use.

Summary.

Naloxone maintenance trials have provided equivocal results. The poor results combined with the short half-life of the medication, requiring oral doses as high as 2-3 gm to provide 24-hour blockade, make it costly to use. It is not a suitable medication for antagonist maintenance, especially in the light of naltrexone's longer duration of action at lower doses.

2.3.4. Naltrexone maintenance.

Naltrexone is a long-acting (up to 72 hours, depending on the dose) opioid antagonist with many advantages as a maintenance drug. It can be administered orally, it blocks both the analgesic and euphoric effects of opioids, and it has only minor side-effects. Despite these advantages, many of the programmes using naltrexone report substantial drop-out rates early in the programme, in some cases, even before the first dose of naltrexone is given. There have been a number of controlled trials comparing naltrexone with methadone or placebo. These are reviewed next, although there are recently completed existing reviews of this area (Tucker & Ritter, 1997).

2.3.4.1. Controlled studies of efficacy against methadone. In a non-randomised quasi-experimental study, 60 patients self-selected into either methadone or naltrexone maintenance were observed (Grey, Osborn & Reznikoff, 1986; Osborn, Grey & Reznikoff, 1986). Compared with methadone maintenance, naltrexone treatment retained fewer patients over a 12-week study period, although there were no differences between the two regimens in terms of extent of illicit drug use. However, the differences in motivation between the two groups flawed confident conclusions about the relative value of methadone and naltrexone maintenance. However, from what we know more generally about the attractiveness of these intervention, it seems reasonable to expect that methadone maintenance is more likely to attract and retain street users than naltrexone maintenance.

2.3.4.2. Controlled studies of efficacy against placebo. In one study of 192 patients entering naltrexone or placebo maintenance, there was a trend towards naltrexone patients having less illicit drug use and better retention, when compared with the placebo. However, the data remained equivocal because of the extremely high drop-out rate in both groups (13/192 completed treatment, as noted earlier) (Report-of-the-National-Research-Council-Committee-on-Clinical-Evaluation-of-Narcotic-Antagonists, 1978). The results, also showed that a narcotic antagonist was acceptable to a small number of patients, typically those who were "opiate-free", and well-motivated to seek treatment .

Consistent results were reported by Lerner and colleagues (Lerner et al., 1992), who randomly allocated 31 "newly abstinent patients" who had undergone detoxification to receive placebo or naltrexone in a double blind study. They found no advantage for naltrexone over placebo, either at two months or at 12 months, although again there was a trend favouring naltrexone maintenance. At two months 60% of the naltrexone patients and 50% of the placebo patients remained opioid-free, while at twelve months the rates were 53% and 37%, respectively. Interestingly, there was significantly less severe craving reported in the naltrexone condition compared with the placebo condition, but more opioid use (presumably the patients were experimenting or "challenging" the naltrexone). Consistent with the broader literature and with the last-mentioned study, motivation was a good prognostic factor. Those who completed treatment (whether in naltrexone or placebo) were more likely to: have graduated from high school; have steady employment; have completed compulsory military service; have had fewer criminal charges; and be married (Lerner et al., 1992). Clearly, the results suggest that the value of naltrexone treatment itself, was less important than being socially stable.

More recently, Israeli researchers (Shufman et al., 1994) have reported on a double-blind placebo-controlled trial which demonstrated that naltrexone had a superior impact on heroin use compared with the placebo. However, possibly because of the small sample size (N = 32), the differences between naltrexone and placebo were non-significant. Again, a trend emerged in favour of the naltrexone group, with fewer heroin positive urine tests in the naltrexone group than in the placebo group, and more drug-free patients in naltrexone than in placebo treatment.

Spanish research had also failed to detect significant differences in favour of naltrexone above placebo (San, Pomarol, Peri, Olle & Cami, 1991). Again the sample size was small with 50 patients entering either naltrexone or placebo treatment in a double blind randomised design. Interestingly, in the current context, all of the 50 patients successfully entered and completed detoxification with clonidine prior to commencing on naltrexone maintenance. Such a result argues strongly that patients can be detoxified successfully, without necessarily resorting to anaesthetising them during the process, consistent with the research on ROD (see earlier).

Italian researchers (Gerra et al., 1995) found naltrexone maintenance was associated with significantly less craving, greater levels of abstinence, better mood and attendance for treatment than placebo or clonidine detoxified controls. Other research also supports the value of naltrexone maintenance for at least some patients (O'Brien, Greenstein, Mintz & Woody, 1975; Rawson, 1984). Much of the rest of the research is observational, and will not be presented in detail here.

2.3.4.3. The role of ancillary services during naltrexone maintenance. In a quasi-experimental study, 117 patients who had completed a trial of LAAM were given the opportunity to transfer to naltrexone (Judson & Goldstein, 1984). Forty patients entered treatment and 77 did not. At the follow-up, more patients who had received naltrexone were opioid-free compared with those who did not receive naltrexone. The authors make the point that the two groups were not comparable in motivation at the outset.

Although retention in naltrexone maintenance has usually proved difficult for even short periods of time with illicit drug using populations, it has been found to be quite successful with highly motivated individuals who wish to cease opioid use. Thomas and her colleagues first described success with naltrexone maintenance in a small sample of opioid dependent medical professionals (Thomas et al., 1976). In a subsequent study, 114 opioid-dependent businessmen and 15 opioid-dependent physicians were treated with naltrexone as part of a structured aftercare program following clonidine detoxification (Washton, Pottash & Gold, 1984). More than 80% of the patients completed at least six months of treatment and remained drug-free 12-18 months later.

It is clear that naltrexone has a potential role as a maintenance medication with these selected and highly motivated patients, but the target population is small. It may prove with time that it also has a role in gradually transferring patients from full opioid agonist therapy to partial agonist treatment (such as buprenorphine). Thereafter, transfer to a full antagonist (naltrexone) as a method of withdrawing those who wish to cease all maintenance therapy, may be easier.

2.3.4.4. The role of ancillary services during naltrexone maintenance. A study of the importance of ancillary services in naltrexone treatment compared the impact of regular supportive psychotherapy with standard case management (Resnick, Washton & Stone-Washton, 1981). The researchers studied 66 patients who were randomly assigned to treatment. They found that the higher level of intervention was associated with a greater rate of success in detoxification and with a greater likelihood of opioid-free status at three months (73% versus 40%) and at six months (54% versus 40%), and of those in the high intervention group who failed to become opioid-free, 70% entered methadone maintenance, whereas only 33% of the failures in the low intervention group entered such treatment. Clearly, psychological support facilitated successful detoxification, success in maintenance therapy, and appropriate treatment seeking if abstinence was unobtainable.

Summary.

Naltrexone maintenance trials have provided evidence of benefit for highly motivated patients who have external pressures to become and stay opioid free. Heroin users tend to fare poorly, as do most methadone patients. Motivated patients with good social supports and strong incentives to remain drug free are most likely to benefit. Ancillary services are associated with better retention in naltrexone maintenance.

2.4. Catecholamines, withdrawal and -2 adrenergic agonists

2.4.1. The endogenous opiate (reward) system.

Opiate receptors (μ-1, μ-2, , ,) are distributed widely throughout the grey matter of the brain and spinal cord. The highest concentration exists in the limbic and limbic associated areas. Each of these receptors are involved in mediating the effects of opioid agonists, both endogenous and exogenous. It is however the μ-1 sub-type of receptor that is responsible for producing the euphoric effects of exogenous agonists, such as morphine and heroin.

Euphoria is mediated by μ1 receptors in the reinforcement pathway of the central nervous system (CNS). This involves the dopamine reward system (opiate receptors in or near the ventral tegmental area of the midbrain) and subsequent activation of the mesolimbic dopamine system expressed through the nucleus accumbens. These systems are presented in Figure 1.

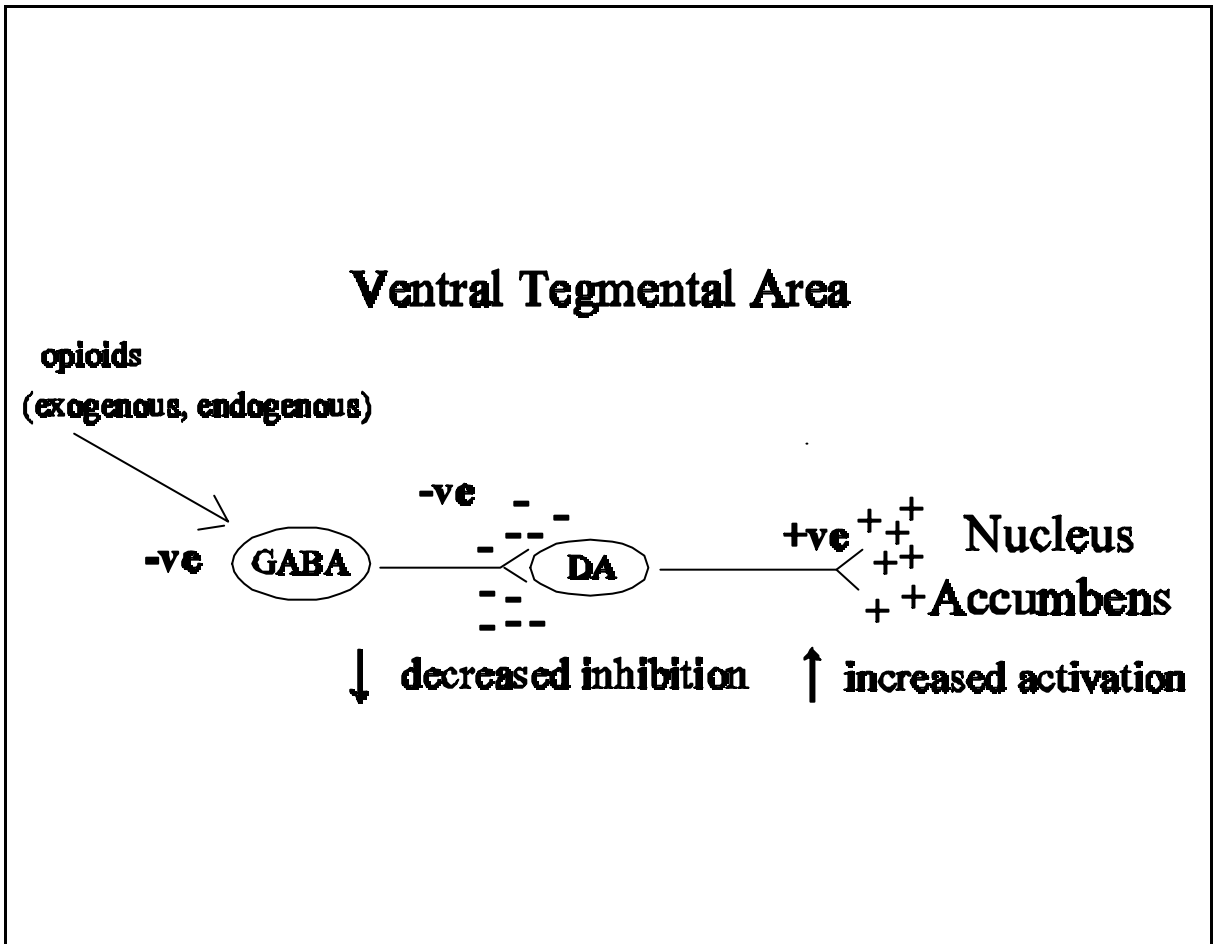

Figure 1. Reward system: mesolimbic dopamine system activation expressed through the nucleus accumbens. Opioids cause a decrease in the activity of GABA releasing neurons in the ventral tegmental area which leads to a decreased inhibition of dopamine releasing neurons. This decreased inhibition means that there is an increase in the release of dopamine. This increased dopamine leads to increased activation of the nucleus accumbens, and thus increased activation of the natural reward system.

Normally within the CNS, GABAergic inhibition of dopamine releasing neurons leads to a decreased activity in the nucleus accumbens and other brain regions. When opioid agonists, either endogenous or exogenous, are present, hyperpolarisation of GABA releasing neurons occurs through an opioid mediated increase in potassium conductance. This then leads to a decreased inhibition of dopamine releasing neurons, which in turn leads to an increased activation of the nucleus accumbens (and other brain regions). This process increases activation of the reward system, and hence, euphoria (Figure 1). This same dopamine reward system is also involved in the rewarding effects of cocaine, benzodiazepines, and alcohol. This activation of the natural reward system produces the reinforcing effects that lead to prolonged abuse of various drugs including opioids. It is this reinforcing behaviour that is a major barrier to sustained abstinence (see later). Repeated administration of exogenous opioids leads to tolerance. When administration is stopped, withdrawal occurs.

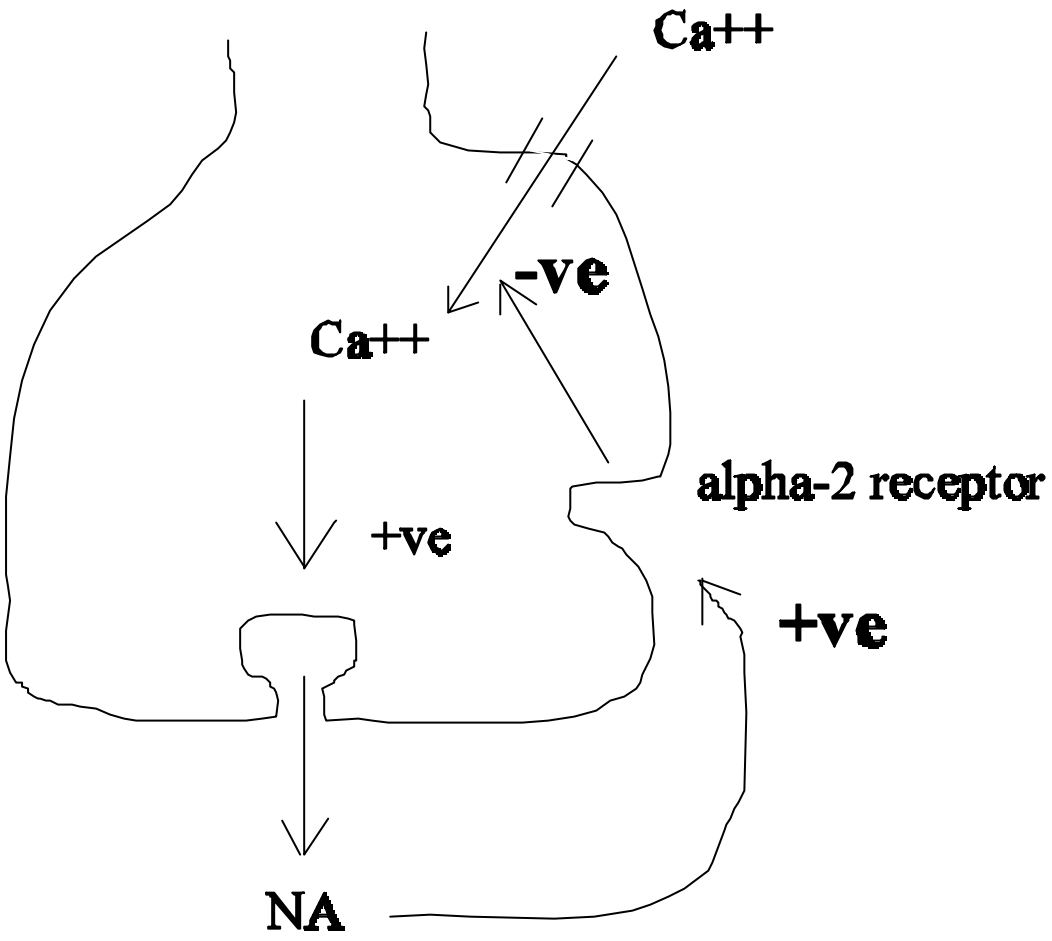

Figure 2 Auto-inhibition of noradrenaline (NA) releasing neurons in the locus coerulus (LC). Activation of the -2 receptor causes a decrease in calcium (Ca++) entry into the cell which in turn causes a decrease of noradrenaline release. -2 adrenergic agonists which also activate the -2 receptor also inhibit Noradrenaline release from these cells.

Opioid receptors are also located in the locus coerulus (LC) of the pons. It is the abnormal activation of these receptors which is likely implicated in the withdrawal syndrome associated with exogenous opioids. The LC is the major area of central noradrenaline innervation. Noradrenaline system activation includes arousal, and regulation of blood pressure, among others. Activation of opioid receptors in the LC inhibits firing in this region and, therefore, decreases the release of noradrenaline. The rebound increase in noradrenaline release after immediate cessation of chronic opioid intoxication is responsible for many of the adverse effects seen in opiate withdrawal (e.g., lacrimation, hypertension, rhinorrhoea, etc).

Also found in the LC are -2 adrenergic receptors. Activation of these receptors has an inhibitory effect on the release of noradrenaline from the LC. This effect is mediated through an auto-inhibitory/auto-regulatory action of noradrenaline neurons (see Figure 2). The LC is inhibited by both opioid and -2 adrenergic receptor stimulation and is implicated in opiate withdrawal (Gold, Redmond & Kleber, 1978). In primates, LC stimulation, dangerous situations, and drugs such as piperoxane (which activate the LC), produce behaviours and physiological changes which are similar to those seen in opiate withdrawal (Gold, Redmond & Kleber, 1979).

2.4.2. Withdrawal and -2 adrenergic agonists.

Because -2 adrenergic receptors are separate entities to opiate receptors but produce similar actions in the LC, -2 adrenergic agonists are successful in ameliorating symptoms of the withdrawal syndrome associated with the discontinuation of chronic exogenous opioid agonists (e.g., heroin, methadone). One such -2 adrenergic agonist is clonidine. Clonidine is widely used as an anti-hypertensive. More recently, however, clonidine has been used to suppress the adverse effects associated with opiate withdrawal. Early animal studies demonstrated that clonidine inhibited many of the withdrawal symptoms precipitated in morphine dependent rats (Meyer & Sparber, 1976; Tseng, Loh & Wei, 1975). The -2 adrenergic receptor agonists are successful in this regard due to their lack of cross-tolerance at opioid receptors and absence of dependence causing capabilities (Gilman, Goodman, Rall & Murad, 1985). Clonidine has been shown to inhibit withdrawal symptoms in as little as 120 minutes after administration (Gold, Pottash, Sweeney & Kleber, 1980a; Gold, Pottash, Sweeney & Kleber, 1980b; Gold et al., 1978; Gold et al., 1979). Clonidine significantly reduces both subjective and objective withdrawal symptoms when compared to controls and placebo controls (Gold et al., 1980a; Gold et al., 1980b; Gold et al., 1978; Gold et al., 1979) (see Table 2). The withdrawal symptoms most reduced by clonidine appear to be, chills, rhinorrhoea, lacrimation, stomach cramps, diaphoresis, and joint and muscle aches (Washton & Resnick, 1983). Clonidine, when used in conjunction with naltrexone and diazepam, reduces the time taken for withdrawal from 3.30 days to 2.32 days when given in larger doses on the first day of treatment (Brewer et al., 1988). Washton and colleagues (Washton, Resnick & Geyer, 1983; Washton, Resnick & Rawson, 1980) showed clonidine, when used in conjunction with naltrexone, to be more effective (in terms of patients remaining drug free for 10 days after treatment), when patients were withdrawn abruptly rather than slowly with reduced doses. Six out of seventy patients, however, experienced unacceptable dizziness or sedation while taking only 0.3mg/day clonidine (Washton et al., 1983; Washton et al., 1980). In studies by Gold and his colleagues, clonidine doses also had to be reduced due to hypotension and over-sedation.

Clonidine, therefore, does appear to have some important limitations for use in opioid withdrawal. Because it produces a marked reduction in both systolic and diastolic blood pressure causing severe dizziness and the possibility of thrombosis, and as it causes sedation, its out-patient use is limited. Lofexidine, also an -2 agonist, suppresses opiate withdrawal effects in morphine-dependent rats (Shearman, Lal & Ursillo, 1980), and is at least as effective for suppressing opioid withdrawal symptoms as clonidine (Kahn, Mumford, Ash-Rogers & Beckford, 1997; Washton & Resnick, 1981; Washton, Resnick, Perzel & Garwood, 1981). It does, however, have little (if any) hypotensive effects (Cox & Alcorn, 1995; Gold, Pottash, Sweeney, Extein & Annitto, 1981; Washton et al., 1983; Wilkins, Winternitz, Oparil, Smith & Dustan, 1981), and produces fewer overall adverse events and less sedation than clonidine (Kahn et al., 1997). It is these attributes which make lofexidine attractive for use on an out-patient basis which has obvious benefits for treatment of opiate dependence.

Lofexidine is, unfortunately, expensive compared to clonidine (Preston & Bigelow, 1985). Clinical trials comparing the efficacy of lofexidine are limited, and those that do exist possess questionable methodology (Cox & Alcorn, 1995). Further, there is no significant difference between the success of lofexidine and methadone when used as an opiate withdrawal treatment (Bearn, Gossop & Strang, 1996). Patients who fail to detoxify successfully with the use of lofexidine, appear to do so because they cannot overcome the craving for opioids (see earlier; 4.4.1) (Cox & Alcorn, 1995). Therefore, it seems that patients would need to be selected (e.g., highly motivated to withdraw from opioids) for detoxification programmes involving -2 agonists.

Summary.

Both pharmacologically and clinically, -2 adrenergic agonists have shown their usefulness in suppressing the adverse effects experienced by patients undergoing withdrawal from chronic self-administration of opioids. Clonidine is limited by its hypotensive and sedative effects, while lofexidine is expensive. Further, certain side-effects exist, and all of the symptoms associated with opioid withdrawal are not inhibited by these drugs. The use of these drugs may, however, provide encouragement and incentive for some patients contemplating detoxification from opioids.

Table 2 : Evidence on the effectiveness of -2 adrenergic agonists in managing opioid withdrawal symptoms

Study Year	Type	Duration	Pre-withdrawal preparation/ medication	Withdrawal medication #	Post-withdrawal preparation/ medication	Status at completion	After care	Comments
Gold *et al.*, 1979	detoxification double blind opioid dependent (2-10 yrs): methadone (15-50mg) (n=6) heroin (n=6)	3 hr baseline 2x consecutive 2 hr trials 1 week out-patient + follow-up at 2 weeks	2 day phased withdrawal from methadone 36 hrs opioid free - heroin	5µg/kg clonidine or placebo orally in matching vehicles 2x doses 120 minutes apart	5µg/kg clonidine orally b.i.d. 1 week	significant reduction in opioid withdrawal signs and symptoms in both methadone and heroin groups during 120 minute medication phase 10 patients clonidine-free and opioid-free at 2 week follow-up	1 week out-patient clonidine admin. follow-up at 2 weeks	all 12 patients reported they were experiencing withdrawal before clonidine admin. but not 120 minutes after clonidine admin. placebo had no significant effect no reports of euphoria with clonidine consistent complaint in both groups was occasional sluggishness and sleep continuity disturbances

Study Year	Type	Duration	Pre-withdrawal preparation/ medication	Withdrawal medication #	Post-withdrawal preparation/ medication	Status at completion	After care	Comments
Gold *et al.,* 1981	detoxification opioid dependent male patients (n=15) opioid dependence for at least 1 yr methadone for at least 6 months patients expressed interest in detoxification all had previous unsuccessful attempts at detoxification	in-patient 120 minutes (initial) 10 days (total)	abrupt withdrawal from opioids at least 36 hrs opioid free	lofexidine 3µg/kg initial dose 20µg/kg/day in divided doses for at least 10 days	none/not specified	100% patients successfully detoxified for the duration of the study (10 days)	none no follow-up data supplied	there was a consistent day-by-day reduction in withdrawal ratings (as assessed by clinical staff) over the first 5 days insomnia was a consistent complaint

Study Year	Type	Duration	Pre-withdrawal preparation/ medication	Withdrawal medication #	Post-withdrawal preparation/ medication	Status at completion	After care	Comments
Washton and Resnick 1982	detoxification male methadone dependent (10-25mg) out-patient volunteers with no evidence of medical or psychiatric illness (n=15)	10 days	usual methadone dose (10-25mg)	day 1: usual methadone dose + 0.1mg self administered lofexidine 2-3x/day day 2: methadone placebo + 0.1mg lofexidine 4x/day - up to 0.4mg 4x/day (=1.2mg/day)	patients given option of starting naltrexone on day 11 if detoxification successful	success was rated as detoxification and induction onto naltrexone 10/15 patients successful	none no follow-up data supplied	insomnia, lethargy, and muscle/bone pain were common withdrawal complaints failure was reportedly due to craving of opioids and not withdrawal effects reported side effects of lofexidine were dry mouth and mild drowsiness no hypotension no side effects when lofexidine reduced gradually

Study Year	Type	Duration	Pre-withdrawal preparation/ medication	Withdrawal medication #	Post-withdrawal preparation/ medication	Status at completion	After care	Comments
Washton and Resnick 1983	detoxification comparing clonidine and lofexidine clonidine (i) opioid dependent out-patients withdrawal from heroin &/or methadone (n=12) (ii) methadone dependence 10-50mg/day (n=20) lofexidine methadone-dependent male out-patients with no evidence of medical or psychiatric illness (n=15)	clonidine (i) 120 minutes (ii) 2 weeks lofexidine 10 days	clonidine patients experiencing withdrawal clonidine at least 2 weeks before detoxification lofexidine usual methadone dose (10-25mg)	clonidine (i) single oral dose - 0.2mg or 0.3mg (ii) 0.5-0.9 mg/day clonidine for 2 weeks concomitant clonidine and methadone 's at 5-10mg/day until 0mg lofexidine day 1: usual methadone dose + self administered 0.1mg 2-3x/day lofexidine day 2: methadone placebo + up to 0.4mg lofexidine 4x/day	clonidine (i) significant reduction in withdrawal severity (ii) 50% (10/20) reached 0mg methadone and remained opioid free for 10 days lofexidine 75% (10/15) successfully completed treatment	none/not specified	none no follow-up data supplied	patients rated lofexidine as moderately to extremely effective reports of insomnia, lethargy, and muscle/bone pain
Study Year	**Type**	**Duration**	**Pre-withdrawal preparation/ medication**	**Withdrawal medication #**	**Post-withdrawal preparation/ medication**	**Status at completion**	**After care**	**Comments**

Brewer and Bailey 1988	detoxification <u>group A</u> (n=37) daily heroin 0.59g abuse time 5.3 yrs (0.7-10) <u>group B</u> (n=23) daily heroin 0.78g abuse time 4.5 yrs (0.7-12)	1-5 days	0.1mg test dose of clonidine	(mg) <u>group A</u> day 1: clonidine 0.64 diazepam 64.7 naltrexone 3.3 day 2: clonidine 0.84 diazepam 67.6 naltrexone 14.7 <u>group B</u> day 1: clonidine 1.22 diazepam 75.4 naltrexone 20.9 day 2: clonidine 0.7 diazepam 38.7 naltrexone 46.7	none/not specified	time to detoxification (days) <u>group</u> A B 3.30 2.32 (2-5) (1-3)	none no follow-up data	only one patient failed to complete (from group A) successful detoxification = 50mg naltrexone in one 24 hr period and patient felt well enough to go home
Study Year	**Type**	**Duration**	**Pre-withdrawal preparation/ medication**	**Withdrawal medication #**	**Post-withdrawal preparation/ medication**	**Status at completion**	**After care**	**Comments**

Bearn *et al.,* 1996	detoxification DSM-IV criteria for opioid dependence (n=86) random assignment to treatment groups: methadone (n=44) lofexidine (n=42)	10 days	patients stabilised on methadone for 3 days prior to treatment (mg methadone) methadone-57.9 lofexidine-64.8	methadone + placebo or placebo + lofexidine x2tabs/day for 10 days methadone reduced linearly to 0mg lofexidine : 0.6-1.4mg (day 1-3) 2mg (day 4-7) 0.8mg (day 8-10)	gradual tapering of lofexidine over 4 days	completed treatment: 36/42 lofexidine 43/44 methadone	ten item short opiate withdrawal scale (SOWS) measured up to day 24	lofexidine group had significantly more severe withdrawal symptoms (SOWS) on day 3-7 and on day 10 there was a similar gradual decline of withdrawal symptoms (SOWS) in both groups over next 14 days
Study Year	**Type**	**Duration**	**Pre-withdrawal preparation/ medication**	**Withdrawal medication #**	**Post-withdrawal preparation/ medication**	**Status at completion**	**After care**	**Comments**

,	detoxification opioid dependent patients actively seeking detoxification (n=28) double-blind study of clonidine (n=14) and lofexidine (n=14)	18 days	patients stabilised on methadone for 3 days prior to treatment	day 0: 0.4mg/day lofexidine or 0.2mg/day clonidine up to a maximum 1.8mg/day lofexidine 0.9mg/day clonidine day 4: methadone placebo + clonidine or lofexidine day 14: methadone placebo stopped day 14-18: clonidine or lofexidine tailed off	none/not specified	total number of daily adverse effects: clonidine- 226 lofexidine-114 patients with hypotension: clonidine-93% lofexidine-53%	none no follow-up data supplied

3. Research Directions

3.1. Possible studies

The previous sections have foreshadowed general research directions for the future, through the critical review of the extant knowledge. The following provides a more detailed suggestion for research directions.

3.1.1. Pre-post (observational) trials.

Single group pre-post studies are unlikely to be of value in developing knowledge of the efficacy of different withdrawal protocols, although they may be helpful in assessing safety and feasibility. If pilot clinical work is carried out to refine the delivery of clinical procedures, this pilot work should be unpublished, except to document safety and adverse events. Problems associated with patient selection bias, motivational differences and other limitations on inferences make such research unhelpful. If ROD or RODA is successful in withdrawing patients, it may be due to the selection of highly motivated patients who want to withdraw from opioid use. Positive results in pre-post studies may lead politicians, the general community, and the profession to mistakenly believe that anaesthesia/sedation is required. Without the appropriate comparison group to determine the relative outcomes of RODA anaesthesia, it becomes impossible to determine which components are necessary. As noted earlier in this Report, is seems that the vast majority of patients who enter ROD can successfully withdraw. It is also our understanding that the Therapeutic Goods Administration of the Commonwealth Department of Health and Family Services will require randomised clinical trials with evidence of efficacy, cost-effectiveness and safety as part of an application for product registration.

3.1.2. Randomised clinical trials.

We argue that any research on the efficacy of ROD or RODA should be through randomised clinical trials. As set out in a recent NIDA report (Herman & Czechowicz, 1996), there are too few randomised clinical studies to allow a rigorous scientific opinion on the value, safety and costs of these procedures. Randomised clinical trials are feasible, although the media publicity surrounding RODA may create some difficulties in retaining patients in the non-preferred treatment.

We suggest that the appropriate design to evaluate RODA is a comparison of the outcome of patients who go through the detoxification with clonidine and other medications to reduce symptoms in an awake state. The reason for this control is to test the claim that the critical component of RODA is the sedation or anaesthesia which allows for rapid infusion or oral dosing with naltrexone. These two groups should be based on random allocation. All patients should then be maintained on naltrexone for a substantial period of time, possibly up to one year. The evaluation would address the efficacy and safety of the two procedures. Comparison with standard treatment would be helpful to determine the efficacy of accelerated detoxification relative to existing procedures.

There are further interesting questions raised by the current review. It is clear that one of the more impressive trials in the literature by Gerra (Gerra et al., 1995) has obtained results which are remarkable. If replicated, detoxification of awake patients and transfer to naltrexone maintenance would be feasible and successful. Of course, others have argued and shown that it is feasible to detoxify the majority of patients in an awake state on an inpatient basis. There is considerable ongoing demand for this form of treatment in Australia at present. It is therefore suggested that a study of the Gerra procedures be considered as a way of achieving accelerated withdrawal from opioids.

There are already funded and underway, or planned, studies into withdrawal that preceded the RODA controversy. These studies will be conducted collaboratively in New South Wales, Victoria, South Australia, the Australian Capital Territory and Queensland (Bammer et al., submitted). Several research groups in Australia and State Government Departments of Health have been negotiating to carry out a study of withdrawal using both buprenorphine and naltrexone. Some research on naltrexone maintenance has recently been completed in Newcastle.

One planned study aims to transfer stable methadone patients from methadone to buprenorphine, to stabilise them on buprenorphine for a period of time and then to transfer them to naltrexone maintenance for up to six months before finally ceasing pharmacotherapy. Another aims to use decreasing doses of buprenorphine to manage withdrawal from heroin. This research should be controlled and the appropriate control group would be patients who are transferred from methadone to buprenorphine and then to placebo and patients who are simply randomised to withdraw from methadone without any further pharmacological assistance. There is no doubt that the details of these protocols needs to be clarified, and that the psychosocial supports need to be developed. A further study aims to withdraw heroin users with buprenorphine. All protocols should include cost-utility or cost-effectiveness analyses.

Summary.
In terms of research directions for Australia, pre-post (observational) research will not be of value in developing an understanding of the efficacy of different withdrawal approaches. Problems associated with patient selection bias, motivational differences and other obvious limitations on inferences make such research unhelpful, and even detrimental to developing knowledge in this area. We argue that any research on ROD or RODA should be in the form of a randomised trial. As set out in a recent NIDA report (Herman & Czechowicz, 1996), there are too few well-controlled studies to allow a rigorous scientific opinion on the value, safety and costs of these procedures. We suggest that the appropriate design to evaluate RODA is a comparison of the outcome of patients who go through the detoxification with clonidine and other medications to reduce symptoms in an awake state. Additionally, research on the value of naltrexone and buprenorphine has been commenced and should be pursued examining the value of these procedures for stabilised methadone patients. The value of buprenorphine in the management of withdrawal of heroin users will be pursued.

3.2. Standard of the Research

The research should be conducted in accordance with appropriate national and international standards. The Guidelines for Good Clinical Research Practice (Therapeutic-Goods-Administration, 1991) should be adhered to in the design and conduct of any such trial. The guidelines for GCRP "provide a basis for ensuring that clinical studies are not only designed to scientific and ethical standards but are also meticulously conducted, recorded, terminated and reported, according to pre-established criteria detailed in the study protocol" (p.1).

The use of such an standard approach will not only maximise the value of the research which is conducted, but will also minimise the extent to which it may be criticised as being of a poor standard and therefore invalid. Given the strength of opinion expressed concerning RODA, it is incumbent upon all participants to conduct trials of broadly acceptable standards, especially to comply with the standards of the regulatory body controlling the registration of medications in Australia.

The GCRP standards are quite stringent in that they require all aspects of a clinical research trial to be controlled and monitored, so that the research can be audited by an independent body should that be desired or required. The standard is derived from methods adopted in the development of pharmacotherapies, but they are presented to be generally applicable. As the requirements under GCRP are quite high, any protocol should be designed to meet those standards. It is important that researchers be aware of the standards prior to the design of the study and completion of the protocol, as it is impossible to raise a trial to GCRP standards retrospectively.

Summary.
Research undertaken in Australia in this area should be conducted in accordance with appropriate national and international standards. The Guidelines for Good Clinical Research Practice should be adhered to in the design and conduct of any trials.

3.3. Research instruments and measures

The research tools which are used should be common to all of the trials conducted. The tools chosen obviously depend on the nature of the questions asked.

3.3.1. The Opiate Treatment Index.

It is recommended that the Opiate Treatment Index is used for the evaluations (Darke, Hall, Heather, Ward & Wodak, 1991a; Darke, Hall, Wodak, Heather & Ward, 1992; Darke, Ward, Hall, Heather & Wodak, 1991b; Darke, Ward, Zador & Swift, 1991c). In the Opiate Treatment Index, recent drug use, HIV risk behaviour, criminal activity, psychological adjustment, physical health and social adjustment are all assessed. For the first five of these areas, the assessment covers the previous month, that being the window which is used for determining the patient's well-being. For the last sub-scale, addressing social adjustment, a six-month window is used and this may not be appropriate for the trials which may be conducted. It is therefore suggested that the first five of these sub-scales be uniformly and broadly accepted and adopted as the core set of information which should be gathered in these trials.

3.3.2. Other measures.

Of course, other measures will be required including measures of retention in treatment (treatment completion) and urinalysis to confirm self-report of drug use. Additionally, investigators may wish to develop or include other measures which are not part of this core instrument group. Measures of opioid craving, withdrawal distress, and adverse events would be useful additions, especially if a standard reporting format was adopted.

Summary.
Future research in Australia in this area should use common measures. The Opiate Treatment Index is suggested as a core instrument, along with measures of retention and urinalysis. Additionally, investigators may wish to develop or include other measures.

3.4. Pooling Research Results

Ideally, the research studies should provide data that can be pooled for analysis of the outcomes of patients from the different procedures, even if those trials are distinct randomised clinical trials. This would allow for some direct comparisons, albeit of a quasi-experimental nature where patients have come from different research studies. We suggest that researchers agree to provide information to a core group or to receive information from others so that pooled analyses can be conducted.

Nonetheless, the research data ownership would always reside with the investigators of the particular project. Any use of the pooled research results for purposes other than the registration of these medications would need to be with the approval of the investigators. It is therefore suggested that agreements be entered into in a cooperative and open fashion. To this end, State and Federal governments that might fund such activities could make explicit recognition of the collaborative nature of these activities. While respecting each Government's right to have its own initiatives in these areas, it should be possible for a core set of data to be pooled in the fashion outlined above.

Summary.
The research studies should provide data that can be pooled for analysis of the outcomes of patients from the different procedures, even if those trials are distinct randomised clinical trials. This approach will allow for some direct comparisons of different research study results, albeit of

a quasi-experimental nature. We suggest that researchers agree to pool data, and that funding bodies foster collaborative arrangements. Funding for pooling data and for the analysis of those data should be made available from governments.

4. Conclusions

4.1. For whom is RODA suitable?

It seems that RODA may be suitable for that small group of patients who find detoxification using alternative, more conventional approaches impossible, although the notion that it yields better outcomes than other approaches to treatment for these patients is unproven and untested. RODA should not be considered a treatment for opioid dependence, as detoxification is not a treatment for dependence (Brewer, 1997a; Gossop & Strang, 1997; Herman & Czechowicz, 1996; Mattick & Hall, 1996), despite claims by some advocates of RODA who have reportedly attempted to patent the process (Brewer, 1997a). RODA certainly should not be considered to be an appropriate first line of intervention for severe opioid dependence, especially in the light of its risks, costs and relative efficacy, as these are currently understood. This view is underscored by the very poor retention of dependent heroin users and unselected methadone patients in naltrexone maintenance, which is arguably the most important component of the intervention in maintaining abstinence.

Some have also speculated that accelerated detoxification may be suitable for those regular dependent heroin users who do not show social disintegration, who remain functioning in their community, employed and in stable relationships, and who have no interest in commencing methadone or other opioid replacement therapy. Patients with iatrogenic dependence, or those who use opioids illicitly also may be suitable for such treatment. But it is not appropriate to assume that all of these individuals will require anaesthesia to be withdrawn successfully. Nor should they be left to their own devices in maintaining abstinence. They should be supported with naltrexone maintenance, supportive aftercare or both. The current debate has had too great a focus on withdrawal and too little on maintenance with naltrexone.

Finally, at present, there is no evidence to support the assertion that the RODA procedure enhances the rate of abstinence above that obtained by other methods. The position taken by Brewer (1997), a supporter of the RODA procedure, seems reasonable in this regard. According to Brewer, RODA may assist a minority of patients to successfully complete detoxification, and it may enhance the likelihood that they will enter naltrexone maintenance, but "I do not think it can be claimed that patients having precipitated withdrawal [with opioid antagonists] show, in general, better long-term results than comparable patients who complete conventional inpatient withdrawal programmes" (p.299) (Brewer, 1997b). RODA cannot be claimed to be the panacea that some have presented it to be, especially in the absence of randomised controlled trials of treatment.

Summary.
What is the place of RODA in the management of opioid dependence? It does not seem likely that it will be an appropriate first line of treatment for heroin users. This group would probably be better offered maintenance therapy to allow them to stabilise their lifestyles and stop opioid use. To do otherwise would expose street heroin users to ongoing risks associated with injecting given the high likelihood of relapse. Similar comments pertain to many methadone patients, who are not likely to benefit from attempts at withdrawal. Yet, it is most likely to be the stable, drug-free, employed, and motivated methadone patient who may benefit most from attempts at detoxification. Even so, this group will not all require anaesthesia, as many will detoxify using more conventional methods. Thus, we are left with a small group who are so sensitive to withdrawal symptoms that they are unwilling to attempt withdrawal.

4.2. What other withdrawal strategies should be considered?

The role of antagonists in withdrawal is important, and as indicated above can hasten the rate of withdrawal. However, RODA has taken attention from a balanced consideration of alternatives. The use of opioid antagonists is not restricted to post-ROD or post-RODA treatment. Naltrexone can be introduced during -2 adrenergic agonist therapy with clonidine or lofexidine. Lofexidine has significant advantages over clonidine for withdrawal management, and it is suggested that it be explored as a suitable pharmacotherapy for this indication in Australia. This will require discussion between the drug company which manufactures it and with the Australian Commonwealth Department of Health and Family Services' Therapeutic Goods Administration.

Alternatively, naltrexone may be used in suitably selected methadone patients who have been transferred to, and stabilised on, buprenorphine. As buprenorphine has a very mild acute withdrawal period and as naltrexone will not displace it, the transfer to naltrexone in such patients should produce quite mild withdrawal symptoms. Research addressing this form of withdrawal has been funded in New South Wales and recently in Queensland. It is also likely to involve Victorian and South Australian research groups.

Psychological adjuncts in the form of simple accurate information about the withdrawal process and about antagonist maintenance therapy must be developed and incorporated in the management of withdrawal processes. Additionally, consideration should be given to the value of ongoing supportive care during the withdrawal period. In considering supportive ancillary services during withdrawal, attention should focus on the financial cost of these services and their acceptability to patients, along with their impact on outcomes. Australia is not in a position where resources can be allocated to expensive interventions if there is not clear evidence of safety, effectiveness and cost-effectiveness.

Summary.
Other withdrawal strategies should be considered including the value of lofexidine as a suitable pharmacotherapy for management of opioid withdrawal. Naltrexone may be used in suitably selected methadone patients who have been transferred to, and stabilised on, buprenorphine. Psychological adjuncts in the form of simple accurate information about the withdrawal process and about antagonist maintenance should be developed.

4.3. What are the research priorities?

Developing research priorities in this area is likely to be a controversial task, given the strength of opinion and the absence of data on RODA. Despite the diverging views, there are some areas that require attention for varying reasons. It would be most unhelpful to develop a wish-list of every question that we might want answered in this area. There is a political imperative for research, given the increasing community pressure on governments to address the issue of heroin dependence, and because of the likelihood that methadone access is being compromised by limited funding.

Before outlining some candidate questions, two general priorities will be suggested as requirements. Consistent with the views of the Health Ministers at the recent Cairns meeting, the research efforts which proceed should be coordinated by adopting a similar clinical and research methodology to maximise the comparability of results from different research centres. Multi-site trials, while bringing their own challenges, will maximise the sample size obtained when examining any procedures. To these ends, research groups and centres should enter into cooperative agreements so that the research data from individual patients will be available for pooling. Such agreement need not restrict the rights of the individual research groups to publish their data, but it would make the best use of the results in advising governments and health care providers about the value of various treatment options.

Research could be valuable in a number of areas (not necessarily in order of priority).

1) It seems politically necessary that the value of RODA be assessed in a randomised clinical trial against ROD for methadone patients, and possible heroin users. A control group where patients remain on methadone to either withdraw or remain on a wait-list would be helpful to determine any adverse effects of withdrawing methadone patients (see earlier). In determining the extent of the resources that should be allocated to researching RODA, its probable uptake in the public hospitals in Australia should be discussed. It seems very unlikely that public hospital ICU beds will be routinely available for opioid detoxification.

2) The value of transferring stable methadone patients from methadone to buprenorphine, and then to naltrexone will be studied, given funding already in place. Candidate control groups are: (a) patients transferred to buprenorphine and then withdrawn or placebo (rather than naltrexone); and (b) patients left on methadone.

3) Additionally, less elaborate methods of accelerated withdrawal deserve to be researched. These include researching the value of ROD in outpatient detoxification for heroin dependent patients compared with conventional outpatient detoxification and/or with buprenorphine, followed by naltrexone maintenance. Naltrexone maintenance, needs to be researched, although there are probably sufficient data already available for its registration in Australia for management of opioid dependence.

Summary.
Research priorities include that RODA be assessed in a randomised trial against ROD. The value of transferring stable methadone patients to buprenorphine and then naltrexone will be assessed. ROD in outpatient detoxification for heroin dependent patients compared with conventional outpatient detoxification and/or with buprenorphine, followed by naltrexone maintenance should be assessed.

5. Outcomes of National Consultation Workshop

5.1. Workshop aims

A workshop, in which over 20 clinicians, health care policy makers and researchers participated (see Appendix for a list of participants), was held at the National Drug and Alcohol Research Centre, in Sydney, on 23rd November, 1997. Others, some of whom were unable to attend on the day, were given the opportunity to read and comment on the Draft Report, and any forwarded comments were integrated into the report as deemed appropriate.

The workshop began with participants considering the Draft Review, which had been circulated prior to the meeting for perusal and comment. The Draft Report was developed further in the light of participants' input. Input from those with clinical experience in, or direct observation and knowledge of, therapy with opioid antagonists was deemed to be most important. Some additional studies provided by participants were integrated into the Draft Report. Then the forms of research to be pursued were discussed, and agreements and disagreements documented.

5.2. Areas of agreement

There was agreement and consensus regarding many areas of importance.

5.2.1. Induction onto naltrexone maintenance

There was clear, unanimous agreement from the workshop participants that the objective from any research conducted in this area should be to trial the efficacy, safety and cost-effectiveness of *naltrexone maintenance and the ability of different methods of inducting patients onto naltrexone maintenance to achieve that end successfully*. It was emphasised that the procedure of rapid naltrexone induction should not be separated from naltrexone maintenance and any measure of effectiveness must primarily take account of the long-tem outcomes of patients in entering and completing naltrexone maintenance. Obviously, adverse events and serious adverse events associated with any of the methods of induction onto naltrexone maintenance and with the maintenance treatment itself require careful documentation and reporting to the sponsor, relevant ethics committee and the regulatory agency, as required under GCRP (Therapeutic-Goods-Administration, 1991).

There are several approaches to induction onto naltrexone maintenance, including:

i accelerated detoxification in conscious patients without sedation/anaesthesia (ROD) delivered as an in-patient or day patient treatment and transfer to naltrexone maintenance;

ii accelerated detoxification with anaesthesia (referred to as rapid opioid detoxification under anaesthesia or RODA) and transfer to naltrexone maintenance;

iii transfer from heroin/methadone to buprenorphine and transfer to naltrexone maintenance; and

iv standard in-patient or outpatient detoxification with clonidine and other medications (lofexidine or buprenorphine) for symptomatic relief and transfer to naltrexone maintenance.

These approaches differ in the medications used to moderate the symptoms of withdrawal, the level of withdrawal symptoms experienced by the patients, the length of delay between detoxification and commencement of naltrexone maintenance, and the ease with which the patient can cease the treatment episode. It can be expected that the different approaches will vary in the proportion of patients successfully inducted onto naltrexone maintenance. It is also possible (although there is no evidence at present to predict the likelihood of this) that the induction process may influence the outcomes of naltrexone maintenance treatment. This is what needs to be investigated. However, it was emphasised that anaesthesia may not be required or beneficial, and that there is a need to trial non-anaesthesia methods of induction onto naltrexone maintenance. It may prove that less intense approaches to minimising withdrawal distress would be acceptable and as effective. It was agreed,

however, that rapid induction, or induction with minimal withdrawal distress associated with it, would potentially lead to more patients successfully commencing naltrexone maintenance, and some felt it would produce more effective ongoing naltrexone maintenance therapy.

An analysis of current and proposed research projects should be undertaken to ensure that there are no substantial gaps in assessment of the different mechanisms of induction onto naltrexone maintenance.

5.2.2. Adoption of GCRP standards

There was general agreement that the guidelines for Good Clinical Research Practice in Australia (Therapeutic-Goods-Administration, 1991), or a similar suitable standard, be adopted in the trials. These guidelines have the objective to "help safeguard the interests of subjects, investigators, sponsors and society in ensuring that only adequately planned and conducted clinical studies are performed. . . . [as] Unless the entire procedure, including the analysis of data, is adequately controlled, there is a risk of failure and hence a waste of human and financial resources with indisputable associated ethical concerns" (p.1) (Therapeutic-Goods-Administration, 1991).

In this regard, there was agreement that patients be made aware of all of the possible adverse effects that could come from induction onto naltrexone maintenance therapy. Care should be taken with patients who have a history of psychiatric disturbance or medical complications which may contraindicate entry into ROD or RODA. The need for a means to identify patients receiving naltrexone maintenance in case of trauma-related need to manage acute pain was emphasised, and the researcher should have a mechanism for advising on the appropriate use of non-opioid analgesia to clinicians caring for patients after trauma. The ethical review process prior to commencement of trials should address this issue.

5.2.3. Combining data from different trials in Australia

It is not feasible to test all the possible induction procedures in a single trial. The methodology would be too complex, the facilities and staff required for each procedure will vary, and most research groups are primarily interested in only a few methods of induction onto naltrexone. However, the opportunity exists for the various research groups to pool results.

Participants in the workshop agreed, in principle, to research results being combined, and there are a range of research projects at different stages of development that will together investigate most, if not all, of the methods of induction identified above. The advantage of being able to conduct quasi-experimental comparisons, plus the potential to conduct analyses to determine which patients fared best with each procedure was recognised. However, the core data set to be collected and the most appropriate mechanism to support the combination of results from the different research projects remained unresolved. The issues of the core minimum data to be gathered and the method of combining and centralising the data requires further consideration. There needs to be agreement on aspects of the initial assessment, outcome domains and measurement instruments, assessment of adverse and serious adverse events, the frequency of assessment, and duration of follow-up. Several participants self-identified as interested in this activity. The agreement reached will need to protect the rights of the individual research groups and only planned and agreed upon analyses will be feasible.

5.2.4. Planned trials

A number of planned or mooted trials were outlined, and there was agreement that they were all important, although the rationale and reasons for the various efforts differed.

5.2.4.1. Methadone to buprenorphine to naltrexone. A group of research centres based in Queensland, NSW and Victoria have been collaborating with the aim of assessing the value of using buprenorphine to transfer stable methadone patients to naltrexone. The details are to be finalised, but the primary aim is to assess the efficacy of naltrexone as an aid to successful withdrawal from opioid maintenance therapy and continued abstinence thereafter. An additional aim is to assess the cost-effectiveness of the procedures. Illicit opioid use, side-effects and adverse events and serious adverse events, patient satisfaction and retention among patients who meet DSM-IV criteria for opioid dependence, will be monitored as a measure of success. Funding has been secured in the three states. There are secondary aims, including assessing the level of interest in and possible barriers to, successful withdrawal, detoxification, and abstinence with buprenorphine and subsequent naltrexone maintenance therapy. Pilot studies will address the best methods of induction onto buprenorphine and then onto naltrexone prior to the commencement of a randomised clinical trial.

5.2.4.2. Rapid induction onto naltrexone without anaesthesia. Staff of the South Eastern Sydney Area Health Service (see list of participants for details) wish to proceed with a controlled study of accelerated detoxification and induction onto naltrexone maintenance treatment.

5.2.4.3. Rapid induction onto naltrexone under anaesthesia. Staff of the Western Sydney Area Health Service (WSAHS; see appendix) wish to pilot anaesthesia-assisted induction onto naltrexone maintenance treatment. The WSAHS team wish to treat 50 methadone patients and 50 heroin users. They will use the methods from Israel, and they are now continuing to assess the treatment protocol (see appendix) and outcomes of the program there. While there was some discussion about the size of the patient sample to be examined in the pilot (and some clinicians and researchers questioned the need for such a large sample), the WSAHS team considered this number to be necessary to gain familiarity with a complex treatment protocol, train staff and optimise the operation and efficiency sufficient to determine effect sizes in order to conduct power analyses for the subsequent randomised clinical trial. Pilot study will also allow entry criteria to be refined. The WSAHS team also noted that once a clinical team is set up to conduct the effort, economies of scale allow for a large pilot group. The team have estimated that induction onto naltrexone under anaesthesia can be delivered by Westmead Hospital at a cost that is comparable to conventional inpatient detoxification and significantly less that the cost of overseas for-profit programs. It was agreed that from a political perspective, it is important that a randomised clinical trial of anaesthesia-based accelerated detoxification proceeds. Clinicians at the workshop were satisfied by the WSAHS team's ability to minimise risks during RODA.

5.3. Concerns expressed about planned research trials

5.3.1. Serious adverse events associated with induction onto naltrexone maintenance.

Deaths have been associated with RODA, but were thought to be relatively unlikely in well-supported intensive care units or similarly supported medical wards. Some workshop participants, however, were not convinced that adverse events would not occur, and pointed to the lack of clear information concerning patient well-being during and soon after the induction onto naltrexone. Additionally, there are sufficient comments in the literature about patients suffering severely under accelerated induction procedures, for extreme caution to be exercised in any trial, and inpatient pilot studies to be preferred. There was also concern expressed about the potential for serious adverse events to increase once RODA is in general use.

One area of concern regarding naltrexone maintenance treatment is that it may increase the risk of overdose for patients who cease naltrexone treatment and relapse to either occasional or regular opioid use. It is not clear from the available research evidence whether the increased risk of overdose is due to the usual loss of tolerance that occurs with the cessation of opioid use, or to naltrexone causing an increased sensitivity to opioids. Although theoretically some hypersensitivity *may* occur at the receptor level, the duration of any such effect and its magnitude and importance are unclear. Some have speculated that naltrexone causes increased levels of depression in some patients on naltrexone maintenance therapy, and that this depression may be a cause of at least a proportion of the overdose deaths observed (Miotto, McCann, Rawson, Frosch

& Ling, 1997). Whatever the basis, it is critically important that people receiving naltrexone are warned of the increased risk of overdose and are advised how to minimise the risk.

Another concern was the potential for induction onto naltrexone maintenance to destabilise patients who were functioning well in methadone maintenance therapy. Specifically, there was a concern that patients whose regular opioid use had declined due to agonist therapy, might recommence when taking naltrexone and return to frequent, regular injecting. It was agreed that it is important to inform patients of the potential risks of such destabilisation, and to provide safeguards for these patients, including ensuring access to methadone maintenance therapy should the patient fare poorly.

5.3.2. Media scrutiny and rational policy development

The level of media attention given to rapid detoxification using naltrexone to date, and the subsequent public perception that this procedure provides a "cure" for heroin dependence remains an issue. Concerns were expressed by some participants that any delivery of anaesthetic based detoxification and induction onto naltrexone maintenance will receive substantial media attention, and reports of even small groups of "successfully" treated patients could result in considerable pressure for this procedure to be implemented more widely. This could lead to a consequent negative impact on other approaches to induction onto naltrexone which may be as effective as RODA, or which may be more easily implemented (given the need for constant patient monitoring in an ICU or with ICU support with RODA). Additionally, some have expressed concerns any pre-post evaluation of RODA patients (without an appropriate randomised control group) runs the risk that methods of induction onto naltrexone maintenance will not be subject to the same standards of evidence required of other interventions for serious and debilitating disorders in Australia (Hall & Mattick, 1997; Hall et al., in press).

One suggestion to minimise this potential problem was to ensure that any assessment of RODA be examined accompanied by a ROD patient group run in parallel (see also section 5.1). It was argued that such an approach would also allow researchers to pilot and refine both intervention procedures in preparation for a randomised clinical trial (as there is very limited experience with either procedure in Australia). Clearly RODA needs to be explored prior to a clinical trial, but so does ROD if it is to be implemented most effectively, with minimal patient distress. The WSAHS team plan to pilot and refine both procedures, prior to undertaking a randomised clinical trial of RODA and ROD. In addition, a wait-list control will be utilised in the pilot phase of refining RODA for methadone patients.

It was also noted by some participants that naltrexone maintenance is only one part of the national effort to develop a broad range of options for the treatment of opioid dependence, as endorsed by the Ministerial Council on Drug Strategy in July, 1997. Other options include improving the effectiveness of methadone maintenance treatment, developing alternative maintenance approaches (buprenorphine and LAAM) and examining ways to help prevent relapses. The media attention given to rapid opioid detoxification with anaesthesia has caused substantial attention to be focused on naltrexone and the process of withdrawal. We need to restore the balance and also ensure the effective national coordination of other areas of research.

6. Appendices

6.1. List of contributors

Participants who attended the one-day workshop on 23.11.1997:
Dr Robert Ali, Drug & Alcohol Services Council, S.A. Health Department
Dr Gabriele Bammer, NCEPH, Australian National University
Ms Anne Bartu, W.A. Alcohol & Drug Authority, W.A. Health Department
Dr James Bell, Drug and Alcohol Unit, Prince of Wales Hospital, N.S.W. Health Department
Dr Jon Currie, Drug and Alcohol Service, WSAHS, N.S.W. Health Department
Dr Erol Digiusto, Drug and Alcohol Service, WSAHS, N.S.W. Health Department
Dr Aidan Foy, Department of Medicine, Mater Hospital, N.S.W. Health Department
Dr Linda Gowing, Commonwealth Department of Health and Family Services
Prof. Wayne Hall, NDARC, University of New South Wales
Mr Simon Harris, NDARC, University of New South Wales
Ms Virginia Hart, Commonwealth Department of Health and Family Services
Dr Nicholas Lintzeris, Turning Point Alcohol & Drug Centre Inc.
Dr Michael Lynskey, NDARC, University of New South Wales
A/Prof. Richard P. Mattick, NDARC, University of New South Wales
Dr Yugan Mudaliar, Intensive Care, Westmead Hospital, WSAHS, N.S.W. Health Department
Ms Susannah O'Brien, NDARC, University of New South Wales
Dr Allan Quigley, West Australian Alcohol & Drug Authority, W.A. Health Department
Dr Alun Richards, Alcohol Tobacco and Other Drugs, Queensland Health Department
Ms Alison Ritter, Turning Point Alcohol & Drug Centre Inc.
Mr Gray Sattler, NSW Health Department
Dr Jeff Ward, Division of Psychology, Australian National University
Ms Patricia Ward, NSW Health Department
Dr Jason White, Behavioural Pharmacology, University of Adelaide

Those sent draft document for comment, included:
Dr Nick Buckley, NCEPH, Australian National University
Dr John Caplehorn, Public Health and Community Medicine, University of Sydney
Mr Keith Evans, Alcohol Tobacco and Other Drugs, Queensland Health Department
Dr George O'Neill, Perth, WA
A/Prof. George Rubin, Australian Centre for Effective Healthcare, University of Sydney
Prof. John B. Saunders, Centre for Drug & Alcohol Studies, University of Queensland
Dr Alex Wodak, Drug and Alcohol Services, St Vincent's Hospital, NSW Health Department
Dr Gilbert Whitton, Drug & Alcohol Services, SWSAHS, NSW Health Department
Dr Wendy Wickes, Drug & Alcohol Services, SWSAHS, NSW Health Department
Dr Deborah Zador, Area Staff Specialist, CSAHS, NSW Health Department

6.2. Observations on the technique of anaesthesia

The following are the observations of Drs. Peter Cox and Yugan Mudaliar of Westmead Hospital, Sydney concerning the technique of anaesthesia used for the MEGAMA procedure of accelerated neuroreceptor blockade.

Premedication

Vitamin C, clonidine, diazepam, ranitidine, omeprazole and a cephalosporin are given according to a strict protocol over a four hour period prior to induction of anaesthesia. The patient will have been fasted for an appropriate time and given an enema. Baseline haematology and renal function tests will have been performed, as well as an ECG. Intravenous fluids are commenced prior to induction. The patient is settled in a quiet environment during this phase.

Induction, maintenance and completion of anaesthesia

General anaesthesia is induced with midazolam and propofol. When a satisfactory depth of anaesthesia has been reached, the vocal chords are sprayed with lignocaine and after a suitable interval, the trachea is intubated. Further doses of propofol may be given to attenuate the autonomic response to laryngoscopy and intubation. An Fi02 of 1.0 is used during induction and this is reduced to 0.75 in air following intubation. The endotracheal tube is connected to a humidified blow-over circuit and 5cms of CPAP is applied. Assisted ventilation may be required during this phase.

An 18G orogastric tube is then inserted, and its position is very carefully checked. Once spontaneous ventilation has been re-established, a propofol infusion is commenced. The patient is nursed slightly head-up.

Between 2.5 and 4.0 litres of intravenous fluids are given over the perioperative period. Hartmanns solution is principally used, with supplements of 5% dextrose in 0.5N saline with 0.2% KCI.

Approximately 30 minutes after induction the stomach is washed out and all gastric contents removed. The first dose of naltrexone combined with clonidine is given and the orogastric tube is closed for 45 minutes. The first signs of withdrawal usually appear after 25-30 minutes. At this stage, it may be necessary to increase the rate of propofol infusion and/or give more midazolam and clonidine.

An attempt is made to keep the level of anaesthesia "light" so that the response to naltrexone is evident to the observers. The first signs of withdrawal are often sneezing or piloerection. The maximum response to naltrexone appears to be within 45-50 minutes and is largely worn off within 1.5 hours.

The second dose of naltrexone is given 1.5 hours after the first. Ten minutes before the dose is given, the stomach is washed out, extra midazolam is given and the propofol rate is increased. A second dose of naltrexone and clonidine is then given and the orogastric tube again clamped for 45 minutes. The patient is then monitored for 2.5 hours.

Extubation is performed 4 hours after the initial dose of naltrexone. Thirty minutes prior to extubation, octreotide is given intravenously. Ten minutes prior to extubation, further diazepam and possibly clonidine are given via the orogastric tube. The propofol infusion is ceased.

Extubation is performed in the usual manner, removing the orogastric tube first. The autonomic response to extubation may be attenuated by the use of bolus doses of propofol or IV lignocaine. The patient is extubated on his/her side and is monitored post-procedure in a quiet environment.

Recommendations

Safety is the paramount consideration of the procedure. It is critical to recognise that the anaesthetist is the primary, active instigator of intervention during the whole procedure ("anaesthetist as chemical surgeon"). Therefore the anaesthetist performing the procedure must be trained and experienced in this specific intervention, and must be present and actively monitoring the procedure at all times. Similarly, the presence of specialist nursing staff with expertise in the procedure is vital. Where multiple numbers of patients are to be treated simultaneously, anaesthetic and nursing cover may need to be increased, depending on local requirements.

Monitoring of patients must comply with at least minimal requirements of the Australian and New Zealand College of Anaesthetists. Temperature regulation and careful fluid balance are mandatory. Air mattresses may be useful. If intravenous preparations of naltrexone and clonidine are used, this should make the response to their effects more predictable.

Personal views of the procedure

We believe that the procedure can be performed safely using current anaesthetic techniques. This situation is no different from other prolonged general anaesthetics in terms of its risks, the management of which should be within the competence of an anaesthetist in regular practice. The cost of the anaesthesia component is likely to be modest.

With our backgrounds in anaesthesia, chronic pain management and intensive care medicine, our recent observation of this programme leads us to believe that accelerated neuroreceptor blockade, using the techniques outlined, offers an extremely useful option in the overall approach to opioid dependence.

7. References

Azatian, A., Papiasvilli, A., & Joseph, H. (1994). A study of the use of clonidine and naltrexone in the treatment of opioid addiction in the former USSR. Journal of Addictive Diseases, 13, 35-52.

Bammer, G., Ali, R., Hall, W., Kutin, J., Lintzeris, N., Mattick, R. P., Ritter, A. J., & White, J. (submitted). New treatments for heroin dependence in Australia. *Medical Journal of Australia*.

Bardo, M. T., Bhatnagar, R. K., & Gebhart, G. F. (1983). Chronic naltrexone increases opiate receptor binding in brain and produces supersensitivity to morphine in the locus coeruleus of the rat. Brain Research, 289, 223-234.

Bardo, M. T., Miller, J. S., & Risner, M. E. (1984). Opiate receptor supersensitivity produced by chronic naloxone treatment. Dissociation of morphine-induced antinociception and conditioned taste aversion. Pharmacology, Biochemistry and Behaviour, 21, 591-597.

Barnao, T. (1997, September, 1997). Mission possible: Heroin - hope at last. Australian Women's Weekly, 82-84.

Bartter, T., & Gooberman, L. L. (1996). Rapid opiate detoxification. American Journal of Drug and Alcohol Abuse, 22, 489-495.

Bearn, J., Gossop, M., & Strang, J. (1996). Randomised double-blind comparison of lofexidine and methadone in the in-patient treatment of opiate withdrawal. Drug and Alcohol Dependence, 43, 87-91.

Brewer, C. (1997a). The case for rapid detoxification under anaesthesia (RODA): A reply to Gossop and Strang. British Journal of Intensive Care(July/August), 137-143.

Brewer, C. (1997b). Ultra-rapid, antagonist-precipitated opiate detoxification under general anaesthesia or sedation. Addiction Biology, 2, 291-302.

Brewer, C., Laban, M., Schmulian, C., Gooberman, L., Kasvikis, Y., & Maksoud, N. A. (July 8-12, 1996). Rapid opiate detoxification and naltrexone induction under general anaesthesia and assisted ventilation: Experience with 510 patients in four countries. Paper presented at the Annual Meeting, Royal College of Psychiatrists/Association of European Psychiatrists, London.

Brewer, C., Rezae, H., & Bailey, C. (1988). Opioid withdrawal and naltrexone induction in 48-72 hours with minimal drop-out, using a modification of the naltrexone-clonidine technique. British Journal of Psychiatry, 153, 340-343.

Brodsky, M., Elliott, K., Hynansky, A., & Inturrisi, C. E. (1995). CNS levels of mu opioid receptor (MOR-1) mRNA during chronic treatment with morphine or naltrexone. Brain Research Bulletin, 38, 135-141.

Caplehorn, J. R. M. (1997). Ultrarapid opiate detoxification: What's all the fuss about? Medical Journal of Australia, 167, 393.

Charney, D. S., Heninger, G. R., & Kleber, H. D. (1986). The combined use of clonidine and naltrexone as a rapid, safe, and effective treatment of abrupt withdrawal from methadone. American Journal of Psychiatry, 143, 831-837.

Charney, D. S., Riordan, C. E., Kleber, H. D., Murburg, M., Braverman, P., Sternberg, D. E., Heninger, G. R., & Redmond, E. (1982). Clonidine and naltrexone: A safe, effective, and rapid treatment of abrupt withdrawal from methadone therapy. Archives of General Psychiatry, 39, 1327-1332.

Cote, T. E., Izenwasser, S., & Weems, H. B. (1993). Naltrexone-induced upregulation of mu opioid receptors on 7315c cell and brain membranes: Enhancement of opioid efficacy in inhibiting adenylyl cyclase. Journal of Pharmacology and Experimental Therapeutics, 267, 238-244.

Cox, S., & Alcorn, R. (1995). Lofexidine and opioid withdrawal. Lancet, 345, 1385-1386.

Danks, J. A., Tortellam, F. C., Bykov, V., Jacobson, A. E., Rice, K. C., Holaday, J. W., & Rothman, R. B. (1988). Chronic administration of morphine and naltrexone up-regulate [3H]D-Ala2, D-leu5 enkephalin binding sites by different mechanisms. Neuropharmacology, 27, 965-974.

Darke, S., Hall, W., Heather, N., Ward, J., & Wodak, A. (1991a). The reliability and validity of a scale to measure HIV risk-taking behaviour among intravenous drug users. AIDS, 5, 181-185.

Darke, S., Hall, W., Wodak, A., Heather, N., & Ward, J. (1992). Development and validation of a multi-dimensional instrument for assessing outcome of treatment among opiate users: The Opiate Treatment Index. British Journal of Addiction, 87, 733-742.

Darke, S., Ward, J., Hall, W., Heather, N., & Wodak, A. (1991b). The Opiate Treatment Index (OTI) Researcher's Manual: National Drug and Alcohol Research Centre Technical Report Number 11. Sydney: National Drug & Alcohol Research Centre.

Darke, S., Ward, J., Zador, D., & Swift, G. (1991c). A scale for estimating the health status of opioid users. British Journal of Addiction, 86, 1317-1322.

De Vries, T. J., Tjon Tien Ril, G. H. K., Van der Laan, J. W., Mulder, A. H., & Schoffelmeer, A. N. M. (1993). Chronic exposure to morphine and naltrexone induces changes in catecholaminergic neurotransmission in rat brain without altering mu-opioid receptor sensitivity. Life Sciences, 52, 1685-1693.

Demaria, P. A., Rodgers, C., & Braccia, G. (1997). Propofol for sedation during rapid opiate detoxification. American Journal of Psychiatry, 154, 290-291.

Everleigh, B. (1997). The use of lofexidine in an opiate community detox. Paper presented at the 8th International Conference on the reduction of drug related harm. Paris, March 1997.

Gerra, G., Marcato, A., Caccavari, R., Fontanesi, B., Delsignore, R., Fertonani, G., Avanzini, P., Rustichelli, P., & Passeri, M. (1995). Clonidine and opiate receptor antagonists in the treatment of heroin addiction. Journal of Substance Abuse Treatment, 12, 35-41.

Gewiss, M. V., Marley, R. J., Thorndike, E. B., Goldberg, S. R., & Schindler, C. W. (1994). GABA receptor-linked chloride channels and the behavioural effects of naltrexone in rats. Pharmacology, Biochemistry and Behavior, 49, 589-597.

Gilman, A. G., Goodman, L. S., Rall, T. W., & Murad, F. (Eds.). (1985). The pharmacological basis of therapeutics (7th ed.). New York: MacMillan Publishing Company.

Gold, M. S., Pottash, A. C., Sweeney, D. R., Extein, I., & Annitto, W. J. (1981). Opiate detoxification with lofexidine. Drug and Alcohol Dependence, 8, 307-315.

Gold, M. S., Pottash, A. C., Sweeney, D. R., & Kleber, H. D. (1980a). Opiate withdrawal using clonidine, a safe, effective, and rapid nonopiate treatment. Journal of the American Medical Association, 243, 343-346.

Gold, M. S., Pottash, A. C., Sweeney, D. R., & Kleber, H. D. (1980b). Efficacy of clonidine in opiate withdrawal: a study of thirty patients. Drug and Alcohol Dependence, 6, 201-208.

Gold, M. S., Redmond, D. E., & Kleber, H. D. (1978). Clonidine blocks acute opiate withdrawal symptoms. Lancet, 2, 599-602.

Gold, M. S., Redmond, D. E., & Kleber, H. D. (1979). Noradrenergic hyperactivity in opiate withdrawal supported by clonidine reversal of opiate withdrawal. American Journal of Psychiatry, 136, 100-102.

Gonzalez, J. P., & Brogden, R. N. (1988). Naltrexone: A review of pharmacodynamic and pharmacokinetic properties and therapeutic efficacy in the management of opioid dependence. Drugs, 35, 192-213.

Gossop, M., Johns, A., & Green, L. (1986). Opiate withdrawal: Inpatient versus outpatient programmes and preferred versus random assignment to treatment. British Medical Journal, 293, 103-104.

Gossop, M., & Strang, J. (1997). Rapid anaesthetic-antagonist detoxification of hertoin addicts: What origins, evidence base and clinical justification? British Journal of Intensive Care, 7(2), 66-69.

Gould, D. B. (1995). Buprenorphine causes pulmonary edema just like all other mu-opioid narcotics. Upper airway obstruction, negative alveolar pressure [letter]. Chest, 107, 1478-1479.

Green, L., & Gossop, M. (1988). Effects of information on the opiate withdrawal syndrome. British Journal of Addiction, 83, 305-309.

Grey, C., Osborn, E., & Reznikoff, M. (1986). Psychosocial factors in outcome in two opiate addiction treatments. Journal of Clinical Psychology, 42, 185-189.

Hall, W., & Mattick, R. P. (1997). Ultrarapid opiate detoxification. Medical Journal of Australia, 167, 393-396.

Hall, W., Mattick, R. P., Saunders, J. B., & Wodak, A. (in press). Rapid opiate detoxification treatment. Drug and Alcohol Review.

Herman, B. H., & Czechowicz, D. (1996). NIDA scientific report of ultra rapid detoxification with anaesthesia (UROD): Opinion of the consultants and criteria relating to the safety and efficacy of UROD . Washington, D.C.: National Institute on Drug Abuse.

Jaffe, J. (1995). Pharmacological treatment of opioid dependence: Current techniques and new findings. Psychiatric Annals, 25, 369-375.

Johnson, S. M., & Flemming, W. W. (1989). Mechanisms of cellular adaptive sensitivity changes: applications to opioid tolerance and dependence. Pharmacological Reviews, 41, 435-488.

Judson, B. A., & Goldstein, A. (1984). Naltrexone treatment of heroin addiction: One-year follow-up. Drug and Alcohol Dependence, 13, 357-65.

Kahn, A., Mumford, J. P., Ash-Rogers, G., & Beckford, H. (1997). Double-blind study of lofexidine and clonidine in the detoxification of opiate addicts in hospital. Drug and Alcohol Dependence, 44, 57-61.

Kleber, H. D., Topazian, M., Gaspari, J., Riordan, C. E., & Kosten, T. (1987). Clonidine and naltrexone in the outpatient treatment of heroin withdrawal. American Journal of Drug and Alcohol Abuse, 13, 1-17.

Kurland, A. A., & Hanlon, T. E. (1974). Naloxone and the narcotic abuser: A controlled study of partial blockade. International Journal of the Addictions, 9, 663-672.

Kurland, A. A., McCabe, L., & Hanlon, T. E. (1975). Contingent naloxone (N-allylnoroxymorphone) treatment of the paroled narcotic addict. International Pharmacopsychiatry, 10, 157-168.

Latowsky, M. (1996). Improving detoxification outcomes from methadone maintenance treatment: The interrelationship of affective states and protracted withdrawal. Journal of Psychoactive Drugs, 28(3), 251-257.

Lee, M. C., Wagner, H. N., Tanada, S., Frost, J. J., Bice, A. N., & Dannals, R. F. (1988). Duration of occupancy of opiate receptors by naltrexone. Journal of Nuclear Medicine, 29, 1207-1211.

Legarda, J. J., & Gossop, M. (1994). A 24-h inpatient detoxification treatment for heroin addicts: a preliminary investigation. Drug and Alcohol Dependence, 35, 91-93.

Lerner, A. G., Sigal, M., Bacalu, A., Shiff, R., Burganski, I., & Gelkopf, M. (1992). A naltrexone double blind placebo controlled trial in Israel. Israeli Journal of Psychiatry and Related Sciences, 29, 36-43.

Lewis, D. C., Mayer, J., Hersch, R. G., & Black, R. (1978). Narcotic antagonist treatment: Clinical experience with naltrexone. International Journal of the Addictions, 13(6), 961-73.

Loimer, N., Lenz, K., Schmid, R., & Presslich, O. (1991). Technique for greatly shortening the transition from methadone to naltrexone maintenance of patients addicted to opiates. American Journal of Psychiatry, 148, 933-935.

Loimer, N., Schmid, R., Lenz, K., Presslich, O., & Grünberger, J. (1990). Acute blocking of naloxone-precipitated opiate withdrawal symptoms by methohexitone. British Journal of Psychiatry, 157, 748-752.

Loimer, N., Schmid, R., Presslich, O., & Lenz, K. (1988). Naloxone treatment for opiate withdrawal syndrome. British Journal of Psychiatry, 153, 851-852.

Loimer, N., Schmid, R. W., Presslich, O., & Lenz, K. (1989). Continuous naloxone administration suppresses opiate withdrawal symtoms in human opiate addicts during detoxification treatment. Journal of Psychiatric Research, 23, 81-86.

Marley, R. J., Shimosato, K., Gewiss, M., Thorndike, E., Goldberg, S. R., & Schindler, C. W. (1995). Long-term sensitization to the behavioral effects of naltrexone is associated with regionally specific changes in the number of mu and delta opioid receptors in rat brain. Life Sciences, 56, 767-774.

Martin, W. R., Jasinski, D. R., & Mansky, P. A. (1973). Naltrexone, an antagonist for the treatment of heroin dependence. Archives of General Psychiatry, 28, 784-791.

Mattick, R. P., & Hall, W. (1996). Are detoxification programmes effective? Lancet, 347, 97-100.

Mattick, R. P., Oliphant, D., Hall, W., & Ward, J. (1997). The effectiveness of other opioid replacement therapies: Buprenorphine, LAAM, heroin and injectable methadone. In J. Ward, R. P. Mattick, & W. Hall (Eds.), Methadone maintenance treatment and other opioid replacement therapies . London: Harwood Press.

Mayor, S. (1997). Specialists criticise treatment for heroin addiction. British Medical Journal, 314, 1365.

McKey, J. (1997). Rapid detoxification: Miracle or myth? Connexions, 17, 20-22.

Merrill, J., & Marshall, R. (1997). Opioid detoxification using naloxone. Drug and Alcohol Review, 16, 3-6.

Meyer, D. R., & Sparber, D. B. (1976). Clonidine antagonises body weight loss and other symptoms used to measure withdrawal in morphine pelleted rats given naloxone. Pharmacologist, 18, 236.

Meyer, M. C., Straughn, A. B., Lo, M.-W., Schary, W. L., & Whitney, C. C. (1984). Bioequivalence, dose-proportionality, and pharmacokinetics of naltrexone after oral administration. Journal of Clinical Psychiatry, 45, 15-19.

Milby, J. B., Gurwitch, R. H., Hohmann, A. A., Wiebe, D. J., Ling, W., McLellan, A. T., & Woody, G. E. (1987). Assessing pathological detoxification fear among methadone maintenance patients: The DFSS. Journal of Clinical Psychology, 43, 528-538.

Millan, M. J., Morris, B. J., & Herz, A. (1988). Antagonist-induced opioid receptor up-regulation. I. Characterisation of supersensitivity to selective mu and kappa agonists. Journal of Pharmacology and Experimental Therapeutics, 247, 721-728.

Miotto, K., McCann, M. J., Rawson, R. A., Frosch, D., & Ling, W. (1997). Overdose, suicide attempts and death among a cohort of naltrexone-treated opioid addicts. Drug and Alcohol Dependence, 45, 131-134.

Morris, B. J., Millan, M. J., & Herz, A. (1988). Antagonist-induced up-regulation. II. Regionally specific modulation of mu, delta and kappa binding sites in rat brain revealed by quantitative autoradiography. Journal of Pharmacology and Experimental Therapeutics, 247, 729-736.

O'Brien, C. P., Greenstein, R. A., Mintz, J., & Woody, G. E. (1975). Clinical experience with naltrexone. American Journal of Drug and Alcohol Abuse, 2, 365-77.

O'Connor, P. G., Carroll, K. M., Shi, J. M., Schottenfeld, R. S., Kosten, T. R., & Rounsaville, B. J. (1997). Three methods of opioid detoxification in a primary care setting. Annals of Internal Medicine, 127, 526-530.

O'Reilly, R. L., & Smith, D. (1991). Benzodiazepines and confusion in medically ill alcoholics. Canadian Family Physician, 37, 2609-2613, 2644.

Osborn, E., Grey, C., & Reznikoff, M. (1986). Psychosocial adjustment, modality choice, and outcome in naltrexone versus methadone treatment. Abuse, 12, 383-388.

Osterwalder, J. J. (1996). Naloxone--for intoxications with intravenous heroin and heroin mixtures--harmless or hazardous? A prospective clinical study. Journal of Toxicology. Clinical Toxicology, 34, 409-416.

Paronis, C. A., & Holtzman, S. G. (1992). Apparent pA2 value of naltrexone is not changed in rats following continuous exposure to morphine or naloxone. Life Sciences, 50, 1407-1416.

Preston, K. L., & Bigelow, G. E. (1985). Pharmacological advances in addiction treatment. International Journal of the Addictions, 20, 845-867.

Rabinowitz, J., Cohen, H., Tarrasch, R., & Kotler, M. (1997). Compliance to naltrexone treatment after ultra-rapid opiate detoxification: An open label naturalistic study. Drug and Alcohol Dependence, 47, 77-86.

Raczynski, J. M., Wiebe, D. J., Milby, J. B., & Gurwitch, R. H. (1988). Behavioral assessment of narcotic detoxification fear. Addictive Behaviors, 13, 165-169.

Rawson, R. A. (1984). Five-year follow-up of opiate addicts with naltrexone and behavior therapy. In L. S. Harris (Ed.), NIDA Research Monograph No.49 - Problems of drug dependence, 1983: Proceeding of the 45th Annual Scientific Meeting, the Committee on Problems of Drug Dependence (pp. 239-95). Rockville, MD.: US Department of Health and Human Services.

Report of the National Research Council Committee on Clinical Evaluation of Narcotic Antagonists. (1978). Clinical evaluation of naltrexone treatment of opiate-dependent individuals. Archives of General Psychiatry, 35, 335-340.

Resnick, R. B., Washton, A. M., & Stone-Washton, N. (Eds.). (1981). Psychotherapy and naltrexone in opioid dependence. (Vol. 34). Rockville, MD: Department of Health and Human Services.

Riordan, C. E., & Kleber, H. D. (1980). Rapid opiate detoxification with clonidine and naloxone. Lancet, 1, 1079-1080.

Rounsaville, B. J., Kosten, T., & Kleber, H. (1985). Success and failure at outpatient opioid detoxification. Evaluating the process of clonidine- and methadone-assisted withdrawal. Journal of Nervous and Mental Disease, 173, 103-110.

San, L., Pomarol, G., Peri, J. M., Olle, J. M., & Cami, J. (1991). Follow-up after a six-month maintenance period on naltrexone versus placebo in heroin addicts. British Journal of Addiction, 86, 983-990.

San, L., Puig, M. A., Bulbena, A., & Farre, M. (1995). High risk of ultrashort noninvasive opiate detoxification [letter]. American Journal of Psychiatry, 152, 956.

Schindler, C. W., Goldberg, S. R., & Katz, J. L. (1993). Pharmacological specificity of enhanced sensitivity to naltrexone in rats. Psychopharmacology, 110, 60-68.

Schindler, C. W., Marley, R. J., & Goldberg, S. R. (1992). Enhanced sensitivity to naltrexone is associated with an up-regulation in GABA receptor function. Life Sciences, 50, 1-6.

Schindler, C. W., Wu, X. Z., Su, T.-P., Goldberg, S. R., & Katz, J. L. (1990). Enhanced sensitivity to behavioural effects of naltrexone in rats. Journal of Pharmacology and Experimental Therapeutics, 252, 8-14.

Self, D. W., & Nestler, E. J. (1995). Molecular mechanisms of drug reinforcement and addiction. Annual Review of Neuroscience, 18, 463-495.

Senft, R. A. (1991). Experience with clonidine-naltrexone for rapid opiate detoxification. Journal of Substance Abuse Treatment, 8, 257-259.

Seoane, A., Carrasco, G., Cabre, L., Puiggros, A., Hernandez, E., Alvarez, M., Costa, J., Molina, R., & Sobrepere, G. (1997). Efficacy and safety of two new methods of rapid intravenous detoxification in heroin addicts previously treated without success. British Journal of Psychiatry, 171, 340-345.

Shearman, G. T., Lal, H., & Ursillo, R. C. (1980). Effectiveness of lofexidine in blocking morphine-withdrawal signs in the rat. Pharmacology Biochemistry and Behavior, 12, 573-575.

Shufman, E. N., Porat, S., Witztum, E., Gandacu, D., Bar-Hamburger, R., & Ginath, Y. (1994). The efficacy of naltrexone in preventing reabuse of heroin after detoxification. Biological Psychiatry, 35, 935-945.

Simon, D. L. (1997). Rapid opioid detoxification using opioid antagonists: History, theory and the state of the art. Journal of Addictive Diseases, 16, 103-122.

Singleton, E. G., Sherman, M. F., & Bigelow, G. E. (1984). The index of choice: Indications of methadone patients' selection of naltrexone treatment. American Journal of Drug and Alcohol Abuse, 10, 209-21.

Taff, R. H. (1983). Pulmonary edema following naloxone administration in a patient without heart disease. Anaesthesiology, 59, 576-577.

Tempel, A., Gardner, E. L., & Zukin, R. S. (1985). Neurochemical and functional correlates of naltrexone-induced opiate receptor up-regulation. Journal of Pharmacology and Experimental Therapeutics, 232, 439-444.

Tempel, A., Zukin, R. S., & Gardner, E. L. (1982). Supersensitivity of brain opiate receptor subtypes after chronic naltrexone treatment. Life Sciences, 31, 1401-1404.

Therapeutic Goods Administration. (1991). Guidelines for good clinical research practice (GCRP) in Australia. Woden, ACT: Commonwealth Department of Health, Housing and Community Services.

Thomas, M., Kauders, F., Harris, M., Cooperstein, J., Hough, G., & Resnick, R. (1976). Clinical experiences with naltrexone in 370 detoxified addicts. In D.Julius & P. Renault (Eds.), Narcotic antagonists: Naltrexone (Vol. 9, pp. 88-92). Rockvile, MD.: National Institute on Drug Abuse.

Tseng, L. F., Loh, H. H., & Wei, E. T. (1975). Effects of clonidine on morphine withdrawal signs in the rat. European Journal of Pharmacology, 30, 93-99.

Tucker, T., & Ritter, A. (1997). Naltrexone: A literature review. Melbourne: Turning Point, Inc.

Unterwald, E. M., Rubenfeld, J. M., Imai, Y., Wang, J. B., Uhl, G. R., & Kreek, M. J. (1995). Chronic opioid antagonist administration upregulated mu opioid receptor binding without altering mu opioid receptor mRNA levels. Molecular Brain Research, 33, 351-355.

Verebey, K., Volavka, J., Mulé, S. J., & Resnick, R. B. (1976). Naltrexone: Disposition, metabolism, and effects after acute and chronic dosing. Clinical Pharmacology and Therapeutics, 20, 315-328.

Vining, E., Kosten, T. R., & Kleber, H. D. (1988). Clinical utility of rapid clonidine-naltrexone detoxification for opioid abusers. British Journal of Addiction, 83, 567-575.

Wall, M. E., Brine, D. R., & Perez-Reyes, M. (1981). Metabolism and disposition of naltrexone in man after oral and intravenous administration. Drug Metabolism and Disposition, 9, 369-375.

Ward, J., Mattick, R. P., & Hall, W. (1992). Key issues in methadone maintenance treatment. Sydney: New South Wales University Press.

Ward, J., Mattick, R. P., & Hall, W. (in press). Methadone maintenance treatment and other opioid replacement therapies. London: Harwood Press.

Washton, A. M., Pottash, A. C., & Gold, M. S. (1984). Naltrexone in addicted business executives and physicians. Journal of Clinical Psychiatry, 45, 39-41.

Washton, A. M., & Resnick, R. B. (1981). Clonidine in opiate withdrawal: Review and appraisal of clinical findings. Pharmacotherapy, 1, 140-146.

Washton, A. M., & Resnick, R. B. (1983). Recent advances in opiate detoxification: Clonidine and lofexidine. In L. S. Harris (Ed.), NIDA Monograph No. 43 - Problems of drug dependence, 1982: Proceedings of the 44th annual scientific meeting, the committee on problems of drug dependence, Inc (pp. 44-50). Rockville, MD: U.S. Department of Health and Human Services, National Institute on Drug Abuse.

Washton, A. M., Resnick, R. B., & Geyer, G. (1983). Opiate withdrawal using lofexidine, a clonidine analogue with fewer side effects. Journal of Clinical Psychiatry, 44, 335-337.

Washton, A. M., Resnick, R. B., Perzel, J. F., & Garwood, J. (1981). Lofexidine, a clonidine analogue effective in opiate withdrawal (letter). Lancet, May, 991-992.

Washton, A. M., Resnick, R. B., & Rawson, R. A. (1980). Clonidine for outpatient opiate detoxification (letter). Lancet, 1, 1078-1079.

Wilkins, L. H., Winternitz, S. R., Oparil, S., Smith, L. R., & Dustan, H. P. (1981). Lofexidine and clonidine in moderate essential hypertension. Clinical Pharmacology and Therapeutics, 20, 752-757.

Yoburn, B. C., & Inturrisi, C. E. (1988). Modification of the response to opioid and non-opioid drugs by chronic opioid antagonist treatment. Life Sciences, 42, 1689-1696.

Yoburn, B. C., Shah, S., Chan, K., Duttaroy, A., & Davis, T. (1995). Supersensitivity to opioid analgesics following chronic opioid antagonist treatment: relationship to receptor selectivity. Pharmacology, Biochemistry and Behavior, 51, 535-539.