

CIRCULAR

File No	00/1287
Circular No	2001/17
Issued	23 February 2001
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Guidelines for Rapid Detoxification from Opioids

This Circular should be read with reference to the NSW Detoxification Clinical Practice Guidelines.

Guidelines for Rapid Detoxification from Opioids have been produced as part of a NSW Health initiative to expand the range of treatment options available to drug dependent people in NSW.

"Rapid detoxification" is the process of accelerating withdrawal from heroin (or other opioids) by administration of an opioid antagonist, while providing symptomatic relief to enable patients to tolerate the procedure. The aim of the "*Guidelines for Rapid Detoxification from Opioids*" is to provide protocols for this process.

The guidelines apply subject to the following conditions:

- They refer to a procedure intended for a carefully selected clinical population.
- They do not relate to detoxification under anaesthetic.
- They are for application in specialist detoxification facilities.
- The procedure should only occur in a facility that has the capacity to retain people as in-patients in the event of severe withdrawal.
- The procedure is NOT recommended for use in primary care or other non-specialist settings.
- The procedure should only occur in a facility following the drugs approval for use in detoxification by that facility's drug committee or other formal approval mechanism.
- The procedure should only occur following the patient being properly informed and consent obtained, which includes information that use of naltrexone in detoxification is off indication. For more information on consent refer to Department Circular 99/16.

Copies of the guidelines can be obtained from the NSW Health Web Site on www.health.nsw.gov.au or NSW Department of Health Drug Programs Bureau (02) 9391 9244.

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GUIDELINES FOR RAPID DETOXIFICATION FROM OPIOIDS

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Acknowledgements: Ms Maureen Steele, Dr Tony Gill, Dr Benny Monheit, Dr Robert Ali, Dr Alex Wodak, and Mr Mario Fantini all contributed valuable advice in the development of this document.

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Introduction

“Rapid detoxification” is the process of accelerating withdrawal from opioids, by the administration of an opioid antagonist (naltrexone or naloxone).

The aim of these guidelines is to describe a procedure which can be performed in specialist detoxification facilities, with medical and nursing staff and the capacity for retaining people as in-patients in the event of severe withdrawal reactions.

This procedure is NOT recommended in primary care or other non-specialist settings.

The objectives of this document are to assist trained D&A clinical staff:

1. To have a clear knowledge and understanding of rapid detoxification
2. to assess patients seeking rapid detoxification
3. to provide accurate information about the procedure
4. to obtain informed consent to treatment
5. to perform rapid detoxification safely and effectively in detoxification units – relatively low level care settings.

There is considerable international research being conducted around all aspects of naltrexone treatment for opioid dependence. Several major Australian trials have been conducted, and results will become available in 2001. Practitioners are urged to keep abreast of research findings relating to naltrexone treatment.

EXECUTIVE SUMMARY

“Rapid detoxification” is the process of accelerating withdrawal from heroin (or other opioids) by administration of an opioid antagonist, while providing symptomatic relief to enable patients to tolerate the procedure.

Naltrexone is not registered in Australia for use in rapid detoxification. Practitioners offering this treatment have an obligation to fully and accurately inform patients of:

- the potential risks and benefits of the procedure
- alternative treatment approaches
- and ensure patients are able to give informed consent to the treatment.

There is considerable consumer demand for rapid detoxification and naltrexone treatment. This protocol is designed to provide access to rapid detoxification in specialist detoxification units.

Consumer demand for rapid detoxification appears to be based on the belief that it offers quick, painless detoxification, which commits patients to abstinence. However, these perceptions are not well-founded. Research consistently shows that rapid detoxification is neither quick nor painless. About 60% or more of patients undergoing rapid detoxification will relapse to heroin addiction within 6 months.

Rapid detoxification appears to improve short-term induction onto naltrexone. The rationale for the technique of rapid detoxification as outlined in this document is to improve induction onto naltrexone without compromising safety and without a major increase in the severity of withdrawal.

Antagonist precipitated withdrawal can be very severe. Untreated, the acute phase of precipitated withdrawal involves 2 major clusters of symptoms –

- gastrointestinal symptoms, comprising unremitting vomiting and diarrhoea, often with cramping abdominal pain, lasting many hours
- psychological disturbances, with agitation, dysphoria, and delirium. Delirium can last for up to 12 hours

To minimize the risks of rapid detoxification, the major measures are:

- to delay the procedure until there are minimal drugs left in the CNS – at least 48 hours after the last use of heroin, or 7 days after the last use of methadone.
- to ensure patients are psychologically prepared and adequately supported
- to exclude patients with intercurrent medical problems which would increase the risk of the procedure.

In view of the unpredictable severity of withdrawal reactions during rapid detoxification, it should only be performed in settings where there are:

- nursing staff adequate to deal with a severe reaction (which may, require a “special” nurse – 1:1 nursing – for 4 hours in the event of a severe reaction)
- medical staff on-site for 4 hours from induction
- access to medications
- access to basic resuscitation equipment – an airway and air viva, and staff trained in the use of this equipment
- the capacity to retain a patient in in-patient care overnight in the event of a significant reaction.

These precautions, combined with careful assessment and patient selection, repeated explanation of the procedure, provision of symptomatic relief based on clonidine and octreotide, and good nursing support, enable rapid induction onto naltrexone to be accomplished straightforwardly and safely.

Rapid detoxification is appropriate for opioid-dependent patients who;

- have no contraindications
- have been informed of the nature of the treatment and of treatment options
- express a wish to undergo the treatment.

Contraindications to rapid detoxification are:

- pregnancy
- a history of cardiac disease, or evidence of heart disease on clinical examination,
- chronic renal impairment
- decompensated liver disease – jaundice and/or ascites, hepatic encephalopathy
- current dependence on benzodiazepines, alcohol, or stimulants
- history of psychosis

Relative contraindications to rapid detoxification are:

- History of treatment for depression (patients may require psychiatric assessment prior to naltrexone)
- Unstable social circumstances – patients who are homeless or in highly unstable social circumstances require a comprehensive plan to stabilize their circumstances preceding their undergoing rapid detoxification

Patients most likely to benefit from naltrexone treatment are those who are strongly committed to abstinence, have good social support (employment, stable relationship, family support), and do not have serious psychological impairment.

Alternate approaches to induction onto naltrexone, involving the use of buprenorphine, are an alternative to rapid detoxification.

Introduction: Opioid drugs - tolerance, withdrawal, and neuroadaptation

The repeated administration of an opioid such as heroin produces two important observable responses – tolerance and withdrawal.

Tolerance is the phenomenon whereby repeated administration of the drug produces a diminished effect, as the body adapts to the presence of the drug. Tolerance to opioids can be dramatic; with repeated exposure to increasing doses of opioids, an individual can appear and function normally despite having taken doses which would be fatal in a non-tolerant individual.

Withdrawal is the phenomenon whereby after a period of prolonged exposure to opioid drugs, stopping the administration of the drug leads to physiological and psychological changes – an “abstinence syndrome”.

Tolerance and withdrawal are manifestations of the same process by which the body adapts to the presence of administered opioids. The term “**neuroadaptation**” is used to describe the changes inferred from observing tolerance and withdrawal. “Neuroadaptation” assumes adaptive changes occur in the CNS as a result of exposure to opioids; however, the mechanisms of neuroadaptation to opioids are not well understood.

Neuroadaptation begins immediately following the administration of an opioid agonist. Four hours after the administration of a single dose of morphine to a non-dependent subject, a mild withdrawal reaction can be precipitated by the administration of large doses of naloxone, indicating that a degree of neuroadaptation has already occurred.

With repeated administration of an opioid, so long as the interval between doses is sufficiently short to ensure that there is time for neuroadaptation to completely reverse between doses, neuroadaptation and tolerance quickly become established. It is possible to progressively raise the administered dose of an opioid until within weeks, tolerance is such that the patient can receive very large doses without evidence of toxicity.

The reversal of neuroadaptation begins quite rapidly when the level of opioid agonist drugs in the CNS begins to decline. Reversal of neuroadaptation is associated with the emergence of an abstinence syndrome – signs and symptoms of withdrawal. After about 3 weeks of regular opioid use, discontinuation is associated with the spontaneous emergence of symptoms and signs of withdrawal.

The severity of opioid withdrawal is determined by two major factors:

- Firstly, the **greater the dose of opioid** being administered regularly, the more severe the withdrawal syndrome on discontinuing
- Secondly, **the more rapid the rate** at which the opioid is withdrawn, the more severe the withdrawal syndrome.

The more rapidly an opioid drug is cleared from the body, the more pronounced is the abstinence syndrome. Withdrawal from short-acting drugs tends to be more severe than withdrawal from long-acting drugs. Morphine has a half-life of about 2-3 hours, which means that morphine blood levels decline fairly rapidly, from a peak following intravenous administration. Abrupt cessation of regular morphine leads to quite a severe withdrawal syndrome. Long acting drugs such as methadone or buprenorphine have much more mild (but more prolonged) withdrawal syndromes on cessation. Even with these drugs, it is recommended that they be tapered over a period to allow more gradual and less symptomatically distressing reversal of neuroadaptation.

The most severe withdrawal reactions occur when an opioid antagonist is administered to a dependent patient who at the time has a high level of circulating opioid agonist.

By competitively inhibiting the agonist, the administration of naloxone or naltrexone abruptly blocks agonist effects – instead of declining over many hours, drug effects are reversed in minutes. The result is a very severe withdrawal reaction, with profound physiological and psychological effects.

Spontaneous opioid withdrawal

In people dependent on heroin, cessation of heroin use results in a withdrawal syndrome. The onset of symptoms of withdrawal is usually 8-24 hours after the last dose of heroin. Symptoms peak at 24-48 hours, then resolves after 5-7 days.

Symptoms of opioid withdrawal include;

Anorexia and nausea, abdominal pain, hot and cold flushes, bone, joint and muscle pain, insomnia and disturbed sleep, cramps, intense craving for opioids

Signs of opioid withdrawal include;

Restlessness, yawning, perspiration, rhinorrhoea, dilated pupils, piloerection, muscle twitching (particularly restless legs while lying down), vomiting, diarrhoea.

Spontaneous withdrawal has been described as “objectively mild but subjectively severe”. Patients are often severely distressed, and in severe withdrawal may lie curled in the foetal position. Their intense craving for opioids is related to the knowledge that a dose of opioid will alleviate distress, and is one reason why many subjects fail to complete withdrawal.

Monitoring the severity of withdrawal

Based on this pattern of symptoms and signs, several scales for monitoring the severity of withdrawal have been developed. However, scales which monitor only objective withdrawal signs often severely underestimate the severity of symptoms, and if symptomatic treatment is to be based on withdrawal severity, it is desirable to use a subjective withdrawal scale. One scale currently in use in several Australian treatment centres is the Subjective and Objective Withdrawal Scale (Handlesman, 1996). Because it was designed for repeated administration over short intervals, it is a useful scale for monitoring severity of withdrawal during detoxification.

Copies of these scales are included as appendix A.

After the acute phase of withdrawal, there appears to be a chronic withdrawal, in which low-grade symptoms of dysphoria and discomfort persist in many patients for 6 months or longer. No-one understands the mechanism of this protracted abstinence syndrome, but it is probably one factor contributing to the high rate of relapse in detoxified heroin users.

Detoxification Services

Spontaneous withdrawal from opioids is not life-threatening. Occasionally subjects with severe vomiting and diarrhoea may become dehydrated. Episodes of acute psychosis in patients with a history of schizophrenia have been reported. Some people harm themselves during withdrawal distress. However, serious adverse events are uncommon, and the majority of dependent heroin users have usually been through multiple episodes of withdrawal, without any symptomatic treatment.

Detoxification is the process of providing symptomatic relief to assist patients to complete withdrawal and avoid adverse events associated with withdrawal.

There has always been considerable consumer demand for detoxification. Patients are fearful of withdrawal, particularly after periods of heavy heroin use. Most commonly, patients present to detoxification services in times of crisis. Almost all people in this situation report wanting to become long-term abstinent.

Withdrawal is often seen as the major barrier to discontinuing drug use. However, contrary to the hopes of patients, families, and health professionals, assisting people to complete withdrawal is not usually followed by long-term abstinence from opioids. The great majority of subjects who undergo detoxification will return to heroin use within the next 12 months (usually, within the next month).

However, many detoxified patients, having reduced their neuroadaptation, resume at much lower levels of heroin use. Often, for many months after an episode of detoxification, subjects heroin use remains substantially lower than before entry to treatment. Thus, while initially aiming for abstinence, a good outcome for some patients is that detoxification interrupts a heavy period of heroin use, allowing them to reduce their level of tolerance and regain – at least for a time – a degree of control.

Those patients who after an episode of detoxification continue in some form of treatment – counselling, naltrexone, or maintenance with methadone – appear to do better than those who do not.

The goals of an episode of detoxification may be summarized as:

- reversing (or at least reducing) neuroadaptation to opioids
- promoting patients involvement in post-detoxification treatment.

To promote these objectives, detoxification services:

- Provide symptomatic relief during withdrawal
- Prevent the occurrence of adverse events (such as dehydration, psychotic decompensation, self-harm during detoxification; and minimizing the risk of overdose post-detoxification)

Even an “unsuccessful” episode of detoxification, in which a patient continues to use heroin, can be the basis for an effective longer-term intervention if the patient takes up methadone or buprenorphine maintenance treatment rather than simply dropping out and continuing heroin use.

Antagonist-precipitated withdrawal

The administration of opioid antagonists (such as naloxone or naltrexone) to opioid-dependent people precipitates an immediate abstinence syndrome, often of considerable severity. This is the basis for the “naloxone challenge test” to diagnose opioid dependence.

Antagonist precipitated withdrawal can be very severe. Untreated, the acute phase of precipitated withdrawal involves 2 major clusters of symptoms –

- (1) gastrointestinal symptoms, comprising unremitting vomiting and diarrhoea, often with cramping abdominal pain, lasting many hours
- (2) psychological disturbances, with agitation, dysphoria, and delirium. Delirium can last for up to 12 hours

- There have been reports of psychotic episodes during precipitated withdrawal.
- Without supportive treatment, patients may become dehydrated and develop electrolyte disturbances as a result of severe vomiting.
- Precipitated withdrawal is associated with significant physiological disturbances, including a marked increase in circulating catecholamines. The manifestations of precipitated withdrawal are atypical, and withdrawal scales do not provide an index of withdrawal severity.

In summary, antagonist-precipitated withdrawal produces can produce severe physiological and psychological distress.

The “trade-off” is that some aspects of antagonist precipitated withdrawal appears to be of shorter duration than the process of spontaneous withdrawal. For example, in anaesthetised patients given a bolus dose of naloxone or naltrexone, signs of physiological withdrawal resolve in 4-6 hours. Once acute withdrawal signs have subsided, further administration of naloxone evokes no further withdrawal signs, and this has been taken as definitive evidence that acute withdrawal is complete.

However, while acute signs of withdrawal subside, many patients remain ill for considerably longer than this acute phase.

Predictors of severity of precipitated withdrawal

The major factor associated with severity of precipitated withdrawal is recency of opioid use – the greater the interval between opioid use and administration of naltrexone, the less severe is the precipitated withdrawal. This is because the severity of withdrawal is proportional to the amount of drug still circulating.

Heroin is a relatively short-acting drug. Heroin-dependent subjects who receive naltrexone within 12 hours of their last use of heroin experience more severe withdrawal reactions than subjects in whom administration of naltrexone is delayed 24-48 hours. With longer half-life drugs such as methadone, much longer intervals are required.

The severity of precipitated withdrawal is also influenced by the level of dependence - people with a high opioid tolerance experience more severe precipitated withdrawal.

People maintained on methadone tend to have very severe precipitated withdrawal when given an antagonist. This reflects 2 factors:

- long term exposure to a high dose of opioid, meaning a high degree of neuroadaptation to opioids
- the long half-life means that there is still circulating methadone up to 80 hours or longer after the last dose. This means that when naltrexone is administered, there is an abrupt displacement of methadone from receptors, leading to severe precipitated withdrawal.

To minimize the physiological stress, severity of withdrawal, and to minimize the risk of delirium, the major measures to increase the safety of rapid detoxification are;

1. to delay the administration of antagonists until there is no circulating opioid drugs – patients must have been opioid free for at least 48 hours after the last use of heroin or other short half-life drugs, or 7 days after the last use of methadone.
2. to ensure patients are psychologically prepared and adequately supported. They need to be clearly informed about procedure, know what to expect, and to receive supportive nursing care during the procedure and for a period afterwards
3. to exclude people with concomitant dependence on benzodiazepines or alcohol, as simultaneous withdrawal from multiple drugs is a high-risk approach – alternative forms of detoxification are indicated
4. to ensure that when antagonists are to be administered, there is an appropriate level of care available in the event of a severe reaction. This means:
 - nursing staff adequate to deal with a severe reaction (which may, require a “special” nurse – 1:1 nursing – for 4 hours in the event of a severe reaction)
 - medical staff on-site for 4 hours from induction
 - access to medications
 - access to basic resuscitation equipment – an airway and air viva, and staff trained in the use of these devices
 - the capacity to retain a patient in in-patient care overnight in the event of a significant reaction.
5. to exclude patients with a history of significant medical problems which may increase the risk of adverse events during rapid detoxification – such as heart disease, psychosis, advanced liver disease.

RAPID DETOXIFICATION

“Rapid detoxification” is the process of accelerating acute withdrawal by administration of an opioid antagonist, while providing symptomatic relief to enable patients to tolerate the procedure.

- **Research evidence to date suggests that the majority of subjects undergoing rapid detoxification will relapse to heroin addiction within 6 months.**
- **There is no firm evidence for recommending which patients are most likely to achieve lasting benefit from this treatment**

Although systematic evidence supporting it is not (yet) available, there remains considerable consumer demand for rapid detoxification and naltrexone treatment.

- **Many prospective patients have unrealistic expectations of rapid detoxification.**
- **careful assessment and provision of accurate information prior to treatment is essential**

At present, all that can be said confidently is that rapid detoxification is an alternative which may benefit some individuals.

Naltrexone is not registered in Australia for the indication of accelerating detoxification.

This places an additional responsibility on practitioners to ensure that patients are fully informed of:

- the potential risks and benefits of the use of naltrexone to accelerate withdrawal
- alternate treatment approaches

Written informed consent for the procedure should be obtained.

Medications used in rapid detoxification

The major symptomatic medications used are:

Clonidine, a centrally acting alpha-2 agonist, to reduce sympathetic overactivity, agitation, and withdrawal distress

Octreotide, a synthetic somatostatin analog, the most effective agent for controlling gastrointestinal symptoms

Most procedures include a degree of sedation – ranging from general anaesthesia to light sedation with a benzodiazepine, usually diazepam.

Other useful medications for specific symptoms include:

Buscopan for abdominal cramps,
quinine sulphate for leg cramps,
metoclopramide or ondansetron for nausea,

Rapid detoxification requires a careful balance between the risks of too much medication and too little medication. Untreated, precipitated withdrawal can involve severe symptomatology and physiological disturbance. Inadequate sedation may be associated with severe distress. However:

- clonidine can produce significant hypotension and bradycardia. In the context of dehydration, this can contribute to acute renal failure.
- benzodiazepines can contribute to worsening of delirium, and to depression of consciousness, respiration and gag reflex and risk of aspiration
- the more drugs used to ameliorate symptoms, the greater the risks of drug interactions and potentiation of cardiovascular and respiratory toxicity.

There have been several documented fatalities associated with rapid detoxification, mostly associated with the administration of multiple medications.

Although most descriptions of rapid detoxification concentrate on the medications used to support patients, critical ingredients include:

- Careful assessment beforehand
- full and repeated explanation of the procedure and what is to be expected
- support during and after the acute phase of withdrawal.

One of the most striking issues concerning rapid detoxification is that published descriptions involve a wide variety of medications and approaches – so much so that the inconsistency makes it difficult to draw any conclusions (see literature review below).

However, among the many approaches reported, it is possible to identify 4 broad approaches:

1. *General anaesthesia* with intubation protects the airway, and should be a safe way to manage patients during precipitated withdrawal. This requires an operating theatre or ICU, with staff capable of administering general anesthetic and monitoring intubated patients. Patients are only suitable for this procedure if they are assessed as having no anaesthetic contraindications to elective surgery.
2. *Deep sedation* without airway protection involves a risk of aspiration.
3. *Light (minimal) sedation*. The problem with performing rapid detoxification in lightly-sedated subjects is the risk of agitation, delirium, vomiting and diarrhoea.
4. *Microdosing* with small, repeated doses of naltrexone (1-2mg) has been reported in the press, but has not been documented in the scientific literature. Such an approach is likely to lead to prolonged withdrawal and has little to recommend it.

Only procedures involving minimal sedation can be carried out in low-level medical settings. In these settings, it is essential to delay administration of opioid antagonists until withdrawal is established, in order to minimize the severity of withdrawal. Delayed introduction of naltrexone can, with care, be performed on an ambulatory basis, or may be performed in low-level medical settings.

The perceived advantages of rapid detoxification

From the perspective of a consumer, particularly the person seeking naltrexone maintenance to assist him/her to achieve stable abstinence, there are 4 potential advantages of rapid detoxification over conventional detoxification.

1. To get it over quickly

Although not life-threatening, withdrawal is very aversive, and many patients are attracted to the idea that detoxification can be completed within a few days instead of involving distress for up to a week.

2. To get it over painlessly

Many patients are attracted to the idea that detoxification performed under general anaesthesia or deep sedation means an essentially painless detoxification, in which the patient “wakes up cured” of their addiction.

3. To commit to detoxification irrevocably

Once a dose of naltrexone has been administered, detoxification proceeds irrevocably, leaving no room for ambivalence or change of mind. Even if a patient “changes his mind” and takes a dose of heroin within 24 hours of receiving naltrexone, the presence of naltrexone blocks the effect, and withdrawal symptoms – and detoxification – continue. This appeals to some patients, and also appeals to relatives and practitioners frustrated at ambivalence and relapse.

5. To improve induction onto naltrexone

The end-point of rapid detoxification is induction onto naltrexone.

Set against these potential advantages there are also many perceived disadvantages of rapid detoxification.

- 1. Rapid detoxification involves complicating a simple procedure.*** Most addicts have been through withdrawal on numerous occasions. There need to be compelling arguments, in terms of long-term outcomes rather than patient preference, for subjecting patients to greater levels of risk and distress.
- 2. Rapid detoxification involves significant risks.*** Risks during the acute procedure are associated with aspiration, electrolyte disturbances, toxic effects of drugs.
- 3. Long-term naltrexone treatment appears to be associated with an increased risk of fatal overdose, as in the event of relapse after naltrexone treatment patients often misjudge their level of tolerance.***

Are the perceived advantages of rapid detoxification real?

In seeking to determine the value of rapid detoxification, it is helpful to determine the extent to which the consumer appeal of rapid detoxification is realistic.

Does rapid detoxification shorten withdrawal symptoms?

While acute withdrawal is complete, many patients continue to experience moderately severe withdrawal symptoms, for days, and occasionally for longer. Australian research investigating precipitated withdrawal has identified 3 phases of withdrawal after rapid detoxification.

1. The acute phase. the acute phase of withdrawal lasts about 4-6 hours from the administration of a bolus of naltrexone. Most approaches to rapid detoxification involve placing patients under a general anaesthetic or deep sedation for the duration of acute withdrawal.
2. Subacute phase. This phase lasts from 12-72 hours in which time subjects report high subjective withdrawal scores, and are often unwell, reporting severe fatigue and asthenia. Vomiting is quite common, and most people are anorectic. Almost all subjects report severe difficulty sleeping. Many report feeling depressed.
3. Chronic phase. Subjective withdrawal symptoms significantly higher than baseline persist for 3-4 weeks in patients who have been detoxified from methadone, and for shorter periods in patients detoxified from heroin.

Thus, while rapid detoxification compresses the phase of acute withdrawal, symptoms – sometimes quite distressing – persist, possibly for periods comparable to the duration of spontaneous withdrawal.

Does rapid detoxification reduce the severity of symptoms?

It is suggested that symptomatic relief – particularly, deep sedation and anaesthesia – successfully abolish the worst of withdrawal symptoms. However, as noted above, most subjects do not “wake up cured” after rapid detoxification:

Persisting symptoms of withdrawal, sometimes quite severe, are common.

Does rapid detoxification increase induction onto naltrexone?

Conventional induction onto naltrexone involves 7 days opioid-free after heroin use, followed by naloxone challenge to confirm that patient is fully withdrawn, and administration of first dose naltrexone. This conventional process of induction involves considerable attrition. Many patients do not complete detoxification. As noted above, those who do complete detoxification often review their goals, and decide – either consciously or unconsciously – that they do not want further treatment, and instead seek to return to using drugs while trying to remain “in control”. All in all, the great majority of people who report wanting naltrexone, but attempt conventional detoxification, do not end up taking a dose of naltrexone.

By shortening the drug free interval, rapid detoxification achieves higher rates of induction onto naltrexone than conventional detoxification.

However, drop-out rates from naltrexone tend to be high, and it may be that over 6 months so few people remain on naltrexone that improving rates of induction contributes little long-term benefit. This remains to be determined in long-term studies.

Is rapid detoxification “irrevocable”?

Once an opioid-dependent person has been administered 25mg or more of naltrexone, they experience a withdrawal reaction and their neuroadaptation appears to be rapidly reversed. Even if they use heroin while taking naltrexone, the blockade of mu-receptors is usually sufficient to prevent the development of neuroadaptation.

However, it should be noted that “irrevocable” is only relative. While patients take naltrexone, they remain physiologically non-dependent, even if they use usual doses of opioids. Unfortunately, despite efforts to enhance compliance with naltrexone treatment, the majority of opioid-dependent people discontinue the drug within a short time, and most relapse to opioid dependence. So while detoxification is in a limited sense irrevocable, long-term maintenance of abstinence is certainly not.

In the sense that swallowing a dose of naltrexone ensures achieving the aim of detoxification – reversal of neuroadaptation – it is an “irrevocable” approach to detoxification. However, subsequent attrition from naltrexone treatment is high, and relapse to heroin use common.

Why offer rapid detoxification?

Given that:

- many of the assumptions about rapid detoxification are not well based
- there are risks associated with the procedure

is there any reason for offering rapid detoxification?

The benefits of rapid detoxification have been exaggerated, but this does not mean the procedure is without value. Rapid detoxification can improve induction onto naltrexone, a valuable treatment option for some heroin users.

The rationale for rapid detoxification is that it improves induction onto naltrexone

The technique of rapid detoxification outlined in this document assumes that by timing the introduction of naltrexone optimally, induction onto naltrexone can be accomplished without markedly exacerbating withdrawal symptoms and without compromising safety.

In heroin detoxification, introduction of naltrexone just as the level of circulating morphine is reaching negligible concentrations means that naltrexone displaces very little morphine at opioid receptors. The patient will already be experiencing significant withdrawal symptoms, and any increase in withdrawal symptoms will be slight. Induction onto naltrexone can thus be accomplished early and without marked increase in symptoms. However, precautions must be followed, as if the level of circulating morphine is higher than expected, a severe reaction may ensue.

Rapid detoxification – Summary

- Rapid detoxification appeals to many people, particularly at the time when their drug use is out of control, and they feel helpless and fearful, and are strongly motivated to achieving long-term abstinence.
- At such times, patients – knowing the likelihood of relapse during conventional detoxification – perceive that rapid detoxification as an opportunity to commit to detoxification, to complete the process quickly and with the greatest likelihood of successfully reversing neuroadaptation.
- In order to minimize the medical risks associated with rapid detoxification, and reduce the severity of symptoms following acute withdrawal, it is desirable to delay the procedure until withdrawal is established. Performed after a suitable delay, there is no need for anaesthesia, and induction onto naltrexone can be performed without the need for an intensive care level of support.
- As with any treatment for dependency problems, the people most likely to benefit from naltrexone treatment are those with good social supports – a stable relationship, employment, stable accommodation – and good psychological functioning. Patients in unstable social circumstances, and those with significant psychological impairment, are probably better managed in agonist maintenance programs.
- The combination of careful assessment and patient selection, repeated explanation of the procedure, provision of symptomatic relief based on clonidine and octreotide, and good nursing support, enable induction onto naltrexone to be accomplished straightforwardly.
- As a precaution against people who have used opioids shortly before induction (despite warnings not to do so), the capacity to retain people as in-patients is essential to perform this procedure safely.
- Intensive follow-up is a critical component of optimizing the benefits of rapid detoxification.
- All patients must be warned of the risks of opioid overdose on discontinuing naltrexone.

RAPID DETOXIFICATION PROTOCOL

Assessment

Best practice in detoxification involves comprehensive assessment of patients prior to treatment (NSW Detoxification Clinical Practice Guidelines, 1999). The aims of the assessment interview are:

1. To foster a therapeutic relationship by empathic and respectful listening and questioning
2. to clarify why the patient has presented, the nature and severity of their problems, and the nature of their social and emotional supports
3. to reflect back this assessment information, and provide information on treatment options
4. to develop a treatment plan.

Assessment also collects relevant information, and needs to document:

- medical and psychiatric history
- drug use history
- current circumstances
- motivation and goals, reason for seeking treatment
- discussion of treatment options
- treatment plan
- informed consent

It is useful to ask patients about their prior experience of withdrawal, which symptoms they found most difficult, and what their expectations are about withdrawal.

A medical practitioner should assess patients prior to settling on rapid detoxification as the treatment plan. Medical assessment of patients seeking rapid detoxification should include:

history of significant medical and psychiatric conditions
physical examination of the cardiovascular and respiratory systems
examination for signs of liver disease
signs of intoxication, withdrawal, and vein damage
mental state examination.

Blood screening may be performed if clinically indicated. A urine drug screen can be of value in confirming self-reported drug use – particularly, in screening for benzodiazepine or stimulant abuse, and in identifying patients who are using “street” methadone.

A critical part of developing a treatment plan involves providing information about treatment options, exploring patient’s responses, in order to make a realistic choice as to how to proceed. **Providing accurate information beforehand is an important aspect of helping patients to deal with withdrawal.** It is desirable that written information be available.

Treatment plan

Rapid detoxification is appropriate option for opioid-dependent patients who;

- have no contraindications,
- have been informed of the nature of the treatment and of treatment options,
- in whom there are no contraindications,
- express a wish to undergo the treatment.

Contraindications to rapid detoxification are:

1. pregnancy
2. a history of cardiac disease, or evidence of heart disease on clinical examination,
3. chronic renal impairment
4. decompensated liver disease – jaundice and/or ascites, hepatic encephalopathy
5. current dependence on benzodiazepines, alcohol, or stimulants
6. history of psychosis

Relative contraindications to rapid detoxification are:

1. History of treatment for depression (needs psychiatric assessment prior to naltrexone)
2. Unstable social circumstances – patients who are homeless or in highly unstable social circumstances require a comprehensive plan to stabilize their circumstances preceding their undergoing rapid detoxification

Patients dependent on heroin (and who have not used methadone within the last 2 weeks) need to complete 48 hours opioid-free before undergoing rapid detoxification. Patients who have used methadone need to have 7 days opioid-free before the procedure. **Failure to observe these intervals can lead to severe withdrawal reactions and serious complications.** It is not acceptable to compromise safety in the hope of a good outcome.

Rapid detoxification is not an end in itself, but should be part of an ongoing treatment plan – usually, naltrexone maintenance. Follow-up arrangements should be discussed prior to embarking on detoxification. Ongoing treatment with naltrexone is covered in Interim National Guidelines.

Informed Consent

For subjects choosing to undergo rapid detoxification, a careful explanation of what is involved should be given. Written information should be supplied as well. Signed consent to treatment should be obtained. A sample consent form is included as appendix B.

In patients seeking to withdraw from methadone, it is both courteous and necessary for safety to discuss the patients planned treatment with their methadone doctor or clinic. **There have been incidents when failure to do this had a fatal outcome.**

Some patients attending for rapid detoxification request to have a support person present during the procedure. In general, this is probably a helpful thing.

Initiating treatment - days 1 and 2

Treatment setting – in-patient or out-patient

Rapid detoxification as outlined in this protocol can be performed in ambulatory patients in a day-patient setting. However, it is recommended that most patients spend two days as in-patients prior to induction. In particular, in units with limited experience with this procedure, all patients should be managed as in-patients, until staff have become familiar with the procedure.

If a patient indicates a preference for rapid detoxification, and gives informed consent, the first decision is whether the patient will:

- begin an ambulatory detoxification, attending daily for medications and support
- undertake residential detoxification.

This choice is not final - patients who start out doing an ambulatory detoxification, but find that they continue heroin use, can be admitted to a residential facility, while those who cannot tolerate residential treatment and would prefer to be at home can be discharged to continue on an ambulatory basis. Even with symptomatic withdrawal medication, many ambulatory patients are unable to abstain from opioids for 48 hours. Such people can be admitted to a residential detoxification unit for the drug-free interval prior to rapid detoxification.

Induction onto naltrexone must be performed in a setting in which there is nursing and medical care on site. **In all cases, the setting must be one in which there is the option of keeping people overnight in the event of a significant withdrawal reaction.** Indeed, even in patients who do not have a serious withdrawal reaction, remaining in a residential setting overnight after commencing on naltrexone probably helps enhance compliance early in treatment.

Medication while awaiting rapid detoxification

Opioids must be entirely avoided in the interval prior to rapid detoxification.

During this opioid-free interval, patients can be treated with clonidine and other symptomatic medications as needed to minimize withdrawal distress.

Clonidine is used in doses up to 300ug (2 tablets) 8th hourly (6 tablets daily is maximal). Clonidine helps control agitation and restlessness. However, the dose which can be employed is limited by side effects – most patients will become somewhat hypotensive, and should be warned of this risk. It is generally safest to start with a dose of 150ug (1 tablet) every 6 hours, monitoring the symptomatic response and the patients blood pressure. Clonidine should be withheld if the systolic blood pressure falls below 90 or patients complain of lightheadedness. Doses as low as 75ug (1/2 tablet) 4-6th hourly can help relieve withdrawal distress.

- Quinine sulphate (300mg bd) can be helpful in patients with muscle cramps.
- Maxolon 10mg (1 tablet) 3 times daily can help control nausea and vomiting.

Many patients complain of insomnia during withdrawal, and it is customary to use a short-acting benzodiazepine – usually, temazepam 20mg – if this is distressing. However, insomnia is common on commencing naltrexone, and it is more useful to reserve the use of benzodiazepines to the first 2 nights of naltrexone treatment.

Medications should not be given as a prescription, but should be dispensed daily to patients during the lead up to rapid detoxification.

Rapid detoxification – day 3

(Although scheduled for day 3, rapid detoxification may occur on later days, depending on whether patients manage to abstain from opioids from the day they are first seen. For patients withdrawing from methadone, rapid detoxification should not occur until day 7, assuming the patient has successfully remained abstinent from opioids throughout that time.)

Re-assess and confirm suitability to proceed

1. The patient presents (or in the case of residential patients, is seen) in the morning
2. The procedure is again explained
3. The clinician confirms that the patient has been opioid-free for the required interval. (Despite warnings, some patients will use heroin, but deny doing so for a variety of reasons. This will occur both in ambulatory and in residential settings - despite the best efforts of staff, residential units can never be guaranteed “drug free”).
4. A urine specimen may be collected and tested by dipstick testing for opioids – if definitely positive, the detoxification should be deferred.

Naloxone (Narcan) challenge

Procedure

- Explain the test and the reason for performing it
- Intramuscular: 0.4mg, repeat another 0.4mg in 10 minutes if no reaction
- Intravenous: give 0.2 mg; if no reaction after 60 seconds, give further 0.6mg and observe for 5 minutes

Withdrawal signs should peak within 10 minutes:

- a) piloerection (palpable and lasting more than 30 seconds);
- b) rhinorrhoea, lacrimation, yawning (more than 3 times);
- c) sweating (wet rather than moist);
- d) vomiting

Piloerection is the most decisive withdrawal sign. Restlessness is also a feature of a positive naloxone reaction.

Interpretation

The naloxone challenge may be interpreted as positive (i.e. the patient is still physically dependent on opioids) if there is:

- a marked reaction to any one of (a), (b), (c) or (d)
- a milder reaction to any two of (a), (b), (c), or (d).

An alternative approach to interpreting the response to a naloxone challenge is to administer the Subjective and Objective Opiate Withdrawal Scales prior to naloxone, then repeat the scales at 10 and 20 minutes post naloxone.

A mild reaction - an increase of 2 points or less on the objective scale, or
 - an increase of less than 5 points on the subjective scale

Positive reaction - an increase >2 on objective or 5 or more on subjective scale

Response

- If there is a **positive** response delay induction, and plan to re-challenge after at least 24 hours. Reassure patient that discomfort will pass in 20 minutes. If there is a **severe** response, administer symptomatic medication and defer induction
- **If there is a mild response to naloxone, it is reasonable to proceed with induction**

Induction onto naltrexone

1. Administer 75-150ug clonidine (so long as pulse >60 and BP >90 systolic)
2. Administer 5mg diazepam
3. Administer 100ug (1 ampoule) subcutaneous octreotide
4. Administer 25mg (1/2 tablet) of naltrexone.
If a withdrawal reaction is going to occur, it will generally be 40-80 minutes after the administration of naltrexone. Occasionally, it is more delayed.
5. Patients should be observed for a minimum of 3 hours after administration of naltrexone. During this time, they should have observations performed every 30 minutes. If they are well, they can be discharged. (Alternatively, it may enhance their compliance to suggest that they remain in the detoxification unit overnight.)
6. Patients who are agitated or distressed at the end of 3 hours should remain under close observation, with regular observations and reassurance. Symptomatic relief is of some benefit. Clonidine may be administered if the patients pulse is above 55 and blood pressure is >90 systolic. Buscopan is helpful for abdominal cramps, and quinine for muscle cramps. On the evening after the procedure, Temazepam (20mg) may be given.
7. Thereafter, patients receive 50mg naltrexone daily each morning. Some patients experience side-effects and may need to be maintained on 25mg naltrexone daily.

Aftercare

Vigorous attempts to follow patients are indicated after rapid detoxification. Generally, patients should be seen daily for 3 days, then at weekly intervals.

There are many approaches to the delivery of aftercare. These include;

- Medical monitoring – regular review with the prescribing doctor, with monitoring of compliance, review of drug use, sometimes with urine testing to confirm self-report
- Counselling – regular scheduled counselling sessions have frequently been used
- Supervised dosing – a family member or friend supervises the daily administration of naltrexone, sometimes administering the tablet crushed to minimize the risk of the patient spitting it out.
- Self-help groups may be a valuable adjunct to people trying to maintain abstinence

These approaches to enhancing compliance are not mutually exclusive. There is no clear evidence as to which approach is most effective, but what is clear is that vigorous follow-up and support enhance the effectiveness of treatment.

Recommendations for monitoring patients on naltrexone are contained in the National Naltrexone Guidelines.

Suitability for rapid detoxification - summary

Criteria	Operational criteria & method of assessment
1. Opioid dependent individuals.	1.1 DSM IV criteria checklist 1.2 Examination for signs of drug use 1.3 Urine drug screen (optional)
2. 16 years of age or over.	2. Proof of identity. Patient who are 16 or 17 years old will need to be assessed by 2 practitioners.
3. If in methadone treatment, discuss with prescriber or clinic	3.1 Self-report 3.2 Confirmation from PSB
4 Not dependent upon, intoxicated or withdrawing from alcohol, BZDs or amphetamines. Dependent cannabis use is not an exclusion criteria.	4.1 Clinical history & examination. Drug use history
5. Not pregnant or breast feeding	5.1 Urine bHCG test at assessment using rapid urine test kits.
6. Social environment suitable	6.1 Assessment of social environment (in particular, client not homeless)
7. No active or unstable medical condition	7.1 Medical assessment 7.2 Blood tests if indicated
8. Able and willing to give informed consent	8.1 Clinician assessment

Ambivalent patients

Many patients are unable to make an immediate decision as to whether or not they wish to participate in rapid detoxification. It is important to take a long view, giving patients time to think about their options, rather than pressuring them to make a decision.

Who is most likely to benefit from naltrexone treatment?

In general terms, patients with good social supports (employment, relationship, family) and with fewer psychological difficulties (less comorbidity) appear to be most likely to benefit from naltrexone treatment.

RAPID DETOXIFICATION PROTOCOL - SUMMARY

Day 1: Comprehensive Assessment

⇒ establish opioid dependence
⇒ identify realistic treatment goals

Discuss treatment options

⇒ treatment plan
⇒ informed consent

Commence clonidine 75-150ug q6h
(May add) quinine 300mg bd, metoclopramide 10mg tds

Day 2: Review

Discuss symptoms and drug use over previous 24 hours
Rate intoxication and withdrawal
Discuss appropriate dose of symptomatic medications
Review treatment plan

Day 3/4: Review and induction

Discuss symptoms and drug use over previous 24 hours
Rate intoxication and withdrawal
Discuss proposed induction onto naltrexone, confirm consent

⇒ **if >48 from last opioid use, commence induction**
⇒ **if in doubt, wait another 24 hours**

Administer naloxone challenge

If reaction is mild (increase on OOWS <3), proceed with naltrexone induction

Induction

Administer clonidine 150ug
diazepam 10mg po
naltrexone 25mg po
octreotide 100ug sc

Observe for 3 hours. If well, may go home (or remain in residential unit – optional)

Thereafter, daily review for 3 days is recommended.

An alternate approach to induction onto naltrexone using buprenorphine

In 2001, the drug buprenorphine will be registered for use in Australia.

Buprenorphine will be available for use in both detoxification and maintenance. The relevance of this is that it is possible to perform a buprenorphine detoxification and initiate naltrexone treatment quite rapidly (indeed, at about the same point as in the rapid detoxification protocol outlined in this document).

National guidelines for the use of buprenorphine, and training programs for practitioners interested in using buprenorphine, are currently being developed. These provide important information about the distinctive pharmacology of buprenorphine. For further information, readers are referred to these documents.

The critical issue about buprenorphine is that it is a mu receptor agonist with high receptor affinity and low intrinsic activity. The high receptor affinity means that buprenorphine is not readily antagonised by naloxone or naltrexone, as it remains bound to receptors. In terms of induction onto naltrexone, this means that following buprenorphine treatment, naltrexone can be introduced earlier than after full opioid agonists, and can even be administered together with buprenorphine. When this is one, the result is a moderate withdrawal reaction, far less severe than the precipitated withdrawal noted when full opioid agonists are reversed.

There are two approaches to induction onto naltrexone using buprenorphine:

- Early introduction on day 3 of detoxification
- Late introduction on day 8 of detoxification

Sample dosing regimes for the two approaches are shown in the table.

Naltrexone induction regimes

Source: Dr Nick Lintzeris

Day	Sample buprenorphine regime (S/L tablets)	Early NTX induction regime (oral)	Delayed NTX induction regime (oral)
1	6 mg	0	0
2	10 mg	0	0
3	8 mg	12.5 mg	0
4	6 mg	12.5 mg	0
5	4 mg	25 mg	0
6		50 mg	0
7		50 mg	0
8		50 mg	0 or 12.5 mg
9		50 mg	12.5 mg
10		50 mg	25 mg
11		50 mg	50 mg

Both procedures result in an increased severity of opiate withdrawal following the first dose of naltrexone. Patients must be warned to expect this. Essentially, the two approaches represent a choice – whether to experience the peak withdrawal symptoms early during detoxification (day 3), when most patients still have residual symptoms, or to delay peak symptoms until day 8 (when most patients who have completed a successful detoxification feel fine).

The withdrawal symptoms associated with the first dose of naltrexone typically commence 90 minutes to 4 hours after the first naltrexone dose, peak around 3 to 6 hours after the naltrexone dose, and generally subside in severity within 12 to 24 hours. The withdrawal is frequently experienced as moderate to severe at its peak.

Subsequent doses of naltrexone produce considerably less severe withdrawal discomfort.

Most clients undergoing this procedure request symptomatic medication, and clonidine (100 to 150 mcgm every 3 to 4 hours as required) and a benzodiazepine (eg diazepam 5 mg 3 to 4 hourly, maximum of 30 mg, as required) should be prescribed. Most clients find either procedure tolerable, and whilst it can be conducted an outpatient settings, it should only be attempted under circumstances where there is a suitable and responsible person to support the client at home and to supervise medications, and the prescribing doctor is available to address any potential complications. Patients and their carers should be prepared in advance for the increase in withdrawal severity, the role of medications, and the risks of using heroin to overcome the withdrawal symptoms.

The potential advantages and disadvantages of each approach are summarized in the next table.

Comparison between early and delayed naltrexone induction (Source: Dr Nick Lintzeris)

	Early NTX induction regime	Delayed NTX induction regime
Potential advantages	Only 36 to 48 hours of abstinence from heroin use is required prior to first dose of naltrexone; hence more clients will get a first NTX dose	Allows more time for consideration and selection of optimal post withdrawal treatment options
	More rapid resolution of withdrawal discomfort: naltrexone precipitated withdrawal peaks early in withdrawal episode, following NTX dose, with resolution of most withdrawal symptoms within days.	Initial withdrawal episode is less severe for the client and less intensive for service providers
Potential disadvantages	Greater drop out reported after first NTX dose than in delayed induction regime	Some clients will drop out or resume heroin use prior to day 8 or 9 of withdrawal episode, and therefore not commence NTX
	May ‘rush’ some clients into NTX treatment, whereas other post withdrawal treatment (eg maintenance substitution treatment) may be preferred.	NTX precipitated withdrawal occurs later in the withdrawal episode (on day of first NTX dose)

Section 2: Literature Review of Rapid Opioid Detoxification

Update 1998-2000

Background

Several comprehensive reviews of Rapid Opioid Detoxification (ROD) and Rapid Opioid Detoxification under Anesthesia (RODA) were undertaken in response to a revived public, commercial and scientific interest in these techniques in mid 1990s (Mattick et al., 1998; O'Connor & Kosten, 1998). These reviews considered evidence from trials, research reports and clinical reports relating to rapid opioid detoxification procedures dating back to the early 1980s. These reviewers concluded that the literature was limited for the following reasons:

- small numbers of subjects evaluated;
- variation in protocols studied;
- lack of randomised designs and control groups;
- and description of only short term outcomes (O'Connor & Kosten, 1998)

The key recommendations of these reviews were that more rigorous research methods be used, that longer-term outcomes be investigated, and that comparisons be made with other methods of treatment for opioid dependence¹.

This review aims to examine the literature published subsequently to provide an up to date summary of the available evidence and clinical practice, and to highlight any issues raised by recent studies.

Review strategy

The electronic databases, MEDLINE and EMBASE were searched for published articles (1998 -2000 inclusive) without language restriction using the key words 'detoxification', 'naloxone', 'naltrexone', and 'opiate'. 69 publications were identified and assessed for their relevance. Included publications were assessed to have rapid detoxification using opioid antagonists as their primary subject matter. 21 studies, 13 letters to Journal Editors, three editorial/commentary articles, one Cochrane Systematic Review and Protocol, and one narrative review article were identified.

32 publications were excluded. Reasons included: reporting on naltrexone maintenance without rapid detoxification, use of buprenorphine (to be reviewed elsewhere), and publication in non-English Journals

¹ A considerable body of well-designed research investigating rapid detoxification using opioid antagonists has been undertaken in Australia in the past two years. Studies have taken place in Sydney, Canberra, Adelaide and Brisbane (ongoing). The relative effectiveness, safety and cost effectiveness of these research trials will be described by the National Evaluation of Pharmacotherapies for Opioid Dependence (NEPOD) project. The final NEPOD report will be delivered to the Commonwealth and jurisdictional governments in July 2001.

Cochrane Systematic Reviews

1. Opioid antagonists and adrenergic agonists for the management of opioid withdrawal (Gowing, Ali, & White, 2000a)

This review examined studies that met the following criteria:

- administration of an opioid antagonist in combination with an alpha2 adrenergic agonist;
- aim of the intervention was the modification of the signs and symptoms of withdrawal;
- participants with a primary diagnosis of opioid dependence;
- focused on the acute phase of withdrawal;
- reported details on drug type and dose and characteristics of participants;
- reported on nature of withdrawal symptoms, side effects or completion rates;
- and were randomised or quasi-randomised controlled clinical trials or prospective controlled cohort studies (less rigorous studies were considered for the narrative component of the review).

This review did not consider studies using anesthesia or deep sedation.

Nine studies were identified but only three studies (Gerra et al., 1995; O'Connor et al., 1997; O'Connor et al., 1995) met the analytical review criteria and a meta-analysis was not undertaken. A narrative review of these and the other six studies (Azatian, Papiasvilli, & Joseph, 1994; Bell et al., 1999; Charney, Heninger, & Kleber, 1986; Kleber, Topazian, Gaspari, Riordan, & Kosten, 1987; Merrill & Marshall, 1997; Vining, Kosten, & Kleber, 1988) was undertaken and yielded the following findings:

- Naltrexone is the most commonly used opioid antagonist used to precipitate withdrawal, with only one study using naloxone
- Naltrexone tends to be administered once a day, using an initial dose of 12.5mg on the first or second day of treatment
- Clonidine doses in the studies ranged from 0.1-0.3mg three times a day
- 5 out of 7 provided the treatment on an outpatient basis, but all provided extended care on the first day of naltrexone administration
- Severity of withdrawal with the naltrexone-clonidine combination is at least equivalent to withdrawal using clonidine only and more severe in the first few days of treatment
- The use of naltrexone-clonidine can result in good completion rates (75-95%), however one study had extremely low completion rates (7%) (Azatian et al., 1994)
- Common side effects were vomiting, diarrhea and delirium lasting several hours following the first dose of naltrexone. Data are insufficient to make reliable estimates of the rates of the occurrence of side effects.
- Methadone patients underwent treatment in 3 studies (mean dose range 32-46mg/day) and withdrawal severity was rated as moderately severe in all of these studies. Delirium was reported in most methadone patients in one study. Data is insufficient to form a view about the effectiveness of the approach for the management of methadone withdrawal relative to heroin or shorter acting opioids.

The authors made the following conclusions about the use of opioid antagonists and adrenergic agonists in the management of opioid withdrawal:

- It is feasible to induce withdrawal from heroin using naltrexone and combine it with clonidine to ameliorate the signs and symptoms of withdrawal.
 - There is insufficient information available to make conclusions about naloxone or use of the technique in the management of withdrawal from methadone.
 - Practitioners should prepare patients for the possibility of delirium following their first dose of naltrexone and the likelihood of moderate to severe symptoms despite medication.
 - Patients should be monitored closely for several hours following their first dose of naltrexone.
2. Opioid antagonists under sedation or anaesthesia for opioid withdrawal (Gowing, Ali, & White, 2000b)

This review is still to be completed and is currently only available as a protocol. The objective of this review is to assess the effectiveness of interventions involving the administration of opioid antagonists (i.e. naloxone, naltrexone, nalmefene) to induce opioid withdrawal with *concomitant heavy sedation or anaesthesia*.

Outcomes to be considered in the review will include intensity of withdrawal syndrome, duration of treatment, completion of withdrawal, occurrence of side effects, attendant risks, patient satisfaction, and costs. Only randomised and quasi-randomised controlled clinical trial and prospective controlled cohort studies will be included in metanalysis. Other studies will be discussed in the narrative component of the review.

Narrative review of studies (published 1998-2000)

Quality of studies

There are very few rigorous studies in the recent literature. Of the 21 studies identified, only three used random allocation (Gerra et al., 2000; Hensel & Kox, 2000; Kienbaum et al., 2000) and eight studies reported on a control group or cohort. The majority (14/21) consisted of prospective single group studies or case series. Moreover, only 10/21 studies report on any long-term outcomes relating to drug use (see Table 3).

Study sample size ranged from 1 to 120 with 80% of studies having sample sizes of 30 or less. The total number of patients in these studies was 641.

The majority of studies (17/21) were investigating RODA. Of these, almost half (9/17) were focused on physiological functioning and related indicators during the anaesthesia phase of withdrawal, for example, respiration rate (Hoffman, Berkowitz, McDonald, & Hass, 1998a; Hoffman, McDonald, & Berkowitz, 1998b) plasma catecholamines (Kienbaum et al., 2000; Kienbaum et al., 1998; McDonald, Hoffman, Berkowitz, Cunningham, & Cooke, 1999) cardiovascular stimulation (Allhoff, Renzing-Kohler, Kienbaum, Sack, & Scherbaum, 1999; Kienbaum et al., 2000; Kienbaum et al., 1998; Lorenzi et al., 1999), endocrine function (Pfab, Hirti, & Zilker, 1999) and monitoring techniques (Allhoff et al., 1999; Hensel, Wolter, & Kox, 2000).

Characteristics of patients

Type of opioid dependence was specified for 40% of patients. Of these 57% were methadone, 34% heroin, and 13% other opioids (e.g. morphine sulfate, codeine, L-methadone, hydrocodone, butorphanol tartrate, oxycodone, L-polamidone, dihydrocodeine).

Commonly cited exclusion criteria in these studies were:

- Pregnancy
- Other drug dependence, in particular benzodiazepines, alcohol, and amphetamines.
- Serious psychiatric or medical illness
- Conditions associated with anesthetic risk or a ASA physical status >II

There are a few reports of patients being assessed regarding their motivation to cease drug use (Cucchia, Monnat, Spagnoli, Ferrero, & Bertschy, 1998; Hensel & Kox, 2000; Lorenzi et al., 1999; Tretter et al., 1998) or only being considered for the study if they had failed conventional detoxification in the past (Cucchia et al., 1998; Tretter et al., 1998).

In some cases, all patients regardless of type of opioid dependence, were stabilised on methadone before rapid detoxification (Cook & Collins, 1998; Scherbaum et al., 1998; Tretter et al., 1998). Gerra et al (2000) stabilised patients with heroin, until 12 hours before treatment.

Detoxification Procedure

Types of detoxification protocols used can be broadly classified according the anesthetic used, the opioid antagonist/s administered, and adjuvant medications used to ameliorate withdrawal signs and symptoms.

In the case of ROD studies, sedation was induced using benzodiazepenes such as:

- midazolam - 45-120mg (Cucchia et al., 1998);
- flunitrazepam - 2mg followed by 1mg (Bell et al., 1999);
- diazepam - 30mg followed by 40-180mg (London, Paul, & Gkolia, 2000);
- oxazepam - 60mg followed by 60mg (Gerra et al., 2000)

Cucchia and colleagues noted that the doses of benzodiazepenes required were relative to the benzodiazepine tolerance of the patient. The reported duration of the acute phase of withdrawal ranged from 4 to 12 hours.

In the case of RODA studies, anesthesia achieved in the majority of cases using propofol, however some studies have used methohexital (Kienbaum et al., 2000; Kienbaum et al., 1998; Scherbaum et al., 1998). In a direct comparison of RODA using propofol with RODA using methohexital, Kienbaum and colleagues (2000) found that the propofol group recovered from anesthesia more quickly and were extubated significantly earlier than the methohexital group. In addition, Hensel and colleagues (2000) found that using EEG threshold monitoring to regulate depth of anesthesia compared with conventional clinical signs significantly reduced the dose of propofol, recovery time and objective withdrawal symptoms for the EEG monitored group.

Reported duration of anesthesia ranges from 6 to 22 hours with most reports between 6-8 hours. The length of anesthesia required also appears to vary for different patient types. Hensel & Kox (2000) compared the duration of anesthesia needed until patients responded negatively to the naloxone challenge test in heroin, morphine, codeine and methadone dependent patients. For methadone patients, the average duration of anesthesia was 325 minutes (SD=62) and this was significantly longer compared to that of the other groups ($p < .05$).

Typically naloxone is used to precipitate withdrawal followed by a dose/s of naltrexone. Some studies have used naloxone alone during the acute phase of the procedure (Gold, Cullen, Gonzales, Houtmeyers, & Dwyer, 1999; Lorenzi et al., 1999; Tretter et al., 1998) while others only administered naltrexone (Bell et al., 1999; Hensel & Kox, 2000; London et al., 2000) (Hoffman et al., 1998a; Hoffman et al., 1998b). Use of nalmefene was also reported in one study (Gold et al., 1999).

Muscle relaxants used in association with anaesthetic agents include rocuronium, atracurium, and cisatracurium.

Adjuvant medications

The most widely used adjuvant medication is clonidine. Other medications used include:

- Anti-emetics (e.g. ondansetron, metaclopramide, prochlorperazine)
- Anti-diarrheal agents (e.g. octreotide, loperamide – although this is an opioid and presumably ineffective when antagonists are used)
- Anti-inflammatory agents (e.g. ketorolac, diclofenac, ketoprofen)
- Anti-spasmodic agents (e.g. hyoscine, baclofen)
- Benzodiazepines (e.g. midazolam, oxazepam, flunitrazepam, lorazepam, temazepam)
- Lofexidine
- Buscopan (abdominal cramps)
- Quinine sulphate (leg cramps)
- Ranitidine, cisapride, omeprazole, famotidine (hyperacidity)
- Neuroleptics (e.g. chlorpromazine, perazine)
- Anti depressants (e.g. Trimipramine)
- Antibiotics (e.g. Ceftriaxone)
- Ant-coagulant (e.g. heparin)
- Fluids (e.g. Ringers lactate, potassium chloride)
- Chlorprothixene
- Chloral hydrate
- Butylscopolamine

Provision of aftercare

There is not a consistent approach to aftercare reported in the reviewed studies and there is limited description of intensity of care provided. Types of aftercare reported include:

- Individual counselling or psychotherapy (Cook & Collins, 1998; Gerra et al., 2000; Gold et al., 1999; Hensel & Kox, 2000; Rabinowitz, Cohen, & Kotler, 1998) .
- Group psychotherapy (Gerra et al., 2000; Scherbaum et al., 1998);
- Residential rehabilitation (Cucchia et al., 1998; Scherbaum et al., 1998);
- Contact with general practitioner (Cucchia et al., 1998; Tretter et al., 1998)
- Support at outpatient clinic (Bell et al., 1999; Gerra et al., 2000; London et al., 2000; Tretter et al., 1998);
- 12 step program (Gold et al., 1999).

Outcomes

Completion of detoxification

There are several definitions of successful completion of detoxification and ways of describing short-term outcomes. For the purpose of this review successful completion of detoxification is defined as induction onto naltrexone maintenance and/or completion of the detoxification protocol. As may be expected given the nature of the procedure, in the RODA studies described here, all patients were inducted on naltrexone and completed the detoxification protocol.

In the ROD studies, the majority of patients were inducted on to naltrexone, 100% (Cucchia et al., 1998; London et al., 2000) to 80% (Bell et al., 1999) to 75% (Gerra et al., 2000).

In terms of rates of induction to naltrexone compared with other forms of detoxification, Gerra and colleagues (2000) randomly allocated patients to detoxification using clonidine and naltrexone, clonidine alone, and 10-day methadone tapering. 75% of the clonidine-naltrexone group commenced naltrexone maintenance which was significantly higher than those commencing naltrexone in the clonidine group (53.1%, $p < .05$) and methadone-tapering group (26.4%, $p < .01$).

Withdrawal severity

11/21 studies reported some form of standard measurement of withdrawal severity. The measure/s used and time intervals vary widely across studies making meaningful comparison difficult. It does appear, however, that in the majority of studies the peak withdrawal severity is approximately 2 hours after first antagonist administration and over the course of that day. In addition, withdrawal signs and symptoms do not return to baseline levels for at least 24 hours and up to 28 days after detoxification. Also withdrawal severity as measured here, does not appear to be systematically greater for methadone patients compared with patients detoxifying from shorter acting opioids. The measure used and the outcomes are described in Table 1.

Table 1: Withdrawal severity

Study	Type	Measure used	Outcomes
Cucchia et al, 1998	ROD Deep sedation	13 items presence/absence symptoms checklist t = 30,60,90,120, 150,180,210, 240 minutes and 5,6,7,8, 10, 12, 16, 18, 24 hours	Peak severity at t=1 hour and remained significantly elevated compared to baseline for 24 hour measurement period
Scherbaum et al 1998	RODA	Modified 10-item version of Short Opiate Withdrawal Scale and Subjective Opiate Withdrawal Scale. T= Baseline Day -5 and-1, Days 1-14, and twice weekly in Weeks 3 and 4.	Short Opiate Withdrawal Scale - Peak severity on Day 1, with scores significantly ($p<.05$) higher than baseline though to Day 7, and still not returned to baseline by Day 28. Significant positive correlation between methadone dose and objective withdrawal symptoms at baseline and 3 and 4 weeks post procedure No differences found on subjective withdrawal
Bell et al, 1999	ROD Light sedation	Objective and subjective withdrawal scales, and patient rating of severity and acceptability of withdrawal 4 hourly. Subjective withdrawal was not recorded in the acute phase and delirium, a prominent symptom, was not measured on either these scales	Objective withdrawal peaked 2 hours after naltrexone administration. Scores decreased within 12 hours and at 24 hours post naltrexone, the median score was 0 (range 0-6). At 24 hours post naltrexone, subjective withdrawal ranged from 0-42 with a median of 23 (max score =64) where 42 is quite severe. No significant differences between methadone and heroin patients in terms of objective and subjective withdrawal Majority of patients rated withdrawal episode as moderately to extremely severe but moderately to completely acceptable
Gold et al, 1999	RODA	Clinical Institute Narcotic Assessment (CINA) withdrawal scale (range 0-31) Measured before detoxification, after emergence and after naloxone challenge.	64% experienced mild withdrawal symptoms (scores between 1-4) 30% showed no signs or symptoms withdrawal. No significant difference in CINA scores across the measurement occasions.

London et al, 1999	ROD Light sedation	Symptoms rated by nurse (present, absent, severe) at 30 and 60 minute intervals for 12 hours after detoxification commenced according to following criteria 1. achievement of symptom control = symptom absent in 90% or more observations 2. Failure to control symptoms = present or severe in 10% or more observations	Restlessness not controlled in 92% of patients Good control of vomiting and diarrhea in 70% and 55% of patients respectively. Severe symptoms above 10% criterion occurred in 20% of patients
Lorenzi et al 1999	RODA	Wang Scale modified for anesthesia based withdrawal, rating of objective signs and symptoms of withdrawal (present, absent) at prior to anesthesia, before infusion of naloxone, and hourly for 5 hours, at emergence, and next day after naloxone challenge test	Peak withdrawal scores two hours after administration of naloxone. After 3 hours withdrawal was considerably reduced. No patient showed withdrawal signs upon emergence from anesthesia, however the naloxone challenge test the following day did evoke a significant withdrawal syndrome (p<.005)
Pfab et al, 1999	RODA	Objective and subjective symptoms measured until urine free of drugs and patients reported no withdrawal symptoms.	All patients experienced moderate to severe withdrawal symptoms and no detoxification was finished within 48 hours.
Gerra et al, 2000	ROD Light sedation Compared with clonidine and methadone detoxification regimes	5 point scale rated by observer ranging from no symptom present to very severe every 24 hours during detoxification period (2-3 days) and following 5 days Craving and mood also measured	Withdrawal signs peaked on day 2 but were slight and transient withdrawal symptoms and easily managed with clonidine Significantly lower percentage of heroin catabolites in urine controls, lesser craving, less mood problems, higher compliance in extended naltrexone treatment compared to the other groups
Hensel et al 2000	RODA +- EEG monitoring depth of anesthesia	Objective Symptom scale.	EEG monitoring group significantly lower scores on symptom scale (p<.01)

Hensel & Kox, 2000	RODA	Objective and subjective opiate withdrawal scales (OOWS and SOWS) measured baseline 6hs after detoxification treatment, 1 st , 2 nd , and 3 rd day after detoxification and day of discharge.	Peak withdrawal severity pre-procedure. Methadone patients significantly greater severity of subjective and objective withdrawal scores from baseline to day two and three respectively compared to heroin, morphine, and codeine patients (p<.05)
Kienbaum et al, 2000	RODA Comparing propofol and methohexital anesthesia	Modified 10 item Short Opioid Withdrawal Scale (range 0-20) measured 1 and 5 days prior to admission, day 1,2, 3,4,5,6,7, 10, 14,21,28.	Peak withdrawal severity day 1 and significantly higher than baseline scores up to Day 14 for both groups (p<.05). Withdrawal severity significantly less for propofol group from day 10 to 28 (p<.05)

Days in hospital

All of the studies reviewed here were conducted on an inpatient basis except for Gerra et al (2000). The withdrawal syndrome in many cases was quite protracted and is reflected in the duration of stay in hospital. Reported length of inpatient stay ranges from 24 hours to 8 days with a median of 3-4 days. Length of inpatient stay does not appear to be systematically different for ROD patients compared with RODA patients. However, length of inpatient stay tends to be longer for patients on methadone compared with shorting acting opioids (Bell et al., 1999; Hensel & Kox, 2000). In many cases, patients undertaking these procedures are not well enough to go home until 2-3 days after the procedure. Please refer to Table 2 for an overview of study type, patient type and the duration of inpatient stay.

Table 2: Duration of inpatient stay

Study	Type	Type of patient	Duration of inpatient stay
Cucchia et al, 1998	ROD Deep sedation	17 methadone 3 Heroin	1.5 days >1.5 days for 20% of patients
Scherbaum et al, 1998	RODA	22 Heroin and methadone, proportion not specified	Average of 8 days
Tretter et al, 1998	RODA	8 Methadone 4 codeine 2 L-methadone	2-4 days
Bell et al, 1999	ROD Light sedation	15 Heroin 15 methadone	1 day- 73% heroin - 47% methadone 2 days- 26% heroin - 33% methadone ≥3 Days - 20% meth
Gold et al, 1999	RODA	10 Heroin 5 Methadone 3 Hydrocodone 1 Butorphanol tartrate	1 day - 30% 1-2 days - 35% 2-3 days -20% 3-4 days -15%
London et al, 1999	ROD Light sedation	N=20 Patient type not specified	5-7 days
Lorenzi et al, 1999	RODA	7 Heroin 5 Methadone	1.5 days
Albanese et al, 2000	RODA	120 Heroin, Methadone, and other opioids. Proportion not specified	2-4 days
Gerra et al , 2000 (outpatient)	ROD Light sedation	98 Heroin	2-3 days ROD group compared with 5 days clonidine group 10 days methadone tapering
Hensel & Kox, 2000	RODA	32 Methadone 25 Heroin 8 Codeine 7 Morphine	Average - intensive care unit 1.9 days methadone 1.75 days morphine 1.6 days heroin 1.6 days codeine
Kienbaum et al, 2000	RODA	25 Methadone	4-6 days

Long term outcomes

Only 10/21 studies investigated long term outcomes, ranging from 8 days to 18 months. The time of follow-up occasion, the method used and outcomes reported varied greatly across studies and are summarised in Table 3 below.

Compliance with naltrexone maintenance tends to be poor and reported relapse rates high, with most individuals relapsing to heroin use in the first 1-2 months after detoxification. The percentage of individuals who were abstinent or had not lapsed to regular heroin use at 3 months ranged from 25-67%, at 6 months ranged from 20%-55%. There do not appear to be differences in long term outcomes between ROD and RODA patients.

It is noteworthy that 'abstinence' and 'relapse to drug use' are not consistently defined and that most outcomes are based on self report of the patient alone, and in some instances corroboration by significant other/family members.

There is little information available on relative relapse rates in the reviewed studies. Gerra and colleagues (2000) report similar relapse rates at 6 months between naltrexone-clonidine (47%) and clonidine (56%) detoxified patients. 74% of methadone tapering patients, had returned to heroin use. Laheij et al (2000) report on abstinence rates at 3 months, with 67% of RODA patients 'cured' and compared with 33% of the methadone tapering group.

Table 3: Long term outcomes

Study	N	Follow-up occasions	Method	Outcomes
Cook & Collins (1998)	1	11 months	Clinical interview	'physically well and free of opioids'
Cucchia et al (1998)	20	6 months	Not specified	80% had relapsed to heroin use at 6 months with 75% relapsing within the first month. If intermittent use while on naltrexone maintenance is excluded as relapse, only 12 patients relapsed. 9 re-entered methadone maintenance
Rabinowitz et al (1998)	120 37 lost to follow-up	12 months	Telephone interview with patients and significant other/family member	Relapse defined as period of routine use with at least 2 weeks of daily use 36 (43%) relapsed, with over half these relapses occurring in the first 2 months. 14 reported episodic use of heroin.

Bell et al (1999)	30	8, 35, 63, 91 days	Regular telephone and in person clinical contact with patients. Research interviews on Day 35 and 91	<p>Day 8, 24(80%) taking naltrexone.</p> <p>Day 35, 17(57%) taking naltrexone</p> <p>Day 63, 7 (23%) taking naltrexone</p> <p>Day 91, 6 (17%) taking naltrexone with 4 occasionally using heroin; 5 patients who stopped naltrexone claimed to be opioid free for a 28 day period, verified by urinalysis.</p> <p>8 patients underwent repeat procedures.</p> <p>11 returned to methadone maintenance 7 relapsed to heroin use 1 died of an overdose</p>
Gold et al (1999)	20	Up to 18 months	Telephone interviews with patient and significant other/family member	<p>2 in opioid treatment for chronic pain 3 abstinent 4 abstinent, but experienced relapse within 1 month to a year after discharge 2 lost to follow-up 3 in methadone maintenance 4 returned to active heroin use 1 fatal overdose</p>
London et al (1999)	20	3 months	Clinical interview and random urinalysis	<p>5(25%) opiate free 1 using intermittently 7 returned to dependent use 7 lost to follow-up</p>
Albanese et al (2000)	120	6 months	Patient self report	<p>61 (55%) abstinence or a single lapse 18 relapses –10 within 8 weeks post procedure 9 lost to follow-up</p>
Gerra et al (2000)	98	6 months	Urinalysis	<p><u>Clonidine Group (32)</u> 18 relapsed (7 had entered naltrexone maintenance)</p> <p><u>ROD Group (32)</u> 15 relapsed (9 had entered naltrexone maintenance)</p>

				<u>Methadone Tapering Group(34)</u> 25 relapsed (9 had entered naltrexone maintenance)
Hensel & Kox (2000)	72	1 week, 3,6,9,12 months	Telephone interview with patients, general practitioners, and next of kin. Random monthly urine screens.	At 12 months: 49 (68%) were abstinent 17 relapsed, 12 in the first two weeks(of these 3 returned to methadone maintenance) 6 lost to follow-up
Laheij et al (2000)	30	3 months	Not specified	RODA group (15) 67% abstinent at 3 months Methadone Tapering Group(15) 8 (53%) completed detoxification 5 (33%) abstinent at 3 months

Associated side effects and adverse events

The side effects associated with rapid detoxification procedure include:

- Cardiovascular stimulation (Kienbaum et al., 1998)
- QT prolongation (Allhoff et al., 1999)
- Bradycardia and/or hypokalemia (Allhoff et al., 1999; Hensel & Kox, 2000; Scherbaum et al., 1998)
- Low body temperature (Cook & Collins, 1998; Scherbaum et al., 1998)
- Severe vomiting (Albanese et al., 2000; Bell et al., 1999; Cucchia et al., 1998)
- Diarrhea (Cucchia et al., 1998; Hensel & Kox, 2000; Tretter et al., 1998)
- Dysphoria (Bell et al., 1999; Cucchia et al., 1998; Tretter et al., 1998)
- Protracted withdrawal symptoms and prolonged hospital stay (Cucchia et al., 1998; Scherbaum et al., 1998; Tretter et al., 1998)
- Anesthetic complications (e.g. prolonged intubation and recovery) (Scherbaum et al., 1998)
- In ROD procedures, acute confusional state and disorientation, restlessness and limited memory of events for first 6-12 hours (Bell et al., 1999; London et al., 2000)
- Mild but persistent hypotension (Hensel & Kox, 2000)
- Suppression of thyroid hormones (Pfab et al., 1999)

Adverse events reported in the identified studies include:

- Bigeminal cardiac arrhythmia (Albanese et al., 2000)
- Pulmonary failure (Pfab et al., 1999)
- Renal failure, 2 cases (Pfab et al., 1999)
- Partial subclavian vein thrombosis related to central venous catheterisation requiring 2 week hospitalisation (Kienbaum et al., 2000)

- Increase in serum transaminases 7 days post procedure and diagnosis of Hepatitis B despite previously normal serology (Scherbaum et al., 1998)
- Severe aesthenia which resolved with termination of naltrexone (Albanese et al., 2000)
- Psychotic episode post procedure requiring halperidol (Albanese et al., 2000)
- Death, 41 hours post-procedure still on ward, cause not specified [Gold, 1999 l#67]
- Suicide attempt on Day 3 post procedure (Albanese et al., 2000)
- Suicide attempt on Day 5 post procedure (Cucchia et al., 1998)
- Fatal overdose, 5 weeks post discharge, three weeks after ceasing NTX maintenance (Bell et al., 1999)
- 2 non-fatal overdoses, after misjudging post NTX cessation tolerance (Bell et al., 1999)

Issues

The review period yielded several editorial and commentary articles. Some of the issues raised include:

- Importance of RODA being undertaken by anesthesiologists in intensive care settings (Gevirtz, Subhedar, & Choi, 1998; Justins, 1998)
- Importance of using an adrenergic agonist such as clonidine during RODA to avoid hyperadrenergic crisis and pulmonary oedema (Gevirtz et al., 1998; Gevirtz, Subhedar, & Choi, 1999)
- Concern that the pharmacological basis of rapid detoxification remains to be clarified (Spanagel, 1999)
- Inadequate description of post detoxification symptoms (Kleber, 1998)
- Objective verification of outcomes lacking (Kleber, 1998)
- Concern about safety (Gaughwin, 1999)
- Concern about unethical promotion of RODA (Brewer, 1998)
- Importance of post detoxification care and treatment plan/options (Kleber, 1998)

Cost effectiveness

Laheij et al (2000) compared the costs of RODA and a methadone-tapering program. The average intention to treat cost of RODA was US\$5850 compared with US\$4230 for the methadone-tapering program. However, the average cost per treatment success where success is defined as completing detoxification was US\$8775 for RODA and US\$12,685 for methadone tapering.

CONCLUSIONS

- The quality of research evidence has not improved greatly over the last two years.
- The majority of studies have involved RODA rather than ROD.
- Rapid detoxification techniques appear to be quite successful in achieving favourable short term outcomes with the majority of patients being inducted onto naltrexone or completing the detoxification protocol.
- Rapid detoxification is not particularly rapid. Withdrawal signs and symptoms can be severe and persist for several days after detoxification with most patients spending between 2-4 days in hospital. Persistent withdrawal in the first month was noted in some studies.
- While there was a wide range of reported outcomes, the majority of studies reported high rates of relapse to heroin use and poor compliance with naltrexone maintenance.
- There are considerable risks and adverse events associated with rapid detoxification techniques.

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Appendix A – Subjective withdrawal scale

INSTRUCTIONS : Please score each of the 15 items below according to how you feel **NOW**. Place a tick (✓) in the appropriate column. Only one tick per question. Use the scoring values as provided. Obtain the total score by adding the score given for each item. Please answer all items.

Patients name _____

A. TIME OF FORM COMPLETION |__| |__| : |__| |__| AM / PM B. FORM NUMBER:

1 2 3 (circle)

SUBJECTIVE OPIATE WITHDRAWAL SCALE

ITEM	0 Not at all	1 A Little	2 Moderate	3 Quite a Bit	4 Extreme
I feel anxious					
I feel like yawning					
I am perspiring					
My eyes are teary					
My nose is running					
I have goosebumps					
I am shaking					
I have hot flushes					
I have cold flushes					
My bones & muscles ache					
I feel restless					
I feel nauseous					
I feel like vomiting					
My muscles twitch					
I have stomach cramps					
I feel like using now					
Column Scores					
Total Score					

Appendix A – Objective withdrawal scale

OBJECTIVE OPIOID WITHDRAWAL SCALE

Patients name _____

INSTRUCTIONS : This form is to be completed by a member of clinical staff. Give a score for each of the observations (No.s 1 - 13) according to the scoring values for each given observation and how the client appears within a 5-10 MINUTE OBSERVATION PERIOD. Add up the total score for all of the observations to get the overall withdrawal score for each administration of naloxone.

Observations	Scoring	Score 1	Score 2	Score 3
1. Yawning	0 = no yawns 1 = > 1 yawn			
2. Excessive nasal discharge	0 = < 3 sniffs 1 = > 3 sniffs			
3. Goose flesh (observe arm)	0 = absent 1 = present			
4. Perspiration	0 = absent 1 = present			
5. Watery eyes	0 = absent 1 = present			
6. Tremor	0 = absent 1 = present			
7. Pupil dilation	0 = absent 1 = > 3mm			
8. Hot and Cold Flushes	0 = absent 1 = shivering / huddling for warmth			
9. Restlessness	0 = absent of position 1 = frequent shifts			
10. Vomiting	0 = absent 1 = present			
11. Muscle twitches	0 = absent 1 = present			
12. Abdominal cramps	0 = absent stomach 1 = Holding			
13. Anxiety	0 = absent 1 = mild – severe			
TOTAL SCORE				

Appendix B

(Name of Centre)

CONSENT FOR RAPID DETOXIFICATION

This form is designed to explain rapid detoxification as it is performed at(Insert Name).

Rapid detoxification is a way of coming off heroin and getting onto naltrexone. The usual way to manage heroin withdrawal is to give clonidine. Heroin withdrawal symptoms usually last about 5 days. After 7-10 days without opioids, they are able to start on the drug naltrexone, a drug which blocks opioid drugs.

The treatment we are offering you is “rapid detoxification”, in which naltrexone is introduced on the third day of detoxification, causing a more intense withdrawal on that day. You are being offered rapid detoxification because you have expressed an interest in withdrawing from heroin and seeking to go onto naltrexone treatment. Naltrexone is not registered in Australia for the purpose of rapid detoxification.

Administered to someone dependent on heroin (someone who has a habit), naltrexone can produce a severe withdrawal reaction. Untreated, this can be very dangerous. The basis of rapid detoxification is to administer naltrexone to shorten withdrawal, while giving drugs to lessen the severity of withdrawal symptoms. Previous studies demonstrate that patients can undergo rapid detoxification from heroin and safely commence naltrexone maintenance within 2-3 days.

If you wish to proceed with this treatment, you will be interviewed and examined to confirm that you do not have any medical reason which would make the procedure unsafe - (such as pregnancy, serious psychiatric illness, heart disease). You will be asked to complete an interview about your health, drug use, and psychological state. This interview takes about 40 minutes. If you are already showing signs of withdrawal, you will be commenced on clonidine immediately. Before the rapid detoxification, you will be examined by a doctor to confirm you do not have any health problems which would make the procedure risky. The doctor will also examine you to check that you do not have any underlying medical problems.

In order to carry out rapid detoxification, you need to be free of all opioid drugs for a minimum of 48 hours, otherwise withdrawal reactions can be severe and prolonged. (If you have been using methadone, you need to be opioid-free for 7 days before induction onto naltrexone.) In order to get through the 48 hours, you will be given symptomatic medication – clonidine, and other drugs as needed. You may be treated on an out-patient basis, attending the centre daily to see your case worker and receive medications. Alternately, you may be admitted to a detoxification unit and be treated as an inpatient. You can discuss which option is most suitable with your case manager.

Once you have gone 48 hours with no opioids (no heroin, morphine-, codeine-, doloxene-containing drugs), you will be asked to attend in the morning for rapid detoxification. You will be reviewed by a doctor, who will confirm whether you are ready for the procedure, and that you wish to proceed. If you do, you will be given doses of clonidine and octroside (a drug to reduce nausea and vomiting). After a small delay,

you will be given an injection of naloxone (Narcan). If this produces a marked withdrawal reaction, it is not wise to proceed to naltrexone. Nursing staff will monitor your reaction, and discuss with you whether to proceed to naltrexone.

If your reaction to naloxone is not severe, 1/2hour later you will be administered 1/4 tablet of naltrexone. This will cause withdrawal symptoms, which will last a couple of hours. Mostly, the symptoms are mild, and if you are well you can go home that afternoon, returning to the Centre next morning for review. Alternatively, you have the option of remaining in the detoxification unit for one further night.

The risks associated with naltrexone are that withdrawal will be severe, with vomiting, diarrhoea, and great discomfort. Occasionally, patients become confused or aggressive during accelerated detoxification. High doses of naltrexone can cause liver damage, but the doses used in this study have not caused liver damage. Among people who discontinue naltrexone, there is increased sensitivity to opioids and an increased risk of death by accidental overdose. As many as 10% of people prescribed naltrexone are at risk of overdose death in the ensuing 12 months.

Clonidine lowers the blood pressure, and makes people feel tired and sometimes light headed. If your blood pressure becomes too low, the clonidine is withheld. Octreotide is a drug which controls nausea and vomiting, and appears to have few side-effects.

If you wish to remain on naltrexone, you will have to pay the cost of further medication.

CERTIFICATION BY DOCTOR AND PATIENT

I hereby certify that I have disclosed the risks that may be involved, in terms readily understood by the patient.

Date

Signature of Doctor

CONSENT BY PATIENT

I hereby certify that I have read and understood all the information provided, have been given the opportunity to ask any questions and agree to undergo the procedure of rapid detoxification described above.

Date

Signature of Patient

Signature of Witness:

Nature of Witness:
