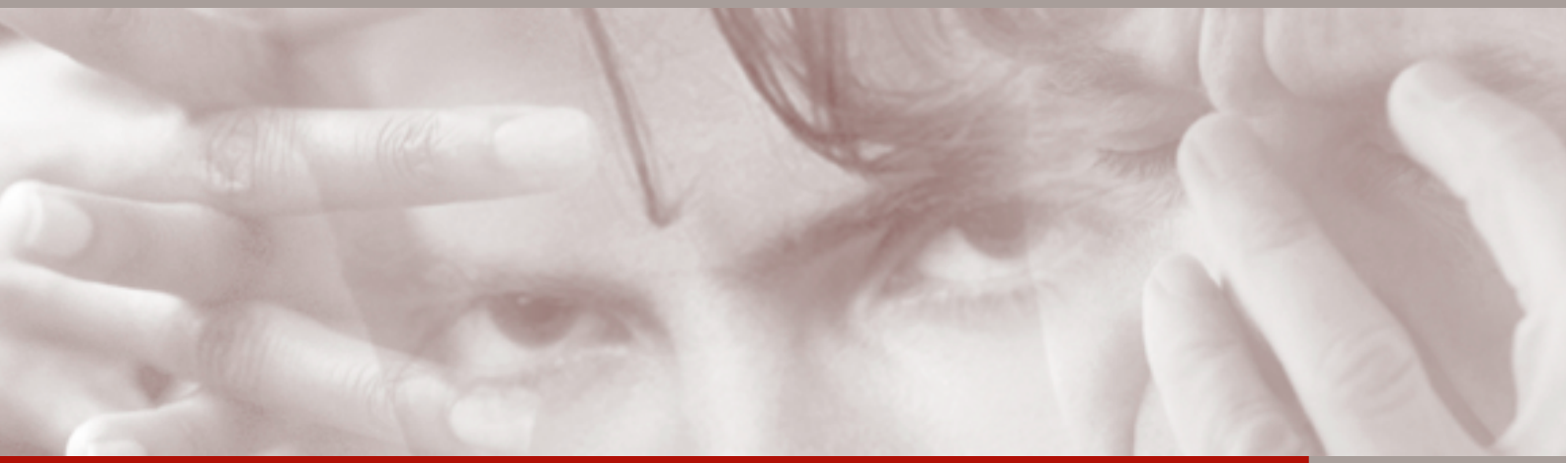
Australian Government

Clinical Guidelines and Procedures for the Use of Naltrexone in the Management of Opioid Dependence



National Drug Strategy

Clinical Guidelines and Procedures for the Use of Naltrexone in the Management of Opioid Dependence

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Introduction

Naltrexone was first used in the treatment of opioid dependence in the USA in the 1970s. However, because there was seen to be only a small demand for the drug, it was not initially registered for use in Australia. During the 1990s, there was an increase in the prevalence of opioid dependence, and increasing interest in using naltrexone. A number of medical practitioners began using the Special Access Scheme (which under certain circumstances allows the prescribing of unregistered drugs) to use naltrexone. Results of the first Australian clinical trial of naltrexone in the management of opioid dependence were published in 1998. In 1999, the drug was registered for use in Australia.

These clinical guidelines have been prepared to aid medical practitioners in the selection and management of patients seeking treatment with naltrexone hydrochloride for management of opioid dependence and to assist medical practitioners to provide patients with accurate information concerning naltrexone.

These clinical guidelines cover the use of naltrexone in the management of opioid dependence – in both relapse prevention and in withdrawal. The approach taken in developing these guidelines was to review published evidence, paying most weight to appropriately controlled trials. Strong research evidence is not available on many issues, and clinical consensus from a panel of experienced clinicians has been employed in developing these guidelines.

The guidelines were prepared under the auspices of the National Expert Advisory Committee on Illicit Drugs (NEACID) in collaboration with the National Evaluation of Pharmacotherapies for Opioid Dependence (NEPOD) project, the Royal Australian College of General Practitioners (RACGP) and the Australian Professional Society on Alcohol and Other Drugs (APSAD), and are funded by the Commonwealth Department of Health and Ageing.

These clinical guidelines are based on international research literature and clinical experience with the use of naltrexone in Australia. The material presented has undergone a rigorous process of review and has been formally endorsed by the RACGP and APSAD.

The contribution of various individuals and organisations in the drafting and review process is gratefully acknowledged.

Commonwealth Government and State Governments support for the National Evaluation of Pharmacotherapies for Opioid Dependence (NEPOD) project allowed extensive clinical and research experience of naltrexone, and underpins the development of these guidelines.

Regulation of Naltrexone in Australia

Naltrexone hydrochloride (REVIA®) is registered in Australia for use in relapse prevention for alcohol dependence and opioid dependence.

Naltrexone is available on the PBS for only one indication, as an authority prescription for relapse prevention in the management of alcohol dependence. Several studies have demonstrated the efficacy of naltrexone in alcohol dependence (Volpicelli, 1992; O'Malley, 1996), although the effectiveness of naltrexone in alcohol dependence is reduced by poor compliance (Volpicelli, 1997).

Naltrexone is available on private prescription for relapse prevention in opioid dependence. This is treatment designed to assist a detoxified and opioid-free former heroin user to remain abstinent from heroin.

Naltrexone is NOT registered in Australia for use in opioid withdrawal although naltrexone is occasionally used to accelerate the process of withdrawal from opioids. "Rapid detoxification" is the name given to a wide variety of techniques employing an opioid antagonist to accelerate the process of opioid withdrawal (O'Connor & Kosten, 1998). The use of naltrexone in rapid detoxification is an "off-label" use of the drug, which places additional responsibility on medical practitioners to ensure that prospective patients are fully informed of:

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

Prescribers must ensure that written informed consent for the procedure is obtained.

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1 Clinical pharmacology of naltrexone

1.1 General Information

What is naltrexone?

Naltrexone is a highly specific opioid antagonist which has a high affinity for opiate receptor sites. It competitively displaces opioid agonists if they are present, such as methadone, heroin, and slow-release morphine.

Naltrexone has few intrinsic actions besides its opioid-blocking properties. It does produce some pupillary constriction by an unknown mechanism. Naltrexone does not cause any physiological tolerance or dependence. It is not known to block the effects of other classes of drug besides opioids, however, naltrexone appears to block some of the euphoriant actions of alcohol, presumably due to its blockade of opioid receptors.

What form does it come in?

Naltrexone hydrochloride is available in Australia as REVIA®, and is presented as a scored pale yellow coated capsule shaped tablet. REVIA is available as 50mg tablets in bottles of 30 tablets.

Because the major limitation of naltrexone is patient compliance with the daily regimen, there is considerable interest in the use of depot preparations of naltrexone, designed to slowly release naltrexone into the circulation over a period of weeks to months. Medical practitioners in Australia and elsewhere have experimented with naltrexone implants designed to do this.

Naltrexone implants are not registered for use in Australia, and their use is experimental. Medical practitioners are advised not to use naltrexone implants, except in the context of clinical trials registered with the Therapeutic Goods Administration.

Absorption, distribution, metabolism, excretion

Naltrexone is rapidly absorbed, with peak blood levels achieved about 1 hour after oral administration (Gonzalez, 1988). Naltrexone has a relatively short plasma half-life of 4 hours. It is primarily metabolised in the liver to a metabolite, 6-β-naltrexol, which has a plasma half-life of about 10 hours and is also an opioid antagonist. Approximately 20% of the active metabolite is bound to plasma protein, and is distributed widely, with relatively high amounts in the brain, fat, spleen, heart, testes, kidney and urine (Gonzalez, 1988). Naltrexone and 6-β-naltrexol undergo enterohepatic recycling and are excreted primarily by the kidney. Less than 1% of naltrexone is excreted unchanged.

Despite both compounds having relatively short half-lives, the duration of naltrexone blockade is much longer. An oral dose of 50mg naltrexone has been shown to produce 80% inhibition of radiolabelled carfentanyl binding for 72 hours (Lee et al, 1988).

Rationale for the use of naltrexone in opioid dependence

The rationale for using naltrexone in relapse prevention is that the patient knows that taking naltrexone blocks the effects of heroin. Detoxified heroin users have described naltrexone as being a form of "insurance", a protection against a sudden temptation to use heroin. Clinical experience indicates that patients who take naltrexone in the hope that it will stop them wanting to use heroin, or will maintain their motivation to remain abstinent, tend to be disappointed. Naltrexone should be seen as a medication which may help motivated patients to remain abstinent, rather than a drug which reduces patients desire to use heroin. Furthermore, it should be remembered that "motivation" to remain drug free can be very variable over time. It is common that people in crisis express a strong intention to become and remain drug free, but within a relatively short time such determination disappears.

Indications

Opioid users:

- Seeking abstinence from opioids
- Capable of giving informed consent to naltrexone treatment

Naltrexone treatment is only appropriate for opioid users committed to long term abstinence.

Contraindications to naltrexone treatment

- Current physiological dependence on opioids. Those currently physiologically dependent should be offered detoxification or referred to specialist services.
- Acute opioid withdrawal. There needs to be a drug free interval before commencing naltrexone.
- Using opioids for chronic pain states. This requires specialist assessment.
- Acute hepatitis or liver failure, as naltrexone can be hepatotoxic in high doses. The margin of separation between the apparently safe dose of naltrexone and the dose causing hepatic injury appears to be only fivefold or less.
- Known adverse reactions/sensitivity to naltrexone.

Precautions

In addition, caution is advised in prescribing naltrexone to the following patients. Assessment by an alcohol and drug specialist is recommended.

- Women who are pregnant or breast feeding as naltrexone is classified as a B3 risk in pregnancy;
- Patients concurrently dependent on multiple drugs;
- Patients with impaired renal function, as naltrexone and its active metabolite are excreted in urine;
- Patients with major psychiatric illness, including depression;
- Children and adolescents as the effects of naltrexone in the treatment of opioid dependence in these populations is also unknown. Referral to specialist alcohol and drug services is recommended.

Side effects

Although major adverse events are very rare, side effects of naltrexone are common, but tend to be transient, mild and improve with time.

Side effects reported by more than 10% of patients include

- difficulty in sleeping
- anxiety
- nausea & vomiting
- headache.
- loss of energy
- abdominal pain
- joint and muscle pain

Safety of naltrexone treatment

The greatest problem associated with naltrexone treatment is the increased risk of death from heroin overdose in patients who return to opioid use after being treated with naltrexone

Increased risk of death for those patients who return to opioid use after naltrexone treatment is thought to be primarily due to loss of tolerance to opioids. An increase in the risk of death by overdose occurs in any recently detoxified group of formerly heroin dependent patients, including people within 12 months of leaving methadone treatment (Zanis, 1999). After discontinuing naltrexone, a dose of heroin which the user had been accustomed to inject during their last period of addiction may now prove fatal. Another factor contributing to the risk of death is that some people become depressed after discontinuing heroin, and may deliberately suicide.

The experience with naltrexone indicates that there are few serious adverse reactions, other than the precipitated withdrawal, which occurs when the drug is administered to someone who is not opioid free.

Although some years ago it was noted that high doses of naltrexone administered to morbidly obese subjects resulted in transaminase elevations, subsequent experience with use of naltrexone in alcohol dependence has found hepatotoxicity to be rare (Croop, 1997).

Effectiveness of naltrexone treatment

The effectiveness of naltrexone treatment for relapse prevention is limited.

Published literature on naltrexone in relapse prevention in general shows:

- that only a small minority of opioid-dependent people seeks naltrexone treatment, and
- among those entering treatment there is a very high rate of dropping out.

A significant proportion of people remaining in naltrexone treatment for periods of 3 months or longer remains abstinent from heroin. However, this represents only a small proportion of heroin users. Furthermore, most of these subjects appear to return to heroin use eventually. The only moderately long-term, published follow-up study of patients treated with naltrexone (Rawson and Tennant, 1984), reported that more than 90% of subjects became re-addicted to heroin at some time over the following 5 years. Patients in that study reported that they had found naltrexone helpful, as it had helped them to remain heroin-free for periods of time. This study concluded that naltrexone is not a "cure" for heroin addiction, but was a useful medication in protecting patients from re-addiction for periods of time.

With more intensive supportive treatment, and with new methods of delivering naltrexone, it is thought that the effectiveness of treatment with this medication can be improved. However, at this time the available evidence suggests only very modest efficacy of naltrexone in relapse prevention for opioid dependence.

2 Entry into naltrtexone treatment

2.1 Patient Selection Issues

Because of concerns over safety in the event of relapse, and the relatively low rates of abstinence achieved with naltrexone, **naltrexone treatment is only appropriate for heroin users committed to long-term abstinence**. It is preferable that such a commitment is assessed over time – at least a few days – rather than in a single interview.

Naltrexone is only one of a range of treatments for opioid dependence. Treatment options include detoxification, self-help groups, drug free counselling, residential therapeutic communities, and maintenance treatment with methadone or buprenorphine. These treatment options are complementary, not competing, and many patients will access a variety of treatments over time, depending on their circumstances. The appropriateness of entry into one of these treatment options should be considered when assessing a patient for naltrexone treatment.

Practitioners should consider how prospective patients are to be inducted onto naltrexone. Induction onto naltrexone involves reversal of neuroadaptation to opioids, and usually produces considerable symptomatic distress for a few days.

Retention in drug dependence treatment programs is generally poor with the exception of agonist maintenance therapies [Ward, Mattick & Hall, 1998]. Patients may be better suited to methadone or buprenorphine maintenance treatment if they are ambivalent about long term abstinence, or if they are at high risk of relapse to heroin use. Such risk may be evidenced by virtue of a chaotic lifestyle, entrenched involvement with drug using friends, and a lack of external supports to assist the patient to maintain abstinence.

Suitability for treatment with naltrexone:

- **committed to long term abstinence**
- **have considered a range of treatment options**
- **have considered how they will be inducted**
- **have external support to maintain abstinence**

2.2 Assessment for Naltrexone Treatment

Motivation and expectations

Motivation for treatment and expectations of treatment should be explored by:

- clarification of reasons for presentation including immediate precipitants
- clarification of patients goals e.g. long term abstinence, respite, attempt to regain control

Many prospective patients see naltrexone as a "wonder drug" which will stop them from wanting to use drugs. Naltrexone can be a useful adjunct in relapse prevention, but it does not motivate people to remain abstinent.

Drug use history

A drug use history comprises:

- current levels of drug use (quantity and frequency of use)
- duration of use
- assessment of dependence (including physiological dependence)
- use of drugs other than the primary drug of dependence
- history of treatment for drug problems

Careful drug use history taking is extremely important.

Patients may say they have been abstinent from heroin for a week, but may have been using street methadone and/or codeine or d-propoxyphene preparations or compound analgesics such as Panadeine forte®, or Digesic ® and still be physiologically dependent on opioids. If a patient is on methadone or has recently been on methadone, or has been using street methadone, it is important to be particularly cautious when initiating naltrexone.

If a patient's primary drug problem is amphetamine, cocaine or cannabis use, it is very unlikely that naltrexone will be of use.

Medical and psychiatric history

- Naltrexone treatment or, possibly, abstinence from heroin may exacerbate or unmask psychiatric problems, particularly depression, in susceptible subjects. Identification and monitoring of depressive symptoms is desirable, and if there is concern about a patient's mood, psychiatric assessment may be helpful.
- In general, patients with a history of medical conditions, which are acute or unstable, should undergo careful assessment prior to initiation of any new treatment.
- Consideration needs to be given to possible drug interactions in people taking prescribed medications.
- Rapid detoxification causes considerable physiological stress. Patients with a history of cardiac disease – particularly, ischaemic heart disease, arrhythmia, hypertrophic cardiomyopathy – should not undergo rapid detoxification.

Psychosocial history

- Current social circumstances – housing, relationships (including children), employment
- Developmental history (family of origin, schooling, occupational history)
- Forensic history (including current charges)
- History of features of depression and anxiety

Physical and mental state examination

- Mental state examination (mood, affect, attention and concentration) is important to screen for depression or thought disorder, and to confirm that the patient is in a fit state to provide informed consent.
- Evidence of drug use (documenting the extent of vein damage, signs of liver disease, nutrition, and self-care) should be sought. This may be of value in monitoring improvements during treatment, and providing patients with positive feedback about their progress.
- Signs of withdrawal (see Appendix 6)
- Signs of intoxication (see Appendix 7)
- General health.
  - — Patients with history or signs of cardiac or respiratory disease should not generally undergo rapid detoxification.
  - — Patients with signs of acute or decompensated chronic liver disease (jaundice, encephalopathy) should not usually be commenced on naltrexone.

Investigations where clinically indicated.

Pregnancy test

- If a patient has a positive pregnancy test at assessment, do not perform a naloxone challenge, and reconsider naltrexone treatment.
- Patients should be advised of the potential risks of naltrexone during pregnancy.

Urinalysis

- Urinalysis can be undertaken as an adjunct to history taking and physical examination in confirming recent drug use. Opioids can be detected in urine for up to 48 hours.
- If a patient has an opioid-positive urine at assessment do not continue with the naloxone challenge test.
- Patients should be advised if random urine drug screens are used for monitoring purposes during treatment.

Liver function test (LFT) and serology for blood-borne viruses

- njecting drug users are a high-risk group for parenterally transmitted diseases. It is therefore appropriate to:
  - — screen new patients for hepatitis B and C,
  - — immunise against hepatitis B,
  - — provide harm reduction information.
- These investigations are not mandatory prior to initiating treatment, and may better be undertaken during the first month of treatment.

Naloxone challenge test.

In situations where patients report having completed detoxification, it is prudent to confirm that they are no longer physically dependent on opioids by performing a naloxone challenge test (see Appendix 1 for how to perform the test)

2.3 Treatment Plan and Informed Consent

Informed consent for naltrexone treatment should include explaining treatment and providing written information.

- Patients should be appraised of the potential risks of treatment, particularly the overdose risks on discontinuing naltrexone.
- Contraindications for treatment should be discussed and excluded, and arrangements for induction onto naltrexone explained.
- The costs of treatment, frequency of appointments, availability of support services, should be explained.
- Clarification should be sought whether the patient wants to enter into an arrangement in which his/her taking of naltrexone is supervised.
  - — This may improve compliance with treatment. Currently, several programs encourage patients to involve a significant other ("carer") to supervise the daily taking of naltrexone, and this may improve compliance and treatment outcomes.
  - — Research has demonstrated that treatment with naltrexone is more effective in highly supervised settings such as prisoners on probation (Brahen, 1984), or medical practitioners under the supervision of medical boards (Washton, 1984). Whether these findings can be extended to having family members or friends as carers remains to be determined.
- Practitioners must document informed consent to naltrexone treatment
- A medical warning card should be issued to patients in case analgesia is required in the event of sudden illness or injury

2.4 Induction Into Treatment

The administration of naltrexone to people physiologically dependent on opioids will precipitate a severe withdrawal reaction

The administration of naltrexone to people physiologically dependent on opioids will precipitate a severe withdrawal reaction. Precipitated withdrawal is much more severe than spontaneous withdrawal, and people undergoing precipitated withdrawal can become very ill. To avoid precipitating withdrawal, there are three approaches to induction onto naltrexone treatment:

1. ***The conventional approach*** is to undertake detoxification, and when patients have been free of short-acting opioids for 5 days, or free of methadone for 10 days, commence naltrexone treatment. As patient history can be unreliable, it is desirable to perform a naloxone challenge test prior to the first dose of naltrexone, to avoid inadvertently precipitating a withdrawal reaction. The procedure for undertaking a naloxone challenge are outlined in Appendix 1.

2. ***Antagonist accelerated induction ("Rapid detoxification")*** involves administration of naltrexone or naloxone to opioid dependent subjects, while providing symptomatic relief to make the ensuing precipitated withdrawal tolerable. This approach is described in Section 4.

3. ***Buprenorphine-assisted detoxification*** can allow the introduction of naltrexone without severe precipitated withdrawal either during buprenorphine treatment, or within days of stopping buprenorphine. This is described in Appendix 2. Details regarding the use of buprenorphine to assist withdrawal from heroin or other opiates are provided in the National Buprenorphine Guidelines.

3 Treatment with naltrexone

3.1 Dose and Duration of Treatment

The usual maintenance dose is 50mg daily. However, 25mg daily produces adequate blockade of opioid receptors, and may be a satisfactory dose in patients who experience side-effects from 50mg/day.

25mg daily produces adequate blockade of opioid receptors

50mg daily is the usual maintenance dose

The optimal duration for treatment with naltrexone is unknown. However, it is known that treatment for dependence is a long-term process, and there is still a substantial risk of relapse to heroin dependence for 2-3 years after last use of heroin. The optimal period of treatment will be different for different patients, and advice about how long to take naltrexone should take into account lifestyle changes, environmental risk factors, and craving.

Patients should generally be encouraged to take naltrexone for at least 6 months.

3.2 Supportive Care for Patients on Naltrexone

Intensive follow-up is a critical component of optimising the benefits of naltrexone treatment. The practitioner performing induction onto naltrexone should review patients, or arrange for a suitably qualified health professional to review them, on two occasions during the first week after induction. Thereafter, clinical reviews should be conducted weekly during the first month of treatment.

There are many approaches to the delivery of supportive care. 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 minimise the risk of the patient spitting it out.
- Self-help groups may be a valuable adjunct to people trying to maintain abstinence

In the treatment of drug dependence, it is conventional to accept that it is only possible to help people change patterns of behaviour if they themselves are motivated to make such changes. Motivation of

treated heroin users to remain abstinent is generally transient (Ling, 1978), and this is one reason why compliance with naltrexone treatment is generally poor, and a large proportion of subjects relapse. It is unclear how far practitioners should go towards trying to improve compliance with naltrexone treatment. In recent years, several practitioners have advocated a more aggressive approach to naltrexone treatment. Rather than accepting the ambivalence and shifting motivation to remain abstinent frequently demonstrated by patients, these practitioners have recommended:

1. initiating treatment with rapid detoxification (to minimise drop-outs prior to commencing naltrexone)
2. supervised dosing, by involvement of family or other carers who provide a high level of supervision, ensuring patients continue to take their naltrexone.
3. aggressive re-induction after an episode of relapse

There has been no systematic evaluation of this approach to treatment, certainly not one involving comparison groups or randomised design. Whether in the long term this approach leads to better, worse, or the same outcomes as conventional approaches to treatment remains to be determined.

It is important to remember that while families are often keen to be involved in patient's care on naltrexone, practitioners must obtain each patients' consent to involve family or discuss treatment with them. Remember that every family is different and that adverse family dynamics can contribute to a person's drug use. While most families try to support family members who stop heroin use, a person ceasing heroin can sometimes lead to considerable family tension. Sensitive handling of such changes could be important in reducing the risk of relapse.

Role of psychosocial interventions

Many people taking naltrexone are keen to engage in some form of counselling, and practitioners who do not feel they have the skills or time to spend in counselling patients should refer patients who express a wish for counselling.

3.3 Monitoring and Review

Patients should be seen regularly while on naltrexone treatment.

It is recommended that clinical reviews should be conducted weekly during the first month of treatment, then fortnightly or monthly as required.

Monitoring of compliance and progress should occur at each clinical review:

- assess drug use, for both heroin and other drugs
- assess compliance with naltrexone regime
- assess changes in social functioning and relationships
- review whether patient is involved in counselling
- monitor side effects especially mood

3.4 Relapse

At review, some patients will report that they have discontinued naltrexone use and returned to using heroin. Just as commonly, they may report that they are complying with treatment – yet have fresh injecting marks, a positive urine test for opioids, or other evidence of return to heroin use. Sometimes it is only the report of a significant other which may alert the doctor to the fact that the patient is not taking naltrexone, and has resumed heroin. Multiple missed appointments and the observations of the dispensing pharmacist can also be valuable indicators that something is wrong.

In these circumstances, the conventional approach is to re-assess the patient, clarifying their motivation. Patients should always be warned of the risks of overdose. Other treatment options should be considered. If the patient wishes to enter a residential treatment program, the program rules may allow them to remain on naltrexone. Some patients prefer to do this, so that they continue naltrexone after leaving residential treatment.

- **If heroin use is ongoing, seek clarification of their goals**
- **Consider residential treatment or methadone or buprenorphine maintenance treatment**
- **Counsel patient about the dangers of overdose**

Re-induction onto naltrexone

Many patients who have relapsed will express a desire to resume naltrexone treatment. However, these patients need to be cautioned that reinstatement of dependence occurs rapidly within days of regular heroin use, and, therefore, somewhat unpredictably, resuming naltrexone can precipitate severe withdrawal.

- If it is more than 5 days since the last dose of naltrexone, and the patient has used heroin each day since then, recommence on naltrexone as though a new patient requiring detoxification.
- If within 5 days of last naltrexone dose, restart naltrexone under medical supervision – patients may experience withdrawal, but this is usually not severe.
- Restart naltrexone in the morning, at least 24 hours after last use of heroin
- Commence with ¼ tablet (12.5mg)
- Patients may need symptomatic medication (see 5.3 below)

Clinical experience to date has been that patients who relapse and return to naltrexone tend to remain in treatment a relatively short time. After multiple relapses, medical practitioners should seriously consider whether it is appropriate to continue naltrexone treatment, as it becomes increasingly likely that the patient will drop out, and **it is preferable to actively manage cessation of treatment than for people to drop out and be receiving no treatment**. Alternative approaches such as residential treatment or methadone or buprenorphine maintenance treatment should be discussed.

3.5 Transfer to Maintenance Substitution Treatment

The patient may wish to transfer to maintenance substitution treatment (methadone or buprenorphine). This involves some risk, because when methadone is commenced too soon after the last dose of naltrexone, its actions will be blocked, and patients may appear to require a higher starting dose of methadone. This can give rise to a situation where people accumulate toxic levels of methadone, and the toxicity only becomes gradually apparent as the naltrexone blockade wears off. This risk needs to be balanced with the risk of people using heroin if the methadone dose is insufficient.

- The first dose of methadone should ideally be delayed until 72 hours after the last dose of naltrexone.
- However, it may be possible to initiate treatment with 20mg of methadone after only 48 hours, although patients should be warned of the possible residual receptor blockade.
- When methadone is initiated within 7 days of last use of naltrexone, the starting dose should not exceed 20mg daily for the first 3 days, as the patient may have low tolerance.
- When inducting onto buprenorphine, the initial dose should not exceed 4 mg, although rapid dose increases can occur following review by the prescribing doctor.

See also:

- ***National clinical guidelines and procedures for the use of methadone in the treatment of heroin dependence and,***
- ***National clinical guidelines for the use of buprenorphine in the treatment of heroin dependence.***

3.6 Management Issues in Naltrexone Treatment

Intermittent naltrexone use

Some patients may wish to use naltrexone in an intermittent way. For example:

- A patient may be abstinent, but when facing a high risk situation, will take one tablet
- A patient may want to avoid heroin use most days, but want to take heroin on weekends

There are serious potential risks with these approaches –

- Overdose on opioids due to risk of misjudging level of tolerance
- Precipitated withdrawal due to resumption of naltrexone following reinstatement of opioid dependence

For these reasons, it is appropriate to caution people against irregular use of naltrexone. Also it may in some situations be prudent to discontinue naltrexone treatment if the patient's level of risk-taking outweighs any observed benefits of the treatment.

Diversion

Patients should be warned against giving or selling their naltrexone to other opioid users as it can precipitate acute withdrawal. Precipitated withdrawal is much more severe than spontaneous opioid withdrawal. Several patients have required hospitalisation after taking naltrexone while still physiologically dependent on heroin.

Guidelines for the management of precipitated withdrawal are included in Appendix 3.

Multiple drug use

Some heroin dependent patients, when they cease heroin, commence or increase their use of other drugs, especially benzodiazepines, cannabis, amphetamines, and cocaine. Naltrexone does not block the effects of these drugs. Practitioners should caution patients against use of these drugs, and should monitor use of these drugs at each appointment.

The risks and benefits of continuing treatment should be assessed when patients are abusing or dependent upon other drugs.

Adjunct pharmacotherapies

There is at this time no evidence to support the routine use of drugs such as antipsychotics, benzodiazepines and anticonvulsants during naltrexone treatment.

Antidepressants

Many heroin users experience dysphoria at treatment presentation, upon completion of withdrawal, and during the induction phase of naltrexone.

- The dysphoria usually resolves within weeks.
- Antidepressants are indicated if there is a diagnosis of depression as indicated by features more substantial than dysphoria, such as suicidal ideation, anhedonia, sleep disturbance, and weight change.
- Although it has been suggested that use of antidepressants (SSRIs) improves outcomes in unselected naltrexone patients, the weight of evidence does not support routine use of SSRIs in conjunction with naltrexone.

Sleep disturbance

One study has reported that naltrexone has fewer adverse effects on sleep than methadone (Staedt, 1996), but despite this many patients complain of insomnia, particularly on initiation of naltrexone treatment. Benzodiazepines can help, but their use should be time limited – a period of less than 2 weeks is recommended.

- Patients need to be advised of non-pharmacological treatment options for sleep disturbance.

Symptomatic medications

There may be a role for the use of symptomatic medications in the first few days of naltrexone treatment to address ongoing withdrawal symptoms. Recommended medications include:

nausea and vomiting –	metoclopramide
abdominal cramps –	hyoscine butylbromide
joint aches –	NSAIDs
agitation/insomnia –	benzodiazepines
diarrhoea –	non-opioid anti-diarrhoeals

Pain management

Mild pain

For mild pain non-opioid analgesics (paracetamol, NSAIDs) should be used. Patients taking naltrexone will not benefit from opioid containing medicines such as cough, cold, and anti-diarrhoeal preparations.

Elective surgery

Naltrexone should be discontinued at least 72 hours before elective surgery including dental surgery, if it is anticipated that opioid analgesia may be required. The treating surgeon/doctor should be informed that the patient has been taking naltrexone. The patient should then be abstinent from the opioid for three to five days before resuming naltrexone treatment, depending on the duration of the opiate use and the half-life of the opiate. A more conservative approach is to wait seven days. As an alternative a naloxone challenge test can be administered.

Emergency pain relief

In an emergency, pain management may consist of regional analgesia, conscious sedation with a benzodiazepine, use of non-opioid analgesics, or general anaesthesia. Ketorolac is an NSAID available for parenteral use.

- **Patients on naltrexone will not respond to opioid analgesics**
- **For mild pain non-opioid analgesics should be used**
- **Discontinue naltrexone at least 72 hours before elective surgery**
- **In an emergency, co-ordinate with an alcohol and drug specialist**

Pregnancy

Patients seeking to remain opioid-free during pregnancy should have additional monitoring and support, as pregnancy can be a time of considerable psychological stress. While pregnancy is often a time when women become motivated to stop drug use, it is also a time when previously stable patients may relapse.

The safety of naltrexone in pregnancy is not established. It has been classified as pregnancy risk B3. If a woman becomes pregnant on naltrexone, it is recommended that:

- If the patient believes she is at low risk of relapse, and the doctor concurs, it is appropriate to cease naltrexone and monitor the patient through pregnancy
- If the patient is highly concerned about relapse, and wishes to continue naltrexone, it is important to inform the patient about the risks of staying on naltrexone, and obtain consent for ongoing treatment.
- If the patient wishes to cease naltrexone but then reports that she has started using heroin again, it may be appropriate to consider methadone treatment. Patients need to be fully informed of the risks involved in doing so, including the risk that the baby will go through withdrawal on delivery.

4 The use of naltrexone in withdrawal ("RAPID DETOXIFICATION")

It is not recommended that practitioners use rapid detoxification as a means of induction onto naltrexone, particularly not on an occasional basis.

These guidelines are intended for those practitioners who have decided to perform rapid detoxification on a regular basis.

4.1 Opioid Antagonist Precipitated Withdrawal.

The administration of opioid antagonists (such as naloxone or naltrexone) to an individual who is currently physiologically dependent on opioids precipitates an immediate abstinence syndrome, **often of considerable severity**. This is the basis for the 'naloxone challenge test" to diagnose opioid dependence (see Appendix 1).

The acute phase of precipitated withdrawal involves two major clusters of symptoms:-

- Gastrointestinal symptoms – vomiting and diarrhoea, often with cramping abdominal pain, lasting many hours.
  - — Without supportive treatment patients may become dehydrated and develop electrolyte disturbances as a result of severe vomiting.
- Psychological disturbances, with agitation, dysphoria, and delirium.
  - — Delirium can last for up to 12 hours.
  - — Significant physiological disturbances, including a marked increase in circulating catecholamines.

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.

The key step to minimising the severity of acute precipitated withdrawal, and the severity of persisting symptoms over the next several days is to delay the introduction of naltrexone until 48 hours after the last use of heroin, or 5 days after the last use of methadone.

Administration of naltrexone without observing such a delay risks severe physiological and psychological reactions.

4.2 Rapid Detoxification

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

It is not recommended that practitioners use rapid detoxification as a means of induction onto naltrexone, particularly not on an occasional basis.

These clinical guidelines are intended for those practitioners who have decided to perform rapid detoxification on a regular basis.

Approaches

The published literature on rapid detoxification is characterised by a marked variation in approaches used, in reported outcomes, in reported severity of symptoms associated with detoxification and in medium term outcomes. Broadly speaking, two approaches to rapid detoxification have evolved:

- rapid detoxification under anaesthesia, and
- rapid detoxification using sedation.

Anaesthetic-based approaches to rapid detoxification involve airway protection to minimise the risk of aspiration. However, many patients are persistently unwell after the procedure. Anaesthetic-based approaches require skilled personnel, high level medical settings (ICU or operating room for 4-6 hours), and are more expensive than procedures involving sedation. Australian studies suggest that outcomes after anaesthetic based procedures are no better than outcomes after rapid detoxification performed with sedation.

What all approaches to rapid detoxification have in common is the:

- administration of an antagonist to precipitate withdrawal.
- use of symptomatic treatment to alleviate the severe precipitated acute withdrawal.
- use of symptomatic treatment to alleviate persisting dysphoria and gastrointestinal symptoms after acute withdrawal has subsided.

The key components of all rapid detoxification are:

- assessment and informed consent
- an adequate interval between last use of an opioid and introduction of naltrexone
- provision of symptomatic medication
- provision of an appropriate setting for care.

Assessment and informed consent.

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

Adequate assessment is the key to obtaining informed consent, and the key to appropriate patient selection.

The provision of accurate information about the procedure and about naltrexone treatment is critical.

Patients (and their families if consent is given for their involvement in care) should be informed of the documented effectiveness of naltrexone treatment. 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. Persisting withdrawal symptoms and malaise can persist for several days after rapid detoxification.
- Rapid detoxification does improve short term induction onto naltrexone, but thereafter attrition from treatment is high. Sixty percent or more of patients undergoing rapid detoxification will relapse to heroin addiction within 6 months.

Poorly motivated patients, and those in unstable social circumstances, are poor candidates for naltrexone treatment.

Patients who are homeless or in highly unstable social circumstances require a comprehensive plan to stabilise their circumstances prior to undergoing rapid detoxification. It is probably best to defer naltrexone treatment in patients who are ambivalent about remaining abstinent from opioids.

Assessment

The assessment documented in the medical record should include:

- Drug use and treatment history
- Medical and psychiatric history
- Psychosocial history
- Physical and mental state examination
- Assessment of motivation.

Contraindications

- 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:

- Moderate or severe depressive symptoms. Psychiatric assessment is recommended.

Provision of information

Prospective patients should be supplied with written and verbal information about:

- The nature of the proposed treatment
- The risks involved
- The steps to minimise the risk of severe withdrawal
- The known benefits and risks of naltrexone treatment
- An indication of the costs of treatment and the services that will be provided.
- The role (if any) of support people.

All patients must be warned at the outset, and at follow-up visits, of the risks of opioid overdose on discontinuing naltrexone and recommencing opioid use.

There have been cases where patients on methadone treatment have undergone rapid detoxification without informing their methadone doctor or their pharmacist, and where resumption of methadone has resulted in fatal overdose.

- Patients on methadone should be asked to consent to their methadone prescriber and dispenser being informed that they are to undergo rapid detoxification.
- Where patient consent is not given, it is not appropriate to proceed with rapid detoxification.

Interval between last opioid use and rapid detoxification

Delaying the administration of antagonists until there are very low levels of circulating opioid drugs minimises the severity of acute withdrawal and greatly reduces the severity of protracted withdrawal in the first week of naltrexone treatment.

- After conventional detoxification, naltrexone should only be introduced after
  - — 5 days free of heroin
  - — 10 days after the last dose of methadone.

- Rapid detoxification reduces the delay in commencing naltrexone. Naltrexone may be introduced after:
  - at least 48 hours free of short acting opioids (heroin, morphine)
  - at least 5 days free of methadone.

After these intervals, most opioid dependent patients will experience moderate precipitated withdrawal and will require symptomatic support and monitoring.

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 minimise withdrawal distress.

Provision of symptomatic medication

Prior to induction to naltrexone

Clonidine is used in doses up to 300ug (2 tablets) 8 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 150µg (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 light-headedness.
- Doses as low as 75ug (1/2 tablet) 4-6th hourly can help relieve withdrawal distress.

Clonidine should be commenced at around the time patients start to experience withdrawal symptoms (about 8 hours after the last use of heroin or 24 hours after the last dose of methadone. It should be continued up until the patient has commenced naltrexone.

Other medications which may be useful in the period prior to induction onto naltrexone include:

- Quinine sulphate (300mg bd) can be helpful in patients with muscle cramps.
- Metoclopramide 10mg (1 tablet) 3 times daily can help control nausea and vomiting.
- Temazepam 20mg at night can assist with insomnia.

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

On commencement of rapid detoxification

Octreotide, a synthetic somatostatin analogue is the most effective agent for controlling gastrointestinal symptoms during precipitated withdrawal.

- Administer 100µg subcutaneous octreotide prior to precipitating withdrawal.

Sedation is usually employed during the acute phase of precipitated withdrawal in non-anaesthetised patients. Medications which depress consciousness (such as high dose benzodiazepines) alleviate psychological distress but increase the risk of aspiration as a result of depressed gag reflex. If patients have observed the appropriate opioid-free interval prior to commencement of naltrexone:

- It is recommended that 5mg diazepam be administered as premedication prior to precipitating withdrawal

Precipitation of withdrawal

It is recommended that precipitated withdrawal be commenced with naloxone rather than naltrexone.

Even with careful explanation to prospective patients, it is not always possible to be confident that people presenting for rapid detoxification will have observed the required opioid free interval. For this reason it is recommended that precipitated withdrawal be initiated with naloxone rather than naltrexone.

Naloxone is a short acting antagonist whereas naltrexone is long acting. If a patient has a severe withdrawal reaction to naloxone, the drug rapidly wears off (usually in an hour or less) and the patient recovers. In contrast, precipitated withdrawal from naltrexone lasts many hours and so it is highly desirable to initiate precipitated withdrawal with naloxone.

- Administer 0.4 mg naloxone by intra muscular injection (IM)
  - If the reaction is too severe the procedure can be aborted
  - If the patient tolerates naloxone 0.4mg IM, naltrexone 25mg can be administered orally.

Safety issues

All approaches to rapid detoxification involve balancing safety against tolerability.

- 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.

Setting for care

Rapid detoxification with anaesthesia

Anaesthetic based approaches to rapid detoxification require skilled personnel and high level medical settings (ICU or operating room for 4-6 hours).

Rapid detoxification with sedation

Rapid detoxification with sedation can be performed in settings with lower levels of care, and can be performed in ambulatory patients. However, as a precaution in the event of a severe precipitated withdrawal, rapid detoxification under sedation should only be performed where there is access to an adequate level of care:

- adequately trained nursing staff to deal with a severe reaction;
  - this may require individualised (one to one) nursing for 4 hours
- medical staff on site for 4 hours from induction, and available on call for at least 24 hours after the first dose;
- access to medications;
- access to basic resuscitation equipment
  - staff trained in the use of these devices.

Management of severe reaction

Occasionally, even after great care in screening patients, a patient has a severe withdrawal reaction.

During rapid detoxification, the first dose of naltrexone should always be administered in the morning to ensure that peak severity of precipitated withdrawal occurs at a time when medical support is most readily available.

Patients should be observed for a minimum of 3 hours after administration of naltrexone.

- If they are well, they can be discharged.
  - On the evening after the first dose, temazepam (20mg) may be given.
  - Thereafter patients receive 50mg naltrexone daily each morning.
- Patients who are agitated or distressed at the end of 3 hours should remain under observation with regular monitoring and reassurance. Symptomatic relief is of some benefit:
  - Clonidine may be administered if the patient's pulse is above 55 and blood pressure is >90 systolic.
  - Buscopan is helpful for abdominal cramps
  - Quinine (one tablet, twice daily) is helpful for muscle cramps.
- Occasionally, the precipitated withdrawal may be of such severity that it is inappropriate to discharge the patient home that evening.
  - Arrangements to ensure a patient can receive inpatient care overnight, if needed, should be in place.

5 Patient information and warnings on naltrexone treatment

Patients should be supplied with take-home patient information and a medical warning card (available from Orphan Australia). Practitioners should cover the following points with patients:

Naltrexone as part of a comprehensive treatment plan

Make clear to the patient (and carer if involved) that naltrexone is not a 'miracle cure' for opioid dependence. It does not influence the underlying reasons for opioid use and this is why appropriate counselling and support are integral to successful naltrexone treatment.

Attempting to overcome naltrexone blockade

Patients should be explicitly warned that attempting to overcome the opioid receptor blockade by naltrexone by using large doses of opioids can result in fatal opioid overdose (i.e. respiratory arrest, coma or circulatory collapse).

Reduced tolerance to opioids after discontinuing naltrexone

Patients should also be warned that when they cease naltrexone treatment they will have an increased sensitivity (diminished tolerance) to opioids and that relatively small doses of heroin may result in fatal overdose. If the patient has decided to use heroin again they should consider themselves a 'new user'.

Naltrexone precipitated opioid withdrawal

Patients should be advised that on ceasing naltrexone, it takes very little exposure to heroin to develop physiological dependence. After only a few days of daily heroin use, further ingestion of naltrexone may precipitate a withdrawal reaction. Patients should be cautioned about sharing their naltrexone with opioid dependent friends or engaging in 'home detoxification'.

Medical warning card

Patients should be advised to carry a medical warning card or bracelet, which states they will not respond to opioid analgesia (obtainable from Orphan Australia). The patient should also inform other relevant clinicians (e.g. pharmacist, dentist, other medical officers) that they are taking naltrexone so that appropriate pain management can be provided.

Pregnancy

Patients should be advised that they may experience increased sex drive and fertility compared to when they were taking opioids and to use reliable contraception to avoid pregnancy.

Female patients in particular should be counselled about avoiding pregnancy while taking naltrexone as its safe use in pregnancy and while breastfeeding has not been established. The decision to continue naltrexone treatment in pregnancy involves careful assessment of the relative risks to the foetus and the likelihood of relapse to heroin use.

Alcohol use while taking naltrexone

It is safe to drink alcohol while taking naltrexone. Naltrexone will not stop an individual becoming intoxicated. However, alcohol intoxication while taking naltrexone has been reported at times to be unpleasant.

After care

The potential for relapse after ceasing treatment is high. Clinical experience suggests that active attempts to contact people who discontinue treatment or miss appointments may improve the outcomes of naltrexone treatment. At the commencement of treatment, it is desirable to confirm with patients that they consent to attempts being made to contact them to arrange another appointment if they drop out.

Appendix 1

Naloxone (Narcan®) challenge

It is strongly recommended that the Narcan® challenge test be undertaken when inducting patients onto naltrexone. There are however, occasions where this may not be clinically indicated. Patients should be provided with information regarding the procedure, including the rationale behind the procedure.

Procedure

- **Explain the test and the reason for performing it**
- **Intramuscular: 0.4mg naloxone, repeat another 0.4mg in 10 minutes if no indications of withdrawal**
- **Intravenous: give 0.2 mg naloxone; if no indications of withdrawal 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. (see Appendix 8)

- 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 mild **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 IM 10mg morphine can be administered, and detoxification should be advised.
- If no signs, but a subjective response to naloxone, ask the patient – 'can you tolerate this for 24 hours?' If the patient feels able to do so, they may take 12.5mg (1/4 tablet) naltrexone and be reviewed later that day.
- If there is a **negative** response, naltrexone treatment may be initiated with a dose of 25mg. If there are no signs of withdrawal or side effects following this initial naltrexone dose, the patient can go home, with instructions to take 50mg (one tablet) daily thereafter. If patients complain of significant withdrawal or side effects hold the patient on 25mg until resolved/symptoms settle.

Appendix 2

Naltrexone induction using buprenorphine

(This is covered in more detail in the *National Guidelines and Procedures for the use of Buprenorphine in the Treatment Of Heroin Dependence*).

The pharmacology of buprenorphine allows the commencement of naltrexone without major delays. This is thought to be because buprenorphine has a higher affinity for opioid receptors than naltrexone, so the naltrexone does not significantly displace buprenorphine or precipitate severe opioid withdrawal.

From buprenorphine to naltrexone:

Two general procedures have been used:

1. commencing low doses of naltrexone whilst continuing buprenorphine;
2. ceasing buprenorphine and commencing naltrexone several days later.

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

NALTREXONE INDUCTION REGIMES

Day	Sample buprenorphine regime (sublingual 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

Which procedure is best?

Both procedures result in an increased severity of opioid withdrawal following the first dose of naltrexone.

- This typically commences 90 minutes to 4 hours after the first naltrexone dose, peaks around 3 – 6 hours after the naltrexone dose, and generally subsides in severity within 12 – 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 patients undergoing this procedure request symptomatic medication.

- clonidine (100 – 150 mg every 3 – 4 hours as required) and a benzodiazepine (eg diazepam 5 mg 3 – 4 hourly, maximum of 30 mg, as required) should be prescribed.

Most patients find either procedure tolerable.

All clients need supervision and access to the prescribing doctor.

Outpatient setting is suitable only:

- where there is a suitable and responsible person to support the patient where they live, and to supervise medications; *and*
- if the prescribing doctor is available to address any potential complications.

PREPARE IN ADVANCE

for the increase in withdrawal severity, the role of medications, and the risks of using heroin to overcome the withdrawal symptoms.

Appendix 3

Management of acute opioid withdrawal precipitated by naltrexone

Introduction

Naltrexone is an opioid antagonist which has recently been registered for use in Australia. There have been a number of reports of opioid-dependent people self-administering naltrexone, precipitating a severe withdrawal reaction requiring hospital treatment. These guidelines are to assist medical and nursing staff to recognise and manage naltrexone precipitated withdrawal.

Precipitated withdrawal

Onset of naltrexone-precipitated withdrawal occurs 20 to 60 minutes following ingestion.

- Gastrointestinal symptoms are usually predominant.
- Severe vomiting and diarrhoea may occur.
- Patients become agitated and distressed, and delirium with confusion is common.
- Signs of sympathetic overactivity, particularly profuse sweating and piloerection, may occur.
- If a patient has taken sedative drugs in conjunction with naltrexone, as commonly occurs, delirium is exacerbated but other signs may be less clear.

There are significant risks associated with precipitated withdrawal.

- Most deaths associated with precipitated withdrawal appear to have been the result of aspiration associated with high doses of sedative drugs.
- In people who have received high doses of sedating drugs, delayed respiratory depression emerging after acute withdrawal has subsided, may have contributed to deaths.
- Fluid and electrolyte problems secondary to vomiting and diarrhoea.
- During acute delirium, confused patients must be considered at risk and require medical care.

Diagnosis and Assessment

History may be difficult to obtain from confused patients, particularly if they are defensive about being identified as heroin users.

- Suspect naltrexone precipitated withdrawal in any patient presenting with signs of opioid withdrawal in conjunction with delirium or intractable vomiting.

- A history of opioid dependence should be gained from the patient, significant others or by inspection of injection sites for recent track marks. (An absence of track marks should not exclude this diagnosis)

Careful assessment of the degree of sedation, and of the patient's capacity to protect their airway, is essential.

- The use of flumazenil to reverse sedation is not recommended due to the chance of the presenting patient having concurrent benzodiazepine dependence and the risk of inducing life-threatening seizures.
- Deeply sedated, vomiting patients may require intubation and ICU management.
- It may be desirable to check electrolytes and arterial blood gases.

Management

Naltrexone precipitated withdrawal is self-limiting, with delirium usually lasting only about 4 hours. Treatment is supportive and symptomatic.

Patients with vomiting may require fluid and electrolyte replacement.

- **Although most patients will experience fluid loss to some degree, the insertion of IV cannulae and administration of fluids should be balanced against potential problems. Patients in delirium frequently remove IV lines.**
- **Most patients will be capable of tolerating oral fluids within 12 hours of ingestion of naltrexone.**

During naltrexone-induced withdrawal delirium, most patients can be reoriented. This is critical in both obtaining a history and in managing the confused patient.

The most important part of management is reassuring the patient that symptoms, although severe, will be short lived.

Treating staff should be aware that the antagonist induced withdrawal syndrome is extremely traumatic and that patients expressing fear of death, for example, should not be treated contemptuously, but given appropriate, repeated reassurance.

The administration of opioid agonists is unlikely to be helpful.
Patients should be warned that taking heroin will not alleviate symptoms.

In managing vomiting and diarrhoea, clinical experience indicates that conventional anti-emetics provide little relief. **Octreotide** (Sandostatin) 100ug sc is the drug of choice in reducing vomiting and diarrhoea.

Agitation and sympathetic overactivity can be treated with **clonidine** (150ug po, or 100ug IM, repeated after 2 hours if agitation persists and hypotension is not a problem).

When urgent sedation is imperative (where patients are violent and confused), **midazolam** 5-10mg IM may be helpful.

When abdominal cramps are a problem, a single dose of 20mg hyoscine-N-butylbromide (Buscopan) can help.

Additional Management

Patients and families should be informed that residual symptoms may persist for up to 7 days. Patients need to be warned of the risk of overdose if they use heroin following naltrexone.

" These guidelines were developed as part of the National Evaluation of Pharmacotherapies for Opioid Dependence (NEPOD) project. The guidelines were written by Malcolm Young, Langton Centre, Sydney. Helpful comments from James Bell, Nick Lintzeris, Robert Ali and Lynn Hawken regarding an earlier draft are gratefully acknowledged.

Appendix 4
Contact List

Pharmaceutical company

Orphan Australia
12 Langmore Lane, BERWICK VIC 3806
Telephone: 03 - 9769 5744
Facsimilie : 03 – 9769 5944
Email: orphan@netspace.net.au

Clinical advice on the management of opioid dependence

AUSTRALIAN CAPITAL TERRITORY

ACT Department of Health, Housing and Community Care
GPO Box 825
Canberra ACT 2601

Alcohol and Drug Program
Acting Director
Management & Administration
Telephone: (02) 6205 0947
Facsimile: (02) 6205 1180

ACT Community Care Alcohol and Drug Program
Senior Medical Officer
Telephone: (02) 6205 4545
Facsimile: (02) 6205 0951
Chief Health Officer
Telephone: (02) 6205 0883
Facsimile: (02) 6205 1884
Chief Pharmacists
Telephone: (02) 6205 9061
Facscimile: (02) 6205 0997
Policy Information
Manager
Alcohol and Drug Priorities
Telephone: (02) 6205 0909
Facsimile: (02) 6205 2037

NEW SOUTH WALES

Alcohol and Drug Information Service
Telephone: (02) 9361 2111
Toll Free: 1800 023 599

NSW Drug and Alcohol Specialist Advisory Service
Telephone: (02) 9557 2905
Toll Free: 1800 023 687

NSW Health Drug Programs Bureau
Telephone: (02) 9391 9244

NORTHERN TERRITORY

Alcohol and Drug Service (ADIS)
Toll free 1800 131 350

Drug and Alcohol Clinical Advisory Service (DACAS)
Toll free 1800 111 092

Alcohol and Other Drugs Program, Policy and Program Development
Telephone: (08) 8999 2691

QUEENSLAND

Alcohol, Tobacco and Other Drug Services
Medical Advisor
Telephone: (07) 3896 3900

Policy and Specific State Information
Senior Advisor
Alcohol, Tobacco and Other Drug Services
Telephone: (07) 3234 1700

TASMANIA

Alcohol and Drug Service State Office

State Manager
Telephone: (03) 6233 3860

Coordinator Illicit Drugs
Telephone: (03) 6233 2269

Deputy Chief Pharmacist
Telephone: (03) 6233 3906

Alcohol and Drug Service
Southern Regional Office

Manager
Telephone: (03) 6222 7511

Opiate Treatment Medical Officer
Telephone: (03) 6222 7511

Pharmacist
Telephone: (03) 6233 3906

Alcohol and Drug Service
North/North West Regional Office

Manager
Telephone: (03) 6336 5577

Opiate Treatment Medical Officer
Telephone: (03) 6233 5577

SOUTH AUSTRALIA

ADIS (Alcohol and Drug Information Service)
Toll Free: 1300 13 13 40

Drug & Alcohol Clinical Advisory Service
Toll Free: 1300 13 13 40
Warinilla Clinic
92 Osmond Terrace
Norwood SA 5067
Telephone: (08) 8130 7500

Northern Methadone Service
22 Langford Drive, Elizabeth SA 5112
Telephone: (08) 8252 4040

Southern Clinic
82 Beach Road, Christies Beach SA 5165
Telephone: (08) 8326 6644

VICTORIA

Victorian Drug and Alcohol Clinical Advisory Service

Exclusively for health and welfare professionals. Provides advice and information on clinical management of patients with drug and or alcohol problems, including:

- advice on recognition and management of withdrawal syndromes
- drug use complications
- drug information
- prescribing information
- assistance with cases of acute intoxication

Metropolitan: (03) 9416 3611
country areas (toll free): 1800 81 2804

Drugs and Poisons Unit, Department of Human Services

The Unit issues permits for approved practitioners to prescribe methadone. It also approves individual medical practitioners and pharmacists to respectively prescribe or dispense methadone.
PO Box 1670N, Melbourne, 3001
Telephone: 1300 364 545
Fax: 1300 360 830

Direct Line

For the general public and health and welfare professionals. Provides counselling, information and referral, including:

- needle syringe exchange and bin location
- drug and alcohol agencies and drug withdrawal beds
- methadone program contact details
- HIV/AIDS information and referral
- drink/drive education and assessment referral.

Metropolitan: (03) 9416 1818
Country areas (toll free): 1800 13 6385

Youth Substance Abuse Service

YSAS provides information, outreach and residential services for young people aged between 12 and 21 experiencing significant problems related to their use of drugs and/or alcohol.

14-18 Brunswick Street, Fitzroy 3065
Telephone: (03) 9415 8881
Fax: (03) 9415 8882
Website: http://www.ysas.org.au

YSASLine

YSASline provides 24 hour access to information, telephone counseling, and referral to YSAS outreach teams. The service is open to young people, their families, health and welfare workers, police and ambulance officers. Call YSASline to contact an outreach team. Access to the YSAS residential service is made by contacting your local outreach team via YSASline.

Metro: (03) 9244 2450
Country freecall: 1800 014 446

VIVAIDS: the Victorian Users Group

VIVAIDS provides information on anything and everything to do with drugs. They also provide peer support, peer education, referrals, needle exchange and advocacy to drug users, while promoting harm reduction to users and the community.

765a Nicholson Street
North Carlton 3054
Telephone: (03) 9381 2211

Specialist Methadone Services

Specialist Methadone Services provide a consultative service to methadone prescribers seeking expert opinion about the management of patients with special problems, such as psychiatric, social, medical or treatment problems. Patients may be referred by arrangement, or advice sought by contacting the service.

Turning Point Drug and Alcohol Centre
54 Gertrude St., FITZROY 3065

Administration
Telephone: (03) 9254 8061
Fax: (03) 9416 3420

Clinical Services
Telephone: (03) 9254 8050
Fax: (03) 9486 9766

South Eastern Methadone Consultancy Clinic
61-69 Brighton Rd., ELWOOD 3184
Telephone: (03) 9525 7399
Fax: (03) 9525 7369

Western Hospital Drug and Alcohol Service
Gordon St., FOOTSCRAY 3011
Telephone: (03) 9317 2217
Fax: (03) 9319 6027

Austin and Repatriation Medical Centre
Specialist Methadone Service
Studley Rd., HEIDELBERG 3084

Administration
Telephone: (03) 9496 5000

Pharmacy
Telephone: (03) 9496 4999
Fax: (03) 9459 4546

Eastern Region Specialist Methadone Service
Whithorse Community Health Service
65 Carrington Street, BOX HILL, 3128
Telephone: (03) 9890 2220

Royal Women's Hospital Chemical Dependency Unit

For women who are pregnant and use drugs. The unit provides a direct service for women who live within a 25 km radius, and secondary consultation for other women. Midwives and social workers are available for consultation.

264 Cardigan Street
Carlton 3053
Telephone: (03) 9344 2363

Health Insurance Commission.

The HIC provides information about medical consultations and pharmaceutical benefits obtained through its Doctor Shopper Hotline. It is also able to provide this information if the patient signs a privacy release form authorising the HIC to provide this information. Forms and explanatory letters are available from the HIC.

Health Insurance Commission
134 Reed Street
Tuggeranong ACT 2900

Doctor shopper hotline (free call):
Telephone: 1800 631 181

Hepatitis C information

Hepatitis C Support Line
Hepatitis C Council

The Hepatitis C Council has produced a booklet ***"Hepatitis C Contact"*** which provides information, and answers frequently asked questions.

Carlow House, Level 9
289 Flinders Lane, Melbourne 3000
Telephone: (03) 9639 3200
Country Calls: 1800 703 003

Hepatitis C Helpline

Telephone: (03) 9349 1111
Country Calls: 1800 800 241
TTY: 1800 032 665
Vietnamese Line: 1800 456 007

Department of Human Services

DHS pamphlet "***Hepatitis: the Facts***" available from the Department of Human Services, or on the internet at:
http://www.dhs.vic.gov.au/phd/9904043/index.htm

The Department of Human Services has produced a booklet ***"Management, Control and Prevention of Hepatitis C: Guidelines for Medical Practitioners"***. It is available from the Department.

Health care providers can obtain information and assistance with counselling from the Hepatitis C Educator (03 9288 4127). Advice on notification of hepatitis C can be obtained from the Infectious Diseases Unit.

AIDS information

AIDSLINE

Telephone: (03) 9347 6099
Country Calls: 1800 133 392
TTY: 1800 032 665

Melbourne Sexual Health Centre

580 Swanston Street, Carlton 3053
Telephone: (03) 9347 0244
Country Calls: 1800 032 017

Needle and Syringe Exchange Programs (NSEPs)

Contact details of Victorian NSEPs is available:

On the internet at:
http://hna.ffh.vic.gov.au/phb/9808109/index.htm
or by calling Direct Line (see above).

WESTERN AUSTRALIA

Alcohol and Drug Information Service

Telephone: (08) 9442 5000
Country Calls: 1800 198 024

Clinical Advisory Service

Next Step
32 Moore Street, EAST PERTH WA 6004
Phone: (08) 9442 5042
Country Calls: 1800 688 847

Pharmaceutical Services (Doctors and Pharmacists)

Health Department of Western Australia
Telephone: (08) 9388 4985

Appendix 5

Naltrexone – A User's Guide

Glossary

abstinence – not using a particular drug; being drug-free.

opioid antagonist – a drug which blocks the effects of opioid drugs.

dependence – the drug has become central to a person's thoughts, emotions and activities. Stopping, or reducing the drug suddenly, can lead to physical withdrawal symptoms.

euphoria – feeling of well being – the 'high' or 'rush'.

opioid – class of drugs including heroin, methadone, codeine, pethidine, morphine etc.

rapid opioid detox – this is an experimental technique to accelerate withdrawal from opioids while the person is under sedation.

receptors – brain structures which bind particular drugs. The effects of a drug are experienced when the drug has attached itself to its corresponding receptor.

tolerance – requiring higher doses of the drug to experience the same effects.

This booklet is about the use of naltrexone to help you maintain abstinence from opioids such as heroin and methadone. It is not about the use of naltrexone in rapid opioid detox.

What is naltrexone?

Naltrexone is a drug prescribed to help people maintain abstinence after they have successfully detoxified from heroin and other opioids. It acts by blocking the opioid receptors in the body. Using heroin or other opioids while on naltrexone will have little or no effect.

Other uses of naltrexone

Naltrexone is sometimes used in the treatment of alcohol dependence. It appears to reduce the desire to drink alcohol in some people. It does **not reduce the effects** of alcohol, or other drugs except for opioids.

How do you get naltrexone?

Naltrexone is only available on prescription from a doctor. Naltrexone goes under the trade name of ReVia[R].

Although any doctor can prescribe naltrexone, it is recommended that you seek a doctor who is experienced in the treatment of alcohol and other drug dependence. This may include:

- doctors who specialise in naltrexone treatment
- doctors in clinics providing alcohol and other drug treatment services
- general practitioners experienced in alcohol and other drug treatment.

Who can undergo naltrexone treatment?

There are a number of factors that need to be considered before a doctor can prescribe naltrexone.

- Before starting your medication your body must be free from heroin for 7-10 days and up to 14 days if you have been using methadone. This means you must completely detox from opioids before you can begin taking naltrexone. The reason for this is that naltrexone will bring on immediate and possibly severe withdrawal symptoms if there are opioids in your body. Your doctor may decide to test you with Narcan (naloxone) to ensure you are opioid free. If you do have opioids in your system, Narcan will immediately bring on withdrawal symptoms which can last approximately 1 hour.
- Certain liver conditions may exclude you from taking naltrexone. These include acute hepatitis and alcoholic liver disease. Inform your doctor of any liver condition that you may have.
- Pregnant and breastfeeding women should seek the advice of their doctor. It has not been established that using naltrexone during pregnancy is completely safe.
- There are better outcomes from naltrexone treatment for people who are highly motivated to become opioid free and who are well supported by friends and family.

What does naltrexone treatment involve?

The treatment involves taking a prescribed course of naltrexone tablets for up to one to two years. These tablets are taken by mouth, once a day.

Naltrexone comes in bottles of 30 tablets. Your doctor however may start you off on a lesser amount and monitor your progress more closely.

Some doctors believe that naltrexone should be taken under the supervision of a family member, pharmacist or a doctor etc.

Naltrexone is dispensed by retail or mail-order pharmacies

As in many other conditions, the medication can be more effective when combined with counselling and ongoing support from friends and family. You should discuss this with your doctor who may be able to suggest some counselling or other support for you.

Why undergo naltrexone treatment?

- It acts as a disincentive to continued drug use. Using heroin or other opioids while taking naltrexone will not produce any of the usual effects. This is because the opioid receptors have been blocked.
- Naltrexone does not produce physical or psychological dependence.
- As long as you no longer inject, naltrexone reduces the risk of hepatitis C, HIV and other health problems.
- It allows you to stabilise your lifestyle.

What naltrexone doesn't do

- It is **not** a miracle cure for opioid dependence. This is why counselling and other support is important when taking naltrexone medication.
- It does **not** produce any euphoric effects.

Side effects

Naltrexone is generally well tolerated in the human body. However, there have been some side effects reported. Some of these may be withdrawal symptoms associated with heroin or other opioid dependence. Side effects may include:

- depression
- sleep disturbances
- headaches
- loss of energy
- nausea and vomiting
- abdominal pain
- constipation
- loss of appetite
- anxiety

Risks

The greatest danger associated with naltrexone is the risk of death by opioid overdose after either **skipping a dose** of naltrexone or **stopping naltrexone**. This is because **naltrexone rapidly reduces your tolerance to opioids**.

If you are considering taking heroin or other opioids once you have stopped or skipped a dose of naltrexone, you need to consider yourself as a new user. Overdose may occur if you use the same – **or even a smaller** – amount of heroin or other opioids than you used before taking naltrexone.

Risks while on naltrexone

- If you have a history of depression you should let your doctor know as naltrexone use can be associated with depression.
- As naltrexone blocks the opioid receptors, taking other opioid-based treatments such as Panadeine Forte or codeine-based cough medicines will be ineffective. Any emergency service provider (ambulance officers, casualty staff etc) or doctor needs to know that you are taking naltrexone. Non-opioid treatment can be used in these situations.

Skipping doses

After each dose of naltrexone, the blocking effect wears off gradually leaving receptor sites vacant. For example, a 50mg tablet wears off in about a day. Higher doses may last longer. Any use of heroin or other opioids while on naltrexone is risky, even if they have no effect.

This situation is more critical when methadone is being used. This is because a dose of methadone can last in the body for 24 hours, during which time the amount of naltrexone in the body is declining. This means that a dose of methadone which initially has no effect may over several hours come to produce serious overdose effects.

Is it the right treatment for me?

Naltrexone is one of a range of treatment options for opioid dependence. Other treatment options include:

- methadone maintenance
- detox, rehabilitation
- counselling.

Deciding to undergo naltrexone requires careful consideration. The important thing to remember is that you must detox first. Naltrexone is not a euphoric alternative to heroin or other opioids. It's a drug which blocks euphoric effects and helps you maintain abstinence.

Taking naltrexone medication is only part of the treatment. Counselling and support are valuable supplements in getting to an opioid free lifestyle.

Talk to a counsellor or your doctor to assess whether naltrexone is the best option for you.

More information

For more advice and information on naltrexone or where to go for treatment call ADIS (Alcohol and Drug Information Service) on:

phone: (02) 9361 2111

Toll free number: 1800 422 599

ADIS provides a 24 hours, 7 days confidential service which includes advice, information and referral to local agencies.

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Appendix 6

Withdrawal States from Commonly Used Drugs

Drug class	Onset	Duration	Symptoms
Opioids	8-12 hours (short acting). Delayed for longer acting opioids.	Peaks 2-4 days Ceases 7-10 days (short acting). Longer for long acting opioids.	Anxiety, muscle tension, muscle and bone ache, muscle cramps, sleep disturbance, sweating, hot and cold flushes, piloerection (goosebumps), yawning, lacrimation, rhinorrhea, abdominal cramps, nausea, vomiting, diarrhoea, palpitations, elevated blood pressure, elevated pulse, dilated pupils.
Alcohol	As blood alcohol falls, depends on rate of fall and hours after last drink.	5-7 days	Anxiety, agitation, sweating, tremor, nausea, vomiting, abdominal cramps, diarrhoea, anorexia, craving, insomnia, elevated blood pressure, elevated pulse, temperature, headache, seizures, confusion, perceptual distortions, disorientation, hallucinations, hyperpyrexia.
Benzodiazepines	1-10 days depending on half-life	3-6 days	Anxiety, insomnia, muscle aching and twitching, perceptual changes, feelings of unreality, depersonalisation, seizures.
Stimulants	8-36 hours	Several days, occasionally 2-3 weeks	Lethargy, depression, irritability, hyperphagia, anhedonia, dysphoria, desire for sleep increased.
Cannabis	Usually days	Weeks	Irritability, anxiety, insomnia, anorexia, sweating, muscle spasms, headaches.

From NSW Methadone Maintenance Treatment Clinical Practice Guidelines. Used with permission.

Appendix 7

Acute intoxication states from commonly used drugs

Class of Drug	Intoxication	Overdose
Opioids (eg methadone, heroin, morphine)	Constriction of pupils Itching/scratching Sedation/somnolence Lowered blood pressure Slowed pulse Hypoventilation	Loss of consciousness Respiratory depression Pinpoint pupils Hypotension Bradycardia Pulmonary oedema
Alcohol	Relaxation Disinhibition Impaired coordination Impaired judgement Decreased concentration Slurred speech Ataxia Vomiting	Disorientation/confusion Respiratory depression Loss of consciousness Loss of bladder control
Benzodiazepines (eg diazepam, oxazepam, flunitrazepam)	Disinhibition Sedation Drooling Incoordination Slurred Speech Lowered blood pressure Dizziness	Stupor/coma Ataxia Confusion Respiratory depression
Stimulants (eg amphetamines, cocaine)	Hyperactivity Restlessness Agitation Anxiety/nervousness Great dilation of pupils Elevated blood pressure Increased pulse Raised temperature Sweating Tremor	Panic Acute paranoid psychosis Seizures Cardiac arrhythmias Myocardial ischaemia Hypertensive crisis Cerebrovascular accidents Hyperpyrexia Dehydration
Cannabis	Relaxation Decreased concentration Decreased psychomotor performance Impaired balance Conjunctival injection	Paranoid psychosis Confusion Agitation Anxiety/panic Hallucinations

From NSW Methadone Maintenance Treatment Clinical Practice Guidelines. Used with permission.

Appendix 8

Assessment of withdrawal from opioids

The Subjective Opiate Withdrawal Scale (SOWS)

Date Time

Please score each of the 16 items below according to how you feel NOW (circle one number)

	Symptom	Not at all	A little	Moderately	Quite a bit	Extremely
1	I feel anxious	0	1	2	3	4
2	I feel like yawning	0	1	2	3	4
3	I am perspiring	0	1	2	3	4
4	My eyes are teary	0	1	2	3	4
5	My nose is running	0	1	2	3	4
6	I have goosebumps	0	1	2	3	4
7	I am shaking	0	1	2	3	4
8	I have hot flushes	0	1	2	3	4
9	I have cold flushes	0	1	2	3	4
10	My bones and muscles ache	0	1	2	3	4
11	I feel restless	0	1	2	3	4
12	I feel nauseous	0	1	2	3	4
13	I feel like vomiting	0	1	2	3	4
14	My muscles twitch	0	1	2	3	4
15	I have stomach cramps	0	1	2	3	4
16	I feel like using now	0	1	2	3	4

Range 0-64. Handelsman, L., Cochrane, K. J., Aronson, M. J. et al. (1987)
Two New Rating Scales for Opiate Withdrawal, *American Journal of Alcohol Abuse*, 13, 293-308.

Objective Opioid Withdrawal Scale (OOWS)

Date Time

Observe the patient during a 5 minute observation period

then indicate a score for each of the opioid withdrawal signs listed below (items 1-13). add the scores for each item to obtain the total score

	Sign	Measures		Score
1	Yawning	0 = no yawns	1 = ≥ 1 yawn	
2	Rhinorrhoea	0 = < 3 sniffs	1 = ≥ 3 sniffs	
3	Piloerection (observe arm)	0 = absent	1 = present	
4	Perspiration	0 = absent	1 = present	
5	Lacrimation	0 = absent	1 = present	
6	Tremor (hands)	0 = absent	1 = present	
7	Mydriasis	0 = absent	1 = ≥ 3 mm	
8	Hot and Cold flushes	0 = absent	1 = shivering / huddling for warmth	
9	Restlessness	0 = absent	1 = frequent shifts of position	
10	Vomiting	0 = absent	1 = present	
11	Muscle twitches	0 = absent	1 = present	
12	Abdominal cramps	0 = absent	1 = Holding stomach	
13	Anxiety	0 = absent	1 = mild - severe	
	TOTAL SCORE			

Range 0-13

Handelsman, L., Cochrane, K. J., Aronson, M. J. et al. (1987) Two New Rating Scales for Opiate Withdrawal, *American Journal of Alcohol Abuse,* 13, 293-308

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