



Australian Government

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

Abbreviated Version



*National
Drug Strategy*

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

Abbreviated Version

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August 2003

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ISBN 0 642 82264 6

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Publication approval number: 3266 (JN 7619)

Publications Production Unit
Australian Government Department of Health and Ageing

Introduction

These guidelines have been prepared to aid medical practitioners in the selection and management of patients seeking treatment with naltrexone hydrochloride for prevention of relapse to opioid dependence.

These 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). This publication is funded by the Australian Government Department of Health and Ageing for the National Drug Strategy.

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

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

Contents

Introduction	3
1 General Information	5
Regulation of Naltrexone in Australia	5
Rationale for use of naltrexone in opioid dependence	5
Indications	5
Contraindications to initiating naltrexone treatment	5
Precautions	6
Side effects	6
Safety of naltrexone treatment	6
Effectiveness of naltrexone treatment	6
2 Selection Issues	7
Assessment 7	
Motivation for treatment/expectations of treatment	7
Drug use history	7
Medical and Psychiatric history	7
Psychosocial history	7
Physical examination	7
Investigations (where clinically indicated).	8
Informed consent	8
Induction onto naltrexone	8
The conventional approach	8
Buprenorphine-assisted detoxification	8
Antagonist accelerated induction (“rapid detoxification”)	8
3 Management of opioid dependent patients on naltrexone	9
Dose and duration of treatment	9
Supportive care for patients on naltrexone	9
Role of psychosocial interventions	9
Coordinated Care	9
Monitoring and review	10
Compliance	10
Relapse	10
Re-induction onto naltrexone	10
Transfer to maintenance substitution treatment	11
Management issues in naltrexone treatment	11
Intermittent naltrexone use	11
Diversion of naltrexone	11
Polydrug use	11
Adjunct pharmacotherapies	11
Pain management	12
Pregnancy	12

1 General Information

- Naltrexone is a highly specific opioid antagonist with a high affinity for opiate receptor sites. It competitively inhibits opioid agonists, such as methadone, heroin and slow release morphine if they are present.
- 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.
- These guidelines refer primarily to the use of naltrexone in **relapse prevention** – for patients already detoxified from opioids (heroin or methadone) and seeking assistance to remain abstinent.
- It is not recommended that medical practitioners use naltrexone to accelerate withdrawal from opioids. However, a section on the use of naltrexone in Rapid Opioid Detoxification is included in the full version of these guidelines for those practitioners who have decided to perform rapid detoxification on a regular basis.

Regulation of Naltrexone in Australia

- Naltrexone is available **on the PBS** for only one indication, as an authority prescription for relapse prevention in the management of **alcohol dependence**.
- Naltrexone is available on **private prescription** for relapse prevention in **opioid dependence**.
- Naltrexone is **NOT** registered in Australia for use in **opioid withdrawal**, although naltrexone is occasionally used to accelerate the process of withdrawal from opioids.

Rationale for use of naltrexone in opioid dependence

The rationale for using naltrexone in relapse prevention is that naltrexone blocks the effects of heroin.

- Naltrexone should be seen as a medication which may help motivated patients to remain abstinent, rather than a medication which reduces patients' desire to use heroin.

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

Indications

- Opioid Users:
- Seeking to remain abstinent from opioids
 - Capable of giving informed consent to naltrexone treatment.

Contraindications to initiating naltrexone treatment

- 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:

- Women who are pregnant or breast feeding as naltrexone is categorised 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 aged less than 18, as the effects of naltrexone in the treatment of opioid dependence in these populations are unknown. Referral to specialist alcohol and drug services is recommended.

Side effects

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

Adverse events reported by more than 10% of patients in clinical trials treating opioid dependence 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 due to loss of tolerance in patients who return to opioid use after being treated with naltrexone.

Effectiveness of naltrexone treatment

The effectiveness of naltrexone treatment for relapse prevention is limited.

- Only a minority of opioid dependent people seeks naltrexone treatment.
- Among those entering treatment there is a very high rate of dropping out.
 - dropout rates in the first two weeks of naltrexone treatment average 39% in published studies.
 - The average time in treatment ranges from 1 to 8 months.

2 Selection Issues

Naltrexone is indicated as an **adjunctive therapy** in the maintenance of formerly opioid-dependent patients who have ceased the use of opioids. Naltrexone can be a useful adjunct to counselling and other rehabilitation options

Assessment

Naltrexone is not a treatment that should be considered suitable for all opioid dependent patients. The clinical utility of naltrexone is optimised with careful screening and selection of patients. Where the risks of treatment outweigh the potential benefits, it is not appropriate to prescribe. Assessment of drug users is based on the following domains.

Motivation for treatment/expectations of treatment

- clarify reasons for presentation
- clarify patient's goals

Drug use history

- current levels of drug use (quantity and frequency of use)
- duration of use
- assessment of physical dependence
- polydrug use
- history of treatment for drug problems

Careful drug use history taking is extremely important

Medical and Psychiatric history

- caution re: depression, psychosis
- caution re: liver disease, cardiac disease

Psychosocial history

- housing, relationships (including children), schooling, employment, family history
- forensic history (including current charges)
- does the patient have an adult sponsor who can help supervise naltrexone dose and provide social support

Physical examination

- evidence of use
- evidence of withdrawal
- evidence of intoxication
- general health

Investigations (where clinically indicated).

- urinalysis
- LFT
- pregnancy
- naloxone challenge test

Informed consent

- Document informed consent to initiating naltrexone treatment
- Counsel patient about overdose risk and reiterate this at regular intervals
- Written patient information should be provided

Induction onto naltrexone

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 extremely ill. To avoid this there are three approaches to induction onto naltrexone treatment.

The conventional approach

- Undertake detoxification
- Commence naltrexone after 5 days free of short acting opioids (eg heroin) or 10 days free of methadone.
- As patient history can be unreliable it is desirable to perform a naloxone challenge test prior to the first dose of naltrexone (see Appendix 1 of the full Clinical Guidelines and Procedures for the use of Naltrexone in the Management of Opioid Dependence).

Buprenorphine-assisted detoxification

- Buprenorphine assisted detoxification can allow the introduction of naltrexone without risk of severe precipitated withdrawal. (See Appendix 2 of the full Clinical Guidelines and Procedures for the use of Naltrexone in the Management of Opioid Dependence and the National Buprenorphine Guidelines).

Antagonist accelerated induction (“rapid detoxification”)

It is not recommended that medical practitioners use rapid detoxification as a means of induction onto naltrexone

- Guidelines for rapid detoxification are included in the full version of these clinical guidelines for those medical practitioners using, or considering using, rapid detoxification on a regular basis. This brief version of the clinical guidelines is intended for those medical practitioners regularly prescribing naltrexone for relapse prevention and assumes familiarity with the full version.

3 Management of opioid dependent patients on naltrexone

Dose and duration of treatment

25mg daily produces adequate blockade of opioid receptors
50mg daily is the usual maintenance dose

Treatment for dependence is a long-term process, and the optimal period of treatment will be different for different patients. This decision should be based on review of achievement of lifestyle changes, environmental risk factors, and craving.

Patients should generally be encouraged to continue on their naltrexone management program for at least 6 months.

Supportive care for patients on naltrexone

Intensive follow-up is a critical component of optimising the benefits of naltrexone.

Role of psychosocial interventions

Clinicians need to be aware of the critical role of broader psychosocial interventions in achieving and maintaining abstinence from opioids. Medical practitioners should attempt to refer patients to appropriate psychosocial treatment service providers if they are not already accessing such services. Useful supports include:

- self help groups
- community health centres
- counselling/life skills at a non government organisation
- private counselling and/or psychotherapy

Coordinated Care

Medical practitioners may not be willing, nor able, to manage all aspects of a patient's problems. Shared care models for naltrexone treatment include:

- induction by a specialist service, with continued prescribing of naltrexone and clinical review by GP
- induction and maintenance of naltrexone and clinical review by a GP, with counselling provided by A&D specialist service
- referral/consultancy for special issues (e.g. pregnancy, polydrug use, depression)

Monitoring and review

Patients should be seen regularly while on naltrexone treatment. Generally patients should be seen daily for the first three days, then at weekly intervals.

Clinical reviews should be conducted weekly during the first month of treatment, then fortnightly or monthly as required.

Compliance

Some people may prefer to have the administration of their naltrexone dose observed by a carer. Others will prefer to be unsupervised. This issue should be resolved before commencing naltrexone treatment, and reviewed during treatment. Supervised naltrexone dosing leads to higher rates of treatment compliance than unsupervised naltrexone dosing.

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

- check drug use, for both heroin and other drugs
- check compliance with naltrexone regime
- assess changes in social functioning and relationships
- monitor side effects (especially mood)

Relapse

- Seek clarification of their goals
- If heroin use is ongoing, consider methadone or buprenorphine maintenance treatment
- Counsel patient about the risks of overdose

Re-induction onto naltrexone

After ceasing naltrexone, there is rapid reinstatement of physiological dependence within days of regular heroin use. Resuming naltrexone can precipitate severe withdrawal. If the patient wishes to restart naltrexone, the recommended approach is:

- If it is more than 5 days since last naltrexone use and patient has used heroin each day since then, start as though new patient requiring detoxification.
- If it is within 5 days of last naltrexone dose
 - can restart naltrexone under medical supervision - patients may experience withdrawal, but usually not severe
 - Restart naltrexone in the morning, at least 24 hours after last use of heroin
 - Commence with 1/4 tablet (12.5mg)
 - Patients may need symptomatic medication
- There are diminishing returns from multiple reinstatements – consider alternative treatments

Transfer to maintenance substitution treatment

See also the *National Methadone Guidelines* and the *National Buprenorphine Guidelines*.

- The first dose of methadone should ideally be delayed until 72 hours after the last dose of naltrexone
- It may be possible to initiate treatment with 20mg methadone after 48 hours, although patients should be warned that it may take some time to reach full effectiveness due to 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 4mg, although rapid dose increases can occur subsequent to review by the prescribing doctor.

Management issues in naltrexone treatment

Intermittent naltrexone use

Some patients may wish to use naltrexone in an intermittent way, such as;

- Abstinent, but facing high risk situation, so takes one tablet
- Wanting to use heroin only on weekends

There is no research in this area and there are potential risks –
Risk of misjudging level of tolerance
Precipitated withdrawal.

Patients should therefore be warned against this practice.

Diversion of naltrexone

Patients should be counselled 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.

Polydrug use

Patients receiving naltrexone treatment may increase other drug use, especially benzodiazepines, cannabis, amphetamines, and alcohol. Medical practitioners should monitor use of these drugs. In a situation of abuse or dependence on other drugs, the risks and benefits of continuing naltrexone treatment should be assessed.

Adjunct pharmacotherapies

Symptomatic withdrawal medication may be warranted for patients experiencing withdrawal symptoms in the first few days of commencing naltrexone. Recommended medications include:

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

Selective Serotonin Reuptake Inhibitors (SSRI) may be prescribed if patient has features of clinical depression. Many heroin users will complain of dysphoria during withdrawal and in the first few days of naltrexone treatment but this usually resolves spontaneously.

There is no evidence to support the routine use of other medications (e.g. antipsychotics, anticonvulsants).

Pain management

- All patients should be provided with a medical warning card
- 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

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

- If the patient and doctor agree that there is a low risk of relapse, cease naltrexone and monitor the patient through pregnancy.
- If the patient is concerned about relapse and wishes to continue on naltrexone, inform the patient of the risks and obtain informed consent to continuing treatment.
- If the patient wishes to cease naltrexone but reports starting to use heroin again, consider methadone treatment.