Naltrexone in the treatment of opioid dependence

Naltrexone is an opioid antagonist that acts by preventing the reinforcing effects of addictive opioids. This article provides an overview of naltrexone, its pharmacology, treatment effectiveness and role as a relapse prevention agent in the treatment of opioid dependence.

Naltrexone is an orally effective, long-acting opioid antagonist. Because of its mu-receptor antagonism, naltrexone prevents the positive reinforcing effects of addictive opioids such as heroin, hence its usefulness as a relapse prevention agent in the treatment of opioid dependence. Apart from its antagonistic property, naltrexone is pharmacologically inert, so is safe and has no potential for misuse. Naltrexone is also effective in treatment of alcohol dependence (Latt et al, 2002), although it is not yet licensed for this in the UK. This article will only discuss its use as a relapse prevention intervention in opioid dependence. Naltrexone is not a controlled drug and received its product license for treatment of opioid dependence in the UK in 1988.

Pharmacological profile

Naltrexone ([17-(cyclopropylmethyl)-4,5α-epoxy-3,14-dihydroxymorphinan-6-one] – *Figure 1*) is a competitive antagonist at mu, kappa and delta opioid receptors. It blocks the euphoric effects of opioids, minimizing the rewarding and positive reinforcing potential associated with their use, as well as blocking their analgesic effects.

Pharmacokinetics

Naltrexone is rapidly and very well absorbed after oral administration but it undergoes extensive first-pass metabolism (Gonzalez and Brogden, 1988). Its plasma half-life is about 4 hours, while its primary (and active) metabolite (6-beta-naltrexol) has a half-life of about 10 hours. Despite this, mu receptor blockade after oral naltrexone lasts for up to 72 hours (Lee et al, 1988). It is eliminated from the body by hepatic metabolism but neither naltrexone nor 6-beta-naltrexol is metabolized by cytochrome P450 enzymes. Hence it is unlikely that the pharmacokinetics of naltrexone are affected by drugs that inhibit or induce the cytochrome P450 system. Only 1% of naltrexone is excreted in urine as free naltrexone (Meyer et al, 1984).

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Side effects and safety

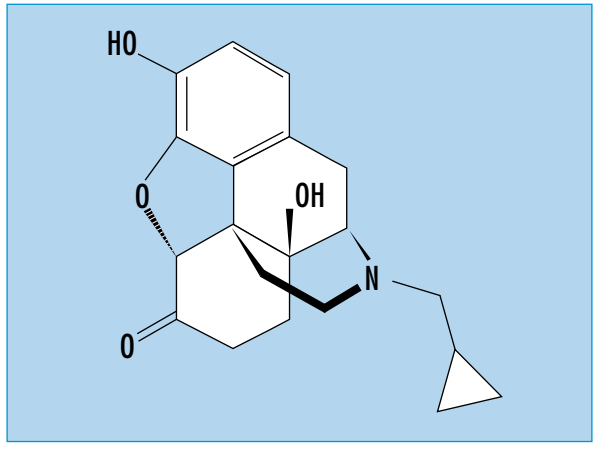
Naltrexone has an excellent side-effect profile – although up to 10% of new starters may experience nausea, headache, dizziness, fatigue or insomnia, almost always these are mild and transient, and very rarely require discontinuation of naltrexone. It is worth noting that some of these symptoms could also be the result of a mild opioid withdrawal syndrome. Hypersensitivity reactions are very unusual. Rarely, naltrexone can cause hepatocellular injury, and in a dose-dependent fashion even hepatotoxicity. Hence particular caution should be exercised in patients with compromised liver function, and routine monitoring of liver functions before and during naltrexone treatment is advised.

Perhaps the only serious risk associated with oral naltrexone treatment is the risk of overdose or death upon cessation of treatment. Because of a drop in tolerance to opioids, the same dose of opioid (such as heroin or methadone) that the patient was used to before treatment can be fatal if taken after stopping naltrexone.

Cautions

Any patient starting naltrexone must be warned against concomitant use of opioid drugs, including opioid-containing cough or common cold remedies and opioid pain killers. Opioid analgesia will be ineffective when taking naltrexone and hence non-opioid analgesics are preferred for the management of pain in these patients. It is rec-

Figure 1. Molecular structure of naltrexone [17-(cyclopropylmethyl)-4,5α-epoxy-3,14-dihydroxymorphinan-6-one].



ommended that naltrexone be stopped at least 72 hours before elective surgery requiring opioid analgesia. Patients taking naltrexone should always carry with them a medical warning card that states their treatment.

Naltrexone is not licensed for use in patients under the age of 18 years. Although naltrexone has not been found to have any specific teratogenic potential, because of insufficient evidence it is not recommended for use in pregnancy. Finally, naltrexone is contraindicated in patients with acute hepatitis, hepatic or renal failure and in those currently using opioids.

Naltrexone for relapse prevention in opioid dependence

Initiation on naltrexone

The National Institute for Health and Clinical Excellence (2007) notes three underpinning principles that should guide the clinician in starting and maintaining a patient on naltrexone:

1. Naltrexone is a treatment option for highly motivated and detoxified, previously opioid-dependent individuals
2. Naltrexone should be offered as part of a comprehensive and supportive treatment programme
3. Its treatment effectiveness should be regularly reviewed and monitored.

Naltrexone should only be initiated 7–10 days after the last intake of an opioid (usually 7 days after a short-acting opioid such as heroin and 10 days after a long-acting opioid such as methadone), as otherwise it can precipitate withdrawal symptoms. It is also essential that subjective patient report of abstinence is corroborated by negative urine or saliva test for opioids. As naltrexone is contraindicated in pregnancy, a pregnancy test should be considered before initiation. Also, because of its potential for hepatotoxicity, it is recommended that liver function tests are carried out before starting naltrexone. If liver function tests are more than three to five times normal, do not start naltrexone; in the absence of more specific guidance, it is suggested that should one or more of the liver enzymes (such as alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase and gamma glutamyl transferase) or other markers of liver function (such as bilirubin and prothrombin time) be raised three to five times, specialist advice should be sought before starting naltrexone.

Some experts (Bell et al, 2003) even recommend carrying out a naloxone (a short-acting, parenterally administered opioid antagonist) challenge before staring naltrexone, to ensure that the person is clean of opioids. This is done by administering naloxone 200 µg intravenously and observing the person for withdrawal symptoms for 1 minute. If there are no withdrawal symptoms, administer another injection of naloxone 600 µg and if there are still no withdrawal symptoms for 5 minutes, start naltrexone. Should withdrawal symptoms be precipitated during the challenge, do not start naltrexone, until the challenge is repeated a few days later. However, in busy clinical settings it may not always be possible to do a challenge and in such instances a negative opioid test should suffice. Although uncommon, because of naltrexone's hepatotoxic potential, liver function tests before starting naltrexone are essential. Thereafter, they should be monitored regularly. It is recommended that naltrexone be initiated by a specialist and the patient monitored regularly for side effects, compliance and safety. *Figure 2* summarizes a typical treatment schedule with naltrexone.

Naltrexone's efficacy as a relapse prevention agent is strongly determined by compliance and patient retention in treatment. Hence, where feasible, naltrexone intake should be supervised by a family member and adjunctive psychosocial interventions to improve retention (e.g. contingency management) should be offered as part of the treatment package (Department of Health et al, 2007). Contingency management, based on operant conditioning principles, when used in the treatment of drug misusers involves giving patients rewards or incentives (e.g. vouchers, other privileges) contingent on certain agreed desirable behaviours (e.g. maintenance of abstinence from opioid use).

Maintenance on naltrexone

There is little accurate guidance as to how long to continue patients on naltrexone, with the suggested duration ranging from months to years. In clinical practice, naltrexone is often continued for as long as it takes the individual to make adequate changes in his/her life that will aid or maintain abstinence, such as changes in lifestyle, friends, job or assertiveness. While these changes are taking place, naltrexone acts as a safeguard or an 'insurance' for the person to prevent use of opioids.

A particular safety concern clinicians have to bear in mind and one that should be discussed with the patient and his/her family or carer is the risk of overdose during naltrexone treatment and immediately following discontinuation of treatment. A patient on naltrexone might take large amounts of opioids in an attempt to override the blockade and to achieve pleasurable effects, resulting in an overdose situation. So too, soon after discontinuation of naltrexone, a patient might take an opioid in doses similar to those he/she is used to but as tolerance would have dropped significantly that dose can prove to be fatal. Finally, clinicians take note that as naltrexone's efficacy as a relapse prevention intervention is strongly determined by patient retention in treatment, psychosocial measures such as contingency management that improve retention should be offered as part of naltrexone treatment, for best results.

Figure 2. Treatment with naltrexone.

Starting dose:	Day 1 = 25 mg Day 2 onwards = 50 mg daily
Maintenance dose: 50 mg daily	
Alternative dosing schedule: three times a week (100 mg on Monday, 100 mg on Wednesday and 150 mg on Friday)	

Evidence base

There have been very few well-designed and sufficiently powered randomized control trials that have evaluated the efficacy of naltrexone in treatment of opioid dependence. Methodological limitations include small sample sizes, short study duration and sample heterogeneity. Earlier systematic reviews (Kirchmayer et al, 1999, 2002) failed to show significantly positive outcomes for naltrexone when used as the sole relapse prevention intervention in opioid dependence. However, Johansson et al (2006) in their meta-analytical review of the efficacy of naltrexone in opioid dependence found that it was significantly superior to control conditions in producing positive treatment outcomes. They also noted that retention in treatment was a powerful mediator for treatment success.

The National Institute of Health and Clinical Excellence (2007), assessing the evidence base and expert consensus in this field, concluded that in clinical practice naltrexone produced high rates of abstinence, use of naltrexone cut down mortality rates among addicts and that naltrexone resulted in significant improvements in the quality of life of patients. All in all, they stated: 'the committee was convinced of the clinical effectiveness of naltrexone treatment in a selected highly motivated group of people' and also that 'it would fall within acceptable cost effectiveness limits'.

Formulations of naltrexone

The most widely used and hence most extensively studied preparation of naltrexone is oral naltrexone tablets, which in the UK come in 50 mg tablets. However, naltrexone is also available in longer-acting formulations, depot injections and implants, both of which are unlicensed preparations. Preliminary evaluations of depot naltrexone are encouraging: Comer et al (2006), in an 8-week, randomized, placebo-controlled trial of depot naltrexone, concluded that depot naltrexone was a feasible, efficacious and well-tolerated treatment for opioid dependence.

Naltrexone implants, although unlicensed in the UK and not yet robustly tested, are available to patients outside the NHS. In a 6-month trial involving 56 opioid abstinent patients, Kunoe et al (2009) showed that naltrexone implant treatment was safe and effective in reducing heroin use in motivated patients. However, significant safety concerns regarding naltrexone implants and the implantation procedure have also been noted in the literature (Lintzeris et al, 2008). Adverse events reported have included severe dehydration, severe opiate withdrawal (in the first few days after implantation, where the implantation has followed a rapid opiate detoxification), relapse of mental disorder and infection of the implant site. Other safety concerns relate to patients attempting to take out the implant themselves, or as noted earlier patients attempting to reverse the blockade effect by taking large doses of heroin, resulting in an overdose. Naltrexone is not to be confused with naloxone – a full opioid antagonist, administered parenterally (inactive orally) that is an effective antidote in reversing the effects of opioid overdose.

KEY POINTS

- Naltrexone is an orally effective opioid antagonist that is licensed for relapse prevention in opioid dependence.
- Naltrexone is safe and well tolerated. It is non-addictive, has no withdrawal symptoms on cessation, has few side effects and has no serious drug interactions.
- Retention in treatment and compliance with treatment are strong mediators of naltrexone's treatment success.
- Naltrexone should only be offered as part of a comprehensive psychosocial treatment package.
- Longer acting preparations of naltrexone such as depots and implants, although as yet unlicensed, offer promise for the future.

Conclusions

Naltrexone is safe and effective as a relapse prevention intervention in opioid dependence. However, patient retention and compliance with treatment are important mediators that determine naltrexone's treatment effectiveness. Although as yet unlicensed, parenteral preparations of naltrexone hold promise for the future. **BJHM**

Conflict of interest: none.

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