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Perioperative management of patients on naltrexone

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INTRODUCTION

Naltrexone is a long-acting opioid receptor antagonist increasingly prescribed in the community for a wide variety of conditions. Patients taking naltrexone present particular challenges in pain management in the perioperative period. Depending on the dose, formulation, and recency of taking naltrexone, patients may be very resistant to opioid analgesics or may also show increased sensitivity to the analgesic and respiratory effects of opioids. This complexity means that patients are at risk of both poorly controlled pain and respiratory depression, potentially within the same presentation. Patients should therefore be managed by multidisciplinary teams with experience in complex acute pain with the availability of respiratory monitoring and support.

This review will examine the current clinical uses of naltrexone including different dosages and administration. We will discuss the implications of naltrexone therapy for elective and emergency procedures and suggest approaches to analgesic and anaesthetic management in these complex patients.

PHARMACOLOGY

Naltrexone is a long-acting competitive antagonist of opioid receptors, with the highest affinity for μ-receptors. It has a half-life of 5 hours. It also has an active metabolite, 6β-naltrexone, which has a much longer half-life of 15 hours.[1] Oral doses are subject to extensive first pass metabolism in the liver, with only 2% excreted unchanged in the urine.[2] Naltrexone has an excellent safety profile, and is generally well tolerated by patients.[3] It has been associated with hepatotoxicity when given in very high doses[4] but has been shown to be safe even in patients with compensated cirrhosis at clinically relevant doses.[5] Common currently prescribed formulations of naltrexone are presented in Table 1.

CLINICAL INDICATIONS

Alcohol or opioid abstinence

Naltrexone is indicated as part of a comprehensive treatment plan for alcohol dependence with a goal of abstinence.[1] Naltrexone has also been show to decrease rates of relapse after abstinence from alcohol.[6,7] The mechanism of action is thought to be via reduction in reward and intoxication associated with drinking alcohol,[8] with the greatest clinical effect being in reducing heavy or excessive drinking.[9] Naltrexone is less commonly used for opioid abstinence as opioid substitution with buprenorphine or methadone is generally preferred in Australia.[10] The oral formulation is also used to treat opioid related side effects such as severe constipation in the palliative care setting as an off-label use.[11] Methylnaltrexone has a methyl group added to reduce its lipid solubility and to limit blood brain barrier crossing, and therefore is more selective for peripheral opioid receptors. It can be given as a subcutaneous injection to relieve severe constipation without counteracting analgesic effects on central nervous system.

In this high dose, naltrexone is available in several formulations. Oral naltrexone is taken in a dose of 50mg per day and this formulation is TGA approved in Australia and Medsafe approved in New Zealand. A subcutaneous implant is available through the Special Access Scheme only. Implants have a variable duration. The formulation accessible in Australia has a stated duration of action of approximately 180 days. A depot formulation, not currently available in Australia or New Zealand, has a duration of action of approximately 28 days.

Table 1. Naltrexone formulations in clinical use in Australia and New Zealand

Formulation (brand name)	Dose (route)	TGA/ Medsafe NZ Approved	Indications
Naltrexone Hydrochloride (Generic health, Naltraccord)	50mg daily (orally)	Yes	For use within a comprehensive treatment program for alcohol dependence. OR as adjunctive therapy in the maintenance of formerly opioid-dependent patients who have ceased the use of opioids such as diamorphine (heroin) and morphine.
O'Neil Long acting naltrexone implant (Go Pharmaceuticals)	1.8g surgical implant, every 6 to 12 months	Special Access Scheme approval only (TGA)	As above
Naltrexone depot for intramuscular injection (Vivitrol)	380mg every 4 weeks (intramuscular)	No	Alcohol dependence or for the prevention of relapse to opioid dependence, following opioid detoxification.
Naltrexone HCl / Bupropion (Contrave)	8-32mg / 90-360mg daily (orally)	Yes	Contrave is indicated, as an adjunct to a reduced-calorie diet and increased physical activity, for the management of weight in adult patients (≥18 years) with an initial Body Mass Index (BMI) of ≥ 30 kg/m^2 (obese), or ≥ 27 kg/m^2 to < 30 kg/m^2 (overweight) in the presence of one or more weight-related co-morbidities (e.g., type 2 diabetes, dyslipidaemia, or controlled hypertension)
Naltrexone Hydrochloride (pharmacy compounded medicine)	1-7mg daily (orally)	Off-label use of oral formulation	Used for a wide range of disorders, including chronic pain conditions and inflammatory conditions

Management of weight loss

A combination weight loss pill (Contrave – naltrexone/bupropion) was approved in 2019 by the TGA for patients with morbid obesity and at least one associated condition (for example, diabetes).[12] Patients on this therapy receive between 8 and 32 mg of naltrexone per day, in combination with sustained release bupropion. Naltrexone and bupropion work synergistically on central neural pathways in the hypothalamus to both reduce appetite and cravings for food[13] resulting in effective weight loss.[14]

Chronic pain and inflammatory conditions

Low dose naltrexone (1-6 mg per day) may be prescribed for the management of chronic pain conditions, and has been described for the treatment of a wide range of conditions such as fibromyalgia, Crohn's disease, multiple sclerosis, complex-regional pain syndrome, Hailey-Hailey disease, and cancer.[15] Low dose naltrexone is currently being explored as a treatment for chronic fatigue syndrome[16] and Post-COVID-19 Syndrome.[17] Anaesthetists may see patients presenting for fertility treatments on low dose naltrexone as it is increasingly utilised in this setting.[18] At low doses it is thought to display differential pharmacodynamics, and in this dose range may act as a glial modulator through actions at toll-like protein receptors in neural cells, as well as enhancing endogenous endorphin release.[19] Although there are promising in vitro studies,[20] high quality clinical evidence for low dose naltrexone in these conditions is lacking.[21] Evidence of clinical efficacy is largely anecdotal, with limited numbers of small randomised controlled trials.

All of these indications are currently off-label uses of naltrexone, and the prescription must be made up by a compounding pharmacy for patients in Australia and New Zealand. Given the wide range of conditions for which low dose naltrexone is prescribed, it is likely that anaesthetists will encounter increasing numbers of patients on this medication in their practice. Familiarisation with these off-label uses of naltrexone is important as it may not be expected or readily detected in the broader patient population.

Ultra-low dose naltrexone (in the range of picograms to nanograms per kilogram) is sometimes used in patients with chronic non-malignant pain who require high doses of opioids. In ultra-low doses, naltrexone appears to enhance analgesic efficacy and decrease certain side effects of opioid analgesics, and potentially reduce tolerance.[22] This is a relatively uncommon off-label use of naltrexone and is beyond the scope of this review.

PERIOPERATIVE CONSIDERATIONS

As a competitive antagonist of all opioid drugs, naltrexone has serious implications for the pain management of all patients presenting to hospital.[23] Patients utilising formulations of naltrexone may experience inadequately controlled pain and exceedingly high opioid requirements, as well as difficult to manage hypertension under general anaesthetic.[24] Without careful titration of opioid analgesia and monitoring of these patients, there is a risk of respiratory depression with the offset of naltrexone.[25]

Patients can be considered opioid naive after the cessation of naltrexone.[26] After discontinuation, enhanced opioid sensitivity may occur due to selective upregulation of μ-receptors. This means that response to opioids may be unpredictable, resulting in potentially higher risk of respiratory depression requiring close monitoring throughout the perioperative period.[27] These patients therefore may not be suitable for day case surgery and a need for post-operative admission to hospital should be assessed in each case.

Management of patients on naltrexone formulations is complex, and the best approach will vary depending on the needs of the patient, the procedure required, the dose of naltrexone and the need for opioid analgesia.

MANAGEMENT OF PATIENTS PRESENTING FOR ELECTIVE PROCEDURES

The approach to patients presenting for elective procedures is summarised in Figure 1. In essence, management of these patients requires identification of those taking naltrexone and then ensuring that this is ceased appropriately prior to surgery. If the patient is taking a combined naltrexone/bupropion preparation, replacement therapy may be required.

It may be appropriate to continue naltrexone therapy throughout the perioperative period. These decisions should be made on a case-by-case basis by surgical and anaesthesia teams in consultation with the naltrexone prescriber. Procedures that are expected to cause mild or no pain, or that can be managed entirely with non-opioid analgesia may be appropriate for this, such as cataract surgery, minor plastic procedures or colonoscopy.[27] This may be of particular benefit in patients at high risk of relapse of opioid or alcohol abuse if naltrexone therapy is ceased.

Management of patients on naltrexone for opioid or alcohol abstinence

Patients who are on naltrexone for opioid or alcohol abstinence will require cessation of therapy prior to most surgeries. Management of naltrexone in the perioperative period should be done in co-ordination with the patient's general practitioner and their naltrexone prescriber.[26] Preoperative patient and family education is important, to set expectations and ensure appropriate supports are in place.[28] Oral naltrexone should be stopped at least 24 hours, and ideally 72 hours, prior to elective surgery due to prolonged opioid receptor antagonism.[26] After 24 hours, a 100mg dose of naltrexone will effectively block 96% of μ-opioid receptors. This

falls to 86.5% at 48 hours and 46.6% at 72 hours.[28] In our institution, we recommend cessation of naltrexone 72 hours preoperatively to ensure best achievable opioid responsiveness for patients during the perioperative period. The period of cessation may need to be further prolonged in patients with renal or hepatic impairment.[1]

Naltrexone implants may need surgical removal in cases of severe acute pain, where opioid responsiveness is required.[26] Duration of action after removal of an implant is unknown, and it may be advisable to plan non-opioid analgesia rather than attempt removal.[29] If patients are on intramuscular injections of extended release naltrexone, this will need to be stopped at least 25 days prior to surgery in order to ensure naltrexone has been cleared.[30] Patients may need to be transitioned to oral naltrexone for this period, which can then be stopped 72 hours prior to surgery. This must be done in co-ordination with the patient's naltrexone prescriber.

Patients may be at high risk of relapse of alcohol or opioid abuse while off naltrexone and may benefit from extra supports during this period.[31] This may include early admission to hospital for observation and support if appropriate. Patients should be educated that the highest mortality risk is from patients taking pre-naltrexone doses of opioids, which may result in overdose and respiratory arrest.[32]

Management of patients on combined Naltrexone/Bupropion (Contrave)

There is no clear guidance from the manufacturer or in the literature about when Contrave should be stopped in the lead up to surgery. Given the dosages, it is prudent to cease 72 hours prior to surgery as for high dose naltrexone as similar issues are encountered intraoperatively.[33] This should be done in consultation with the patient's naltrexone prescriber as consideration needs to be given as to whether to continue bupropion as a single agent. The manufacturers do not recommend a taper for discontinuation of Contrave as no withdrawal syndromes were seen in initial randomised controlled trials.[12] However there have been case reports of withdrawal symptoms associated with bupropion discontinuation[34] and tapering regimens are recommended.[35] If the patient wishes to avoid antidepressant discontinuation syndrome, bupropion can be continued as a single agent. In Australia, bupropion is only available as an extended-release preparation, which should not be split.[36] A suggested dosing regimen is shown in Table 2, which facilitates minimal change in dose of bupropion.

It should be noted in these patients some opioid alternative medications must be used with caution. Bupropion is an inhibitor of CYP2D6, which may prevent tramadol being converted to its active metabolite and decrease its effectiveness.[37] Bupropion also lowers the seizure threshold.[38]

Table 2. Suggested replacement dosing of bupropion as a single agent for patients on Naltrexone/Bupropion (Contrave)

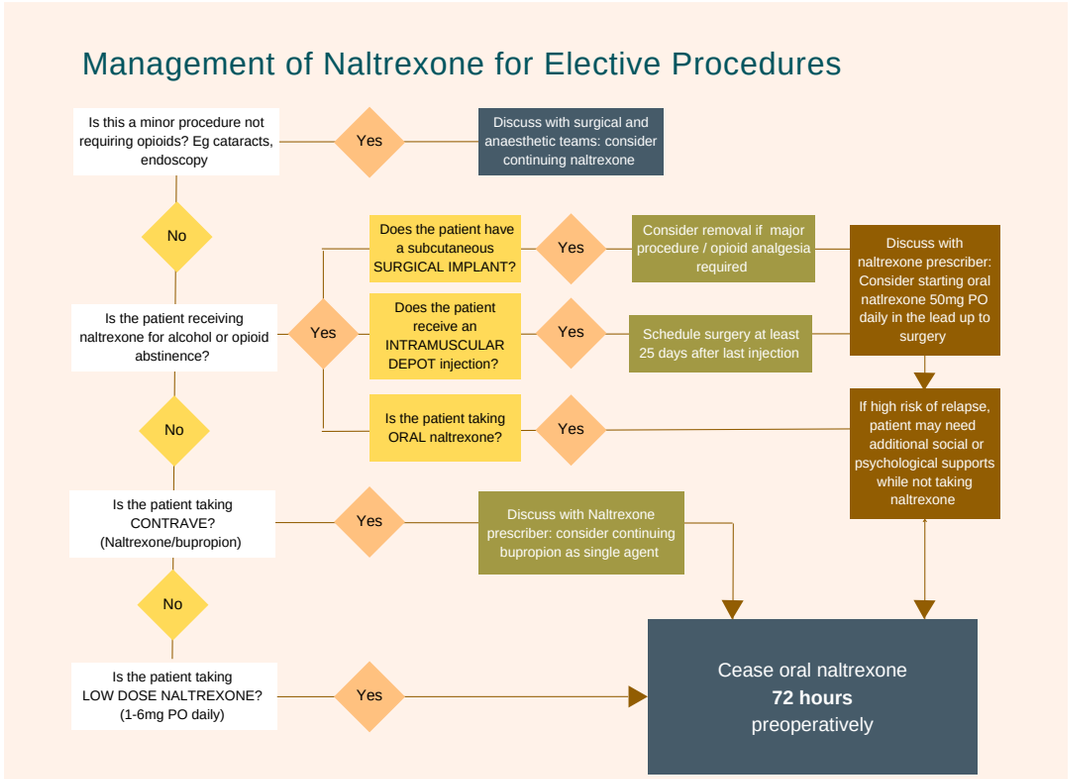
Daily dose of Contrave (Naltrexone/Bupropion)	Replacement dose of Zyban (Bupropion Extended Release)
One tablet per day (Total dose 8mg/90mg)	No replacement bupropion required
One tablet twice per day (Total dose 16mg/180mg)	150mg PO once daily
Three to four tablets per day (Total dose range 24mg/270mg to 32mg/360mg)	150mg PO twice daily

Management of patients on low dose naltrexone for chronic pain or inflammatory conditions

There is little data available regarding the impact of low dose naltrexone on analgesia and anaesthesia. Research into combined preparations of morphine and naltrexone have shown that low dose naltrexone (1.2mg) co-administered with oral and intravenous morphine significantly reduces both the subjective opioid effects as well as objective measures such as pupillometry.[39] In one study, low dose naltrexone co-administered with morphine resulted in significantly reduced end tidal CO_2, equivalent to placebo levels, when compared to morphine alone.[40] Patients taking these low doses of naltrexone will likely require higher than expected doses of opioid medication to achieve adequate pain control. It is not clear if cessation of naltrexone at this low dose results in similar opioid sensitivity as seen with cessation of high dose naltrexone.

Evidence is lacking as to the optimal timing for cessation of low dose naltrexone. General patient advice recommends cessation anywhere from 24 hours to 7 days before a procedure.[41,42] There are descriptions in the literature of uneventful anaesthesia 24 hours after low dose naltrexone,[43] however no detailed case reports are available. In our clinical experience, low dose naltrexone (1-6mg per day) continued throughout the perioperative period results in significantly increased opioid requirements, even when maximising non-opioid analgesia. Pain may also be more difficult to manage post operatively as a result. On the basis of this, we suggest low dose naltrexone to be withheld for 24 to 72 hours preoperatively. Our institutional guideline recommends a 72-hour period, for consistency across all naltrexone formulations.

Figure 1. Preoperative management of naltrexone for elective procedures



MANAGEMENT OF PATIENTS PRESENTING FOR EMERGENCY SURGERY OR WITH TRAUMA

All patients on naltrexone presenting for emergency surgery or with trauma should be managed by an experienced team with input from an acute pain service.

It is important to determine the timing of the last dose of naltrexone.[25] If this was within the last 72 hours, patients may require higher than usual doses of opioids to manage their pain. As a competitive antagonist, the effects of naltrexone can be overcome with sufficiently high dose opioid. In rats, the dose of opioids needed to accomplish this may be 10–20 times the standard clinical doses.[44] These doses may be associated with severe respiratory depression and non-opioid receptor related side-effects including erythema and bronchoconstriction.[45] The offset of the naltrexone may be abrupt and cause respiratory depression secondary to the un-antagonised action of now excessive opioids.[46] After cessation of naltrexone, patients are at risk of respiratory depression due to transient increased opioid receptor sensitivity as well as direct decrease in effect of naltrexone resulting in lower analgesic opioid dose requirements.[26] Patients should therefore be monitored in a high dependency environment with the capacity for ventilatory management.[47]

Cessation of naltrexone will allow the most analgesic options for patients with major surgery or multi-trauma during their recovery. If a patient is taking a naltrexone/bupropion preparation (Contrave), consider continuing bupropion as a single drug to avoid anti-depressant withdrawal symptoms. It may be appropriate for patients having only minor surgery with minimal postoperative pain to continue naltrexone uninterrupted. Patients on low dose naltrexone may be able to continue their naltrexone, compensating for this by utilising higher doses of opioids, but this remains an individual risk:benefit decision. An approach to patients presenting for emergency procedures is summarised in Figure 2.

Opioid medications

Intraoperative management can be particularly challenging in patients who are still on naltrexone. Profound hypertension may be seen with laryngoscopy and surgical stimulation.[48,49] Short acting opioids are preferred to manage these effects, given the high doses required and high risk of respiratory depression post-operatively. High dose remifentanil is a pharmacologically favourable opioid which can be titrated to effectively overcome naltrexone blockade with rapid and predictable offset.[49] Use of remifentanil can be associated with opioid induced hyperalgesia and there are concerns that this may contribute to difficult postoperative pain management.[50] Opioid antagonists are protective against the development of hyperalgesia[51] meaning this effect may be less relevant in this population.

Short acting opioids are most suitable for analgesia to facilitate titration to patient response given inter-individual variation.[52] Because naltrexone competitively binds to μ-receptors, utilising opioids with higher affinity for μ-receptors such as fentanyl and hydromorphone may result in greater effect.[53] The high doses required of histamine releasing opioids such as morphine may result in unacceptable non-opioid mediated side effects such as erythema, bronchospasm, and hypotension. Hydromorphone and fentanyl do not stimulate histamine release,[54] further reinforcing their utility in this setting. Although tramadol exerts some of its analgesic effects through action at μ-receptors, it may still have analgesic efficiency in the presence of naltrexone. This is however associated with increased nausea and vomiting.[55]

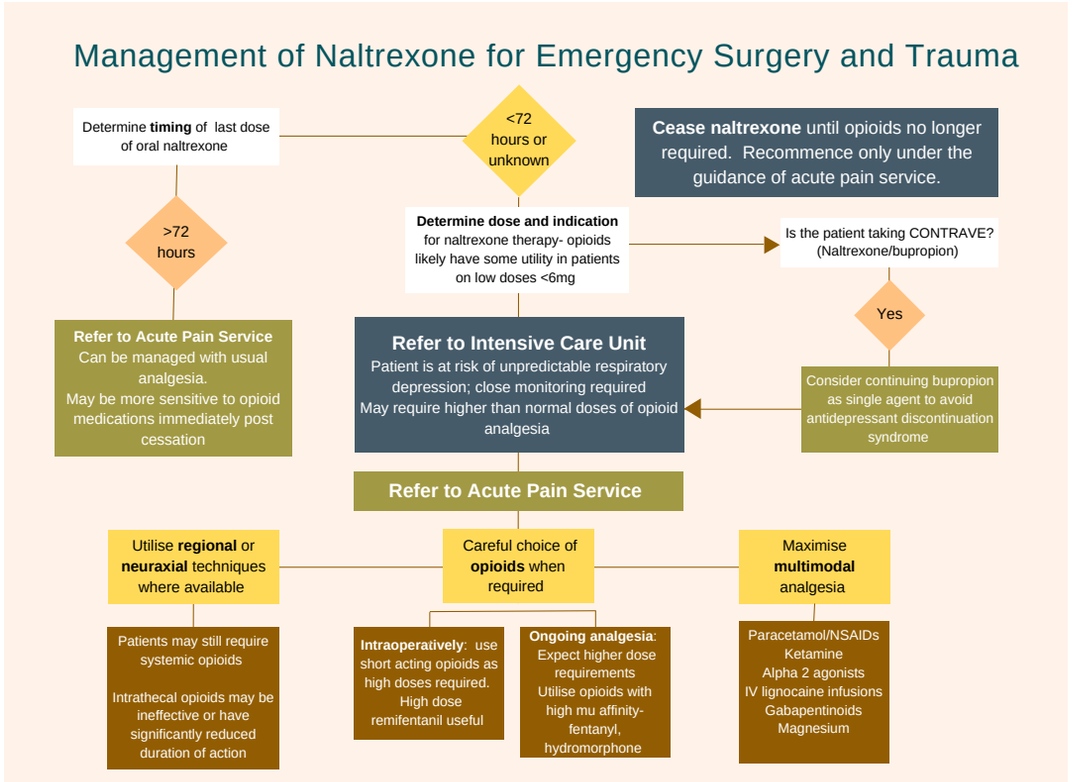
In patients on low dose naltrexone, opioids are likely to still have some clinical utility; albeit requiring higher than normal doses. Low dose naltrexone has been used to prevent adverse effects associated with intrathecal and high dose oral morphine. A 250 microgram dose of intrathecal morphine was shown to provide analgesia for Caesarean section in the presence of low dose naltrexone (6mg) although with significantly shorter duration of action.[56] There is some suggestion that a 1mg dose of naltrexone does not significantly impact analgesia in patients on high dose oral morphine or continuous intrathecal morphine for chronic pain.[57] Patients should be monitored carefully for adequate analgesic effect and adverse side effects of opioid medications.

Opioid sparing anaesthesia and analgesia

Due to the prolonged opioid antagonist action of naltrexone, patients will require maximisation of non-opioid analgesia, including regional or neuraxial analgesia, as appropriate.[58] Regional anaesthesia can provide superior analgesia to parenteral opioids.[59] Where neuraxial or peripheral nerve blocks are used, placement of catheters should be considered to facilitate extended postoperative opioid-sparing analgesia. Neuraxial or regional analgesia may not be completely effective in controlling pain and this may require the addition of short acting opioids in a monitored environment.[47]

Ketamine has been used effectively as an adjunct for both anaesthesia and analgesia in patients receiving naltrexone.[48,49] Multimodal analgesia is recommended, including paracetamol, non-steroidal anti-inflammatory medications, gabapentinoids, magnesium, lignocaine infusions and alpha-2 agonists such as clonidine and dexmedetomidine.[26] Doses that can be utilised for analgesia are limited by side effects[54] and opioid medications may still be required in the presence of severe pain.

Figure 2. Management of naltrexone for emergency surgery and trauma



TRANSITIONAL PAIN MANAGEMENT

The decision of when to recommence naltrexone is complex and requires multidisciplinary collaboration. All patients on naltrexone formulations should be referred to a specialist acute pain management service postoperatively. Manufacturers recommend recommencement of naltrexone 5 to 7 days after last dose of opioid.[1,12] Naltrexone has a higher affinity for μ-receptors than most opioid agonists and so can preferentially displace circulating opioids and precipitate acute withdrawal.[60] Abrupt precipitated opioid withdrawal is dangerous and potentially lethal.[61] Clear communication with the multidisciplinary team is important to ensure thorough understanding of the pain management plan[29] and to ensure that naltrexone is not inadvertently given too soon. We have found adding an alert to the patient's medication chart helps to communicate the importance of avoiding naltrexone while the patient is receiving opioids.

Careful planning of transition back to naltrexone should start early in the admission. As patients may be recommencing naltrexone after discharge from hospital, it is important that hospital teams work closely with community providers to ensure patients are well informed and well supported. Patients may benefit from the involvement of alcohol and other drug services as they may require extra support during this high-risk time for relapse.[30]

Timing of recommencement is a case-by-case decision, requiring specialist input especially where shorter time frames may be desired. Shorter intervals should only be considered where very limited doses of short acting opioids have been used. Australian guidelines for the introduction of high dose naltrexone for opioid abstinence recommend an interval of 5 days between last buprenorphine and first naltrexone and up to 10-14 days if methadone was the last opioid used.[10] There is an absence of guidance as to when it is safe to recommence low dose naltrexone, and this should be a risk:benefit decision made on a case-by-case basis.

If there are any concerns about recommencement of naltrexone, a naloxone challenge test should be performed, as outlined in Table 3.[1]

Table 3. Naloxone Challenge Test[1]

- Gain intravenous (IV) access.
- Monitor vital signs – Heart rate, blood pressure, oxygen saturation, temperature.
- Observe patient for signs and symptoms of withdrawal:
- E.g. Nausea and vomiting, abdominal cramps, sweating, rhinorrhoea, bone and joint pain, piloerection, anxiety, irritability, pupillary dilatation.
- Give initial dose of naloxone: 200 micrograms Naloxone IV
- Observe for 30 seconds for signs or symptoms of withdrawal.
- If no evidence of withdrawal, give full test dose of naloxone: 600 micrograms IV
- Observe for an additional 20 minutes.
- If there are any indications of opioid withdrawal, the test is positive. Do not administer further naloxone.
- If the test is **positive**, do not administer naltrexone and repeat the test in 24 hours.
- If the test is **negative**, naltrexone can be administered as long as there are no other contraindications.

CONCLUSION

Naltrexone is increasingly commonly used in the community, particularly in low doses for off label indications. Patients on naltrexone present particular challenges in both their anaesthetic and analgesic management when they present in both elective and emergency settings. Management requires close communication of the multidisciplinary team and should involve an acute pain management service wherever possible. Decisions regarding the use of opioids in these patients requires consideration of dosage, timing and indication for naltrexone and the impact on the patient when naltrexone is recommenced. More research is needed, especially to help guide the management of patients on low dose naltrexone.

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