Therapeutic Reviews

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Opioid Antagonists AHFS 28:10

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This article focuses on naloxone and naltrexone, and discusses the use of methylnaltrexone. For international educational and comparative purposes, this article also refers to some formulations not available in the USA, e.g., nalmefene.

Indications: Reversal of opioid-induced respiratory depression (naloxone), acute opioid overdose (naloxone), prevention of relapse in opioid and †alcohol addiction (naloxone, naltrexone), opioid-induced constipation or post-operative ileus (methylnaltrexone, alvimopan), †pruritus caused by cholestasis[1] or spinal opioids (naloxone, naltrexone), and possibly, chronic renal failure (naltrexone).[2,3]

Contraindications: these vary by drug and indication, see manufacturers' Prescribing Information for details, e.g.:
Naloxone: none when used to reverse opioid-induced respiratory depression or acute opioid overdose
Naltrexone: patients physically dependent on opioids (i.e., after 2 weeks of regular PO use); acute hepatitis or hepatic failure; severe renal impairment (creatinine clearance <10mL/min)
Methylnaltrexone: known or suspected bowel obstruction.

Pharmacology

Naloxone, naltrexone and nalmefene (not USA) are generally thought of as pure antagonists; they have a high affinity for opioid receptors but no intrinsic activity. They reversibly block access to the opioid receptors and, if given after an opioid agonist, they displace the latter because of their higher receptor affinity.[4]

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However, the discovery that ultra-low doses of naloxone and nalmefene given postoperatively potentiate the analgesic effect of morphine and/or reduce undesirable effects (nausea and vomiting, and pruritus) means that the situation is more complex.[5–9]

In fact, it is over 30 years since it was shown in post-dental extraction pain that naloxone could produce either analgesia (low-dose) or hyperalgesia (high-dose).[10] Further, in the same circumstances, naloxone 400microgram neutralizes the analgesic effect of morphine 8mg IV (as expected) but more than doubles the analgesic effect of pentazocine 60mg IV.[11] (Pentazocine is a partial μ and κ agonist and δ antagonist.[12]) Naltrexone appears to demonstrate similar effects.[13–15] In patients, *ultra-low* dose naltrexone potentiates the analgesic effect of methadone, oxycodone and intrathecal morphine.[13,16,17]

These phenomena are best explained by opioid antagonists having other effects in addition to classical opioid receptor antagonism. For example, a ligand binding to an opioid receptor can trigger either an inhibitory or excitatory response, dependent on the type of G protein coupled to the receptor, either G_I/G_O (inhibitory) or G_s (excitatory). Typically, with an opioid agonist, the G_I/G_O (inhibitory) activity predominates, resulting in analgesia and other opioid effects. In such circumstances, a usual clinical dose of an opioid antagonist like naloxone will displace the opioid agonist from the receptor and thereby reverse its effects. However, the G_s excitatory response can increase in various circumstances, e.g. chronic opioid use, nerve damage.[18] This may contribute to opioid tolerance and, when predominant, to opioid-induced hyperalgesia.[19] Ultra-low levels of naloxone interfere with the scaffolding protein (filamin A), which couples Gs to the opioid receptor and thereby inhibits the excitatory response.[20]

Naloxone also binds to the non-opioid toll-like receptor 4 on glial cells; this interaction inhibits glial cell activation, which appears important in CNS sensitization.[21,22] Glial cell activation is associated with a reduction in glutamate transporters, which impedes the synaptic clearance of this excitatory neurotransmitter. In an animal model of neuropathic pain, ultra-low dose naloxone prevented the loss of glutamate transporters and enhanced the analgesic effect of morphine.[23]

These effects of ultra-low dose naloxone at non-opioid receptor binding sites, which can improve analgesia, are lost with higher doses because of classical opioid receptor antagonism. Thus, despite the potential benefits of ultra-low dose naloxone, the inherent risk of reversal of analgesia limits the widespread clinical application of this approach and it should only be undertaken by specialists in pain or palliative medicine. In practice, if opioid-induced hyperalgesia is suspected, the first and most important step is to reduce the dose of the offending opioid.[24]

Opioid antagonists are used in various clinical settings:

Reversal of opioid-induced respiratory depression: The most important clinical property of naloxone is reversal of opioid-induced respiratory depression (and other opioid effects) caused by either an overdose of an opioid or an exaggerated response to conventional doses. Compared with other opioids, antagonism of buprenorphine requires higher doses of naloxone because buprenorphine also has high receptor affinity (see Dose and Use).[25]

Naloxone has been reported to be only partially effective in reversing the effects of tramadol.[26,27] However, in a series of 11 patients with a tramadol overdose, seven had a good response to naloxone, and only one had no response.[28]

Patients with opioid overdose may develop pulmonary edema. The exact mechanism is unclear. Because pulmonary edema has been seen both in older patients with typical doses of naloxone, e.g., 200–400microgram, and in healthy teenagers with doses as low as 40–80microgram, it has been suggested that naloxone can trigger a central neurogenic response which leads to vasoconstriction of the pulmonary vasculature followed by pulmonary edema.[29] Alternatively, because pulmonary edema is almost universal in fatal opioid overdose,[30,31] naloxone, by increasing respiratory rate and tidal volume, may simply unmask pulmonary edema which has developed secondary to severe hypoxemia and acidemia.[32]

Delayed-onset pulmonary edema (48h after overdose treated with naloxone) due to acute cardiomyopathy also has been reported, possibly the result of cardiac muscle damage caused by hypoxemia.[33]

Prevention of relapse in opioid addiction: Naltrexone 100mg blocks the effect of a challenge of IV diamorphine (diacetylmorphine, heroin) 25mg by 96% at 24h, and 46% at 72h.[34] Thus, naltrexone is primarily used to prevent relapse in opioid addiction by blocking opioid "highs." It also is used PO off-label to reduce the relapse rate in alcohol addiction. Naloxone is given PO either once daily or three times per week. It also is available as a long-acting depot IM injection (duration of action >1 month; authorized

for use in alcohol and opioid addiction) and a SC pellet implant (not USA; duration of action weeks–months).[35–37]

Opioid combination products to deter opioid abuse: In an attempt to reduce the risk of opioid abuse, PO formulations containing both a strong opioid and an opioid antagonist have been developed:

- Suboxone® (buprenorphine + naloxone) given SL for opioid dependency
- Embeda® (morphine + naltrexone)[38]
- Targinact® (oxycodone + naloxone)[39]
- OxyNal® (oxycodone + naltrexone).[40,41]

When administered PO, the opioid antagonist either remains sequestered or the amount released is insufficient to antagonize the analgesic effect of the opioid. However, if abused (e.g., the tablets crushed and administered by insufflation or IV), the opioid antagonist is then released in sufficient amounts to antagonize the opioid.

Opioid-induced GI disorders: Methylnaltrexone and alvimopan are quaternary compounds which do not readily cross the blood-brain barrier and thus act as peripheral opioid antagonists. SC methylnaltrexone is authorized for use in "advanced illness" to treat opioid-induced constipation despite treatment with laxatives (see Dose and Use), and PO alvimopan is indicated for use in postoperative ileus.[42,43] In the past, PO naloxone and naltrexone have been used to correct delayed gastric emptying and constipation.[42] However, because both are centrally acting, there is a risk of reversal of analgesia and systemic withdrawal and methylnaltrexone is now preferable.

A recent systematic review and meta-analysis calculated that to prevent one patient with opioid-induced constipation failing to respond to therapy, the NNT with methylnaltrexone is 3 (95% CI 2–10) with a NNH of 14 (95% CI 9–33).[44] Because constipation in advanced disease is generally multifactorial in origin,[45] methylnaltrexone augments rather than replaces laxatives. Off-label uses of methylnaltrexone include opioid-induced constipation in postoperative[46,47] or non-surgical critical care patients[48] and opioid-related acute colonic pseudo-obstruction.[49] Methylnaltrexone also may improve other peripheral effects of opioids, e.g., urinary retention.[46]

Targinact® (SR oxycodone + SR naloxone) also is marketed as a product which helps reduce opioid-induced constipation. Although primarily added to deter abuse (see above), the naloxone appears to reduce the impact of the opioid on the GI tract.[39] The SR formulation helps ensure that most of the naloxone is removed by first-pass metabolism, minimizing the amount reaching the systemic circulation and the risk of reversal of analgesia.

Marketing Authorization is being sought for a once daily PO formulation of a peripherally acting opioid antagonist for opioid-induced constipation (Naloxegol).

Pruritus: In cholestasis, pruritus is a consequence of increased opioidergic tone caused by a raised plasma enkephalin concentration.[50–53] Opioid antagonists counteract the increased tone, and thus relieve the pruritus.

Naloxone by CIVI/CSCI decreases scratching activity by patients with cholestatic pruritus[54–56] and has a place in the emergency treatment of acute exacerbations of cholestatic pruritus. PO naltrexone[1,57] (or nalmefene[58]) can then be used long-term.

However, opioid antagonists can precipitate an opioid withdrawal-like reaction in patients with cholestasis, including hallucinations and dysphoria.[52,59] To avoid or minimize such a reaction, treatment must be started cautiously with a low dose (see Dose and Use).

The use of naltrexone to relieve cholestatic jaundice may sometimes unmask or exacerbate underlying pain, necessitating discontinuation of naltrexone.[60] Thus, patients with cholestatic jaundice and pruritus and severe pain should *not* be treated with an opioid antagonist.[61] Instead, an alternative treatment for pruritus should be used (e.g., sertraline, rifampicin[53,62]) and the pain treated appropriately with both non-opioid and opioid analgesics.

There are reports of patients with cholestatic pruritus who have responded to buprenorphine alone or in combination with ultra-low doses of naloxone.[63–66] Sometimes ultra-low doses of naloxone or naltrexone improved both the pruritus and the pain.[67] However, there are insufficient data at present to recommend this approach.

In uremic pruritus, the situation is more complex because there are several causal mechanisms, both peripheral (cutaneous) and central (neural).[68] The opioid system is involved, but in uremia there is no

increase in opioidergic tone (and thus no danger of a withdrawal syndrome if an opioid antagonist is given). Instead, the ratio between μ-opioid (pruritus-inducible) and κ-opioid (pruritus-suppressive) receptors alters in favor of the former.[69,70] This predisposes to the onset or exacerbation of pruritus. It also suggests that both κ *agonists* and μ *antagonists* could bring relief. Thus, in an RCT lasting 2–4 weeks of nalfurafine, a novel κ agonist, 36% of subjects responded (at least 50% reduction in worst itching) compared with 15% in the placebo group.[71] Naltrexone also has been tried in this setting.[72] However, RCTs have given conflicting results, e.g., benefit was seen in uremic patients with very severe pruritus[2] but not in those with moderately severe pruritus.[3] One explanation is that, in uremia, an opioid mechanism is important only in severe pruritus. The fact that naltrexone is non-selective and antagonizes both μ- and κ-opioid receptors also may be relevant.

In an open study of patients with various skin and systemic disorders associated with pruritus, good relief was obtained with naltrexone in 70% of patients.[51] However, in the absence of controlled data, the results should be interpreted with caution. Pruritus associated with chronic disease generally requires alternative specific measures.[73]

Ultra-low dose naloxone also is used to relieve pruritus caused by spinal opioids, when other treatments have failed.[74]

Miscellaneous: Naloxone is reported to benefit patients with septic shock,[75] morphine-induced peripheral vasodilation,[76] ischemic central neurological deficits[77,78] and post-stroke central pain.[79]

Endogenous opioids inhibit cell proliferation, an effect which intermittent low-dose naltrexone appears to augment by provoking a compensatory elevation in opioid growth factor (OGF, an enkephalin) and OGF receptor, (a non-classical opioid receptor). This interaction impacts upon the cell cycle, inhibiting proliferation. The potential roles of low-dose naltrexone and OGF in cancer and auto-immune diseases (e.g., multiple sclerosis, Crohn's disease) are being explored.[80–82]

Pharmacokinetics: Table 1 contains selected pharmacokinetic data. Compared with naloxone, naltrexone has a higher PO bioavailability and a longer duration of action; it undergoes extensive first-pass metabolism.[83,84] The major metabolite, 6-β-naltrexol, is a *neutral* antagonist, i.e., it inhibits activation of opioid receptors but, unlike naloxone and naltrexone, it does not suppress basal receptor signaling, thereby reducing the risk of severe withdrawal. The antagonist effect of 6-β-naltrexol also shows peripheral selectivity. Accordingly, it may be developed commercially as a treatment for opioid-induced GI disorders.[85]

Table 1
Pharmacokinetic profiles of selected opioid antagonists

	Naloxone	Naltrexone
Bioavailability (%)	6 PO	5–40 PO
Onset of action	1–2min IV; 2–5min SC/IM	may precipitate withdrawal symptoms in <5min in opioid-dependent patients
Time to peak plasma concentration (h)		1–2 PO
Half-life (h)	about 1	4; 13 for 6-β-naltrexol[86]
Duration of action	IV 15–90min	1–3 days

Cautions

For full list, see manufacturers' Prescribing Information.

In patients receiving opioids for pain relief, naloxone should *not* be used for drowsiness and/or delirium which is not life-threatening because of the danger of reversing the opioid analgesia and precipitating a major physical withdrawal syndrome. Instead, omit or reduce the next regular dose, and subsequently continue at a reduced dose.

The use of naltrexone also will impede opioid analgesia (see below),[87] and can precipitate an opioid withdrawal-like syndrome in patients with cholestatic pruritus.

Naltrexone may cause occasional hepatotoxicity;[88] the manufacturer advises checking LFTs before and at intervals during treatment.

Undesirable Effects

For full list, see manufacturers' Prescribing Information.

Naloxone: nausea and vomiting; occasionally severe hypertension, pulmonary edema (see above), rarely tachycardia, arrhythmias, and even cardiac arrest.[89]
Naltrexone: *very common (>10% in detoxifying opioid addicts)* insomnia, headaches, anxiety, nausea and vomiting, intestinal colic, lack of energy, joint and muscle pain.

The long-term use of naltrexone increases the concentration of opioid receptors in the CNS and results in a temporary enhanced response to the subsequent administration of opioid analgesics.[90] The management of severe acute and postoperative pain in patients receiving long-term naltrexone requires careful consideration and detailed planning (Box A).[87]
Methylnaltrexone: *common* abdominal pain/colic (generally mild-moderate),[91] diarrhea, flatulence, nausea (these generally resolve after a bowel movement), dizziness (postural hypotension can occur). *Rare* syncope, severe diarrhea and cardiovascular collapse, and GI perforation (stomach, small and large bowel).[92]

Box A Management of acute pain in patients receiving naltrexone

Elective surgery
The use of naltrexone must be identified well before the operation.
Ensure effective liaison between the substance misuse and acute pain teams.
Consider switching patients on IM depot injections to PO tablets before surgery.
For minor surgery, when non-opioids are considered sufficient to manage the postoperative pain, leave SC pellet *in situ*; if severe postoperative pain anticipated, remove SC pellet.
Discontinue PO naltrexone 72h before the operation.
Maximize the use of non-opioid analgesics, e.g., IV paracetamol, NSAID.
Note: if an opioid analgesic is required, a larger than usual dose may be needed but, conversely, there may be an increased response to opioids (see Pharmacology above).

Unexpected severe acute pain, e.g., trauma, emergency surgery
If possible use non-opioid analgesics, e.g.:
- IV paracetamol and/or NSAID
- ketamine 100microgram/kg IV every 5min until satisfactory analgesia obtained, plus a single dose of midazolam 20–40microgram/kg IV to minimize dysphoria; may be repeated after 30min; give further midazolam only if dysphoria present.

Note: there is a risk of marked sedation when ketamine and midazolam are combined in this way; to be used only by those competent in airway management.

If venous access is difficult, ketamine can be given SC; use the same doses as for IV but allow 15min between doses.
The above are generally used to achieve rapid pain relief until other measures can be instituted, e.g.:
- local anesthetic blocks
- epidural analgesia (local anesthetic ± clonidine).

Dose and Use
Naloxone is best given IV but, if not practical, may be given IM or SC.

Opioid overdose (naloxone)
Dose recommendations vary, and the following is offered as a guide:
- start with 400microgram–2mg IV every 2–3min p.r.n., up to a total of 10mg
- if necessary, set up an IVI set to deliver an hourly dose which is 50–100% of the stat dose which had previously maintained satisfactory ventilation for ≥15min
- the recommended IVI concentration is 200microgram/mL, diluted in 0.9% saline or 5% glucose
- titrate the IVI as necessary.[93]

Although significant respiratory depression is rarely seen with clinically recommended doses of buprenorphine, serious or fatal respiratory depression has occurred in addicts abusing buprenorphine, generally high dose IV and/or in combination with benzodiazepines or other CNS depressants, e.g., alcohol.[94,95] Because buprenorphine has very strong receptor affinity (reflected in its high relative potency with morphine), naloxone in standard doses does *not* reverse the effects of buprenorphine and higher doses must be used (Box B).[96,97] The non-specific respiratory stimulant doxapram also can be used, 1−1.5mg/kg IV over 30sec, repeated if necessary at hourly intervals or 1.5−4mg/min CIVI.[97,98]

Box B Reversal of buprenorphine-induced respiratory depression

Discontinue buprenorphine (stop CSCI/CIVI, remove TD patch).
Give oxygen by mask.
Give IV naloxone 2mg stat over 90sec.
Start naloxone 4mg/h by CIVI.
Continue CIVI until the patient's condition is satisfactory (probably <90min).
Monitor the patient frequently for the next 24h, and restart CIVI if respiratory depression recurs.
If the patient's condition remains satisfactory, restart with a lower dose buprenorphine, e.g., half the previous dose.

If following the administration of naloxone there is unexpected breathlessness and persistent hypoxemia despite oxygen, the possibility of pulmonary edema should be considered. Delayed-onset pulmonary edema (48h after overdose) also may occur, associated with acute cardiomyopathy, and possibly the result of hypoxemic cardiac muscle damage.[33] Treat as necessary with oxygen, IV furosemide, IVI nitrates, and ventilation. The pulmonary edema generally responds to these measures and resolves within 24−48h.

Reversal of respiratory depression caused by the medicinal use of opioids (naloxone)

If respiratory rate ≥8 breaths/min, and the patient easily rousable and not cyanosed, adopt a policy of "wait and see"; consider omitting or reducing the next regular dose, and subsequently continuing at a reduced dose.

If the overdose is associated with a long-acting opioid (particularly methadone or dextropropoxyphene) or an SR formulation, the duration of action of the opioid will exceed that of naloxone. Even if there is an initial response to naloxone, further IV doses are likely to be needed, and it may be necessary to continue treatment with a closely monitored IVI of naloxone for up to 24h, and sometimes longer.

In patients taking a strong opioid for severe pain and who have become physically dependent, naloxone 400microgram (a standard ampoule) will precipitate an acute withdrawal syndrome, severe pain with hyperalgesia, and marked agitation.[99] Small doses must be used.

Thus, if respiratory rate <8 breaths/min, and the patient comatose/unconscious and/or cyanosed:

- give 100−200microgram IV stat
- if necessary, give 100microgram every 2min until respiratory function is satisfactory
- further IV doses should be given after 1−2h if there is concern that further absorption of the opioid will result in delayed respiratory depression.

The dose is titrated to maintain adequate respiratory function, *not* level of consciousness. The American Pain Society recommends even smaller doses:[100]

- dilute a 1mL ampoule containing naloxone 400microgram to 10mL with 0.9% saline for injection
- administer 0.5mL (20microgram) IV every 2min until the patient's respiratory status is satisfactory
- further doses may be necessary because naloxone is shorter-acting than most opioid analgesics.

Consider the possible cause(s) of the opioid overdose, e.g., reduced elimination because of renal impairment (morphine, hydromorphone) or accumulation because of a long half-life (methadone). Wait until there has been a sustained improvement in consciousness before restarting with a lower opioid dose. It may be preferable to switch to another opioid; seek specialist advice.

Treatment of opioid-induced constipation (methylnaltrexone)

Methylnaltexone is relatively expensive and should be considered only as a supplement to a stimulant laxative (e.g., senna)[101] when an optimized dose of the latter is insufficient. A survey in the USA found that about one quarter of prescriptions for methylnaltrexone (mainly by generalists) were inappropriate with regard to indication or dose.[102]

Methylnaltrexone is contraindicated in cases of known or suspected bowel obstruction; it should be used with caution in patients with conditions which may predispose to perforation (e.g., GI cancer, peptic ulcer, colonic pseudo-obstruction). Between 1/3−1/2 of patients given methylnaltrexone defecate within 30min−4h without loss of analgesia or the development of opioid withdrawal symptoms.[103−107] Dose recommendations:

- for patients weighing 38−62kg, start with 8mg on alternate days
- for patients weighing 62−114kg, start with 12mg on alternate days
- outside this range, give 150microgram/kg on alternate days
- the interval between administrations can be varied, either extended or reduced, but not more than once daily

The dose of methylnaltrexone should be halved in severe renal impairment (creatinine clearance <30mL/min).

Cholestatic pruritus (naloxone, nalmefene, naltrexone)

To try and avoid or minimize an opioid withdrawal-like syndrome, start with a low dose. Although some recommend the initial use of naloxone, others have successfully used naltrexone *de novo* 12.5−25mg b.i.d. and subsequently titrated as below:

- start with a low dose of naloxone by CIVI, e.g., 0.002microgram/kg/min (about 160−200microgram/24h)[52]; long-term administration by CSCI also has been reported[56]
- if no withdrawal-like symptoms occur, the rate can be doubled every 3−4h; but if symptoms occur, continue with the current dose until resolved
- after 18−24h, when a rate known to be associated with opioid antagonistic effects is reached (0.2microgram/kg/min), the infusion is stopped and naltrexone 12.5−25mg PO b.i.d. is started)[52,57,59]
- the dose is increased every few days until a satisfactory clinical response is obtained; at this stage, the effective dose should be consolidated into a single daily maintenance dose
- the effective dose range for PO naltrexone is 25−250mg once daily;[52]
- some centers use PO nalmefene: start with 2mg b.i.d.; double the dose every 2 days until pruritus is relieved or no further improvement; individual maximum doses 30−120mg b.i.d.[108]

Uremic pruritus (naltrexone)

- start with 50mg once daily[2,3]
- if ineffective after 1 week, consider increasing dose to 100mg once daily.

Supply

Naloxone

Naloxone (generic)
Injection 400microgram/mL, 1mL vial = $13; 1mL syringe = $9; 10mL vial = $82.
Injection 1mg/mL, 2mL syringe = $20.

Naltrexone

Naltrexone (generic)
Tablets *(scored)* 50mg, 28 days @ 50mg once daily = $120.

ReVia® (DuPont)
Tablets *(scored)* 50mg, 28 days @ 50mg once daily = $252.

Methylnaltexone

Relistor® (Wyeth)
Injection 8mg, 0.4mL vial = $72; 12mg, 0.6mL vial = $72.

Abbreviations

†	Unauthorized use
b.i.d.	Bis in die, twice daily
CI	Confidence interval
CIVI	Continuous intravenous infusion
CNS	Central nervous system
CSCI	Continuous subcutaneous infusion
GI	Gastrointestinal
IM	Intramuscular
IV	Intravenous
IVI	Intravenous infusion
LFT	Liver function test
NNH	Number needed to harm
NNT	Number needed to treat
NSAID	Nonsteroidal anti-inflammatory drug
OGF	Opioid growth factor
PO	Per os, by mouth
RCT	Randomized controlled trial
SL	Sublingual
SC	Subcutaneous
SR	Sustained-release
TD	Transdermal

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