

## Pure Narcotic Antagonists

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### **Key Words:**

Narcotic antagonist  
Naloxone  
Naltrexone  
Nalmephephene  
Methylnaltrexone  
Alvimopan®  
Opioid receptors  
Opioid agonist  
Opioid agonist and antagonist combination medications  
Periaqueductal grey matter  
Substantia gelatinosa  
G (guanine nucleotide) protein-coupled transmembrane receptors  
 $\mu$  MOP receptor  
 $\delta$  DOP receptor  
 $\kappa$  KOP receptor  
NOP receptor  
Acute withdrawal symptoms  
Titration  
Hepatotoxic  
Naloxone Challenge Test  
Opioid-induced bowel dysfunction

## Pure Narcotic Antagonists

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### **Key Concepts:**

- Narcotic antagonists are chemical derivatives of opioid molecules.
- Therapeutic uses for each of the narcotic antagonists are due to a unique pharmacokinetic profile, coupled with differing routes of administration.
- There are currently four identified opioid receptors located throughout the central nervous system.
- The highest concentrations of opioid receptors lie within the periaqueductal grey matter of the midbrain and the substantia gelatinosa of the spinal cord.
- Narcotic antagonists compete for all four opioid receptors and displace opioid agonists.
- Displacement of an opioid agonist from an opioid receptor followed by binding of a pure narcotic antagonist to an opioid receptor reverses all of the effects of opioids.
- Several narcotic antagonists are used for management of some diseases and conditions unrelated to opioid reversal.

**Introduction ~~Introduction~~ This paper has to be referenced like one of our AANA Journals. AMA Format does not allow referencing everything in the beginning subtitle. Also, any sentence that comes from a reference must**

**be referenced. I did not find anywhere in the AMA Manual Style that a whole paragraph can be referenced. Generic drug names are only capitalized when beginning a sentence.**

The use of a narcotic antagonist began as early as 1915, when J. Pohl discovered that an allyl compound of codeine (N-allylnorcodeine) stimulated respiration, and antagonized the effects of morphine and heroin. Pohl's work remained untended, until Hart (1941), followed by Hart and McCawley (1944) synthesized (N-allylnormorphine [nNalorphine]), and demonstrated its effects. Later studies showed the ability of nNalorphine to antagonize the effects of morphine, act as an antidote to morphine poisoning, and maintain abstinence in morphine-dependent patients<sup>1</sup>.

Naloxone, an analog of nNalbuphine (N-allylnoroxymorphine) [Narcan<sup>®</sup>, Narcan<sup>®</sup> Neonatal, Naloxone HCl, Nalone<sup>®</sup>, Narcanti<sup>®</sup>] began human clinical trials in 1967, and was later discovered to competitively displace narcotics from opioid receptors.<sup>1,2,3,4</sup>

Later, Naltrexone [Depade<sup>®</sup>; ReVia<sup>®</sup>; Vivotrol<sup>TM</sup>], an analog of nNaloxone (1974)<sup>4,5,6</sup> and nNalmefene (6-methylene naltrexone) [Revex<sup>®</sup>], an analog of nNaltrexone (1985)<sup>4,7</sup> were introduced. Differences in routes of administration and pharmacokinetics between nNaloxone, nNaltrexone, and nNalmefene provide unique therapeutic uses for each of these narcotic antagonists.

Methylnaltrexone [Relistor<sup>®</sup>]<sup>8</sup>, a quaternary methyl analog of nNaltrexone, is a new narcotic antagonist (FDA approved April 2008)<sup>9</sup>. It is devoid of central nervous system activity, and affects only peripheral narcotic mu-opioid (MOP)/μ

opioid receptors. Peripheral narcotic receptor antagonism allows treatment of negative opioid side effects without antagonism of analgesia<sup>8,10</sup>.

Alvimopan<sup>®</sup> is a new [FDA approved 2008] peripherally acting MOP/ (if MOP means mu-opioid, do you repeat  $\mu$  opioid after it)  $\mu$ opioid receptor

antagonist used to restore normal bowel function for post surgical bowel surgery when opioid analgesics are used. Alvimopan<sup>®</sup> is used off-label for opioid-induced constipation<sup>8,11,12</sup>.

Finally, nNaloxozone binds covalently and irreversibly to the MOP/  $\mu$ opioid receptor and can only be eliminated by cell endocytosis. Naloxozone is devoid of use in patients<sup>13</sup>.

There are four opioid receptors with individually identified genetic substrates located throughout the entire central nervous system. Table 1 lists detailed information of the four opioid receptors.

The highest concentrations of opioid receptors are found along the periaqueductal grey matter of the midbrain and within the substantia gelatinosa of the spinal cord. The opioid receptors occur as presynaptic and postsynaptic G (guanine nucleotide) protein-coupled transmembrane receptors. Opioid agonists couple to the receptors, which initiates a series of reactions resulting in potassium efflux from the neurons. Potassium efflux creates hyperpolarization across the neuronal membrane, making it less likely to respond to a conductive pain stimulus<sup>15,16</sup>. Figure 1 depicts the G protein-coupled opioid receptor<sup>17</sup>.

Narcotic antagonists compete with opioid ligands for all opioid receptors, but especially for the MOP/  $\mu$ receptor. Several opioid agonist peptides have been synthesized which are selective to only one specific opioid receptor: ( $\mu$ receptor – DAMGO peptide;  $\delta$ receptor – BUBU peptide ;  $\kappa$ receptor – U69693 peptide) and are currently being investigated for clinical use<sup>18,19</sup>.

The binding of a pure narcotic antagonist to an opioid receptor reverses all of the effects of opioids. They are used to treat opioid side effects, and have found several uses for management of some diseases and conditions unrelated to opioid reversal. Table 2 summarizes the current uses for the pure opioid receptor antagonists.

Long-term use of narcotic antagonists causes up-regulation to the population of opioid receptors in the brain, so that subsequent administration of opioid agonists causes a temporary exaggeration of opioid effects<sup>33,34</sup>.

There are several narcotic agonist and pure narcotic antagonist combination medications available. Current studies show that mixtures of opioid agonists with low-dose opioid receptor antagonists enhance the analgesic efficacy and analgesic specificity of the opioid<sup>35,36</sup>. Table 3 lists the currently available mixtures of opioid agonists with low-dose opioid antagonists.

This chapter will discuss only the pure narcotic antagonists **nN**aloxone, **nN**altrexone, **mM**ethylnaltrexone, **nN**almefene, and **aA**lvimopan which clinicians may use or encounter in their practice.

Naloxone [Narcan<sup>®</sup>, Narcan<sup>®</sup> Neonatal, ( I think since you have already given the trade names, you do not have to repeat them in subtitles)]

Naloxone HCl, Nalone, Narcanti]<sup>3,6,8,15,16,20,40,41,42,43</sup> As mentioned above, the references need to be cited in the body of the text where the reference applies

Naloxone is an analog of mMorphine, and is pharmacologically categorized as an antidote.<sup>3,6,15,20</sup> It is used for partial or complete antagonism of opioid depression of patient vital signs. Naloxone competes for opioid binding sites and displaces opioids on all opioid receptors. It exhibits a high affinity for the MOP/  $\mu$ opioid receptor, and has no significant agonist activity, even at high doses.<sup>3,6,16</sup>

**Absorption:** Naloxone may be administered via endotracheal (ET), intramuscular (IM), subcutaneous (SubQ), or intravenous (IV) routes. The IV route may be administered either as a bolus or by infusion. Naloxone is rapidly inactivated after oral (PO) administration, but can be administered orally (PO) in high doses.<sup>6,8,20</sup>

**Distribution:** ~~Via~~ Distribution is via the bloodstream to body fluids and tissues, with high concentrations found in the brain, kidneys, spleen, lungs, liver, heart, and skeletal muscles. Naloxone will cross the placenta, and can be found in breast milk. Naloxone exhibits weak protein binding.<sup>6,20</sup>

**Metabolism:** Metabolism is by hHepatic glucuronidation, ~~whose~~ The major metabolite is naloxone-3-glucuronide which has ~~with~~ no listed antagonistic

activity. Metabolites are excreted by the kidney. Onset, duration, and elimination half-life are summarized in Table 4

~~Excretion: Renal as various metabolites~~

~~Dosage; Onset; Duration; Elimination Half-life are summarized in Table 4~~

I condensed this above to get rid of so many subtitles<sup>6,8,20</sup>

### In Vitro Pharmaceutical Interactions

When administered IV, IV route: nNaloxone may be diluted with sSterile wWater for Injection (SWFI), nNormal sSaline (NS), or 5% dDextrose and wWater (D<sub>5</sub>W). Naloxone is compatible with the following medications: verapamil, benzquinamide, heparin, ondansetron, gatiflo~~x~~acin, (is gatiflxacin spelled correctly?) linezolid, and propofol.

Do not mix nNaloxone with preparations containing the preservatives bisulfite, metabisulfite;<sup>;</sup> long-chain anions, high molecular weight anions, or solutions with an alkaline pH.<sup>20</sup> (Could you give some drug examples of these and also tell what happens when naloxone is mixed with them?) I obtained this from reference 20. I think this will suffice, as I cannot produce an exhaustive list of anesthesia drugs with these properties.

### In Vivo Pharmacokinetic / Pharmacodynamic Interactions

A, Naloxone may alter urine levels of vVanillylmandelic acid (VMA), 5-hydroxyindoleacetic acid, and glucose.<sup>20</sup> (Can you elaborate on how this is causes problems)

b. \_\_\_ Naloxone may cause an allergic hypersensitivity reaction due to preparation with preservatives methylparaben or propylparaben. Preservative-free preparations of nNaloxone are available.<sup>20</sup>

~~c.~~ \_\_\_ Antagonism of opioids results in the release of catecholamines due to sudden acute pain, which may precipitate acute withdrawal symptoms, which are is summarized in Table 5.<sup>40,42,43</sup> Do not administer nNaloxone to newborns of mothers suspected of long-term opioid abuse because this could precipitate withdrawal in the newborn. Careful titration of naloxone in the operating room (OR) or post anesthesia care unit (PACU) can reverse the side effects of excessive opioid dosing without complete reversal of analgesia, which would precipitate sudden acute pain.<sup>42,43,47</sup>

~~d.~~ Careful titration of Naloxone in the operating room (OR) or Post Anesthesia Care Unit (PACU) can reverse the side effects of excessive opioid dosing without complete reversal of analgesia precipitating sudden acute pain<sup>47</sup>.

e. \_\_\_ Rapid administration of nNaloxone can precipitate nausea and vomiting. Additionally rapid administration of naloxone in patients with cardiovascular disease may precipitate pulmonary edema. (are there mechanisms for causing N & V and the pulmonary edema?) Due to the intense catecholamine release, and the associated hypertension and intense pain.

~~f.~~ Rapid administration of Naloxone in patients with cardiovascular disease may precipitate pulmonary edema.

Summary

~~Naloxone is the prototype narcotic antagonist whose molecular structure has become the basic substrate for other opioid antagonists. It competitively binds to all four opioid receptors, and displaces opioids already bound to all G Protein-coupled opiate receptors. Naloxone has been the mainstay for rapid reversal of adverse opioid effects in patients seen in the emergency room (ER), OR, and the physician's office. Naloxone may induce symptoms of acute withdrawal and should be administered cautiously as directed. See Table 5 for symptoms of acute withdrawal. I do not think a summary is needed at the end of each drug. A summary of course is great at the end of the chapter.~~

Naltrexone [Depade<sup>®</sup>; ReVia<sup>®</sup>; Vivotrol<sup>™</sup> ] [3,8,15,16,21,41,42,43,46](#)

### Introduction

Naltrexone is a cyclopropyl derivative of oxymorphone, similar in structure to ~~n~~Naloxone, and is pharmacologically categorized as an antidote. It is used for the treatment of ethanol dependence, and blockade of the effects of opioids due to opioid dependence and addiction. It is used off-label for nicotine withdrawal, premenstrual syndrome, adverse reaction to morphine, self-injurious behavior, and pruritis. Naltrexone competes for all four opioid binding sites and displaces already bound opioid agonists from receptors. Naltrexone exhibits a high affinity for the MOP/ $\mu$ -opioid receptor. [3,8,15,16](#)

Naltrexone is available as tablets of Depade<sup>®</sup> (25mg, 50mg, 100mg) and ReVia<sup>®</sup> (50mg). Naltrexone for injection [Vivotrol<sup>™</sup> 380mg] consists of an extended-

release microsphere powder for suspension. Vivotrol™ comes supplied as a kit with a syringe, needle, and diluent.<sup>21</sup>

**Absorption:** Naltrexone is administered predominately PO, or by IM injection. Do not administer ~~n~~Naltrexone IV, or SubQ.<sup>6,20</sup> Why? Naltrexone is formulated to be either po, or IM for long-term narcotic antagonist effects for the treatment of opioid abuse.?

**Distribution:** The volume of distribution ( $V_d$ )  $V_d$  of naltrexone is 19L/kg, and this drug is ~~is~~ widely distributed throughout the body. Naltrexone is 21%-28% protein bound and it. ~~Naltrexone will~~ crosses the placenta, which can have profound physiological effects for the opioid-addicted fetus, similar as to the mother (see below). (would there be a problem with placenta crossing in drug-addicted pregnant women?)

**Metabolism:** Naltrexone is metabolized to conjugated glucuronide byproducts by a cytosolic non-cytochrome mediated family of enzymes. Dihydrodiol dehydrogenase is the principle non-cytochrome metabolic enzyme, which converts ~~n~~Naltrexone to 6- $\beta$ naltrexol, with antagonistic properties. Naltrexone exhibits a significant first pass effect when administered PO, but this effect is ~~is~~ significantly reduced when administered IM. The first pass effect accounts for reduced bioavailability of a medication due to metabolism of the medication by the liver.<sup>9</sup> (Can you elaborate on what happens with first-pass hepatic effect?)  
Naltrexone is eliminated in the urine as various metabolites and is also found in breast milk.

~~Excretion: Naltrexone is eliminated in the urine as various metabolites and unchanged drug, and can be found in breast milk.~~

Dosage; Onset; Duration; Elimination Half-life are summarized in Table 4

In Vitro Pharmaceutical Interactions (no underline)

Naltrexone has only been studied with the concomitant administration of opioid agonists. Administration with other drugs has not been studied. Vivotrol™ is a microsphere preparation of naltrexone. Components of the Vivotrol™ kit must be assembled and prepared only with the supplied diluent. Vivotrol™ must be administered immediately after preparation with the supplied syringe and needle.

~~Vivotrol™ Vivotrol™~~ must be ~~stored stored~~ refrigerated at 2°C – 8°C (36°F - 46°F). (I think it is preferred to use the generic name throughout once the trade name has been identified as you have already done in the beginning of the paper.) Non-refrigerated ~~Vivotrol™ Vivotrol™~~ may be stored up to 7 days at room temperature of 25°C (77°F) (If this drug must be stored refrigerated, how can it be stored non-refrigerated for up to 7 days at room temperature?). Once Vivotrol is removed from the refrigerator, it is alright to leave it at room temperature for up to seven days, but then the drug must be discarded. If it is kept properly refrigerated, it will remain useable until its expiration date. Tablets may be stored at room temperature.<sup>20</sup>

~~Tablets may be stored at room temperature.~~

### In Vivo Pharmacokinetic / Pharmacodynamic Interactions

~~Vivotrol™ is a microsphere preparation of Naltrexone. Components of the Vivotrol™ kit must be assembled and prepared only with the supplied diluent. Vivotrol™ must be administered immediately after preparation with the supplied syringe and needle.~~

Naltrexone is hepatotoxic in high doses. It is contraindicated in patients with acute hepatitis or liver failure.<sup>6,21</sup> (Why is this drug contraindicated in acute hepatitis or liver failure). Naltrexone is metabolized chiefly by the liver. Acute hepatitis or liver failure will result in high blood levels of Naltrexone along with competition with metabolism of other medications or metabolic products.<sup>2,41,42,43</sup>

Concomitant use of nNaltrexone with other medications that alter hepatic metabolism must be considered. (Why does naltrexone induce or inhibit metabolism of other drugs?) Naltrexone will compete with other hepatically metabolized medications, and could prolong the effects and/or the side-effects of these other medications. Induration and/ or pruritis can occur following IM injection.

Naltrexone is contraindicated in patients who require opioid analgesics for pain, patients experiencing acute opioid withdrawal, opioid dependent patients, and patients who present with a positive drug urine screen for opioids. ~~the following patients:~~

- ~~a. Patients who require opioid analgesics for analgesia~~
- ~~b. Patients experiencing acute opioid withdrawal~~

~~c. Opioid-dependent patients~~

~~d. Patients who present with a positive opioid urine screen test~~

Naloxone should be the first drug of choice for opioid overdose because of easy titration to effect, and a shorter half-life. Before patients are administered

~~n~~Naltrexone, a Naloxone Challenge Test shown in Box 1, can be used as the first line of treatment, with follow-up ~~n~~Naltrexone administration. Failure of the Naloxone Challenge Test is a contraindication for the follow-up use of ~~n~~Naltrexone.<sup>21</sup>

Naltrexone used for nicotine-induced withdrawal symptoms has been shown to attenuate nicotine alertness and nicotine euphoria, but ~~n~~Naltrexone did not affect nicotine's ameliorating effect on nicotine withdrawal symptoms<sup>49</sup>:

(Is there a mechanism for this? It would be nice to add it if there is.) It is postulated that opioids modulate nicotine-induced neurotransmission.<sup>46</sup>

Summary

~~Naltrexone is suitable for long duration blockade of opioid effects for opioid dependence, opioid addiction, and as a treatment for ethanol dependence. The inability to titrate Naltrexone precludes its clinical anesthesia in the OR, but could be used in the PACU.~~

~~Naltrexone and Naloxone administration may induce symptoms of acute withdrawal, which is summarized in Table 5.~~

Methylnaltrexone is a new narcotic antagonist (FDA approved April 2008)<sup>9</sup>. It is a quaternary methyl analog of ~~n~~Naltrexone. The methyl moiety makes the ~~m~~Methylnaltrexone molecule highly ionized, ~~therefore it which~~ will not cross the lipid-based blood-brain barrier. ~~This, making~~ it devoid of central nervous system activity, which ~~means that this drug only~~ affects ~~only~~ peripheral narcotic MOP/  $\mu$  opioid receptors.<sup>2,8</sup>

Antagonism of purely peripheral opioid receptors attenuates the opioid-induced decrease of gastric emptying, constipation, and nausea without affecting central opioid analgesia receptors. Nausea is attenuated because the chemoreceptor trigger zone (CTZ) lies outside of the blood-brain barrier, and ~~this drug~~ will displace opioids occupying receptors in the CTZ.<sup>10</sup> Methylnaltrexone is also used off-label to treat pruritis, nausea ~~and /~~ vomiting related to morphine administration, and opioid-induced urinary retention.

~~Absorption:~~ Methylnaltrexone is administered ~~SubSubQ~~ for treatment of constipation, and PO for pruritis and nausea / vomiting prior to morphine administration. ~~OralPO~~ dosing is currently investigational.<sup>44,45</sup>

~~Distribution:~~ Methylnaltrexone is 11%-15.3% protein bound. Its volume of steady-state distribution ( $V_{ss}$ ) is 1.1L/kg.

~~Metabolism:~~ Methylnaltrexone metabolism is negligible. Approximately 50% of methylnaltrexone is eliminated unchanged by renal excretion while less than 50% is excreted in the feces as unchanged drug.

~~Excretion: Approximately 50% of Methylnaltrexone is eliminated primarily via renal excretion, and less than 50% is excreted in the feces, both routes as unchanged drug.~~

~~Dosage; Onset; Duration; Elimination Half-life are summarized in Table 4~~

In Vitro Pharmaceutical Interactions (These are not pharmaceutical interactions. I think that they would be pharmacodynamic. )

Methylnaltrexone ~~is~~ demonstrates weak intrinsic binding affinity to MOP/  $\mu$ - and kappa opioid receptors (KOP/ koioid) receptors relative to morphine.<sup>8,45</sup>

Methylnaltrexone inhibits endothelial cell proliferation and migration as well as opioid and non-opioid induced human pulmonary endothelial cell barrier disruption. Methylnaltrexone is a weak inhibitor of hepatic cytochrome P450

CYP2D6. (Could you list some drugs that this might affect?)(Some anesthetic medications which are metabolized by CYP2D6 are: diphenhydramine, morphine, ondansetron, oxymorphone, tramadol,- No drug interaction studies have been performed between methylnaltrexone bromide and drugs that are actively secreted by the kidney.<sup>45</sup>

Syringes or vials should be stored at ambient room temperature, and away from light. Do not allow the medication to freeze. (This I think would be a pharmaceutical interaction but can you say what happens if the drug is frozen?)

In Vivo Pharmacokinetic / Pharmacodynamic Interactions

Methylnaltrexone is indicated for the treatment of opioid-induced

constipation in patients with advanced or terminal illness who are receiving palliative care, when response to laxative therapy has been insufficient. Use of ~~m~~Methylnaltrexone beyond four months has not been studied. No dosage adjustment is necessary for patients with mild or moderate renal or hepatic impairment. Dosage should be adjusted for patients with severe renal impairment (creatinine clearance <30ml/minute). No studies have been performed for use in patients with severe hepatic impairment. Methylnaltrexone should not be used in patients with mechanical bowel obstruction, lesions of the gastrointestinal tract, or with severe or persistent diarrhea.<sup>44</sup>

### Summary

~~Although Methylnaltrexone is indicated for the treatment of opioid-induced constipation, its use as a treatment for opioid-induced nausea could make it suitable for use in clinical anesthesia.~~

Nalmefene [Revex<sup>®</sup>]<sup>7,8,15,22,28,29,30,31,32,33,41</sup>

### Introduction

Nalmefene is a 6-methylene analog of ~~n~~Naltrexone. It is pharmacologically categorized as an antidote. Nalmefene is equipotent to ~~n~~Naloxone but has a longer duration of action. Nalmefene is used for the treatment of opioid dependence and addiction, reversal of postoperative opioid depression, and management of acute opioid overdose. This drug Nalmefene competes for opioid binding sites and displaces opioids on all opioid receptors, and exhibits a

high affinity for the MOP/  $\mu$ opioid receptor. Nalmefene precipitates the sudden release of catecholamines, which may result in acute withdrawal symptoms similar to ~~n~~Naloxone.<sup>7,8,22,28</sup> See the summary of acute withdrawal symptoms summarized in Table 5.

Nalmefene is available in two concentrations which are 100 mcg/mL for postoperative use and 1000 mcg/mL for management of opioid overdose.

~~Blue Labeled Ampule – 100mcg/ml, intended for post-operative use~~  
~~Green Labeled Ampule – 1000mcg/ml, intended for management of opioid overdose~~

~~Absorption:~~ Nalmefene may be administered IM, IV, PO, or ~~Sub~~SubQ

~~Distribution:~~ ~~Nalmefene~~ This drug is rapidly distributed with a  $V_d$  of 8.6L/kg. It is 45% protein bound. Nalmefene has 100% bioavailability when administered IM or ~~Sub~~SubQ, and 40% bioavailability when administered PO.<sup>41</sup>

~~Metabolism:~~ Nalmefene is metabolized to glucuronide byproducts in the liver. Metabolites show little or no activity, which differs from ~~n~~Naltrexone.

~~Excretion:~~ Nalmefene is excreted primarily in urine, feces (17%), with a small amount in the bile.<sup>8,22,28</sup>

~~Dosage; Onset; Duration; Elimination Half-life are summarized in Table 4~~

In Vitro Pharmaceutical Interactions

Nalmefene must be stored at controlled room temperature and may be diluted with NS or SWFI.-(Why only these two solutions and what happens to it if it is refrigerated?| If you could find out, it would be good to put this information in.)

~~Nalmefene may be diluted with NS or SWFI~~

#### In Vivo Pharmacokinetic / Pharmacodynamic Interactions

Nalmefene requires no dosage adjustment for patients with renal impairment or hepatic impairment for a one time single use.

Nalmefene must be carefully titrated intravenously for use in the OR or PACU so that side effects of excessive opioid dosage are reversed without precipitating acute pain by reversing opioid analgesic effects.

Nalmefene, nNaloxone and nNaltrexone may induce symptoms of acute withdrawal, ~~and are summarized in (see Table 5 for symptoms).~~<sup>8,22,31,32,33</sup> Oral PO-administration of nNalmefene produces long-term inhibition of opioid effects.

Nalmefene for use in opioid withdrawal is not documented.

Nalmefene should not be used as the drug of choice for treatment of opioid-induced ventilatory failure, or for complete reversal of buprenorphine-

(Buprenex<sup>®</sup>)-induced respiratory depression. (Why?) Nalmefene should not be used in neonates.<sup>22</sup> (why?)

~~Nalmefene should not be used in neonates.~~

#### Summary

~~The long duration of Nalmefene makes it primarily suitable blockade of opioid effects from opioid dependence and addiction. Nalmefene is used in clinical anesthesia either in the OR or the PACU. Naltrexone and Naloxone may induce~~

~~symptoms of acute withdrawal and should be administered cautiously. Symptoms of acute withdrawal are summarized in Table 5.~~

Alvimopan [Entereg<sup>®</sup>]<sup>8,11,12,48</sup>

### Introduction

Alvimopan is a selective MOP/  $\mu$ opioid receptor antagonist used to accelerate upper and lower gastrointestinal (GI) recovery following partial large or small bowel resection surgery with primary anastomosis by blocking the effects of opioid-induced bowel dysfunction. Alvimopan is pharmacologically classified as a functional gastrointestinal (GI) disorder agent, and is only administered to hospitalized patients for a short-term of 15 doses.<sup>8,11,12</sup>

Studies show patients who have taken ~~a~~Alvimopan are more susceptible to myocardial infarction, but no causal relationship has been established. The drug is only available to hospitals that have registered and met all of the requirements for the ~~A~~Alvimopan [ENTEREG<sup>®</sup>] Access Support & Education Program. (E.A.S.E.™)

~~Absorption:~~ Alvimopan is administered PO, and it is rapidly distributed with a  $V_d$  30 +/- 10L. Alvimopan and its metabolites are 80% to 94% protein bound therefore bioavailability is 6% with oral administration.<sup>12</sup>

~~Distribution:~~ Alvimopan is rapidly distributed with a  $V_d$  of 30 + 10L. Alvimopan and its metabolite are 80-94% protein bound, therefore bioavailability is 6% with PO administration.

**Metabolism:** Alvimopan is absorbed into the bile, and displays no recognizable hepatic metabolism. Biliary secretion of both unabsorbed and unchanged drug occurs. Alvimopan is hydrolyzed to a glucuronide conjugate metabolite, and other minor metabolites by intestinal microflora. The metabolite [also](#) displays antagonistic activity. (Does this pose a problem with duration of action?)

**Excretion:** Biliary secretion is the primary pathway for [a](#)Alvimopan elimination. Renal excretion accounts for approximately 35% of total clearance. Unabsorbed and unchanged [a](#)Alvimopan ~~and~~ are eliminated in the feces and in urine<sup>11,12</sup>.

~~Dosage; Onset; Duration; Elimination Half-life are summarized in Table 4~~

#### In Vitro Pharmaceutical Interactions

High gastrointestinal fat content absorbs ~~PO~~ [a](#)Alvimopan [taken po](#), and delays its entry into the bloodstream. (Is there a reason for this? Is there something about the molecule that causes this? Would be an interesting fact to add if you could.)

#### In Vivo Pharmacokinetic / Pharmacodynamic Interactions

Postoperative ileus is a multifactorial process that involves inhibitory sympathetic input, effects of endogenous opioids, release of hormones, inflammation, and the absence of both neurotransmitters and other mediators. The co-administration of morphine, administered for acute postoperative pain, with [a](#)Alvimopan, which binds to gastrointestinal MOP/  $\mu$ opioid receptors, results in increased gastrointestinal motility and secretion, while still allowing analgesia.<sup>12</sup>

Can you do a summary paragraph of two here?

Summary

There are several narcotic antagonists available on the market in the United States for treatment of conditions associated with opioid overdose or withdrawal. As research recognizes the interactions of opioid modulation with other non-opioid ligands and receptors, novel medications are developed which help with treatment for other addictions. Clinical anesthesia providers are best suited to use only naloxone during the perioperative period because of its intravenous route of administration, and its ability to be titrated to effect.

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Table 1

International Union of Pharmacology Recognized Opioid Receptors<sup>2,3,14,15</sup>

<u>Opioid Receptors</u>				
<u>Official Designation</u>	<u>MOP</u>	<u>DOP</u>	<u>KOP</u>	<u>NOP*</u>
Other Designations	μ	δ	κ	

	OP <sub>3</sub>	OP <sub>1</sub>	OP <sub>2</sub>	<del>OP<sub>4</sub></del>
OP <sub>4</sub>	<u>Have I moved this to the right place?</u>			

Subtypes	$\mu_1, \mu_2$	$\delta_1, \delta_2$	$\kappa_1, \kappa_2, \kappa_3$	
Prototype Agonist	morphine	Ala-leu-enkephalin	ketocyclazocine	
Endogenous Ligand	Leu-enkephalin	Leu-enkephalin	dynorphin	nociceptin
Ion Channel Effects	Opens Potassium Channels	Opens Potassium Channels	Closes Calcium Channels	Closes Channels

#### Location

$\mu$  Pre and Post Synaptic primary afferent neurons

- Peripheral sensory neurons
- Periaqueductal grey matter
- Nucleus raphe magnus
- Rostral ventral medulla
- Thalamus
- Cerebral Cortex

$\delta$  Olfactory bulb

- Cerebral cortex
- Presynaptic Primary afferent neurons
- Motor integration areas
- Nociception areas

$\kappa$  Hypothalamus

- Nociception areas

NOP Nucleus Raphe Magnus  
Primary afferent neurons

#### Broad Effects

$\mu_1$   
Analgesia (supraspinal and spinal)

Euphoria  
Low abuse potential  
Miosis  
Bradycardia  
Hypothermia  
Urinary retention

$\mu_2$

Analgesia (spinal)  
Depressed ventilation (Especially due to agonist stimulation of receptors along the brain stem)  
Physical dependence  
Constipation (Especially due to agonist stimulation of receptors along the gastrointestinal tract)  
Urinary retention

$\delta$

Analgesia (supraspinal and spinal)  
Depressed ventilation  
Physical dependence  
Constipation (Especially due to agonist stimulation of receptors along the gastrointestinal tract)  
Urinary retention

$\kappa$

Analgesia (supraspinal and spinal)  
Dysphoria, psychomimetic reactions (hallucinations, delirium)  
Sedation  
Low abuse potential  
Miosis  
Diuresis

\*Nociceptin-orphanin receptor

Table 2

## Summary of Current Recognized Uses for Pure Opioid Receptor

### Antagonists<sup>3,8,15,16,20,21,22,23,24,25,26,27,28,41</sup>

#### A. Naloxone

a. FDA labeled indications: Overdosage of opioids (known or suspected);

Reversal of adverse opioid activity (Respiratory depression, rigidity, nausea/vomiting, urinary retention, biliary spasm)

b. Non-FDA labeled indications: Antidiarrheal overdose; opioid dependence; opioid induced constipation; pruritis of skin (chronic and opioid-induced); urinary retention; IBS (Irritable Bowel Syndrome); Phencyclidine (PCP) ingestion; septic shock; cardiogenic shock; high altitude pulmonary edema; acute respiratory failure; senile dementia; ischemic neurological deficits; partial reversal of the effects of alcohol, barbiturates, and benzodiazepines

#### B. Naltrexone

a. FDA labeled indication: alcohol dependence; opioid dependence

b. Non-FDA labeled indications: drug withdrawal; prophylaxis for adverse reactions to morphine; premenstrual syndrome; self-injurious behavior; antagonism of cannabinoid effects; substance abuse associated with schizophrenia; cocaine and alcohol dependence

#### C. Methylnaltrexone

a. FDA labeled indication: Treatment of opioid-induced constipation in patients with advanced or terminal illness who are receiving palliative care, when response to laxative therapy has been insufficient.

b. Non-FDA labeled indications: Pruritis, nausea / vomiting related to opioid agonists, urinary retention due to opioid agonists.

#### D. Nalmefene

a. FDA labeled indication: In treatment for prolonged opioid use

b. Non-FDA labeled indications: treatment of opioid overdose; alcohol dependence; alcohol withdrawal syndrome and eating disorders (further study is ongoing and necessary); chronic interstitial cystitis;

Nalmefene is also undergoing Investigative use for impulse control disorders such as pathological gambling, compulsive shopping, trichotillomania (excessive self-grooming such as pulling out hair), sex addiction, and

kleptomania<sup>22,,29,30,31,32</sup>.

#### E. Alvimopan

FDA labeled indications: Used only short term following partial large or small bowel resection surgery with primary anastomosis to restore bowel function in patients with post-operative ileus and opioid-mediated bowel dysfunction.

Alvimopan accelerates the time for upper and lower gastrointestinal recovery<sup>11,12,16</sup>.

Table 3 Currently Available Mixtures of Opioid Agonists with Low-Dose Opioid Antagonists

- a. Suboxone<sup>®</sup> and Subutex are a 4:1 mixture of Buprenorphine with Naloxone. They are used for the treatment of opioid dependence<sup>35</sup>.
  - b. ValoronN is a mixture of the opioid agonist Tilidine with Naloxone and is used as a moderate analgesic. It is only available in Germany, Belgium, and Switzerland<sup>37</sup>.
  - c. TalwinNX is a mixture of Pentazocine with Naloxone.
- Suboxone, ValoronN, and TalwinNX are used as analgesics for opioid dependent patients, because of reduced abuse potential<sup>38,39</sup>.
- d. Embeda<sup>®</sup> is a new [2009] and unique formulation of polymer coated Extended Release (ER) Morphine agonist surrounding a sequestered core of Naltrexone. Embeda<sup>®</sup> allows the use of a potent opioid for chronic, moderate, and severe pain, with no potential for abuse and misuse. It is only to be administered to opioid-tolerant patients experiencing long-term pain who have become tolerant to high doses of opioid. Embeda<sup>®</sup> is not prescribed to treat occasional pain. It can cause fatal respiratory failure in patients intolerant to high dose opioids. Tampering with the Embeda<sup>®</sup> tablet releases Naltrexone which negates the effects of the high-dose morphine<sup>36,39,40</sup>.

Table 4 Summary of Pure Narcotic Antagonists Dosage, Onset, Duration, Elimination Half-life<sup>8,12,20,21,22,41,42,44,46,47</sup>

## Naloxone

### Dosage

#### **Opiate intoxication**

Premature, Neonate, Children to 5 years or < 20kg

IV: 0.1mg/kg q 2-3 minutes, May repeat dose q 2-3 minutes PRN. May repeat dose q 20-60 minutes.

IM/SubQ in divided doses of 0.1 mg/kg.

Children > 5 years or  $\geq$  20 kg

IM, IV, SubQ: 0.2 mg/kg q 2-3 minutes.

As a continuous IV drip: Titrate dose 0.04-0.16 mg/kg/hour for 2-5 days.

Adult

IV: Titrate by 50-100mcg increments to 0.4-2mg q 2-3 minutes PRN. May repeat dose q 20-60 minutes PRN.

As a continuous IV drip 0.25-6.25 mg/hour

IM/SubQ: 0.4-0.8 mg, repeat PRN.

#### **Post-operative respiratory depression**

Child; IM, IV, SubQ: 5-10 mcg/kg q 2-3 minutes

Adult; IV: 100-200 mcg q 2-3 minutes

#### **Opioid Overdose**

Adult (Non-opioid dependent); IM, IV, SubQ: 0.4mg (10mcg/kg) q 2-3 minutes

Adult (Opioid dependent); IM, IV, SubQ: 100-200 mcg q 2-3 minutes

### **Onset / Duration / Elimination Half-Life**

IM/SubQ: Onset 2-5 minutes / Duration 45-60 minutes / Elimination half-life

Neonates 3-4 hours, Adults 0.5-1.5 hours

IV: Onset 1 minute / Duration 45 minutes / Elimination Half-life Neonates 3-4 hours, Adults 0.5-1.5 hours

## **Naltrexone**

### **Dosage**

Oral: Alcohol dependence, or opioid antidote – Initially 25mg (Naltrexone challenge); if no withdrawal symptoms in one hour then 25 mg. Afterward with no withdrawal symptoms exhibited, 50-150mg/day in divided doses

Oral: As an adjunct to alcoholism treatment, and maintenance of abstinence – 50 mg/day with food for 12 weeks

IM: As an adjunct to alcoholism treatment and maintenance of abstinence – 380mg q 4 weeks

Oral: Pruritis – 50mg/day for 7 days to 4 weeks

Oral: Nicotine withdrawal – 50mg/day

### **Onset / Duration / Elimination Half-life**

Oral: Onset 15-30 minutes / Duration of 50mg is 24 hours; Duration of 100mg is 48 hours; Duration of 150mg: 72 hours / Elimination half-life of Naltrexone is 4 hours; Elimination half-life of 6-  $\beta$ naltrexol is 13 hours.

IM: Onset is gradual with an initial peak at 2 hours, with a secondary peak 2-3 days later / Duration 4 weeks / Elimination half-life of Naltrexone and 6-βnaltrexol is 5-10 days.

### **Methylnaltrexone**

#### **Dosage**

SubQ Dosing:

Methylnaltrexone is available in three forms:

8mg pre-filled syringe

12mg single-use vial

12mg pre-filled syringe

Administer as follows:

Patient weight 38-62 kg; give 8mg Sub Q

Patient weight 62-114 kg; give 12mg Sub Q

Dosage adjustment can be made for patients outside these ranges at

0.15mg/kg

One dosage of Methylnaltrexone should be administered only every other day, as needed, but no more frequently than one dose in a 24-hour period

PO Dosing:

19.2 mg/kg 20 minutes prior to the administration of Morphine

#### **Onset / Duration / Elimination Half-life**

SubQ

Onset absorbed rapidly, with peak at 30 minutes / Duration half-life 8hours / Elimination approximately 50% of unchanged drug primarily renal; <50% via feces.

## **Nalmefene**

### **Dosage**

1. IM, IV, SubQ: (IV is the preferred route)

A. Postoperative opioid depression in non-opioid dependence, use Blue Labeled Ampule (100mcg/ml): 0.25 mcg/kg q 2-5 minutes titrated to effect, up to 1 mcg/kg.

Dilute Nalmefene 1:1 in NS or SWFI for patients with increased cardiovascular risks, titrate 0.1 mcg/kg doses.

B. Opioid overdose in non-opioid dependence Green Labeled Ampule (1000mcg/ml): 0.5mg/kg, may repeat with 1mg/70kg in 2-5 minutes up to 1.5mg/70kg.

C. Opioid overdose in opioid dependence (IV) Green Labeled Ampule (1000mcg/ml): 0.1mg/70kg while observing for opioid withdrawal symptoms for 2 minutes, then give 0.5mg/70kg. Repeat as needed (PRN) 1mg/70kg after 2-5 minutes up to 1.5mg/kg.

2. PO

D. Chronic interstitial cystitis: 0.5mg twice daily (bid) up to 60mg bid. (Dosing was less  $\leq$  2mg/week for the first three months up to 10mg/week up to 15 months).

Onset is moderately rapid with peak dose seen from 1 hour – 2.5 hours.

### **Onset / Duration / Elimination Half-life**

IM, SubQ: Onset 5-15 minutes / Duration 10 hours / Elimination half-life 8.5-10.8 hours.

IV: Onset < 2minutes / Duration 4-8 hours / Elimination half-life 8.5-10.8 hours.

## **Alvimopan**

### **Dosage**

Take 12mg PO 30 minutes to 5 hours before surgery; then 12 mg PO daily beginning the day after surgery for 7 days or until discharge. The patient should receive no more than 15 total doses. Do not administer if the patient has had therapeutic doses of opioids for more than 7 days prior to the day before surgery. Dosages are not to be given to patients who have been discharged. The drug is only available to hospitals who have registered and met all of the requirements for the Alvimopan [ENTEREG<sup>®</sup>] Access Support & Education (E.A.S.E.™) Program.

### **Onset / Duration / Elimination Half-life**

PO dosing peaks at 2 hours. Onset for the metabolite of Alvimopan is highly variable among patients / Duration 12 hours / Elimination half-life of Alvimopan 10-17 hours; of Metabolite 10-18 hours

Table 5 Symptoms of Acute Withdrawal<sup>8,41,42,47</sup>

Administration of an opioid antagonist displaces an opioid agonist, resulting in sudden acute pain with intense sympathetic nervous system stimulation.

Sudden acute hypertension

Abdominal cramping

Pain

Tachycardia

Cardiac dysrhythmias

Lethal dysrhythmias (ventricular tachycardia, ventricular fibrillation)

Nausea

Vomiting

Diaphoresis

Nasal Stuffiness

Lacrimation

Piloerection

Agitation

Anxiety

Yawning

Myalgia

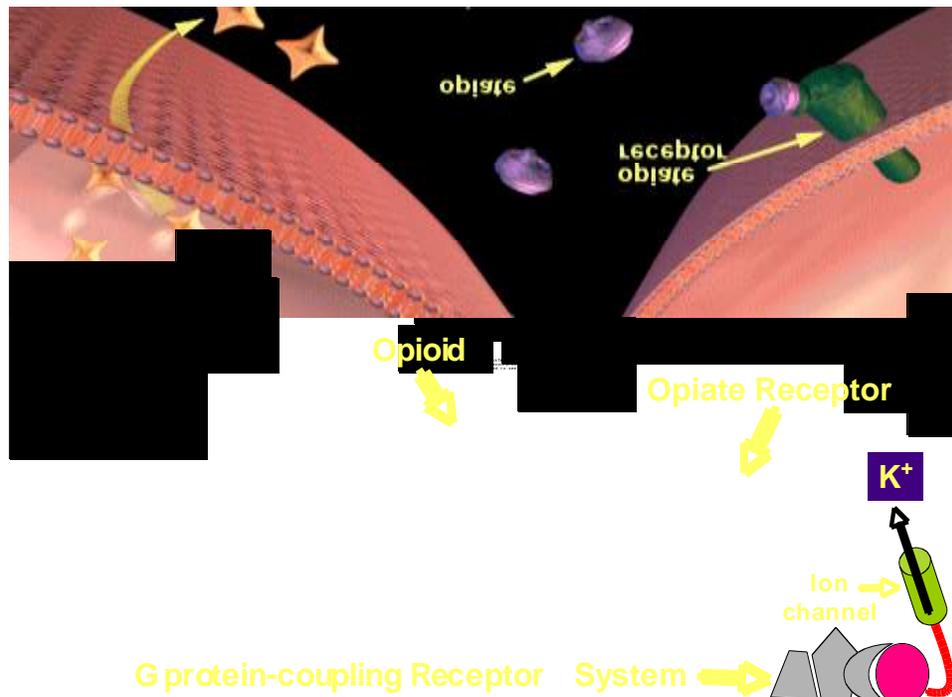
Skin crawling

Tremor

Seizures

Pulmonary edema in susceptible patients with cardiac disease

Figure 1 The G Protein-Coupled Opiate Receptors



Adapted by Allan Schwartz, CRNA, DDS from the National Institute of Health, National Institute on Drug Abuse<sup>17</sup>

### Box 1 The Naloxone Challenge Test<sup>42</sup>

Administer 0.8mg of Naloxone SQ, or 0.2 mg IV followed under 15 minutes of close observation for signs or symptoms of acute withdrawal, which is summarized in Table 5.

## Study Questions

1. What is the backbone molecular structure for each of the Pure Narcotic Antagonists?

- a) methyl group
- b) phenyl group
- c) benzyl group
- d) sterol group
- e) n-allyl opioid group

Answer e

2. What property of each of the Pure Narcotic Antagonist allows it to have a unique therapeutic use?

- a) protein binding
- b) polarity
- c) pharmacokinetic profile
- d) hepatic metabolism
- e) renal clearance
- f) all of the above

Answer f

3. Identify the for current genetically-identified opioid receptors:

- a) Mu Kappa Delta NOP
- b) Mu Kappa Delta Sigma
- c) Mu Kappa Delta Alpha

Answer a

4. Where are the highest concentrations of opioid receptors?

- a) substantia gelatinosa
- b) prefrontal gyrus
- c) substantia nigra
- d) tentorium
- e) periaqueductal grey matter

Answer a,e

5. Naloxone specifically affects only mu opioid receptors? True False

Answer false

6. Administration of a Pure Narcotic Antagonist reverses the following opioid effects:

- a) analgesia
- b) decreased respiration
- c) nausea/vomiting
- d) mioiosis
- e) constipation
- f) all of the above

Answer f

7. Pure Narcotic Antagonists have found therapeutic use in:

- a) alcohol withdrawal
- b) pruritis
- c) cocaine, alcohol, marijuana dependence
- d) premenstrual syndrome

e) all of the above

Answer e