Ultra Low Dose Naltrexone – For Lower Opiate Tolerance – Research Summary

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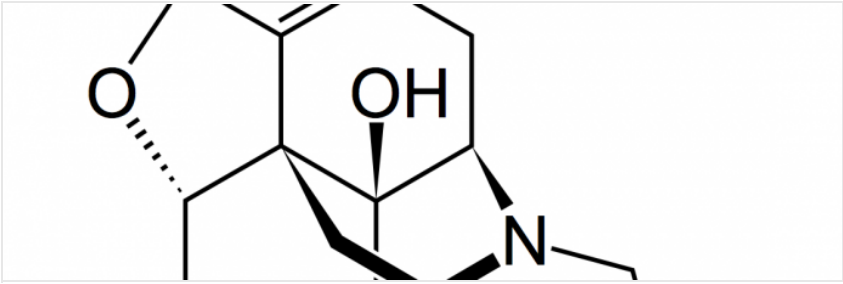

What is Naltrexone?

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Naltrexone's primary use (in normal doses) is in the management of opioid and alcohol dependency. It is also often used to reduce Benzodiazepine withdrawal symptoms as both Benzodiazepines and alcohol rely on agonizing GABA receptors, which is also why addiction to alcohol or benzodiazepines are also notoriously difficult to treat.

Naltrexone reversibly blocks the effects of opiates to manage opiate dependency and also modulates the dopaminergic mesolimbic pathway – the reward center in the brain, together these reduce the feel good factor in the drugs and thus in theory allowing a reduction.

Obviously this doesn't work very well…because simply put it also cancels a portion of the Opiates primary effects.

The interesting part about Naltrexone is when it is diluted into micrograms it changes into a totally different drug.

What is Ultra Low Dose Naltrexone?

Ultra Low Dose Naltrexone is an extremely diluted liquid solution of the drug Naltrexone.

It is even more diluted than the popular solution used for treating multiple sclerosis known as "Low Dose Naltrexone.

Note that Ultra Low Dose Naltrexone is NOT Low Dose Naltrexone.

Normal Naltrexone, ULDN (Ultra Low Dose Naltrexone) and LDN (Low Dose Naltrexone) all have different effects due to the differing effects on the Opiate receptors depending on dosage.

This will be covered in detail further on.

How Does Ultra Low Dose Naltrexone Potentiate Opioids?

Yes, studies show that ultra low dose Naltrexone show improvement in analgesic efficacy and an increased duration of

analgesia, alleviation of tolerance and reversal.

6 Papers publish by Crain and Shen from 1990 to 2000 show reliably ULDN enhanced the level of analgesia as well as the duration from morphine.

> a novel drug that combines oxycodone with ultralow-dose naltrexone, an opioid antagonist. Ultralow-dose opioid antagonists have been demonstrated to enhance and prolong opiate analgesia and alleviate opioid tolerance and withdrawal in rodents. This 3-week, Phase II clinical trial assessed safety and analgesic efficacy of Oxytrex in patients with moderate to severe pain from osteoarthritis. Patients with a pain score or =5 received placebo, oxycodone 4 times a day (qid), Oxytrex qid, or Oxytrex twice a day (bid). All active treatment groups received the same total daily dose and dose escalation of oxycodone starting at 10 and ending at 40 mg/day. Importantly, the Oxytrex bid group received a lower daily dose of naltrexone than Oxytrex qid (0.002 vs 0.004 mg/day). Oxytrex bid produced a 39% reduction in pain intensity, which was significantly greater than that of placebo (P < .001), oxycodone qid (P = .006), and Oxytrex qid (P = .003). Oxytrex bid was also superior to placebo in quality of analgesia (P = .002), duration of pain control each day (P = .05), patients' global assessments (P = .04), and the Western Ontario and MacMaster Universities Osteoarthritis Index total score (P = .03). The incidence of side effects was comparable between active treatments. In this Phase II dose-ranging study, Oxytrex bid demonstrated greater pain relief with a more convenient dosing schedule compared to oxycodone qid.
> *J Pain. 2005 Jun;6(6):392-9.*
> *Adding ultralow-dose naltrexone to oxycodone enhances and prolongs analgesia: a randomized, controlled trial of Oxytrex.*
> *Chindalore VL1, Craven RA, Yu KP, Butera PG, Burns LH, Friedmann N.*
> *Anniston Medical Clinic, Anniston, Alabama, USA.*

For those who don't know – Tolerance happens because as a person takes the same chemical many times, the body adapts and down-regulates the receptors to reduce the effect of the drug.

In addition ultra, low dose Naltrexone also prevents the development of drug tolerance to Opiates.

> Recent preclinical and clinical studies have demonstrated that cotreatments with extremely low doses of opioid receptor antagonists can markedly enhance the efficacy and specificity of morphine and related opioid analgesics. Our correlative studies of the cotreatment of nociceptive types of dorsal-root ganglion neurons in vitro and mice in vivo with morphine plus specific opioid receptor antagonists have shown that antagonism of Gs-coupled excitatory opioid receptor functions by cotreatment with ultra-low doses of clinically available opioid antagonists, e.g. naloxone and naltrexone, markedly enhances morphine's antinociceptive potency and simultaneously attenuates opioid tolerance and dependence.
> These preclinical studies in vitro and in vivo provide cellular mechanisms that can readily account for the unexpected enhancement of morphine's analgesic potency in recent clinical studies of post-surgical pain patients cotreated with morphine plus low doses of naloxone or nalmefene. The striking consistency of these multidisciplinary studies on nociceptive neurons in culture, behavioral assays on mice and clinical trials on post-surgical pain patients indicates that clinical treatment of pain can, indeed, be significantly improved by administering morphine or other conventional opioid analgesics together with appropriately low doses of

Naltrexone opiate tolerance reversing tolerance

A B C D E F G
H I J K L M N
O P Q R S T U
V W X Y Z #

A
ADHD
Adderall
Agmatine
Alprazolam
Anxiety disorder
Armodafinil
Asperger syndrome
Attention deficit hyperactivity disorder
Autism
Autism spectrum

B
Benzodiazepine

C
Chronic pain
Cognitive behavioral therapy

D
Depression (mood)
Diazepam
Dihydrocodeine
drug tolerance

E
Eczema

F
Flumazenil
fight or flight

G
Generalized anxiety disorder

K
Kratom

an excitatory opioid receptor antagonist.
Crain SM, Shen K-F (2000) Antagonists of excitatory opioid receptor functions enhance morphine's analgesic potency and attenuate tolerance/dependence liability. Pain 84:121-131.

Note that physical drug tolerance is independent of receptor tolerance, but somehow Naltrexone also prevents physical withdrawals that cause pain, known as Hyperalgesia.

Allowing lower levels of Naloxone to be used, also reduced additive potentiation.

Related articles

OPIATE TOLERANCE REVERSING TOLERANCE

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How Does ULDN Work to Reverse Opiate tolerance or tolerances of Other Drugs?

Naltrexone acts on the mu opioid receptor, using allometric scaling from research in rats 1mg per kg will work out to be 1 picograms per kg

Mice were able to stay on the same dosage by adding Naltrexone 3 days later, without the need to increase the drug as you would normally need to.

Ultra Low Dose Naltrexone is speculated to have high affinity for an unknown site and is not acting as a classical antagonists. Only 1% of the opioid receptors are occupied at ultra low dose.

Higher dosages may cause interference with the above mechanism by binding at the classical receptor site instead of the unknown site.

Whatever this mechanism it is, ULDN is shown by scientists to work by preventing a switch in the G protein coupling that has been shown to occur drug chronic opiate administration.

The current standing theory is that ULDN acts to block receptor coupling tp G proteins

> Opiates produce analgesia by activating mu opioid receptor-linked inhibitory G protein signaling cascades and related ion channel interactions that suppress cellular activities by hyperpolarization. After chronic opiate exposure, an excitatory effect emerges contributing to analgesic tolerance and opioid-induced hyperalgesia. Ultra-low-dose opioid antagonist co-treatment blocks the excitatory effects of opiates in vitro, as well as opioid analgesic tolerance and dependence, as was demonstrated here with ultra-low-dose naloxone combined with morphine. While the molecular mechanism for the excitatory effects of opiates is unclear, a switch in the G protein coupling profile of the mu opioid receptor and adenylyl cyclase activation by Gbetagamma have both been suggested. Using CNS regions from rats chronically treated with vehicle, morphine, morphine+ultra-low-dose naloxone or ultra-low-dose naloxone alone, we examined whether altered mu opioid receptor coupling to G proteins or adenylyl cyclase activation by Gbetagamma occurs after chronic opioid treatment. In morphine-naïve rats, mu opioid receptors coupled to Go in striatum and to both Gi and Go in

L

- Lidocaine
- Limbic System
- loop

M

- Magnesium deficiency (medicine)
- Memantine
- Methylphenidate
- Modafinil
- Morphine

N

- Naltrexone
- Nasal spray
- Neurotypical
- Nicotine
- neurotypicals

O

- Oxytocin
- Oxytocin
- opiate tolerance

P

- Panic attack
- Phenylalanine
- Posttraumatic stress disorder
- Proglumide
- potentiation

R

- Reverse Tolerance
- reducing tolerance
- reversing tolerance

S

- Social anxiety
- Social anxiety disorder
- Social skills
- Sublingual administration

T

- Testosterone
- the loop

W

- WAY-267,464

> periaqueductal gray and spinal cord. Although chronic morphine decreased Gi/o coupling by mu opioid receptors, a pronounced coupling to Gs emerged coincident with a Gbetagamma interaction with adenylyl cyclase types II and IV. Co-treatment with ultra-low-dose naloxone attenuated both the chronic morphine-induced Gs coupling and the Gbetagamma signaling to adenylyl cyclase, while increasing Gi/o coupling toward or beyond vehicle control levels. These findings provide a molecular mechanism underpinning opioid tolerance and dependence and their attenuation by ultra-low-dose opioid antagonists.
> *Neuroscience. 2005;135(1):247-61.*
> *Ultra-low-dose naloxone suppresses opioid tolerance, dependence and associated changes in mu opioid receptor-G protein coupling and Gbetagamma signaling.*
> *Wang HY1, Friedman E, Olmstead MC, Burns LH.*
> *1Department of Physiology and Pharmacology, City University of New York Medical School, 138th Street and Convent Avenue, New York, NY 10031, USA. hywang@sci.ccny.cuny.edu*

Why Ultra Low Dose Naltrexone, rather than Low Dose or even just Naltrexone?

First of all, pure Naltrexone is a scary undesirable experience. Naltrexone is an opioid antagonist that means it's pretty much the opposite of pain relief, misdoing can yield some extremely uncomfortable experiences.

Ultra Low Dose Naltrexone acts in a very different way than Low Dose Naltrexone. The referenced research shows ULDN is also capable of reversing tolerance on multiple papers referenced at the end of this article.

What's the Dosage and How Should It Be Taken?

The studies shows that less is better, having more than (20micrograms) blocks the effects of opiates and removes the anti-tolerance effect.

The greatest level of tolerance reversal and reduction came from the lowest levels of Naltrexone!

This is an important point, anecdotally people are trying up from 1 microgram to 20 micrograms.

The suggested regiment from the research is 3 times a day, taken with the opiate together.

In the studies using allometric scaling only 1 to 2 micrograms would be used, if translated to human levels – however allometric scaling is not always accurate given the differences between

> Extensive preclinical data have shown ultra-low-dose opioid antagonists to enhance and prolong the analgesic efficacy of opiates and prevent opioid tolerance (Crain and Shen, 1995; Powell et al., 2002; Shen et al., 2002a, b). The enhancement of analgesia is both an increase in potency and an increase in efficacy of the opiate. For example, in the mouse hot water tailflick assay, the antinociceptive effect of the EC50 dose of oxycodone (1 mg/kg, s.c.) was enhanced by the addition of 1 pg/kg naltrexone, while the antinociceptive effect of an EC100 dose of oxycodone (3 mg/kg, s.c.) was also enhanced by ultra-low-dose naltrexone, here at 3 pg/kg (Fig. 1). In addition, the duration of action is prolonged.
> Recent Developments in Pain Research, 2005: 115-136 ISBN:
> 81-308-0012-8 Editor: Anna Capasso
> Ultra-low-dose opioid antagonists enhance opioid analgesia while reducing tolerance, dependence and addictive properties
> Lindsay H. Burns
> Pain Therapeutics, Inc., South San Francisco, CA, USA

What's the Upper Ceiling?

20 micrograms appears to be the upper limit.

It is highly likely that trying anything 1 to 10 micrograms is feasible. Allometric scaling is notoriously unreliable.

Potential Interactions and Risks to Watch Out

At such low doses Naltrexone should have next to no side effects, in fact it should reduce the side effect profile of Opiates (when tolerance has developed and higher dosages are in play).

Normal Naltrexone can be overdosed at levels beyond 1500mg, it is a common mistake to think Naltrexone cancels out the dangerous fatal depressive effects of opiates like Morphine or Heroin. It does not, it is entirely common for people to overdose on Opiates because they think Naltrexone will block the effects of the Opiates completely.

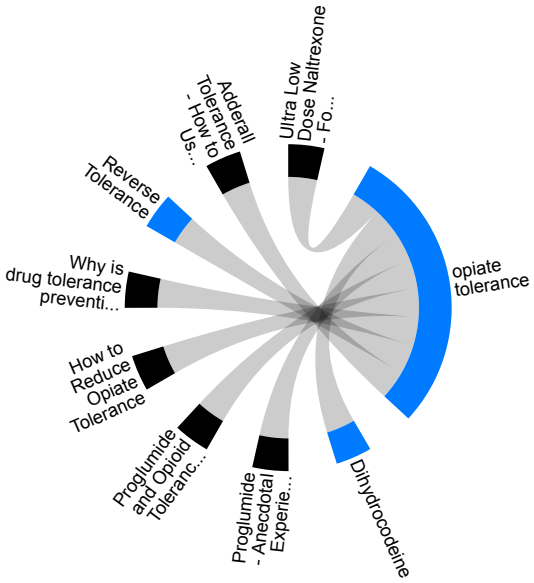
A Naltrexone overdose can cause liver damage, cause pain and extreme fatigue and even become fatal. On normal doses it can cause stomach cramps, diarrhoea, headaches, and muscle aches and more.

Bonus Information

Mice Deficient in B-Arrestin-2 pkcy or the delta opioid receptor do not develop opioid tolerance. Naltrexone happens to target delta opioid receptors.

Low Dose Naltrexone (A little higher dosage than ULDN but still much lower than tablet form) is a very popular liquid solution for a whole bunch of other ailments such as Multiple Sclerosis.

– Khemcorp



Disclaimer: All thoughts and advice expressed are the personal opinions and gatherings of the author and do not constitute medical advice. If you are seeking medical advice please consult a doctor.

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