Naltrexone

The Story of Opioids

Before the concept of low-dose naltrexone was born, high doses of this drug were used in conventional medicine for completely different purposes.

Naltrexone is a drug that blocks the activity of opioids in the brain. Your body normally produces endorphins and enkephalins, natural opioids that contribute to feel-good sensations. In fact, these chemicals are the body's most powerful reward and pleasure system.

Opioid drugs can provide relief from chronic, intense pain. But they don't come without risks: high doses can slow or even stop breathing and exaggerate feelings of calm, euphoria, and pleasure when abused.

Opioid drugs include both prescription painkillers like Vicodin and Percocet, as well as drugs of abuse like fentanyl.

The opioid blocker naltrexone was synthesized in the 60s and approved in the 80s for treating opioid addiction.

Doctors gave naltrexone to opioid addicts in recovery to prevent relapse. The rationale was to completely shut off the 'high' of abused narcotics. By blocking all receptors in advance, naltrexone renders narcotics powerless.

The dosage needed to achieve opioid blockage is high, ranging from 50 – 100 mg/day.

Note: Naltrexone shouldn't be confused with *naloxone* (Narcan), although both drugs are opioid blockers. You may have heard about naloxone kits (spray or injection) that can save lives in opioid overdose. Naloxone is a better choice for reversing overdose because it starts to act faster and lasts for a shorter time, as is desirable in emergency situations. Naltrexone, on the other hand, takes a couple of hours just to kick in.

The Discovery of LDN

Around the same time when naloxone was being used for opioid addiction in mainstream clinics, New York-based physician Dr. Bernard Bihari started using the drug in very low doses in the midst of the first AIDS epidemic.

By attempting the impossible – using an opioid blocker to enhance the immune response in people with an "untreatable" disease – Dr. Bihari spurred a lot of attention.

He was initially working with opiate addicts when he observed that high-dose naltrexone seemed to make the body triple endorphin production. However, it caused too many side effects, such as insomnia and the inability to handle stress. Few would stay on it.

To re-wind: opioid-like endorphins are not only released to help us cope with everyday social situations free of fear, pain, and anxiety. They also play an important role in acute stress and the fight-or-flight response.

Interested in the drug's immune effects, Dr. Bihari started prescribing a range of naltrexone doses to HIV patients. His goal was to find the best dose that would boost endorphins without causing negative effects.

Surprisingly, it turned out that a small naltrexone dose (3 – 5 mg) increased endorphins to the same extent as a high dose.

Next, he ran a 9-month LDN trial in people with AIDS and described the results as promising. After realizing the immune-normalizing potential of LDN for AIDS, Dr. Bihari hypothesized its application for a wide range of autoimmune diseases.

However, it wasn't until 2007 that the first low-dose naltrexone (LDN) clinical trial was published. All the while, science has been gaining a lot of insight into the intricate workings of endorphins and opioids in the body.

Some small LDN studies have been published and LDS has gained attention as a potential complementary approach to many chronic diseases. Yet the opinions about its clinical use are mixed, and rightly so.

Despite some encouraging findings and anecdotes, we still know less than we don't about LDN. Proper, large-scale trials are lacking. Most of the data relies on Dr. Bihari's observations, small-scale studies, and clinical and personal experiences. Because of this, **there's still insufficient evidence to recommend LDN for any indication.**

Proponents

- Used off-label for autoimmune diseases, chronic pain, and inflammation
- Claimed to increase natural opioids and balance the immune system
- Limited studies suggest side effects are mostly rare and mild
- Likely few drug interactions

Skeptics

- Large-scale studies lacking
- Not enough data to rate effectiveness
- Unapproved, unofficial use (off-label)
- Dosing usually has to be adjusted to each individual
- Use largely relies on clinical expertise
- Long-term safety unknown

Proposed Mechanism

The mechanism outlined here and proposed by Dr. Bihari is considered to be a controversial scientific hypothesis. It hasn't been confirmed in large trials or, therefore, accepted by most medical doctors and experts. Proper clinical studies have yet to verify most of Dr. Bihar's claims.

With this in mind, let's take a look at how LDN is hypothesized to work.

Dr. Bihari considered that low naltrexone doses block opioid receptors for a short time – about 3 hours. In response, the body seems to increase the production of endorphins. According to Dr. Bihari, a small late-evening dose of naltrexone will boost endorphin production by 300%.

He said that although naltrexone is cleared away by the morning, endorphins stay high all the next day. The endorphin blockage from low-dose naltrexone is described as mild and short. Essentially, it's thought to increase the activity of opioids.

In comparison, high dose naltrexone doses raise endorphins but keeps the receptors constantly blocked, *reducing* their activity as the end result.

Dr. Bihari believed that the rise in endorphin levels remains for as long as a person is taking the low dose every night.

Beta-endorphin, one of our main natural opioids, has a long half-life of about 20 hours in the body. It's unknown for how long other endorphins stay high in the blood.

Endorphins act on different opioid receptors:

- **Mu receptors** are in the brain and help with pain relief.
- **Delta receptors** may play a role in cancer and the immune system.

There are several other receptor types that may be important for the action of LDN, but these two appear to play the largest role.

Does it Block or Stimulate Endorphins?

The concept of "stimulating by blocking" is not an easy one. Let's dive a bit deeper.

The hypothalamus is a structure in the base of the brain and part of the limbic system, which orchestrates emotions, motivation, and learning. Low-dose naltrexone is thought to block opioid receptors in the hypothalamus.

In response to the short-term blockage, Dr. Bihari said that the brain begins producing more of a prohormone called proopiomelanocortin during the night. Next, this hormone is broken up into 3 others in the pea-sized "master gland" called the pituitary:

- Beta-endorphin
- Adrenocorticotropic hormone (ACTH)
- Melanin-stimulating hormone

Aside from these direct effects on the brain, Dr. Bihari thought that LDN may also signal the adrenals to make more enkephalin via another prohormone called proenkephalin.

This is a normal response, as the body interprets blocked receptors as a signal that endorphins are low. To compensate, it increases their production. For this reason, Dr. Bihari would say that LDN increases natural opioids – endorphins and enkephalins – by blocking.

He said that if the receptors are blocked by a high dose, they don't get to recover and stay shut off. According to him, the ideal dose should maximally increase endorphins while minimally blocking them.

The Missing Link Between Cancer, Autoimmunity, and Depression?

To understand how LDN might work, some scientists are trying to get to the bottom of how complex diseases like cancer, autoimmunity, and mood imbalances may be connected to endorphins. Their work is still in the early stages and nobody yet has any conclusive answers.

According to one theory that has yet to be verified, low blood levels of endorphins might contribute to immune deficiencies, and this link has been implicated in cancer and autoimmune diseases. Similarly, HIV/AIDS is accelerated by a deficiency of endorphins. Of course, they are not the only potential cause, but might be a piece of the puzzle.

Low endorphins are highly unlikely to be the only causative factor of autoimmune problems, mood disorders, or any other complex disease. These diseases always involve multiple possible factors–including the body's chemistry, environment, health status, and genetics–that often vary from one person to another.

Another interesting scientific concept is the so-called "sickness response" or "sickness behavior." When people are faced with a disease – be it cancer or depression – they tend to isolate themselves while the body increases inflammation and alters the immune response.

To draw a parallel, sickness behavior is well-known to scientists in the animal world: animals will isolate themselves for a short period of time when faced with an infection or disease to avoid contaminating others.

Sickness behavior can become devastating if it stops to serve a purpose and turns into chronic low mood and energy. It turns out that low endorphins may be the culprit of this complex psychological and emotional response in humans, at least according to certain research groups.

By boosting endorphins, LDN is hypothesized to help reverse this kind of behavior while also balancing the immune system. However, this hypothesis has yet to be tested in clinical trials.

Is It Legal?

LDN is an experimental approach. Despite ongoing scientific efforts, there's not enough clinical data about its effectiveness. Thus, it is often thrown into the "alternative treatments" bucket, but it is not illegal.

Naltrexone is a drug licensed and approved by the FDA, meaning that doctors can prescribe it. However, it's not approved for the indications we focus on in this article. That makes the use of LDN "off-label."

LDN Dosage

Consult with your physician before taking low-dose naltrexone. **This medication requires a prescription and should only be used under the guidance of a qualified healthcare professional**.

Typical Protocol & Dosage

- LDN is usually taken only once a day before bedtime as 90% of endorphins are hypothesized to be made during the night.
- The dosage typically ranges from 1.5 mg to 5 mg/day*.
- Slow/timed-release naltrexone and LDN capsules that contain calcium carbonate filters should be avoided.
- Pills are the most common form, but topical creams and patches have also been developed; they may work better for children or people who have difficulty swallowing.
- Naltrexone is commercially available only at a 50mg dose, which means that people need to get their prescribed low-dose formulation from a compounding pharmacy.

*Dr. Bihari considers that the dose should be no less than 1.75 – 2 mg/day and no higher than 4.5 – 5 mg/day. He used to say that 3 mg/day is a good dose that works for most people.

Ultra-low Dosage

This is where the confusion kicks in, as some studies used so-called "ultra low-doses," ones that range from 0.125 – 0.5 mg/day. On the other hand, borderline doses of 0.5-1 mg/day are considered "very low-dose."

There is no clear benefit to very or ultra-low doses, based on the published studies. However, each person is different and your doctor may consider that doses in this range will work better for you.

LDN Side Effects and Interactions

This list does not cover all possible side effects. Contact your doctor or pharmacist if you notice any other side effects.

Call your doctor for medical advice about side effects. In the US, you may report side effects to the FDA at 1-800-FDA-1088 or at www.fda.gov/medwatch. In Canada, you may report side effects to Health Canada at 1-866-234-2345.

Sleep Issues

Some people experience vivid dreams (or rarely nightmares), which tend to go away with time. Insomnia is another possible side effect. In such cases, dosing can be moved to the morning.

Dr. Bihari added that poor sleep is the only side effect he noticed in a very small percentage of people on 3 mg/day. He considers that lowering the dose (to 1.5 – 2 mg/day) is a better solution than moving it to the morning.

In such cases, some practitioners recommend natural calming supplements or lifestyle adjustments to help people overcome mild sleep issues while on low-dose naltrexone. They include magnesium, melatonin, and hops.

Other

According to the published studies, mild headaches are also possible. Some physicians reported anxiety, but this was mostly in people undergoing opioid withdrawal and possibly not related to naltrexone.

There are anecdotes of people with chronic fatigue and "mold illness" not reacting well to LDN, though these diagnoses are considered controversial. Be sure to see a board-certified physician to get an accurate diagnosis and treatment.

Major side effects in the published clinical trials to-date have not been reported.

Drug Interactions

Keep in mind that the side effects profile and drug interactions of LDN are relatively unknown, given the lack of well-designed clinical studies.

Limited evidence suggests that LDN should not be used with opioid painkillers: codeine, morphine, fentanyl, hydrocodone, and methadone. Low doses of naltrexone may block opioid receptors and temporarily reduce their effectiveness.

People who used (or abused) opioids long-term may require 10 days to 2 weeks before LDN treatment. Your doctor will be able to assess this based on your individual situation.

People who have had organ transplants and are taking immunosuppressive drugs permanently are cautioned against the use of LDN.

According to some anecdotes, LDN may affect thyroid hormone balance.