Section A-Research paper

NALTREXONE PAST THE PSYCHIATRIC FIELD: A REVIEW

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ABSTRACT

Opioid receptor (OR) antagonist naltrexone is a medicine that has been approved by the FDA for the treatment of opioid and alcohol use disorders when taken in the usual doses. Naltrexone, on the other hand, has been found to have unique applications in inflammatory, neoplastic, insulin sensitivity-related, and chronic pain diseases since the identification of the effects of OR signalling at low doses that are not neuropsychiatric in nature. Its harmful effects are also mitigated when it's taken in smaller dosages. Its use outside of the manufacturer's instructions in the aforementioned scenarios has been shown to be cost-effective in comparison to expensive immunomodulation and anticancer medications. Because of its cheaper cost and extremely low margin of interest, in-depth research on the topic has been prevented by the pharmaceutical industry. Animal studies, cell culture studies, and case reports are the only types of research that have been carried out so far; some of these types of research have shown encouraging results. There are not nearly enough high-quality trials being conducted.

Keywords: Opioid, Malignancy, Inflammation, Insulin, Alcohol

INTRODUCTION

The "*Opioid Receptor* (OR)" antagonist naltrexone is a medication approved by the United States "*Food and Drug Administration* (FDA)" for the treatment of opioid and alcohol use disorders when taken at the recommended doses. Traditionally, naltrexone is recommended in oral doses of at least 50 mg per day. It is a competitive OR antagonist that can be taken orally and has a longer duration of action than its predecessors, nalorphine, naloxone, and cyclazocine, allowing once-daily dosage.[1] With typical doses of 50 mg to 100 mg per day, it is still only used for alcohol and opioid use disorders, according to the "*US Federal Drug Administration* (USFDA)".[2] It has been demonstrated to reduce alcohol consumption and prevent relapse.[3] Since naltrexone is hepatotoxic, liver chemistries must be monitored after therapy. Dr. Bernard Bihari, the deputy medical commissioner for New York City during the AIDS crisis in the 1980s, observed that naltrexone increased the irritability and depressive symptoms of heroin addicts when administered at the recommended levels. At modest dosages, it simultaneously increased endorphin levels, which enhanced immunity.[4] He titrated doses to reduce side effects while maintaining endorphin levels.

"*Low-dose naltrexone* (LDN)" is the term for these 1–5 mg dosages, which were successfully utilized as AIDS adjuncts. The discovery of LDN sparked an interest in understanding the non-neuropsychiatric bases of OR down signalling.[1-5] This narrative review focuses on the areas where LDN as well as ultra low levels have been demonstrated to offer significant advantages. With a focus on its intracellular mechanisms of action, influencing the immune system, postponing the advancement of cancer, and utility in disorders associated with chronic pain has been thoroughly discussed.

EVOLUTION

Naloxone, its short-acting counterpart, should be addressed while discussing naltrexone. Naloxone was a unique opioid system pharmacology research tool when initially manufactured. Naloxone blocks opioid actions by binding to the neuronal "Mu" opioid receptor. It reverses opioid overdose as a "Mu opioid receptor (MOR) antagonist." Drs. Jack Fischman and Mozez Lewenstein of Memorial Sloan Kettering Center for Cancer Research developed and patented naloxone in 1961 based on a theory by Dr. Harold Blumberg of Endo Laboratories in Long Island. Intravenous naloxone (Envizio) was FDA-approved for opioid overdose reversal in 1971 and became a common emergency treatment at several of the nation's top academic medical institutes. Naloxone was intravenous exclusively until recently. The FDA approved a self-administered subcutaneous/intramuscular autoinjector in 2014. Nasal spray was approved in 2017. As psychiatric and addiction specialists, one must rescue, resuscitate, and revive the patient to give them another chance to change. Long-acting naltrexone blocks MOR like naloxone. In 1963, Endo Labs created it, which DuPont Pharmaceuticals bought in 1969. After years of dormancy, Congress approved the Drug Abuse Office and Treatment Act in 1972 to discover non-addictive (nonagonist) heroin addiction treatments. Opioid addiction treatment was only methadone, a long-acting MOR agonist. It reduced cravings without the "high" or cognitive inhibition of heroin. If methadone-compliant, heroin-dependent patients can work, have relationships, and live productively. Methadone, which binds to opioid receptors and is addictive, reduced cravings. However, the medicine must be supplied at a registered clinic and carefully monitored because it is prone to abuse and diversion and can cause overdose and death when taken with other sedating pharmaceuticals including barbiturates, benzodiazepines, and alcohol. Consequently, naltrexone, without methadone's sedating, euphoric, and sometimes lethal side effects, was a popular office-based opioid-use disorder treatment.[3]

Clinical application at low doses

Many diseases have been proven to improve and change in course when treated with low-dose naltrexone. There is some complexity in terms of its several pharmacological targets and modes of action. The sources of clinical evidence range widely, from early case reports to more contemporary randomized controlled trials. For conditions like Crohn's disease and fibromyalgia that include chronic inflammation or immunological dysregulation, low-dose naltrexone may be helpful.[1-10] **Box 1**

Box 1: Clinical application at low doses

Dose Range	Dose Specific Mechanism of Action	Clinical Use
Standard (50–100 mg)	Opioid receptor antagonism	Alcohol and opiate abuse
Low-dose (1–5 mg)	Toll-like receptor 4 antagonism, opioid growth factor antagonism	Fibromyalgia, multiple sclerosis, Crohn's disease, cancer, Hailey-Hailey disease, complex-regional pain syndrome
Very low-dose (0.001–1 mg)	Possibly same as low-dose	Add-on to methadone detoxification taper
Ultra low-dose (<0.001 mg)	Binding to high affinity filamin-A (FLNA) site and reducingμ-opioid receptor associated Gs-coupling	Potentiating opioid analgesia

(Adapted from: Toljan K.[1])

ALTERNATE MEDICAL APPLICATIONS

Multiple sclerosis

Endorphins, enkephalins, and dynorphins, which are endogenous opioids, were mostly thought of as neuromodulators until the 1980s. Yet, it was later discovered that a particular enkephalin, known as (Met5)-enkephalin, also controlled growth.[1-3] It was demonstrated to work on the-OR later on and is known as the opioid growth factor (OGF) (zeta-OR or OGF receptor [OGFr]). Subsequent research indicated that OGFr did not have sequence homology with the other OR.[2] The G-S phase of the cell cycle is where the OGF-OGFr axis controls both healthy and cancerous cell proliferation.[2]

In animal models of MS, this axis' modification with LDN resulted in a delay in the onset of symptoms. In a 2015 retrospective analysis, Turel et al.,[11] stated that LDN decreased tiredness in relapsing-remitting MS, improved quality of life, and slowed disease progression through animal and human research. There were no new adverse effects that were recorded (other than those already present in literature). Despite the expensive immunomodulating treatments that are a mainstay for MS patients, LDN may be a hope.

Polycystic ovary syndrome

In patients with polycystic ovary syndrome (characterized by a state of IR), there appears to be a potential role of standard-dose naltrexone. However, it is contraindicated in hepatic insufficiency and in those using opioids chronically. It is considered a pregnancy category C drug.[12]

Crohn's disease

Philippe et al.,[13] demonstrated that sick enterocytes and T-cells overexpressed -ORs in a case-control French study of individuals with inflammatory bowel disease conducted in 2006. In order to treat auto-inflammatory disorders, this prompted study into the possible value of medications that act on opioid receptors.

In a 2018 database review by Parker et al.,[14] they performed an intention-to-treat analysis on two randomized controlled trials (RCTs) involving Crohn's disease patients - one adult and one pediatric - and discovered that the studies were unable to draw any meaningful conclusions about the ability of LDN to cause remission in the condition.

Since January 2021, a double-blind placebo-controlled trial has been running in The Netherlands to determine whether LDN can cause remission in mild-to-moderate Crohn's disease. The major outcome criterion for the trial is endoscopic remission, while additional outcomes include, among others, patient-reported outcomes. [15]

Psoriasis

The most likely mechanisms of action in this situation are: (1) a decrease in pro-inflammatory markers through the inactivation of TNF produced by macrophages; and (2) a reduction in pain and itchiness through an increase in circulating endogenous opioids like ß-endorphin due to paradoxical endogenous opioid release caused by low-dose naltrexone.[1,2] This finding may have clinical ramifications for patients who are unable to tolerate conventional medications or for whom other treatments have failed. Although though it is often impossible to prove cause and effect from a single instance, this is a fascinating and original finding that calls for more research. Low-dose naltrexone therapy for psoriasis may be tempting because to its low risk of side effects, affordable price, and effectiveness in individuals with inflammatory chronic diseases. Patients with psoriasis may benefit from modulating the OGF-OGFr axis, just like MS sufferers might. Long-term treatment with LDN (three months) resulted in clearing of skin lesions with no return of flare throughout the follow-up period of six months in two distinct clinical case reports on patients with psoriasis vulgaris and erythrodermic psoriasis.[16,17]

Rheumatoid arthritis

According to a 2019 published pharmacoepidemiological study from Norway that used the Norwegian Prescription Database, LDN use in rheumatoid arthritis patients led to a decrease in the need of steroids, analgesics, and disease-modifying antirheumatic medications. The result was statistically noteworthy. However this study was a quasi-experimental one. Therefore, there is an unmet demand for blinded RCTs in individuals with rheumatoid arthritis.[18]

Severe acute respiratory syndrome coronavirus‐2 (SARS‐CoV‐2)

It has been demonstrated that "cytokine storm" is a secondary cause of the acute respiratory distress syndrome and associated multi-organ dysfunction in SARS-CoV-2. The extracellular signal-regulated kinase (ERK), also known as the mitogen-activated protein kinase (MAPK) pathway, has a unique significance in this context. Viral load and MAPK/ERK phosphorylation are closely connected.[19] In murine models, Choubey et al.,(2022)[20] shown that LDN had an inhibitory effect on ERK. LDN, which has previously received US-FDA certification for being free of clinical toxicity, can be used in human RCTs to potentially provide conclusive proof of benefit in SARS-CoV-2.

Other medical conditions

Cholestasis, pruritus, Osteoarthritis, Low back pain, Axillary brachial plexus blockade analgesia, Postoperative pain control following colorectal surgery are all the other medical conditions that have been discussed for the treatment with the ultra-low-dose naloxone/naltrexone.[1]

CANCER

The key mechanism of action for stopping the spread of cancer by naltrexone appears to be its effect on cell cycle regulation via the OGF-OGFr axis.[11] There may be a mortality advantage from LDN use in patients with skin, lung, bladder, liver, colon, and rectum malignancies. Liubchenko et al.,[21] came to the conclusion that low dosages (vs. standard dose) of naltrexone when administered in intermittent dosing had a favourable effect on tumour progression in their extensive systematic review, which included trials on humans, animals, and cell culture. Figure 1

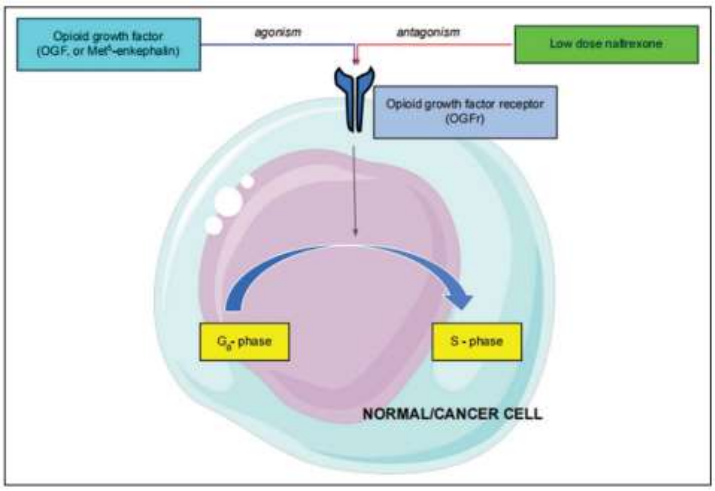

Figure 1: Low dose naltrexone (Adapted from: Garg et al[2])

CHRONIC PAIN CONDITIONS

As naltrexone is an OR antagonist, using it as an analgesic seems unscientific. Only LDN has this paradoxical effect, and its recommended levels are unaffected. There have been many explanations put out, but two in particular stand out: the action of LDN on TLR-4 located on microglia cells (the macrophages of the central nervous system) and the up-regulation of endogenous opioid levels and OR.[22]

First, a non-OR mechanism, such as TLR-4, which is present on a variety of cells including microglial cells, appears to be responsible for the seemingly counterintuitive impact of naltrexone in lowering pain. TLR-4 functions downstream of NF-B to control inflammatory activity, similar to how IR is described. LDN acts as an anti-inflammatory drug by stifling this cascading mechanism. LDN, however, has demonstrated efficacy in conditions like fibromyalgia, which is not often thought of as an inflammatory condition. Fibromyalgia is

more likely to make people more sensitive to pain sensations. Thus, LDN's anti-inflammatory properties could be considered to be complemented by a modulation of pain response.[1,3]

Second, studies using persistent doses of opioid agonists and LDN in in vivo models have demonstrated that endogenous opioid levels rise and OR is upregulated.[23] Similar survey-based and pilot studies have demonstrated that LDN may have a significant role to play in the treatment of complicated regional pain syndrome and irritable bowel syndrome.[1,2,24,25] These research' data, however, cannot be generalized to support their usage in clinical settings. RCTs are required to support (or deny) the claims made.

ADVANTAGES

Low price

LDN costs roughly $35 per month, compared to the typical US monthly cost of $100 for fibromyalgia treatment.[22] For non-psychiatric uses, naltrexone is currently unavailable in India. In their 2020 trial comparing the effectiveness of naltrexone and acamprosate in the treatment of alcohol dependence, Kumar et al.,[27] obtained the former medication free of charge from government supply. Until indigenous data are available, the price in the United States can be used as a proxy for the Indian market.

Low negative consequences

According to Turel et al. (2015)[11], more than 77% of MS patients taking LDN did not report any negative side effects. In this study, immune thrombocytopenic purpura was noted, although it was unclear whether it was a result of the disease or the treatment. Only dosages of 300 mg/day or higher were associated with liver damage in a placebo-controlled investigation. Warfarin and other drugs have not been found to interact. LDN use in the nonpsychiatric setting is based on the idea that only normal doses of naltrexone have the potential to be toxic, but LDN has not yet demonstrated any negative side effects other than insomnia and vivid dreaming.[1,22] Nevertheless, there aren't enough powerful controlled studies.

Low abuse liability

Unlike regular dose naltrexone, LDN doesn't seem to be abuse-vulnerable. Patients are cautioned against using opioids along with LDN because of the possibility of opioid misuse and overdose.[1,2]

DISADVANTAGES

Adverse outcomes

There have been cases of immune thrombocytopenic purpura developing in MS patients who received LDN; however, the presence of other immunomodulating medications and the effects of the disease itself appear to be confusing variables. There have also been reports of other problems like sleeplessness (6%), and nightmares (5%).[28]

Low-dose pills are not readily available.

LDN must now be obtained through special issue pharmacies because the only USFDA-approved use of naltrexone appears to be treating alcohol and opioid use disorders, and that too for standard dose naltrexone.[2,28]

Outside the purview of insurance

Insurance companies do not cover LDN and it continues to be an off-label medicine in relation to the USFDA approved restriction. Given that LDN is used to treat the majority of chronic illnesses, the cost per capita gains significance even though the long-term cost of LDN compared to traditional therapy is arguably negligible.[1,2]

CONCLUSION

Via LDN, OR antagonism has expanded the range of OR signalling beyond the narrow field of neuropsychiatry. The medicine has entered previously unexplored territory thanks to its ability to modulate insulin sensitivity, regulate normal cellular growth, stop the spread of cancer cells, moderate pain sensitivity, and lower inflammation. Its impact on TLRs, ATMs, microglial cells, NF-B, SIRT-1, the OGF-OGFr axis, and the MAPK/ERK pathway, among other things, has been studied using animal and cell culture models. Case studies have demonstrated the therapeutic advantages of long-term usage.[1,2,28]

There are, however, significant gaps in the data because there aren't many high-quality studies or long-term follow-ups. One restriction in and of itself is the lack of low-dose pills on the market. It is essential that excellent and thorough investigations be carried out before naltrexone is made available to people in need due to the discovery of novel cascade mechanisms in the drug's effect.

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