FACT SHEET LOW DOSE NALTREXONE (LDN)

A therapeutic intervention for improved disease management

Naltrexone is an oral Opiate and Toll-Like Receptor Antagonist medication that modulates the immune system to improve health outcomes in many diseases: these include autoimmune & inflammatory illness, cancer, hormonal dysfunction & infertility, autism as well as chronic fatigue.

The Naltrexone History

Opiates

For six thousand years the opium poppy has been used for its sedative and pain relieving properties; botanically it was known as *somniferum* the 'sleep-bringing poppy'. Opium is rich in alkaloids and with the emergence of chemistry research its main component was extracted in 1806 and named *morphine* after Morpheus the Greek God of dreams. Later *diamorphine,* also known as *heroin,* was synthesized. In 1939 *pethidine* was discovered and not many years later *methadone* formulated. They are known as the *opiates* which relieve pain but in excess are harmful and extremely addictive, suppressing breathing and even cause death. Such adverse effects prompted researchers to find a molecule that could reverse the negative effects of the opiate drugs.

Naloxone was the first opiate antagonist to be discovered which when injected immediately blocked the effects of morphine. In 1967 an oral medication, initially known as 'Endo1639A', was conceived which had similar effects and later become known as *naltrexone*.

Endorphins

Opiate drugs mimic the action of the body's *'natural neuropeptides'* known as *endorphins.* The best known is *beta-endorphin* which has the greatest analgesic properties influencing both the central nervous system (CNS, brain) and body's peripheral nervous system (PNS) but endorphins also have other biological activities which are not well understood. Under stress the brain's hormone control centre, the hypothalamus and pituitary, releases a *precursor protein POMC (known as proopiomelanocortin)* which can be broken down in any part of the body to form endorphins.

The peripheral nervous system (PNS) connects all parts of the body like electrical wiring to the central nervous system (CNS). Where the nerve junctions or *synapses* meet *neurotransmitter* chemicals are released sending their information to specific receptor areas that continue the transmission of data. For example when pain is experienced '*substance P'* is released from the *pre-synaptic* terminal and travels across the nerve junction to the *post-synaptic* receptor to relay the pain-danger signal. In the PNS opiate medications and endorphins bind to the pre-synaptic opiate receptors preventing *substance–P* being released blocking the pain sensation.

But nerve transmission is much more complex than this simple example. There are numerous other neurotransmitter substances that act like *substance-P* with a variety of opiate receptors (especially *mu* receptor) which modulate the pain signal.

In the brain-CNS opiate receptors are everywhere but act differently increasing the release of the happy chemical *dopamine* by inhibiting the neurotransmitter GABA (Gamma-Amino-Butyric Acid) which controls the release of dopamine. Increased *dopamine* has analgesic action and promotes the 'high' which opiate abusers desire.

Note: In 1979 proteins in wheat and milk were shown to have opiate-like effects, known as exorphins, which could be blocked by naloxone. This may explain addictive nature of these foods.

Toll-Like-Receptors guardians of the immune system

As earlier as 1985 researchers recognised that endorphins influence the immune system and within a year Toll-Like-Receptors (TLR) were also discovered. TLR are found in white blood cells and the cells of various organs where they perform the first line of defense for the *innate immune system* against microbial invasion.

Once TLR recognize foreign microorganism small inflammatory molecules, known as *cytokines,* are liberated to mobilize white cells that fight the invader. TLR is also able to release *NF-kappa-B* one of the most potent signaling molecules involved in the response to severe stress, infection and inflammation, including the initiation of autoimmune disease and cancer.

It is now recognised that opiate receptors are similar to TLR and both are inhibited by naltrexone.

Note: Vitamin D also modulates the Toll-like receptors of the innate immune system and can be used in conjunction with Naltrexone.

Current knowledge of Naltrexone

Many diseases are an expression of a malfunctioning immune system.

The immune system is regulated by endorphins which have a primary action on opiate receptors.

The immune system identifies intruders with Toll-like receptors which release cytokines which initiate the white cell response.

A naltrexone capsule is a mixture of both LEFT (levo) and RIGHT (dextro) handed molecules - like our hands, mirror images of the each other.

Levo - Naltrexone action:

- Initially antagonizes the opiate/endorphins receptors
- Leading to upregulation of endorphin release and modify the immune system
- And reduction in cell proliferation

Dextro – Naltrexone action:

- Antagonizes the Toll-like Receptors (TLR) suppressing cytokine response and modifying the immune system, and
- Antagonizes the TLR - 4 involved in release of NF kappa B reducing inflammation & potentially down-regulating oncogenes that initiate cancer growth.

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Naltrexone in clinical practice

High dose naltrexone (HDN) was first used for opiate addiction but proved ineffective due to the troublesome side effects of anxiety, mood changes and agitation which led to poor patient compliance. However the Finnish physician Dr Davis Sinclair had success using HDN in alcoholics wishing to stop drinking; commonly known as the Sinclair Method of treatment.

The first clinician to demonstrate Low Dose Naltrexone (LDN) effectiveness was Dr Bernard Bihari in 1985 who began using LDN in immune suppressed HIV patients and showed it could lessen susceptibility to infection, prevent the destruction of the immune system and lower death rate. At the same time Dr Ian Zagon for the next three decades published over 300 papers on LDN unravelling the endorphin, opiate receptor and immune system connections.

Endorphin Deficiency

Low endorphins levels, as Dr Bihari found with his HIV patients, may also be present in those who cry easily (e.g. watching a TV commercial), have low mood and depression, greater sensitivity of emotions and to pain, desire pleasurable rewards and cravings for chocolate, tobacco, sex, alcohol and drugs. Some have called this the *endorphin deficiency syndrome*.

As mentioned earlier naltrexone increases endorphin levels and may be a useful therapy, with lifestyle changes and medications, in conditions such as fibromyalgia, chronic fatigue, and depression and pain states.

Note: Exercise, massage, meditation, rodiola, chamomile & lavender, omega-3 oils and a healthy high protein diet are known to increase endorphins. The withdrawal of the milk and gluten foods, that contain exorphins, might be worth considering.

Hypothalamic-pituitary hormone disturbance and high cytokines levels from inflammation are known to disturb sleep but both are normalized by naltrexone. A trial of LDN be useful for insomnia, thyroid disorders, premenstrual syndrome, polycystic ovarian disease, endometriosis, infertility and in obesity.

Dr Bernard Bihari's Story

In 1985 Dr Bihari working in New York with HIV/AIDS patients with compromised immune systems, many of whom were drug users, had no available effective therapies to treat these people. He was aware that endorphins, the natural morphine like substance which are produced under pleasure and stress states, were involved in the regulation of the immune system.

Dr Bihari's brilliant insight was to imitate a twelve week trial of LDN in 22 HIV patients with low endorphins levels which he compared with a non-treated control group. During the trial not one person developed opportunistic infections in the LDN group whereas 5 of the 16 controls became ill.

He then went on to actively use LDN in his patients and observed that when naltrexone was taken regularly it appeared to prevent the destruction of the immune system and lower their death rate.

When the new HIV anti-retroviral drugs became available he noted that LDN acted synergistically to improve the clinical response.

In 2014 he also reported on 354 advanced cancer patients who had failed traditional therapy who received low dose LDN with other possible complementary therapies. He found that 20% of patients had an objective response to LDN therapy and 25% stabilization of their cancer. He noted that most of those who died were terminally ill before they commenced LDN.

Many cancer types responded positively to LDN. An independent review confirmed that LDN alone did appear to invoke complete cancer remission in some patients. A recent study has also shown that LDN heightens the sensitivity of chemotherapy agents increasing cancer cell death.

Inflammatory and immune disorders

I have already mentioned how naltrexone influences the Toll-like receptors that directly reduce cytokine mediated inflammation and also inhibits NF-Kappa-B signaling which has been linked to the onset of infection, autoimmune & other inflammatory disease and the initiation of cancer. A number of LDN trials have shown positive response in the treatment of crohn's disease, multiple sclerosis, thyroid disorders and cancer. See table opposite for diseases that may respond to LDN

Conditions that may respond to LDN Therapy

Inflammatory states

- Autoimmune conditions – multiple sclerosis, Lupus, rheumatoid arthritis etc
- GI inflammatory bowel disease – crohn's disease, ulcerative colitis & IBS
- Lung - COPD, asthma
- Cancer

Hormone dysfunctions

- Thyroid - hyper- & hypo-thyroid states
- PMS, PCOD, infertility, obesity

Brain connections

- Insomnia, depression, ADHD, autism
- Parkinson's, motor neuron disease, neuropathic pain, restless leg syndrome

Side effects

Side effects of naltrexone therapy are minimal the most common being sleep disturbance which usually settles when a lesser amount is taken.

Naltrexone is a non-subsidised prescription medicine in New Zealand

Remember the principles for treating disease:

Remove the toxic source(s) and normalize the healing process.

In chronic disease treatment - begin low and go slow.

Many diseases are an expression of a malfunctioning immune system and Low Dose Naltrexone may be a useful therapy to trial in chronic illness.

General Reference – 'The LDN Book' edited Linda Elsegood, Chelsea Green Publishing (2016), a great resource for LDN information. Also available as an e-book.

Websites worth exploring – www.lowdosenaltrexone.org, www.ldnresearchtrust.org

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