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Low-dose naltrexone for disease prevention and quality of life

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SUMMARY

The use of low-dose naltrexone (LDN) for the treatment and prophylaxis of various bodily disorders is discussed. Accumulating evidence suggests that LDN can promote health supporting immune-modulation which may reduce various oncogenic and inflammatory autoimmune processes. Since LDN can upregulate endogenous opioid activity, it may also have a role in promoting stress resilience, exercise, social bonding, and emotional well-being, as well as amelioration of psychiatric problems such a autism and depression. It is proposed that LDN can be used effectively as a buffer for a large variety of bodily and mental ailments through its ability to beneficially modulate both the immune system and the brain neurochemistries that regulate positive affect.

Introduction

Preventive medicine has excelled in reducing the risk factors of high cholesterol with various statins, and accruing cardiac damage with baby aspirin blood thinners. There is considerable controversy about general health sustaining effects of adequate vitamins, minerals, herbals and specific purified nutritionals, but there is relatively little medical research on discrete biochemical supplements to facilitate general health and well-being. In this essay we introduce low-dose naltrexone (LDN) as a potential way to strengthen brain and bodily resources to facilitate emotional homeostasis and also provide background prophylaxis against and potential treatment of various cancers and autoimmune disorders – an idea that has already been extensively discussed on the web (e.g., www.Lowdosenaltrexone.org).

Naltrexone, an orally effective, long-lasting opiate receptor antagonist, was approved by the FDA for treating alcohol and opiate addiction in 1984, but its general patent expired the following year. It is a non-selective antagonist, with robust effects on pleasure promoting mu opioid receptors (MOR) and delta opioid receptors (DOR) [1], with less antagonism of aversion-mediating kappa opioid receptors (KOR) [2] but substantial effect on the more recently discovered orphanin FQ or nociceptin [N/OFQ] opioid family [3]. The benefits of high dose naltrexone in narcotic addiction are explained by blockade of all pleasure producing effects of opioids, and similar mechanisms may explain the ability of naltrexone to reduce binging on alcohol.

Here we will consider the potential benefits of low-dose naltrexone (LDN) as a way to strengthen both brain and bodily resources to promote psychological well-being as well as bodily health, especially along the dimension of reduced likelihood of cancers and autoimmune problems. Intermediate levels of LDN (at ~0.25 mg/kg given every other day) were initially found to have some benefits in the treatment of a subset of autistic children [4,5]. One of the clinical impressions was an increased social initiative and cheerfulness, especially on the non-medication days, as if a rebound effect of positive social chemistries (e.g., opioids) was occurring. There is now increasing data that would suggest that a temporary blockade of opioid receptors with LDN may lead to an upregulation of mood enhancing endogenous opioids, and hence perhaps dopamine activity, which may further promote positive frames of mind. As importantly, endogenous opioids have robust immune modulatory properties, which may be harnessed through LDN to facilitate body resources to retard and combat oncogenic and autoimmune processes and reduce the impact of allostatic load on the body.

Although the data is only now emerging for beneficial endogenous brain and body opioid rebound effects from LDN supplementation, indirect evidence does exist for such effects, including the ability of ultra-low LDN to facilitate the analgesic effects of opioids [6], and the ability of LDN to facilitate maintenance of drug abstinence in former opiate addicts [7]. In this essay we will focus on the potential ability of LDN to serve as a facilitator of immunocompetence that may provide prophylaxis for a variety of disorders, from oncogenesis to neurological disorders, where a compromised immune system hastens bodily decline.

Hypotheses

When administered in low-doses of 3–4.5 mg daily, naltrexone increases the expression of mu, delta, and epsilon opioid receptors as well as central and circulating met-enkephalin (ME) and beta-endorphin (BE), which may improve psychological well-being.

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The associated bodily changes result in enhanced immune functions that may stop inflammation and the progression of rheumatoid, gastrointestinal and neurological autoimmune disorders. These hypothesized disease-modifying effects of enhanced immune functions contradict current medical opinion that immune functions must be globally suppressed to retard the progression of autoimmune diseases. Yet evidence is mounting that LDN may have substantial therapeutic effects in such disorders. Furthermore, naltrexone's enhancement of the immune system is a novel approach to arresting or preventing a variety of cancers. Resistance to viral diseases may also be enhanced, with a trial currently in progress to evaluate efficacy of LDN for treating AIDS.

Background evidence: Since naltrexone entered the public domain in1984, little funding has been available for researching treatment for any diseases except alcoholism and opiate addiction, both heavily supported by federal grants. Now, however, there have been widespread anecdotal reports of successful treatments of various cancers, AIDS [8,9], and Multiple Sclerosis [10], and autoimmune diseases such as lupus, arthritis, and fibromyalgia [11]. If chronic LDN could potentiate and regulate the immune system in health promoting ways, it may serve to combat AIDS and some cancers and reduce autoimmunological self-destructive actions in various disorders.

The first successful clinical trials were for Crohn's disease in 2006 [12] and in late 2007 for Multiple Sclerosis [13]. Trials for MS and fibromyalgia are underway at medical centers in California and Cleveland, along with an AIDS trial in Mali.

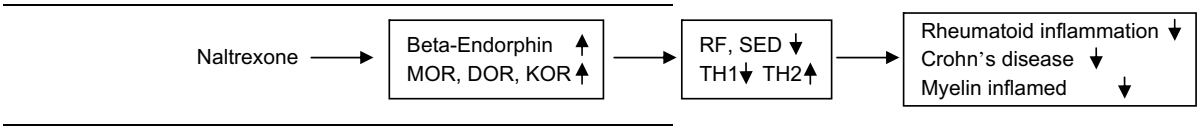
The normal 50 mg naltrexone dose that blocks opioid receptors 24 h per day is commonly prescribed for alcoholics and heroin addicts who wish to resist a relapse. This typically amounts to more than 0.5 mg/kg for most adults. In contrast, the most common LDN use is typically 4.5 mg, which generally means most adults get no more than 0.08 mg/kg per day, which can block mu opioid receptors for only a few hours, perhaps up to 6 h. If taken at bedtime, this would mean that an individual might wake up the next morning with a homeostatic rebound-induced over-activity of their own endogenous opioid systems. It is this type of bodily change in opioid dynamics that we focus on here. Until recently significant increases in mu, delta and perhaps epsilon opiate receptor expression have only been documented in animal models for chronic opiate blockade with high dose naltrexone [14,15], which leads to elevated morphine analgesia [16]. However, a recent animal study confirmed that a low-dose (0.1 mg/kg of naloxone) could elevate mu opioid receptor density as well [17]. More significantly, the recently completed Italian Multiple Sclerosis trial utilizing 5 mg of naltrexone daily found significant increases in circulating beta-endorphin, along with widespread reports of symptom relief [13].

Chronic naltrexone affects both immune and endorphin systems

While high dose naltrexone can counteract the reduction of immune system activity caused by opiate analgesics [18,19], when given alone, it can facilitate immune system parameters [20,21]. Zagon and McLaughlin [22] clearly delineated differences between high and low-dose naltrexone while studying mice with transplanted neuroblastoma tumors. The full dose of naltrexone [10 mg/kg] producing constant blockade of opiate receptors had no beneficial effect and actually facilitated tumor growth. In contrast, a low-dose [0.1 mg/kg] decreased oncogenesis significantly [23]. Zagon and McLaughlin concluded that LDN increased opiate receptors and elevated circulating BE and ME after a 4–6 h period of receptor blockade. This "rebound phase" may release the increased density of mu and delta opioid receptors for endogenous opioid stimulation with the increasingly available BE and ME. The general principle operative here may be that the increased concentrations of BE and ME that gain access to increased density of MOR and DOR receptors may "functionally supersensitize" [24] endogenous opioid functions throughout the body with beneficial downstream effects on various body parameters, especially immunocompetence.

The beta-endorphin pathway in immune regulation

To grasp potential LDN paths of action, let us consider the following well articulated opioid antagonist's pathways for treating autoimmune disease. The potential action of BE in ameliorating autoimmune disease is sketched below.



Naltrexone modulation of immune regulation and treatment of autoimmune disease

Recent studies have shown BE concentration in circulating blood cells to be dramatically low in rheumatic diseases such as arthritis, lupus and gout, with significant inverse correlations between BE and both rheumatoid factor and erythrocyte sedimentation rate and hence the likelihood of inflammation [25]. Levels of BE were as low as 1/8 to 1/4 normal in other autoimmune-related diseases, including fibromyalgia [26], Crohn's disease [27], multiple sclerosis [28], chronic migraine [29] and cluster headaches [30] and endometriosis [31].

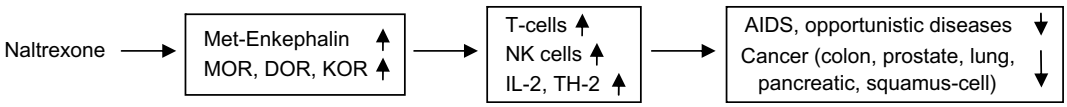
A preliminary pilot trial of 4.5 mg naltrexone for Crohn's Disease, completed at Penn State in 2005, yielded promising results. In 3 months 89% of the patients achieved significant reduction in symptoms and improvement in quality of life measures, and 67% went into remission. These results were maintained after 4 weeks of no naltrexone [12].

Recent work on collagen-induced arthritis in rats have found BE treatment to reduce clinical arthritis manifestations by shifting the balance of TH-1 and TH-2 cells toward TH-2. This comes from down-regulating the NF-kappa2 pathway, including tumor necrosis factor alpha, Interleukin-1beta, Interleukin-6, inducible nitric oxide synthase, and mRNA for matrix metalloproteinase-2 and mmp-9 [32]. Dr. Sacerdote and her colleagues in Milan have reached the same conclusion that BE increases ameliorate autoimmune diseases by suppressing TH-1 and augmenting TH-2 cells [33].

Low-dose naltrexone may work through methione-enkephalin as well

The scientific case for LDN's positive effect on immune parameters is strengthened by studies that have evaluated infused ME in the treatment of cancers. Plotnikoff et al. [34] report that ME stimulates expression of interleukin-2 receptors and blood levels of interleukin-2, along with increases in white blood cells, natural killer cell activity, gamma-interferon, active T-cells and other ele-

ments of the immune system. These results were obtained both *in vitro* and *in vivo* and with normal volunteers as well as people suffering from a variety of cancers, including Kaposi's sarcoma, lung cancer, melanoma, and hypernephroma. These benefits might be sketched as follows:



Naltrexone's potential for cancer prevention and treatment

Potential benefit for cancer treatment has arisen largely from the work of Penn State investigators Ian Zagon and his colleagues. Zagon published initial evidence that chronic LDN (0.1 mg/kg in mice) reduced neuroblastoma tumor incidence by 66%, retarded tumor development by 98% and lengthened survival by 36% over controls [35]. The apparently intermittent receptor blockade via LDN significantly reduced cancer cell development, in contrast to a constant blockade that accelerated tumor growth [36]. Furthermore, the specific mu receptor blocker beta-Funaltrexamine did not significantly retard tumor development, yet the nonspecific blocker naltrexone did [37].

Both ME and BE may enhance NK cell activity via the mu receptor [38] and also by binding to receptors on cancer cells themselves [23]. Animal studies have shown full dose naltrexone to reduce tumor activity in mammary cancer [39]. In humans, high dose naltrexone has been involved (along with IL-2) in arresting 6 of 10 metastasized renal cancers [40] and [along with IL-2 and melatonin] in retarding metastasized cancer growth in terminal cases of kidney, stomach, pancreatic, colorectal, and thymus cancer [41].

While studying the efficacy of ME for neuroblastoma and squamous cell, colon, and pancreatic cancer, Zagon and colleagues used full dose naltrexone to block ME's retardation of tumor growth [42]. This contrasts with their prior studies which have shown low-dose treatments to be effective on colon cancer [43], and neuroblastoma [35]. Though acute high doses of naltrexone effectively block opioid retardation of the growth of some cancer cells, chronic low-doses foster that retardation. Furthermore, LDN has arrested B-cell lymphoma in one published case [44] and, along with alpha-Lipoic Acid, metastasized pancreatic cancer for 3 years in another [45]. Anecdotal reports of LDN causing remission include colorectal, mammary, ovarian, small-cell and non-small-cell lung, and prostate cancers, as well as Hodgkins and non-Hodgkins lymphoma, multiple myeloma, and neuroblastoma [46]. Intravenous ME may turn out to be a better treatment for some cancers, or more effective when combined with LDN. But the paradoxical effect of low-dose generic naltrexone of increasing *both* circulating BE and ME *and* the density of their *mu* and *delta* receptors bears further study because of its impressive cost-effectiveness.

LDN also holds promise for prostate cancer prevention and early treatment, since all of the anecdotal prostate cancer cases in one report that had not undergone hormone treatments went into remission [46]. Independently, medical interest has begun to focus on the immune system for a first defense against this cancer [47]. Furthermore, Dr. Bihari, whose experiences with LDN have been extensively summarized [46], reported success retarding or arresting AIDS in 1988 [9]. Low concentrations of naltrexone in vitro have also been shown to potentiate the effectiveness of the antiretroviral drugs zidovudine (AZT) and indinavir, lending support to Bihari's claims [48].

Thus, LDN, through its enhancement of immune functions [21] and specifically of natural killer cell activity [49] may promote prevention and treatment of viral diseases and bacterial infections. Evidence from animal models suggests that naltrexone's path to supporting immune defenses against viral disease begins by increasing both beta-endorphin and met-enkephalin, which may then bind to sensitized mu opioid receptors to increase natural killer cell activity for quelling viral infection [50]. Since we only have clinical evidence from uncontrolled observations in the many disorders mentioned above, well-controlled double-blind clinical studies are warranted, despite the difficulty in financing studies off-patent medicines.

Conclusion

Low-dose naltrexone's potential for enhancing the quality of life through both reward and energy functions arises from the well-demonstrated links between mu opioid receptors and central dopamine neurons in the mesencephalon [51,52]. Solid evidence for safety and tolerability of chronic LDN is present in the recent Crohn's trial [12] and MS trial [13], as well as decades of FDA approved daily 50 mg doses for alcoholism. There is *no* published evidence to support the old "black box" warning about potential liver damage from chronic high doses [53]. This only happened at extremely high doses that were used in some of the early toxicology trials.

In sum, we conclude that low-dose naltrexone presents a safe and promising approach to prevention and/or treatment of many autoimmune diseases and cancer variants, as well as potentially various viral (e.g., AIDS) and neurological diseases (Multiple Sclerosis) that are exacerbated by compromised immunity. LDN's potential for modulating both opioid and immune systems yields a very wide field for clinical experimentation as well as novel research directions for strengthening the scientific evidence for linkages between opioid and immune systems in the regulation of various disease processes. There are solid reasons to believe LDN can also promote positive emotional states through the endogenous opioid amplification of positive affect and energy [52]. From a psychiatric perspective, the facilitation of endogenous opioids should alleviate depression since, to some degree, that multifaceted problem reflects reduced ability to experience pleasure. Evidence also exists for resilience against cardiovascular stress [54,55] and for specific enhancement of the reward system for exercise [56], palatable tastes [57,58], laughter [59,60], sex [61], social bonding [4,62], and even the placebo effect of positive expectations [63].

In a time of imperative health care reform, the prospect of so many novel contributions to both disease suppression and quality of life by a generic pharmaceutical presents significant challenges and opportunities for government, the medical research community, the pharmaceutical industry and health care management.

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