Minireview

Intermittent blockade of OGFr and treatment of autoimmune disorders

Ian S Zagon and Patricia J McLaughlin

Department of Neural & Behavioral Sciences, Penn State University College of Medicine, Hershey, PA 17033, USA
Corresponding author: Patricia J McLaughlin. Email: pxm9@psu.edu

Impact statement

This mini-review presents information on the intermittent blockade of the opioid growth factor (OGF)–OGF receptor (OGFr) axis by low-dose naltrexone (LDN), and the role of enkephalin (i.e. OGF) in autoimmune disorders, specifically multiple sclerosis, Crohn's, and fibromyalgia. Clinical reports on subjects taking LDN have documented reduced fatigue, few side-effects, and improved overall health. Preclinical studies on mice with experimental autoimmune encephalomyelitis (EAE), the animal model of multiple sclerosis, revealed that immunization for EAE reduces serum OGF. Intermittent OGFr blockade with LDN restores serum enkephalin levels that correlate with reduced behavioral and pathological signs of EAE; LDN also increases enkephalin levels in naïve mice. The interplay between LDN, and the onset and treatment of autoimmune diseases, chronic pain, and other addictive behaviors requires further investigation, but highlights a central role for enkephalins and intermittent blockade of the OGF–OGFr pathway in pathogenesis and treatment of these disorders.

Abstract

The opioid growth factor (OGF)–OGF receptor (OGFr) axis is present in normal and abnormal cells and tissues, and functions to maintain homeostatic cell replication. OGF is an inhibitory growth factor that upregulates p16 and/or p21 cyclin-dependent inhibitory kinases to slow cell replication. Blockade of this regulatory pathway can be intermittent or complete with the end result being depressed or accelerated, respectively, cell proliferation and growth. Intermittent blockade of the OGF–OGFr pathway with lose doses of naltrexone (LDN), a general opioid receptor antagonist, has been studied clinically in a number of autoimmune diseases, including fibromyalgia, Crohn's, and multiple sclerosis (MS). Serum enkephalin levels were decreased in patients with MS relative to subjects with other neurological disorders. The intermittent blockade of OGFr by LDN results in a biofeedback mechanism that upregulates serum enkephalin levels. Clinical studies have reported that LDN is beneficial in enhancing quality of life, reducing fatigue, and increasing motor activity in humans with fibromyalgia, Crohn's, or MS. LDN treatment is well tolerated even after several years of therapy. Preclinical investigations using experimental autoimmune encephalomyelitis (EAE), an animal model of MS mediated by T and B lymphocyte activation, demonstrate that immunization alone resulted in reduced enkephalin (i.e. OGF) levels. Therapy with LDN restored serum enkephalin levels in EAE mice resulting in improved EAE behavioral scores and diminished CNS pathology. This mini-review summarizes both preclinical and clinical data and focuses on the role of serum enkephalins resulting from intermittent blockade of OGFr by LDN in autoimmune disorders.

Keywords: Enkephalin, fibromyalgia, low-dose naltrexone, multiple sclerosis, opioid growth factor, opioid growth factor receptor

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Introduction

The endogenous opioid [Met^5]-enkephalin was first discovered in 1975[1,2] following the identification in 1973 of opioid binding proteins/receptors in rodent brain and the gastrointestinal tract.[3,4] Approximately a decade later, another opioid receptor termed opioid growth factor receptor (OGFr) was identified in developing rat brain and neuroblastoma.[5–8] The specific agonist for OGFr appears to be OGF, chemically termed [Met^5]-enkephalin. Enkephalins also mediate their action through binding with classical opioid receptors.[9] Mu, delta, and kappa opioid receptors share molecular and protein structure homology,[10] but little or no amino acid or molecular homology with OGFr.[8,11,12]

The pharmacology of OGFr shares some resemblance to that of classical opioid receptors in that opioid receptor antagonists bind to each receptor blocking endogenous ligand activity.[13,14] Receptor antagonist blockade is reversible, and the resultant action is dependent on the duration

of opioid receptor blockade. Because antagonists bind with different affinities to receptors, the longevity of the antagonist-receptor complex is important in conferring action. In 1983, it was first published that different dosages of naltrexone resulting in different durations of opioid receptor blockade led to dichotomous biological responses.[15] Dosages (0.1 mg/kg) of naltrexone inhibited neuroblastoma tumor growth, whereas 100-fold more drug did not inhibit tumor growth more. Rather 10 mg/kg naltrexone injections to nude mice accelerated tumor onset, increased tumor growth, and advanced death suggesting that a true pharmacological dose response was not in play.[15]

Intermittent blockade of OGFr

Investigations on the duration of opioid receptor blockade by naltrexone were conducted both *in vivo* and *in vitro*. In thermal response studies, dosages of naltrexone that enabled the mouse or rat to remain on the hot plate until removed even after 12 h were considered to confer "continuous opioid receptor blockade." Dosages of naltrexone that blocked the effects of morphine desensitization to heat for only 6–8 h produced an "intermittent opioid receptor blockade".[16]

In vivo studies demonstrated that low dosages of naltrexone (i.e. 1 mg/kg) that conferred an intermittent blockade in newborn rats decreased cell replication in brain, body, and somatic organ development.[17–20] Mice inoculated with neuroblastoma cells and receiving 0.1 mg/kg naltrexone had decreased tumor growth.[15,16] This concept of intermittent blockade of the OGFr resulting in a biofeedback production of OGF (enkephalin) and thus facilitating robust inhibitory action between OGF and OGFr is an important concept in the treatment of autoimmune disorders.

In vitro studies designed to investigate the mechanism underlying short-term OGFr blockade by naltrexone utilized human cancer cells treated with 10^{-5} M naltrexone.[21] After 6 h, media was removed to mimic an intermittent receptor blockade and replaced with fresh media containing sterile water. Cell number of each human cancer line (representative of ovarian (SKOV-3, OVCAR-3), pancreatic (MiaPaCa-2), and colon (HCT-116) cancers) was determined at designated times. Short-term receptor blockade by naltrexone inhibited the growth of all cell lines. If classical opioid receptors were effectively knocked down by siRNAs specific for the mu, delta, and kappa opioid receptor, and cultures exposed to short-term naltrexone, growth was inhibited, as was protein expression of OGF and OGFr.[21]

Some investigators suggest that low doses of naltrexone (LDN) act directly as immunomodulating agents,[22,23] or by interaction with toll-like receptor 4.[24] Investigations focused on T and B cell proliferation *in vitro*[25] and *in vivo*[26] have demonstrated that the modulation of the immune system is likely a direct response to increased or decreased proliferation of lymphocytes as well as activation of peripheral lymphocytes and resultant cytokine production. Direct evidence for LDN's mechanistic effects emanates from preclinical work documenting that LDN administration to mice results in measurable increases in serum OGF levels. The biofeedback mechanism of LDN is still being investigated but appears to suggest that LDN initiates release and/or greater secretion of OGF. The concept that LDN's action results in increased serum OGF levels remains an interesting biofeedback loop in autoimmune disorders.

LDN treatment results in increased secretion/production/release of methionine enkephalin, renamed OGF because of its ability to modulate the growth of normal and abnormal cells and tissues.[27] OGF is a negative growth regulator that mechanistically upregulates p16 and/or p21 cyclin-dependent inhibitory kinases.[28] The inhibitory effects are reversible, species and tissue non-specific,[29] and obey intrinsic biological rhythms of the cell (e.g. circadian rhythm).[30] The pentapeptide is autocrine and paracrine produced at concentrations consistent with physiological behavior, but is quickly degraded.

Role of the OGF-OGFr axis and autoimmune disorders

LDN appears to be an effective compound – used either alone or as an adjuvant – for the treatment of a variety of autoimmune disorders. Based on the clinical data described below, our laboratory investigated LDN and exogenous OGF in a mouse model of experimental autoimmune encephalomyelitis (EAE) – the animal model of MS. Animal models of both chronic EAE (Ch-EAE) and relapsing-remitting EAE (RR-EAE) have demonstrated the efficacy of enkephalins to reverse the progression of clinical behavior in both forms of EAE and to reduce CNS pathology. In the course of study, it was discovered that immunization alone of C57Bl/6 mice resulted in depressed serum OGF levels within days of inoculation suggesting that the autoimmune response was correlated with serum enkephalins. Blood levels of OGF were restored following systemic OGF or LDN indicating that enkephalins were responsive to OGFr modulation.

While the dysregulation of the OGF-OGFr axis is not the sole cause for autoimmune disorders, it may contribute to our knowledge on the etiology and pathogenesis of MS, and possibly other autoimmune disorders. Given the broad spectrum of autoimmune disorders that are currently treated with LDN invoking an intermittent OGFr blockade, the hypothesis that low serum enkephalins are unable to control the heightened proliferation of immune cells during a trigger event warrants further study. Currently, there are animal models of MS, as well as limited clinical studies and anecdotal case reports that support the relationships of intermittent receptor blockade, LDN, endogenous opioids, and autoimmune disorders.

Preclinical studies on enkephalins and EAE

EAE is the only one of several models used to study MS. EAE can be induced by different peptides that lead to either Ch-EAE or RR-EAE. In Ch-EAE, C57Bl6/J black mice are immunized with myelin oligodendrocytic glycoprotein (MOG_{35-55}), whereas immunization of SJL/J white mice with proteolipid protein ($PLP_{131–165}$) produces RR-EAE.[31–

[38] Both animal models have been studied for the effects of OGF or LDN on clinical behavior, pathology, sensitivity, motor activity, and immune system responses.[31–38] In some investigations, treatment was initiated at the time of immunization (induction of disease), while in other studies, treatment was initiated two days after disease symptoms became visible mimicking the established disease, a more clinically relevant model.

Chronic EAE with OGF treatment beginning at the time of disease induction

OGF treatment beginning at the time of disease induction decreased disease indices in comparison to controls.[31–33] Spinal cord pathology was modified following OGF treatment with significant decreases in the number of activated astrocytes and damaged neurons observed in CNS tissue of animals treated with OGF. Intermittent OGFr blockade with LDN treatment also disrupted disease progression and prevented the onset of neurological dysfunction over a considerable period of time. Notably, OGF or LDN never exacerbated EAE.

Chronic EAE with OGF treatment beginning with established disease

In another series of experiments, OGF was administered to mice with established EAE.[34,35] Within six days of OGF treatment, animals demonstrated significant decreases (45%) in behavioral scores relative to saline-injected mice.[34] The reduced clinical behavioral scores were evident for OGF-treated mice for 40 days. OGF treatment in mice with established Ch-EAE also reduced the number of activated astrocytes and decreased the area of spinal cord demyelination relative to controls. Within 40 days of immunization, Ch-EAE mice receiving saline had approximately 13% demyelinated white matter in spinal cord cross-sections in comparison to 8% or less in OGF-treated Ch-EAE mice. After 20 days of drug treatment, CD3+ cell infiltration was reduced 68% in Ch-EAE mice receiving OGF in comparison to control (saline) Ch-EAE animals suggesting that enkephalins (i.e. OGF) target the pathobiology of EAE.[34,35]

RR-EAE with OGF treatment beginning at the time of immunization

Because nearly 85% of the 2.5 million MS patients worldwide have relapse-remitting MS (RR-MS), the efficacy of OGF and LDN to modulate disease progression was investigated using the SJL mouse model.[36–38] Behavioral (clinical) signs of RR-EAE begin to appear within 9–10 days of $PLP_{139–151}$ immunization. OGF therapy starting at the time of disease induction resulted in RR-EAE animals with less severe behavior than mice receiving saline. On average, there were increased numbers, and longer phases, of remission with fewer periods of clinical relapse in the group of mice receiving OGF therapy.[36] Coinciding with the reduction in behavioral scores, neuropathological examination of the lumbar spinal cord revealed decreased numbers of T lymphocytes, microglia/macrophages, and activated astrocytes following OGF treatment. Demyelination and neuronal damage in the spinal cord were markedly reduced in OGF-injected mice during the nearly two-month observation period. Importantly, OGF treatment led to prevention of behavioral relapse for more than 36 days following the initial flair, with 85% of the mice returning to behavioral scores of 0 or 0.5 over the course of 5.5 weeks, and more than 70% of the mice showing remissions that lasted longer than 2 days. However, neither OGF nor LDN "cured" EAE.

RR-EAE and OGF or LDN treatment beginning at the time of established disease

Studies on SJL mice immunized with synthetic myelin proteolipid protein, and treated with OGF[37] or LDN[38] beginning two days after the first clinical signs of disease ($\sim$ day 9) were initiated. Some RR-EAE mice receiving LDN or OGF treatment beginning on day 9 continued to develop behavioral symptoms and were considered "non-responders". For those mice considered "responders," OGF reduced clinical behavioral scores, and increased the number and duration of remissions.[37] Over the course of 40 treatment days, 42% of mice in the RR-EAE+OGF group had at least one remission and 5 mice remained in permanent remission; only 1 of 13 mice in the RR-EAE+saline group displayed a brief remission. Astrogliosis was markedly reduced in comparison to saline-treated animals with RR-EAE. In the study using LDN, mice responding to the intermittent OGFr blockade had mean clinical (behavioral) scores of 79 ± 9 in comparison to RR-EAE mice receiving saline with behavioral scores of 141 ± 9; the higher the score, the more debilitated motor behavior.[38] Many of these studies were conducted multiple times strengthening our confidence that elevated enkephalins resulting from intermittent OGFr blockade by LDN or direct OGF injections are beneficial therapy for the relapsing-remitting form of MS.

Mechanistic studies on OGF and autoimmune diseases

The mechanism underlying the efficacy of OGF to arrest progression of Ch-EAE or RR-EAE is not completely understood. EAE results from immunization with adjuvant containing myelin proteins, followed by the activation of T and B lymphocytes in peripheral tissues (e.g. spleen and lymph nodes), and some stimulated lymphocytes migrate to the central nervous system and secrete inflammatory cytokines. The roles of enkephalins, and the OGF-OGFr regulatory pathway, in these processes were studied both *in vivo* and *in vitro*.[25,26,39] *In vitro*, direct application of OGF or LDN to activated splenocytes inhibited T and B cell proliferation within hours of treatment without requiring intervention from other immune system mediators.[25] *In vivo* injections of OGF or LDN inhibited nodal T and B cell expansion after 5, 12, and 15 days of therapy.[26] Examination of peripheral lymphocyte dynamics following immunization of mice with antigen and treatment with OGF or LDN was conducted over a two-week period.[26,39]

Isolated lymphocytes from spleens and draining inguinal lymph nodes were counted by flow cytometry, and the subpopulations of CD4+ and CD8+ T-cells, as well as B lymphocytes, were noted. Within five days of treatment with exogenous OGF or LDN, the number of CD4+ and CD8+ T lymphocytes in MOG-injected Ch-EAE mice treated with OGF or LDN was reduced on average 30% from immunized saline-treated mice. Importantly, at this time point, there was no evidence of disease. After 12 days of injections, Ch-EAE mice receiving OGF or LDN had 32–37% reductions in the number of CD4+ T cells, and 35–42% reductions in CD8+ T cells isolated from the spleen relative to the cell number for saline-injected mice. As expected following immunization, B cell number was elevated 2-fold in MOG-immunized mice relative to non-immunized normal mice, and within five days of OGF and LDN treatment, there was a marked reduction (29%) in the number of B220+ B cells relative to values in saline-injected MOG mice.[26]

Other investigations on the intracellular distribution of CNS-derived lymphocytes from lumbar spinal cord tissue were conducted using CNS tissues from Ch-EAE mice collected on day 15 of OGF or LDN treatment. Cell homogenates were labeled with markers for CD4+ T cells, as well as for cytokines expressed on Th1, Th2, and Th17 subsets of T cells.[26] OGF treatment for approximately two weeks increased the percentage of CD4+ T cells by 2-fold relative to the number recorded for saline-treated MOG-immunized mice, as well as increasing the percentage of Th1 and Th17 cell subpopulations compared to saline-treated mice. Receptor blockade by LDN did not alter the number of Th1, Th2, and Th17 subsets within 15 days.[26] From these data, we can conclude that enkephalins suppressed T and B lymphocyte proliferation in the spleen and inguinal lymph nodes in the Ch-EAE model and repressed replication of CD4+ and CD8+T cells isolated from the spleen and lymph nodes of immunized mice.

Preliminary studies on the immunological mechanisms of enkephalins in the RR-EAE model were conducted. Autoreactive $CD4^+$ T cells were followed as they migrated from peripheral tissues into the CNS.[38] Immunohistochemical studies revealed that the number of CNS-infiltrating $CD3^+$ T cells was diminished in RR-EAE mice receiving OGF or LDN administration. The pilot preclinical data suggested that modulation of the OGF-OGFr axis did not result in changes in the expression or conversion of Th1 to Th17 pro-inflammatory cytokines IFNγ and IL-17, respectively, nor were there changes in the activity of anti-inflammatory Th2, IL-4 secreting cells. However, the overall cell number was diminished, supporting the concept that the immunomodulatory function of OGF is an anti-proliferative action.

Clinical studies and low-dose naltrexone

Preclinical studies are important for establishing efficacy and mechanism, but the test of an effective drug is in the clinic. Naltrexone prescribed at low, or even very low dosages, appears to be an effective therapeutic for pain management and other symptoms (e.g. fatigue) related to a variety of autoimmune diseases.[24,40–59] The research behind the selection of dosage that constitutes "low dose" in humans is not well documented and most physicians use a daily dose of 3–4.5 mg per human, without regard of body weight, size, or age. This dose is well below the FDA-approved systemic dose of 50 mg naltrexone frequently cited to reverse drug or alcohol use. Some reports have begun to demonstrate that even very low (VLDN) or ultra-low dosages (ULDN) of naltrexone are effective in maintaining abstention from drugs or alcohol.[60,61] Preclinical studies have shown that 1 mg of naltrexone per kg body weight in a rat decreases cell replication.[14]

LDN as a treatment for autoimmune disorders

Fibromyalgia, Crohn's disease, and multiple sclerosis share characteristics such as depression, fatigue, memory loss, and neurological pain. These disorders are difficult to diagnose, have no cures, and occur in a random manner without defined risks. A common characteristic among them is that many patients find relief following daily LDN therapy. Whether receiving LDN for treatment of fatigue, pain, or depression, patients on daily LDN regimens report an improved quality of life and reduced physiological symptoms. Our hypothesis is that autoimmune disorders are associated with decreased enkephalins and endorphins, a condition that possibly exacerbates the associated inflammation, pain, and other immune-mediated metabolic deficits.

Multiple sclerosis and LDN

Multiple sclerosis (MS) is a chronic disease, with normal life expectancy rates, and thus sustained periods of compromised quality of life. Disease-modifying treatments for MS often require injections, have side-effects, are costly, and are not always effective causing patients to search for alternative therapies. A relatively large number of MS patients have tried, or are currently on, LDN, in part related to the social media support for LDN to enhance mood and decrease pain, as well as the reported lack of side-effects.[40–45]

Unfortunately, only a few small trials and case reports have been published on intermittent OGFr blockade through LDN.[40–45] In some studies, LDN is taken alone, while in others it is prescribed as adjuvant therapy to FDA-approved disease-modifying therapies. The efficacy of LDN taken alone is unclear, as it is difficult to design a clinical trial without offering patients a disease-modifying therapy. However, nearly all of the published studies conclude with a recommendation to design and support larger, randomized, double-blind trials to study the LDN therapy. In a pilot study of 60 patients who completed an 8-week course of 4.5 mg naltrexone daily, no adverse side effects were noted, and LDN was associated with improved quality of life.[40] Data from several questionnaires (i.e. General Health Survey, Mental Health Inventory, Pain Effects Scale, and Perceived Deficits Questionnaire) indicated significant improvement in scores related to mental and physical

health.[40] A larger cohort of patients was enrolled in a second trial that showed that LDN therapy had no adverse effects.[42] An in-depth retrospective chart review of prescriptions for LDN versus standard therapies for MS revealed that requests for LDN stabilized over a two-year period with no drop-off of LDN usage. In this report, the standard of care was baclofen, and its usage did not change suggesting that LDN is tolerable and could be used as an adjunctive therapy.[45]

Several retrospective studies examined the clinical profiles of relapsing-remitting MS individuals.[43,44] Ludwig *et al.*[44] reported on 50 or more MS patients using LDN only for a sustained period (more than three years) of time and compared biological parameters in these individuals with MS subjects receiving Copaxone® and LDN; the mean length of disease was 14 years. Patients receiving LDN alone had comparable levels in measures of hemoglobin, hematocrit, platelet count, and the number of RBCs and WBCs to those patients on the disease-modifying therapy, suggesting that LDN therapy alone did not alter blood chemistry. Further analyses of liver chemistry demonstrated that LDN treatment alone did not adversely affect values of creatinine, BUN, alkaline phosphatase, bilirubin, or other liver transferases.[44] Subjects receiving only LDN were comparable to those prescribed both Copaxone and LDN with regard to timed walking trials, an indicator of behavior. In conclusion, the lack of significant differences in biochemical data was the positive outcome expected, suggesting that LDN alone did not place the patients' health in jeopardy or compromise their medical recovery.

Chart reviews from the Penn State Hershey Neurology Clinic revealed that individuals diagnosed with MS and offered LDN reported no discernible side effects over extended periods of time.[43,44] Evaluation of approximately 200 confirmed MS patients performed through RedCap database who were provided a prescription for oral LDN suggested that the patients self-reported benefit from LDN, with no unexpected or severe side effects. A second analysis of medical charts from MS patients prescribed LDN alone were compared to those of patients treated with glatiramer acetate (Copaxone) and offered LDN as an adjunct therapy.[47] Although sample size was small for both groups ($n = 23$, $n = 30$), the data were collected over a 50-month period and no differences in laboratory values from standard blood tests, timed 25-foot walking trials, and magnetic resonance imaging (MRI) reports were noted, again supporting LDN as an inexpensive, non-toxic, stand-alone biotherapy.

Fibromyalgia and LDN

Fibromyalgia is a chronic, debilitating disorder that is characterized by musculoskeletal pain, fatigue, and memory loss.[46–51] A definitive cause for this disorder is unknown, women are at higher risk than men, and the disease is often associated with depression, irritable bowel syndrome, and tension headaches. Because endogenous opioids such as endorphins and enkephalins are involved in many of these pathologies, there is some validity to the hypothesis that low-dose naltrexone which upregulates these endogenous opioids may be an effective therapy.

Parkitny and Younger[48] reported that in a small (10-week) single-blinded, crossover trial, LDN treatment (4.5 mg/day) to humans was effective at decreasing fibromyalgia-related pain and overall disease symptoms. Importantly, LDN reduced pro-inflammatory cytokines measured in blood samples collected throughout the 10-week trial. LDN is well-rated by patients and was considered the second best treatment as reported by CureTogether – an internet forum.[51] A survey by Raknes and Smabrekke[45] found that the number of prescriptions for opioids requested by individuals was significantly decreased (46%) if the patient was also taking low-dose naltrexone. Younger and Mackey[46] reported in a single-blinded, cross-over study with eight weeks of drug followed by a two-week washout period that 10 individuals with fibromyalgia receiving 4.5 mg naltrexone daily showed neutralization of mechanical and heat sensitivities. Patients with the greatest inflammatory index as reflected by the erythrocyte sedimentation rate had the largest reduction of symptoms following LDN. In a follow-up study, Younger *et al.*[47] recruited 31 women with fibromyalgia receiving 4.5 mg naltrexone daily and reported that self-assessed pain levels were substantially reduced after LDN relative changes in pain reported by subjects receiving placebo ($P < 0.02$); in addition, mood was improved ($P < 0.05$), as was general quality of life ($P < 0.04$). Furthermore, LDN was well-tolerated by the patients with no serious side effects noted.

In an interesting study by Johnson *et al.*[49,50] on similarities resembling autism detected among patients with fibromyalgia and those leaving opioid detoxification programs, they found that the three diseases may have inter-related etiology through hormonal production as evidenced by the return to normalcy in all situations following low-dose naltrexone.

Crohn's disease, inflammatory bowel disease, and LDN

Crohn's disease is a chronic inflammatory bowel disease that affects any part of the gastrointestinal tract and can be characterized by symptoms of pain, diarrhea, skin rashes, and fatigue.[52–56] The cause of Crohn's is not well-defined but genetics often predispose individuals to environmental risks, over-reactive immune systems, and bacterial infections. In 2018, Parker *et al.*[52] reported on the safety and tolerability of LDN for pediatric Crohn's patients, and the efficacy and safety of LDN for adults with Crohn's disease. In small but well-designed clinical trials, adults treated with 4.5 mg/day LDN for 12 weeks were found to have 30% clinical remission of Crohn's symptoms in comparison to 18% of patients receiving placebo, and nearly twice the number of LDN patients achieved higher endoscopic response rates and clinical response rates relative to untreated patients. Importantly, no adverse events were reported for either study. Pediatric patients were prescribed LDN for only eight weeks, but 25% of those on LDN achieved clinical remission in comparison to no subjects in the placebo group. A small clinical

study was conducted with LDN treatment for Crohn's; two-third of the subjects had clinical remission of Crohn's after 12 weeks, with tolerable side-effects related to sleep disturbances.[53] This group conducted a larger (40 subject, 12 week) randomized, placebo-controlled trial and showed that 4.5 mg naltrexone resulted in significant declines in disease activity scores in 88% of patients.[54] This work has been substantiated by other reviews on LDN and Crohn's or ulcerative colitis.[55,56]

Pain, addiction, and LDN

Enkephalins are endogenous opioids and bind to opioid receptors that are also targeted by exogenous opiates such as morphine and heroin, and possibly induce similar euphoric effects. Alcohol dependence and food addictions may also trigger opioid receptors that share enkephalins as agonists. Thus, intermittent opioid receptor blockade following LDN, along with the biofeedback mechanisms that trigger enkephalin secretion, has been considered for the treatment of pain[24,57–60] and management of dependence.[61–63]

Conclusions

Investigations on the role of intermittent OGFr blockade, enkephalins, and autoimmune disorders are understudied. Clinical studies suggesting that low dosages of naltrexone are effective at treating fatigue or enhancing quality of life outnumber basic science studies using animal models to study fibromyalgia, Crohn's, or MS. In fact, this "bed to bench" phenomenon encouraged our laboratory to begin investigating the EAE model of MS. The discoveries that immunization alone alters serum enkephalins,[64] and that intermittent OGFr blockade following LDN restores serum enkephalin levels in mice and humans with MS[65] supports our hypothesis. The safety of LDN in small clinical trials indicates that short-term or extended use of LDN alone is tolerable and safe. LDN in combination with other therapies also appears to be well tolerated, and LDN does not appear to interfere with the disease-modifying drug. In summary, the clinical data support the need for larger human trials. An issue that is remaining to be debated is whether LDN requires FDA-approval. Regulatory approval may be unnecessary as naltrexone is already FDA-approved for systemic use at much higher doses treatment of narcotic and alcohol overuse, as well as for diet control (Contrave®). LDN is a repurposed drug, and low (LDN), very low (VLDN), and even ultra-low (ULDN) doses may never receive FDA approval given that higher doses are already approved. The safety, tolerability, and efficacy appear to substantiate use by clinicians. Another limitation of marketing LDN is that naltrexone is a general opioid receptor antagonist and binds to all classical opioid receptors, as well as OGFr. There remains a need for specific antagonists that express greater affinity to OGFr so that long-term use would not interfere with other opioid-based medications. Finally, the concept that it is the duration of receptor blockade that determines the effectiveness of LDN is important, and "more is not better." Consumption of LDN more than once a day will not provide greater efficacy, and may even lead to complications. Direct enkephalin treatment for humans is unlikely as enkephalins are easily degraded and sustained relapse capsules are not available. Thus, triggering the body's own source of enkephalin by intermittent opioid receptor blockade following low doses of naltrexone remains a viable therapy for autoimmune disorders.

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ORCID iD

Patricia J McLaughlin http://orcid.org/0000-0002-4630-8225

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