

Low-Dose Naltrexone in Diseases' Treatment: Global Review

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ABSTRACT – Naltrexone is a non-selective opioid antagonist, which shows effects on delta, mu and kappa receptors. Its therapeutic use is designed for drug addicts' treatment, reducing withdrawal side effects. However, several researchers have used low-dose Naltrexone (LDN) for therapeutic purposes in diseases associated to immune system deficiency and inflammatory and tumor processes. Consequently, enhance evidences that LDN use hypothesis promotes, through a compensation mechanism, an increase of endorphins and enkephalins, in addition to opioid receptors up-regulation mechanism, in Central Nervous System (CNS), becoming it a potentially effective clinical practice in these pathologies. Thus, we present a review about LDN use in different pathologies, all they published in literature, and its therapeutic effects, enabling us to conclude that 3.0-4.5mg/day dose use in humans is effective for idiopathic diseases with alterations in immune system, as well as those ones with inflammatory and tumor characteristics.

Keywords – Diseases, Low dose Naltrexone, Treatment.

I. INTRODUCTION

Naltrexone is a non-selective antagonist drug of opioid receptors, mu, kappa and delta, approved by Federal Drug Agency (FDA) in 1984 for alcohol dependence disorder treatment, where several studies involving men and women demonstrate its effectiveness in reducing consumption of this substance, withdrawal period adverse effects, and possible relapses prevention [1-5]. Possibly the mechanism that provide Naltrexone benefits in addicts individuals may be related to aforementioned receptors blocking, reducing binding narcotics group generally [6,7].

In 1983, endogenous opioid systems have been associated with cells and tissues growth in general, and immune system proper functioning [8,9]. Since then, Naltrexone has been studied in low dose and prolonged use for treating various diseases, such Crohn's disease, Multiple sclerosis, Fibromyalgia, Neuroblastoma, among others [10-13]. Low dose Naltrexone (LDN) possibly increase opioid receptors expression, as well as enkephalins and endorphins levels by a compensatory mechanism due to temporary blocking of these receptors [6,7,14].

Naltrexone is capable to block opioid receptors for 24 hours period at 50 mg/day dose, being usually the initial dose for prescription to reduce alcohol consumption. However, Naltrexone daily and reduced dose (3-4.5mg/day) possibly imply to a temporary blocking of these receptors in Central Nervous System (CNS) for a 4-6 hours period, thus promoting a receptors up-regulation and their endogenous ligands [6,8].

Thus, the aim of this study is to present different studies results using LDN in their materials and methods in several pathologies, highlighting disease type and therapeutic effects observed in this new approach. Therefore, it was conducted a literature review about subject in question, using information from scientific journal indexed articles among 2000-2015. Search websites, like Pubmed, Scielo, ScienceDirect, Medline, Lilacs, among others, were accessed. They were considered original articles and case studies contained keywords: "Low dose Naltrexone" or "LDN", in different languages (Portuguese and English).

II. LOW-DOSE NALTREXONE IN DISEASES' TREATMENT

Among gastrointestinal tract pathologies, Crohn's disease, which is characterized by intestine granulomatous inflammation, most common at ileocecal area, with symptoms such diarrhea, abdominal pain, and weight loss, is responsible for life quality impairment and increased individuals mortality worldwide [15,16]. In a study, using LDN (4.5mg/day) in Crohn's disease patients (confirmed by histological analysis and endoscopy) for twelve weeks period, it was observed that 89% of patients showed significant disease symptoms improvement after treatment and 67% achieved disease remission [10].

In another study with 40 patients resistant to conventional treatments, all of them with inflammatory bowel diseases (IBD) generally, including Crohn's disease and ulcerative colitis, it was used LDN (5mg/day) as

alternative therapy and clinical and endoscopies responses were considered. It is emphasized that clinical responses is supported in disease symptoms remission after three months of treatment and endoscopic response considered reduction in pathological condition (quantitative and/or qualitative) for same treatment period. Of the 40 patients, 27 showed desirable clinical responses, while the remaining 13 ones had a favorable endoscopic response, where these results remained for an average of 21 months, total study period. In conclusion, authors have identified benefits of using LDN in different inflammatory diseases on gastrointestinal tract, it not showing side effects, justifying this therapy in these pathologies types [17].

Multiple sclerosis (MS) is a progressive disease of Unknown etiology that affects thousand people worldwide and it is characterized by axonal myelination loss, causing neuronal damage. The main theories proposed as disease cause are related to viral infections and immune system impairment [18,19]. Evidence s suggest that peroxy nitrite and glutamic acid levels are elevated in MS patients, and it is possible a reduction in cerebrospinal fluid occur after three to six months after treatment period [11,20].

Autism is a neurodegenerative disorder that affects one in 150 children only in United States, and it is characterized by difficulties in social approaches, socio-emotional relationships, communication, behaviors related to isolation, and some motor and sensory dysfunction [21,22]. A study on clinical and biological effects of LDN use by a 12 weeks period in 11 children diagnosed with autism, it was observed a positive result on disorder symptoms, attenuating significantly identified weaknesses [23]. In another study, Good asserts autism may be related to high levels of nitric oxide in CNS and use LDN benefits can contribute to this disorder treatment possibly by an anti-inflammatory action [20].

Neuroblastoma is a tumor type that affects Sympathetic Nervous System mostly during childhood, representing approximately about 8% of all malignant neoplasms in patients younger than 15 years old [24,25]. In a study of Neuroblastoma model in mice, it was observed LDN was able to reduce tumor onset time in 65-90% and increase animals' survival time in 10-24% when compared to control group, concluding then LDN can modulate tumoral response and endogenous opioid system plays an important role in neuro-oncogenic events [8,9].

Fibromyalgia is a disease with no cure, and it is characterized by widespread pain permanence, chronic fatigue, sleep disorders, muscle rigidity, cognitive losses, and in some cases it is reported depression. Its pathophysiology is not completely known, but evidences suggest CNS disorders affect different afferent processes and its diagnosis is by clinical evaluations. Several treatments are used for this patients, including opioid, antiepileptic and antidepressant drugs, although without completely effective results [26,27].

In a case study in literature, a 37-year-old patient presenting pain, muscle stiffness, chronic fatigue, and sleep problems, after he had been diagnosed with Fibromyalgia, he started LDN treatment and reported improvements in pain (using a subjective scale) and cold sensitivity after eight weeks of treatment. Although patient had varied the dose, starting at 2mg/day up to 4.5mg/day, the dose which showed best results was the last one. Among improvements, patient enumerates those related to fatigue, working capacity and mood. It is therefore concluded that Fibromyalgia treatment with LDN may be used safely with a relatively low cost and it presents improvements over main disease symptoms [28]. Another LDN study at 4.5mg/day dose for two weeks, it was observed that there was a reduction in disease symptoms in about 30% of patients compared to placebo group. Furthermore, it was identified also that pain thresholds were significantly better in treated group [29].

Chronic pain syndrome was studied using LDN because of its possible analgesic and anti-inflammatory on CNS microglia effect. That is, using 4.5mg/day Naltrexone dose in 300 patients during a year, this study demonstrated that one third of these individuals had pain relief and reported greater physical disposition and increases in physical strength, relating these results to a better life quality of these people, concluding LDN may be used in treatment of this syndrome with safe and effective results [28,29].

In another study conducted by Bernad Bihari (American physician) involving 50 patients with HIV in 1985-1986, it was observed that these individuals were not affected by opportunists' infections, common in these patients. Doses were used at 50mg, 10mg, 5mg, and 3mg/day, seeking a lower dose that promotes endorphin levels increase by opioid system up-regulation. In this way, 3 and 5mg/day doses were effective in raising endorphin production levels up to 300%, and its administration during in the night is most recommended, because from 2:00-4:00 a.m. there is a peak in endorphin endogenous production, taking better use advantage of LDN. LDN significant efficacy has been extended for more than 12 years in his private practice in patients with HIV/AIDS and there were no reported side effects in its use [30].

III. CONCLUSION

According to literature presented, it may be concluded that LDN use is effective in various pathologies, such as Crohn's disease, AIDS, Multiple sclerosis, Neuroblastoma, Fibromyalgia, among others, possibly due to its actions on immune system, anti-inflammatory and antitumor properties. Thus, LDN may be characterized as a new generation of potential drugs in these disorders' treatment, aiming improvement and/or remission of their symptoms, opening up new possibilities for research into immunological abnormalities, inflammatory and/or cell growth/development diseases.

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