

## Restless Legs Syndrome: Sequential Treatment with Rifaximin and Low Dose Naltrexone

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### Abstract

**Background:** Restless legs syndrome (RLS) has been linked to small intestinal bacterial overgrowth (SIBO) and in small studies the antibiotic rifaximin is reported to be efficacious. In light of recent findings that RLS may be associated with inflammation and endorphin deficiency, low-dose naltrexone (LDN) was administered to patients following rifaximin and a case series is presented.

**Methods:** Chart review study of RLS patients who had a positive lactulose breath test for SIBO. Those with low ferritin levels had diagnostic studies and were treated with iron before receiving further therapy. Rifaximin was administered: 550 mg/TID/2-weeks. Immediately after finishing rifaximin, LDN was administered long-term. Three dosages of LDN (2.5 mg/day, 2.5 mg/BID and 4.5 mg/day) were studied since doses have varied in different disease states.

**Results:** Global RLS symptom improvement for this sequential therapy were: marked improvement in 21/40 (52.5%), moderate improvement in 5/40 (12.5%), slight improvement in 3/40 (7.5%), or no improvement in 11/40 (27.5%). LDN was administered for mean of 80-weeks (range 1-364, SD  $\pm 112$ ). A numerically greater percentage on 2.5 mg LDN compared to 2.5 mg BID and 4.5 mg daily LDN had marked/moderate improvement: 78.3% vs. 45.5%. Adverse events occurred in 6 (15%) and led to discontinuation of LDN.

**Conclusions:** Sequential therapy appears to improve RLS symptoms. Bacterial overgrowth and inflammation may be factors in RLS. Endorphin deficiency appears to place a role in RLS and thus increasing these levels by LDN may be of benefit. Further prospective studies using the International RLS scale are warranted.

### Introduction

Links between restless legs syndrome (RLS) and small intestinal bacterial overgrowth (SIBO), as well as the effect of antibiotic therapy in RLS associated with SIBO have been reported (1-4). Most secondary RLS conditions are associated with inflammation, thus there was interest in reducing inflammation as part of RLS therapy (5). In two of the author's clinical practice (LBW, TM), RLS patients who have SIBO (with or without gastrointestinal symptoms) are treated with rifaximin (a non-absorbed, gut directed antibiotic) immediately followed by prokinetic (promotility) therapy to reduce relapse of SIBO, which is often caused by small intestinal stasis (6). Initially low dose erythromycin, which has motilin hormone activity, was used for this purpose; subsequently, low dose naltrexone (LDN) has been chosen since, in addition to promotility activity, it reduces inflammation, pain, and improves central nervous system endorphin activity which appears to be important in RLS pathophysiology (6-13). In this brief

communication we describe the results of treating RLS patients with sequential therapy using rifaximin followed by LDN.

## Methods

A chart review was carried out on patients (N=52) who were prescribed rifaximin and LDN for RLS from January 2006 to December 2014. Twelve patients were eliminated from further analysis for the following reasons: 6 did not fill their prescription, 4 did not have a follow up office visit, and 2 did not receive rifaximin prior to LDN treatment. In the remaining 40 patients who had clinical follow up, a detailed chart review was performed. Patients were included if their lactulose breath test indicated SIBO. Those with low ferritin levels had diagnostic studies and were treated with iron before receiving further therapy. Gastrointestinal symptoms and disorders were evaluated.

Rifaximin had been prescribed based upon an abnormal lactulose breath test. Prior to 2009, criteria for a positive lactulose breath test was a >20 ppm rise in hydrogen and/or methane above baseline by 180 minutes. In 2009 the criteria changed to a >20 ppm rise of either gas above baseline by 90 minutes. The breath tests were reviewed in 2015 to determine if there were false positive readings. The outcome of RLS symptoms was determined by the chart review and/or a telephone call in March 2015 when the response was not well documented in the follow up office visits. The assessment determined if their global RLS symptom improvement were markedly improved, moderately improved, slightly improved, unchanged or worsened. Adverse events were assessed as part of normal clinical practice administering an antibiotic and LDN.

Patients were required to have the four international criteria of RLS: 1) compelling urge to move extremities, usually the legs, often associated with discomfort, 2) occurrence during rest or inactivity, 3) occurrence or worsening typically in evening, and 4) temporary improvement with movement, including stretching or walking. None of the patients had been treated with rifaximin or naltrexone in the past.

## Results

Clinical characteristics of 40 patients included: 36 women, 4 men, mean age 58 years, and mean body mass index of 27 kg/mm<sup>2</sup>. Irritable bowel syndrome was diagnosed in 28 patients (diarrhea predominant in 9, constipation predominant in 9, both forms in 10). Chronic idiopathic constipation was diagnosed in 6 patients. One had bloating alone. One had excess flatulence alone. Two had no gastrointestinal symptoms. Two patients had been diagnosed with celiac disease in the distant past but had been on a gluten free diet and were found to have SIBO and had normal ferritin levels.

Rifaximin 550 mg was prescribed three times a day for 2 weeks. Immediately after receiving rifaximin, LDN was administered long-term as follows: 2.5 mg once daily (N=23), 2.5 mg twice daily (N=9), or 4.5 mg daily (N=8). Low-dose-naltrexone was administered for mean of 80-weeks (range 1-364, SD ±112).

Global RLS symptom outcomes were as follows: markedly improved in 21/40 (52.5%), moderately improved in 5/40 (12.5%), slightly improved in 3/40 (7.5%), unchanged in 11/40 (27.5%), and worsened in none. The subtotal of 26 patients who had either marked or moderate improvement were treated with LDN for a mean duration 106 weeks (range 4 - 364, SD ±122). More patients on the 2.5 mg LDN dose compared to the higher doses of LDN had marked/moderate improvement: 78.3% vs.

45.5%. Seven patients diagnosed with SIBO prior to 2009 by breath test has a negative breath test by current standards nonetheless four had a marked/moderate improvement with treatment.

Self-limited adverse events occurred in 6 (15%) patients, led to cessation of LDN, and were equally divided in those who received the lower vs. higher LDN doses. These events included: insomnia (5), vivid dreams (1), headache (1), drowsy (1), dizzy (1), muscle pain (2), and abdominal pain (1).

## Discussion

The current study expands on prior antibiotic studies by adding long-term LDN therapy to short-term antibiotic therapy. In the first multimodality therapy study with rifaximin followed by promotility therapy and anti-inflammatory therapy (probiotic and zinc), long-term efficacy was seen in 13 patients (2). Using a short course of rifaximin alone, RLS improved but this was followed by a relapse of symptoms (3, 4). The RLS symptom outcome of the patients in the present study appeared to be favorable and many patients had long-term remission of symptoms while taking LDN which has been hitherto unreported. Many of the patients had significant improvement for 2 years with some up to 6 years.

The limitations of drawing conclusions includes retrospective analysis, absence of a placebo arm, small number of patients subdivided into different LDN doses, and lack of validated symptom score analysis (e.g., IRLS scale). The range of LDN dose varies in studies between 0.5 mg to 9 mg per day, and different doses appear to be more effective in various diseases (e.g., Crohn's disease responds best to 4.5 mg whereas autoimmune diseases require a lower dose of LDN). This is the first study of LDN in RLS and the ideal dose was unknown. Furthermore, one could argue that it is not clear which therapy was active since the medications were used in succession and symptom assessment was carried out at the latest office visit. In other SIBO conditions such as IBS, relapse after antibiotic therapy occurs earlier compared to following it with prokinetic therapy (6). LDN may be playing an additional therapeutic role since not only is there long-term improvement of RLS symptoms in many patients, but in the 4 of 7 patients where the breath test was reread as negative, there was a marked/moderate clinical response.

LDN increases endorphin levels by temporarily blocking the opioid receptors, causing a rebound via a positive feedback mechanism (10). In contrast to the 50-100 mg dosing which blocks the opioid receptors long-term, the 4 hour blockade by LDN results in the cells sensing less opioids and responding by increasing production of the endorphins and receptors. The collective evidence supports the view that LDN operates as a novel peripheral- and central-acting anti-inflammatory agent, reducing pain in inflammation-driven conditions (8). Endorphins can directly attenuate microglia activation and pro-inflammatory cytokine release via blockade of the Toll-like receptor 4 pathway (9). RLS is often accompanied by discomfort or pain and thus there may be a direct effect on this symptom by endorphins.

Recently the endogenous opiate system has been suspected as having a role by stabilizing dopaminergic substantia nigra degeneration under conditions of iron deprivation. Interactions of endorphins and iron on the dopamine cell appear to be critical for adequate dopamine functioning. In

a study by Sun et al, application of enkephalin significantly protected the substantia nigra cells from damage by iron deficiency (11). The implications of this mouse model are that in RLS patients with iron deficiency, dopaminergic system dysfunction may result, and an intact endogenous opioid system or opioid treatment may improve dopamine receptor function. This theory is supported by a study examining autopsy tissue of RLS brains compared to controls. In this study there was a 37.5% reduction in beta-endorphin and met-enkephalin cells in the thalamus (12). As a functional corollary to this research, a PET scan study found regional negative correlations between endorphin binding and RLS severity in various parts of the brain; thus the lesser degree of endorphin binding, the greater the severity of RLS symptoms (13). This begets the theory that there may be a relative endorphin deficiency in RLS and supports a role for LDN which can increase central nervous system endorphin levels (14).

Further studies of RLS patients treated with rifaximin followed by LDN and patients treated with LDN alone utilizing randomized, placebo-controlled studies are warranted.

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