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Rifaximin Improves Restless Legs Syndrome Associated With Small Intestinal Bacterial Overgrowth

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INTRODUCTION

- Restless legs syndrome (RLS) is compelling urge to move legs at night and is often associated with discomfort[1]
- RLS causes insomnia, negative daily functioning, and poor quality of life[2]
- RLS has been reported as comorbid condition in diseases associated with small intestinal bacterial overgrowth (SIBO) such as irritable bowel syndrome (IBS),[3] Crohn's disease,[4] and celiac disease[5]
  - Prospective multicenter study found that 43% of patients with Crohn's disease (93 of 218) had RLS (see poster P308 by Weinstock et al presented at this meeting)
  - Prospective single-center study found that 35% of patients with celiac disease (30 of 85) had RLS (see poster P447 by Weinstock et al presented at this meeting)
- Treatment of RLS with dopamine agonist, ropinirole (Requip®; GlaxoSmithKline, Research Triangle Park, NC), is only marginally more effective than placebo, with only 60% of ropinirole-treated patients achieving much or very much improvement in global symptoms compared with 40% of patients who received placebo[6]
- Rifaximin[a] is broad-spectrum, gastrointestinal (GI)-targeted antibiotic with low systemic absorption (<0.4%) that is effective treatment for SIBO[7,8]
- Rifaximin has been effective in reducing RLS symptoms in patients with IBS
  - In prospective clinical trial of 13 patients with IBS and RLS, 77% of patients reported ≥80% improvement of RLS symptoms following treatment with rifaximin 1200 mg/d for 10 days[9]

OBJECTIVES

- To evaluate efficacy of rifaximin for treatment of patients with idiopathic RLS and SIBO
- To evaluate prevalence of GI symptoms in idiopathic RLS and effect of rifaximin in patients with RLS and SIBO

METHODS

Inclusion criteria

- Patients were either previously diagnosed with idiopathic RLS by neurologist or had RLS diagnosis confirmed using international RLS (IRLS) diagnostic criteria[10] and abnormal lactulose breath test (LBT)
- Patients were screened by nurse coordinator using IRLS scale to document that all patients had severity score ≥15
  - Set of 10 questions rated on scale that assessed frequency of symptoms and severity of RLS impact on sleep, mood, and activity of daily living[11]
    - Each question on scale ranged from 0 (no impact) to 4 (very severe impact)[11]

Study design

- Prospective, open-label, single-center study conducted from November 2007 to March 2008
- Rifaximin (Xifaxan®; Salix Pharmaceuticals, Inc, Morrisville, NC) 400 mg 3 times daily for 10 days followed by rifaximin 400 mg every other day for 20 days

Assessments

- Lactulose breath test
  - Hydrogen and methane excretion were assessed every 20 minutes for 180 minutes after ingestion of 10 mg lactulose
  - Abnormal result was defined as increase in hydrogen and/or methane excretion >20 ppm
- Symptoms were assessed by self-report patient questionnaires at 0, 12, 20, and 30 days during course of treatment
  - RLS symptom assessment as measured by IRLS severity scale[11]
  - Global improvement of RLS and GI symptoms as measured using separate Likert scales (0: not improved or worse; 1: slightly improved; 2: moderately improved; 3: markedly improved)
    - Responders were defined as patients reporting slight, moderate, or marked improvement of symptoms following rifaximin treatment
    - Nonresponders were those who reported no change or worsening of symptoms following rifaximin treatment
  - Report of improvement of abdominal pain and bloating using Likert scale (0: not at all bothered; 1: hardly bothered; 2: somewhat bothered; 3: moderately bothered; 4: good deal bothered; 5: great deal bothered; 6: very great deal bothered)

RESULTS

- Of 21 patients with RLS who were screened, 6 had normal LBT and were excluded
- One patient with abnormal LBT result was diagnosed with *Helicobacter pylori*–associated gastritis in workup for iron deficiency and was also excluded
- Total of 14 patients with RLS with concomitant SIBO received rifaximin treatment (Table)

Table. Baseline Demographics and Characteristics of Patients With RLS With Concurrent SIBO

Parameter	Patients (N=14)
Mean age ± SD, y	54.3 ± 16.5
Male:Female, n	6:8
Mean duration of RLS ± SD, y	6.8 ± 7.5
GI disorder, n (%)[a]	
IBS	6 (43)
Bloating	3 (21)
Crohn's disease	1 (7)
Celiac disease[b]	1 (7)
Mean duration of GI disorders ± SD, y	16 ± 17.3
Ferritin level ± SD (range), ng/dL	79 ± 74 (3-222)
LBT results, n (%)	
High hydrogen excretion	8 (57)
High methane excretion	4 (29)
High methane and hydrogen excretion	2 (14)
Mean baseline IRLS severity score[c] ± SD	23.1 ± 6.2
Mean baseline GI symptom severity score[d] ± SD	
Abdominal pain	2.8 ± 1.6
Bloating	2.9 ± 1.7

GI, gastrointestinal; IBS, irritable bowel syndrome; IRLS, international restless legs syndrome; LBT, lactulose breath test; RLS, restless legs syndrome; SD, standard deviation; SIBO, small intestinal bacterial overgrowth. [a] Two patients did not display any GI symptoms despite having positive LBT result. [b] Patient was initially diagnosed with IBS but was later found to have celiac disease. [c] Maximum score = 40. [d] Maximum score for each symptom = 6.

- Sixty-four percent (9 of 14) of patients with RLS and SIBO reported slight, moderate, or marked global improvement of RLS symptoms following rifaximin treatment (Figure 1)

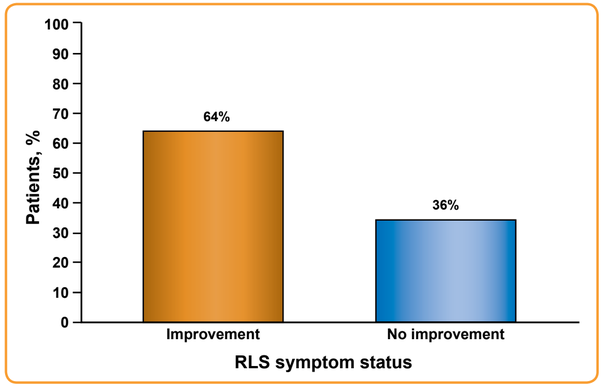

Figure 1. Restless legs syndrome (RLS) symptom status following rifaximin treatment. Sixty-four percent (9 of 14) of patients reported slight, moderate, or marked improvement in RLS symptoms following rifaximin 400 mg 3 times daily for 10 days followed by 400 mg every other day for 20 days compared with 36% of patients who reported no change or worsening of symptoms (5 of 14 patients).

- Responders to rifaximin treatment displayed greater improvement of IRLS severity scores than nonresponders (Figure 2)

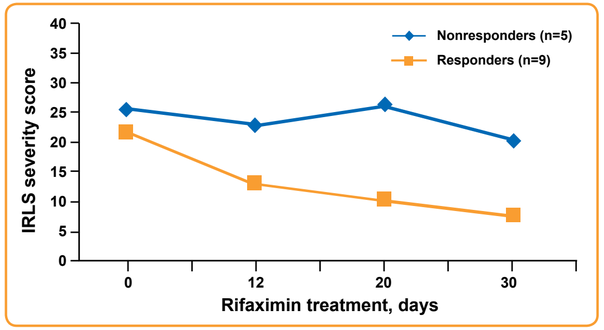

Figure 2. International restless legs syndrome (IRLS) severity scores in clinical responders (reported improvement of RLS symptoms on global Likert scale during rifaximin treatment) versus nonresponders. IRLS severity scores improved in responders 12 days following initiation of rifaximin and were maintained throughout study.

- Abdominal pain and bloating scores improved in majority of patients (Figure 3)

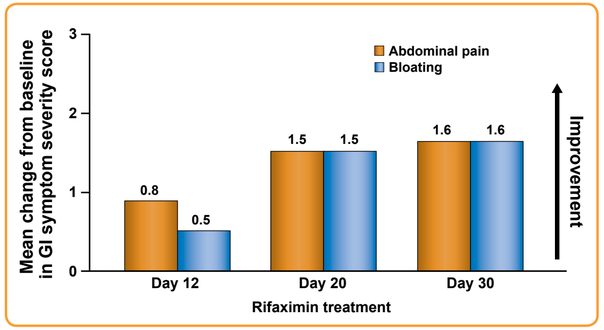

Figure 3. Rifaximin improved abdominal pain and bloating in patients with RLS and concurrent SIBO. In general, patients with both RLS and SIBO displayed improvement in abdominal pain and bloating during rifaximin treatment. GI, gastrointestinal; RLS, restless legs syndrome; SIBO, small intestinal bacterial overgrowth.

- 5 of 14 patients (36%) did not respond to course of rifaximin
  - 2 patients responded to treatment with additional combination antibiotics
  - 2 patients showed no improvement following additional antibiotic treatment
  - 1 patient was diagnosed with celiac disease; symptoms improved on gluten-free diet

DISCUSSION AND CONCLUSIONS

- GI disturbances may be common in patients with idiopathic RLS[9]
- In this small, prospective, open-label study, rifaximin 1200 mg/d for 10 days followed by 400 mg every other day for 20 days substantially improved both RLS and GI symptoms
- These results provide additional evidence of link between SIBO and RLS
- Breath testing for SIBO may be useful diagnostic tool in patients with RLS, and antibiotic therapy with small intestine–targeted antibiotic appears to be warranted
- Randomized, double-blind, placebo-controlled trial is currently under way to evaluate efficacy of rifaximin 1650 mg for treatment of RLS and GI symptoms in patients with idiopathic RLS and SIBO

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[a] Rifaximin is indicated for treatment of travelers' diarrhea caused by noninvasive strains of *Escherichia coli* and is not labeled for treatment of small intestinal bacterial overgrowth or restless legs syndrome.

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