SLEEPJ, 2021, 1–2

doi: 10.1093/sleep/zsaa282
Editorial

EDITORIAL

Restless legs from the urge to reduce gastric acid secretion?

Brian B. Koo*

Department of Neurology, Yale University, New Haven, CT

*Corresponding author. Brian B. Koo, Department of Neurology, Yale University, PO Box 208018 15 York Street New Haven, CT 06520-8018. Email: Brian.koo@yale.edu.

Restless legs syndrome (RLS) is a common sensorimotor disorder, occurring in approximately 5% to 10% of adults in the Western hemisphere [1]. Although abnormalities in iron metabolism appear to be a constant feature in the pathophysiology of RLS, much about the biological mechanisms underlying RLS is incompletely understood. There are multiple neurobiological pathways, which modulate the clinical expression of RLS by some, up to this point ill-defined mechanism. Exemplifying this assertion, the dopamine system has long been known to play a role in RLS pathophysiology, largely driven by clinical observations that dopamine blocking antipsychotic medications provoke RLS [2], and that dopamine precursor medications treat RLS [3]. Other neurobiological pathways that appear to be involved in the pathophysiology of RLS include the serotonin, glutamate, opioid, adenosine, and histamine pathways [4].

Needless to say, the neurobiology of RLS is complex. Mirroring this neurobiological complexity, clinically, RLS symptoms are either exacerbated or mitigated by a myriad of medications and substances which act on some of the above mentioned neurobiological pathways. Substances that exacerbate RLS include serotonin promoting medications, histamine blocking medications, and alcohol (likely through increasing glutamate), while RLS is ameliorated by opioid medications, adenosine promoting medications (e.g. dipyridamole), and glutamate suppressing medications (e.g. gabapentin).

In general, RLS can be divided into primary idiopathic RLS in which RLS occurs in the absence of a condition or substance which leads to its emergence and secondary RLS, which occurs concomitantly with an RLS-promoting condition or substance. It is likely that all humans are capable of experiencing RLS symptoms, if the right combination of provoking conditions or substances align. It is also likely that the threshold to develop RLS differs between individuals based upon inherent genetic factors, treatable disease factors (hypothyroidism [5], renal disease), modifiable dietary and medication factors, and dynamic metabolic factors such as iron status. For example, frequent blood donation may be sufficient to provoke RLS in one individual, while another individual who donates blood with regularity may not express RLS until they develop hypothyroidism. Yet another person may not express an RLS phenotype in the setting of blood donation and hypothyroidism, until they begin taking an antidepressant medication. Many of these factors occur commonly and thus have broad population implications. In the United States, according to the National Center for Health Statistics, during any given 30-day span, over 13% of adults have taken an antidepressant medication [6]. Even if RLS will develop in only 1% of persons taking an antidepressant medication, this still equates to hundreds of thousands of adults with RLS arising from an antidepressant medication.

In this issue of *SLEEP*, Earley et al.[7] study the potential association between RLS and another group of commonly used medications, the antacid medications to treat gastric reflux disease. In their cross-sectional cohort study, the authors have found that in two large independent cohorts of blood donors from the United States (n = 13,403) and Denmark (50,323), the use of either a proton pump inhibitor (PPI) or a histamine H_2-receptor antagonist (H_2A) was associated with the presence of RLS, independent of age, sex, race, BMI, or blood donation frequency. The authors logically lay out the case that both PPI and H_2A medications are linked to reduced iron [7], the latter being a known contributor to RLS, and hence there is likely to be an association between taking a PPI or H_2A medication and having RLS. Indeed, an independent association was found between PPI or H_2A medication usage and having RLS, such that those taking a PPI or H_2A had a 41% increased odds of RLS (OR = 1.41; 95% CI, 1.13–1.76; p = 0.002) in the US cohort and a 29% increased odds of

RLS (OR = 1.29; CI, 1.20–1.40; $p < 0.001$) in the Danish group. There were some notable nuances to this association.

First, the association between PPI or H_2A use and RLS was not mediated by serum ferritin. The authors found that there was evidence for association between PPI or H_2A use and RLS directly, as well as between PPI or H_2A use and ferritin when controlling for RLS, but not for ferritin and RLS when controlling for PPI or H_2A use, suggesting that the association between PPI or H_2A use and RLS was not mediated by serum ferritin. They did not include, however, a multivariate regression model where serum ferritin was included along with PPI or H_2A use and other covariates to determine association with RLS. An inclusion of this model would have made a stronger argument for the association between RLS and PPI or H_2A use being independent of low iron. Furthermore, a statistical finding or lack thereof does not indicate a lack of actual biological causality or mediation. It should be noted, however, that histamine H_1-receptor blocking medications (e.g. diphenhydramine) taken by those with RLS typically cause an acute exacerbation of RLS, occurring within hours. The acuity of this reaction makes iron deficiency an unlikely mediator of the H_1 antagonist-RLS relationship.

Second, RLS prevalence was higher for those taking two or more antacid medications versus those taking only one antacid medication. While in the US cohort, PPI and H_2A medications considered separately were both independently associated with RLS, in the Danish cohort, H_2A but not PPI medications were associated with RLS, even though taking a PPI or H_2A was associated with RLS. These medications have different mechanisms of action, one blocking the histamine H_2 receptor and the other blocking the parietal cell H+ / K+ ATP pump, thereby suppressing gastric acid secretion. As mentioned above, the association between PPI or H_2A use and RLS may be mediated by iron deficiency even though the results from the present study did not support this. This would make some sense as both PPIs and H_2As have been independently associated with iron deficiency [8]. On the other hand, if iron deficiency does not mediate the PPI/H_2A-RLS association, then what does? Considering H_2A, these drugs likely have effects on the brain. The histamine H_2 receptor is excitatory and exists in different brain regions, including hypothalamus, basal ganglia, cortex, cerebellum, and dorsal raphe nucleus, and activation of the H_2 receptor in these regions may modulate vigilance, feeding, movement, and likely a myriad of other functions [9]. That it could cause RLS would not be surprising, and in fact, there is a case report of a patient taking cimetidine chronically who developed RLS [10]. PPIs causing RLS? Could this be from an alteration of the gut microbiome and small intestinal bacterial overgrowth, which has been associated with RLS? [11] Or do PPIs act in the brain, suggested by findings that PPIs increase beta-amyloid levels in the brain, thereby increasing dementia risk [12]. The possibilities seem endless.

Regardless of the mechanism by which PPIs and H_2As may be associated with RLS, the study by Earley et al. provides convincing population-level evidence that these commonly used antacid medications are associated with and potentially causative of RLS. The cross-sectional nature of the study precludes a definitive conclusion of causality, but given the brittle track record of RLS being caused by numerous factors and the biological plausibility for at least the H_2As interacting with brain regions thought key in RLS, it appears very possible that the antacids may in fact cause RLS. For the sleep medicine provider managing patients with RLS (particularly chronic severe RLS), these medications should be added to the long list of substances that can exacerbate or cause RLS.

Funding

None declared.

Conflict of interest statement. None declared.

References

1. Allen RP, *et al*. Restless legs syndrome prevalence and impact: REST general population study. *Arch Intern Med*. 2005;**165**(11):1286–1292.
2. Blom S, *et al*. Comparison between akathisia developing on treatment with phenothiazine derivatives and the restless legs syndrome. *Acta Med Scand*. 1961;**170**:689–694.
3. Akpinar S. Treatment of restless legs syndrome with levodopa plus benserazide. *Arch Neurol*. 1982;**39**(11):739.
4. Ferré S, *et al*. In search of alternatives to dopaminergic ligands for the treatment of restless legs syndrome: iron, glutamate, and adenosine. *Sleep Med*. 2017;**31**:86–92.
5. Ahmed N, *et al*. Hypothyroidism in restless legs syndrome. *J Sleep Res*. 2020:e13091.
6. Brody DJ, *et al*. *Antidepressant Use Among Adults: United States, 2015–2018. NCHS data brief, no 377*. Hyattsville, MD: National Center for Health Statistics; 2020:377.
7. Earley EJ, *et al*. Association of proton pump inhibitor and histamine H2-receptor antagonists with restless legs syndrome. *Sleep*. 2021;**44**(3). doi:10.1093/sleep/zsaa220.
8. Lam JR, *et al*. Proton pump inhibitor and histamine-2 receptor antagonist use and iron deficiency. *Gastroenterology*. 2017;**152**(4):821–829.e1.
9. Lakoski JM, *et al*. Interaction of histamine H2-receptor antagonists with GABA and benzodiazepine binding sites in the CNS. *Eur J Pharmacol*. 1983;**88**(2-3):241–245.
10. O'Sullivan RL, *et al*. H2 antagonists, restless leg syndrome, and movement disorders. *Psychosomatics*. 1993;**34**(6):530–532.
11. Weinstock LB, *et al*. Restless legs syndrome is associated with irritable bowel syndrome and small intestinal bacterial overgrowth. *Sleep Med*. 2011;**12**(6):610–613.
12. Ortiz-Guerrero G, *et al*. Proton pump inhibitors and dementia: physiopathological mechanisms and clinical consequences. *Neural Plast*. 2018;**2018**:5257285.