NEW RESEARCH

JCSM
Journal of Clinical Sleep Medicine

pii: jc-00278-14
http://dx.doi.org/10.5664/jcsm.4296

CASE REPORTS

Asenapine-Induced Restless Legs Syndrome: Differentiation from Akathisia

W. Vaughn McCall, M.D., M.S., F.A.A.S.M.[1]; Mary Anne Riley, M.A.[1]; Chelsea Hodges, M.A.[1]; Laryssa McCloud, Ph.D.[1]; Marjorie Phillips, M.S.[2]; Peter B. Rosenquist, M.D.[1]

[1]Department of Psychiatry and Health Behavior, The Medical College of Georgia, Georgia Regents University, Augusta, GA; [2]Pharmacy Department, Georgia Regents Medical Center, Augusta, GA

Akathisia and restless legs syndrome (RLS) share some common clinical features and a common relationship with dopamine dysfunction. However, the underlying causes and appropriate treatments for akathisia and RLS are different. Herein we describe a case of RLS that was precipitated by a single dose of asenapine, which is an atypical antipsychotic, and dissect the features that support the contention that this was indeed a case of RLS and not akathisia.

Keywords: restless leg syndrome, akathisia, asenapine

Citation: McCall WV, Riley MA, Hodges C, McCloud L, Phillips M, Rosenquist PB. Asenapine-induced restless legs syndrome: differentiation from akathisia. *J Clin Sleep Med* 2014;10(12):1341-1342.

Restless legs syndrome (RLS) is defined by the "essential criteria," which include "(1) an urge to move the legs, usually accompanied by uncomfortable and unpleasant sensations in the legs…, (2) The urge to move or unpleasant sensations begin or worsen during periods of rest or inactivity…, (3) The urge to move or unpleasant sensations are partially or totally relieved by movement…and (4) The urge to move or unpleasant sensations are worse in the evening…"[1] Sleep disturbance and periodic limb movements (PLM) are associated features of RLS. There are primary and secondary forms of RLS, but hypofunctioning of central dopamine (DA) transmission is common to a variety of RLS presentations.[2] A sensation of restlessness is also a characteristic of akathisia, which is defined as the "subjective complaint of restlessness, often accompanied by observed excessive movements (e.g., fidgety movements of the legs, rocking from foot to foot, pacing, inability to sit or stand still) developing within a few weeks of starting or raising the dose of a medication (such as a neuroleptic)…"[3] Akathisia is most commonly seen in patients receiving medications that block central DA2 receptors, such as typical antipsychotic medications.[4]

RLS and akathisia share some common features, such as a sensation of restlessness, urgency to move, and hypofunctioning of DA, but there are also important differences. Akathisia does not usually present with the dysaesthesia focused in the legs; indeed most patients with akathisia describe restlessness in the absence of discomfort. Instead, akathisia produces a sense of restlessness that is described as emanating from the central core of the patient.[5] Secondly, akathisia is not present with a marked diurnal variation in symptom intensity, while an evening-dominance of symptoms is a characteristic feature or RLS.

A variety of psychotropic medications can cause RLS and/or akathisia, including antipsychotics and antidepressants with serotonergic (5-HT) effects.[6,7] Herein we describe a case in which the novel antipsychotic asenapine rapidly induced symptoms that were consistent with RLS, and not akathisia.

REPORT OF CASE

A 60-year-old Caucasian woman participated in a major depression treatment research study in which patients who were already taking an antidepressant would be randomized to also receive either placebo or the novel atypical antipsychotic asenapine. Standard doses for asenapine are 5 mg twice per day or 10 mg twice per day. It is rapidly absorbed when taken as a sublingual dissolvable lozenge (T_{Max} 1 hour), with a half-life ($t_{1/2}$) of 24 hours.[8] The study was approved by the local institutional review board (IRB).

The informed consent document covered the common risks of asenapine but did not mention restless legs syndrome. After providing informed consent, the baseline assessment revealed an average sleep duration reported as 4-6 h nightly and an unremarkable medical history. Her medications included citalopram 40 mg daily and clonazepam 0.5 mg at bedtime as needed. She denied daytime sleepiness.

On the first night of participation in the study, the patient ingested her first and only dose of blinded study medication by the sublingual route, and within 30 minutes the patient began to experience a disagreeable sensation in both legs that was described as "shakiness in her legs," accompanied by periodic involuntary jerking of her left leg while awake. The leg discomfort was briefly relieved by movement. Her sleep onset was remarkably delayed and her husband reported the jerking continued during sleep. The sensation was not present in any other part of her body besides her legs. The disagreeable sensations had dissipated by morning.

On a follow-up visit the patient reported a similar experience with diphenhydramine and family history positive for a formal diagnosis of RLS in her mother. The patient's iron status was unknown.

The patient refused to continue in the study, and hence the study drug assignment was unblinded, revealing that she had received a single dose of asenapine 5 mg sublingual.

DISCUSSION

This patient's experience with asenapine is consistent with a medication-induced RLS. This conclusion is strengthened by (1) the discovery of a similar response to other psychoactive medications, (2) a positive family history (which is a "supportive clinical feature"),[1] (3) the spontaneous report of symptoms to a blinded medication in the absence of specific information in the informed consent form regarding RLS, and (4) the husband's report of movements during sleep consistent with PLMs. This adverse event might have been coded as akathisia, but the symptoms were described as confined to the legs and not the central core, as might be expected in akathisia. It is unknown whether this occurrence of RLS would have happened in the absence of her concurrent treatment with citalopram or clonazepam. Other investigators have reported RLS with administration of the atypical antipsychotic olanzapine, and the need to distinguish RLS from akathisia.[9]

Differentiating between RLS and akathisia is clinically relevant. While the initial approach for treating both RLS and akathisia may include reducing or discontinuing the offending medication, thereafter the treatment approaches for RLS and akathisia diverge. While dopamine agonists have a dominant role in the treatment of RLS,[2] they have a minor role in the treatment of akathisia. Conversely, mirtazapine has been suggested as a treatment for akathisia,[4] yet mirtazapine is among the drugs most often cited in instances of drug-induced RLS.[6]

The primary teaching points of this case include (1) the need to distinguish between RLS and akathisia, (2) RLS can be rapidly induced in susceptible individuals with certain psychotropics, and (3) susceptibility can be defined as prior experience of RLS induction with other psychotropics, and/or a positive family history of RLS.

REFERENCES

1. Allen R, Picchietti D, Hening WA, et al. Restless legs syndrome: diagnostic criteria, special considerations, and epidemiology: a report from the restless legs syndrome diagnosis and epidemiology workshop at the National Institutes of Health. *Sleep Med* 2003;4:101-19.
2. Cervenka S, Palhagen S, Comley RA, et al. Support for dopaminergic hypoactivity in restless legs syndrome: a PET study on D2-receptor binding. *Brain* 2006;129:2017-28.
3. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 5th ed. Arlington, VA: American Psychiatric Association, 2013
4. Kumar R, Sachdev PS. Akathisia and second-generation antipsychotic drugs. *Curr Opin Psychiatry* 2009;22:293-9.
5. Benes H, Walters AS, Allen RP, et al. Definition of restless legs syndrome, how to diagnose it, and how to differentiate it from RLS mimics. *Mov Disord* 2007;22:S401-8.
6. Perez-Lloret S, Rey M, Bondon-Guitton E, et al. Drugs associated with restless legs syndrome: a case/noncase study in the French Pharmacovigilence Database. *J Clin Psychopharmacol* 2012;32:824-7.
7. Basu B, Gangopadhyay T, Mandal B, et al. A case of akathisia induced by citalopram: case report and review of the literature. *Curr Drug Saf* 2014;9:56-9
8. Stoner SC, Pace HA. Asenapine: a clinical review of a second-generation antipsychotic. *Clin Ther* 2012;34:1023-40.
9. Aggarwal S, Dodd S, Berk M. Restless leg syndrome associated with olanzapine: a case series. *Curr Drug Saf* 2010;5:129-31.

SUBMISSION & CORRESPONDENCE INFORMATION

Submitted for publication July, 2014
Submitted in final revised form July, 2014
Accepted for publication July, 2014

Address correspondence to: W. Vaughn McCall, M.D., M.S., Dept Psychiatry; MCG, 997 St Sebastian Way, Augusta GA 30912; Tel: (706) 721-6719; E-mail: wmccall@gru.edu

DISCLOSURE STATEMENT

This work was supported by Merck & Co. Dr McCall has received research support from NIH and Merck, has been a consultant to Merck and Otsuka, and has received honoraria from Wolters Kluwer. The other authors have indicated no financial conflicts of interest. This paper describes the investigational use of asenapine for treatment of treatment-resistant depression