



Restless Legs Syndrome Caused by Quetiapine

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In addition to patients presenting with primary restless legs syndrome (RLS), clinicians may also encounter patients presenting with drug-induced RLS. Drug-induced RLS is a commonly observed adverse event in patients receiving atypical antipsychotics (AAP). The individual AAPs have been shown to induce RLS at varying frequencies. In particular, olanzapine and quetiapine have been reported to induce RLS at higher rate than do the other AAPs. Considering quetiapine's low affinity for the dopamine receptor, AAP-induced RLS cannot be attributed to the degree of dopamine blockade alone. Observations from previous pharmacokinetic studies indicating that quetiapine exhibits transiently high D2 occupancy when initially administered could offer an explanation for this high rate of RLS induction. Several additional reports have indicated that the symptoms of RLS may be exacerbated by administration of anti-histaminic drugs, which is of interest in the context of quetiapine's high affinity for the H1 receptor. Still, the exact mechanism by which AAPs induce RLS remains unclear. This article will review the current clinical evidence regarding quetiapine-induced RLS.

Key Words: Quetiapine; Restless legs syndrome; Atypical antipsychotics

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INTRODUCTION

While in clinical practice, clinicians may encounter patients presenting with drug-induced restless legs syndrome (RLS) in addition to those presenting with primary RLS. RLS is particularly and commonly observed in patients receiving atypical antipsychotics (AAP), which as a class are known to exert their clinical effect through antagonism of the dopamine receptor. However, the probability at which administration of the individual AAPs may induce RLS has been seen to be inconsistent. Quetiapine and olanzapine in particular have been observed to be potent inducers of RLS. As such, it is difficult to ascribe AAP-induced RLS to dopamine antagonism alone when considering quetiapine's low affinity for the dopamine receptor.

PATHOPHYSIOLOGY OF QUETIAPINE-INDUCED RLS

RLS has previously been associated with iron deficiency, pregnancy, kidney disease, and rheumatoid disease as well as disruption of dopamine and histamine signaling [1]. Additionally, asso-

ciations between drug-induced RLS and dopamine (D2) receptor blockers, histamine receptor blockers, antidepressants, lithium, and caffeine have been described [2].

Dopamine and quetiapine-induced RLS

The mechanism by which AAPs may induce RLS remains unclear. The primary mechanism has been suspected to be related to a disruption in dopaminergic signaling [3]. However, by this reasoning, quetiapine would be expected to induce RLS at a lower rate than that of olanzapine and risperidone owing to its lesser occupancy of the D2 receptor [3]. This supposition is further questioned by additional observations that quetiapine only loosely binds to the D2 receptor and readily dissociates from it [4]. To that end, other studies have even shown that quetiapine induces akathisia at a similar rate to placebo [5,6]. Investigators have hypothesized that quetiapine's tendency to transiently bind D2 at high occupancy [7] when initially administered could be a contributing factor to the high rate of RLS reported during its use [8]. However evidence in support of this mechanism remains inconclusive.

Histamine and quetiapine-induced RLS

Quetiapine has been found to display a high affinity for the H1 receptor, and several reports have described exacerbation of RLS symptoms on administration of antihistaminic medication [9]. In addition, some investigators have reported that administration of antihistamines, antidepressants, antipsychotics, and antiemetics may increase the risk of RLS in patients with end stage renal disease [10]. However, at the same time, a recent study has revealed the possible involvement of a striatal histamine mechanism in the pathogenesis of iron-deficiency anemia-induced RLS, and that histamine H3R antagonism may be efficacious in its management [11]. Therefore further study of the relationship between histamine and RLS continues to be warranted.

Iron deficiency and quetiapine-induced RLS

Other studies have suggested involvement of iron dysregulation in the pathogenesis of quetiapine-induced RLS [9]. Iron deficiency has been shown to be a common cause of secondary RLS. Insufficient supply leads to a disruption in dopamine synthesis, increasing variation in the diurnal cycle [9]. An underlying iron deficiency may increase susceptibility to RLS, and supplementation could possibly mitigate symptom severity [12]. Thus, clinicians may benefit from remaining cognizant of a patient's iron status when management has been complicated by the presence of RLS.

DIFFERENCE BETWEEN ANTIPSYCHOTIC-INDUCED AKATHISIA AND ANTIPSYCHOTIC-INDUCED RLS

Because severe cases of antipsychotic-induced RLS that have lost circadian variation may be challenging to distinguish from those of akathisia, discerning between the two is sometimes difficult [13]. The symptoms of antipsychotic-induced RLS increase during the night and the discomfort is localized to the lower extremities [1,14]. However, patients may describe either condition as an inner restlessness. Given this, RLS should be considered with a higher index of suspicion than akathisia in patients managed on quetiapine, as quetiapine is much more likely to induce the former rather than the latter [3,4].

CASE SERIES OF QUETIAPINE-INDUCED RLS

A literature search was conducted using the term 'quetiapine' OR 'restless legs syndrome,' OR 'RLS' in Medline, EMBASE, and PsycINFO. Table 1 summarizes the results of that search limited to case reports of quetiapine-induced RLS [8,15-24]. Dosages of quetiapine administered in the studies ranged from 25 mg to 600 mg. Low as well as high dosages of quetiapine were seen to be capable of inducing RLS.

Table 1. Summary of case reports on restless legs syndrome caused by quetiapine

Reference	Onset age (yr)/sex	Dosage (mg)	Diagnosis	Concomitant psychotropics
Fountoulakis et al. [15]	28/F	200	BD	Li
Catalano et al. [16]	43/F	50	MDD	VFX, BZD
	27/F	25	MDD	None
Pinninti et al. [17]	68/F	200	BID	None
Urbano and Ware [18]	53/F	600	BIID	BZD, BUP, OCZ
	52/F	600	BID	BZD, OCZ
Chou et al. [19]	47/M	200	BID	VPA
Webb [20]	44/M	600	BID	None
Rittmannsberger and Werl [8]	65/M	250	MDD	VFX
	41/F	25	BIID	OCZ, TZD
	54/F	100	MDD	AMT, BZD
	66/F	50	MDD	DXT, MZP
	33/F	75	BPD	VPA, DXT, OCZ
	49/F	200	MDD	ESC, MZP
Michopoulos et al. [21]	61/M	150	MDD	VFX, BZD
	47/F	150	BIID	VFX
Vohra [22]	40/F	N/A	SAD	AMT
	43/F	300	BD	CTP
	39/F	250	MDD	FLX
	38/F	300	MDD	STR
Chen [23]	46/M	150	BIID	ESC, Li
Soyata et al. [24]	39/F	100	MDD	None

F: female, M: male, BID: bipolar I disorder, BIID: bipolar II disorder, MDD: major depressive disorder, BPD: borderline personality disorder, SAD: schizoaffective disorder, BD: bipolar disorder, Li: lithium, VFX: venlafaxine, BZD: benzodiazepine, BUP: bupropion, OCZ: oxcarbamazepine, VPA: valproate, TZD: trazodone, AMT: amitriptyline, DXT: duloxetine, MZP: mirtazapine, ESC: escitalopram, CTP: citalopram, FLX: fluoxetine, STR: sertraline

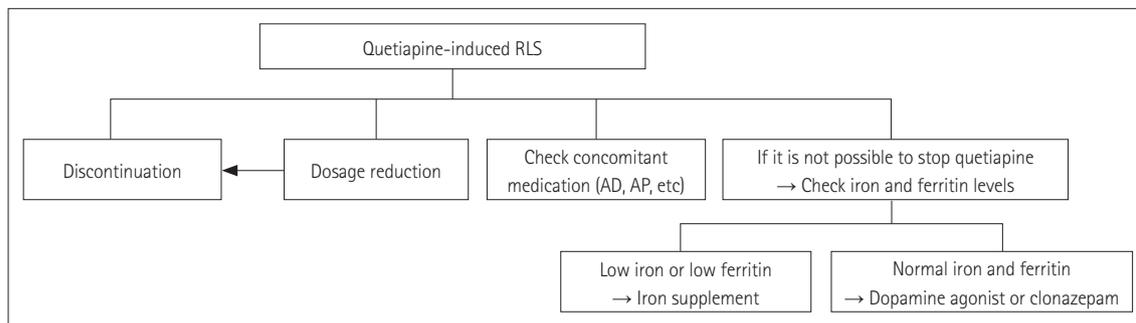


Figure 1. Treatment of quetiapine-induced RLS based on case reports. RLS: restless legs syndrome, AD: antidepressant, AP: antipsychotics.

A total of 22 cases of quetiapine-induced RLS have been reported. Among them, 17 patients were females, and 5 patients were males. These results were consistent with previous studies that reported a higher prevalence of primary RLS in women compared to men [25]. However, the small sample size limits the statistical power of this observation.

Mean age of all patients was 46.5 years. Mean ages of the males and females were 52.6 years and 44.7 years, respectively. A majority of the patients carried psychiatric diagnoses (bipolar disorder, $n=10$; major depressive disorder, $n=10$; schizoaffective disorder, $n=1$; borderline personality disorder, $n=1$). Investigators have hypothesized that depression and RLS could synergistically increase susceptibility to RLS [26]. And although strong evidence is lacking, the effects of concomitant administration of other medications such as antidepressants cannot be discounted. A proposed mechanism for this phenomenon involves inhibition of dopaminergic signaling by selective serotonin reuptake inhibitors [26]. Fourteen patients were being managed on a combination of quetiapine and an antidepressant (Table 1). Thus, the effects of antidepressant administration as well as quetiapine administration alone, and that of a possible interaction between an antidepressant and quetiapine on the incidence of RLS could not be individually assessed in those patients. However, in four of the other patients it was possible that quetiapine alone was responsible for the onset of RLS. In one of those patients, a single low dose (100 mg) of quetiapine is believed to have induced RLS. However, at the same time, there has been another report submitted to the literature that documents the mitigation of clonazepam-refractory RLS in a female patient after a single dose of low-dose (25–50 mg) quetiapine [27]. Thus, continued investigation of this matter is required.

The patients were on a wide variety of medications (venlafaxine, $n=4$; amitriptyline, $n=2$; mirtazapine, $n=2$; duloxetine, $n=2$; escitalopram, $n=2$; citalopram, $n=1$; fluoxetine, $n=1$; trazodone, $n=1$; sertraline, $n=1$; bupropion, $n=1$). Four patients were on oxcarbamazepine and two patients were on valproate.

TREATMENT OF QUETIAPINE-INDUCED RLS

Quetiapine-induced RLS is often readily identified, and symptoms usually improve on termination of quetiapine or a dosage re-

duction (Figure 1) [8,22]. In times when taking the patient off of quetiapine may be disadvantageous, the addition of a dopamine agonist such as ropinirole or pramipexole, and possibly clonazepam, may serve to mitigate RLS symptoms (Figure 1) [8,18,22]. In specific cases, determining serum iron and ferritin levels may be of benefit, as if there were to be a concurrent iron deficiency in a patient with quetiapine-induced RLS, iron supplementation may mitigate symptoms like other secondary RLS. Although there has been no report on iron supplement in a patient with quetiapine-induced RLS, some investigators reported the improvement in antipsychotic-induced akathisia with iron supplement in a patient with iron deficiency [28].

CONCLUSIONS

Quetiapine-induced RLS is more commonly encountered than that caused by other AAPs [8]. Although the primary pathophysiology has yet to be clearly identified, clinicians should be aware of this adverse effect of quetiapine. Further studies on this matter are necessary.

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Conflicts of Interest

The author has no potential conflicts of interest to disclose.

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REFERENCES

- Ekblom K, Ulfberg J. Restless legs syndrome. *J Intern Med* 2009;266:419-431.
- Satija P, Ondo WG. Restless legs syndrome: pathophysiology, diagnosis and treatment. *CNS Drugs* 2008;22:497-518.
- Aggarwal S, Dodd S, Berk M. Restless leg syndrome associated with atypical antipsychotics: current status, pathophysiology, and clinical implications. *Curr Drug Saf* 2015;10:98-105.
- Goldstein JM. Quetiapine fumarate (Seroquel): a new atypical antipsychotic. *Drugs Today (Barc)* 1999;35:193-210.
- Kumar R, Sachdev PS. Akathisia and second-generation antipsychotic drugs. *Curr Opin Psychiatry* 2009;22:293-299.
- Kane JM, Fleischhacker WW, Hansen L, Perlis R, Pikelov A 3rd, Assunção-

- Talbot S. Akathisia: an updated review focusing on second-generation antipsychotics. *J Clin Psychiatry* 2009;70:627-643.
7. Kapur S, Zipursky R, Jones C, Shammi CS, Remington G, Seeman P. A positron emission tomography study of quetiapine in schizophrenia: a preliminary finding of an antipsychotic effect with only transiently high dopamine D2 receptor occupancy. *Arch Gen Psychiatry* 2000;57:553-559.
 8. Rittmannsberger H, Werl R. Restless legs syndrome induced by quetiapine: report of seven cases and review of the literature. *Int J Neuropsychopharmacol* 2013;16:1427-1431.
 9. Ondo WG. Restless legs syndrome. *Curr Neurol Neurosci Rep* 2005;5:266-274.
 10. Blwise DL, Zhang RH, Kutner NG. Medications associated with restless legs syndrome: a case-control study in the US Renal Data System (USRDS). *Sleep Med* 2014;15:1241-1245.
 11. Lai YY, Hsieh KC, Cheng YH, Chew KT, Nguyen D, Ramanathan L, et al. Striatal histamine mechanism in the pathogenesis of restless legs syndrome. *Sleep* 2019 Oct 31 [Epub]. Available at: <https://doi.org/10.1093/sleep/zsz223>.
 12. Patatanian E, Claborn MK. Drug-induced restless legs syndrome. *Ann Pharmacother* 2018;52:662-672.
 13. Kang SG, Lee HJ, Jung SW, Cho SN, Han C, Kim YK, et al. Characteristics and clinical correlates of restless legs syndrome in schizophrenia. *Prog Neuropsychopharmacol Biol Psychiatry* 2007;31:1078-1083.
 14. Ferini-Strambi L. RLS-like symptoms: differential diagnosis by history and clinical assessment. *Sleep Med* 2007;8 Suppl 2:S3-S6.
 15. Fountoulakis KN, Iacovides A, Kaprinis SG, Kaprinis GS. Diffuse muscle pain with quetiapine. *Br J Psychiatry* 2003;182:81.
 16. Catalano G, Grace JW, Catalano MC, Morales MJ, Cruse LM. Acute akathisia associated with quetiapine use. *Psychosomatics* 2005;46:291-301.
 17. Pinninti NR, Mago R, Townsend J, Doghramji K. Periodic restless legs syndrome associated with quetiapine use: a case report. *J Clin Psychopharmacol* 2005;25:617-618.
 18. Urbano MR, Ware JC. Restless legs syndrome caused by quetiapine successfully treated with ropinirole in 2 patients with bipolar disorder. *J Clin Psychopharmacol* 2008;28:704-705.
 19. Chou KJ, Chen PY, Huang MC. Restless legs syndrome following the combined use of quetiapine and paroxetine. *Prog Neuropsychopharmacol Biol Psychiatry* 2010;34:1139-1140.
 20. Webb J. Co-occurring akathisia and restless legs syndrome likely induced by quetiapine. *J Neuropsychiatry Clin Neurosci* 2012;24:E46-E47.
 21. Michopoulos I, Ferentinos P, Oulis P, Gournellis R. Restless legs syndrome associated with the combined use of quetiapine and venlafaxine. *J Clin Psychopharmacol* 2014;34:159-161.
 22. Vohra A. Quetiapine induced restless legs syndrome: a series of four cases. *Asian J Psychiatr* 2015;16:73-74.
 23. Chen PH. Restless leg syndrome induced by escitalopram and lithium combined with quetiapine treatment in bipolar II disorder: a case report. *Clin Neuropharmacol* 2016;39:118-119.
 24. Soyata AZ, Celebi F, Yargc LI. Restless legs syndrome after single low dose quetiapine administration. *Curr Drug Saf* 2016;11:172-173.
 25. Garcia-Borreguero D, Egatz R, Winkelmann J, Berger K. Epidemiology of restless legs syndrome: the current status. *Sleep Med Rev* 2006;10:153-167.
 26. Picchiatti D, Winkelmann JW. Restless legs syndrome, periodic limb movements in sleep, and depression. *Sleep* 2005;28:891-898.
 27. Boku S, Hirota M, Yoshida H, Homma H, Iwasaki S, Matsubara S. A case of restless legs syndrome successfully treated with quetiapine. *Sleep Biol Rhythms* 2006;4:193-195.
 28. Cotter PE, O'Keefe ST. Improvement in neuroleptic-induced akathisia with intravenous iron treatment in a patient with iron deficiency. *J Neurol Neurosurg Psychiatry* 2007;78:548.