Restless legs syndrome induced by quetiapine: report of seven cases and review of the literature

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Abstract
We report on seven cases of restless legs syndrome (RLS) in patients treated with quetiapine. Small doses (50–250 mg at bedtime) provoked RLS in a dose-dependent way. Most patients suffered from an affective disorder and all were treated concomitantly with antidepressants. A search of the literature revealed a further nine cases of RLS concerning quetiapine, also afflicting only patients with affective disorders. Quetiapine seems to carry a special risk for RLS in this sort of patient. Possible causes for this concurrence are discussed.

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Key words: Affective disorder, antidepressant, quetiapine, restless legs syndrome, second generation antipsychotic.

Introduction
Restless legs syndrome (RLS) is defined as: an urge to move the legs, usually accompanied by unpleasant sensations in the legs; beginning or worsening during inactivity; relief by movement; preponderance in evening or night (Allen et al., 2003). RLS occurs as an illness in its own right with major genetic factors as an aetiological background but also in a secondary form with iron deficiency, pregnancy, kidney diseases and rheumatic diseases as the most important risk factors (Ekbom and Ulfberg, 2009). Beyond this, multiple drugs have been described to induce or to exacerbate RLS, among them dopamine D2 receptor antagonists, histamine receptor antagonists, antidepressants, lithium and caffeine (Satija and Ondo, 2008).

We report seven cases of RLS in which initiation or increase of dose of quetiapine rapidly induced marked RLS.

Case reports
Patient 1 was a male aged 65 yr, referred to psychiatric inpatient treatment for a major depressive episode, recurrent type. For various medical conditions he had been on a regimen of 3 mg phenprocoumon, 5 mg nebivolol, 20 mg lisinopril, 25 mg hydrochlorothiazide, 20 mg simvastatin and 40 mg pantoprazole for >6 months. Psychopharmacological treatment was started with 75 mg venlafaxine and up-titrated to 225 mg (225–0–0 mg) within 1 wk. At the same time 50 mg quetiapine was added at bedtime for difficulties with falling asleep and as an add-on antidepressant medication. Dose was increased to 100 mg (25–25–50 mg) after 4 d and to 200 mg (50–50–100 mg) after 10 d (counting from starting-day of quetiapine). When on day 15 the major part of the dose was shifted towards the evening (25–25–150 mg) the patient started complaining of nightly aches in both knees, which made him uncomfortable and restless and prevented him from sleep. Since the patient was known to suffer from gonarthrosis an analgesic was added, first 50 mg diclofenac p.r.n. Because of the difficulties with sleeping the dose of quetiapine was increased to 250 mg (25–25–200 mg) on day 30, but sleep did not improve and pains got rather worse. Since diclofenac did not prove effective the treatment was changed to 500 to 1000 mg metamizole and finally 100 mg tramadol was added. The patient was severely disturbed by the nightly pains and the accompanying restlessness and neither analgesics nor quetiapine brought any relief. He observed that the aches started every night at the same time, about 1.5 h after receiving his bedtime medication. In order to explore whether the symptoms were in conjunction with the medication he varied the time of ingestion, taking quetiapine very early one night and the next very late. Indeed the onset of the aches was coupled with the ingestion of quetiapine. Cessation of treatment with quetiapine then led to immediate and complete disappearance of the pains.

Patient 2 was a female aged 41 yr suffering from bipolar II disorder, depressive episode, on a stable medication with 300 mg oxcarbazepine t.i.d. and 150 mg trazodone at bedtime for >1 yr. Quetiapine was started with 25 mg at bedtime. About 3 h later the patient...
complained about unpleasant feelings and an urge to move in both lower legs. The complaints extended to the upper legs and lasted for approximately 12 h. This was the first and only dose of quetiapine. Cessation of quetiapine ended the complaints and no symptoms of RLS were observed during further treatment.

Patient 3 was a female aged 54 yr suffering from major depressive disorder, recurrent. Treatment was started with 50 mg amitriptyline q.h.s., 50 mg quetiapine q.h.s. and 1 mg lorazepam t.i.d. The next day quetiapine was increased to 100 mg q.h.s. That night the patient complained about an ‘unquiet’ feeling in her legs and continuous movements of her legs, preventing her from falling asleep. Treatment with quetiapine was stopped and no further complaints of RLS were reported. Amitriptyline was continued with a maximum dose of 150 mg q.h.s. without recurrence of RLS. The patient reported that she had experienced RLS once before when she had been treated with 45 mg mirtazapine q.h.s. (whereas a 15 mg dose was tolerated).

Patient 4 was a female aged 66 yr diagnosed with major depressive disorder, recurrent. She suffered from tinnitus and tension headaches and had undergone an evaluation of sleep to rule out epilepsy. On that occasion periodic limb movement syndrome (PLMS) had been diagnosed. On admission she had been on a regimen of 60 mg duloxetine (60–0–0 mg) and 150 mg trazodone q.h.s. for about 3 yr. When trazodone was replaced with 15 mg mirtazapine she complained about 2 d about uncomfortable sensations in her legs and an urge to move when in bed. In this patient treatment of RLS was started with 0.088 mg pramipexole q.h.s., which proved effective. An increase of mirtazapine to 30 mg was feasible without provoking symptoms of RLS. Treatment with 50 mg quetiapine q.h.s. was started 10 d later, which led to recurrence of the same symptoms of RLS on the first night. Quetiapine (50 mg) was given for 3 d more, always leading to the same symptoms. Omission of quetiapine led to immediate cessation of the complaints.

Patient 5 was a female aged 33 yr with borderline personality disorder on a steady medication with 90 mg duloxetine (90–0–0 mg) that had been on-going for 3 yr. Treatment was started with 300 mg valproate b.i.d. and increased to 500 mg b.i.d. the next day. After 2 d, 15 mg oxazepam b.i.d. and 50 mg quetiapine q.h.s. were added. Quetiapine was increased to 75 mg 2 d later. On the second night the patient complained of a ‘prickling’ feeling in her feet, worse at rest and in bed. The patient reported that she had been on quetiapine previously (100–200 mg q.h.s.) and had been suffering from the same sensations. Since quetiapine’s effect on sleep was beneficial, 0.35 mg pramipexole was added, which improved the symptoms immediately. At time of discharge the patient was on quetiapine (100 mg q.h.s.) and took pramipexole on a p.r.n. basis about every other night.

Patient 6 was a female aged 49 yr, an in-patient suffering from a first episode of major depression with psychotic features, which had been lasting for 3 months. She was treated with 20 mg escitalopram (20–0–0 mg), 3.5 mg lorazepam (0.5–0.5–2.5 mg) and 150 mg trazodone at bedtime for about 3 wk when 100 mg quetiapine was added at bedtime. After 3 d, quetiapine was increased to 200 mg q.h.s. After another 4 d trazodone was replaced by 15 mg mirtazapine, which was raised to 30 mg q.h.s. 2 d later. That night the patient started complaining about a ‘twITCHING’ of her legs and an inability to hold them still. Over the next week dosage of quetiapine was gradually reduced to 100 mg q.h.s. With this dosage RLS disappeared. As the patient still complained about difficulties falling asleep an increased dosage of quetiapine to 200 mg q.h.s. was tried 1 wk later. That same night symptoms of RLS reappeared. She was kept for two further nights on the same regimen, which resulted in the same problems. Then quetiapine was stopped and so did complaints from RLS. Afterwards the patient was given 80 mg prothipendyl for sleep instead of quetiapine without recurrence of RLS.

Patient 7 was a male aged 61 yr, who had been suffering from recurrent major depressive episode for about 3 months. Treatment was started with venlafaxine (up-titrated to 300–0–0 mg until day 7), 4.5 mg lorazepam (1–1–2.5 mg) and quetiapine (up-titrated to 150 mg q.h.s. until day 12). The dose of lorazepam was then gradually reduced to a daily total dose of 2.5 mg (0.5–0–2 mg). When the evening dose of lorazepam was lowered from 2 to 1 mg at day 22 the patient started to complain about multiple interruptions of sleep caused by uncomfortable feelings in the legs and an urge to move the legs. He was kept on the same medication for a further 8 d with the nightly complaints waxing and waning. The symptoms abated when the dose of quetiapine was reduced to 100 mg q.h.s.

Discussion

These cases have some features in common (Table 1): all but one patient suffered from affective disorders; all patients were on a treatment with some kind of antidepressant when quetiapine was added; RLS occurred at very small to moderate doses (25–250 mg) in a dose-dependent way, manifesting itself with an increase of dose and abating with reduction (patients 1, 6 and 7).

There are special features about some of these cases. In patient 1 we attributed his pains to his gonarthrosis until he himself discovered the relation with quetiapine. Now there is no doubt that these pains had been caused by quetiapine, since they were intractable with various analgesics but resolved miraculously with cessation of quetiapine. It might be questionable whether it is appropriate to list this case under the title of RLS, yet some authors mention that occasionally RLS can manifest as ‘true pain’ (Allen et al., 2003; Ekbom and Ulfborg, 2009). Fountoulakis et al. (2003) reported a quite similar case. Patient 4, with PLMS, a condition closely related to RLS...
(Allen et al., 2003), had been diagnosed some months earlier, yet with us she had complained neither about PMLS nor RLS until treatment with mirtazapine was started. There are some reports about RLS induced by mirtazapine (Prospero-Garcia et al., 2006; Kim et al., 2008). In this case we decided to treat RLS symptomatically with a dopaminergic agent, which proved successful, as has been shown in some other cases (Urbano and Ware, 2008). Under concomitant treatment with 0.088 mg pramipexole it was possible to raise the dose of mirtazapine to 30 mg without recurrence of RLS. Adding quetiapine started the symptoms anew, demonstrating the liability of quetiapine to promote RLS. That pramipexole can be helpful in cases of drug-induced RLS was also demonstrated by patient 5. In patient 7 we presume that lowering the dose of lorazepam had unmasked RLS.

We conducted a literature search using the term ‘quetiapine’ in conjunction with ‘restless legs’, ‘RLS’ and ‘Ekbom syndrome’ in Medline, EMBASE and PsychINFO and were able to identify nine cases of quetiapine actually inducing RLS (Table 2). In all instances the patients suffered from affective disorders. One report resembles the complaints that patient 1 had suffered (Fountoulakis et al., 2003). The patients presented by Catalano et al. (2005) are diagnosed with akathisia although the description very clearly points to an additional RLS. This leads to the question of differential diagnosis between RLS and akathisia. RLS differs from akathisia as it occurs only at bedtime and the accompanying paresthesia predominantly affects the lower extremity, whereas akathisia mainly occurs during daytime and is characterized by a general inner restlessness (Ferini-Strambi, 2007; Ekbom and Ulfberg, 2009). There certainly exists some overlap between syndromes as there are cases in which both are present (Catalano et al., 2005; Webb, 2012) and, under treatment with antipsychotics, patients with pre-existing RLS have been shown to develop akathisia much more frequently than patients without RLS (Young et al., 2003). In our patients diagnosis was performed applying the criteria proposed by the International Restless Legs Syndrome Study Group (Allen et al., 2003) and none suffered from clinically obvious symptoms of akathisia.

Considering the worldwide use of quetiapine for about the last 20 yr, the number of reports is small. On the other hand our seven cases seem to indicate that this side-effect is not so rare and might affect quetiapine more than other antipsychotics. We are monitoring the patients in our department for side-effects in the framework of the AMSP project (Grohmann et al., 2004). The cases collected here stretch over a period of >4 yr and during this time we observed only cases involving quetiapine and no other antipsychotic. Thus, the question is whether there is something special about quetiapine to induce RLS. Assuming a causative role of a hypodopaminergic state (Ekbom and Ulfberg, 2009) quetiapine should be the least likely candidate among second generation antipsychotics to cause RLS. Quetiapine has an especially low propensity to induce extrapyramidal symptoms and its likelihood to induce akathisia is comparable to placebo (Kane et al., 2009; Kumar and Sachdev, 2009). The low level of motoric side-effects has been contributed to its loose binding to dopamine D_2 receptors (Seeman and Tallerico, 1999) and limbic selectivity (Nemeroff et al., 2002). Maybe its initial transient high binding to D_3 receptors (Kapur et al., 2000; Nemeroff et al., 2002) could explain the occurrence of RLS about 1 h after ingestion. Also quetiapine’s high affinity for histamine H_1 receptors might be of importance, since antihistaminic agents have also been found to induce RLS (Ondo, 2005). Nevertheless, it is hard to explain why quetiapine should have a higher propensity to induce RLS than other antipsychotics.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Diagnoses</th>
<th>Sex, age (yr)</th>
<th>Co-medication and dose</th>
<th>Quetiapine dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Major depression</td>
<td>Male, 65</td>
<td>Venlafaxine ER 225 mg</td>
<td>250 mg q.h.s.</td>
</tr>
<tr>
<td>2</td>
<td>Bipolar II disorder, depressive episode</td>
<td>Female, 41</td>
<td>Trazodone 150 mg</td>
<td>25 mg q.h.s.</td>
</tr>
<tr>
<td>3</td>
<td>Major depression</td>
<td>Female, 54</td>
<td>Oxcarbazepine 900 mg</td>
<td>50 mg q.h.s.</td>
</tr>
<tr>
<td>4</td>
<td>Major depression</td>
<td>Female, 66</td>
<td>Amitryptiline 50 mg</td>
<td>50 mg q.h.s.</td>
</tr>
<tr>
<td>5</td>
<td>Borderline personality disorder</td>
<td>Female, 33</td>
<td>Lorazepam 3 mg</td>
<td>75 mg q.h.s.</td>
</tr>
<tr>
<td>6</td>
<td>Major depression</td>
<td>Female, 49</td>
<td>Duloxetine 60 mg</td>
<td>200 mg q.h.s.</td>
</tr>
<tr>
<td>7</td>
<td>Major depression</td>
<td>Male, 61</td>
<td>Lorazepam 3 mg</td>
<td>150 mg q.h.s.</td>
</tr>
</tbody>
</table>

Table 1. Overview of patients with restless legs syndrome: diagnoses and medications

Restless legs syndrome induced by quetiapine
A possible explanation for the accumulation of cases involving quetiapine could be found in its special patterns of clinical use. It is not only licensed for the treatment of depression but is also known to have good hypnotic properties (Cohrs et al., 2004). This makes quetiapine a quite popular drug in the treatment of affective disorders (Philip et al., 2008) and it is given preferentially at bedtime. The observed frequency of RLS then might reflect the fact that no other second generation antipsychotic is used so often in this way. All patients found in the literature and all but one patient of our cases suffered from affective disorders. Remarkably, no patient with psychotic disorders, where quetiapine is used far more frequently and in higher dosage, came to our attention for RLS. Depression and RLS can mutually induce each other and depressive patients therefore carry a heightened risk for RLS (Picchietti and Winkelman, 2005). Probably more important is the fact that all of our patients were treated concomitantly with antidepressants, where especially selective serotonin reuptake inhibitors, mirtazapine, and tricyclic antidepressants (as well as lithium) have been reported to cause RLS (Ondo, 2005; Prospero-Garcia et al., 2006; Kim et al., 2008; Chopra et al., 2011). Two of our patients (4 and 6) first developed RLS during treatment with antidepressants and initiation of quetiapine led to recurrence. Antidepressant × quetiapine interactions are most probably of a pharmacodynamic and not of a pharmacokinetic nature since RLS occurred in conjunction with quite different antidepressants, at low doses and rather quickly after start of treatment. Quetiapine then only appeared as causative as it is used mostly as an add-on therapy augmenting a pre-existing antidepressant therapy. In conclusion, our observations indicate that quetiapine as an add-on therapy for depression might increase the risk for RLS. The pathophysiologic mechanisms remain obscure. Further investigations concerning

<table>
<thead>
<tr>
<th>Author</th>
<th>Diagnoses</th>
<th>Sex, age (yr)</th>
<th>Co-medication and dose</th>
<th>Quetiapine dose</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fountoulakis et al. (2003)</td>
<td>Bipolar disorder</td>
<td>Female, 28</td>
<td>Lithium</td>
<td>200 mg</td>
<td>Pain in knees 24 h after first dose; no EPS, no restlessness reported</td>
</tr>
<tr>
<td>Catalano et al. (2005)</td>
<td>Depression, pain</td>
<td>Female, 43</td>
<td>Venlafaxine ER 150 mg, Lorazepam 2 mg</td>
<td>50 mg q.h.s.</td>
<td>Daytime akathisia; awakes nightly and has to walk around ‘to get the nervous energy out of my legs’</td>
</tr>
<tr>
<td>Catalano et al. (2005)</td>
<td>Depression, panic, Pain</td>
<td>Female, 27</td>
<td>Oral contraceptive</td>
<td>25 mg q.h.s.</td>
<td>Typically RLS</td>
</tr>
<tr>
<td>Pinninti et al. (2005)</td>
<td>Bipolar I</td>
<td>Female, 68</td>
<td>Lithium</td>
<td>200 mg q.h.s.</td>
<td>Reduction to 150 mg resolved the symptoms. Rechallenge with 200 mg led to reappearance of RLS</td>
</tr>
<tr>
<td>Anon. (2006)</td>
<td>Bipolar disorder</td>
<td>Female, 68</td>
<td>Lithium</td>
<td>200 mg</td>
<td>Reduction to 150 mg resolved symptoms, increasing dose lead to reoccurrence</td>
</tr>
<tr>
<td>Urbano and Ware (2008)</td>
<td>Bipolar II, pain</td>
<td>Female, 53</td>
<td>Clonazepam, lorazepam, bupropion, oxcarbazepine, narcotic</td>
<td>200 mg q.h.s.</td>
<td>Additional 1 mg ropinirole allows a dosage of 600 mg quetiapine without complaints with RLS</td>
</tr>
<tr>
<td>Urbano and Ware (2008)</td>
<td>Bipolar disorder</td>
<td>Female, 52</td>
<td>Atenolol</td>
<td>600 q.h.s.</td>
<td>Start with increase of dosage to 600 mg. Successful treatment with 0.25 mg ropinirole</td>
</tr>
<tr>
<td>Chou and Chen (2010)</td>
<td>Bipolar disorder</td>
<td>Male, 47</td>
<td>Valproic acid 700 mg, Paroxetine 12.5 mg</td>
<td>200 mg q.h.s.</td>
<td>Start of RLS with first dose</td>
</tr>
<tr>
<td>Webb (2012)</td>
<td>Bipolar disorder</td>
<td>Male, 44</td>
<td>None</td>
<td>600 mg q.h.s.</td>
<td>Severe RLS with mild daytime akathisia</td>
</tr>
</tbody>
</table>

EPS, Extra-pyramidal symptoms.
the frequency and possible pathomechanisms are necessary.

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