

Quetiapine-Induced Enuresis: Two Case Reports

Forouzan Elyasi,^{1,2,*} and Hadi Darzi³

¹Department of Psychiatry, School of Medicine, Mazandaran University of Medical Sciences, Sari, Iran

²Psychiatry and Behavioral Sciences Research Center, Addiction Institute, Mazandaran University of Medical Sciences, Sari, Iran

³School of Medicine, Mazandaran University of Medical Sciences, Sari, Iran

*Corresponding author: Forouzan Elyasi, Psychiatry and Behavioral Sciences Research Center, Addiction Institute, Zare Hospital, Neka Road, Sari, Mazandaran, Iran. Tel: +98-9111551097, Fax: +98-1133285659, E-mail: forouzan.el@gmail.com

Received 2016 April 03; Revised 2016 July 03; Accepted 2017 April 15.

Abstract

Quetiapine is an effective and well-tolerated atypical dibenzothiazepine antipsychotic with higher affinity for 5-hydroxytryptophan than D2 dopamine receptors. It is a generally well-tolerated drug, yet, is remotely associated with urinary incontinence. Urinary incontinence is an embarrassing and distressing side effect of antipsychotic drugs. This paper reports on 2 patients with bipolar disorder, who developed urinary incontinence after treatment with quetiapine, and suggests dose reduction as the proper method for addressing this side effect. Nocturnal enuresis should be enquired through direct yet sensitive questions. The inevitable corollary is that patients treated with quetiapine should be properly monitored for nocturnal enuresis. A proper response to this side effect does not necessarily cease the antipsychotic medication.

Keywords: Antipsychotics, Bipolar Disorders, Enuresis, Quetiapine, Urinary Incontinence

1. Introduction

Quetiapine fumarate (ICI 204,636, (Seroquel)) is a widely prescribed atypical anti-psychotic. Urinary incontinence is a rare side effect of quetiapine with potentially adverse impacts on the efficacy of treatment. The first appearance of chlorpromazine-induced Urinary Incontinence (UI) in psychiatry literature dates back to 1955 (1). In 1979, Nurnberg and Ambrosini reported several cases of UI in patients taking phenothiazines and haloperidol (2). Several conventional antipsychotics, including chlorpromazine, thioridazine, chlorprothixene, thiothixene, trifluoperazine, fluphenazine (including enanthate and decanoate), haloperidol, and pimozide are known to be associated with UI (3, 4). Nocturnal Enuresis or bed-wetting is a less-known side effect of atypical antipsychotics (5). A growing number of evidence attributes this side effect to second-generation antipsychotics, especially clozapine (6). The prevalence of risperidone-induced enuresis is less than 1% (7).

There are very few reports on olanzapine-induced UI (8). A clinical trial has reported the incontinence/nocturia rates of olanzapine, risperidone, and quetiapine as 1%, 3%, and 4%, respectively (9). Until 2003, there was no evidence of quetiapine and ziprasidone-induced UI (10). Aripiprazole-induced UI is a very rare side effect that was first observed during pre-marketing evaluations of the drug's oral form (11). This paper reports on 2 patients with bipolar disorder, who experienced quetiapine-induced urinary incontinence.

2. Case Presentation

2.1. Case 1

The patient in case 1 was a 34-year-old male diagnosed with bipolar disorder. He had been initially treated with lithium and perphenazine until lithium-induced renal failure, which occurred months before the start of this study, and forced the physician to stop this treatment. The treatment was then changed to sodium valproate (1200 mg/day), perphenazine (24 mg/day), and biperiden (4 mg/day). At that point, the patient had a serum creatinine of 2 mg/dL, yet about a month before the start of this report, the patient exhibited an irritable mood with racing thoughts and jealousy delusions. This made his physician add quetiapine to the previous treatment. The starting dose was 100 mg/day and was increased after 4 days to 400 mg/day. One week after the start of the new treatment, the patient was hospitalized because of lethargy as well as daytime and nighttime urinary incontinence. At that point, the serum creatinine of the patient was 5.9 mg/dL. Physical and neurological examinations did not indicate any abnormal issues. Fasting blood glucose, urinalysis, thyroid function tests, and urine drug screening were all normal and negative.

The episodes of urinary incontinence stopped 24 hours after reducing the dose of quetiapine. After reducing the dose of sodium valproate and perphenazine, serum creatinine of the patient decreased to 2 mg/dL. This patient was observed for 2 years after hospitalization and did not ex-

perience any other episode of urinary incontinence even after taking 150 mg/day of quetiapine.

2.2. Case 2

The second case was a 65-year-old female, who had been referred to the psychosomatic clinic due to hallucinations and disorientation regarding time and place. Her family reported a 4-week history of verbal aggression, irritability, labile mood, self-talk, loss of appetite, and insomnia. Her psychiatric history showed 2 previous episodes of mania, which had occurred 35 and 20 years earlier. She had not experienced any other mood-change episode during the past 20 years. There was no history of substance abuse. The history and clinical interviews led to the diagnosis of bipolar disorder type I. Four days prior to her visit, the patient had visited another psychiatrist, who had prescribed lithium (900 mg/day), perphenazine (24 mg/day), trihexyphenidyl, (6 mg/day), and risperidone (2 mg/day).

Delirium became superimposed on mixed episodes of bipolar disorder. The patient's family strictly opposed hospitalization. The psychotropic treatment was stopped and only haloperidol (0.5 mg/day) was administered. Meanwhile, several laboratory tests were performed leading to normal results except for blood glucose, which was affected by diabetes. Delirium subsided after 1 week, yet symptoms of mixed episodes were still prominent. Haloperidol treatment was stopped and the patient was given quetiapine, starting with a dose of 12.5 mg/day (taken at night), which was then to 25 mg after 3 days and to 300 mg after 2 weeks (100 mg at noon and 200 mg at night). The patient showed an acceptable response to this treatment. Five days after increasing the quetiapine dosage to 300 mg, the patient started to experience nocturnal enuresis. There was no personal and family history of urinary incontinence, dysuria, pelvic trauma, and urgency. There was also no history of urinary tract symptom. Neurological examination did not reveal any relevant findings and urine cultures were negative. To address the issue, the authors reduced the nightly doses of quetiapine (changing it to 50 mg in the morning, 100 mg at noon, and 150 mg at night). The patient's UI problem subsided 1 week after rearranging the daily intake of quetiapine.

3. Discussion

In both of the cases outlined above, quetiapine was the most likely cause of urinary incontinence, since UI symptoms started after the patients started to take quetiapine and disappeared shortly after the dosage reduction. Urinary incontinence is a rarely reported side effect of quetiapine. Interestingly, some articles have stated that re-

placement of risperidone with a low potent peripheral (α -1)adrenergic antipsychotic like quetiapine and olanzapine is a potentially good therapeutic strategy for dealing with risperidone-induced urinary incontinence (7, 12).

Quetiapine-induced urinary incontinence seems to be as rare as urinary incontinence caused by other neuroleptics. In 2011, a study compared the prevalence of nocturnal enuresis in patients treated with clozapine against those treated with risperidone, olanzapine, or quetiapine.

The pathophysiology of antipsychotic-induced urinary incontinence is still unclear, yet several mechanisms have been proposed. One of these suggested mechanisms is associated with anticholinergic effects of atypical antipsychotic on the bladder, which leads to inhibition of detrusor contraction with consequent overflow of urine (13). A general explanation for neuroleptic-induced urinary incontinence is that it is caused mostly by α -adrenergic blockade, moderately by dopamine blockade, and minimally by cholinergic effects on the bladder (10).

Urinary incontinence and enuresis associated with α -adrenergic blockade causes urinary sphincter relaxation in anatomically predisposed patients (1). The absence of other systemic hypo adrenergic effects such as hypertension shows that α -adrenergic blockade cannot accurately explain urinary incontinence. The early speculations about neuroleptic-induced UI leads to a centrally mediated mechanism (2). An experimental study on animals has shown that the olanzapine and to a lesser extent risperidone, effect a number of voiding parameters, which collectively lead to reduced micturition volume, increased residual volume of the bladder, and decreased activity of external urethral sphincter. The study elucidated that the mechanism of these effects may be more central rather than peripheral (14).

In a study on participants, who experienced UI after treatment with an atypical antipsychotic, urodynamic examinations showed that one-third of participants had detrusor over-activity, while another one-third had reduced bladder compliance (15). It was then suggested that neuroleptics may cause UI through several mechanisms, and there may be different individual susceptibilities. In support of this belief, case reports and case series have shown that clozapine-induced enuresis could be successfully treated with anticholinergics (trihexyphenidyl and oxybutynin), α -1 agonists (ephedrine), antidepressants (amitriptyline), desmopressin, or by adding a second antipsychotic to clozapine (aripiprazole) (16-18). As postulated in a case report, central dopaminergic-serotonergic activity combined with peripheral α -adrenergic blockade may act synergistically and predispose a patient to urinary dysfunction.

The lower urinary tract is controlled by several neuro-

transmitter pathways, to which antipsychotics have affinity. These neurotransmitters include serotonin (which facilitates urine storage and inhibits voiding), dopamine (blockade in the basal ganglia, which may cause involuntary enuresis), acetylcholine (which has a direct effect on bladder contractility) and adrenergic (which has significant impact on the regulation of bladder outlet function, especially in males).

The sedative effects of antipsychotics may lead to the inability of the patients to wake-up, leading to enuresis (19). Quetiapine is also sedative, and it can therefore be argued that some patients may enjoy a deeper sleep, thus failing to notice the need for voiding.

This hypothesis cannot properly explain this urinary incontinence because deep sleep is not exclusively sedation-induced, and is by no means strongly associated with enuresis (6).

In the cases reported in this paper, the improvement of urinary incontinence after administration of lower nightly doses of quetiapine and shifting the dose to day hours may support the hypothesis of the sedative role of these drugs in developing urinary incontinence.

3.1. Conclusion

Urinary incontinence is a stressful and awkward side effect of antipsychotics. Once left untreated, it may lead to noncompliance of patients undergoing distress. The prevalence of urinary incontinence and enuresis may be under-reported. This side effect has a profound impact on both patients and their caregivers. The ignominious and uncomfortable nature of this symptom, coupled with constant need for cleaning and laundering the bed linens and the ongoing concern about the cause of symptoms, may lead to mental exhaustion and subjective burden. This can leave significantly adverse effects on the quality of life of a patient.

Mental health clinicians and personnel should directly ask patients about this issue, explain it to them, and discuss the options available to patients for managing symptoms.

Footnotes

Authors' Contribution: Forouzan Elyasi performed primary and psychiatric evaluation of the cases and interpretation of clinical data, drafted the manuscript, and revised it according to the reviewers' comments. Hadi Darzi performed the English editing of the manuscript. Both authors read and approved the final manuscript.

Declaration of Interest: The authors declared that they have no competing interests.

Consent: Written informed consent was obtained from the 2 patients for the publication of this report.

Funding/Support: There was no funding.

References

1. Lomas J, Boardman RH, Markowe M. Complications of chlorpromazine therapy in 800 mental-hospital patients. *Lancet*. 1955;**268**(6875):1144-7. doi: [10.1016/S0140-6736\(55\)90642-5](https://doi.org/10.1016/S0140-6736(55)90642-5). [PubMed: [14382518](https://pubmed.ncbi.nlm.nih.gov/14382518/)].
2. Nurnberg HG, Ambrosini PJ. Urinary incontinence in patients receiving neuroleptics. *J Clin Psychiatry*. 1979;**40**(6):271-4. [PubMed: [36372](https://pubmed.ncbi.nlm.nih.gov/36372/)].
3. Shapiro AK. Pimozide-induced enuresis. *Am J Psychiatry*. 1981;**138**(1):123-4. [PubMed: [6934699](https://pubmed.ncbi.nlm.nih.gov/6934699/)].
4. Ambrosini PJ, Nurnberg HG. Enuresis and incontinence occurring with neuroleptics. *Am J Psychiatry*. 1980;**137**(10):1278-9. doi: [10.1176/ajp.137.10.aj137101278](https://doi.org/10.1176/ajp.137.10.aj137101278). [PubMed: [6106394](https://pubmed.ncbi.nlm.nih.gov/6106394/)].
5. Harrison-Woolrych M, Skegg K, Ashton J, Herbison P, Skegg DC. Nocturnal enuresis in patients taking clozapine, risperidone, olanzapine and quetiapine: comparative cohort study. *Br J Psychiatry*. 2011;**199**(2):140-4. doi: [10.1192/bjp.bp.110.087478](https://doi.org/10.1192/bjp.bp.110.087478). [PubMed: [21653944](https://pubmed.ncbi.nlm.nih.gov/21653944/)].
6. Barnes TR, Drake MJ, Paton C. Nocturnal enuresis with antipsychotic medication. *Br J Psychiatry*. 2012;**200**(1):7-9. doi: [10.1192/bjp.bp.111.095737](https://doi.org/10.1192/bjp.bp.111.095737). [PubMed: [22215862](https://pubmed.ncbi.nlm.nih.gov/22215862/)].
7. Ghanizadeh A, Kianpoor M. Cessation of risperidone-induced incontinence by valproate in a child with pervasive developmental disorder. *Prim Psychiatry*. 2008;**15**(4):324.
8. Sagar R, Varghese ST, Balhara YP. Olanzapine-induced double incontinence. *Indian J Med Sci*. 2005;**59**(4):163-4. [PubMed: [15876782](https://pubmed.ncbi.nlm.nih.gov/15876782/)].
9. Stroup TS, Lieberman JA, McEvoy JP, Swartz MS, Davis SM, Rosenheck RA, et al. Effectiveness of olanzapine, quetiapine, risperidone, and ziprasidone in patients with chronic schizophrenia following discontinuation of a previous atypical antipsychotic. *Am J Psychiatry*. 2006;**163**(4):611-22. doi: [10.1176/appi.ajp.163.4.611](https://doi.org/10.1176/appi.ajp.163.4.611). [PubMed: [16585435](https://pubmed.ncbi.nlm.nih.gov/16585435/)].
10. Clark N. Conventional antipsychotic and clozapine-induced urinary incontinence. *J Coll Psychiatr Neurolog Pharma*. 2003;**2**:1-8.
11. Bozkurt H, Abali O. Aripiprazole-induced enuresis in a child with autistic disorder. *Arch Neuropsych*. 2011;**48**:164-6.
12. Kantrowitz JT, Srihari VH, Tek C. Three cases of risperidone-induced enuresis. *Schizophr Res*. 2006;**84**(1):174-5. doi: [10.1016/j.schres.2006.01.023](https://doi.org/10.1016/j.schres.2006.01.023). [PubMed: [16564679](https://pubmed.ncbi.nlm.nih.gov/16564679/)].
13. Warner JP, Harvey CA, Barnes TR. Clozapine and urinary incontinence. *Int Clin Psychopharmacol*. 1994;**9**(3):207-9. doi: [10.1097/00004850-199409000-00010](https://doi.org/10.1097/00004850-199409000-00010). [PubMed: [7814831](https://pubmed.ncbi.nlm.nih.gov/7814831/)].
14. Vera PL, Miranda-Sousa A, Nadelhaft I. Effects of two atypical neuroleptics, olanzapine and risperidone, on the function of the urinary bladder and the external urethral sphincter in anesthetized rats. *BMC Pharmacol*. 2001;**1**:4. [PubMed: [11580866](https://pubmed.ncbi.nlm.nih.gov/11580866/)].
15. Torre DL, Isgro S, Muscatello MR, Magno C, Melloni D, Meduri M. Urinary incontinence in schizophrenic patients treated with atypical antipsychotics: urodynamic findings and therapeutic perspectives. *Int J Psychiatry Clin Pract*. 2005;**9**(2):116-9. doi: [10.1080/13651500510018329](https://doi.org/10.1080/13651500510018329). [PubMed: [24930792](https://pubmed.ncbi.nlm.nih.gov/24930792/)].
16. Kho KH. Clozapine-induced nocturnal enuresis: diagnostic and treatment issues. *Psychiatric Bulletin*. 2001;**25**(6):232-3. doi: [10.1192/pb.25.6.232](https://doi.org/10.1192/pb.25.6.232).
17. Lee MJ, Kim CE. Use of aripiprazole in clozapine induced enuresis: report of two cases. *J Korean Med Sci*. 2010;**25**(2):333-5. doi: [10.3346/jkms.2010.25.2.333](https://doi.org/10.3346/jkms.2010.25.2.333). [PubMed: [20119596](https://pubmed.ncbi.nlm.nih.gov/20119596/)].
18. Saddichha S, Kumar M. Antipsychotic-induced urinary dysfunction: anticholinergic effect or otherwise? *BMJ Case Rep*. 2009;**2009** doi: [10.1136/bcr.02.2009.1547](https://doi.org/10.1136/bcr.02.2009.1547). [PubMed: [21686994](https://pubmed.ncbi.nlm.nih.gov/21686994/)].
19. Steingard S. Use of desmopressin to treat clozapine-induced nocturnal enuresis. *J Clin Psychiatry*. 1994;**55**(7):315-6. [PubMed: [8071296](https://pubmed.ncbi.nlm.nih.gov/8071296/)].