CASE REPORT

# From Urinary Retention to Increased Urinary Frequency: A Case Report on Mirtazapine's Unusual Side Effect

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## Abstract

Mirtazapine is a noradrenergic and specific serotonergic antidepressant (NaSSA). It is used off-label for the treatment of insomnia, panic disorder, generalized anxiety disorder, posttraumatic stress disorder (PTSD), obsessive–compulsive disorder (OCD), headaches, and migraines. The common side effects include sedation, increased appetite, weight gain, and dry mouth. Changes in urinary function are an uncommon side effect, predominantly as urinary retention and very rarely as an increase in urinary frequency. Here is a case of depressive episode in a middle-aged female, where mirtazapine precipitated a rapid and troublesome increase in micturition frequency.

**Keywords:** Adverse drug reaction, Case report, Micturition frequency, Mirtazapine.

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## Introduction

Mirtazapine is a tetracyclic piperazinoazepine compound which has been approved by the US FDA in 1995 for the treatment of depression.[1] It exerts its effects by inhibition of alpha-2 adrenergic receptors and postsynaptic serotonin type 2A, 2C (5-HT2) and type 3 (5-HT3) receptors. It also blocks histamine 1 (H1) receptors.[2] Mirtazapine is well suited for depression with melancholic features.[3,4] Its side effects include sedation (54%), xerostomia (25%), weight gain (17%), and dizziness (7%). Less common side effects include orthostatic hypotension, elevation of serum cholesterol, triglycerides, alanine aminotransferase (AST), and agranulocytosis.[5,6] Urinary side effects in the form of retention have been documented and have been attributed to anticholinergic action. An Increase in the frequency of micturition is a very rare phenomenon and only one case has documented dose-dependent increase in micturition frequency.[7] We are reporting a case of mirtazapine-induced micturition frequency in a middle-aged woman with a moderate depressive episode which was successfully managed by switching to an alternative antidepressant.

## Case Description

A 51-year-old widow was brought to psychiatry outpatient department (OPD) in late February 2021 with a history of insidious onset gradually progressive; persistent and pervasive sadness of mood and easy fatiguability since January 2021. Since early February 2021, her symptoms progressed and she developed a loss of interest in previously pleasurable activities, terminal insomnia, and loss of appetite associated, resulting in significant and unintentional weight loss. These symptoms were preceded by the accumulation of significant stressors in the form of the death of her two siblings in November 2020 and January 2021.

She was earlier treated for moderate depressive episodes from January 2020 to December 2021 and is under adequate glycemic control with oral hypoglycemic agents for diabetes mellitus type 2 since 2016.

No history of persistent or pervasive high mood, suicidal/homicidal ideas, no history of hearing disembodied voices/seeing strange things which others couldn't hear/see, beliefs that others are persecuting/following/constantly talking about her, beliefs that her thoughts were being controlled/inserted/withdrawn/broadcasted by an external agency, no history of substance abuse.

Physical examination was within normal limits and systemic examination revealed no abnormalities. Mental status examination revealed depressed facies with a downcast gaze and crying incessantly during the interaction, low rate, and tone of speech. She described her mood as "feeling sad all the time", her affect was depressed and was reduced in range and reactivity, the thinking was normal in the stream, goal-directed and without any depressive cognitions, and biodrives were deranged in the form of initial and terminal insomnia, decreased appetite, and low energy.

She was diagnosed with a case of recurrent depressive disorder, current episode moderate (F33.1) as per the diagnostic criteria of the International Classification of Diseases, 10th Edition [ICD-10]. In view of the depressive episode with somatic symptoms, she was started on mirtazapine 7.5 mg HS.

From day 1, she developed increased micturition frequency (4–5 times at night, more than her usual self). She also started having a sensation of numbness and a burning sensation around her mouth. On day 4, the dose of mirtazapine was the increased to 15 mg following which her symptoms worsened further and she would awaken 5–6 times at night. She felt incapacitated due

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to increased frequency of micturition and reported to Psychiatry OPD.

There was a history of urge incontinence, neurological deficits suggestive of upper motor neuron lesion, and fever with burning micturition. Gynecological and medical consultation for other causes of micturition frequency including urinary tract infection and hyperglycemia did not reveal any pathology. Her hematological and biochemical profile including thyroid function tests were within normal limits.

In the absence of any secondary cause and debilitating difficulties due to increased micturition frequency, mirtazapine induced micturition frequency was considered and mirtazapine was stopped immediately. By day 8, her micturition frequency reduced and reached an earlier pattern. She was started on nortriptyline up titrated to 125 mg HS over the next 10 days. Her depressive symptoms improved gradually over the next 6 weeks. The Naranjo adverse drug reaction probability scale of this case scored 8 suggestive of a definite adverse drug reaction.

## Discussion

The urinary retention caused by mirtazapine can be explained by its alpha2 adrenergic receptor-blocking action. Alpha 2c receptors are located in the adrenal medulla, and stimulation of these receptors causes inhibition of catecholamine release. Hence inhibition of these receptors by mirtazapine causes increased release of noradrenaline (NA) and this increased NA leads to the urinary retention caused by constriction of urinary sphincter.[8] The urinary retention is often clustered into the anticholinergic side effects produced by mirtazapine which paradoxically includes urinary frequency as well.[4,9] A possible mechanism of increased urinary frequency can be understood by pondering over how urinary continence is mediated. Whenever the urinary bladder is distended urothelium senses this distension and sends afferents through Aδ fibers that relay information via the spinal cord to the pontine storage centers. This leads to the activation of sympathetic innervation of the lower urinary tract via the hypogastric nerves and causes a release of noradrenaline which stimulates β3-adrenoceptors in the detrusor and α1-adrenoceptors in the bladder neck and proximal urethra. Stimulation of β3-adrenoceptors causes smooth muscle relaxation and increases bladder compliance, α1-adrenoceptors stimulation causes contraction of smooth muscles thus increasing bladder outlet resistance. At the same time, pudendal and sacral nerves are activated which release acetylcholine which acts on nicotinic receptors in the distal urethra and pelvic floor which contract and further increase bladder resistance. Mirtazapine may relax the internal urethral sphincter through alpha antagonism, thus potentiating stress urinary incontinence.[10]

The Naranjo adverse drug reaction probability scale of this case scored 8 (definite adverse drug reaction).[11] Unusual features of this case are sudden onset intolerable micturition frequency post-mirtazapine which was reversed post-cessation of the drug. Only one case report could be found implicating mirtazapine in urinary incontinence.[7] However, no study till now has implicated mirtazapine directly to increased micturition frequency sans urinary incontinence.

Principles of management include immediate cessation of the drug and switching to an alternate antidepressant. Complete recovery usually occurs within a week after halting the drug. There are currently no specific recommendations to assess the risk of micturition symptoms and their management due to mirtazapine.

## Conclusion

A middle-aged female, with a case of Recurrent Depressive Disorder developed unusual and troublesome micturition after gradual uptitration of mirtazapine to 15 mg/day. This is a rare side effect of the antidepressant. Her symptoms resolved after a change of medication to nortriptyline and micturition frequency reverted to normal within a week. This case report aims to highlight a rare and bothersome yet reversible adverse effect of increased micturition frequency by mirtazapine.

### Ethical Considerations

Informed consent has been taken prior to publishing this article from the patient. The participation of the patient is voluntary, and every step has been taken to maintain the patient's confidentiality and anonymity. There are no conflicts of interest.

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