# Clozapine-Induced Urinary Incontinence: A Novel Management Option and Review of the Literature

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## Introduction

The superior efficacy of clozapine over other antipsychotics for treatment-resistant schizophrenia is well-recognized, and great attention is given to monitoring for its dangerous potential adverse effects, such as agranulocytosis. However, a host of less risky but unpleasant side effects can limit clozapine's tolerability and quality of life in those prescribed it.

Nocturnal enuresis and urinary incontinence may affect 10 - 43% of patients taking clozapine and have the potential to negatively impact patient self-perception and social functioning, yet these symptoms may be underreported by patients and underrecognized by prescribers [1,2,3]. Several possible mechanisms have been proposed for clozapine-induced urinary incontinence (CIUI), and a variety of pharmacological and behavioral management strategies have been described in case reports and series [2].

We present the case of a 38 year-old male with clozapine-induced urinary incontinence successfully treated with mirabegron, a β3-agonist used in the treatment of overactive bladder. To our knowledge, this is the first report of the successful use of mirabegron for this indication.

We also review the body of literature on treatment options for CIUI and propose a basic approach to its management.

## Previously Reported Treatments for Clozapine-Induced Incontinence and Enuresis

| Intervention | Dose/Day | n | Complete or Partial Symptom Resolution | Safety Considerations |
|---|---|---|---|---|
| Desmopressin | 10mcg/1mL spray (1-2 spray) | 11 | 10 (91%) | Hyponatremia (5-15% of patients); may be life-threatening. Use caution in elderly, monitor Na closely. |
| Oxybutynin | 5 - 15 mg | 14 | 10 (71%) | Anticholinergic side effects, particularly that of worsening constipation and risk of paralytic ileus, warrant extreme caution in combination with clozapine. |
| Trihexyphenidyl | 5 - 6 mg | 3 | 3 (100%) | |
| Imipramine | 25 mg | 3 | 3 (100%) | Anticholinergic side effects as above. Also consider risk of lethal overdose, sedation, increased seizure risk. |
| Amitriptyline | 25 mg | 3 | 2 (67%) | |
| Aripiprazole | 10 - 15 mg | 3 | 3 (100%) | Dual antipsychotic treatment may increase metabolic and extrapyramidal side effect risk. Combination with aripiprazole in particular may increase risk of akathisia. |
| Ephedrine | 25 - 75 mg | 19 | 18 (95%)) | Risk of psychosis, misuse or diversion, hypertension. |
| Various studies showed self-resolution without intervention (n=4), resolution with clozapine dose reduction (n=12), transition from clozapine to olanzapine (n=1), and a 40% response rate to behavioral interventions (n=5). Dividing clozapine dosing to twice-daily was unsuccessful for one patient. | | | | |

**Table 1: Summary of efficacy results and safety considerations for select treatments for CIUI, adapted from the 2022 systematic review by Tanzer et al [2].**

## Case Presentation

Mr. D is a 38 year-old man diagnosed with treatment-resistant schizophrenia after at least four trials of typical and atypical antipsychotics failed due to inefficacy in treating positive symptoms or intolerable extrapyramidal side effects. He had no history of previous urologic symptoms.

- **Aug 2021**: Mr. D started clozapine and gradually titrated to 450 mg daily with improvement in positive symptoms and adverse effects of sialorrhea, mild tremor, and weight gain.
- **June 2022:** Mr. D reported daytime and nocturnal urinary frequency (Q 0.5hr), urgency, and urge incontinence. Notably, his identical twin brother developed similar symptoms months after starting clozapine.

  He was referred to Urology for further evaluation of urge incontinence:
  - Urodynamic studies were largely unremarkable
  - Recommended fluid and caffeine restriction
  - Urology determined symptoms most likely due to clozapine
  - Trials of **trospium 20mg BID, oxybutynin 10mg QD, darifenacin ER 15mg QD** yielded little improvement
- **Sept 2022:** Due to limited improvement in urinary symptoms, Mr. D desired to transition to an alternate antipsychotic
  - Cross-taper from clozapine to cariprazine attempted, limited by EPS and episode of acute urinary retention
- **Nov 2022:** Urinary symptoms had minimally improved. Urology discussed bladder Botox or sacral nerve stimulation
  - Mr. D and family remained hopeful about transitioning off clozapine secondary to urinary symptoms
  - Cross-taper from clozapine to loxapine initiated
- **Jan 2023**: Mr. D's outpatient team coordinated with Urology to discuss alternative management options; **mirabegron 50mg QD started with darifenacin ER 15mg QD**
- **March 2023:** Mr. D's urinary frequency decreased to Q1h voids, less nocturia and urgency. Urge incontinence resolves, going outside more.
- **June 2023:** Mr. D is admitted to inpatient psychiatry for severe EPS and concern for anticholinergic toxicity
  - Loxapine was discontinued and clozapine re-titrated
  - Mirabegron was discontinued, darifenacin continued
- **Aug 2023 - Feb 2024**: Urinary symptoms return to 6/2022 baseline and remain impairing. Mr. D hesitates to restart mirabegron due to concern for anticholinergic polypharmacy, though mirabegron is not anticholinergic. Urology continues darifenacin ER 15mg.
- **March 2024**: Mr. D re-trialed mirabegron, reported urinary retention and declined to continue the medication.

**Figure 1: Suggested management framework for urinary incontinence or nocturnal enuresis arising during clozapine treatment**

## Literature Review

PubMed and Embase were queried with the following terms: 'clozapine AND enuresis;' 'clozapine AND incontinence' (n=695). Results were reviewed for systematic reviews and meta-analyses. One systematic review (Tanzer et al 2022) was identified.

PubMed and Embase were also queried for 'clozapine AND mirabegron' (n=19). Results were reviewed for systematic review, meta-analyses, randomized controlled trials, clinical trials, case series, and case reports. One case report (Filipe and Marques 2018) was identified.

## Conclusions

Urinary incontinence and nocturnal enuresis are common complications of clozapine treatment and can negatively impact patient quality of life and treatment adherence. Mr. D's case highlights several best practices in identifying and managing CIUI identified in the extant literature:

- Pre-treatment counseling and active screening for urinary incontinence and enuresis during clozapine treatment are important, as patients may not spontaneously disclose these symptoms [3].
- Rule-out of other medical or iatrogenic causes of incontinence is critical before attributing symptoms to clozapine. Urology referral should be considered for expertise in workup of urinary symptoms and ongoing collaboration in their management.
- Nonpharmacologic interventions including caffeine and nocturnal fluid restriction, pre-bedtime voiding, and voiding alarms may be helpful initial interventions regardless of symptom etiology [2].
- If symptoms are attributed to clozapine and causing significant distress or functional impairment, dose reduction or transition to an alternate antipsychotic may be considered. CIUI may be less likely to resolve over time without intervention [3].
- Desmopressin may be considered a first-line pharmacology treatment for CIUI in patients <65 years old given its lack of anticholinergic action, though warrants careful monitoring for hyponatremia. Anticholinergics should be reserved as second-line treatments due to potential to worsen clozapine-associated GI hypomotility.

As Mr. D's case demonstrates, for patients with CIUI and evidence of overactive blader the selective β3-agonist mirabegron may also be a useful treatment option. One published case report documents a case of Pisa syndrome resulting from the coadministration of mirabegron and clozapine; however, to our knowledge, Mr. D's case is the first report of the successful use of mirabegron in treating CUIC [4]. Mirabegron is metabolized by CYP2D6 and 3A4 and may impact clozapine levels through 2D6 inhibition; thus, clozapine levels should be monitored in the setting of mirabegron use. Common adverse effects to monitor for include hypertension, constipation, dizziness, and urinary retention [5].

## References

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