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Review

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Treatment strategies for clozapine-induced nocturnal enuresis and urinary incontinence: a systematic review

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Abstract

Background. Clozapine is the most effective medication for treatment-refractory schizophrenia but is associated with significant adverse drug reactions, including nocturnal enuresis and urinary incontinence. This side effect can be burdensome and lead to medication nonadherence and psychotic relapse. Evidence to guide treatment of clozapine-induced nocturnal enuresis and urinary incontinence is sparse. We therefore aimed to synthesize the evidence base to guide management for clinicians, patients, and their carers.

Methods. We systematically searched PubMed, Embase, PsycInfo, CINAHL, and the Cochrane Trial Registry databases from inception to May 2021 for publications on management of clozapine-induced nocturnal enuresis and urinary incontinence using a PROSPERO preregistered search strategy.

Results. We identified 22 case reports and case series describing 74 patients. Interventions included clozapine dose reduction, nonpharmacological treatment, and pharmacological treatments. Among pharmacological treatments, desmopressin, oxybutynin, trihexyphenidyl, tolterodine, imipramine, amitriptyline, ephedrine, pseudoephedrine, aripiprazole, and verapamil were associated with complete resolution of nocturnal enuresis and urinary incontinence. Balancing evidence for effectiveness against risk of adverse effects, we developed a management framework for clozapine-induced nocturnal enuresis and urinary incontinence.

Conclusions. Following assessment of urological, psychiatric, pharmacological, and common comorbid medical issues, first-line treatments should be nonpharmacological, including bathroom alarms, voiding before bedtime, and nocturnal fluid restriction. If these interventions do not provide adequate relief, aripiprazole should be trialed. Desmopressin may be considered for severe refractory cases, but monitoring for hyponatremia is essential.

Introduction

Clozapine is the gold standard antipsychotic for treatment-refractory schizophrenia[1] and has been shown to reduce rates of hospitalisation,[2] as well as to reduce overall mortality compared with other antipsychotics.[3] Haematological,[4] metabolic,[5] and cardiac[6] adverse events are well known. However, clozapine can also be associated with other side effects, such as nocturnal enuresis and urinary incontinence, which significantly impact on quality of life, and is associated with noncompliance.[7] The prevalence of nocturnal enuresis and urinary incontinence is thought to be underreported and may affect up to 40% of those prescribed clozapine.[7] Some cases may spontaneously resolve, although many demonstrate chronicity and impact quality of life. Patients may experience stigma, embarrassment, loss of quality sleep, impaired sexual function, and dissatisfaction with hygiene, in addition to the cost of incontinence supplies and additional laundry.[7–11]

Clozapine has a higher incidence of nocturnal enuresis and urinary incontinence than other second-generation antipsychotics, the mechanisms likely being multifactorial in nature.[12] For instance, bladder continence is mediated by β-adrenergic relaxation of smooth bladder muscle and α-adrenergic constriction of the trigone muscle and internal sphincter.[11,13,14] Clozapine-induced α1 blockade may therefore cause urinary sphincter relaxation, as well as blockade of parasympathetic neurons innervating the bladder, known as the pudendal reflex, via antagonism of 5-HT2 or 5-HT3 receptors.[13] Clozapine use may also result in urinary retention and overflow incontinence through anticholinergic action, while agonism on 5-HT1A receptors may stimulate

the micturition reflex. Furthermore, clozapine-induced sedation and prolongation of non-rapid eye movement (REM) sleep may prevent patients from waking in response to a full bladder.[15] Urinary incontinence may also be the result of a decrease or imbalance of dopaminergic or noradrenergic systems in the basal ganglia secondary to clozapine treatment.[16] In addition, urinary incontinence is a well-established symptom of psychosis and may indicate clinical deterioration or relapse of psychotic symptoms.[17]

A range of medications are currently used to treat nocturnal enuresis and urinary incontinence, including desmopressin, anticholinergics, tricyclic antidepressants, α-agonists, sodium valproate, bethanechol, aripiprazole, and verapamil. However, there is limited guidance for the pharmacological treatment of clozapine-induced nocturnal enuresis and urinary incontinence. We conducted a systematic review to assess the effectiveness of pharmacological and nonpharmacological options, their associated side effect profiles, and the quality of evidence, in order to provide guidance to clinicians, patients, and carers.

Methods

PubMed, Embase, PsycInfo, CINAHL, and the Cochrane Trial Registry databases from inception to May 2021 were searched using the terms: Clozapine OR Clopine OR Clozaril OR Zaponex AND enuresis OR incontinence OR urin* OR "bed wetting." Studies were not limited by language, and all article types, including conference posters and abstracts, were included. References for selected articles were cross-checked for further studies. Search and screening at title, abstract, and then full text level was conducted independently by three authors (T.T., L.M., and E.W.). The Preferred Reporting Items for Systematic Reviews and Meta Analyses statement recommendations were followed, and this study was preregistered with The International Prospective Register of Systematic Reviews (PROSPERO) (CRD42020138221).[18,19]

Studies were included if the participants experienced clozapine-induced nocturnal enuresis and urinary incontinence and reported an intervention. There were no restrictions on age, gender, comorbidities, adjunct therapies, or diagnosis. All study designs were included where available, including case reports, case series, observational studies, and RCTs. Study quality was assessed using the Joanna Briggs Institute critical appraisal tool appropriate for that design.[20]

The prespecified variables for collection included demographics, medical and psychiatric history, medications, including clozapine dose and plasma level, clozapine-associated adverse events, and the enuresis intervention. Complete enuresis treatment response was defined as continence, either based on reports from patients or staff or the absence of urine stains on sheets or clothing. Partial enuresis treatment response was defined as a reduction in volume or a reduction in enuresis frequency. Missing data or nonindividualized data from case series were noted and documented as "not reported." Data extraction was conducted by two researchers (L.M. and E.W.) and validated by a third (T.T.). Descriptive statistics and qualitative analysis were employed.

Results

There were 1283 unique articles identified after removal of duplicates in the databases (Figure 1). Of these, 1261 studies were excluded at title and abstract level. This left 22 included studies (14 case reports and 8 case series) published between 1994 and 2020 that described pharmacological and nonpharmacological treatment of clozapine-induced nocturnal enuresis and urinary incontinence. There were no other study designs.

The 22 case reports and case series described 74 patients (Table 1). There were 35 males and 22 females, with gender not reported in 17 patients. Age was reported in 53 patients and ranged from 16 to 69 years old with a mean age of 38.6 years (SD 9.5). Patient diagnoses included schizophrenia, schizoaffective disorder, and bipolar disorder. Clozapine dose ranged from 50 to 900 mg. Clozapine plasma levels were reported in seven patients and ranged from 290 to 760 ug/L.[14,21–24] Seven studies were recorded in an inpatient setting,[23–28] and one in an outpatient setting,[29] whereas the remaining studies did not report the setting. Timing of enuresis ranged from 1 to 90 days after commencement of clozapine (median: 21 days). Four patients (5%) had urinary incontinence prior to commencing clozapine. Other reported clozapine-induced adverse events included sialorrhea (eight patients),[26,30–35] sedation (three patients),[26,33,34] constipation (two patients),[32,34] weight gain (two patients),[32,33] tremor (one patient),[32] worsening OCD symptoms (one patient),[32] diaphoresis (one patient),[32] tachycardia (one patient),[33] and overeating (one patient).[33] Table 1 provides a summary of the results and safety considerations.

The studies were of varying quality, as assessed using the Johannes Briggs clinical appraisal tool. In particular, a failure to report patient demographics and characteristics, psychiatric symptoms and diagnosis, lack of validated rating scales for nocturnal enuresis and urinary incontinence, and adverse events of interventions was common. A summary of the study quality and a composite score has been presented in Table 2.

Nonpharmacological and Other Management Options

Four studies trialed clozapine dose reduction, with data for 12 patients.[23,28,31,36] All 12 patients achieved full resolution, although three achieved resolution alongside the use of intranasal desmopressin,[23,28] and aripiprazole.[31] Splitting clozapine into twice-daily dosing was unsuccessful for one patient.[30] Cessation of clozapine and change to olanzapine was successful for one patient.[14] Two of five patients managed with behavioral interventions showed full resolution.[9,22,26,35,37] For four patients, symptoms of nocturnal enuresis and urinary incontinence self-resolved with no change in clozapine therapy, behavioral, or pharmacological intervention.[29,36]

Pharmacological Interventions

Antipsychotics

Aripiprazole

Two studies[31,37] used aripiprazole with data on three patients at a dose of 10 to 15 mg/d. All three participants experienced complete resolution of symptoms approximately 2 to 3 months after commencement of aripiprazole. Neither study reported on adverse effects.

Antidiuretic hormone

Desmopressin

Five case reports and two case series[9,23,24,28,38–40] used desmopressin spray at doses of 1 to 2 sprays (10 mcg/0.1 mL) into each nostril once daily with data for 11 patients. Four studies[9,24,28,38] reported that desmopressin was used at nighttime, whereas three

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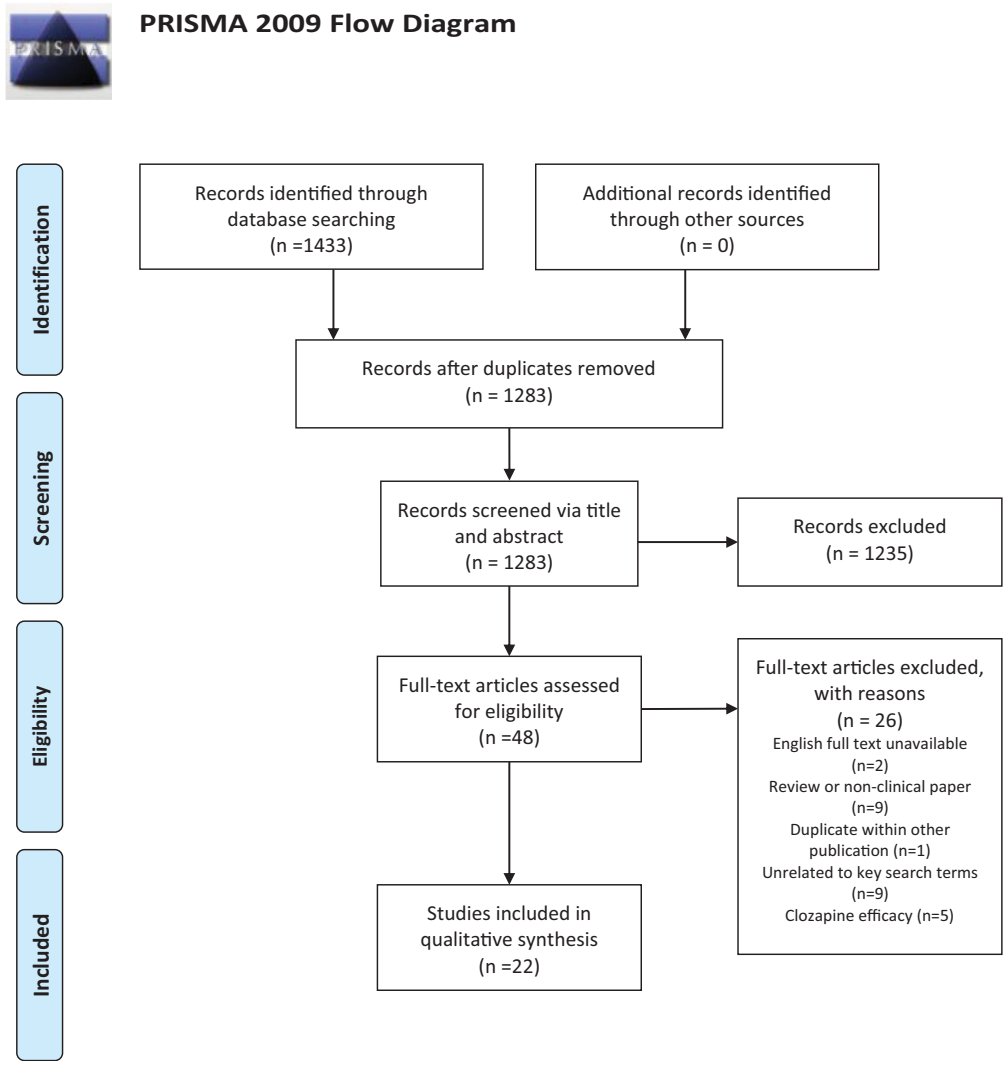

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta Analyses (PRISMA) flow diagram.
Source: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med.* 2009;**6** (7):e1000097. doi:10.1371/journal.pmed.1000097. For more information, visit www.prisma-statement.org.

studies[23,39,40] did not report the time of administration. Nocturnal enuresis fully resolved in 10 of 11 patients. In one case,[24] desmopressin was ceased due to life-threatening hyponatremia before any response was observed. In two cases,[23,28] the patients experienced no adverse events. Adverse events were not reported for eight cases.[23,24,28]

Anticholinergics

Oxybutynin

Two case series[9,39] used oxybutynin at doses of 5 to 15 mg daily with outcome data for 10 patients. Symptoms completely resolved in all 10 patients. Three other publications[21,22,26] reported data for four patients whom previously trialed oxybutynin without success. No studies reported on adverse effects.

Benztropine

One case series[26] reported five patients who had previously taken benztropine for sialorrhea. They reported that benztropine had no effect on urinary incontinence in all patients. No studies reported on adverse effects.

Trihexyphenidyl

One case series and one case report[30,33] used trihexyphenidyl at a dose of 5 to 6 mg/d as either divided doses or as a single nighttime dose with data for three patients. In two out of three patients, nocturnal enuresis completely resolved. One patient experienced two incidences of nocturnal enuresis and urinary incontinence after commencement of trihexyphenidyl followed by complete resolution.[33] Only one case[30] commented on adverse events, with none reported.

Tolterodine

One case report[35] used tolterodine at a dose of 1 mg/d for 2 weeks and achieved a partial response. The dose was then increased to 2 mg/d, and complete resolution was achieved. The patient did not experience any adverse events. One case report[23] trialed tolterodine unsuccessfully for 2 weeks before switching to desmopressin.

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Table 1. Summary of Results

Drug	Daily Dose	n	Complete Resolution (%)	Partial Resolution (%)	No Response (%)	Adverse Effects (%)
Desmopressin	10 mcg/0.1 mL spray (1-2 sprays)	11	10 (91%)	–	–	1 case (9%), desmopressin ceased due to life-threatening hyponatremia None reported (two cases) No data (eight cases)
			Anticholinergics			
Oxybutynin	5-15 mcg	14	10 (71%)	–	4 (29%)	No data
Benztropine	Not reported	5	–	–	5 (100%)	No data
Trihexyphenidyl	5-6 mg	3	3 (100%)	–	–	None reported (one case) No data (two cases)
Tolterodine	2 mg	2	1 (50%)	–	1 (50%)	None reported
			Tricyclic Antidepressants			
Imipramine	25 mg	3	3 (100%)	–	–	No data
Amitriptyline	25 mg	3	2 (67%)	–	–	1 case (33%), amitriptyline ceased due to excessive sedation and dizziness No data (two cases)
			α-agonists			
Ephedrine	25-75 mg	19	15 (79%)	3 (16%)	1 (5%)	None reported
Pseudoephedrine	120 mg	1	1 (100%)	–	–	No data
			Other Agents			
Sodium valproate	1500 mg	3	3 (100%)	–	–	No data
Bethanechol	30 mg	2	–	2 (100%)	–	No data
Aripiprazole	10-15 mg	3	3 (100%)	–	–	No data
Verapamil	40-80 mg	1	1 (80 mg; 100%)	–	–	1 case (100%), experienced temporary bradycardia at each dose increase. Verapamil was continued.
Doxazosin	2 mg at night	1	–	–	1 (100%)	No data
Nonpharmacological or other interventions	–	23	4 (17%) self-resolved; 9 (39%) dose reduction; 3 (13%) dose reduction alongside pharmacological intervention; 2 (9%) behavioral interventions; 1 (4%) changed to olanzapine		3 (13%) behavioral interventions; 1 (4%) changed to twice-daily dosing	No data

[a]Unable to calculate mean and SD of dosage due to lack of data.

Table 2. Johannes Briggs Study Quality and Composite Score

Case Studies											
Paper	1	2	3	4	5	6	7	8	–	–	Total (of 8)
Aggarwal et al[30]	N	Y	Y	Y	Y	Y	Y	Y	–	–	7
Aronowitz et al[38]	N	N	Y	Y	Y	Y	N	N	–	–	4
Dadlani and Austin[22]	Y	Y	Y	Y	Y	Y	Y	Y	–	–	8
Demirkol and Temam[25]	N	Y	Y	Y	Y	Y	N	Y	–	–	6
English et al[23]	Y	Y	Y	N	Y	Y	Y	Y	–	–	7
Ginsberg[24]	N	Y	Y	N	Y	Y	Y	N	–	–	5
Hanes et al[27]	N	N	Y	N	Y	Y	N	Y	–	–	4
Luche and Francois[40]	N	N	Y	N	Y	Y	N	Y	–	–	4
Mehtar and Ucok[29]	N	Y	Y	Y	N/A	Y	N	N	–	–	4
Palaniappan[37]	N	Y	Y	Y	Y	Y	N	Y	–	–	6
Poyurovsky et al[33]	Y	Y	Y	N	Y	Y	Y	Y	–	–	7
Praharaj and Arora[34]	N	Y	Y	N	Y	Y	N	Y	–	–	5
Selvaraj et al[35]	N	Y	Y	N	Y	Y	Y	Y	–	–	6
Steingard[28]	N	Y	Y	N	Y	Y	Y	N	–	–	5
Case Series											
Paper	1	2	3	4	5	6	7	8	9	10	Total (of 10)
Apantaku-Olajide[21]	N	N	Y	Y	Y	Y	N	Y	–	–	5
Bhirud and Shah[36]	N	N	Y	N	Y	Y	N	N	–	–	3
Fuller et al[26]	N	Y	Y	Y	Y	Y	Y	Y	–	–	7
Frankenburg et al[9]	N	Y	Y	N	Y	Y	N	Y	–	–	5
Kho and Nielsen[14]	N	N	Y	N	Y	Y	N	N	–	–	3
Lee and Kim[31]	N	N	N	N	Y	Y	N	Y	–	–	3
Lurie et al[39]	N	N	Y	N	Y	Y	N	N	–	–	3
Poyurovsky et al[33]	Y	Y	Y	N	Y	Y	N	Y	–	–	6

Tricyclic antidepressants

Imipramine

One case series[36] provided data for three patients using imipramine 25 mg daily. All three patients experienced complete resolution of symptoms. Neither case series reported on adverse effects.

Amitriptyline

Two case reports[25,34] provided data for three patients using amitriptyline at a dose of 25 mg/d. In both patients, symptoms completely resolved. Neither case report commented on adverse events. One other case[30] reported a background of excessive sedation and dizziness with amitriptyline use prior to a trial of trihexyphenidyl. This publication did not report the dose.

α-Agonists

Ephedrine

One case series[26] of ephedrine provided data for 16 patients. Ephedrine was given at a dose of 25 to 75 mg/d. Twelve participants had complete resolution of symptoms, three had partial response, and one had no response. The study reported no adverse effects.

Pseudoephedrine

One case report[27] provided data for one patient on pseudoephedrine. A dose of 30 mg four times a day was used, and the patient showed complete resolution of symptoms. The study did not report on adverse effects.

Other agents

Sodium valproate

One case series and one case study[14,21] used sodium valproate, an anticonvulsant, with data for three patients. Two patients suffered from tonic–clonic seizures, and another had inconclusive EEG activity, and were started on sodium valproate. All three patients experienced complete resolution of symptoms. One case used a dose of 500 mg three times a day,[14] and the other did not report the dose.[21] Neither study reported on adverse effects.

Bethanechol

One case report[22] used bethanechol, a muscarinic receptor agonist which may improve detrusor contractility in bladder dysfunction.[41,42] A dose of 10 mg three times a day was used, and the patient's symptoms reduced in frequency. The study did not report on adverse effects. Another study[31] reported previous partial response to bethanechol in the patient's treatment history.

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Verapamil

One study[32] provided data on a single patient using the calcium channel blocker verapamil. The study had a single-blind design, and the participant saw a temporary response at 40 mg/d, and complete resolution at 80 mg/d. Temporary bradycardia was observed at each dose increase and self-resolved.

Doxazosin

One case report[26] provided data for one patient using doxazosin, a selective α_1 receptor blocker. A dose of 2 mg at night was used for 1 week, and the patient showed no response. The study did not report on adverse effects.

Discussion

This study provides the first systematic review of treatments for clozapine-associated nocturnal enuresis and urinary incontinence. All studies were either case reports or case series. Despite this, the cases demonstrate that there are multiple effective pharmacological treatment options. Complete resolution of clozapine-induced nocturnal enuresis and urinary incontinence was seen with the use of aripiprazole, desmopressin, oxybutynin, trihexyphenidyl, tolterodine, imipramine, amitriptyline, ephedrine, pseudoephedrine, and verapamil. These medications were generally well tolerated, although 63% of studies did not discuss adverse effects.

Despite the high incidence of clozapine-induced nocturnal enuresis and urinary incontinence,[7] there is limited available literature on management and interventions. This may be in part due to the underreporting of urinary symptoms due of stigma leading to a lack of attention to the issue.[7] Therefore, direct questioning about the frequency and severity of symptoms should be used to ensure timely identification of nocturnal enuresis and urinary incontinence.

In light of our findings, we have provided a management framework for clinicians, patients, and carers faced with clozapine-associated nocturnal enuresis and urinary incontinence (Figure 2). Given the self-limiting nature of clozapine-induced nocturnal enuresis, long-term use of pharmacological treatment should be avoided where possible. Given the limited evidence available in the literature, treatment options provided are preferred based on the safety of short-term use, rather than solely the number of available studies and cases. The framework is a suggestion designed to assist in making informed treatment decisions. The risk and benefit of each agent must be considered for each individual patient.

In the first instance, it is important to exclude medical issues such as benign prostatic hyperplasia or pelvic floor weakness especially as 5% of cases in this review reported preexisting urinary incontinence.[9,26,39] This may be aided by a urological consult for transabdominal ultrasound or urodynamic testing.[43,44] Review of concomitant medications that may exacerbate nocturnal enuresis and urinary incontinence, such as benzodiazepines or other sedating medications, and consideration of clozapine dose reduction may be effective.[23,31,37] Treating other adverse effects of clozapine, including seizures, constipation, and polyuria associated with insulin resistance, diabetes mellitus, or diabetes insipidus, is advised.[5,14,45,46] Nonpharmacological treatment approaches, such

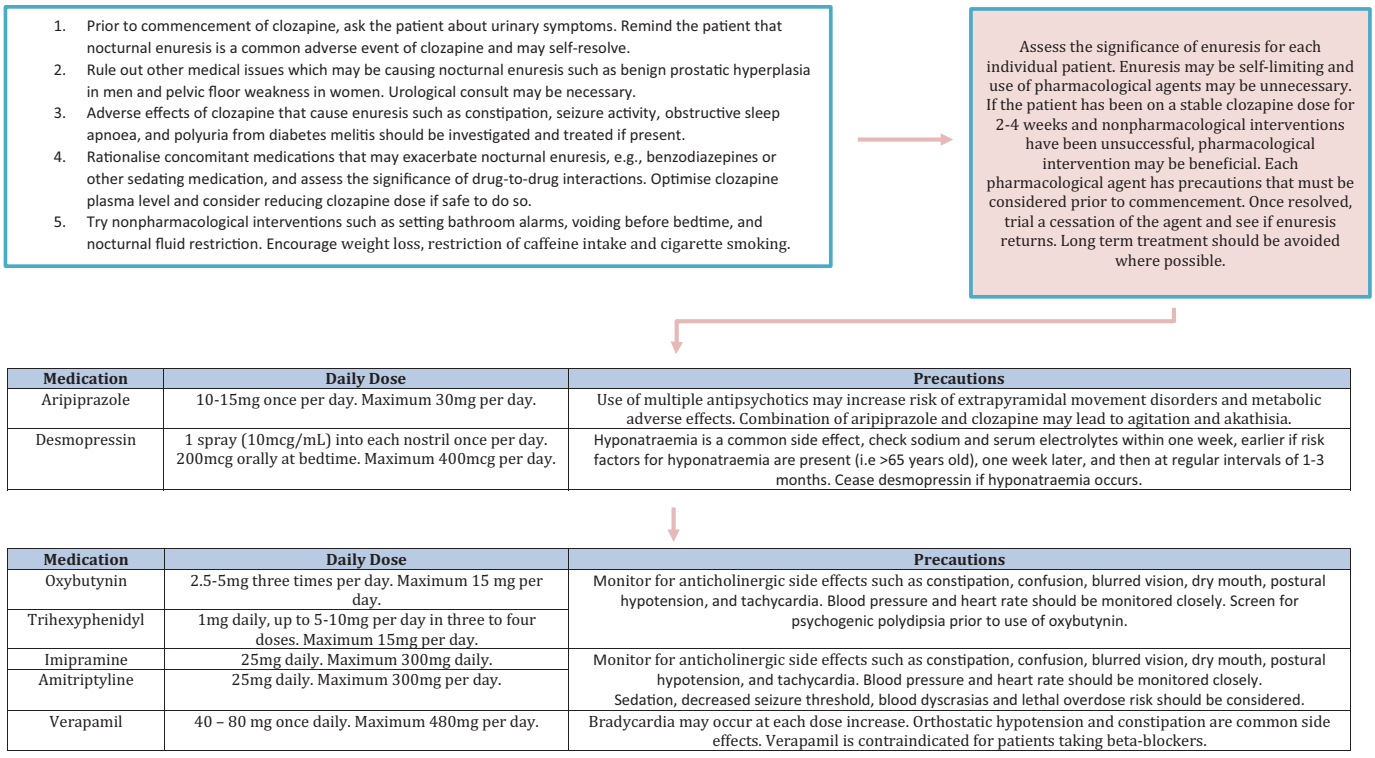

Figure 2. Management framework of clozapine-induced nocturnal enuresis and urinary incontinence.
Notes: Avoid use of α-agonists due to CNS stimulation and risk of exacerbation of psychosis. Benztropine is unlikely to be effective and should be avoided due to the risk of anticholinergic side effects, particularly the worsening of life-threatening constipation. Mirabegron may be an option if urodynamic studies show overactive bladder. Monitor clozapine levels and common adverse events, such as hypertension, constipation, tachycardia, and dizziness.

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as bed-wetting alarms, voiding before bedtime, and nocturnal fluid restriction, should be trialed before pharmacological management. However, as many cases reported significant sedation, some consumers may find implementing these difficult.[26,33,35,47]

Nonpharmacological treatment approaches should be tried in the first instance, particularly as spontaneous resolution is common.[11] Patients should be reminded that clozapine is sedating and may cause temporary bed-wetting. The average time to nocturnal enuresis and urinary incontinence being reported in these cases was 30 days from clozapine initiation, indicating that this discussion may be a priority during in-patient admission. Setting alarms, voiding before bedtime, and nocturnal fluid restriction were trialed in the case reports with varying success and should be considered prior to pharmacological intervention.[9,22,26,35,37] Concomitant medications that may exacerbate nocturnal enuresis and urinary incontinence should be reviewed, as well as an assessment of significant drug-to-drug interactions which may exacerbate nocturnal enuresis and urinary incontinence. Although a recent review of clozapine and norclozapine levels and adverse drug reaction did not find a relationship between either clozapine or norclozapine levels and nocturnal enuresis and urinary incontinence,[48] the case reports included in our review suggest that decreasing clozapine levels could reduce rates of nocturnal enuresis and urinary incontinence. Reduction in clozapine dose may not be practical in some people with treatment resistant schizophrenia.

If symptoms persist and behavioral measures are not successful, aripiprazole can be trialed due to its relatively low risk of adverse events (Figure 2). Aripiprazole may act as a D_2 agonist in a hypodopaminergic state caused by clozapine treatment and thus improve nocturnal enuresis and urinary incontinence by maintaining dopamine transmission in the basal ganglia.[16] Although aripiprazole has little α-1 activity, dopamine is known to cross-activate adrenoreceptors, and thus aripiprazole may improve sphincter tone by interacting with α-1 receptors.[49] Aripiprazole may also reduce bladder dysfunction by acting as a 5-HT1A partial agonist and inhibiting bladder contraction.[31] Another benefit may be improvement in psychotic symptoms, leading to improved continence.[50] Aripiprazole augmentation of clozapine has been found to reduce psychotic symptoms in clozapine-refractory schizophrenia,[50] and to reduce rates of rehospitalisation.[51] Although use of aripiprazole may be associated with akathisia, agitation, and anxiety in the short term, overall it is well tolerated in combination with clozapine.[52] The use of aripiprazole in combination with clozapine has been shown to attenuate other clozapine-related adverse events, such as weight gain and obesity,[53] obsessive–compulsive symptoms,[54] and sedation.[55] Importantly, unlike desmopressin (see below), and anticholinergic medication, aripiprazole is not associated with hyponatremia, or paralytic ileus.[56]

Desmopressin is a synthetic analogue of 8-arginine vasopressin, an antidiuretic hormone which acts on the renal collecting duct to limit urine volume and thus reduce overflow incontinence.[57] Although there are more case reports and case series demonstrating its effectiveness for clozapine-associated nocturnal enuresis and urinary incontinence than for aripiprazole, the incidence of life-threatening hyponatremia requiring close monitoring should be noted. This is a common side effect with an incidence rate of 5% to 15% and must be managed with fluid restriction.[58–60] Psychogenic polydipsia and ability to comply with potential fluid restrictions are therefore important considerations prior to desmopressin commencement. Although all cases in this review used nasal formulation, the use of oral desmopressin may be a preferred option. Hyponatremia occurs less frequently with oral desmopressin formulations and is the preferred method of administration for children with diabetes insipidus and nocturnal enuresis and urinary incontinence.[61]

Anticholinergic medications are second-line treatments. Acetylcholine is the key neurotransmitter involved in bladder contraction and emptying, and as such, anticholinergic medications block muscarinic receptors, thereby decreasing the frequency of involuntary detrusor contractions and increasing bladder capacity.[13] Antimuscarinic drugs, such as oxybutynin and trihexyphenidyl, are therefore likely to be effective in treating nocturnal enuresis and urinary incontinence. Tolterodine, an antimuscarinic agent already marketed for overactive bladder, has the advantage of greater selectivity for bladder function than oxybutynin, whereas the latter is more selective for salivary function.[62,63] However, tolterodine may take 8 to 10 weeks to reach full effect, as opposed to up to 4 weeks for oxybutynin, and thus may be impractical for promoting clozapine adherence.[63] Benztropine, despite showing efficacy for sialorrhea, does not improve symptoms of nocturnal enuresis and urinary incontinence.[64] The use of antimuscarinic agents alongside clozapine may be contraindicated due to the risk of exacerbating clozapine's anticholinergic burden and the associated side effects of constipation, confusion, blurred vision, dry mouth, postural hypotension, tachycardia, and increased risk of paralytic ileus.[56] As a result, bowel function, blood pressure, and heart rate should be monitored closely if these agents are prescribed, as well as concurrent treatment with aperients considered. Finally, oxybutynin may cause hyponatremia-induced seizures, and so screening for psychogenic polydipsia is recommended.[65]

Other anticholinergic agents include tricyclic antidepressants. Amitriptyline, specifically, also increases vasopressin secretion and shortens REM sleep, thereby counteracting clozapine's prolongation of REM and so improving nocturnal enuresis and urinary incontinence.[25,34] However, tricyclic antidepressants share the same side effects as other antimuscarinic agents and have several further disadvantages. One is their antihistaminergic effects resulting in sedation (29%) and dizziness (28%). Others are prolongation of the QT interval, blood dyscrasias, and the risk of fatal overdose risk. Imipramine has 10-fold less potency for muscarinic receptors than amitriptyline and may be a more appropriate choice for patients sensitive to anticholinergic side effects.[66,67]

Another treatment option is verapamil, a calcium channel blocker that may inhibit bladder contraction. This is because voltage-gated calcium channels are implicated in the regulation of bladder smooth muscle tone.[68] There was only a case report on a single patient, so information on side effects in clozapine-induced enuresis is limited. However, side effects in hypertensive patients, including bradycardia, hypotension, and palpitations, are rare at less than 1%.[69] Nevertheless, verapamil should be used with caution in patients taking clozapine due to its risk of constipation (5%).[70] Finally, sodium valproate may be useful in treating seizure activity which may be leading to nocturnal enuresis and urinary incontinence. Seizures appear to occur most frequently at low doses of clozapine during titration and at high doses of clozapine during maintenance phase.[71,72]

Other medications are less suitable given their side effect profile and potential for abuse. For instance, stimulant medications, such as ephedrine and pseudoephedrine, showed benefit in reducing or eliminating nocturnal enuresis and urinary incontinence. These medications stimulate α-adrenergic receptors, facilitating contraction of the trigone and internal sphincter and increasing urethral closure pressure.[13] A further theory that was subsequently

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Table 3. Table of Included Studies

Paper	Intervention	No. of Participants	Setting	Country/Ethnicity	Gender (M/F)	Age (years)	Diagnoses	Presenting Symptoms	Clozapine Duration	Clozapine Dose/ Day (Plasma Level µg/L)	Outcome (Time to Resolution)	Adverse Events
Aggarwal et al[20]	Trihexyphenidyl (6 mg undivided doses)	1	Not reported	India	M	21	Schizophrenia; Harmful cannabis use	Bed wetting	Not reported	350 mg/d	Complete resolution (5 d)	Excessive sedation and dizziness (amitriptyline Nil for trihexyphenidyl
	Splitting clozapine into twice-daily dosing										No response	
Apantaku-Olajide[21]	Sodium valproate	2	Not reported	Not reported	1 M; 1 F	32; 26	Paranoid schizophrenia; Schizoaffective disorder	Bed wetting; anytime urinary incontinence	Not reported	150 mg; 600 mg (350-400 µg/L)	Complete resolution	Not reported
Aronowitz et al[38]	Intranasal desmopressin 10 mcg in each nostril daily	1	Not reported	Not reported	M	32	Schizoaffective disorder depressive type	Nocturnal enuresis; Bladder urgency	2 wk	150 mg	Complete resolution	Not reported
Bhirud and Shah[36]	Imipramine 25 mg at night	3	Not reported	Not reported	Not reported	Not reported	Schizophrenia; Bipolar disorder	Nighttime urinary incontinence	2-3 wk	50-100 mg	Complete resolution	Not reported
	Clozapine dose reduction	9									Complete resolution	
	Self-resolved	3									Self-resolved	
Dadlani and Austin[22]	Bethanechol 10 mg three times a day	1	Not reported	Australia	F	47	Schizophrenia	Daytime and nighttime urinary incontinence	Not reported	200 mg (290 µg/L)	Partial resolution	Nil
	Behavioral intervention with support worker										No response	
Demirkol and Temam[25]	Amitriptyline 25 mg daily	1	Inpatient	Turkey	F	38	Not reported	Daytime and nighttime urinary incontinence	4 wk	250 mg	Complete resolution	Not reported
English et al[23]	Intranasal desmopressin daily and clozapine dose reduction	1	Inpatient	Hispanic	F	16	Bipolar mixed disorder with psychotic features	Nocturnal enuresis	3 mo	600 mg (642 µg/L)	Complete resolution	Nil
	Tolterodine 2 mg twice a day										No response	
Frankenburg et al[9]	intranasal desmopressin (10 mcg in each nostril daily)	4	Not reported	Not reported	6 M; 4 F	Mean age: 36	Not reported	Enuresis; Bladder urgency	Not reported	Mean: 402 mg/d	Complete resolution	Not reported
	oxybutynin (5-15 mg/d)	5										
	Nighttime alarm	1										
Fuller et al[26]	Ephedrine 25-75 mg/d (47 mg average)	19	2 inpatient; 17 not reported	Not reported	13 M; 7 F	32-47 (mean age: 44.9)	Schizophrenia; Paranoid schizophrenia; Schizoaffective disorder	Urinary incontinence; Nocturnal enuresis; Bladder urgency	2 wk to several months	Mean: 439.7 mg	15 complete resolution;3 partial resolution;1 no response	Nil
	Doxazosin 2 mg at night	1	Not reported					Urinary incontinence			No response	Not reported
	Behavioral program	1	Not reported								Complete resolution	Not reported
Ginsberg[24]	Intranasal desmopressin 10 mg in each nostril daily	1	Inpatient	Not reported	M	47	Schizophrenia	Nocturnal enuresis	3 wk	700 mg (760 µg/L)	Ceased due to life-threatening hyponatremia	
Hanes et al[27]	Pseudoephedrine 30 mg four times a day	1	Inpatient	Not reported	M	58	Paranoid schizophrenia	Urinary incontinence	Not reported	Not reported	Complete resolution	Not reported
Kho and Nielsen[14]	Sodium valproate 500 mg three times a day	1	Not reported	Not reported	F	Unknown	Schizophrenia	Bed wetting	Not reported	400 mg (480-590 µg/L)	Complete resolution	Not reported
	Changed to olanzapine	1			M	27		Bed wetting			Complete resolution	
	Insulin (for glucose positive urine)	1			M	29		Nocturnal enuresis			Complete resolution	

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Table 3. *Continued*

Paper	Intervention	No. of Participants	Setting	Country/Ethnicity	Gender (M/F)	Age (years)	Diagnoses	Presenting Symptoms	Clozapine Duration	Clozapine Dose/ Day (Plasma Level μg/L)	Outcome (Time to Resolution)	Adverse Events
Lee and Kim[31]	Aripiprazole 10-15 mg daily	2	Not reported	Not reported	2 M	52; 27	Paranoid schizophrenia	Not reported	Not reported	200 mg; 450 mg	Complete resolution	Not reported
Luche and Francois[40]	Desmopressin 10 mcg into each nostril once per day	1	Not reported	Not reported	F	69	Schizoaffective disorder	Nocturnal enuresis	1 d	150 mg		Not reported
Lurie et al[39]	Intranasal desmopressin	2	Not reported	Not reported	2 M; 5 F	26-43	Treatment-refractory psychosis	Urinary incontinence	Not reported	300-900 mg	Complete resolution	Not reported
	Oxybutynin 5-15 mg/d	5										
Mehtar and Ucok[29]	Self-resolution	1	Outpatient	Not reported	M	35	Paranoid schizophrenia	Double incontinence	3 wk	350 mg	Self-resolved	Not reported
Palaniappan[37]	Aripiprazole 10 mg/d	1	Not reported	Not reported	M	35	Paranoid schizophrenia	Nocturnal enuresis	3 mo	150 mg	Complete resolution (2 mo)	Not reported
	Fluid restriction and voiding before bed										No response	
Poyurovsky et al[33]	Verapamil 80 mg/d	1	Not reported	Ashkenazi Jew	Not reported	42	Paranoid schizophrenia	Nocturnal enuresis	Not reported	150 mg	Complete resolution	Temporary bradycardia for first 5 d of therapy and again at dose increase
Poyurovsky et al[33]	Trihexyphenidyl 5 mg at night	2	Not reported	Ashkenazi Jew	2 M	24; 21	Paranoid schizophrenia; Schizophrenia disorganized type	Nocturnal enuresis	4 wk; 6 wk	300 mg; 400 mg	One partial resolution (immediate); one complete resolution (immediate)	Not reported
Praharaj and Arora[34]	Amitriptyline 25 mg at night	1	Not reported	Not reported	M	35	Paranoid schizophrenia	Nocturnal enuresis	<4 wk	400 mg	Complete resolution	Not reported
Selvaraj et al[35]	Tolterodine 1 mg/d for 2 wk then 2 mg/d	1	Not reported	Not reported	F	37	Treatment resistant schizophrenia	Urinary urge incontinence	10 d	150 mg	Partial resolution at 1 mg; complete resolution at 2 mg	Nil
	Fluid restriction and voiding before bedtime										No response	
Steingard[28]	Intranasal desmopressin 10 mcg into each nostril once a day and clozapine dose reduction	1	Inpatient	Not reported	M	24	Schizophrenia	Nocturnal enuresis	Not reported	Not reported	Complete resolution	Nil

disproved was that both agents increase alertness and so patients would be more likely to wake from the urge to void.[26] However, the danger of misuse, diversion, and psychosis mean that these agents should be used with caution in patients with treatment resistant schizophrenia.[73] The selective β3 adrenergic receptor agonist, mirabegron, may be useful if urodynamic studies show overactive bladder activity. However, it should be noted that mirabegron has a theoretical pharmacokinetic interaction with clozapine as it is metabolized by the cytochrome P450 (CYP) enzymes 3A4 and 2D6.[74] Only one case study is available in the published literature which reported Pisa syndrome with the introduction of mirabegron in a patient taking clozapine.[75,76] Common adverse events of mirabegron include hypertension, constipation, dizziness, tachycardia, angioedema, and urinary retention.

There are significant limitations which need to be considered with these results. We were unable to find study designs other than case reports or case series and unable to quantitatively combine results. Case reports and case series data may be subject to selection, reporting, and publication bias. Included studies were small, and our recommendations for the use of aripiprazole are based on only three cases and supplemented with clinical and pharmacological reasoning. There was often poor reporting of psychiatric symptoms, side effects, concomitant medications, and a short duration of follow-up which may limit the accuracy and generalizability of the results. There were no validated scales employed to measure the severity of nocturnal enuresis and urinary incontinence, and clozapine plasma levels were reported in only five studies, and thus no conclusions can be made regarding the impact of a plasma-level relationship on the symptoms of nocturnal enuresis and urinary incontinence. There remains a need for randomized controlled trials of pharmacological intervention for nocturnal enuresis and urinary incontinence, notably aripiprazole and oral desmopressin, that use validated rating scales to assess symptoms of nocturnal enuresis and urinary incontinence.

Conclusion

Nocturnal enuresis and urinary incontinence are a common and underreported side effect of clozapine that is associated with significant stigma, reduced quality of life, and impaired treatment compliance. The exact mechanisms behind clozapine-induced nocturnal enuresis and urinary incontinence are unclear, although several pharmacological agents and nonpharmacological interventions appear beneficial. As there is a clear lack of quality evidence available for the management of clozapine-associated nocturnal enuresis and urinary incontinence, we have developed a management framework of treatment options to assist clinicians, patients, and carers. Any intervention should follow an assessment of urological, psychiatric, pharmacological, and common comorbid medical issues. Using a systematic approach to treatment, as recommended here, may best serve to address this complex issue.

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