



Conventional Antipsychotic and Clozapine-Induced Urinary Incontinence

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Abstract

Urinary incontinence (UI) is an embarrassing and distressing adverse effect of antipsychotic agents. Untreated UI may even lead to noncompliance in distressed patients. The incidence of UI and enuresis may be underreported. Although UI associated with antipsychotic use has been recognized, the etiology and optimal treatment strategies have not been fully established. This article was written to review the published literature and to explore the reported treatment options.

Several conventional antipsychotics have been associated with UI, including chlorpromazine, thioridazine, chlorprothixene, thiothixene, trifluoperazine, fluphenazine, fluphenazine (enanthate and decanoate), haloperidol, and pimozide. During the late 1980's, the incidence of clozapine-induced enuresis had been 0.23%. By 2000, many case reports and a few studies had labeled the incidence up to 48%.

A general explanation for the mechanism responsible for antipsychotic-induced UI and enuresis is that these side effects are due to mostly alpha-adrenergic blockade, some dopamine blockade, and a minimum of cholinergic effects on the bladder. Desmopressin seems to be an effective but expensive treatment. There are a myriad of oral treatments including pseudoephedrine, oxybutynin, benztropine, trihexyphenidyl, and dopamine agonists to incorporate with non-pharmacological approaches for UI.

Background

Urinary incontinence (UI) is an embarrassing and distressing adverse effect of antipsychotic agents. Untreated urinary incontinence may even lead to noncompliance

in distressed patients. Although UI associated with antipsychotic use has been recognized, the etiology and optimal treatment strategies have not been fully established. This article was written to re-

view the published literature chronologically through clozapine and to explore the reported treatment options.

A Medline search was conducted using the following terms limited to human and English: urinary incontinence, enuresis, bladder, antipsychotics, neuroleptics, clozapine, risperidone, olanzapine, quetiapine, and ziprasidone. Searching strategies revealed many case reports about risperidone or olanzapine inducing urinary incontinence or enuresis. None were published about quetiapine or ziprasidone. This article will include a compilation of the reviewed material discussing the conventional antipsychotics and clozapine only. After reading this article, I invite you to share your clinical experience regarding the four most recent serotonin-dopamine antagonists with other CPNP members by discussing this topic at list@cpnp.org.

Clinical Presentation

Several conventional antipsychotics have been associated with UI, including chlorpromazine, thioridazine, chlorprothixene, thiothixene, trifluoperazine, fluphenazine (including enanthate and decanoate), haloperidol, and pimozide.^{1,2,3,4} UI has been reported with a broad range of antipsychotic dosages.⁴ The clinical presentation is variable. It has been noted as usually nocturnal, not overflow or stress incontinence, without urgency, and endures for a limited time.⁵ A few years later, UI was reported to occur in daytime or at night.⁶ It can occur within hours after initiating an antipsychotic. In some patients though, UI may occur after two to four weeks of antipsychotic therapy.^{1,4} It often remits spontaneously during antipsychotic continuation.^{1,5,6} UI is noted in patients without prior bladder dysfunction and those with preexisting urinary problems.^{1,6} Schwarcz published a report of four cases of antipsychotic-induced enuresis in

patients with preexisting uninhibited urinary bladder.⁷ Furthermore, UI seems unrelated to gender or age.⁶

Psychotic regression and “neuroleptic catatonia” should be ruled out as causes of UI.⁵ Some patients become incontinent as a functional behavior. Other patients may be incontinent due to “atonic overflow bladder”.⁴ The provider should always rule out medical reasons for incontinence, such as a urinary tract infection.

Incidence

The incidence of UI and enuresis may be under recognized. Due to the embarrassing nature of UI, patients often underreport occurrences. Clinicians may fail to inquire about it.⁸

UI from chlorpromazine was mentioned in psychiatric literature as early as 1955⁹. Stress incontinence was noted in 1972¹⁰. Nurnberg and Ambrosini published a case series of UI associated with phenothiazines and haloperidol in 1979. The cases represented a 3% to 6% rate among the authors’ total sample.⁵ This was their first of several documents on the subject.

Clozapine

For several years, antipsychotic-induced UI and enuresis were rarely mentioned in psychiatric literature. The incidence of clozapine-induced enuresis had been 0.23% during the late 1980’s.¹¹ Steingard reported a case of clozapine-induced enuresis in 1994. This 24-year-old male experienced enuresis for the first eleven months of clozapine use. The enuresis improved when the patient lowered his clozapine dose to 100 mg/day. Unfortunately, he began experiencing hallucinations. Desmopressin 10 mcg intranasally was initiated. The enuresis stopped, but then recurred when desmopressin was discontinued. Desmopressin was restarted, and, in conjunction with nightly

desmopressin, the clozapine dose eventually rose to 350 mg/day.¹²

The next clozapine report was from Warner and associates. They describe a retrospective assessment that revealed five of twelve patients receiving clozapine had experienced “nocturnal incontinence”. None of the five had preexisting bladder difficulties. All of the cases occurred in the first three months of treatment and resolved spontaneously. Notably, only one of the five patients had documentation of self-reporting enuresis to the staff.¹³

In 1995, Aronowitz, Safferman, and Lieberman reported about a 32-year-old male who was randomized to clozapine in a research protocol. Within the first two weeks of treatment, the patient developed enuresis and urinary urgency. He was treated with antibiotics for a presumptive urinary tract infection. Even after the urine culture was negative, the man still endured enuresis at an increasing frequency. Desmopressin 10 mcg at bedtime rapidly relieved the enuresis.¹⁴

Frankenburg and colleagues published a letter about ten patients who experienced enuresis or bladder urgency. The urinary problems started after clozapine initiation, in both male and female patients taking a mean dose of 402±244 mg/day, and some without preexisting bladder dysfunction. Non-pharmacological measures did not help nine of the ten patients. Oxybutynin 5–15 mg/day was helpful in five patients and intranasal desmopressin 10 mcg at bedtime in the other four. This report, in addition to two earlier studies by the authors, observed the prevalence of clozapine-induced enuresis to be 28%.¹⁵

Similarly, Lurie and Hosmer report effectiveness of oxybutynin 5–15 mg/day in five outpatients with clozapine-induced UI. The authors also noted that two patients had a

trial of and responded to intranasal desmopressin. A total of seven of 71 patients at this practice site self-reported UI. This translates to an approximately 10% incidence.¹⁶

In 1996, Fuller and colleagues published a study of 57 patients receiving clozapine 75–900 mg/day. Seventeen of those 57 (30%) had clozapine-induced UI that was treated with ephedrine 25–150 mg/day at bedtime. Thirteen of the 17 (76%) experienced complete remittance of UI after starting ephedrine. The authors also found that significantly more females and patients who received higher dosages of concomitant conventional antipsychotics developed clozapine-induced UI.¹⁷

The incidence of clozapine-induced UI was retrospectively studied by Lin and colleagues. Sixty-one men and women had received clozapine therapy for at least three months (mean duration of 12.8 months). The authors found that 27 of the 61 (44%) patients complained of incontinence. Most incontinence occurred at nighttime, but about half of the 27 experienced UI both during the daytime and at night. Twelve of the 27 (44%) patients’ UI resolved over time. Contrarily, UI persisted during the study period in fifteen patients (56%), mostly males.¹⁸ The authors reply to a comment about the limitations of their retrospective methodology by mentioning the preliminary results of a prospective trial in clozapine-induced UI patients.¹⁹ The prospective trial shows a UI incidence of 48%.²⁰

Interestingly, a 1998 article quotes clozapine-induced UI at 1%, but that it is still underreported.²¹ This is much lower than many of the above reports. Most likely, the wide range of UI incidence, 1–48%, is due to clinicians being more vigilant about asking patients if they experience UI during

studies. As clinicians become more aware of antipsychotic-induced UI and enuresis they will be more attuned to asking patients about urinary side effects. Thus, the incidence may rise.

Urologic physiology⁷

The stimulation of muscarinic cholinergic receptors in the bladder cause smooth muscle contraction and bladder emptying. Stimulation of the alpha-adrenergic receptors promotes urinary continence via contraction of the bladder trigone and internal sphincter. Stimulation of beta-receptors in the bladder result in smooth muscle relaxation of the bladder wall. Thus, sympathetic stimulation causes bladder wall relaxation and internal urethral-sphincter contraction resulting in urinary continence. The urination reflex, micturition, is mediated by afferent pelvic nerves and efferent parasympathetic fibers. In the brain, the basal ganglia is partially responsible for inhibiting spontaneous bladder contraction.

Mechanism of Urinary Incontinence

Urinary incontinence and enuresis had been thought to occur due to alpha-adrenergic blockade that caused urinary sphincter relaxation in anatomically predisposed patients.⁹ The absence of other systemic hypoadrenergic effects, like hypotension, indicate that alpha-adrenergic blockade does not fully explain UI. Early speculation about antipsychotic-induced UI led to a centrally mediated mechanism.⁵ Support for this theory was derived from the observation that patients who experienced UI and enuresis lacked systemic alpha-adrenergic blockade symptoms, like hypotension.^{1,3,5,22}

Obsolete hypotheses suggested that UI was a form of extrapyramidal side effects⁶ or induced by urinary retention from anticholinergic side effects²³. These hypotheses are outdated since both low and high potency antipsychotics cause UI.

UI and enuresis are common in diseases that affect the basal ganglia, such as Parkinson's Disease, idiopathic orthostatic hypotension, and striatonigral degeneration.^{1,7} Ambrosini developed a hypothesis about UI and enuresis induced by antipsychotics. He proposed that UI results from an imbalance of the dopaminergic and noradrenergic systems within the basal ganglion structures.⁴ The work of Antelman and Caggiula proposed that noradrenergic neurons facilitated dopaminergic systems.²⁴ Therefore, Ambrosini suggested that pharmacological agents that block norepinephrine or dopamine would induce UI and enuresis in susceptible individuals, while drugs increasing norepinephrine or dopamine release would facilitate continence and urinary retention. This hypothesis was compatible with the observation that conventional antipsychotics, by creating a hypodopaminergic state, caused UI. Furthermore, he substantiated this theory by noting that enuresis is treated by tricyclic antidepressants which increase norepinephrine. To summarize, Ambrosini postulated that enuresis is a primary hypodopaminergic state with a secondary decrease in noradrenergic activity. Thus, treatment with tricyclic antidepressants, which increase norepinephrine, would counteract the dopamine blockade and induce continence.⁴

Ambrosini's hypothesis worked until reports of clozapine-induced UI became known. Clozapine blocks dopamine to a substantially lesser degree than conventional antipsychotics. Therefore, dopamine blockade cannot be the only etiological factor involved in antipsychotic-associated UI. Thus, clinicians looked back to Van Putten and colleagues' theory that the alpha-adrenergic blockade caused UI by decreasing internal bladder sphincter tone.⁹ Early speculation on the explanation for clozap-

ine-induced enuresis involved clozapine's anticholinergic properties causing overflow incontinence or sedation leading to an inability to awaken and urinate.¹⁴

According to Fuller and colleagues, the alpha-adrenergic hypothesis and the failure of anticholinergic treatments for UI led them to propose that an alpha-adrenergic agonist could reverse the clozapine-induced UI. They used ephedrine, an alpha-adrenergic agonist that was commercially available at the time. It was proposed that ephedrine would stimulate both alpha and beta-adrenergic receptors in the bladder, thus facilitating the contraction of the trigone and internal sphincters, as well as relax the smooth muscle of the bladder. These actions would lead to urinary continence.¹⁷

Nearly thirty years after the alpha-adrenergic blockade hypothesis was introduced, Hsu and associates conducted a study to determine if clozapine-induced UI is related to a genetic variant of the α_1 -adrenoceptor. Using the results of successful treatment with ephedrine, an alpha-adrenergic agonist, published by Fuller and colleagues,¹⁷ Hsu *et al.* postulated that α_1 -adrenoceptors might be involved with clozapine-induced UI. Molecular biology advances revealed subtypes of α_1 -adrenoceptors, the α_{1a} , α_{1b} , and α_{1c} -adrenoceptors. Hsu and his associates felt that since the α_{1a} -adrenoceptor is involved in controlling smooth muscle, it might be the genetic variant seen with clozapine-induced UI. However, no correlation between polymorphism and UI was found.²⁵

Most of the above theories have at least partial relevance in the etiology of UI. Fuller and colleagues' study revealed that a statistically significant greater number of clozapine patients developed UI when they received a mean of 440 mg chlorpromazine equivalents in addition to clozapine, com-

pared to those who did not take as high of adjunct antipsychotic dose.¹⁷ Perhaps this indicates that antipsychotic-induced UI and enuresis are mediated by both alpha-blockade and a hypodopaminergic state, as Ambrosini suggested.⁴ This coincides with a published table in Lieberman's article about side effects of clozapine.²¹ Research is needed to establish more evidence to support this theory.

Treatment

Non-pharmacological approaches to diminish the frequency of enuresis and UI include limiting fluids before bedtime and administering medications in the morning and midday instead of bedtime.^{4,7}

Other suggested approaches to treatment for antipsychotic-induced UI are drug continuation at the same dose, dose reduction, switching to a different antipsychotic, or changing the time of medication administration.⁴ Lomas and colleagues noted UI would diminish after lowering the chlorpromazine dose.⁸ The probable influence of alpha-blockade on UI would suggest that low potency antipsychotics may be more likely to cause urinary problems. Avoiding thioridazine and chlorpromazine in patients with a history of UI is reasonable.⁷ Loxapine and molindone are options that have not been reported to induce UI.⁷

Ambrosini and Nurnberg felt that anticholinergic agents, benztropine and trihexyphenidyl, do not diminish the frequency of UI.^{1,4,6} Contrarily, Jose found benztropine 1 mg once or twice daily to relieve the UI.²⁶ Much later, Poyurovsky wrote about treating clozapine-induced UI with trihexyphenidyl 5 mg at bedtime.²⁷ The competitive, nonsubtype-selective antimuscarinic agent, tolterodine (Detrol) was used in the attempt to treat one patient's clozapine-induced enuresis. Due to the "bladder-selective"-ity of tolterodine, the authors

hoped that the medication would cause less anticholinergic side effects when coupled with clozapine, compared to benztropine and clozapine. The patient did not report anticholinergic side effects, however, the tolerodine was ineffective for relief of enuresis.²⁸

Pollack suggests the use of oxybutynin 5 mg up to four times daily for UI. However, caution should be applied to oxybutynin for patients with overflow incontinence, since it causes urinary retention.⁷ Oxybutynin was reported to be useful in ten patients taking clozapine.^{15,16}

It was proposed that since drugs that block dopamine induce enuresis or incontinence, conversely, dopamine agonists could be effective in some patients for the treatment of UI.⁴ The dopamine agonist, amantadine, was successful in treating UI in a case of “neuroleptic-induced catatonia”.²⁹ Bromocriptine, another dopamine agonist, relieves bladder symptoms of frequency, urgency, nocturia, and incontinence in patients with Parkinson’s Disease.¹ Perhaps this could be applied to antipsychotic-induced UI. A disadvantage of dopamine agonists, such as bromocriptine and levodopa, is that psychotic patients may experience an exacerbation of psychosis.⁷

As early as 1991, desmopressin (DDAVP) was utilized for clozapine-induced enuresis.³⁰ Desmopressin is a highly selective antidiuretic agent with longer duration of action than vasopressin and with little vasopressor activity. It has been established that patients exhibit a decrease in nightly urine production due to an increase in plasma antidiuretic hormone (ADH) overnight.³¹ The overall effectiveness appears to be comparable to imipramine, but less effective than an enuresis alarm. (An enuresis alarm is an alarm clock that notifies the patient to awaken and urinate in the bathroom.) The

dose of desmopressin starts as low as 5 mcg intranasally at bedtime, then increases gradually to a maximum of 40 mcg based upon response. One “spray” is 10 mcg. Electrolytes should be checked early during the treatment to monitor for signs of overhydration.³¹

Ephedrine was beneficial for patients with clozapine-induced UI in the study reported by Fuller and colleagues. Despite earlier reports of ephedrine inducing psychosis, none of the patients had ill effects.¹⁷ Nonetheless, monitoring patients by performing mental status exams is important. In 2002, ephedrine is not commercially available from prescription drug vendors, but is available via Internet suppliers. The unavailability of ephedrine is due to abuse potential and a large number of cardiac related adverse events reported to the FDA.³² Pseudoephedrine 30 mg may be an alternative to ephedrine 25 mg.³³

Conclusion

In summary, a general explanation for antipsychotic-induced UI and enuresis is that these side effects are due to mostly alpha-adrenergic blockade, some dopamine blockade, and a minimum of cholinergic effects on the bladder. Desmopressin seems to be an effective but expensive treatment. There are a myriad of oral treatments including pseudoephedrine, oxybutynin, benztropine, trihexyphenidyl, and dopamine agonists to incorporate with non-pharmacological approaches for UI.

Application of the following will help your patients deal with embarrassing urinary incontinence and maintain compliance. Question patients about past and current urinary incontinence, enuresis, or bladder problems. Take the pharmacology of a chosen antipsychotic into consideration along with the patient related urinary system factors. An elementary example would be: a

patient divulges that he has overflow incontinence. Therefore, do not choose an extremely anticholinergic antipsychotic as first choice. Improve patient self-reporting by counseling patients that the treatment team can help if the patient is willing to re-

port any urinary problems.

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**Clark N. Conventional Antipsychotic and Clozapine-Induced Urinary Incontinence.
JCPNP 2003:2(2)**

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