

---

# FOR YOUR INFORMATION



## PHARMACY NEWSLETTER



Volume #22, Issue #04 – April, 2002

### **Clozapine-Induced Urinary Incontinence**

#### **Introduction**

Clozapine is an atypical antipsychotic that is used in the treatment of refractory schizophrenia. Its use, however, has been associated with urinary incontinence or enuresis. Although the nature of this side effect does not pose a major health risk, it contributes negatively to a patient's quality of life and may lead to medication noncompliance.

#### **Incidence of Clozapine-Induced Urinary Incontinence**

The incidence of urinary incontinence has been estimated at 1%.<sup>1</sup> Recent studies, however, have shown that the incidence of clozapine-associated urinary incontinence may be higher than what was previously reported. In one retrospective study<sup>2</sup>, 17 of 57 inpatients (29.8%) treated with clozapine (75 – 900mg/day) for refractory schizophrenia developed urinary incontinence. Urinary incontinence in this population was more likely to occur in women (p=0.03) and in those who were receiving concomitant typical antipsychotic agents (p=0.024). Warner et al<sup>3</sup> assessed 12 patients established on a therapeutic dose of clozapine and found that 5 (41.7%) had experienced nocturnal incontinence. Incontinence in these patients occurred within the first three months of initiating clozapine therapy and resolved spontaneously. Lurie et al<sup>4</sup> report urinary incontinence in 7 of 71 outpatients (9.9%) treated with clozapine (300 - 900mg/day) for resistant psychosis. Finally, a retrospective study<sup>5</sup> of clozapine and urinary incontinence in Chinese inpatients showed that 27 of 61 patients (44.3%) developed urinary incontinence. This

study found no statistically significant differences in age, sex, clozapine dose, duration of clozapine use, duration of illness, age at onset of schizophrenia, or concurrent treatment with other psychiatric medications between patients who developed urinary incontinence and those who did not. The variations in the incidence of urinary incontinence may be in fact due to approaches to identifying patients with urinary incontinence (i.e. subjective complaints vs evidence of bed-wetting) as well as differences in patient populations (i.e. inpatients vs outpatients; severity of psychosis etc.).

#### **Mechanism of Clozapine-Induced Urinary Incontinence**

Presently the mechanism that explains clozapine-associated urinary incontinence is not well defined. It is known that bladder function is under the control of the sympathetic, parasympathetic and somatic nervous systems.

Continence is maintained by both  $\beta$ -adrenergic mediated relaxation of the bladder wall smooth muscle and  $\alpha$ -adrenergic mediated contraction of the trigone and internal sphincter. Micturition is controlled by cholinergic mediated bladder wall contraction. Somatic mechanisms are cortically mediated via the spinal reflex arc as well as through the control of the external sphincter and perineal muscles.<sup>2</sup>

Although the pathophysiological mechanisms remain unclear for clozapine-associated urinary incontinence, many theories have been proposed.

Steingard<sup>6</sup> suggests that sedation prevents patients from waking up during sleep to empty bladder, especially when used in combination with other sedative medications. Clozapine's  $\alpha$ -adrenergic blocking properties could lead to stress urinary incontinence by decreasing internal bladder sphincter tone.<sup>2</sup> Clozapine's potent anticholinergic properties can lead to urinary retention with subsequent overflow incontinence.<sup>3,7</sup> A central component of urinary incontinence has also been suggested. Urinary incontinence could be a result of reduced dopamine transmission with secondary noradrenergic hypoactivity in the basal ganglia. It has been suggested that treatment-resistant individuals may have a greater degree of dysregulation of dopamine/noradrenaline systems, which may make them more susceptible to developing urinary incontinence mediated via central mechanisms.<sup>8</sup> Others have associated resolution of enuresis to the control of seizure and hyperglycemia related to clozapine therapy.<sup>9</sup>

The relationship between clozapine dose and urinary incontinence as well as timeframe to expect incontinence has not been clearly established. Warner et al<sup>3</sup> report the occurrence of clozapine-induced urinary incontinence in 5 of 12 patients within the first three months of initiating clozapine therapy. However, Centorrino et al<sup>10</sup>, report enuresis as a late side effect, which is not correlated with plasma level of the drug. Furthermore, urinary incontinence has been reported to resolve with a dose reduction; however, worsening of the patient's psychosis resulted.<sup>6</sup>

### **Treatment of Clozapine-Induced Urinary Incontinence**

Treatment approaches for clozapine-induced urinary incontinence have included the following: 1) Decreasing the dose of the antipsychotic agent, 2) switching to an agent with less potent anticholinergic activity, 3) administering the antipsychotic agent earlier in the evening if nocturnal incontinence is the

issue, 4) behavioural modification (i.e. toileting schedules) and 5) treating the incontinence with a pharmacological agent.<sup>2,11</sup> The pharmacological agent chosen will depend on the type of urinary incontinence the patient is experiencing. At present, there have been no published randomized controlled trials investigating effective treatments for clozapine-induced urinary incontinence. Effective treatments have, however, been documented in case reports and in one prospective study (Table 1).

Pharmacological treatment of overflow incontinence secondary to urinary retention and/or constipation should be considered once any existing outflow obstruction has been removed. Bethanecol (10-50mg bid-qid), a cholinergic agonist, can be used short-term to stimulate bladder contraction. Prazosin (0.5-2mg bid-qid), an  $\alpha$ -adrenergic antagonist, has been used to relax smooth muscle of the urethra and prostate capsule allowing for improved outflow of urine from the bladder.

Drugs used in the management of stress incontinence secondary to  $\alpha$ -adrenergic blockade include  $\alpha$ -adrenergic agonists and imipramine. Alpha-adrenergic agonists stimulate urethral smooth muscle sphincter contraction, thereby increasing sphincter resistance to outflow. Fuller et al<sup>2</sup> investigated the use of ephedrine (25-150mg/day) in 16 patients who experienced urinary incontinence after initiating clozapine therapy (75-900mg/day) for refractory psychosis. Twelve of 16 patients (75%) had a complete remission of their urinary incontinence, 3 (17.8%) had a reduction in frequency of urinary incontinence and 1 (6.2%) had no response to therapy. Imipramine (10-50mg od-tid), a tricyclic antidepressant, has also been used to treat stress incontinence. Imipramine has both anticholinergic effects as well as a direct relaxant effect on the bladder smooth muscle and some alpha-agonist activity which enhances urethral resistance.

Oxybutynin (2.5-5mg od-tid) has been reported to be effective in treating clozapine-induced urinary incontinence.<sup>4,12</sup> Oxybutynin exerts a direct spasmolytic and antimuscarinic action on the detrusor muscle of the bladder, which results in increased urinary bladder capacity, diminished frequency of uninhibited contractions of the detrusor muscle, and a delay in the initial desire to void. Tolterodine, an antimuscarinic similar to oxybutynin, has been effective in the treatment of urge incontinence, although it was unsuccessful in treating clozapine-associated urinary incontinence in one case report.<sup>11</sup>

The use of intranasal desmopressin (10µg per nostril) for clozapine-induced urinary incontinence has been documented in 10 cases.<sup>6,7,11,12</sup> Desmopressin acts to decrease the formation of urine by increasing water absorption by the renal collecting ducts.

## **Conclusion**

Urinary incontinence is an unpleasant and embarrassing side effect of clozapine therapy. Identifying appropriate pharmacological and non-pharmacological strategies in the management of urinary incontinence is important for the improvement in a patient's quality of life and the prevention of noncompliance with antipsychotic drug therapy.

*Written by: Katie Lencaria, Bsc (Pharm), VGH Pharmacy Resident*

*Reviewed by: Dr. Sylvia Zerjav, Pharm. D.*

*If you would like to be added to the Inpharmation Newsletter mailing list, please call (604) 524-7012 or email address [bthompson@bcmhs.bc.ca](mailto:bthompson@bcmhs.bc.ca). Please ensure you include your entire mailing address (including postal code).*

Table 1. Summary of Case Reports of Clozapine-Induced Urinary Incontinence

Author(s)	Gender	Age	CLZ dose/day	Time to develop UI	Hx UI	Treatment Used	Response to Treatment
Lurie et al 1997 <sup>1</sup>	5W 2M	26-43	300-900mg	?	1 yes	Oxybutynin 5-15mg/day Intranasal desmopressin	Resolved
Steingard 1994 <sup>6</sup>	M	24	300	?	No	Intranasal desmopressin 10µg per nostril HS	Resolved Desmopressin d/c after 1 wk with reemergence of UI. Restarted with no episodes of UI at 2 month f/u.
Frankenburg et al 1996 <sup>12</sup>	4F 6M	35.5± 11.6	402 ± 244mg	?	2 yes	Oxybutynin 5-5mg/day (5 pts) Intranasal desmopressin 10µg per nostril HS (4 pts) Behaviour tx with alarm clock (1 pt)	Resolved
Aronowitz et al 1995 <sup>7</sup>	M	32	150mg	2 wks	?	Intranasal desmopressin 10µg per nostril HS	Resolved
English et al 2001 <sup>11</sup>	F	16	600mg	3 mos	?	Intranasal desmopressin HS & ↓ CLZ 500mg/day	Resolved in 2 days
						1 wk later tx Δ tolterodine 2mg bid	UI returned & continued with 14 days of therapy.
						2 wks later tx Δ desmopressin	Resolved in 2 days
Lin et al 1990 <sup>5</sup>	11F 16M	36.2± 7.5	381.5 ± 133.1mg	?	?	N/A	N/A
Fuller et al 1996 <sup>2</sup>	9M 4F	32-56	200-700	?	?	Ephedrine 25-75mg/day	Resolved (Oxybutynin & Doxazosin not effective prior to ephedrine in 3 patients)
	1M 2F	36-69	200-650	?	?	Ephedrine 25-75mg/day	Reduction in frequency of UI
	M	50	600	?	?	Ephedrine 150mg/day	No change
Kho et al 2001 <sup>9</sup>	F	?	400	?	?	Δ Olanzapine	Enuresis resolved; No relapse experienced
	M	27	400	?	?	Add VA 500mg tid 2° seizures	Enuresis resolved; no further episodes of seizures
	M	29	400	?	?	Add insulin 2° hyperglycemia	Enuresis resolved with control of blood glucose
Warner et al 1994 <sup>3</sup>	4M 1F	33-54	300-450	Within 3 months	No	None	Resolved spontaneously

M=male; F=female; CLZ=clozapine; UI=urinary incontinence

## References

1. Repchinsky C (ed). *Compendium of Pharmaceuticals and Specialties*. 36<sup>th</sup> ed. Ottawa: Canadian Pharmacists Association 2001.
2. Fuller MA, Borovicka MC, Jaskiw GE, Simon MR, Kwon K et al. Clozapine-induced urinary incontinence: Incidence and treatment with ephedrine. *J Clin Psychiatry* 1996;57:514-518.
3. Warner JP, Harvey CA, Barnes TRE. Clozapine and urinary incontinence. *Int Clin Psychopharm* 1994;9:207-209.
4. Lurie SN, Hosmer C. Oxybutynin and intranasal desmopressin for clozapine-induced urinary incontinence. *J Clin Psychiatry* 1997;58:404.
5. Lin CC, Bai YM, Chen JY, Lin CY, Lan TH. A retrospective study of clozapine and urinary incontinence in Chinese in-patients. *Acta Psychiatr Scand* 1999;100:158-161.
6. Steingard S. Use of desmopressin to treat clozapine-induced nocturnal enuresis. *J Clin Psychiatry* 1994;55:315-316.
7. Aronowitz JS, Safferman AZ, Lieberman JA. Management of clozapine-induced enuresis. *Am J Psychiatry* 1995;152:472.
8. Ambrosini TL. A pharmacological paradigm for urinary incontinence and enuresis. *J Clin Psychopharm* 1984;4:247-253.
9. Kho KH, Nielsen O. Clozapine-induced nocturnal enuresis: diagnostic and treatment issues. *Psych Bulletin* 2001;25:232-233.
10. Centorrino F, Baldessarini RJ, Kando JC et al. Clozapine and metabolites: concentration in serum and clinical findings during treatment of chronically psychotic patients. *J Clin Psychopharm* 1994;14:119-125.
11. English BA, Still DJ, Harper J, Saklad SR. Failure of tolterodine to treat clozapine-induced nocturnal enuresis. *Ann Pharmacother* 2001;35:867-868.
12. Frankenburg FR, Kando JC, Centorrino F, Gilber JM. Bladder dysfunction associated with clozapine therapy. *J Clin Psychiatry* 1996;57:39-40.