A Comment on Clozapine-Induced Enuresis: An Underrecognized and Undertreated Problem

To the Editor: Recently, Luche and Francois[1] reported on an interesting case of a 69-year-old woman with schizoaffective disorder, bipolar type who developed clozapine-induced incontinence and nocturnal enuresis early in treatment and responded favorably to adjunctive desmopressin. A few points are worthy of mention.

Incontinence and enuresis are more common with, but not unique to, clozapine than with other antipsychotics. Incontinence and enuresis might even be related to schizophrenia diagnosis itself and can occur in up to 40% of patients early in treatment. Approximately 20% of patients report persistent nocturnal enuresis.[2]

I agree with the authors[1] that this particular side effect must be assessed by direct inquiry (akin to sexual dysfunction)—patient embarrassment leads to underreporting and underdiagnosis.

Mechanisms of clozapine-induced incontinence are protean. It might be ascribed to α_1-adrenolytic actions, oversedation, anticholinergic actions resulting in retention with overflow, constipation, metabolic derangement with glycosuria, or epileptogenecity just to mention a few possibilities.[3] Central dopaminergic blockade (causing detrusor muscle hyperactivity) and serotonergic inhibition (affecting parasympathetic innervations of the bladder) might be contributory as well.

An approach to this problem might entail the following strategies. (1) Rule out/in constipation, urinary tract infections (with poor personal hygiene as negative symptom domain in schizophrenia and pelvic floor relaxation in postmenopausal females as in the case by Luche and Francois[1]), diabetes, nocturnal seizures, spinal lesions, and benign prostatic hyperplasia in older men. Abdominal ultrasonography/sonography and urodynamic studies (eg, postvoid residual volume > 200 mL can be regarded as inadequate) if indicated may be part of the initial workup. (2) Slow titration of clozapine and divide the dose if given at night, as tolerance might develop over time in the first 2 to 3 months. Although, it is not clearly a dose-related side effect, if oversedation is suspected, lowering the dose might be helpful. (3) Minimize evening fluid intake. (4) Encourage the patient to empty the bladder before sleep and discuss bladder training and Kegel exercises. (5) Avoid diuretics (including caffeinated beverages). (6) Taper off other antipsychotics, if any, as their presence can increase risk for nocturnal enuresis × 6. (7) Consider the following medications: ephedrine, pseudoephedrine, desmopressin acetate (beware of hyponatremia), clonidine,[4] bupropion (beware of psychotomimetic effects), aripiprazole (might mitigate metabolic syndrome), duloxetine (serotonin-norepinephrine reuptake inhibitor), atomoxetine[5] (norepinephrine reuptake inhibitor), mirtazapine,[6] or mirabegron (β-3 agonist; if urodynamic studies show overactive bladder). (8) Avoid anticholinergics, as this can increase risk for ileus (clozapine is strongly anticholinergic). (9) Remember that stopping the offending agent might be impractical, as with the case of treatment resistance wherein clozapine has an edge over other antipsychotics.

Dr Francois was shown this letter and declined to reply.

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