

Editorial

Nocturnal enuresis with antipsychotic medication

Thomas R. E. Barnes, Marcus J. Drake and Carol Paton

**Summary**

Nocturnal enuresis can be discomfiting and troublesome. There is increasing evidence that as a side-effect of second-generation antipsychotics, particularly clozapine, it may be underrecognised. Direct but sensitive questioning may be required to elicit this side-effect. We briefly review possible mechanisms of this problem, and management and treatment options.

Declaration of interest

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The results of a comparative cohort study in people prescribed second-generation antipsychotics, reported by Harrison-Woolrych *et al*,¹ suggest that approximately one in five adults taking clozapine experience nocturnal enuresis, a higher proportion than those taking some other second-generation antipsychotics, specifically, risperidone, olanzapine and quetiapine. Reference to another relevant information source, the spontaneous reports of adverse events collected by the yellow-card system,^{2,3} reveals that urinary incontinence and/or enuresis have been associated with all these antipsychotics, and make up the highest proportion of all reports for risperidone, followed in descending order by olanzapine, clozapine and quetiapine. Although these data reinforce that this is a risk with all these drugs, the vagaries of this reporting system (not least, a far higher overall number of adverse event reports for clozapine) preclude any interpretation of relative liability. Nevertheless, yellow-card reports of incontinence and/or enuresis for first-generation antipsychotics are far rarer.

In our own early case series of patients with enuresis and taking clozapine,⁴ the problem had occurred within 3 months of treatment and resolved spontaneously in all cases. This was in line with clinical observation that incontinence as a side-effect of antipsychotic medication tended to develop early in treatment, typically within the first few days, and is usually self-limiting, although subsequent studies showed that the condition may persist in a proportion of individuals.⁵ We noted that the problem was often missed by the clinical team, perhaps partly because affected individuals can be embarrassed and reluctant to report it to staff, and partly because individuals may not attribute the problem to medication. We suggested that specific enquiry may be necessary to elicit this phenomenon. This was a view reinforced by our later study⁶ comparing an open question about side-effects with systematic enquiry, administering a comprehensive checklist of potential antipsychotic side-effects. We found that nearly 40% of a sample of people established on clozapine treatment had

experienced nocturnal enuresis, although this problem was identified almost exclusively by responses to the systematic checklist. Lack of recognition of the problem by clinicians, and underreporting by discomfited patients may partly explain the wide variation in published incidence figures,⁷ ranging from 0.23 to 30%.

The paper by Harrison-Woolrych *et al*¹ may help to raise awareness of this problem among clinicians, in a way that relevant case reports over the past 15 years or so have failed to do. Clinicians' understanding of the side-effect profiles of individual antipsychotic drugs, and their relative liability for particular side-effects, will be partly based on clinical experience: the side-effects observed in, or reported by, their patients. Knowledge about side-effects will also derive from published case reports and research studies, predominantly clinical trials. However, in trials of antipsychotic medication, while data relevant to certain side-effects such as extrapyramidal side-effects and weight gain are commonly provided, problems that may be more challenging to assess or elicit such as urinary incontinence, sexual dysfunction and aversive subjective experiences are consistently overlooked. Thus, the outcome data from clinical studies do not provide clinicians with reliable descriptions of the overall tolerability of individual antipsychotics or their relative liability for all the common adverse effects.

Mechanism

Enuresis signifies the occurrence of voiding at inappropriate times. An enuretic episode is essentially a normal void, mediated by the micturition reflex in the brainstem/midbrain, but not in the appropriate context (i.e. volitionally initiated once in a suitable environment). Nocturnal enuresis is thus normal voiding during sleep. Enuresis has to be distinguished from incontinence, which is an involuntary loss of urine resulting from bladder overactivity (urgency incontinence), weakness of the bladder outlet (stress incontinence) or incomplete bladder emptying (urinary retention leading to overflow incontinence). Mechanisms underlying emergence of enuresis or incontinence can be hard to determine, mainly because the main diagnostic test (invasive urodynamics) can only effectively study the problem if it occurs during the test. This is not an easy requirement for nocturnal enuresis, where the timing is usually unpredictable and sporadic, and because of logistical issues (a urodynamic unit is not a restful environment for sleep). Assumptions therefore have to be made, and resulting presumptions have to be treated circumspectly. Nonetheless, in

the absence of new-onset urinary urgency, stress incontinence or voiding dysfunction, enuresis would be a reasonable diagnosis.

A variety of mechanisms may underlie nocturnal enuresis in people treated with antipsychotic medication. In the context of a psychotic illness, a predisposition to changes in autonomic function may be present, conceivably through the illness itself,⁸ drug treatment or lifestyle factors. For example, some people with psychotic illness consume excess caffeine, which has a diuretic action and also inhibits the metabolism of clozapine. The limited understanding of cerebral control mechanisms makes it hard to conclude responsible processes, but the emergence of enuresis with medication does offer an interesting perspective. Antipsychotic drugs have a wide range of pharmacological actions. For example, many antipsychotics are sedative and it has been postulated that some individuals may sleep so deeply that they fail to recognise that their bladder is full and they need to void. This does not seem entirely satisfactory as an explanation, given that 'deep sleep' is not exclusively sedation-induced, and is by no means strongly associated with enuresis. Most antipsychotics also have the potential to lower the seizure threshold and it is possible that nocturnal incontinence is associated with seizures that occur only during sleep. Drug-induced diabetes mellitus could result in polyuria, which could lead to nocturnal polyuria thus increasing the demands on the lower urinary tract.

Clozapine is the drug most commonly implicated in urinary incontinence, and there has been speculation about the relevance of its cholinergic mechanisms, including agonist activity at muscarinic M4 receptors. Specifically, it has been suggested that the potent anticholinergic action of clozapine may lead to urinary retention and subsequent overflow incontinence. However, a continuously distended bladder should be clinically apparent if this is the mechanism. There have also been case reports of diabetes insipidus with clozapine.

An animal study has shown that olanzapine, and to a lesser extent risperidone, affects a number of voiding parameters with the net result being a decrease in micturition volume, an increase in the residual volume of the bladder and decreased activity of the external urethral sphincter; the authors suggested that the mechanism of these effects may be central rather than peripheral.⁹ In a small study of participants who developed urinary incontinence after starting treatment with a second-generation antipsychotic drug, urodynamic investigations revealed that a third had detrusor overactivity and a further third reduced bladder compliance.¹⁰ This suggests that antipsychotic drugs may cause urinary incontinence through a number of mechanisms and that individual susceptibility may differ. In support of this hypothesis, case reports and case series claim the successful treatment of clozapine-induced enuresis with drugs as diverse as anticholinergics (trihexiphenidyl, oxybutynin), alpha-1 agonists (ephedrine), antidepressants (amitriptyline), addition of a second antipsychotic to clozapine (aripiprazole), and desmopressin.^{11–15} Central dopaminergic-serotonergic effects combined with peripheral 1-adrenergic blockade may act synergistically and predispose to urinary dysfunction; this has been postulated in a case report.¹⁶ The lower urinary tract is controlled by various neurotransmitter pathways for which antipsychotic drugs have affinity. These include serotonin (facilitates urine storage and inhibits voiding), dopamine (blockade in the basal ganglia may cause involuntary enuresis), acetylcholine (directly affecting bladder contractility) and adrenergic (important in regulating bladder outlet function, particularly in men).

The weakness of this evidence base and the diversity of proposed interventions lead inevitably to uncertainty about optimal treatment recommendations in what is a challenging clinical setting. This is exemplified by the fact that risperidone,

a potent alpha-1 adrenergic antagonist, has been reported to both cause¹⁰ and treat¹⁶ urinary incontinence. The mechanisms are likely to be multifactorial in view of the broad actions of antipsychotics and further research is required.

Management

Simple management strategies that are tried in practice include antipsychotic dose reduction where possible or reducing the proportion of the daily dose given at night. Other practical measures include advising individuals to limit fluid intake during the evening, avoid caffeine and alcohol, and empty their bladder before going to sleep. Given the absence of a known relative liability of antipsychotics for this side-effect or a predictable risk (based on pharmacological profile), clinicians may turn to a review of an individual's tolerability of past antipsychotic treatment in this respect to inform a possible trial switch to another antipsychotic.

Appropriate risk management need not necessarily involve cessation of the antipsychotic medicine. There have been claims of successful treatment of clozapine-induced enuresis with various adjunctive medications, all of which seek to exploit some of the different pharmacological mechanisms noted above; these include amitriptyline, desmopressin, ephedrine and anticholinergics such as oxybutynin and trihexiphenidyl.^{12,17–20} Some anticholinergic agents (thought to increase bladder capacity and thus reduce symptoms of urgency) are licensed for the management of urgency urinary incontinence. Alpha-blockers are licensed for the management of voiding symptoms due to benign prostatic hyperplasia. However, for all of these agents the limited evidence for benefit and risks when used for antipsychotic-induced enuresis falls well short of justifying any treatment recommendation.

Conclusion

The impact of this side-effect on patients and carers is profound: the ignominious and uncomfortable nature of the problem, the need for regular washing and laundering of bed linen, and worry about the cause of the bedwetting, can add to a individual's subjective burden and adversely affect quality of life. Night-time bedwetting, in common with some other recognised antipsychotic side-effects such as sexual dysfunction and menstrual irregularities is only likely to be elicited by direct but sensitive questioning. The inevitable corollary is that people prescribed clozapine or any other second-generation antipsychotic should be monitored appropriately for nocturnal enuresis.

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poems
by
doctors

Section

Nitesh Painuly

You need to come to the hospital.
No, I don't.

We will look after you.
Please don't bother.

You are unwell.
I know.

I am concerned.
Don't be.

I am afraid, I have to be.
Yes, you are at risk too.

You have no insight.
Do you have?

You have no capacity.
I have no capacity to resist you.

I have to decide on your behalf.
I'll let you believe that.

Section! How do you feel?
How do *you* feel?

Well . . . I have to keep *us* safe.
Staying alive is not safe for me, don't know about you.

Nitesh Painuly has been writing poems in English and in his native language Hindi. His work as a consultant psychiatrist in the NHS informs a great degree of his writing.

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