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Letter to the Editor

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Desmopressine is and remains the drug of first choice for clozapine-induced nocturnal enuresis or urinary incontinence

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We would like to address 2 points of the systematic review of all case reports of clozapine-associated nocturnal enuresis or urinary incontinence by Tanzer et al.[1]

The authors present the reports on 74 patients. Drug treatment varied widely: a total of 10 different drugs were found. Clozapine is known for its strong anticholinergic effect, causing among other, gastrointestinal hypomotility (GIH) that can develop into subileus, ileus and even result in death. While the prevalence of GIH matches that of agranulocytosis, its mortality rate is 4 to 8 times higher. Of the 10 drugs prescribed for the treatment of urine incontinence, 5—amitriptyline, imipramine, oxybutynine, tolterodine, and trihexfenidyne—are strong anticholinergics; the other five - aripiprazole, desmopressine, (pseudo-)ephedrine, verapamil - are weak anticholinergics.

While nocturnal enuresis or urinary incontinence is considered to be both widely prevalent—up to 40%—and underreported, the authors do not address the issue of early detection of this disturbing side-effect. We think the frequent and systematic use of the Glasgow Antipsychotic Side-effect Scale[2] is the best way for the timely detection of unreported nocturnal enuresis or urinary incontinence. This is our first point.

Our second point touches on the author's recommendation of aripiprazole as the authors' drug of first choice. Their motivation is clear: aripiprazole has, on top of antipsychotic effect, a neutral anticholinergic profile, it attenuates several of clozapine's well-known side effects (weight gain, sedation, and obsessive-compulsive) and it is well-tolerated when combined with clozapine. Their choice has many limitations. The first is acknowledged by the authors: their choice is based on very limited evidence: only 3 of the 74 patients were treated with aripiprazole. This is not all: information on such essentials as publication bias, dropout, and/or treatment failure rate is missing. This is especially relevant as the long interval between treatment initiation and treatment effect can undermine patients compliance with the add-in treatment. The authors' claim of beneficial effect of aripiprazole addition—improvement in psychotic symptoms leading to improved continence—is an understandable and interesting hypothesis and suggestion, but one that is not even mentioned, let alone confirmed, in the 3 case reports. With all this information missing, there can be only 1 conclusion: 3 cases are too few for a recommendation and the authors' recommendation is premature. The cases can be a stimulus for further studies to (try to) answer all currently open questions.

Tanzer et al motivate their choice in favor of aripiprazole at the cost of, among other substances, desmopressine by pointing to the risk of hyponatremia, which occurs in 5% to 15% of the cases,[3,4] with increased age and low sodium baseline as high-risk factors,[3] initiation of desmopressine treatment for nocturia is contraindicated in patients >65 years old.[4] The relevance of this side-effect for clozapine-treated patients with schizophrenia below 65 years, is not an established fact; it rather is a question that deserves further study. Secondly: an established side-effect of 1 drug is no evidence of the efficacy of another drug that lacks this side-effect. As yet the evidence in favor of aripiprazole is few and far in between.

Oxybutynine and tolteridone, 2 drugs of first choice for the treatment of nocturnal enuresis or urinary incontinence, are anticholinergic agents that could initiate or worsen preexistent GIH. While the incidence rates of agranulocytosis and GIH are identical incidence, their mortality rates differ widely: 2.2% to 4.2% (agranulocytosis) vs 15.0% to 27.5% (GIH) in population studies. A review of all published case reports found a mortality rate of GIH of 43.7%.[5]

Due to its lack of anticholinergic properties, desmopressine is and remains the drug of first choice for the treatment of clozapine-induced nocturnal enuresis or urinary incontinence in patients below 65 years, independent of whether these symptoms are also clozapine-induced or not. The verdict on the efficacy of treatment of clozapine-induced nocturnal enuresis or urinary incontinence is still out.

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