Aripiprazole as a treatment option for clozapine-induced enuresis

Sir,

Nocturnal enuresis was initially thought to be a rare adverse effect in patients who were prescribed antipsychotic medicines. A cohort study[1] had shown that the prevalence was as high as 20.7% in clozapine, 9.6% in olanzapine, 6.7% in quetiapine, and 6.2% in risperidone exposed patients. Clozapine is known to have a higher risk for enuresis when compared with other atypical antipsychotics,[2] but the mechanisms underlying the adverse effect are yet to be fully understood. Mechanisms postulated are inhibition of detrusor activity by anticholinergic action and resultant retention overflow, sedation and lowering of the seizure threshold, drug-induced diabetes mellitus associated polyuria, clozapine-induced diabetes insipidus, and hypodopaminergia in central pathways controlling micturition reflex.[3] Though a variety of interventions such as trihexyphenidyl[4] were tried, the response was not consistently satisfactory, possibly explaining the existence of many other mechanisms of enuresis, which are not targeted by these medications.

Aripiprazole being a dopamine D2/D3 partial agonist can target hypodopaminergia in the central pathways that control micturition reflex. This case report briefs about off label use of aripiprazole for clozapine-induced enuresis.

Mr. A, 35-year-old male, working as a laborer in machinery factory, presented with 6 years of continuous illness characterized by somatic passivity, the delusion of persecution, thought broadcasting and delusion of infidelity. He was diagnosed to have paranoid schizophrenia with baseline Brief Psychiatric Rating Scale score of 35. In view of the past poor response to adequate trials of olanzapine, trifluoperazine, and risperidone, he was started on clozapine 25 mg and was gradually titrated up to 150 mg. Further increase in dosage of clozapine was not possible secondary to severe sedation. Reduction of the dosage of risperidone was attempted but resulted in worsening of psychotic symptoms, and thus, he was continued on the combination of clozapine 150 mg and risperidone 4 mg. With 3 months of treatment, his Brief Psychiatric Rating Scale score reduced to 8 with a return to premorbid level of occupational functioning. By February 2013, he reported of episodes of enuresis (nocturnal) at least 5 times/month, fluctuating in its course but never ceased. Enuresis was highly distressing to patient and caregivers, which by itself was endangering the adherence to medications. There were no symptoms and signs of urinary tract infection. His fasting blood glucose was 91 mg/dl, urine specific gravity was within normal limits, urine microscopy-bacteria and pus cells were negative. He was advised to restrict fluid intake and void urine before going to bed, with which there were no difference in the frequency of enuresis. An attempt to reduce either clozapine 150 mg or risperidone 4 mg resulted in exacerbation of psychotic symptoms, which resolved with reinstitution of the same dosage. In view of persisting enuresis, aripiprazole 10 mg HS was added, after which the frequency of enuresis gradually reduced to once per month and got completely subsided by the 2nd month of adding aripiprazole 10 mg. This improvement persisted even during subsequent follow-ups with no additional adverse effects or exacerbation of psychotic symptoms.

In our report, enuresis was highly distressing and endangering the adherence to the treatment. Enuresis had occurred after 15 months of the use of a combination of clozapine and risperidone, both of which were related independently to enuresis. This is in line with the previous finding that the presence of a concurrent antipsychotic increases the risk for clozapine enuresis.[5] This improvement could be claimed to be a spontaneous remission.

References

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However, unlike the previous literature, which had observed transient enuresis as an early side effect (within 3 months of starting clozapine), enuresis observed in our subject was late onset (after 15 months starting of clozapine and risperidone), and thus, the underlying mechanisms could be different. Complete cessation of enuresis after 2 months of the addition of aripiprazole (no changes in the baseline dosage of clozapine or risperidone) supports the role of aripiprazole as a treatment option in antipsychotic-induced enuresis.\textsuperscript{4}

Enuresis is postulated to be occurring in hypodopaminergic and noradrenergic deficit state,\textsuperscript{2} and thus, aripiprazole by its unique mechanism, that is, partial D2/D3 agonism can improve the dopaminergic tone in the higher and lower neural centers, thereby controlling enuresis. Literature suggests that dopamine cross activates adrenoceptors, both central and peripheral, notably $\alpha_1$ adrenoreceptors,\textsuperscript{5,6} probably resulting in improved sphincter tone, thereby inhibiting nocturnal enuresis. Improved sphincter tone could also be secondary to aripiprazole’s action on $\alpha$ adrenergic receptors, thereby improving sphincter tone. As 5HT1A antagonism could result in bladder dysfunction,\textsuperscript{7} aripiprazole could also exhibit anti-enuresis effect by 5HT1A partial agonism as well.

This case report is highly relevant, especially in a subset of patients with enuresis, who are already stabilized with antipsychotics in whom a reduction of dosage may lead to profound deterioration of psychotic symptoms. In such situations, off label use of aripiprazole may improve the antipsychotic-induced enuresis and probably may also augment the antipsychotic response as well.

**Financial Support and Sponsorship**

Nil.

**Conflicts of Interest**

There are no conflicts of interest.

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