



## Clozapine induced enuresis treated with Amitriptyline: A case report

### Amitriptilin ile tedavi edilen Klozapine bağı enüresis: Bir olgu sunumu

Clozapine induced enuresis treated with Amitriptyline

Mehmet Emin Demirkol, Lut Tamam  
Department of Psychiatry, Cukurova University Faculty of Medicine, Adana, Turkey

#### Öz

Tardiv diskinezi, genelde antipsikotik kullanımı sonrasında dopamin 2 reseptörlerinin uzun süreli blokajına bağlı olarak ortaya çıkan istemsiz hareketlerle karakterizedir. Aripiprazole bağı nadiren gelişen tardiv diskinezi olgularında tedavi seçeneklerinden biri klozapindir. Klozapin eşsiz reseptör profili ile etki gücü ve yan etki anlamında diğer antipsikotiklerden ayrılır. Klozapin farklı mekanizmalar üzerinden enüresise neden olabilir. Klozapine bağı enüresis tedavisinde farmakolojik seçenekler arasında desmopressin, oksibütinin, triheksifenidil, amitriptilin, aripiprazol, efedrin, verapamil bulunmaktadır. Hastanın psikiyatrik tanısı, seçenekler arasında bulunan ilaçların olası yan etkileri ilaç tercihi konusunda belirleyici olmaktadır.

#### Anahtar Kelimeler

Amitriptilin; Aripiprazol; Klozapin; Enüresis; Tardiv Diskinezi

#### Abstract

Tardive dyskinesia is characterized by involuntary movements which appear in connection with long-term blockage of dopamine 2 receptors following the use of antipsychotics. One of the treatment options in cases of tardive dyskinesia which occasionally induced by aripiprazole is clozapine. Clozapine is distinguished from other antipsychotics by its effective strength because of its unique receptor profile and its side effects. Clozapine may cause enuresis by various mechanisms. Among the pharmacological choices for the treatment of clozapine-related enuresis are desmopressin, oxybutynin, trihexyphenidyl, amitriptyline, aripiprazole, ephedrine, and verapamil. The patient's psychiatric diagnosis determines the choice of medication with their possible side effects.

#### Keywords

Amitriptyline; Aripiprazole; Clozapine; Enuresis; Tardive Dyskinesia

DOI: 10.4328/JCAM.5277

Received: 08.08.2017 Accepted: 26.08.2017 Printed: 01.06.2017 J Clin Anal Med 2017;8(suppl 3): 234-6

Corresponding Author: Mehmet Emin Demirkol, Department of Psychiatry, Cukurova University Faculty of Medicine, Balcalı Hospital, 01160, Adana, Turkey.

GSM: +905355849684 E-Mail: emindemirkol@gmail.com

## Introduction

Tardive dyskinesia (TD) is characterized by involuntary athetoid, choreiform, ballistic dyskinetic movements which appear after Dopamine-2 (D<sub>2</sub>) receptor blockage related to the long-term use of the first generation (conventional, typical) antipsychotics such as haloperidol or fluphenazine [1,2]. Among the risk factors for TD are advanced age, movement disorders present before the use of medication or a diagnosis of neurodegenerative disease, the use of lithium and the use of antipsychotics for more than six months [1,3]. After the discovery of the second generation (atypical) serotonin 2 (5-HT<sub>2</sub>) receptor blocking antipsychotics such as quetiapine, risperidone, and olanzapine, the rate of occurrence of TD was partly reduced. Because of its partial agonistic activity, aripiprazole is distinct from other second generation antipsychotics and is known as an atypical antipsychotic [1]. The incidence of tardive dyskinesia in the population of non-geriatric users of second generation antipsychotics in a study was found to be 0.8% [1]. As well as this expected low level with the use of aripiprazole, there are also cases in the literature of dyskinetic movements among cases with persistent depression, bipolar disorder, obsessive compulsive disorder, schizoaffective disorder, and schizophrenia. The average daily dose of aripiprazole used with these patients was 10-20 mg [1,4].

Clozapine is an atypical antipsychotic with proven effectiveness in TD developing after the use of antipsychotics [5]. Although it has fewer extrapyramidal side effects, it causes more agranulocytosis, an increase in the risk of stroke, sedation, an increase in obsessive-compulsive symptoms, weight gain and sialorrhea compared with other antipsychotics. In addition to these side effects, 6-44.3% of patients who use clozapine complain of urinary system symptoms, especially enuresis [6]. Various hypotheses have been advanced to explain clozapine-related enuresis. These are urinary retention and overflow incontinence related to the antimuscarinic effect of clozapine, the cholinomimetic effect of clozapine, reduction in internal sphincter tone in connection with  $\alpha$ -1 receptor blockage, the sedative effect of clozapine, and an increase in urinary retention relating to a lowering of the seizure threshold and constipation [6]. Among the options for the treatment of clozapine-related enuresis are reducing the dose of clozapine, behavioral recommendations and use of several different drugs (desmopressin, oxybutynin, trihexyphenidyl, amitriptyline, aripiprazole, ephedrine, and verapamil). Amitriptyline and aripiprazole are foremost among these treatments in patients with an affective component [6]. In this case report, we would like to report a clozapine induced enuresis which has been resolved by the addition of amitriptyline.

## Case Report

A female patient who was 38 years old, a university graduate, a teacher and single, attended our outpatients' department accompanied by her family in October 2011, with complaints of irritability and sleeplessness. In her mental examination performed at that time, she was observed to have reduced care for herself, to have persistent ideas of persecution towards her husband and principal, to have emotions of anger and irritability. She was admitted to our hospital with a preliminary diagnosis of a schizoaffective disorder bipolar type manic episode.

The patient stayed in our clinic for 36 days and a treatment of lithium 1200 mg/day and paliperidone 6 mg/day was started. She was discharged with full remission. In February 2012, she stopped taking the medication without the consent of her physician. One month after stopping the medication, she began to accuse herself and her family, to talk to herself, and to spend money unnecessarily. At that time she also had complaints of inappropriate laughing, an increase in sexual desire, and sleeplessness. As her complaints recurred, she was hospitalized again with the same diagnosis. The patient had auditory hallucinations and remained in our clinic for 32 days. She was prescribed lithium 1200 mg/day and aripiprazole 30 mg/day. She responded well to this treatment and discharged one month later with full remission. Between 2012 and 2016, the patient received her medication as suggested and has regularly been followed up in the outpatient clinic. She was able to continue her job as a teacher, and she experienced no manic, depressive or psychotic symptoms. At the beginning of June 2016, she began to have sleeplessness, twitches in her eyes, contraction, numbness in her face, contraction in her mouth and involuntary movement of her lips. Thinking that the complaints would recede by themselves over time, she did not seek medical help. Later she went to ophthalmology and neurology. The patient was referred to our outpatients' department by neurology with suspected TD, and was admitted to our clinic.

In her initial psychiatric evaluation at the time she was admitted to our clinic, she did not have thoughts of irritability, suspiciousness, depressive elements, or grandiose thoughts. She had no visual or auditory hallucination. Her memory and orientation were normal. Involuntary movements were observed around her mouth and eyes. She scored 26/42 on the Abnormal Involuntary Movement Scale (AIMS). After neurological consultation, it was decided that these involuntary movements could be consistent with TD, and it was recommended that drugs which could give rise to this should be discontinued or changed. No further recommendations were made after ophthalmology consultation. Being female, having mood components, taking lithium and taking antipsychotics for more than six months were considered as risk factors for TD. In the first laboratory examination, her hemogram, liver, renal, thyroid functions and fasting blood glucose were within normal limits. Her blood lithium level was 0.71 mEq/ liter. No pathology was found in her brain magnetic resonance imaging (MRI). Assessment of her medication history revealed that her current dyskinetic movements could be related to aripiprazole, and that her use of lithium might contribute to this. As the patient had been benefitting from lithium for approximately six years, it was first planned to discontinue aripiprazole and begin clozapine, vitamin E, and diazepam. Before initiation of clozapine, hemogram, electroencephalography, and echocardiography tests were conducted and found to be normal. The clozapine dose has been increased gradually. The patient's involuntary eye movements decreased (AIMS: 19/42) in the third week of treatment when the clozapine dose was raised to 250 mg/day. At this time her blood lithium level was 0.82 mEq/ liter. In the fourth week of clozapine treatment, the patient began to have complaints of enuresis nocturna. After a few days, she began to have daytime urinary incontinence. Hemogram and urine tests were within normal limits. Neurologi-

cal, internal medicine and urological consultations' results eliminated other possible causes of enuresis (i.e., urinary infection, diabetes mellitus, renal failure, epilepsy). Lithium and diazepam doses were reduced and terminated. Despite the cessation of all other drugs, enuresis continued. This has shown us possible association between clozapine and patient's enuresis. One week after this, the complaint of enuresis was continuing, and it was decided to start amitriptyline 25 mg/day. Urinary incontinence ceased after the second day of amitriptyline treatment, and after a follow-up of seven days, the amitriptyline dose was stopped. Four days after this, the complaint of enuresis began again, and the patient was once more prescribed amitriptyline 25 mg/day. In the second day of treatment, the enuresis complaint ceased again. The patient was discharged from hospital after a stay of 99 days. In her follow up she was in good condition about tardive dyskinesia (AIMS:16/42) and enuresis after six months with a treatment regimen of clozapine 250 mg/day and amitriptyline 25 mg/day.

### Discussion

Clozapine is distinguished from other antipsychotics by its high  $D_1$  and low  $D_2$  receptor activity. It has been suggested that  $D_1$  receptor affinity is effective in the treatment of TD. Clozapine has side effects like agranulocytosis, hypotension, seizures, constipation, weight gain, sialorrhoea and enuresis [5]. Recent publications have shown that 6-44.3% of patients using clozapine have urinary system symptoms, especially enuresis [6]. Presence of enuresis contributes to poor medication adherence so has deleterious effects on the prognosis of psychosis [7]. Although there are various treatment options (desmopressin, oxybutynin, trihexyphenidyl, amitriptyline, aripiprazole, ephedrine, and verapamil) for the complaint of enuresis induced by clozapine, amitriptyline 25 mg/day was preferred in our case because of the existing diagnosis of schizoaffective disorder and the recurring depressive symptoms.

Amitriptyline, a tricyclic antidepressant, has antimuscarinic, antihistaminic and antiadrenergic effects. Amitriptyline is effective in the treatment of enuresis and clozapine-induced sialorrhoea because of its anticholinergic effect. It also increases vasopressin secretion and shortens the period of REM sleep, these effects contribute to the treatment of enuresis. Adding amitriptyline to clozapine treatment can give rise to anticholinergic side effects, lowering the seizure threshold and sedation. So adding low doses of amitriptyline to clozapine treatment can be rational. Our case, in which the complaint of enuresis ceased from the second day of amitriptyline treatment, is the second in the literature in which amitriptyline was beneficial in the treatment of clozapine induced enuresis [7].

In conclusion, this case report presents a treatment option with amitriptyline for clozapine induced enuresis cases but needs to be supported by further studies.

### Competing Interests

The authors declare that they have no competing interests

### Funding Statement

The authors declare that they have no funding to report

### References

1. Schwartz T, Raza S. Aripiprazole (Abilify) and Tardive Dyskinesia. *P T* 2008;33(1):32-4.
2. Kane JM, Jeste MD. Tardive Dyskinesia: A Task Force Report of the American Psychiatric Association. Washington DC: American Psychiatric Association; 1992. P.12-51.
3. Dolder CR, Jeste DV. Incidence of tardive dyskinesia with typical versus atypical antipsychotics in very high risk patients. *Biol Psychiatry*. 2003;53(12):1142-5.
4. Zacher JL, Hatchett AD. Aripiprazole-induced movement disorder. *Am J Psychiatry*. 2006;163(1):160-1.
5. Spivak B, Mester R, Abesgaus J, Wittenberg N, Adlersbeg S, Gonen N, et al. Clozapine treatment for neuroleptic-induced tardive dyskinesia, parkinsonism, and chronic akathisia in schizophrenic patients. *J Clin Psychiatry*. 1997;58(7):318-22.
6. Lee MJ, Kim CE. Use of aripiprazole in clozapine induced enuresis: report of two cases. *J Korean Med Sci*. 2010;25(2):333-5.
7. Praharaj SK, Arora M. Amitriptyline for clozapine-induced nocturnal enuresis and sialorrhoea. *Br J Clin Pharmacol*. 2007;63:128-9.

### How to cite this article:

Clozapine Induced Enuresis Treated with Amitriptyline: A Case Report. Demirkol ME, Tamam L. *J Clin Anal Med* 2017;8(suppl 3): 234-6.