

# Aripiprazole Augmentation of Clomipramine Therapy in Treatment-Resistant Obsessive-Compulsive Disorder: Case Series

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## ABSTRACT

Aripiprazole augmentation of clomipramine therapy in treatment-resistant obsessive-compulsive disorder: case series

Obsessive-compulsive disorder (OCD) is a chronic disorder characterized by recurrent intrusive thoughts and repetitive rituals, causing significant distress and functional loss. Studies show evidence about serotonergic and dopaminergic mechanisms in neuropathogenesis of OCD. Selective serotonin re-uptake inhibitors (SSRI) are considered first line treatment in OCDs, but treatment resistance may occur in 40-60% of cases treated with SSRIs. Augmentation of antidepressants with atypical antipsychotics is an important treatment option in treatment-resistant patients with OCD. In this article, we aimed to present five OCD cases with treatment-resistance in which we obtained good outcomes, with addition of aripiprazole 10-30mg per day to clomipramine therapy.

**Keywords:** Aripiprazole, clomipramine, obsessive-compulsive disorder, treatment resistance

## ÖZET

Tedaviye dirençli obsesif kompulsif bozukluk hastalarında klomipramin tedavisinin aripiprazol ile augmentasyonu: Vaka serisi

Obsesif-kompulsif bozukluk (OKB) yineleyen, istenmeyen düşünceler ve törensel davranışlarla giden, belirgin sıkıntı ve işlev kaybına neden olan kronik bir hastalıktır. Yapılan çalışmalarda OKB nöropatogenezinde serotonerjik ve dopaminerjik mekanizmaların rol oynadığına ilişkin çeşitli kanıtlar gösterilmiştir. Tedavisinde ilk tercih ilaç olarak Seçici Serotonin Geri Alım inhibitörleri (SSGİ) kabul edilmektedir, ancak buna karşın SSGİ ile tedavi edilen hastaların yaklaşık %40-60'ında tedavi direnci görülebilmektedir. Tedaviye dirençli OKB'de antidepressanların atipik antipsikotiklerle augmentasyonu önemli bir tedavi seçeneğidir. Biz de bu yazımızda; tedaviye dirençli 5 OKB hastasının klomipramin tedavisine aripiprazolün 10-30mg/gün dozlarının eklenmesiyle tedavide olumlu yanıt elde ettiğimiz olgularını sunmayı amaçladık.

**Ahtar kelimeler:** Aripiprazol, klomipramin, obsesif-kompulsif bozukluk, tedavi direnci



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Date of receipt / Geliş tarihi:  
Julne 1, 2015 / 1 Haziran 2015

Date of the first revision letter /  
İlk düzeltme öneri tarihi:  
July 13, 2015 / 13 Temmuz 2015

Date of acceptance / Kabul tarihi:  
August 26, 2015 / 26 Ağustos 2015

## INTRODUCTION

Controversies about treatment strategies and resistance in obsessive compulsive disorder (OCD) still remain, despite various medication combination and augmentation options in OCD. About 40-60% of patients with OCD do not show adequate response to SSRI treatment (1). Resistance to OCD therapy is defined as; a decrease less than 35% in Yale-Brown Obsessive Compulsive Scale (Y-BOCS) score after at least 10 weeks' treatment, and after two different SSRIs

or clomipramine trials, with or without cognitive-behavioral therapy (CBT) (2-4). Treatment period, dose of medicine, treatment compliance, presence of insight, social support and personal features may play important roles in treatment resistance (5-8). Antipsychotic augmentation, especially with risperidone, haloperidol, aripiprazole, and CBT have shown the best evidence. Ondansetron, memantine, riluzole, clomipramine, mirtazapine and repetitive transcranial magnetic stimulation over supplementary motor area show some preliminary evidences. Ablative neurosurgery or deep

brain stimulation may be effective in some well-chosen patients with treatment resistance (1). Besides, mood stabilizers, gamma-amino-butyric acid (GABA) analogues and GABA reuptake inhibitors, benzodiazepines and glutamatergic agents are other treatment options (9). Many studies and case reports revealed efficacy of augmentation with antipsychotics, such as aripiprazole, an antipsychotic showing partial agonism at serotonin 5-hydroxytryptamine (5-HT)-1A receptors, and antagonism at 5-HT<sub>2A</sub> receptors (13), in patients who had inadequate OCD treatment response (10-12).

In this article, we aimed to present good outcomes with the augmentation of clomipramine, considered as gold standard treatment option, with aripiprazole, in five patients with treatment-resistant OCD. Written informed consent.

### CASE 1

Male patient, who was 34 years old was consulted because of self-violation and hostile behaviors for his environment, intrusive thoughts about sexual aggression, repetitive praying behaviors and distress, sleeplessness, nervousness, and loss of functionality due to his obsessions and compulsions. He was suffering from OCD for ten years. He had various medications, such as paroxetine, sertraline, venlafaxine, risperidone, clonazepam, alprazolam, escitalopram and clomipramine at different time periods, and had no clinical remission. He was on fluvoxamine 300mg per day, risperidone 2mg per day, quetiapine 100mg per day for the past 6 months. There were no significant finding neither in his personal nor family history. The patient's biochemical and radiological screenings were within normal limits with normal cranial Magnetic Resonance Imaging (MRI), Electroencephalography (EEG) and Electrocardiography (ECG) results. In his psychiatric examination, his thought content revealed sexual and damaging obsessions, praying and avoidance compulsions. Anxiety with somatic signs, insomnia and irritability were denoted. Hamilton Anxiety Rating Scale (HARS) score was 21, and Y-BOCS score was 24 points. The patient was

diagnosed with OCD according to DSM-IV diagnostic criteria clomipramine 75mg/day, aripiprazole 5mg/day as an add-on treatment for augmentation, and clonazepam 2mg/day were started. Clomipramine dose was increased up to 150mg/day and aripiprazole dose was increased up to 10mg/day gradually. Clonazepam dose was tapered down, and stopped when his anxiety symptoms were disappeared. After 4 weeks, HARS and Y-BOCS scores were decreased to 7 and 8, respectively, and patient did not report any symptoms about obsessions.

### CASE 2

Female patient who was 38 years old presented with symptoms of hand washing and cleaning frequently, spending a long time in bathroom and toilet distress. She was diagnosed with and treated for OCD diagnosis for ten years. She reported that she received sertraline, paroxetine, risperidone, sulpride, amisulpride, and citalopram treatments at different time periods. Her symptoms were persistent despite clomipramine 150mg/day combined with paroxetine 20mg/day treatment within the last year. There was no significant finding neither in her personal, nor family history. Biochemical and radiological examinations were within normal limits. In her psychiatric examination, obsession of contamination, compulsions of cleaning and washing; anxiety, somatic signs of anxiety, insomnia and irritability were determined. HARS score was 15, and Y-BOCS score was 22 points. The patient was diagnosed with OCD according to DSM-IV diagnostic criteria, clomipramine 150mg/day, aripiprazole 5mg/day as an add-on treatment for augmentation, and clonazepam 2mg/day treatment was started. Clomipramine dose was increased up to 225mg/day and aripiprazole dose was increased up to 10mg/day gradually. Clonazepam dose was tapered down, and stopped when her anxiety symptoms were disappeared. After 6 weeks, during her control examination HARS and Y-BOCS scores were decreased to 7 and 7, respectively, and the patient reported that severity of her compulsive behaviors was decreased.

### CASE 3

Male patient who was 31 years old presented with symptoms of hand washing, uncertainty and repetitive behaviors. He was diagnosed with OCD, treated for six years. He stated that he used citalopram, sertraline, clomipramine, fluvoxamine, risperidone, amisulpride at different time periods. He was taking clomipramine 150mg/day and clonazepam 1mg/day for the last three months. He reported no significant finding in his personal or family history. His biochemical and radiological investigations were within normal range. In psychiatric examination, obsessions of contamination and uncertainty; compulsions of cleaning, controlling and counting; anxiety, perseverative talking, irritability and impulsivity were detected. HARS score was 14, and Y-BOCS score was 25 points. The patient was diagnosed with OCD according to DSM-IV diagnostic criteria. Clomipramine 150 mg/day, aripiprazole 5mg/day as an add-on treatment for augmentation, and clonazepam 2mg/day combination treatment was started. Clomipramine dose was increased up to 225mg/day and aripiprazole dose was increased up to 15mg/day gradually. Clonazepam dose was tapered down, and stopped when anxiety symptoms were disappeared. After 6 weeks, during his control examination HARS and Y-BOCS scores were decreased to 8 and 9, respectively, and the patient reported that severity of his compulsive behaviors was decreased.

### CASE 4

Male patient who was 30 years old was diagnosed with Tourette Syndrome (TS) at the primary school 20 years ago. The presenting symptoms were involuntary movements in his both upper extremities, and vocal tics. He stated that he was treated with various agents for many years due to symptoms, such as hyperactivity disorder due to his tics. During adolescence, symmetry obsessions, and uncertainty symptoms were observed. In outpatient clinic, he was prescribed clomipramine, sertraline, fluoxetine, fluvoxamine, risperidone, carbamazepine and clonazepam during different time

periods. He was hospitalized after two suicidal attempts triggered by severe obsessions and stressors in 2006 and 2013. However, he had no complete remission with these treatment modalities. He attended to an outpatient clinic with symptoms of unwillingness, anhedonia, avolition, decrease in self-care, obsessions about colors and lines, and preoccupation with his symptoms for the past two weeks. He was hospitalized with pre-diagnosis of OCD and Major Depressive Disorder (MDD). In his family history, he reported that his cousins and grandfather were diagnosed with OCD. In psychiatric examination, his self-care was deficient; his mood was depressive, and his affect was anxious. Psychomotor activity, speed of speech and thinking process were slowed. There was various symptoms, such as anhedonia, insomnia, irritability, decreased impulse control, and obsessions and compulsions about colors and lines. His insight was poor. We observed stereotypical movements on both his upper and lower extremities. The patient's routine biochemical and radiological investigations were within normal range. Hamilton Depression Rating Scale (HDRS), HARS and Y-BOCS score were 20, 18 and 22 points, respectively. He was diagnosed with OCD, MDD and TS according to DSM-IV diagnostic criteria. Clomipramine 75mg/day, aripiprazole 5mg/day as an add-on treatment for augmentation, and clonazepam 1mg/day combination treatment was started. Clomipramine dose was increased up to 150mg/day and aripiprazole dose was increased up to 10mg/day gradually. Clonazepam dose was tapered down, and stopped in tenth day of treatment. He was hospitalized for 20 days, his obsessive thoughts were improved; severity of depressive symptoms and vocal tics were significantly decreased. After four weeks, during his follow-up HDRS, HARS and Y-BOCS scores were decreased to 8, 7 and 13, respectively. He reported significant improvements in severity of all of his symptoms.

### CASE 5

Male patient, who was 25 years old applied with symptoms of cleaning compulsions, such as frequent hand washing, and checking compulsions which were

started eight years ago. His treatment compliance was poor. In recent months, he started to use sharp materials to penetrate into his eyes, because some voices told him to injure his eyes. Therefore, he bought many sharp materials. Finally, he was hospitalized, because he could not cope with these obsessions and his eyes were infected. He also had vision impairment. He reported that he was prescribed various medications such as clomipramine, fluvoxamine, paroxetine, sertraline and amisulpride for many years. There was no significant finding in his personal or family history. In the psychiatric examination, psychical and somatic signs of anxiety, irritability, impulsivity, self-violation and uncertainty obsessions; checking compulsions; and insomnia were determined. His insight and judgement were adequate. Y-BOCS score was 24 and HARS score was 18 points. Biochemical and radiological examinations were within normal range. Clomipramine 75mg/day, clonazepam 1mg/day, and aripiprazole 5mg/day were started. CBT treatment was initiated, but he could not continue. During his hospitalization, he could not reach sharp materials, but in spite of that he started to press his eyes with blunt materials, and due to his eye infection and vision impairment, he was examined and treated by an ophthalmologist. Clomipramine doses were increased up to 225mg/day and aripiprazole doses increased up to 20mg/day gradually. He was discharged at the sixth week with decreased Y-BOCS and HARS scores to 9 and 8, respectively.

## DISCUSSION

SSRI and CBT treatment are evidence based first line treatment modalities in OCD treatment (14). A decrease less than 35% on Y-BOCS score, or getting at least twelve points from Y-BOCS after being treated at least 10 weeks, and with at least two different SSRIs or with three different medication categories (one of them must be clomipramine), is defined as resistance to OCD therapy (22).

Recommended approach for patients who do not respond to SSRI treatment, is to increase SSRI doses at first, then switching to another SSRI (15).

Pharmacological options in cases with treatment resistance with two different SSRIs include clomipramine treatment during adequate doses and period, and if they are non-responsive to augmentation treatment with atypical antipsychotics, such as risperidone, olanzapine and quetiapine and also with lithium, clonazepam, buspirone, monoamine oxidase inhibitors and other mood stabilizers (14-16). Studies investigating atypical antipsychotic augmentation among adults indicated a moderate response rate, ranging from 33% to 50% (17). Aripiprazole augmentation in treatment-resistant OCD patients was already mentioned in some reports (17,18-20). Aripiprazole, a third line atypical antipsychotic, has D2 receptor antagonism in dopaminergic hyperactivity states, and has partial receptor agonism in dopaminergic hypoactivity. It has also partial agonistic activity on 5-HT<sub>1A</sub> receptors, and antagonistic activity on 5-HT<sub>2A</sub> receptors (13). Aripiprazole has antidepressant effects as well as its effectiveness in different psychiatric disorders like schizophrenia, bipolar disorder and anxiety disorders (21). In OCD pathogenesis, dopaminergic and serotonergic pathways play important roles, and it is considered that an imbalance between these pathways cause the disorder (16,22). Due to imbalance between dopamine and serotonergic pathways in OCD neurobiology, effect of aripiprazole may be explained with its partial agonistic activity on D<sub>2</sub>, and 5-HT<sub>1A</sub> receptors, as well as antagonistic activity on 5HT<sub>2A</sub> receptors (26,30,31). Aripiprazole may be administered as monotherapy or as a combination treatment with SSRIs (17,19,24,25). In a case report of treatment-resistant OCD which was prescribed clomipramine (150mg/day) augmented with aripiprazole (12.5mg/day), it was reported that augmentation with high dose aripiprazole improved patient symptoms markedly rather than augmentation with risperidone or quetiapine after administration of clomipramine in adequate dose and period. This can be explained by diverse pharmacological mechanisms of aripiprazole (25). Results of a double-blind, randomized, placebo controlled study supported the notion that adding aripiprazole to SSRIs could be a valid strategy for treatment-resistant OCD patients (26,27). Another

study performed on 30 subjects provided evidences that aripiprazole augmentation of clomipramine treatment was well tolerated, and might be proposed as an effective therapeutic strategy to improve outcome in treatment-resistant OCD (27). Successful treatment result in an OCD subject with treatment of escitalopram and aripiprazole proved that dopaminergic pathways might play an important role in OCD pathogenesis as well as serotonergic pathways, and that imbalance between these pathways might cause this disorder. Not only inhibitory effect of aripiprazole on dopamine release, but also regulatory effect of augmented escitalopram with aripiprazole agonistic activity on serotonergic pathways, and stabilization effects of dopamine and serotonin were effective (18,28). Aripiprazole 5mg/day augmentation was shown to improve in a treatment-resistant case with sertraline and CBT treatment (22). In a systematic review and meta-analysis, it was reported that short period augmentation with aripiprazole to treatment-resistant OCD patient was an effective treatment strategy (29). OCD patients showing clomipramine resistance and not responding to augmentation with olanzapine and risperidone might respond to an aripiprazole augmentation 7.5mg/day of clomipramine (24).

The majority of samples had already used various psychopharmacological agents before they applied to

our hospital, yet they reported no significant improvement with previous treatments. As they did not adequately respond to previous clomipramine treatment, we prescribed aripiprazole in a range of 10-30mg per day for augmentation of clomipramine, and clonazepam for their severe anxiety. Clonazepam doses were reduced when anxiety levels were improved, and a progressive decrease was observed in Y-BOCS and HARS scores. According to many case reports, studies and our cases, we suggest that aripiprazole may increase the anti-obsessional effect of clomipramine possibly due to its partial agonistic activity on D2 and 5 HT1A receptors, as well as antagonistic activity on 5HT2A receptors.

| Contribution Categories        | Name of Author                   |
|--------------------------------|----------------------------------|
| Follow up of the case          | F.I., S.Y.K.C., Y.S.             |
| Literature review              | F.I., Y.S., R.B., M.Y., S.Y.K.C. |
| Manuscript writing             | F.I., Y.S., R.B., M.Y., S.Y.K.C. |
| Manuscript review and revision | F.I., M.Y., R.B.                 |

**Conflict of Interest:** Authors declared no conflict of interest.

**Financial Disclosure:** Authors declared no financial support.

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