INTRODUCTION

Obsessive Compulsive Disorder (OCD) in children and adolescents is characterized by obsessions and compulsions, symptoms causing significant distress and dysfunction (1,2). With its reported prevalence between 2-4% (3), initial treatment approach of OCD includes family counseling and psychoeducation, along with cognitive behavioral therapy (4,5). Selective Serotonin Reuptake Inhibitors (SSRIs) have long been used in the pharmacological treatment of OCD in children (6). A recent review has also reported the efficacy of serotonergic agents in short and medium-term treatment of OCD (7). However, due to the lack of treatment studies that compare the efficacy of various SSRIs, no systematic proof exists for the recommendation of any SSRI (8).

Strategies that involve increasing the medication and augmentation have so far only been considered in cases with treatment resistance. As a consensus among specialists of the field, the term “treatment resistance” reflects presence of persistent and severe OCD symptoms even though efficient and recommended line of treatment strategies have been used at therapeutic doses for recommended period. This might indicate clinical unresponsiveness following the use of at least two different SSRIs or one SSRI and clomipramine, accompanied by sufficient number of CBT sessions. Many drugs have been tried for augmentation, in the face of treatment-resistance. However, such drug trials mainly have been conducted with adult samples, and studies that assess augmentation in children and adolescents have been scarce. Some of these have focused on aripiprazole as a fine alternative to be used for augmentation. This series comprises clinical course and treatment of six adolescents diagnosed with OCD from three different centers in Turkey, who had all responded well to early augmentation treatment with aripiprazole, indicating the possible need to further discuss the given issue.

Keywords: Aripiprazole, augmentation, children, obsessive-compulsive disorder, psychopharmacology
treatment resistance in OCD is defined by lack of clinical improvement following the trial of at least two SSRIs or one SSRI and clomipramine, along with recommended duration of CBT sessions. In order to use this term, children need to have used either an SSRI or clomipramine for at least 10 weeks, within maximum dose range (or highest tolerable dose) recommended and no change in the medication occurred for the past 3 weeks (7). In the face of treatment resistance, adjunctive agents are used for augmentation strategies. Clonazepam, haloperidol and atypical antipsychotic agents are among such drugs to be used under these circumstances (9). Nevertheless, it must also be recognized that these strategies recommended to be used for treatment-resistant cases solely, might also not be always beneficial in clinical practice. It is crucial to address and manage relevant comorbidity, familial factors, past treatment history or aspects of treatment that might hinder the improvement of OCD symptoms, along with appropriate diagnosis and formulation of pediatric OCD. In this context, sometimes there inevitably are children and adolescents in clinical practice that require altered and individualized treatment steps, in turn causing us clinicians to take on novel strategies that differ from recommended guidelines (8). This might create a medium where the clinician needs to decide on whether to start treatment with a psychotropic medication, cease treatment or use an adjunctive treatment regimen, by calculating associated risks and benefits. One consequence out of this decision process might be existing literature that includes studies reporting more positive outcome following the use of augmentation strategies at the initial phase of treatment, under certain circumstances. One example to this might be the condition of cases with OCD and comorbid tic disorders. These patients have been reported to respond well to SSRI treatment augmented with haloperidol (10). Some researchers have suggested patients with OCD and comorbid tic disorder might benefit better from a treatment regimen that included augmentative antipsychotic medication used in the initial phase of treatment (11-13). Another factor related to the probable better outcome with augmentation therapy used in the initial phase is related to the time of treatment response. It is commonly known that therapeutic effects of SSRIs might emerge around 8-12th week of treatment, in cases with OCD. In order to reduce this delay, Pallanti et al. (2004) evaluated the results of augmentation treatment with mirtazapine in patients with OCD. In their study conducted with OCD patients with no clinical depression, citalopram and mirtazapine combination as the initial treatment was reported to create an earlier positive response compared to citalopram and placebo (around 4th week of treatment) (14).

With this case series, we aimed to present and discuss the clinical courses of OCD cases that were resistant to treatment with an SSRI, and were started on low doses of add-on aripiprazole that was used for augmentation purposes, without using another SSRI or clomipramine as suggested in the guidelines, in order to have a rapid treatment response due to significant functional deterioration observed.

CASE PRESENTATION

CASE 1

Case 1 was an 11 year old girl, who had been attending 6th grade at the time of her application. She had been living with her nuclear family that included her father who was a long-distance truck driver, her mother who was a housewife, and her 2 sisters. She had initially applied to a child and adolescent psychiatry outpatient unit accompanied by her mother. Her initial complaints at application were "doubts about whether she had completed her daily chores or not", "being afraid of the possibility that people close to her might be harmed", and other thoughts about "behaving sinfully towards her mother", and certain behavior and actions in the face of these thoughts such as "asking the same questions persistently, in order to have approval", "counting to reach a certain number", and "asking for forgiveness from her mother", respectively. She had stated that these thoughts and behavior interfered extensively with her daily life. It was learned that her symptoms had started approximately
2 years prior to her initial application, had increased as time passed by, and due to significant deterioration observed in her daily functioning for the past three months, she had decided to seek help from our unit. The interview conducted with the mother revealed negative family history for any psychiatric disorder.

As a result of the assessment and diagnostic procedures applied, the case was diagnosed with "Obsessive Compulsive Disorder", and her initial CY-BOCS scores had been measured as 33. She was then started on oral fluoxetine, 20 mg/day and since no clinical improvement was observed, the dose was increased to 40 mg/day. At 12th week of treatment, there was no significant symptomatic improvement (CY-BOCS: 28), and although the family had been continuing the medication as recommended, it was also seen that they had been struggling to maintain their control sessions regularly. Low-dose oral aripiprazole (2.5 mg/day) was added to the ongoing medication regimen, and the dose was increased to 5 mg/day, within a week. In the control session held four weeks after the add-on of aripiprazole, significant reduction in the case's symptoms were noted. Her compulsions of counting had totally diminished, and her compulsions of "asking for forgiveness from her mother" had been significantly reduced. Her initial CY-BOCS score that had been measured as 33, decreased to 9, following add-on low dose aripiprazole treatment. The case had tolerated the add-on treatment well, no significant side-effect was identified other than drowsiness, that had gradually decreased through the course of the treatment. The case is being followed up in the outpatient unit for 8 months with a medication regimen as 40 mg/day fluoxetine and 5 mg/day aripiprazole.

CASE 2

Case 2 was a 15 year old boy, who had been going to high school at the time of referral. He had been living in a family that consisted of his father who was working as a factory employee, a mother who was a housewife, and a sister. He had initially been referred to our outpatient unit, accompanied by his mother, due to his thoughts of "scary images appearing in his mind, that were mostly about his deceased relatives", and "something bad might happen"; followed by behaviors identified as "repenting" and "touching a nearby object". It was learned that the case frequently included his family members to his routines and rituals, and spent extended amounts of time to relieve his obsessions. His initial symptoms had started a year prior to referral, with sexual and contamination obsessions, and had irregular use of SSRI agents throughout his prior visits. The case had felt the need to get help again, as his daily functioning significantly deteriorated, with his increasing symptomatology within the past 2 months. It was learned that there was no history of psychiatric disorders in the family.

Following psychiatric evaluation and differential diagnostic assessment, the case was diagnosed with OCD, and his initial CY-BOCS score was 31. He was started on 20 mg/day oral fluoxetine, and since there was no measurable clinical improvement, the dosage was increased to 40 mg/day. At the 9th week of his treatment, it was seen that the case had no significant clinical and functional improvement (CY-BOCS: 28); and moreover intrafamilial conflicts had become much more severe due to his family members being forced to be included in his compulsive and ritualistic behavior, in turn, creating severe decline in both the patient’s and the family's treatment motivation. Observing these, 2.5 mg/day oral olanzapine was added to the ongoing treatment regimen and was increased to 5 mg/day. However, due to severe drowsiness as the side effect, the medication was not well-tolerated by the case. Approximately 2 weeks after, olanzapine was ceased and aripiprazole 2.5 mg/day was added, and was increased to 5 mg/day within 1 week. In the control session 4 weeks later, it was seen that the case had significant symptomatic improvement (CY-BOCS: 6), and the overall decline in his obsessive thought content and compulsions which he had included the family members were specifically stated. Add-on aripiprazole was well tolerated by the case, and no side-effect was identified. The case is being followed up in the outpatient unit for 6 months with a medication regimen as 40 mg/day fluoxetine and 5 mg/day aripiprazole.
CASE 3

Case 3 was a 15 year old boy who was attending 9th grade at the time of his index referral. He had been living in a family including his father who worked as an engineer, a mother who was a housewife, and his identical twin-sister. He was referred to the child psychiatry outpatient unit due to his thought content about "the need to have his stuff organized and in symmetry at all times", and in turn, repetitive behavior in order to maintain organization and symmetry for any object around him. During the assessment, it was observed that the case had no insight regarding his symptoms, and was actually brought to the unit by his parents who felt very distraught with his behavior. It was learned that the case had severe angry outbursts whenever the family attempted to hinder his actions, did not let anyone enter his room and touch his stuff. It was learned that the symptoms had actually started early on, during his childhood; however they had not sought help before, and only decided to come this time, because of the severe incline in his symptomatology for the past 3 years and significant deterioration in overall functioning. The family history revealed presence of OCD symptoms in the paternal grandfather and mother’s brother.

Upon psychiatric evaluation, the case was diagnosed with OCD; and his initial CY-BOCS was measured as 39. He was started on 50 mg/day oral sertraline, and due to lack of clinical improvement, the dose was increased to 100 mg/day. At 10th week of treatment, expected clinical improvement was not met (CY-BOCS: 31), while severe symptoms of the case were causing significant distress and conflict among family members as well as the decline in his adherence to treatment. He was started on 2.5 mg/day aripiprazole and increased to 5 mg/day in a week. Following 5 weeks into add-on aripiprazole, it was seen that the case had significant clinical improvement (CY-BOCS: 21), and his family reported a relief regarding his outbursts and overall attitude when they attempted to hinder his compulsive behavior. Add-on aripiprazole was well tolerated by the case, with no significant identifiable side-effects. The case is still being followed up with sertraline 100 mg/day and aripiprazole 5 mg/day.

CASE 4

Case 4 was a 10 year old boy, who had been attending 4th grade at the time of his application to the child psychiatry outpatient unit. He was living with his family that included his father working as a laborer, his mother as a housewife, and a sister. His main complaints at the time of his initial application were "the sense that something bad would happen", such as in situations comprising his academic performance and grades. In addition to that, he also reported thought content such as "being unsure about whether he had successfully completed his chores or not"; and behavior in return, such as "the urge to touch the closest object nearby", and "the need to control and check if he did a certain thing or not". It was learned that the case had spared significant amount of time and energy throughout the day, for these forementioned thoughts and actions. The symptoms were reported to have emerged 5-6 months prior to the application, and while initially only observed at home, had started to increase and become more severe, manifesting at school as well. The family history revealed a positive diagnosis of "Panic Disorder", for the father.

Following psychiatric evaluation, the case was diagnosed with OCD, and initial CY-BOCS score was measured as 35. He was started on fluoxetine 20 mg/day, and since no significant clinical improvement was observed, the dose was increased to 30 mg/day at the 4th week of treatment. However, at 7th week of treatment, it was seen that the case had no significant clinical improvement (CY-BOCS: 30), his symptoms seemed to much more interfere with his school life, and he was bullied because of his symptoms at school. Aripiprazole 5 mg/day was added to the ongoing treatment protocol, and the dose was increased to 5 mg/day. Three weeks after this, significant improvement was reported by the case and his parents (CY-BOCS: 11). Aripiprazole treatment was well tolerated by the case, with no significant side-effects. The case is being followed up in
the outpatient unit for 8 months with a medication regimen as 30 mg/day fluoxetine and 5 mg/day aripiprazole.

CASE 5
Case 5 was a 15 year old boy who had been attending 10th grade at the time of his application to the child psychiatry outpatient unit. He was living in a family of three, the father was a computer technician, his mother a housewife, and his older brother who was a college student. His presenting complaints were thoughts as such "if he had done a bad thing to his mother", "if he had harmed himself", "if he had looked into another person's eyes for a long time, would that person harm him?", that could be summarized as thought content comprising harming himself and others, and being harmed by others, and in turn, behavior emerging in that context, such as "rolling his eyes four times", "waving his hands towards his face twice", "turning towards a table or a wall and hitting these surfaces twice". The case was unable to visit the kitchen or the bathroom at night, due to his severe thought content of harming himself and was reported to have been calling his mother and father by phone at least 6-7 times a day, in order to have their approval of nothing bad had happened. The case was sparing very long time to these thoughts and behavior during the day, that were significantly interfering with his overall life quality and daily functioning. It was learned that the symptoms had started following a school change and him failing in a couple of exams approximately 6 months ago, and increased drastically 2-3 weeks prior to admission. The family history was positive for Major Depressive Disorder, afflicting both parents and OCD in the maternal uncle.

Upon psychiatric assessment, the case was diagnosed with OCD, and his initial CY-BOCS score was measured as 33. He was started on sertraline 25 mg/day, and the dose was gradually increased to 150 mg/day. However, since he developed side-effects such as excessive sweating, headache and nausea at this dosage and he was unable to tolerate them, sertraline was dropped to 100 mg/day. Since he had severe anxiety due to his symptoms, and his compulsions increasingly affecting his school functioning negatively, risperidone 1 mg/day was added to his ongoing medication regimen at 10th week of treatment, and was increased to 2 mg/day within 2 weeks. The case had symptomatic relief with the combination treatment (CY-BOCS: 21); however he started experiencing severe side effects secondary to risperidone use such as sedation, increase in appetite and 6 kg weight gain within 1.5 month, hypersalivation and general motor slowing. The case and his family reported significant distress and discomfort regarding the forementioned adverse effects, therefore risperidone was gradually ceased and he was started on aripiprazole 2.5 mg /day, increasing the dose to 7.5 mg/day within 6 weeks. A control session was held 2 months after add-on aripiprazole, and it was seen that the case had prominent symptomatic improvement (CY-BOCS:8); mainly his anxiety level decreasing significantly, with both him and his family reporting that he voluntarily started participating in school activities. It was also stated that add-on aripiprazole treatment was well- tolerated by the case, as no significant side-effect was identified. The case is being followed up in the outpatient unit for 14 months with a medication regimen as 100 mg/day sertraline and 7.5 mg/day aripiprazole.

CASE 6
Case 6 was a 14 year old girl who had been in the 9th grade at the time of application to the child psychiatry outpatient unit. She was the daughter of a family that consisted of a father who worked as an engineer, a mother who was a school teacher, an identical twin sister and big sister. She had applied to the child psychiatry outpatient unit due to her presenting symptoms of thought content reported as "something bad might happen if she sits on a damp surface", "she might contract a disease if she passes by a garbage", "a family member might be harmed if she does not open and close the bathroom door three times before getting out", and corresponding behavior identified as, "hitting the table three times while saying touch wood!", counting from inside until she reaches a certain number, and saying it will not happen three times afterwards", asking for approval from her mother that nothing bad shall happen, whirling around three times, and spending long time in the bathroom, and using excessive amounts of hygiene products to make sure she
is clean after using the bathroom. It was learned that these symptoms affected her daily life in a very negative way, causing her to be unable to leave the house from time to time and made it impossible for her to use the bathroom at school. Her symptoms were reported to have started 4 months prior to application and increased dramatically within a month. None of the family members were being treated for any psychiatric condition, at the time of her application.

As a result of the assessment, the case was diagnosed with "Obsessive Compulsive Disorder", along with subthreshold depressive symptoms. Her CY-BOCS score was 29 at the time of application. The case was started on fluoxetine 20 mg/day orally, and the dosage was increased to 40 mg/day, within two weeks. She was evaluated as an emergency case following her referral to the emergency unit, due to her symptoms of intense distress, uncontrollable crying episodes, inability to fall asleep, and suicidal ideation. Since no marked improvement had been obtained, as revealed in her control appointments (CY-BOCS score: 24), the case was started on 2.5 mg/day oral aripiprazole along with alprazolam 0.5 mg/day add-on treatment, and a control appointment was scheduled a week later. In her control session, the case reported a significant relief of her anxiety and diminished suicidal thought content, therefore, alprazolam was stopped and aripiprazole was increased to 5 mg/day. A month later, the case was found to have significant reduction regarding her symptoms (CY-BOCS score:12), and her affective state was more positive than earlier. She was also observed to better engage in a conversation with the clinician, since she was less anxious than before. The case reported mild levels of headache and weight gain, as side effects observed by add-on aripiprazole; however since these adverse reactions were reported to be tolerable and did not interfere with overall quality of life, the pharmacological treatment was resumed with same dosages of given drugs. The case is being followed up in the outpatient unit for 10 months with a medication regimen as 40 mg/day fluoxetine and 5 mg/day aripiprazole.

Patient characteristics were summarized and presented in Table 1.

DISCUSSION

OCD is related to a specific cluster of symptoms; and in that sense diagnosis of OCD seems relatively easy; however there is also a long time of latency before a formal diagnosis is made, in general. A valid diagnosis of the disorder is crucial for access to an efficient treatment process. Nonetheless, a group that comprises significant number of cases with chronic OCD that do not respond well to current recommended medication options despite recent progression, still exists (8). SSRIs have long been recognised as an efficient pharmacologic agent in the treatment of pediatric OCD (6). However, data regarding the efficacy of augmentation treatment strategies in the face of treatment resistance to SSRIs, are still fairly limited (15-20). Limited number of studies have been carried out in this field, one being the study conducted by Fitzgerald et al., in 1999. This study reported findings regarding successful treatment outcome by using risperidone as part of an augmentation therapy regimen in four children who were resistant to treatment with SSRIs (16). Another study that assessed the efficacy of augmentation therapy with aripiprazole in cases with treatment-resistant OCD was carried out by Thomsen, in 2004. This study reported clinical improvement in treatment-resistant OCD symptoms of adolescent cases with risperidone, used as the augmentation agent, administered in daily doses up to 2 mg (17). Clinical efficiency of aripiprazole in pediatric OCD treatment was initially demonstrated with a case report of a 13-year old boy, by Storch et al., in 2008. This case that was unresponsive to sertraline and CBT treatment was reported to have clinically improved with 5 mg/day aripiprazole. Authors of this case report have stated that aripiprazole was superior to sertraline regarding relief over OCD-related distress and dysfunction (18). In a study conducted by 39 adolescents 12 years and older who were resistant to treatment with two SSRIs, augmentation with aripiprazole was well-tolerated by the patients and found efficient in more than half of the sample (15). Again, in a 3-case series by Ulay, augmentation treatment with aripiprazole was linked to positive outcome (19). Another study that comprised 16 cases with OCD that were resistant to at least two different SSRIs and CBT reported positive clinical response to add-on aripiprazole (21). Such findings were supported with those reported in
another study with similar design conducted with a larger sample size (20). While aforementioned studies report data regarding possible measures for intervention in the face of treatment resistant OCD, none presents any novel information on situations where therapeutic effect is delayed and this causes more harm to the patient. Delayed therapeutic effect of SSRIs in the treatment of OCD and suggestions of using another SSRI or clomipramine at times of insufficient response to treatment might create certain difficulties in clinical practice from time to time. Delayed effects of the medication and ongoing clinical symptoms might pose serious adversity regarding family, school and social functioning of the developing child. With this report, we have once again witnessed the severe impact of delayed response to SSRI treatment on our cases’ functioning (family, school, peer relationships), due to significant distress caused by OCD-related symptoms. On the other hand, it was also noticed that most of the cases

<table>
<thead>
<tr>
<th>Cases</th>
<th>GEN-DER</th>
<th>Age</th>
<th>Diagnosis</th>
<th>Initial CY-BOCS score</th>
<th>Index treatment and duration</th>
<th>Second CY-BOCS score</th>
<th>Time of add-on aripiprazole to on going treatment</th>
<th>CY-BOCS score following add-on aripiprazole</th>
<th>Current treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case 1</td>
<td>F</td>
<td>11</td>
<td>OCD</td>
<td>33</td>
<td>Fluoxetine 20—40 mg/day, 12 weeks</td>
<td>28</td>
<td>12th week</td>
<td>9 (4th week while on 5 mg/day aripiprazole)</td>
<td>Fluoxetine 40 mg/day + aripiprazole 5 mg/day</td>
</tr>
<tr>
<td>Case 2</td>
<td>M</td>
<td>15</td>
<td>OCD</td>
<td>31</td>
<td>Fluoxetine 20—40 mg/day, 9 weeks</td>
<td>28</td>
<td>11th week (olanzapine was added in 9th week, however was stopped after 2 weeks due to emerging side effects)</td>
<td>6 (assessment at 4th week while on 5 mg/day aripiprazole)</td>
<td>Fluoxetine 40 mg/day + aripiprazole 5 mg/day</td>
</tr>
<tr>
<td>Case 3</td>
<td>M</td>
<td>15</td>
<td>OCD</td>
<td>39</td>
<td>Sertraline 50—100 mg/day, 10 weeks</td>
<td>31</td>
<td>10th week</td>
<td>Sertraline 100 mg/day + aripiprazole 5 mg/day</td>
<td></td>
</tr>
<tr>
<td>Case 4</td>
<td>M</td>
<td>10</td>
<td>OCD</td>
<td>35</td>
<td>Fluoxetine 20—30 mg/day, 7 weeks</td>
<td>30</td>
<td>7th week</td>
<td>Fluoxetine 30 mg/day + aripiprazole 5 mg/day</td>
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</tr>
<tr>
<td>Case 5</td>
<td>M</td>
<td>15</td>
<td>OCD</td>
<td>33</td>
<td>Sertraline 25—100 mg/day (well-tolerated dosage by the patient), 10 weeks</td>
<td>21</td>
<td>16th week (sertraline 100 mg/day + risperidone 2 mg/day, risperidone was stopped due to side-effects)</td>
<td>8 (assessment at 8th week while on 7.5 mg/day aripiprazole)</td>
<td>Sertraline 100 mg/day + aripiprazole 7.5 mg/day</td>
</tr>
<tr>
<td>Case 6</td>
<td>F</td>
<td>14</td>
<td>OCD</td>
<td>29</td>
<td>Fluoxetine 20—40 mg/day, 11 weeks</td>
<td>24</td>
<td>11th week</td>
<td>Fluoxetine 5 mg/day + aripiprazole 5 mg/day</td>
<td></td>
</tr>
</tbody>
</table>

Table 1: Characteristics of cases with OCD
experienced a decrease in treatment motivation due to minimal response to treatment. For all these reasons, augmentation with aripiprazole was used as an add-on strategy during the early phases of treatment. Clinical improvements were observed in all cases as a result of this, and was documented by significant decline in CY-BOCS scores. Our initial motivation for initiating augmentation treatment in the early phase was to manage increasing levels of functional deterioration, specifically the negative impact on school and family functioning. However, one must also note that this study did not aim to suggest a standardized algorithm for when to initiate early-on augmentation therapy in treatment resistant OCD, and more controlled trials and studies need to be planned in order to propose such guidelines.

Apart from these, existing proof of dopaminergic and serotoninergic dysfunction in the neurobiology of OCD might hold a key to explain why aripiprazole is efficient in the improvement of OCD-related clinical symptoms (22,23). As an atypical antipsychotic agent, aripiprazole exerts partial agonistic effect on dopamine D2 receptors and is a regulator of the intrinsic dopamine D2 receptors. This causes an equilibrium within dopamine D2 receptor-mediated neurotransmission without over blockage (22). Aripiprazole acts as a partial agonist for serotonin 5-HT1A and 5-HT2c receptors, as well as an antagonist for 5-HT2A receptor (24).

**CONCLUSION**

Even though a diversion from recommended treatment guidelines, we believe if replicated by more studies, conducted with research samples and control groups, early-term aripiprazole augmentation to SSRIs in the treatment of resistant OCD might be a useful alternative, for selected patients. We hope this case series shall make a contribution to current relevant literature, and prompt future studies that focus on improving treatment options and guidelines, for the disorder.

**Ethics Committee Approval:** Written consent was obtained from all cases.

**Patient Informed Consent:** Written consent was obtained from all cases.

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