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PREVALENCE AND ASSOCIATED FACTORS OF ADVERSE EFFECTS IN CHILDREN AND ADOLESCENTS TREATED WITH SELECTIVE SEROTONIN REUPTAKE INHIBITORS: A CHART REVIEW STUDY*

SEÇİCİ SEROTONİN GERİ ALIM İNHİBİTÖRLERİYLE TEDAVİ EDİLEN ÇOCUK VE ERGENLERDE YAN ETKİLERİN SIKLIĞI VE İLİŞKİLİ FAKTÖRLER: BİR DOSYA TARAMA ÇALIŞMASI

Hanım Hülya ALINAY[1], Ali KARAYAĞMURLU[2], Murat COŞKUN[2]

[1]Sirnak State Hospital, Child and Adolescent Psychiatry Department, Sirnak, Turkiye
[2]Istanbul University, Istanbul Faculty of Medicine, Child and Adolescent Psychiatry Department, Istanbul, Turkiye

ORCID IDs of the authors: H.H.A. 0000-0003-3029-5439; A.K. 0000-0001-5464-2891; M.C. 0000-0002-4808-5870

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ABSTRACT

Objective: This study aims to examine the prevalence and associated clinical and sociodemographic factors of adverse effects in medication among naïve young subjects who received selective serotonin reuptake inhibitor (SSRI) monotherapy.

Material and Methods: The medical records of 85 patients who had received SSRI monotherapy in a university hospital's child and adolescent psychiatry clinic were reviewed. The subjects who met the inclusion criteria were included in the study.

Results: A total of 67 subjects (10.82±3.63 years) were included. More than half (n=39, 58.9%) developed at least one adverse effect possibly associated with SSRI treatment, with psychic (n=25, 37.3%) and autonomic (n=20, 29.9%) adverse effects as well as behavioral activation (n=13, 19.4%) being the most frequently reported. Medication was discontinued in 13 subjects (19.4%) due to adverse effects, with behavioral activation (6 out of 13 subjects) being the most frequent reason for discontinuation. The development of behavioral activation was significantly associated with younger age, diagnosis of obsessive compulsive disorder in the subjects, and psychiatric history in the subjects' fathers (p value<0.05).

Conclusions: Despite the fact that SSRIs are generally safe and well-tolerated in young subjects, adverse effects may be fre-

ÖZET

Amaç: Bu çalışma, seçici serotonin geri alım inhibitörü (SSRI) monoterapisi alan genç hastalar arasında ilaç yan etki sıklığını ve bu yan etkilerle ilişkili klinik ve sosyodemografik faktörleri incelemeyi amaçlamaktadır.

Gereç ve Yöntem: Bir üniversite hastanesinin çocuk ve ergen psikiyatrisi kliniklerinde SSRI monoterapisi alan 85 hastanın tıbbi kayıtları incelendi. Dahil edilme kriterlerini karşılayan hastalar çalışmaya dahil edildi.

Bulgular: Toplam 67 hasta (10,82±3,63 yıl) dahil edildi. Hastaların yarısından fazlası (n=39, %58,9) muhtemelen SSRI tedavisi ile ilişkili en az bir yan etki geliştirdi. En sık bildirilen yan etkiler; psişik (n=25, %37,3) ve otonomik yan etkilerin (n=20, %29,9) yanısıra davranışsal aktivasyondu (n=13, %19,4). Yan etkiler nedeniyle 13 hastada (%19,4) ilaç tedavisi sonlandırıldı ve en sık ilaç kesme nedeni davranışsal aktivasyondu (13 hastanın 6'sı). Davranış aktivasyonunun ortaya çıkması; daha küçük yaş, hastada obsesif kompulsif bozukluk tanısı varlığı ve babada psikiyatrik hastalık varlığı ile anlamlı olarak ilişkiliydi (p değeri<0,05).

Sonuç: SSRI'lar genç hastalarda genellikle güvenli ve iyi tolere edilmesine rağmen, yan etkiler sık olabilir ve bazı durumlarda ilacın kesilmesi gerekebilir. Bu nedenle, genç hastaları tedavi eden klinisyenler, özellikle davranışsal aktivasyonun gelişimi konusun-

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Corresponding author/İletişim kurulacak yazar: Hanım Hülya ALINAY – hnmozkan@gmail.com

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quent, and medication discontinuation may be required under some conditions. Thus, clinicians treating young subjects should be cautious, particularly about the development of behavioral activation. They should also be mindful of the clinical and sociodemographic factors associated with the adverse effects that may arise during SSRI treatment.

Keywords: Adolescents, Adverse Effects, Children, Side Effects, Selective Serotonin Reuptake Inhibitors, Behavioral Activation

da dikkatli olmalıdır. Ayrıca SSRI tedavisi sırasında ortaya çıkabilecek yan etkilerle ilişkili klinik ve sosyodemografik faktörleri de dikkate almalıdırlar.

Anahtar Kelimeler: Ergen, Yan Etki, Çocuk, Seçici Seratonin Geri Alım İnhibitörü, Davranışsal Aktivasyon

INTRODUCTION

Selective serotonin reuptake inhibitor (SSRI) drugs have been widely used among the young population to treat psychiatric disorders with or without FDA-approved indications (1, 2). In clinical practice, major depressive and obsessive compulsive disorders (OCD) are FDA-approved indications, and SSRIs have also been used with several other indications, including anxiety and post-traumatic stress disorders. CDC data show that, between 2011 and 2014, 12.7% of young people aged 12 years and older received antidepressant treatment in the USA (1-4). Although the overall efficacy and safety of SSRIs are supported by large controlled multicenter studies, the adverse effects of SSRI treatment in children and adolescents may be different from adults mainly due to the pharmacodynamic and pharmacokinetic developmental differences between these age groups (5, 6). Indeed, many studies have reported that the adverse effects associated with SSRIs show significant differences across age groups, and children may be more susceptible to such adverse effects of SSRIs, which may be partially explained by their biological immaturity (2, 7, 8). In a review of the side effects of SSRIs in children and adolescents, the commonly reported side effects were behavioral activation, insomnia, somnolence, and gastrointestinal system (GIS)-related symptoms; some of these side effects were reported to be more common in younger children (2). Physical adverse effects due to SSRIs were more commonly reported than psychiatric adverse effects. However, the severity of the latter is significant, as these symptoms result in higher rates of treatment discontinuation (9). Such adverse psychiatric effects can be categorized as follows: signs of behavioral activation (increased activity, impulsivity, and behavioral disinhibition without manic symptoms), manic symptoms (mania, hypomania, and elevated moods), depressive symptoms (worsening depression, crying, irritability, anger, and hypersensitivity), agitative symptoms (agitation, akathisia, restlessness, and irritability), anxiety and panic symptoms, apathy, tremor, and feelings of emptiness (9, 10). Psychiatric adverse effects of SSRIs, especially bipolar disorder, behavioral activation, apathy, and suicidality, can have serious impacts on the patient and his/her family. However, the majority of studies concerning this age group have focused on the efficacy of SSRIs, and relatively few studies have examined the safety profile of SSRI treatment in children and adolescents. To date, no satisfactory data have been presented that recognize adverse effects and how adverse effects relate to SSRI dosages and types as well as the clinical and sociodemographic characteristics of subjects (9, 10). Additionally, data regarding the safety and adverse effects of SSRIs in the young population may sometimes come from studies in which participants received multiple psychotropic drugs during the study period or had experienced previous psychotropic drug use (8). Therefore, it may be important to assess the adverse effects of SSRI treatment and the potential relationship between sociodemographic and clinical variables in medication among naïve young subjects undergoing SSRI monotherapy.

In this retrospective chart review study, we aimed to investigate the prevalence and nature of SSRI-related adverse effects among young subjects receiving SSRI monotherapy and to evaluate the possible relationships between several clinical (i.e., psychiatric diagnosis) and sociodemographic variables (i.e., age and gender).

MATERIAL AND METHODS

Patient selection and procedure

This study was conducted in the Child and Adolescent Psychiatry Department of the Istanbul Faculty of Medicine. The subjects were among the children and adolescents referred to the outpatient clinic from January to June 2018 who had received SSRI monotherapy for any psychiatric diagnosis. The study protocol was approved by the Istanbul University, Istanbul Faculty of Medicine Clinical Research Ethics Committee (Date: 04.05.2018, Decision No:09). All patients provided written informed consent prior to the study procedures. During the initial clinical interview, the subjects were assessed in terms of reason(s) for referral, provisional diagnosis, and the need for psychopharmacological treatment. The subjects then underwent a detailed clinical assessment, which included a diagnostic interview, if they were lined up to start treatment with SSRIs. The inclusion criteria were as follows: participants must a) be receiving SSRI monotherapy, b) undergo a complete and detailed

psychiatric examination and assessment using routine clinical instruments for the efficacy and safety of SSRI monotherapy, and c) have been followed up for at least three months following the initiation of SSRI monotherapy. Among the 85 subjects, a total of 67 met the inclusion criteria and were subsequently included in the study.

Before SSRI treatment was started, each subject was assessed by an experienced child psychiatry fellow and supervisor for a complete psychiatric diagnostic evaluation using the DSM-5 criteria. Upon receiving a psychiatric diagnosis, each subject was asked to fill out relevant instruments to measure symptom severity, such as those for anxiety and depression. Next, every subject was given SSRI treatment on a routine clinical basis, which included fluoxetine and sertraline as the most commonly prescribed SSRIs in the clinic. As a routine clinical practice, each subject who started SSRI monotherapy was assessed after two or three weeks. The efficacy and safety of SSRI treatment were evaluated using the Clinical Global Impression Scale (CGI), the Screen for Child Anxiety and Related Disorders (SCARED), the Children's Depression Inventory (CDI), the Udvalg for Kliniske Undersogelser (UKU) Side Effect Rating Scale, and a screening tool for investigating SSRI-associated behavioral activation, mania, apathy, and suicidality (SABAMAS). These scales were used in most of the clinical visits. Evaluations in this study occurred subsequent to three months of medication treatment.

Measures

Sociodemographic data

Several parameters, including gender, age, education status, medical history, psychiatric diagnoses, and family characteristics, as well as the type, dosage, and duration of SSRI treatment, were coded depending on the information in the patients' charts.

Clinical Global Impression (CGI) Scale

CGI has three subscales, which assess symptom severity (CGI-S), global improvement (CGI-I), and side effects. The CGI scale has been widely used in clinical studies for all age groups (11). In the present study, the CGI-S (with scores from 1 to 7, with 1= normal or not at all ill and 7= extremely ill) and the CGI-I (with scores from 1 to 7, with 1= very much improved and 7= very much worse) subscales were used to measure symptom severity and improvement, respectively.

Udvalg for Kliniske Undersogelser Side Effect Rating Scale (UKU)

The UKU is a frequently used 48-item scale that measures adverse effects and tolerability related to psychotropic medication (12). The internal consistency coefficients (Cronbach's alpha) were 0.76 for females and 0.82 for males (13). It investigates the side effects among four domains (psychic, neurological, autonomic, and other) for the prior three days, with severity scores ranging from 0 (no, or doubtful, side effects) to 3 (severe side effects).

SSRI-Associated Behavioral Activation, Mania, Apathy, and Suicidality (SABAMAS)

SABAMAS was previously developed by the author (M.C.) and used in clinical practice to investigate the four domains of adverse effects, including behavioral activation (8 items), mania (3 items), apathy (4 items), and suicidality (3 items), which may emerge during treatment with SSRIs. It consists of a total of 18 items, with scores ranging from 0 (no adverse effect) to 3 (a severe adverse effect that requires medication discontinuation). The rationale and the need to develop SABAMAS was that despite there being particularly important adverse effects that may emerge during treatment with SSRIs in young subjects, the UKU did not include the majority of these adverse effects. This scale was developed with respect to the present literature (14) and to accumulated clinical experience. If subjects experienced any symptoms in any of these four domains, they were considered to have developed a particular adverse effect. For example, if the subject had even one symptom in the behavioral activation domain, it was considered an emergence of behavioral activation. The internal consistency was measured using Cronbach's α coefficient; the Cronbach's α coefficient of the SABAMAS in the current study was 0.79.

Statistical analysis

The SPSS 21.0 software program was used for the statistical analysis. The mean, percentage, and standard deviations were used to evaluate the descriptive and clinical characteristics of the subjects. A chi-squared test was employed to compare qualitative data between groups. Binary logistic regression analyses were used to predict the development of behavioral activation as well as psychic and autonomic adverse/side effects. For behavioral activation, the independent variables (age, body mass index, comorbidity, diagnosis of OCD, and psychiatric diagnosis in the father) were used in the regression model.

RESULTS

A total of 67 subjects aged 5–17 years (10.82± 3.63 years) were included in the study. Almost half of the subjects were male (n=33, 49.3%), and slightly more than half of the subjects were under 10 years of age (n=35, 52.2%). The most frequent diagnoses were social anxiety disorder (SAD) (n=48, 71.6%), generalized anxiety disorder (GAD) (n=29, 43.3%), attention deficit hyperactivity disorder (ADHD) (n=28, 41.8%), and specific phobia (SP) (n=17, 25.4%). The most frequent diagnoses for SSRI treatments were anxiety disorders (n=50, 74.6%) and OCD (n=10, 14.9%). The most frequently prescribed SSRIs were

sertraline (n=43, 64.2%) and fluoxetine (n=20, 29.9%). There was a history of diagnosed psychiatric disorder(s) in the first-degree relatives in the majority of the subjects (n=50, 74.6%). The rates of diagnosed psychiatric disorder(s) in mothers and fathers were 41.8% (n=28) and 23.9% (n=16), respectively. Table 1 shows the clinical and sociodemographic characteristics of the subjects.

At the end of the 12th week of SSRI treatment, 23.8% of the subjects (n=16) had at least one adverse effect according to SABAMAS and 70.1% (n=47) had at least one side effect according to the UKU scale. While irritability was the most frequently reported adverse effect (n=13, 19.4%) in SABAMAS, nausea/vomiting was the most frequent side effect for the UKU scale (n=15, 22.4%). According to the UKU scale, none of the subjects developed neurological side effects during treatment. Tables 2 and 3 show the details of the SABAMAS and UKU scales, respectively.

Binary logistic regression was employed to assess the variables that predicted behavioral activation as well as autonomic and psychic adverse/side effects. The regression model for behavioral activation (R2=0.338, p=0.007) showed statistical significance. In particular, behavioral activation was associated with the age of the subject (B=6.4, CI: 1.05; 39.3, p=0.044), a diagnosis of OCD in the subject (B=6.3, CI: 1.05; 39.3, p=0.034), and psychiatric disorder(s) in the father (B=4.9, CI: 1.1; 22.7, p=0.036). There was no significant difference

Table 1: Clinical and sociodemographic characteristics of the subjects

	n	%
Age	**10.82±3.63 years**	
Gender		
Female	34	50.7
Male	33	49.3
Psychiatric disorders		
Social anxiety disorder	48	71.6
Generalized anxiety disorder	29	43.3
Attention deficit hyperactivity disorder	28	41.8
Predominantly inattentive	19	28.3
Combined	9	13.5
Specific phobia	17	25.4
Obsessive-compulsive disorder	12	17.9
Separation anxiety disorder	11	16.4
Tic disorders	8	11.9
Major depressive disorder	6	9
Enuresis	4	6
Post-traumatic stress disorder	2	3
Panic disorder	1	1.5
Encopresis	1	1.5
Oppositional defiant disorder	1	1.5
Indications of SSRI initiation		
Anxiety disorders	50	74.6
Obsessive-compulsive disorder	10	14.9
Major depressive disorder	6	9
Post-traumatic stress disorder	1	1.5
Type of SSRI		
Sertraline	43	64.2
Fluoxetine	20	29.9
Paroxetine	2	3
Escitalopram	2	3
Mean doses of SSRIs/mg		
Sertraline	41.2±18.6	
Fluoxetin	16.9±7.9	
Paroxetin	10.0±0.0	
Escitalopram	3.5±0.7	

Note: SSRI: Selective serotonin reuptake inhibitor

Table 2: SSRI Associated Behavioral Activation, Mania, Apathy and Suicidality (SABAMAS)

	Severity			n (%)
	Mild	Moderate	Severe	
Behavioral activation				13 (19.4)
Irritability	8	4	1	13 (19.4)
Oppositional behaviors	5	4	-	9 (13.4)
Excessive talking	3	4	-	7 (10.4)
Aggressive behaviors	2	3	2	7 (10.4)
Hyperactivity	4	2	-	6 (9)
Risky behaviors	1	2	-	3 (4.5)
Talking with unfamiliar people	1	-	-	1 (1.5)
Apathy				2 (3)
Laziness	-	2	-	2 (3)
Not to care anything	-	2	-	2 (3)
Suicidality				2 (3)
Suicidal ideation	-	2	-	2 (3)
Suicidal behavior	-	-	1	1 (1.5)
Suicide attempt	-	-	1	1 (1.5)

Table 3: UKU side effects in the subjects

	Severity			n (%)
	Mild	Moderate	Severe	
Psychic				25 (37.3)
Concentration difficulties	2	5	3	10 (14.9)
Asthenia/lassitude/increased fatigability	3	5	2	10 (14.9)
Sleepiness/sedation	2	2	-	4 (6)
Failing memory	1	2	-	3 (4.5)
Tension/inner unrest	-	5	1	6 (9)
Increased duration of sleep	4	-	-	4 (6)
Reduced duration of sleep	6	-	1	7 (10.4)
Increased dream activity	2	1	-	3 (4.5)
Emotional indifference	1	1	-	2 (3)
Autonomic				20 (29.9)
Nausea/vomiting	7	5	3	15 (22.4)
Diarrhea	1	1	-	2 (3)
Constipation	1	-	-	1 (1.5)
Polyuria/polydipsia	-	1	-	1 (1.5)
Orthostatic dizziness	6	1	-	7 (10.4)
Palpitations/tachycardia	1	-	-	1 (1.5)
Other				6 (9)
Rash	2	-	-	2 (3)
Headache	2	2	-	4 (6)

Table 4: Results of binary logistic regression models for the variables predicting behavioral activation

Model 1: Binary logistic regression analysis for predictors of behavioral activation adverse/side effects (R^2=0.338, p=0.007)		
Variables	**OR (95%CI)**	**p value**
BMI (Weight/Height^2)	1.04 (0.88-1.22)	0.612
Comorbidity (Absence Presence)	1.73 (0.24-12.16)	0.578
Age (Above 10 → Below 10)	6.44 (1.05-39.38)	**0.044**
Diagnosis of OCD (Absence →Presence)	6.35 (1.15-35.04)	**0.034**
Psychiatric diagnosis in the father (Absence →Presence)	4.95 (1.10-22.17)	**0.036**

Note: Bold data, p<0.05 (significance). CI: Confidence interval. OR: Odd ratio. BMI: Body Mass Index. OCD: Obsessive Compulsive Disorder.

Table 5: Details of Medication Discontinuation in the Subjects

Case	Age (years)/ Gender	Indication for SSRI treatment	SSRI Medication and dosage that adverse(s) effect emerged	Adverse effect(s) led to discontinuation
1	7/F	Separation anxiety disorder	Fluoxetine 10 mg/day	Apathy
2	9/F	Separation anxiety disorder	Sertraline 50 mg/day	Rash
3	10/F	Social anxiety disorder	Paroxetine 10 mg/day	Behavioral activation
4	15/M	Obsessive-compulsive disorder	Sertraline 50 mg/day	Sedation
5	16/F	Generalized anxiety disorder	Sertraline 50 mg /day	Tooth grinding
6	13/F	Social anxiety disorder	Sertraline 50 mg/day	Headache
7	5/F	Obsessive-compulsive disorder	Fluoxetine 5 mg/day	Behavioral activation
8	8/M	Generalized anxiety disorder	Sertraline 25 mg/day	Behavioral activation
9	8/F	Obsessive-compulsive disorder	Sertraline 25 mg/day	Behavioral activation
10	10/M	Generalized anxiety disorder	Sertraline 25 mg/day	Suicidal ideation
11	8/M	Social anxiety disorder	Sertraline 25 mg/day	Behavioral activation
12	15/F	Major depressive disorder	Fluoxetine 20 mg/day	Suicide attempt
13	6/M	Obsessive-compulsive disorder	Fluoxetine 10 mg/day	Behavioral activation

Note: F: Female, M: Male

between fluoxetine (n=20) and sertraline (n=43) in terms of the frequency of behavioral activation (p=0.732). The results of the binary regression model for the variables predicting behavioral activation are presented in table 4.

In our study, none of the cases developed bipolar shift and neurological adverse/side effects. The frequency of apathy and suicidal behavior was lower than the frequency of behavioral activation as well as the frequencies of autonomic and psychological adverse/side effects. Medication was discontinued in 13 subjects (19.4%) due to adverse/side effects. The most frequent adverse effect that led to medication discontinuation was behavioral activation which occurred in six subjects. Table 5 presents the details of medication discontinuation.

DISCUSSION

This study investigated the various extents of adverse effects seen in children and adolescents being treated with SSRI drugs; these included autonomic, psychic, and neurological side effects as well as SABAMAS. Additionally, cases in which SSRI treatment was discontinued due to adverse effects were analyzed with respect to their clinical characteristics. Adverse effects were observed in 58.2% (n=39) of our study cases, with the most common effects being autonomic and psychic problems as well as behavioral activation.

In the present study, behavioral activation was observed in 19.4% (n=13) of children and adolescents. This finding is consistent with those of other studies. For example,

in a study of 82 children and adolescents, Wilens et al. determined that the frequency of behavioral activation was 22% (15). Similarly, a current retrospective study that involved 139 children and adolescents undergoing SSRI therapy reported that adverse effects related to behavioral activation were present in 20.9% of cases (8). Coskun et al. reported high rates of symptoms of behavioral activation in preschool children treated with fluoxetine for distressing OCD symptoms (83%), and with escitalopram for anxiety disorders (45%) (16-17). They concluded that younger age and the presence of high comorbidity particularly ADHD may be associated with high rates of symptoms of behavioral activation. While these symptoms were managed by medication discontinuation or dosage reduction in some subjects, risperidone had been used for pre-existing behavioral problems or to manage symptoms of behavioral activation in some of them (18). In some other reports, Coskun (2017) reported an escitalopram-induced manic switch, and Coskun and Karayagmurlu (2020) reported fluoxetine-induced behavioral activation in two preschool subjects who were treated for distressing symptoms of OCD both having comorbid diagnoses of ADHD and anxiety disorders (19-21).

In our study, the factors associated with the emergence of behavioral activation included younger age, psychiatric disorder(s) in the father, and an OCD diagnosis. Our study results are similar to the findings of other studies when comparing activation and age (16, 17). For instance, Carlson et al. reported that the incidence of medication-induced behavioral activation was more frequent in younger people compared to older people (22). In addition, a systematic review revealed an 11% frequency rate of SSRI-induced behavioral activation in children, with rates ranging from 2% to 4% in teenagers and adults (5). The serotonergic system's maturity at a young age is widely considered to be the mechanism behind the high prevalence of behavioral activation in children compared to adults (2, 8, 23). This theory supports the concept that although SSRI therapy has a high efficacy in children and adolescents, it is also more likely to lead to behavioral activation in children in comparison to adults (24).

Another factor associated with the frequency of behavioral activation is the history of psychiatric disorder(s) in the father. This finding is consistent with the research of Strawn, who reported that children who had family members with medical histories of bipolar disorder were at an increased risk of behavioral activation with SSRI use (25). In addition, children diagnosed with OCD have been shown to be at an increased risk of experiencing behavioral activation. Coskun et al. reported higher rates of behavioral activation with fluoxetine in preschool children for the treatment of OCD than with escitalopram treatment for anxiety disorders (16, 17). However, it is unclear whether this difference is due mainly to medication or diagnosis. Moreover, the literature reveals that the signs of activation syndrome intensify as the SSRI dose increases (26, 27). These results are thought to be related to the poor response of OCD to SSRI drugs compared to the response of other psychiatric disorders, thus requiring higher doses for treatment.

The most common adverse effects associated with SSRI use were psychic side effects (37.3%). Of this group, the most frequently observed adverse effects were concentration problems, sedation, and insomnia. The findings observed in this study mirror those of previous studies that have also examined SSRI-related adverse effects (10, 28, 29). The Treatment for Adolescents with Depression Study (TADS) showed that sedation was among the most common side effects experienced by children using SSRIs (10). Two randomized controlled studies were conducted on the efficacy of sertraline in treating children and adolescents, and the most commonly observed adverse effects were concentration problems, sedation, and insomnia (22, 23).

In the present study, 29.9% of children and adolescents using SSRIs experienced autonomic side effects, with GIS problems and orthostatic hypotension being the most common. Two systematic reviews evaluated the efficacy and safety of SSRI treatment in children and adolescents, and the results showed that GIS side effects, such as nausea, vomiting, and dry mouth, were common in patients (30, 31). In addition, the TADS found that nausea, vomiting, and abdominal pain were among the most frequent side effects (10).

In our study, SSRI-induced neurological side effects or manic shifts were not observed in any of the cases, and apathy and suicidality were observed in 3% of the patients. These findings resemble the results of other studies in the literature. In particular, a systematic review regarding the use of SSRIs in children and adolescents showed that the neurological side effects had a very low rate of occurrence (32). A randomized controlled study that evaluated the risk of manic shift during SSRI treatment revealed that the highest risk was during the peripubertal period and that children and adolescents had a less than 2% risk of experiencing manic shift (33). To the best of the researchers' knowledge, the literature does not contain any data regarding the prevalence of SSRI-induced apathy in this age group, although it alternatively includes case series (34). As mentioned above, 3% of the cases in our study experienced apathy. Data regarding SSRI-induced suicidal behavior in children and adolescents were obtained from multicentered, randomized double-blind placebo control studies, including TADS, TORDIA, TASA, and ADAPT. Although no suicides were realized following SSRI treatment, the

rate of suicidal behavior ranged from 10% to 17% (35). While the samples in the previously mentioned studies consisted mostly of children and adolescents diagnosed with major depressive disorder (MDD), our study mainly included patients with anxiety disorders. The lower occurrence of suicide or suicidality in our study could be explained by the differences in the diagnoses of the samples. In a contemporary meta-analysis study, Sørensen et al. evaluated the risk of suicidality in children and adolescents receiving SSRI treatment, and their results showed that suicide risk was associated with older age and the diagnosis of depression (36).

Although SSRIs have been known to be safe and tolerated well by children and adolescents, two meta-analysis studies reported that 12%–26% of patients using SSRIs discontinued treatment due to adverse effects (37,38). In our study, 58.2% (n=39) of cases experienced adverse effects, and 19.4% (n=13) discontinued SSRI treatment as a result. The most common reason for discontinuing treatment in our study was behavioral activation (n=6). Even though behavioral activation was present in 13 patients, various methods were applied to reduce activation; of these 13 patients, 6 were managed through discontinued treatment, 4 through lowered doses, 1 through the addition of an anti-psychotic dose, and the remaining 2 were monitored in the clinic, as their signs of behavioral activation were mild. Although the literature does not present precise, collective data on how to reduce activation signs, most of the studies recommend lowering the dose as the first approach (8, 39-40). In our study, many methods were applied to reduce signs of activation; however, discontinuing treatment was the initial approach in six cases due to the severity of these symptoms. In conclusion, longitudinal studies must be conducted to further illuminate SSRI-induced adverse effects and their predictive clinical and sociodemographic characteristics.

CONCLUSION

In this study, children and adolescents undergoing SSRI monotherapy were extensively evaluated for potential adverse effects over a period of 12 weeks. The results of this study indicated that children using SSRIs commonly experienced adverse effects, with behavioral activation being the most common reason for discontinuing treatment. Therefore, clinicians treating young subjects should weigh the potential benefits and risks associated with SSRI treatment and be aware of the possible factors associated with the development of adverse effects during SSRI treatment for better compliance and success in children and adolescents.

The current study has certain limitations, such as having a retrospective design, not including a control group, being conducted in a single center, and consisting of a relatively small sample. Additionally, the number of subjects using paroxetine and escitalopram was very low compared to sertraline and fluoxetine which may affect the results of the study.

Ethics Committee Approval: This study was approved by Istanbul Faculty of Medicine Clinical Research Ethics Committee (Date: 21.05.2018, No: 696).

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