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Does augmentation with antipsychotic agents affect the medication adherence of the child with obsessive-compulsive disorder?

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Abstract

Antipsychotic agents can be used for augmentation when the response to treatment is insufficient in children with obsessive compulsive disorder. Our aim was to investigate adherence to treatment between patients with and without antipsychotic augmentation and factors potentially related to this. One hundred fourteen children and adolescents aged 8-18 years diagnosed with OCD and still receiving treatment were included in the study. Fifty-two subjects were received antipsychotic therapy for augmentation, while 62 were not receiving it. All subjects were evaluated using a sociodemographic data form, the 8-item Morisky Medication Adherence Scale (MMAS-8), and the Udvalg for Klinikse Undersegelser (UKU) side-effects rating scale. The results were then subjected to statistical analysis. Total MMAS-8 scores were statistically significantly lower in the augmentation group than in the monotherapy group (p: 0.01). Sex, receipt of psychotherapy and family monitoring of treatment had no effect on total MMAS-8 scores (p: 0.949, p: 0.394, and p: 0.198, respectively). Higher UKU side-effect rating scale scores were determined in the augmentation group compared to the monotherapy group ($p<0.05$). Correlation analysis revealed that UKU total score (r:-0.272, p:0.003) and UKU psychological side-effects subscale score (r:-0.263, p:0.005) were significantly inversely correlated with MMAS-8 total scores. Side-effects deriving from medications affected adherence to treatment more significantly than several other environmental factors in children with OCD. Our findings show the need for side-effects, and particularly psychological side-effects, the frequency of which increases with augmentation, to be monitored in terms of adherence to treatment.

Keywords: Adherence, medication adherence, antipsychotic, augmentation, obsessive compulsive disorder

Introduction

Obsessive compulsive disorder (OCD) is characterized by the presence of obsessions, involuntary, repetitive or intrusive thoughts, and unnecessary repetitive behaviors or mental activities. It is a frequent cause of distress for children and adolescents [1]. OCD is a psychiatric disorder that can begin in childhood and affects 1-2% of the population [2]. It causes numerous problems with adverse impacts on children's academic functions, peer relations and home life. Pharmacotherapy and psychotherapy are used in the treatment of OCD. Cognitive behavioral therapy (CBT) is one psychotherapeutic method successfully used in childhood, and also in the adult literature [3]. Pharmacotherapy studies have shown the efficacy of serotonin reuptake inhibitors (SRIs) in the treatment of young people with OCD [4]. However, a satisfactory level of symptom improvement may not be achieved in a significant proportion of children with OCD. Approximately one in three or four of these children fails to respond to first-line treatment, and complete remission of OCD symptoms is not achieved in 46% of cases [5]. Treatment-refractory OCD cases are treated using pharmacological augmentation strategies, the most widespread method, involving the addition to medication of an antipsychotic agent [6]. Studies have shown the effectiveness of augmenting SRI pharmacotherapy in OCD with low-dose typical and atypical antipsychotics. However, it is still unclear which antipsychotic agent is more effective in this augmentation therapy [7].

Medication adherence is defined as the extent to which the behavior

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of an individual using a medication responds to the medication use advice of a health service provider. Studies have shown that failure to comply with medication therapy advised by the physician renders the treatment ineffective and can lead to a decrease in health-related quality of life in patients with psychiatric disorders [8]. Approximately 30-50% of patients with chronic disease fail to take medications as prescribed, for which reason failure to adhere to medication therapy represents a general public health problem [9]. It is very important to increase adherence to treatment in clinical psychiatry. Establishing a therapeutic relationship with patients requires understanding their needs and adjusting treatment accordingly. This can only be achieved when the effectiveness of treatment, the side-effect burden, and its acceptability to patients are monitored on a regular basis [10]. Adherence is frequently low in psychiatric treatments, affecting 15-25% of hospitalized patients and 50% of outpatients. Twenty percent of psychiatric patients do not take their medications, and 30-50% of purchased drugs are not consumed. Low treatment adherence can have serious consequences, and is associated with high direct and indirect costs associated with recurrence, readmission, chronification, and low productivity [11]. Non-adherence to medication is also reported to be widespread in the pediatric population. Medication adherence rates in pediatric patients range between 11% and 93%. Poor adherence to treatments results in prolonged duration of disease for children and in difficulties in the patient-physician relationship [12]. One review reported that long-term medication therapy and the prescription of numerous drugs reduced medication adherence in children [13]. Drug side-effects are known to impact on adherence to treatment and are of major importance [14].

Adherence to treatment is affected by factors related to the medication prescribed, the environment and the patient. The purpose of this study was to investigate adherence to treatment in children and adolescents with and without augmentation of medical treatment and factors potentially related to this.

Material and Methods

The study was performed at the Bakırköy Dr. Sadi Konuk Training and Research Hospital Child and Adolescent Mental Health and Diseases polyclinic. One hundred fourteen subjects age 8-18 years were included. Fifty-two participants were receiving antipsychotic agents for augmentation for treatment of OCD, while 62 were using no such agents. Two groups were constituted, augmentation and monotherapy. An information form consisting of structured multiple choice questions to be completed in writing was prepared by psychiatric specialists to determine cases' sociodemographic and clinical characteristics. The forms were completed by patients and their families. Ethical committee approval was obtained for the study (No. 2017-03-17 dated 15.05.2017), and verbal and written consent was given by all participants and their parents. Patient enrolment was performed between June 2017 and June 2018. Patients consisted of subjects diagnosed with OCD following clinical evaluation by a child and adolescent psychiatry specialist working in this field based on DSM-V criteria. Subjects with comorbid psychiatric disorders or known organic diseases were excluded. Patients receiving multidrug therapies (more than two medications) or whose forms could not be accurately analyzed were also excluded. The OCD treatment protocol published by the American Academy of Child and Adolescent Psychiatry (AACAP) is used as a treatment guideline in the center where the study was carried out [15]. As recommended in the guideline, agents were added for augmentation to patients without sufficient responses to treatment with SSRI over at least 12 weeks.

Medication adherence was assessed using the 8-item Morisky Medication Adherence Scale (MMAS-8). This scale, with confirmed reliability and validity in Turkish, classifies the medication behavior of the individual completing it with eight self-report items. Total scores lower than 6 indicate low adherence, scores of 6-8 indicate moderate adherence, and scores greater than 8 indicate high adherence [16,17].

The Udvalg for Klinikse Undersegelser (UKU) side-effects rating scale was used to assess side-effects caused by the medications used. This scale, developed by Lingjærde et al., is used to assess clinical side-effects associated with psychotropic drug use. It consists of subscales evaluating psychological, neurological, autonomic, and other side-effects. Each item consists of four options scored between 0 and 3, with "0" indicating no side-effect and "3" a severe side-effect. The presence or absence of a causal relation between symptoms and the medication used is assessed by the investigator following evaluation. The investigator prioritizes clinical observations when there is thought to be a discrepancy between the patient's own symptoms and information obtained at interview [18].

Descriptive statistics (mean, standard deviation, minimum, median, and maximum) were used to define continuous variables. The Mann Whitney U test was employed to examine relations between two independent, non-normally distributed continuous variables. The chi-square test (or Fisher's Exact test where applicable) was used to examine relations between categorical variables. Significance was set at 0.05. Analyses were carried out on MedCalc Statistical Software version 12.7.7 (MedCalc Software BVBA, Ostend, Belgium; http://www.medcalc.org; 2013).

Results

The 114 subjects in our study were divided into two groups based on receipt of augmentation therapy. The augmentation group consisted of 52 patients, and the monotherapy group of 62. The age range in the augmentation group was 8-18, with a mean age of 13.04+2.67. The age range in the monotherapy group was also 8-18, with a mean age of 13.08+2.98. The augmentation group consisted of 31 boys and 21 girls, and the monotherapy group of 32 boys and 30 girls. The two groups were similar in terms of age and sex distributions (p: 0.802, and p: 0.451, respectively). Mean duration of treatment was 1.3+1 years in the augmentation group and 1.1+1.05 years in the monotherapy group. Although duration of treatment was longer in the augmentation group, the difference was not statistically significant (p: 0.072). The augmentation and monotherapy groups were similar in terms of receipt of psychotherapy (p: 0.146) and of treatment being monitored by families (p: 0.099) (Table 1). Duration of augmentation therapy was 0.51+0.32 years. Mean time to transition to augmentation was 0.81+0.89 years. The most commonly used SRIs in both groups were sertraline and fluoxetine. The most commonly used antipsychotics in the augmentation group were risperidone in 52% and aripiprazole in 36.6%. Distributions of the drugs used by the groups are shown in Table 1.

At statistical analysis, MMAS-8 total scores were significantly lower (indicating poor adherence to treatment) in the augmentation group compared to the monotherapy group (p: 0.01). At the same time, scale score distributions revealed lower levels of adherence to treatment in the augmentation group and higher levels of adherence in the monotherapy group. Distributions of MMAS-8 total scores based on sex, receipt of psychotherapy and family monitoring of treatment revealed that these factors had no effect on total MMAS-8 scores (p: 0.949, p: 0.394, and p: 0.198, respectively) (Table 2).

Comparison of UKU side-effect scale scores revealed higher total scores (greater side-effects) in the augmentation group compared to the monotherapy group. The difference was statistically significant (p<0.001). All UKU subscale scores were also higher in the augmentation group than in the monotherapy group (Table 2).

Our data were subjected to correlation analyses with MMAS-8 total scores in order to compare the effect on adherence to treatment. No statistically significant correlation was determined between participants' ages (r: -0.039/p: 0.681) or times to diagnosis (r: -0.127, p: 0.179) and adherence to treatment. No significant correlation was also determined between times to transition to augmentation therapy (r: 0.171, p: 0.226) and duration of augmentation therapy (r: 0.115, p: 0.417) and adherence to treatment. Significant inverse correlation was determined between UKU total scores (r: -0.272, p: 0.003) and UKU psychological side-effect subscale scores (r: -0.263, p: 0.005) and MMAS-8 total scores (Table 3). Adherence to treatment decreased as UKU total and psychological side-effects scores increased.

Table 1. A comparison of the groups' sociodemographic characteristics and medications

		Augmentation Group (n=52)		**Monotherapy Group (n=62)**		p*
		Mean±SD **Median (Min-Max)**		**Mean±SD** **Median (Min-Max)**		
Age		13.04+2.67 13.5 (8-18)		13.08+2.98 13.5 (8-18)		0.802
Time to diagnosis		1.3+1 1 (0.5-5)		1.1+1.05 0.75 (0.5-6)		0.072
		n	**%**	**n**	**%**	**p****
Sex	**Male**	31	59.6	32	51.6	0.451
	Female	21	40.4	30	48.4	
Psychotherapy	**Yes**	19	36.5	14	22.6	0.146
	No	33	63.5	48	77.4	
Treatment monitored by family	**Yes**	32	61.5	48	77.4	0.099
	No	20	38.5	14	22.6	
		n (Mean dose)	**%**	**n (Mean dose)**	**%**	
Principal medication	**Sertraline**	34 (83,8 mg)	65.4	45 (66,8)	72.6	
	Fluoxetine	8 (40 mg)	15.4	13 (26,9)	21.0	
	Clomipramine	9 (88,9 mg)	17.3	1 (75 mg)	1.6	
	Citalopram	0	0.0	2 (30 mg)	3.2	
	Fluvoxamine	1 (100 mg)	1.9	0	0.0	
	Other	0	0.0	1 (20 mg)	1.6	
Antipsychotic	**Risperidone**	27(0,91 mg)	52			
	Aripiprazole	19 (4,9 mg)	36.6			
	Olanzapine	2 (5 mg)	3.8			
	Quetiapine	2 (75 mg)	3.8			
	Other	2 (3 mg)	3.8			

*Mann-Whitney U p. **Fisher's Exact p, Numbers in bold text denote significant differences (p<0.05)

Table 2. Comparison of MMAS-8 and UKU side-effect scores

		Augmentation Group (n=52)		Monotherapy Group (n=62)		p*
		Mean±SD Median (Min-Max)		Mean±SD Median (Min-Max)		
Age		4.6+1.9 5 (1-9)		5.6+1.9 6 (2-8)		**0.010**
		n	**%**	**n**	**%**	
Morisky-Adherence	**Low**	32	61.5	30	48.4	
	Moderate	16	30.8	19	30.6	
	High	4	7.7	13	21.0	
		Mean±SD Median (Min-Max)				
MMAS-8 Total		**Male** 5.2+1.6 5 (2-8)		**Female** 5.1+2.3 5 (1-9)		0.949
		Receiving psychotherapy 5.4+2.1 5 (2-9)		**No psychotherapy** 5.1+1.9 5 (1-9)		0.394
		Family monitoring 5+1.9 5 (1-9)		**No family monitoring** 5.5+2.05 6 (2-9)		0.198
		Augmentation Group (n=52)		**Monotherapy Group (n=62)**		
		Mean±SD Median (Min-Max)		**Mean±SD Median (Min-Max)**		
UKU-Total		10.4+7.1 10 (0-34)		4.9+5.7 3 (0-28)		**<0.001**
UKU-Psychological		6.1+3.9 6 (0-16)		3.05+2.9 2 (0-10)		**<0.001**
UKU-Nuerological		0.85+1.6 0 (0-7)		0.24+0.7 0 (0-3)		**0.003**
UKU-Autonomic		1.8+2.4 1 (0-12)		1.08+2.3 0.7 (0-9)		**0.001**
UKU-Other		1.6+1.9 1 (0-9)		0.6+1.3 0 (0-6)		**<0.001**

* Mann–Whitney U test, The 8-item Morisky Medication Adherence Scale (MMAS-8), and the Udvalg for Klinikse Undersegelser (UKU) side-effects rating scale, Numbers in bold text denote significant differences (p<0.05)

Table 3. Adherence to treatment-related correlation analyses

		MMAS-8	
		r	**p**
For all subjects	UKU-Psychological	-0.263	0.005
	UKU-Neurological	-0.129	0.170
	UKU-Autonomic	-0.165	0.079
	UKU-Other	-0.103	0.277
	UKU-Total	-0.272	0.003
	Time to diagnosis	-0.127	0.179
	Age	-0.039	0.681
Augmentation group	Duration of augmentation	0.115	0.417
	Time to transition to augmentation	0.171	0.226

Rho (p) Spearman Correlation Analysis, The 8-item Morisky Medication Adherence Scale (MMAS-8), and the Udvalg for Klinikse Undersegelser (UKU) side-effects rating scale, Numbers in bold text denote significant differences (p<0.05)

Discussion

Studies have shown that OCD frequently follows an inflexible course in a chronic pattern, and that long-term treatment may be necessary to prevent relapse. Preliminary data have shown that patients whose symptoms recur following medication discontinuation respond positively but with relatively lower effectiveness compared to the first treatment when the same drug is resumed [19]. These observations underline the need to determine markers of treatment dependence in OCD. Although adult-based studies have been performed, ours is the first study to assess medication side-effects and adherence to treatment in a pediatric OCD population.

OCD has a tendency to chronification, and the importance of early treatment has been shown in the literature. Recovery can be achieved with monodrug or multidrug medication and psychotherapy. Psychotherapy is effective, but pharmacotherapy is widely employed as the first and sole form of treatment [20, 21]. In one study of 246 children diagnosed with OCD and with a mean age of 11.9 years, SRIs were general prescribed (55%), and antipsychotics were added, either alone or in combination with another medication, in 22%. The level of receipt of psychotherapy plus at least one medication was 36% [22]. The rate of antipsychotic use was higher in our study (45%). Only 33 (29%) of the 114 patients in our study were receiving psychotherapy. However, the rates of psychotherapy receipt were very low in and similar between both the augmentation and monotherapy groups. Although pharmacotherapy represents the current foundation of OCD treatment due to the availability of effective medication, CBT is also reported to be effective in the disease [23]. Wilson and Roman reported that problems concerning difficulty of access to CBT and inadequate education represented the greatest obstacles to the use of this effective therapeutic method [24]. We attributed the low psychotherapy and high augmentation rates in our study to difficulties in accessing psychotherapy.

Non-adherence to treatment is common in patients with OCD. Sixty-one percent of patients with OCD receiving drug therapy are reported either to use their medications less frequently and/or at lower doses, or else to discontinue the medication entirely [25]. This has been attributed to medication side-effects (78%), insufficient therapeutic efficacy (41%), and high levels of concern over drug use (41%) [26]. In our study, we focused on the effect on adherence to treatment of one of these causes, medication side-effects. Establishing an augmentation strategy resulting in fewer drug side-effects has been reported to increase adherence to treatment in cases in which an antipsychotic agent is added for augmentation in patients with refractory OCD [27]. In our study, total UKU side-effect rating scale scores and psychological subscale scores were directly correlated with adherence to treatment. At the same time, patients receiving augmentation had higher side-effect scale scores. The probable side-effects of the antipsychotics administered for augmentation in order to increase patients' adherence to treatment in fact reduced adherence to treatment. Non-adherence to treatment can be reduced either by selecting medication that will cause fewer side-effects, or else by providing information for patients. Patients generally experience concerns over side-effects. It may be useful to provide advice about side-effect management strategies in order to reduce this fear to a minimum; written prescription information can be provided, and follow-up visits at intervals of 1-4 weeks can be performed following the first visit [28]. The side-effect profile of various pharmacological agents used to treat children with refractory OCD is problematic. Therefore, before considering augmentation strategies for OCD in children, it is recommended that all possible efforts should first be made to ensure that patients have received the best first-line treatment [5].

One of the main limitations of this study is that patient-based characteristics that might affect adherence to treatment and types of obsession and compulsion were not evaluated. Another important limitation is that severity of OCD and therapeutic efficacy were not examined. Previously, in evaluating adherence to treatment in OCD, obsessions with violent content and hoarding symptoms, and the presence of lower introspection levels, have been observed to exhibit an adverse effect on adherence [27]. Due to our study's cross-sectional design, it reveals the relation between adherence to treatment and side-effects in statistical terms, rather than showing a causal effect between them. In our study, families' economic and social status were not evaluated. Non-adherence to treatment is reported to be widespread in low-income patients starting treatment due to chronic disorders [29]. However, since both groups in our study consisted of subjects under monitoring by a public hospital and from a single center, we think that the probability of this affecting our results is low.

Conclusion

Lower adherence to treatment in the pediatric OCD population was significantly associated with more drug-related side-effects. More side-effects observed with augmentation, and particularly psychological side-effects, were related to lower adherence to treatment. Psychoeducation for children and families concerning the treatment of OCD and potential drug side-effects will contribute to increasing adherence to treatment. We think that in managing the treatment of children with OCD, physicians should take particular care over potential medication-related side-effects, and that this will enhance the success of treatment by increasing adherence to it. We think that although adult studies are already available, further studies are needed on the subject of patient-related characteristics on adherence to treatment in pediatric OCD.

Competing interests
The authors declare that they have no competing interest

Financial Disclosure
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Ethical approval
Ethical committee approval was obtained for the study (No. 2017-03-17 dated 15.05.2017), and verbal and written consent was given by all participants and their parents.

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