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Psychotropic Drug Use in Children with Autism Spectrum Disorder Admitted to a Training and Research Hospital Outpatient Clinic: A Retrospective Cross-Sectional Study

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Abstract

This study aimed to examine demographic and clinical variables, psychiatric comorbidities, the prevalence of psychotropic drug use, relationships between drug use, demographic and clinical variables, and predictors of drug use in children with autism spectrum disorder (ASD) admitted to a training and research hospital outpatient clinic. Four hundred and eleven children with ASD admitted to the Department of Child and Adolescent Psychiatry, Dr. Sami Ulus Maternity and Children's Health and Diseases Training and Research Hospital, between October 1, 2019 and December 31, 2019, were retrospectively reviewed. Demographic and clinical variables, psychiatric comorbidities, and characteristics of drug use for the cases were recorded. Psychotropic drug use was found in 34.3% ($n = 141$) of the cases. Our results revealed male sex and psychiatric comorbidity as predictors of psychotropic drug use. Antipsychotics were the most prescribed drugs, and the most common psychiatric comorbidity was conduct disorder. Also, children with ASD who had been toilet-trained, and could express sentences but were illiterate, were using psychotropic drugs more often than others. Future multicentered, large clinic-based studies from training and research hospitals should focus on trends of treatment in psychiatric comorbidities accompanying ASD, and constitute a systematic approach for the psychopharmacological treatment of these cases.

Keywords

- autism
- pharmacotherapy
- comorbidity
- child psychiatry

Introduction

Autism spectrum disorder (ASD), a neurodevelopmental condition characterized by impairments in social communication and restricted and repetitive behavior, has a prevalence of approximately 1.7% (1 in 59 children).[1] It is more common in males, and the appearance and severity of symptoms may vary as per chronological age and degree of development. Its early onset and chronicity cause significant financial and sentimental burdens to the individual, family, as well as society.

The main treatment for ASD is a structured, intensive, multidisciplinary, and continuous educational intervention; however, no pharmacological interventions are available for its core symptoms.[2] Autism is mostly accompanied several psychiatric comorbidities including attention deficit hyperactivity disorder (ADHD), depressive disorders, and anxiety disorders.[1,3] Medications are commonly used in these individuals to treat psychiatric symptoms such as hyperactivity, inattention, impulsivity, irritability, aggression, mood lability,

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anxiety, compulsions, and sleep problems.[4] Except for risperidone and aripiprazole—which are approved by the Food and Drug Administration for associated behavioral symptoms like irritability and aggression—most agents such as antipsychotics, antiepileptics, mood stabilizers, selective serotonin reuptake inhibitors, stimulants, and nonstimulant ADHD medications are used off-label.

While very few studies in our country have examined the characteristics and predictive factors of psychotropic drug use in children with ASD in university hospitals,[5–7] none have evaluated these parameters in a training and research hospital, especially in a region with financially disadvantaged communities like ours. In this study, we aimed to examine demographic and clinical variables, psychiatric comorbidities, the prevalence of psychotropic drug use, the relationship of drug use to demographic and clinical variables, and predictors of drug use in children with ASD admitted to the Department of Child and Adolescent Psychiatry of Dr. Sami Ulus Maternity and Children's Health and Diseases Training and Research Hospital.

Methods

Sample

Electronic medical records of children with ASD admitted to the Department of Child and Adolescent Psychiatry, Dr. Sami Ulus Maternity and Children's Health and Diseases Training and Research Hospital, between October 1, 2019 and December 31, 2019, were retrospectively reviewed. Medical information of 455 children with ASD was obtained from these records; however, 44 were excluded due to missing data. Four hundred and eleven children with complete demographic and clinical data in the records were finally included in the study. Psychiatric disorders were diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition criteria via clinical interviews by child psychiatrists. Approval for the design and data collection procedures was obtained from the ethics review committee at the University of Health Sciences, Ankara City Hospital.

Statistical Analysis

All statistical analyses were performed by using SPSS version 17 for Windows (Statistical Package for Social Sciences; version 17.0, SPSS Inc., 2008, Chicago, Illinois, United States). Continuous variables were presented as median, minimum, and maximum values. The consistency of continuous variables toward normal distribution was tested with Kolmogorov–Smirnov test, and Mann–Whitney *U* test was used for binary comparisons. Categorical variables were presented as frequency (n) and percentage (%) and analyzed with Pearson's chi-square test. The predictors of psychotropic drug use were analyzed with binary logistic regression analysis. The inclusion criteria of the variables in the binary logistic regression model were set among those significant by Pearson's chi-square comparisons. Correlations of estimates and Hosmer–Lemeshow goodness-of-fit test were used to evaluate the model (chi-square $(8) = 24.051$, $p = 0.02$) suggesting that the model was well fit to the data. In all the evaluations, a p-value of < 0.05 was considered statistically significant.

Results

The demographic and clinical analysis of 411 diagnosed cases with ASD with respect to psychotropic drug use is summarized in ►**Table 1**. The median age of the cases was 6.5 years, distributed within the range of minimum of 1.5 years and maximum of 18 years. While 84.7% ($n = 348$) of the cases were in the children age group (under 12 years of age), 15.3% ($n = 63$) were adolescents. Of the cases, 315 (76.6%) were male. About 16.5% ($n = 68$) of children were seen in their first consultation during the 3 months. The remaining (83.5%, $n = 343$) were seen as follow-up consultations (►**Table 1**).

Psychotropic drug use was found to be 34.3% ($n = 141$) of the cases. Twenty-nine percent ($n = 119$) of the cases used only one drug, 3.4% ($n = 14$) used two drugs, and 1.9% ($n = 8$) used three or more drugs (►**Table 1**). The most commonly used drug group was antipsychotics (29%, $n = 119$) which included risperidone, aripiprazole, haloperidol, olanzapine, chlorpromazine, and zuclopenthixol. It was followed by ADHD medications (9.2%, $n = 38$) such as methylphenidate and atomoxetine, and antidepressants (1.9%, $n = 8$) such as sertraline, mirtazapine, and escitalopram (►**Table 2**). The median age of the children who used psychotropic drugs was found to be higher than those who did not (9 vs. 5.2; $z = -8.891$, $p < 0.001$). The rate of psychotropic drug use was higher in the children's age group as compared to the adolescents (71.6% vs. 28.4%; chi-square $[1] = 28.121$, $p < 0.001$). The rate of psychotropic drug use in males was significantly higher than in females (86.5% vs. 13.5%; chi-square $(1) = 11.709$, $p = 0.001$). The rate of psychotropic drug use in follow-up patients was found to be significantly higher than the patients who were first-time applicants (97.2% and 2.8%; chi-square $(1) = 29.210$, $p < 0.001$; ►**Table 1**).

The ability to express words, speak sentences, walk, be toilet-trained, and read were found in 90.3% ($n = 371$), 58.2% ($n = 239$), 96.4% ($n = 396$), 60.6% ($n = 249$), and 17% ($n = 70$) of the cases, respectively. The rate of psychotropic drug use in cases who were able to speak sentences was found to be significantly higher than in those who did not (72% vs. 27%; chi-square $(1) = 19.577$, $p < 0.001$). The rate of psychotropic drug use in the toilet-trained cases was significantly higher than in those without it (78.7% vs. 21.3%; chi-square $(1) = 29.574$, $p < 0.001$). The rate of psychotropic drug use was significantly lower in children who could read and write compared to young children and those who were expected to read and write by age but could not read and write (24.1% vs. 75.9%; chi-square $(1) = 7.618$, $p = 0.006$; ►**Table 1**).

The presence of a concomitant physical disorder was found in 17.3% ($n = 71$). Also, epilepsy was detected in 13.4% ($n = 55$). The rate of psychotropic drug use in the cases without epilepsy was significantly higher than in the cases with epilepsy (80.1% vs. 19.9%; chi-square $(1) = 7.766$, $p = 0.005$). Of these cases, 6.6% ($n = 27$) were using a single antiepileptic drug while 5.8% ($n = 24$) were on multiple antiepileptic drugs (►**Table 1**).

The presence of intellectual disability (ID) accompanying ASD was found in 67.4% ($n = 277$) of the cases. The rate of psychotropic drug use was significantly higher in those with

Table 1 Analysis of 411 cases diagnosed with autism spectrum disorder according to the presence of psychotropic drug use

	Total ($n = 411$)	Psychotropic drug use		Statistics	*p*-Value
		No ($n = 270$)	Yes ($n = 141$)	*z* or chi-square	
Age (y)[a]	6.5 (1.5–18)	5.2 (1.5–17.5)	9 (2.1–18)	–8.891	**0.000**
Age groups, *n* (%)				28.121	**0.000**
Children	348 (84.7)	247 (91.5)	101 (71.6)		
Adolescents	63 (15.3)	23 (8.5)	40 (28.4)		
Sex, *n* (%)				11.709	**0.001**
Females	96 (23.4)	77 (28.5)	19 (13.5)		
Males	315 (76.6)	193 (71.5)	122 (86.5)		
Consult, *n* (%)				29.210	**0.000**
First consultation	68 (16.5)	64 (23.7)	4 (2.8)		
Follow-up	343 (83.5)	206 (76.3)	137 (97.2)		
Ability to say words, *n* (%)				1.703	0.192
Yes	371 (90.3)	240 (88.9)	131 (92.9)		
No	40 (9.7)	30 (11.1)	10 (7.1)		
Ability to say sentences, *n* (%)				19.577	**0.000**
Yes	239 (58.2)	136 (50.4)	103 (72.0)		
No	172 (41.8)	134 (49.6)	38 (27.0)		
Ability to walk, *n* (%)				3.093	0.081
Yes	396 (96.4)	257 (95.2)	139 (98.6)		
No	15 (3.6)	13 (4.8)	2 (1.4)		
Toilet training, *n* (%)				29.574	**0.000**
Yes	249 (60.6)	138 (51.1)	111 (78.7)		
No	162 (39.4)	132 (48.9)	30 (21.3)		
Ability to read and write, *n* (%)				7.618	**0.006**
Yes	70 (17.0)	36 (13.3)	34 (24.1)		
No	341 (83.0)	234 (86.7)	107 (75.9)		
ID, *n* (%)				19.595	**0.000**
Yes	277 (67.4)	162 (60.0)	115 (81.6)		
No	134 (32.6)	108 (40.0)	26 (18.4)		
ID subtypes, *n* (%)				25.770	**0.000**
No	134 (32.6)	108 (40.0)	26 (18.4)		
Borderline functioning	48 (11.7)	31 (11.5)	17 (12.1)		
Mild	153 (37.2)	91 (33.7)	62 (44.0)		
Moderate	51 (12.4)	23 (8.5)	28 (19.9)		
Severe	17 (4.1)	11 (4.1)	6 (4.3)		
Profound	8 (1.9)	6 (2.2)	2 (1.4)		
Physical disorders, *n* (%)				3.333	0.068
No	340 (82.7)	230 (85.2)	110 (78.0)		
Yes	71 (17.3)	40 (14.8)	31 (22.0)		
Epilepsy, *n* (%)				7.766	**0.005**
No	356 (86.6)	243 (90.0)	113 (80.1)		
Yes	55 (13.4)	27 (10.0)	28 (19.9)		

(*Continued*)

Table 1 (*Continued*)

	Total ($n = 411$)	Psychotropic drug use		Statistics	*p*-Value
		No ($n = 270$)	Yes ($n = 141$)	*z* or chi-square	
Antiepileptic drug use, *n* (%)				7.202	**0.027**
No	360 (87.6)	245 (90.7)	115 (81.6)		
Single drug	27 (6.6)	13 (4.8)	14 (9.9)		
Multiple drugs	24 (5.8)	12 (4.4)	12 (8.5)		
Other treatments, *n* (%)				1.111	0.292
No	346 (84.2)	231 (85.6)	115 (81.6)		
Yes	65 (15.8)	39 (14.4)	26 (18.4)		
Psychiatric comorbidity, *n* (%)				315.674	**0.000**
Yes	164 (39.9)	24 (8.9)	140 (99.3)		
No	247 (60.1)	246 (91.1)	1 (0.7)		
Number of psychiatric comorbidities, *n* (%)				262.993	**0.000**
None	246 (59.9)	246 (91.1)	0		
1 disorder	61 (14.8)	7 (2.6)	54 (38.3)		
2 disorders	16 (3.9)	15 (5.6)	1 (0.7)		
3 disorders	84 (20.4)	1 (0.4)	83 (58.9)		
4 and above disorders	4 (1.0)	1 (0.4)	3 (2.1)		
Number of psychotropic drugs used, *n* (%)				NA	NA
No	270 (65.7)	270 (100.0)	0		
1 drug	119 (29.0)	0	119 (84.4)		
2 drugs	14 (3.4)	0	14 (9.9)		
3 and above drugs	8 (1.9)	0	8 (1.9)		

Abbreviations: ID, intellectual disability; NA, not applicable.
[a]Median (minimum–maximum).
Note: *p*-Value < 0.05 are statistically significant.

Table 2 The proportion of psychotropic drugs used in the cases with autism spectrum disorder based on psychiatric comorbidity

	None	APs	ADHD TX	ADs	S-H	Melatonin
	$n = 270$	$n = 119$	$n = 38$	$n = 8$	$n = 3$	$n = 2$
ADHD ($n = 61$)	7 (2.6)	36 (30.3)	37 (97.4)	3 (37.5)	1 (33.3)	1 (50.0)
CD ($n = 101$)	1 (0.4)	97 (81.5)	16 (42.1)	4 (50.0)	2 (66.7)	0
Anxiety D/O ($n = 2$)	0	1 (0.8)	1 (2.6)	1 (12.5)	0	0
Speech D/O ($n = 18$)	15 (5.6)	3 (2.5)	0	0	0	0
Depression ($n = 4$)	0	3 (2.5)	1 (2.6)	4 (50.0)	0	0
Sleep D/O ($n = 2$)	0	1 (0.8)	0	0	1 (33.3)	2 (100.0)
LD ($n = 1$)	1 (0.4)	0	0	0	0	0

Abbreviations: ADHD, attention deficit hyperactivity disorder; ADHD TX, ADHD treatment (methylphenidate, atomoxetine); Ads, antidepressants (sertraline, mirtazapine, escitalopram); APs, antipsychotics (risperidone, aripiprazole, haloperidol, olanzapine, chlorpromazine, zuclopenthixol); CD, conduct disorder; D/O, disorders; LD, learning disorder; S-H, sedative-hypnotic (clonazepam).

ID (81.6% vs. 18.4%; chi-square (1) = 19.595, $p < 0.001$). The most common ID subtype was mild ID (37.3%, $n = 153$), followed by moderate ID (12.4%, $n = 51$) and borderline functioning (11.7%, $n = 48$), respectively. Excluding ID, psychiatric comorbidity accompanying ASD was found in 39.9% ($n = 164$) of the cases. The rate of psychotropic drug use in those with any psychiatric comorbidity was significantly higher (99.3% vs. 0.7%; chi-square (1) = 315.674, $p < 0.001$; ►**Table 1**). The most common psychiatric comorbidity was conduct disorder (CD) (24.6%, $n = 101$), followed by ADHD (14.8%, $n = 61$) and speech disorders (4.4%, $n = 18$) (►**Table 2**). Since psychotropic drug use was significantly related to age, age group, sex, ID, psychiatric comorbidity, epilepsy, the abilities of verbal communication, reading and

Table 3 Factors predicting psychotropic drug use in the cases diagnosed with autism spectrum disorder

	B	SE	Wald	*p*-Value	Exp (*B*)	95% CI for Exp (*B*)	
						Lower	Upper
Age (y)	0.123	0.136	0.820	0.365	1.131	0.867	1.475
Age group	1.131	1.205	0.880	0.348	3.099	0.292	32.904
Sex	−1.326	0.633	4.393	**0.036**	0.265	0.077	0.918
Intellectual disability	−1.124	0.592	3.603	0.058	0.325	0.102	1.037
Comorbidity	−7.653	1.152	44.136	**0.000**	0.000	0.000	0.005
Ability to say sentences	0.244	0.751	0.105	0.745	1.276	0.293	5.558
Toilet training	0.352	0.848	0.172	0.678	1.422	0.270	7.496
Ability to read and write	−0.649	0.737	0.775	0.379	0.523	0.123	2.216
Epilepsy	−0.948	0.883	1.154	0.283	0.387	0.069	2.185

Abbreviations: CI, confidence interval; SE, standard error.

writing, and toilet training; a binary logistic regression analysis was carried out on these variables. The predictors of psychotropic drug use were found to be the following: male sex ($B = -1.326$, $p = 0.036$, 95% CI [0.077–0.918]) and psychiatric comorbidity ($B = -7.653$, $p < 0.001$, 95% CI [0.000–0.005]; ►**Table 3**).

Discussion

In this study, we aimed to examine demographic and clinical variables, psychiatric comorbidities, the prevalence of psychotropic drug use, relationships between drug use and demographic and clinical variables, and predictors of drug use in children with ASD. This study is the first to evaluate these parameters in a training and research hospital where the most socioeconomically disadvantaged people are intensely cared for in Turkey.

In studies investigating the prevalence of drug use in children with ASD worldwide, the prevalence rates were found between 33.8 and 60%.[8–13] The prevalence rates of drug use in Turkey through the period 2005 to 2014 were reported as 37.5, 41.2, and 56.3% in previous studies conducted in university hospitals.[5–7] When the temporal changes in drug use are examined, it can be realized that the prevalence of drug use has increased significantly between 1995 and 2014 in children with ASD.[7,11,14,15] The rate observed in our sample (34.3%) was lower than the findings of the aforementioned studies. Recognition of psychiatric symptoms in children with ASD, who are more disorganized and unpredictable as compared to typically developing children is difficult, because of their inability to describe their experiences and feelings verbally. Our patients are generally from a socioeconomically disadvantaged population and may have difficulty in accessing health care services. Therefore, only parents of children with ASD with serious psychiatric comorbidities causing additional difficulties may apply to the hospital. To not overlook emotional and behavioral symptoms in these children, screening tools enabling clinical assessment of comorbid disorders such as developmental behavior checklist and aberrant behavior checklist should be applied in every child admitted to a training and research hospital, irrespective of the reason. Thus, early diagnosis and appropriate treatment of comorbid disorders can reduce disability and family burden, as well as improve the quality of life in these cases.

Previous studies have determined that stay in a foster home, behavioral problems (e.g., hyperactivity, attention deficit, self-mutilation, eating problems, and perseveration), ID, the severity of autism, and age are the predictors of drug use.[6,8–10] Our results reveal male sex and psychiatric comorbidity as predictors of psychotropic drug use. Not surprisingly, ASD is more common in males and its symptoms in males are also more severe.[1] Additionally, the presence of psychiatric comorbidity leads to a significant reduction in terms of quality of life. Since our sample size is small, age, ID, epilepsy, and developmental stages may not have been found as significant determinants. However, similar to available literature, our study noted that the median age of children who used psychotropic drugs was significantly higher than those who did not; and cases with ID used psychotropic drugs more often. Interestingly, higher drug use rates in the child age group may be associated with adaptation skills, which increase in parallel with neurodevelopmental maturation of prefrontal areas (related to executive functions).[16,17] Also, the fact that autism is more common in males may explain gender bias in drug use rates in our sample.[18] During their first consultation, clinicians in our hospital take a detailed description of behavioral and emotional problems such as time, place, activity, context, possible triggers, sequence, and possible consequences of these problems for these children. Thereafter, they apply the most appropriate behavioral intervention to the formulation of the cases, which requires the active participation of families.[19] In follow-up consultations, after behavioral intervention and psychoeducation, medications are added to the treatment plan, targeting challenging behaviors and emotional problems.[20] Therefore, the rate of drug use in follow-up patients was found to be higher than the first-time appliers. In another study at a university hospital in Turkey, all cases could walk, 92% could express words, 69.6% could express sentences, and 78.5% had toilet training,[7] in comparison to 96.4, 90.3, 58.2, and 60.6% of all cases, respectively, in our

study. The relatively lower rates may be related to the sociodemographic characteristics of our sample. When the developmental stages were evaluated, children with ASD with toilet-training, who could speak sentences but were illiterate, were using psychotropic drugs more often than others. Presumably, the cases who had an insight about their condition had more problems than others.[21] Contrary to the study by Gürkan et al,[6] children without epilepsy used psychotropic drugs more often than those with epilepsy in our sample. This can be explained by the fact that most cases have ADHD accompanying their ASD, and their families may have refused medication, fearing that stimulants would trigger epileptic seizures.[22]

Akin to the literature, the most commonly used drug group in our study was antipsychotics.[5,6] It was followed by stimulants and nonstimulant ADHD treatment and antidepressants. Evidence-based treatment algorithms are followed in our clinic. As it is expected, approved drug groups are used often in accordance with international treatment guidelines.[23] Although relatively lower as compared to the literature,[7–10] more than one drug use was detected in 22 of 141 patients using psychotropic drugs. Clinicians working in a training and research hospital may tend to avoid polypharmacy due to the risk of side effects and the difficulty in monitoring them.[24] Most common psychiatric comorbidities were CD, ADHD, and speech disorders. Both ASD and CD may have similar neurological abnormalities for impairments in empathy.[3]

There are some limitations to our study. Its design was cross-sectional and retrospective. Our study focused on only medication use of children with ASD rather than other treatments like psychosocial–educational–behavioral therapies. Besides, the evaluation of psychotropic drug use was based on electronic data from a single training and research hospital, which may not be reliable. Finally, our findings cannot be generalized to all children with ASD in the community.

Conclusion

Our retrospective cross-sectional study examining predictors of psychopharmacologic interventions in children with ASD admitted to a training and research hospital has revealed that medication use is recommended in the case of males and those with psychiatric comorbidity. Our results could be useful for clinicians from training and research hospitals in Turkey for the treatment of children with ASD. Future multicentered, larger clinic-based studies from training and research hospitals should focus on trends of treatment in psychiatric comorbidities accompanying ASD and establish a systematic approach for the psychopharmacological treatment of these cases.

Ethical Approval
This study obtained ethical approval from University of Health Sciences Ankara City Hospital.

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Conflict of Interest
None declared.

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