KASTAMONU MEDICAL JOURNAL

Original Article

Kastamonu Med J. 2026; 6(1): 64-71

DOI: 10.66235/kumj.1906761

Clinical and adverse effect profiles of paediatric polypharmacy by gender and ADHD status

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ABSTRACT

Aims: This study aims to investigate the prevalence of concurrent psychotropic polypharmacy systematically, its associated adverse effects, and their relationship with individual factors such as diagnosis and gender in a child and adolescent outpatient population. While most existing literature on polypharmacy focuses on adults, there is a lack of recent, field-based data concerning children and adolescents.

Methods: Among 4,928 outpatient admissions in January 2024, 595 children receiving two or more concurrent psychotropic medications were included. Polypharmacy was operationalized as the concurrent use of two or more psychotropic medication classes for a minimum duration of 30 consecutive days, consistent with thresholds described in previous guidelines (e.g., AACAP, NICE). Over a six-month follow-up, diagnostic profiles, medication regimens, comorbidities, adverse effects, and adherence were evaluated using clinical records and national e-Nabız data.

Results: The sample was 57.1% male, with a median age of 13. Polypharmacy was most common among 16–18-year-olds. ADHD (52.8%), generalized anxiety disorder (19.5%), and depression/dysthymia (9.2%) were the most frequent diagnoses. Comorbidity was present in 76.6% of cases. Anxiety and mood disorders were more common in females, whereas specific learning disorder and enuresis were more prevalent in males. Stimulant-antipsychotic combinations were more typical in males; antidepressant-antipsychotic combinations were more common in females. Reported adverse effects included sleep disturbances, appetite changes, and irritability, with no significant differences between medication groups.

Conclusion: Polypharmacy was more frequent in adolescents and those with ADHD, anxiety, or depression. Gender differences in medication patterns likely reflect underlying psychopathology. Given the high rates of adverse effects, structured monitoring protocols, including sleep and appetite checklists, should be routinely implemented. The findings support the integration of scheduled medication reviews and age- and gender-sensitive pharmacotherapy planning in child and adolescent psychiatry.

Keywords: Psychotropics, polypharmacy, child and adolescent psychiatry, adverse effects

INTRODUCTION

In recent years, there has been a marked increase in the use of psychotropic medications in child and adolescent psychiatry, with polypharmacy becoming increasingly prevalent in clinical practice [1]. This growing trend, however, raises important concerns regarding efficacy, safety, and long-term outcomes in youth populations. In line with this trend, clinical practice often involves the concurrent prescription of multiple psychotropic agents to accelerate therapeutic response, manage treatment-resistant symptoms, or address comorbid psychiatric disorders. For the purposes of this study, polypharmacy is defined as the concurrent use of two or more psychotropic medication classes for at least 30 consecutive days, consistent with thresholds described in established clinical guidelines (e.g., AACAP, NICE) [2]. However, data regarding the safety, efficacy, and long-

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Received: 29.08.2025 * **Accepted:** 02.10.2025 * **Published:** 12.03.2026

term effects of psychotropic drug combinations in children and adolescents remain limited.

Evidence from international studies indicates a rising trend in antipsychotic medication use among children and adolescents, often prescribed for off-label indications [3]. Polypharmacy rates have been reported to be particularly high in conditions such as attention-deficit/hyperactivity disorder (ADHD) and anxiety disorders [4]. A comprehensive study examining polypharmacy from 1970 to 2023 found that although polypharmacy was more prevalent among adults, its use has also significantly increased in paediatric populations, with rates rising from 7.0% to 19.9% in clinical samples [5]. ADHD, one of the most prevalent neurodevelopmental disorders, is frequently complicated by comorbid anxiety, depression, or oppositional defiant disorder, which often necessitates complex pharmacological regimens [6]. While stimulant medications are commonly employed as the first-line treatment to manage core ADHD symptoms, patients who do not respond adequately or present with additional symptoms are often prescribed adjunctive medications such as atypical antipsychotics, alpha-2 adrenergic agonists (e.g., clonidine, guanfacine), or atomoxetine [7]. Importantly, further research is needed regarding the potential adverse impacts of these combinations on metabolic syndrome, cardiovascular risk, and cognitive development [8].

Similarly, in autism spectrum disorder (ASD), polypharmacy is commonly employed not only to manage aggression and irritability but also to address co-occurring symptoms such as sleep disturbances, hyperactivity, and anxiety, which frequently drive complex treatment regimens [9]. Across ADHD, ASD, and other paediatric conditions, a persistent gap is the lack of long-term safety data on multi-drug regimens, particularly their metabolic, cardiovascular, and cognitive implications. A comprehensive meta-analysis published in 2024, analysing data from 517 studies encompassing 4.5 million participants across both adult and paediatric populations, concluded that research on polypharmacy has predominantly focused on schizophrenia, with limited representation of child and adolescent samples. This extensive analysis highlighted that multi-drug combinations significantly increase the likelihood of adverse reactions - including irritability, sleep disturbances, appetite changes, and emotional dysregulation- while also demonstrating potential elevation in all-cause mortality risk across age groups [5].

Local evidence from Türkiye reflects similar trends. One study reported that among adolescents, the prevalence of antidepressant–antipsychotic combination therapy was 21.5%, while stimulant–antipsychotic combinations were reported in 8.7% of cases [10]. An evaluation of hospitalised patients in Denizli in 2023 revealed that 16.2% of patients were using multiple antipsychotics before admission, a rate that increased to 31.0% upon discharge [11]. Between 2013 and 2022, the rate of polypharmacy among patients presenting with behavioral problems was reported to be as high as 68.2% [12]. These findings suggest not only clinical complexity but also potential systemic drivers, including prescribing habits during hospitalisation and limited access to non-pharmacological interventions.

The present study, therefore, aims to systematically examine the prevalence of concurrent psychotropic polypharmacy, associated adverse effects, and their relationships with individual variables such as diagnosis and gender in a child and adolescent outpatient population monitored at Ankara Etlik City Hospital. Despite growing recognition of paediatric polypharmacy, most existing studies are adult-focused, and few have stratified findings by diagnostic categories, gender, or adverse effect profiles. By addressing these gaps, the present study seeks to contribute to the limited body of research by providing real-world data on prescribing patterns and adverse effects in a large paediatric outpatient sample from Türkiye, a context that continues to be underrepresented in international studies.

METHODS

This study was conducted using a retrospective and descriptive design. A total of 4,928 cases that presented to the Child and Adolescent Psychiatry Outpatient Clinic at Ankara Etlik City Hospital in January 2024 were reviewed through electronic and written medical records. Inclusion criteria were defined as being between 0 and 18 years of age and concurrently using at least two different classes of psychotropic medications. Patients who used two different psychotropic medications concurrently for at least 30 days were considered to be receiving polypharmacy. Exclusion criteria included cases with incomplete medical records and those using only different pharmaceutical formulations of methylphenidate. Diagnostic classification was based exclusively on the current psychiatric status of each patient at the time of evaluation. Both primary and comorbid diagnoses were coded according to clinical assessment, while past psychiatric history or previously resolved conditions were not included in the analysis.

Among the total applications, 614 were found to be related solely to the issuance of the "Special Needs Report for Childhood" and contained no information

regarding psychotropic medication use. Additionally, 544 cases were excluded due to incomplete data. From the remaining eligible cases, 640 patients who were identified as using multiple psychotropic medications concurrently were included in the study. However, 45 patients who were using only different formulations of methylphenidate were excluded based on the predefined criteria, as they were considered to be within the same pharmacological agent class. Consequently, 595 patients were included in the final analysis.

Psychotropic medications used in the study were categorised into seven main classes according to their therapeutic mechanisms of action: stimulants, antipsychotics, antidepressants, non-stimulant ADHD agents, mood stabilisers, anxiolytics, and others. These categories were further subdivided based on their pharmacodynamic properties and receptor-level activity profiles for detailed analysis. Reported adverse effects were classified as either physiological or psychiatric based on clinical findings noted in patient histories. Additionally, variables such as psychiatric diagnoses, comorbid conditions, medication combinations, presence of organic pathology, special education needs, and treatment adherence were comprehensively analysed. All data were obtained retrospectively through the hospital information management system and patient records.

Ethical approval for this study was obtained from the Scientific Research Evaluation and Ethics Committee of Ankara Etlik City Hospital (No: AESH-BADEK1-2025-062, Date: 14/05/2025). As the study was retrospective, the requirement for informed consent was waived in accordance with the approval of the institutional ethics committee. Personal information of the individuals was not recorded during data collection.

Statistical Analysis

Data were analysed using IBM SPSS Statistics version 26.0 (SPSS Inc., Chicago, IL, USA). The normality of continuous variables was assessed using the Shapiro–Wilk test and inspection of histograms, skewness, and kurtosis values. For descriptive analyses, means and standard deviations were calculated for normally distributed variables, while medians and interquartile ranges were reported for non-normally distributed or ordinal variables. Group comparisons were conducted using the independent samples t-test or the Mann–Whitney U test, depending on the distribution of the data. Categorical variables were compared using chi-square tests or Fisher's exact test, as appropriate. Effect sizes were reported for significant results (e.g., Cohen's d for t-tests, r for Mann–Whitney U tests, and Cramer's V for chi-square tests) to complement p-values. A p-value of < 0.05 was considered statistically significant.

RESULTS

Among the 595 patients included in the study, 57.1% (n=340) were male, with a mean age of 12.59 years (Standard Deviation = 3.598; median = 13.00; range = 4–18 years). When age groups were stratified as children versus adolescents, a significant difference was observed in polypharmacy patterns by gender ($\chi^2(1) = 42.98$, $p < .001$). In the child group, polypharmacy was more common among boys (n=189 (72.1%) vs n=73 (27.9%)), whereas in the adolescent group it was more frequent among girls (n=182 (54.7%) vs n=151 (45.3%)).

Analysis of primary psychiatric diagnoses among patients receiving multiple psychotropic medications revealed that

Table.1 Distribution of Comorbid Psychiatric Disorders by Gender in Patients with ADHD

	Male (n=167)		Female (n=88)				
	Present	**Absent**	**Present**	**Absent**	**p**	**χ2**	**Effect Size**
Anxiety Disorders, n (%)	53 (31.7)	114 (68.3)	41 (52.6)	37 (47.4)	**0.002**	9.753	0.2
ODD/CD, n (%)	89 (53.3)	78 (46.7)	25 (32.1)	53 (67.9)	**0.002**	9.643	0.198
Mood Disorders, n (%)	8 (4.8)	159 (95.2)	19 (24.4)	59 (75.6)	**<0.001**	20.762	0.291
SLD, n (%)	44 (26.3)	123 (73.7)	11 (14.1)	67 (85.9)	**0.032**	4.579	0.137
Enuresis, n (%)	16 (9.6)	151 (90.4)	0	88 (100)	**0.005**	7.995	0.181

ADHD: Attention Deficit Hyperactivity Disorder **ODD:** Oppositional Defiant Disorder, **CD:** Conduct Disorder, **SLD:** Specific Learning Disorder

ADHD was the most common diagnosis, present in 52.8% of cases. This was followed by generalised anxiety disorder (GAD) at 19.5% and depression/dysthymia at 9.2%. Mild intellectual disability and ASD were observed in 4.2% and 5.0% of patients, respectively. Less common diagnoses included obsessive-compulsive disorder (OCD) (2.0%), bipolar disorder (0.5%), eating disorders (0.7%), and dissociative disorders (0.2%). These findings suggest that the majority of patients requiring psychotropic polypharmacy present with common mental health conditions such as ADHD and anxiety-related disorders (**Figure 1**).

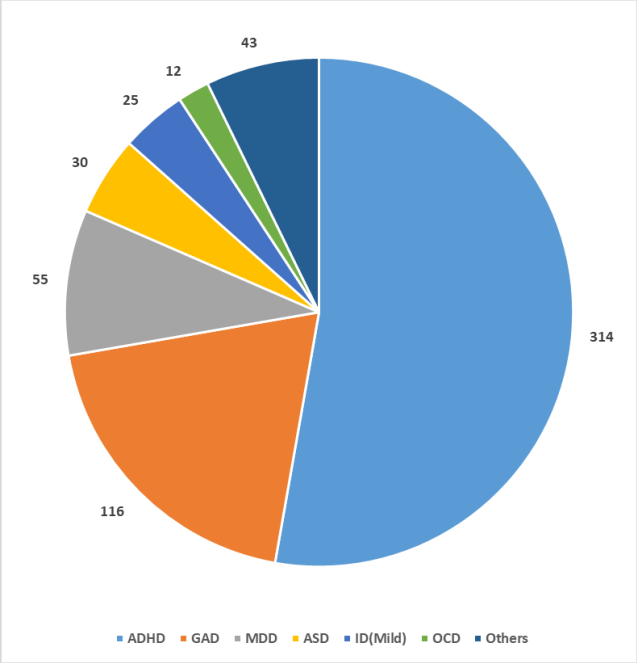


Figure 1. Current Primary Psychiatric Diagnoses of Patients with Polypharmacy
ADHD: Attention Deficit Hyperactivity Disorder, GAD: Generalised Anxiety Disorder, MDD: Major Depressive Disorder, ASD: Autism Spectrum Disorder, ID: Intellectual Disorder, OCD: Obsessive Compulsive Disorder, Others: (SAD: Social Anxiety Disorder, TTM: Trichotillomania, BAD: Bipolar Affective Disorder, PTSD: Post-Traumatic Stress Disorder)

Comorbid psychiatric disorders were identified in 456 out of 595 patients (76.6%). The gender-based distribution of comorbidities among patients diagnosed with ADHD is presented in **Table 1**. Among those with ADHD receiving multiple psychotropic medications, anxiety disorders were significantly more prevalent in females (52.6%) compared to males (31.7%) ($p = 0.002$, effect size = 0.2). Mood disorders were observed in 24.4% of females and 4.8% of males, with the difference reaching statistical significance ($p < 0.001$, effect size = 0.291). Specific learning disorder was more frequently diagnosed in males (26.3%) than in females (14.1%) ($p = 0.032$, effect size = 0.137). Enuresis was observed exclusively in males (9.6%), and this difference was statistically significant ($p = 0.005$, effect size = 0.181). No significant gender differences were found in the prevalence of tic disorders, OCD, or sleep disorders (**Table 1**).

The usage rates of different medication classes were compared by gender. Stimulant use was significantly higher among males (67.4%) compared to females (38.8%) ($p < 0.001$, effect size = 0.284). In contrast, the use of antidepressants was significantly more common in females (72.5%) than in males (40.3%) ($p < 0.001$, effect size = 0.320). The use of non-stimulant ADHD medications (atomoxetine/guanfacine) was observed in 13.8% of males and 7.8% of females, with a statistically significant difference ($p = 0.022$, effect size = 0.094). No significant gender differences were found in the use of antipsychotics, mood stabilisers, or anxiolytics (**Table 2**).

The combined use of different psychotropic medication classes was compared by gender, and statistically significant differences were observed. The combination of stimulants and antipsychotics was more frequently used in males ($p < 0.001$, effect size = 0.266). In contrast, the combination of antidepressants and antipsychotics was more commonly prescribed to females ($p < 0.001$, effect size = 0.236). No significant gender difference was found regarding the combination of stimulants and antidepressants ($p = 0.267$). Similarly, no significant difference was observed in the combination of stimulants with other psychotropics ($p = 0.173$). However, the combination of antidepressants with other psychotropic medications was significantly more common among females ($p < 0.001$, effect size = 0.180). Gender-based comparisons of psychotropic medication combinations are presented in **Table 3.**

An analysis of medication-related adverse effects revealed no statistically significant difference in the overall incidence of adverse effects between genders ($p = 0.486$, $\chi^2 = 0.485$). The most frequently modified medication class due to adverse effects was antipsychotics (n = 38), followed by stimulants (n = 34), antidepressants (n = 19), non-stimulant ADHD medications (n = 5), and other psychotropics (n = 4).

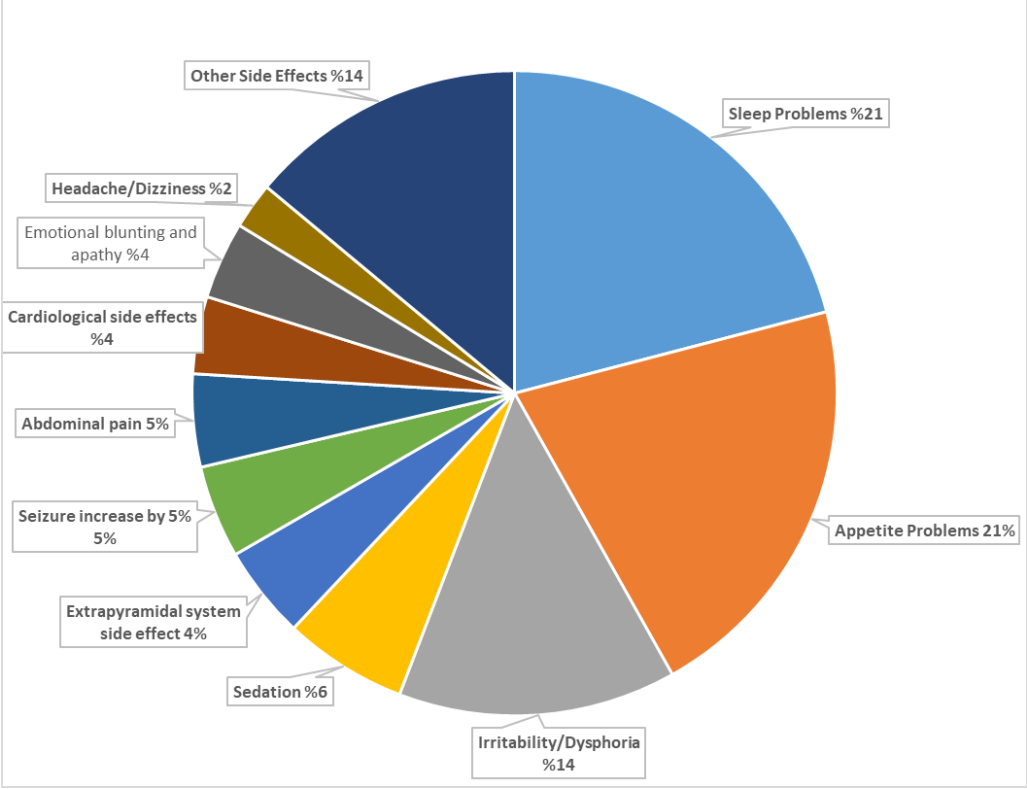
The most commonly reported adverse effects included sleep disturbances (n = 27), appetite changes (n = 27), irritability/dysphoria (n = 18), sedation (n = 8), extrapyramidal symptoms (n = 6), increased frequency of epileptic seizures (n = 6), abdominal pain/vomiting (n = 6), cardiological adverse effects (n = 5), emotional blunting/apathy (n = 5), and headache/dizziness (n = 3).

Table.2 Distribution of Use of Psychotropic Drug Groups by Gender

	Male (n=340)		Female (n=255)				
	Received	**Not Received**	**Received**	**Not Received**	**P**	**χ2**	**Effect Size**
Stimulants, n (%)	229 (67.4)	111 (32.6)	99 (38.8)	156 (61.2)	**<0.001**	47.944	0.284
Antipsychotics, n (%)	265 (77.9)	75 (22.1)	186 (72.9)	69 (27.1)	0.159	1.986	
Antidepressants, n (%)	137 (40.3)	203 (59.7)	185 (72.5)	70 (27.5)	**<0.001**	61.053	0.320
Nonstimulants, n (%)	47 (13.8)	293 (86.2)	20 (7.8)	235 (92.2)	0.022	5.215	0.094
Mood Stabilizers, n (%)	7 (2.1)	333 (97.9)	4 (1.6)	251 (98.4)	0.895	0.017*	
Anxiolitics, n (%)	3 (0.9)	337 (99.1)	6 (2.3)	249 (97.7)	0.265	1.243*	
Other Psychotropics, n (%)	31 (9.1)	309 (90.9)	36 (14.1)	219 (85.9)	0.056	3.646	

* Yates Correction, Nonstimulants: Atomoxetine, Guanfacine

Figure.2. Adverse Effect Profiles of Patients with Multiple Psychotropic Use



Other miscellaneous adverse effects were reported in 18 cases (Figure 2). No statistically significant differences were found in the incidence of adverse effects across different psychotropic medication classes.

DISCUSSION

This study analysed patterns of multiple psychotropic medication prescriptions over a six-month period in a large sample of children and adolescents presenting to a child and adolescent psychiatry outpatient clinic. It aimed to examine the associations of these prescribing patterns with gender, diagnostic profiles, and adverse effects. Our findings indicate that polypharmacy has become a common clinical practice in child and adolescent

psychiatry, and that both gender and comorbid psychiatric disorders play a significant role in determining medication combinations.

Consistent with the existing literature, ADHD, GAD, and mood disorders were more frequently observed among patients receiving polypharmacy. Notably, among male patients diagnosed with ADHD and receiving polypharmacy, the rates of oppositional defiant disorder (ODD), specific learning disorder (SLD), and enuresis were significantly higher, whereas among female patients impair quality of life in young patients. Therefore, integrating structured metabolic and cardiovascular screening protocols into routine follow-up is essential to minimise risk. No significant gender differences were found in overall antipsychotic use. However, the clinical indications appear to diverge by gender: in males, antipsychotics are more commonly prescribed as adjuncts for aggression, impulsivity, and oppositional symptoms associated with ADHD, whereas in females they are frequently used in combination with antidepressants for

Table 3. Rates of Use of Different Psychotropic Drug Classes in Combination by Gender

	Male (n=340)		Female (n=255)				
	Received	**Not Received**	**Received**	**Not Received**	**p**	**χ2**	**Effect Size**
Stimulant-Antipsychotics, n (%)	166 (48.8)	174 (51.2)	58 (22.7)	197 (77.3)	<**0.001**	42.216	0.266
Antidepressants-Antipsychotics, n (%)	82 (24.1)	258 (75.9)	119 (46.7)	136 (53.3)	<**0.001**	33.121	0.236
Stimulants-Antidepressants-Antipsychotics, n (%)	14 (4.1)	326 (95.9)	11 (4.3)	244 (95.7)	0.906	0.014	
Stimulants-Nonstimulants-Antipsychotics, n (%)	9 (2.6)	331 (97.4)	1 (0.4)	254 (99.6)	0.073	3.223*	
Stimulants-Antidepressants, n (%)	61 (17.9)	279 (82.1)	50 (19.6)	205 (80.4)	0.606	0.267	
Stimulants-Nonstimulants, n (%)	17 (5.0)	323 (95.0)	3 (1.2)	252 (98.8)	**0.01**	6.558	0.105
Stimulants-Other Psychotropics, n (%)	9 (2.6)	331 (97.4)	2 (0.8)	253 (99.2)	0.173	1.854*	
Antidepressants-Other Psychotropics, n (%)	17 (5.0)	323 (95.0)	40 (15.7)	215 (84.3)	<**0.001**	19.210	0.180
Nonstimulants-Antipsychotics, n (%)	29 (8.5)	311 (91.5)	10 (3.9)	245 (96.1)	0.025	5.051	0.092
Two Different Antipsychotics, n (%)	23 (6.8)	317 (93.2)	14 (5.5)	241 (94.5)	0.524	0.406	

* Yates Correction, Nonstimulants: Atomoxetine, Guanfacine

with ADHD receiving polypharmacy, anxiety and mood disorders were more prevalent. These findings align with current meta-analyses [13] and underscore the importance of considering gender-based diagnostic differences when planning treatment strategies [14,15].

Antipsychotics were the most frequently prescribed agents, particularly for behavioural regulation and as adjuncts to SSRIs. However, their widespread use in paediatric populations raises significant ethical and clinical concerns. These concerns are amplified by class-specific risks: metabolic disturbances and cardiac side effects are most prominent, while extrapyramidal symptoms and hormonal changes may substantially mood instability or anxiety-related symptoms. This highlights the importance of contextualising pharmacotherapy within the underlying psychopathology rather than reporting crude prevalence alone [14,16]. These results are consistent with the observed gender-related differences in psychopathology.

The most frequently prescribed psychotropic medication combinations identified in the study were stimulant–antipsychotic, antidepressant–antipsychotic, and stimulant–antidepressant. Patterns of use varied by gender: stimulant–antipsychotic combinations were more common among males, which likely reflects the higher prevalence of ADHD accompanied by comorbid ODD,

hyperactivity, and aggression in boys. Antipsychotics are often used as adjuncts to stimulants to manage these disruptive and externalising symptoms, indicating that the pharmacotherapy profile mirrors the clinical presentation of behavioural dysregulation among male patients, while antidepressant–antipsychotic combinations were more prevalent among females, a pattern that is consistent with the greater incidence of anxiety and depressive disorders in girls. The use of antipsychotics as augmentation to SSRIs in this group likely reflects the severity of mood dysregulation, irritability, or treatment-resistant anxiety symptoms, suggesting that gender-specific symptom clusters drive pharmacotherapy choices [17]. Additionally, combinations of stimulants with atomoxetine and guanfacine were observed more frequently in male patients [18]. The addition of antipsychotics to these regimens may reflect a more severe clinical presentation of ADHD or more pronounced difficulties in behavioural regulation among boys. These gender-specific prescribing patterns underscore the need for clinicians to integrate diagnostic comorbidity profiles into treatment planning. Rather than interpreting gender as a stand-alone predictor, it is essential to consider how age, comorbidities (e.g., ODD, anxiety, depression), and symptom clusters contribute to the observed differences in polypharmacy.

Our findings showed that appetite and sleep disturbances, as well as irritability/dysphoria, were common. These observations should be interpreted with caution, as adverse effects differ substantially by drug class: antipsychotics are primarily associated with metabolic syndrome and cardiac risks, stimulants with sleep disturbance and cardiovascular events, and antidepressants with suicidality and behavioural activation. Moreover, adolescence represents a period of heightened vulnerability to metabolic changes, emphasising the need for age-specific monitoring strategies. Furthermore, age-related vulnerability patterns—such as heightened metabolic sensitivity during adolescence—necessitate tailored monitoring protocols. Routine screening, including metabolic and cardiovascular assessments, should be integrated into standard clinical care [19]. Although previous literature has reported that triple drug combinations are associated with a higher incidence of adverse effects, our study did not find a statistically significant difference in the frequency of adverse effects between patients using two versus three different classes of psychotropic medications [4]. This finding may have been influenced by factors such as sample size, the subjectivity of assessment methods, individual variability in patient-reported outcomes, and the limited duration of adverse effect monitoring. To strengthen clinical practice, routine adverse effect checklists and family education should be integrated into follow-up visits. Structured, single-centre monitoring could also reduce fragmented prescribing, ensuring consistency in medication planning and minimising unnecessary polypharmacy. In addition, scheduled medication reviews should be prioritised to evaluate ongoing necessity, dose appropriateness, and tolerability.

One of the strengths of this study lies in the detailed classification of prescribed psychotropic medications within a large patient sample and the integration of these distributions with relevant clinical parameters. By linking frequently used medication combinations to underlying comorbidities and clinical symptom profiles, and by emphasising class-specific risks, age-related vulnerabilities, and the need for structured monitoring, this study provides actionable insights that may guide safer and more rational prescribing practices in real-world child and adolescent psychiatry.

Study Limitations: The single-centre and retrospective design of the study limits the generalizability of the findings. The evaluation of adverse effects relied solely on clinical observation and parental/patient self-report. Since no standardised or validated adverse event scales (e.g., UKU, PAERS) were employed, the reliability and reproducibility of these findings are limited. Additionally, the lack of data on treatment-related parameters, such as dosage and duration, restricts the ability to conduct an in-depth analysis of drug efficacy and adverse effect profiles. To better understand the systemic factors contributing to polypharmacy—such as clinical treatment resistance, barriers to healthcare access, and continuity of care—there is a need for multicentre, longitudinal, and prospective studies.

CONCLUSION

This study demonstrated that in child psychiatry, polypharmacy most commonly involves the combination of antipsychotics with other psychotropic medications, and that these prescribing patterns are significantly associated with both diagnostic profiles and gender. The findings indicate that multiple medication use is particularly prevalent among patients diagnosed with ADHD, anxiety disorders, and mood disorders, and that gender-related clinical differences may play a determining role in pharmacotherapeutic decisions. These results highlight the importance of careful monitoring of antipsychotic polypharmacy and prioritisation of treatment coordination in clinical practice. Furthermore, given the current prescribing trends in Türkiye, the

development of national guidelines for psychotropic use in children and adolescents appears to be an urgent need. Based on these implications, future prospective multicentre studies utilising standardised assessment tools are warranted to promote rational and evidence-based prescribing practices in child and adolescent psychiatry.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study protocol was conducted in accordance with the Declaration of Helsinki and approved by Ankara Etlik City Hospital Ethics Committee on 14/05/2025 with decision number; AESH-BADEK1-2025-062.

Acknowledgements

We would like to thank patients who supported us during the conduct of this study.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Data Availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Financial Disclosure

The authors declared that this study has received no financial support.

Informed Consent

Participants (or their parents/legal guardians) were asked to sign a written informed consent form.

Referee Evaluation Process

Externally peer-reviewed.

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