The utilization of psychopharmacological treatments for individuals with autism spectrum disorder (ASD) in a middle-income European country

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ABSTRACT

Background: Studies examining the utilization of psychopharmacological treatments (psychotropic medications) for autism spectrum disorder (ASD) have primarily been carried out in affluent nations. Nonetheless, there is an evident dearth of data originating from low- and middle-income countries. Our study sought to comprehensively evaluate the usage of psychopharmacological treatments and the effectiveness of those treatments as perceived by the parents of individuals with autism spectrum disorder (ASD) in Macedonia, a middle-income country in South-Eastern Europe.
Methods: We conducted a survey involving 103 parents of individuals with ASD and analyzed the questionnaire responses using descriptive statistics and non-parametric tests.
Results: Our research uncovered that 62% of individuals diagnosed with ASD were prescribed psychopharmacological treatments, yet only 48% actually utilized them. Among the medications prescribed, antipsychotics (55%) and antiepileptics (44%) were the most common, with risperidone and valproate being the preferred options. Psychopharmacological treatments were found to be more commonly used among individuals aged 15 years and above, with children under 8 years closely following suit at a rate of 56%. Furthermore, we discovered a noteworthy association between the severity of ASD symptoms and the utilization of these interventions. Intriguingly, the majority of parents (73%) regarded the effectiveness of psychopharmacological treatments as only partially effective.
Conclusion: Our study emphasizes the prevalent utilization of psychotropic medication, especially among young individuals, and underscores the necessity for enhanced dissemination of information to parents regarding prescribed medications. By integrating our research findings, medical professionals and policymakers can enhance the strategies and initiatives used to improve the quality of care and support for individuals on the autism spectrum.

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1. Introduction

The increasing prevalence of autism spectrum disorder (ASD) necessitates the development of appropriate treatments. Current estimates suggest that ASD affects approximately 1% of the global population, with variations across countries and regions and a continuous increase in the recent decades (Fombonne, 2020; Salari et al., 2022; Zeidan et al., 2022). However, despite the progress made, there has been limited improvement in management or treatment strategies for ASD-related burden (Solmi et al., 2022). The complexity of treatment needs has expanded to include various age groups and populations, taking into account co-occurring neuropsychiatric and other co-morbid conditions.

Autism Spectrum Disorder (ASD) is usually treated with a combination of behavioral and medical approaches. Behavioral treatments are the primary method for addressing the core symptoms of ASD (Aishworiya et al., 2022). Psychopharmacological treatments manage associated symptoms and co-occurring conditions like irritability, sleep disorders, ADHD, anxiety, and depression (Persico et al., 2021). In addition to mental health conditions, autistic individuals face a significantly higher risk of suicidality, including suicidal thoughts, plans, attempts, and death by suicide, compared to non-autistic individuals. Research suggests that heightened HPA axis activity and demoralization are linked to increased suicide risk in this population (Berardelli et al., 2020; Costanza et al., 2022; Curtis, 2022). Despite advancements in understanding autism spectrum disorder (ASD), limited progress has been made in developing pharmacological interventions for its core deficits. No medication has been approved for treating the core symptoms of ASD (Persico et al., 2021). Challenges in targeted drug development include weaknesses in translational research, clinical trial design and execution, and the complex nature of ASD itself. This complexity includes its etiological and clinical heterogeneity, overlapping diagnostic boundaries, and co-occurring conditions.(Baribeau & Anagnostou, 2022; Diaz-Caneja et al., 2021; Lombardo et al., 2019; McCracken et al., 2021). To address this issue, there is a proposal which suggests utilizing biomarker-guided stratification of ASD, considering its cause and potential response to treatment. The aim is to enable personalized and precise ASD treatment, in line with the principles of precision medicine. (Beversdorf & Missouri Autism Summit, 2016; Kostic & Buxbaum, 2021).

In 2022, the "Commission on the Future of Care and Clinical Research in Autism" introduced a pioneering proposal to cater to the distinctive requirements of individuals with Autism Spectrum Disorder (ASD) (Lord et al., 2022). This personalized and stepped care approach emphasizes tailoring treatments and support, considering cultural backgrounds and social systems. The proposal also highlights the disparities between low- and middle-income countries (LMIC) and high-income countries (HIC) acknowledging the scarcity of treatment resources as well as underrepresentation in autism treatment research of the former.

Presently, research and data on support and treatment options, including medication use in ASD are predominantly skewed towards high-income countries (HICs) with well-established autism care systems and this emphasis persists despite the fact that the majority of the global ASD population resides in low- and middle-income countries (LMICs). (de Leeuw et al., 2020; McConkey, 2022). Our comprehensive literature search has revealed a scarcity of studies examining the use of psychopharmacological treatments in low- and middle-income countries, as opposed to high-income ones. Existing research on medication use in Autism Spectrum Disorder (ASD) mainly comes from countries with established autism care systems. Therefore, it is important to explore psychopharmacological treatment for individuals with ASD in Macedonia. As a middle-income country in South-Eastern Europe, Macedonia (World Bank, 2023) presents a valuable case study that can inform and guide the enhancement of ASD care systems in less developed settings. Addressing the limited research on the use of psychopharmacological therapies in these contexts is of utmost importance.

Our study aimed to investigate the utilization of psychopharmacological treatments in our population, with a specific focus on the prevalence, types, and parents' awareness of these treatments among individuals affected by ASD. Additionally, our research aimed to assess the perceived effectiveness of these treatments from the perspective of parents/caregivers of individuals with ASD. While parental evaluations may be subjective and prone to bias, they hold great significance in assessing treatment effectiveness as parents have a unique understanding of their child's condition and can observe even subtle changes over time (Goin-Kochel et al., 2009).

Our further goal was to identify possible differences among the individuals diagnosed with ASD in the usage and perceived effectiveness of psychopharmacological treatments. We analyzed the socio-demographic attributes of parents and families, along with the demographic and medical characteristics of their children with ASD. In earlier published studies, the individual's characteristics (e. g., age, severity of ASD symptoms, cognitive functioning, co-occurring conditions) and parent/family-specific attributes (e.g., income, cultural background, parents' education and perceptions of ASD) were found to direct ASD treatment choices (Goin-Kochel et al., 2007; Jonkman et al., 2023; Mire et al., 2017). The terms "psychopharmacological treatments" and "psychotropic medications" are used interchangeably in this manuscript.

2. Methods

2.1. Participants

Parents of individuals diagnosed with autism spectrum disorder (ASD) were eligible to participate in our research. The age range of the individuals with ASD was not restricted in this study, meaning it included both children and adults. Therefore, in the context of this study, the terms "child" or "children" pertain to the parent-child relationship, where the child is the offspring of the participating parent, rather than being indicative of a specific age group.

Through a web-based survey, parents shared their opinions on the psychopharmacological treatments used by their children with ASD. We considered the responses from 103 parents (and their 103 children with ASD), after excluding two respondents due to insufficient and unclear answers. Since the survey was anonymous, diagnosis verification documents were not / could not be required

from the participants. Nonetheless, aiming to ascertain that the questionnaire reaches the desired population only, the web-link to the questionnaire was distributed specifically through associations and support groups for parents of individuals with ASD and developmental disabilities, undoubtedly knowledgeable and very familiar with the ASD diagnosis, as well as through personal contacts of the researchers. Both autistic individuals with and without intellectual disability were welcome to participate, as intellectual disability was not a criterion for inclusion or exclusion. The severity of ASD was assessed by parents, which aligns with the prevailing approach in similar web-based studies (Coleman et al., 2019). Although the survey was conducted anonymously, parental rating seemed like a reasonable and adequate way to measure severity. However, to ensure the most accurate evaluation possible, the corresponding questionnaire item explicitly described the factors to consider when assessing severity, such as functionality, independence/self-reliance, and behavioral and communication issues.

2.2. Quantitative research

For our planned quantitative research, we selected a parental survey as the appropriate method to investigate the actual utilization of psychopharmacological treatments. This choice was made as investigations of prescribed treatments primarily rely on data from healthcare and insurance systems. The questionnaire was made accessible to parents through a web link that remained active for a duration of six months, from December 2021 to May 2022, or alternatively, as a paper copy. The questionnaire was meticulously prepared by the researchers after conducting an extensive literature search and selecting relevant topics. The opening section of the questionnaire provided information to potential participants about the survey's purpose and its anonymous nature. Due to the fact that it did not collect any unique identifiable patient data, ethical approval for this study was deemed unnecessary and not sought. Nonetheless, ethical principles were strictly adhered to, and utmost confidentiality of participants' data was maintained throughout the entire research process. The questionnaire, completed by parents, gathered demographic information and inquired about the use of psychopharmacological treatments for their children, as well as complementary and alternative medicine (CAM) treatments, including special diets. Due to the substantial amount of data generated and analyzed, this article focuses solely on the results related to psychopharmacological treatments. The findings regarding the use of CAM treatments and special diets are published separately (Stojanovska & Trajkovski, 2023).

2.3. Statistics

Descriptive statistics, including mean, standard deviation, and median, were utilized to characterize the sample and the usage of

Table 1

The socio-demographic characteristics of parents and families, along with the demographic and medical characteristics of children with ASD.

Parents and families (n = 103)	n	%	Children with ASD (n = 103)	n	%
Sex of the parent			Sex		
male	9	8.7	male	85	82.5
female	94	91.3	female	18	17.5
Age of the parent (years)			Age (years) ($\overline{X}$=11.6, s = 6.22; M=10)		
up to 20	1	1.0	3 to 5	11	10.7
20 to 29	2	1.9	6 to 8	35	34.0
30 to 39	42	40.8	9 to 11	11	10.7
40 to 49	49	47.6	12 to 14	15	14.6
50 to 59	7	6.8	15 to 17	16	15.5
60 to 69	2	1.9	18 to 20	9	8.7
Educational level of the parent			above 20	6	5.8
less than high school	5	4.9	Severity of ASD		
high school	33	32.0	mild	38	36.9
university degree	65	63.1	moderate	49	47.6
Employment of the parent			severe	16	15.5
unemployed	20	19.4	Other neurodevelopmental or neuropsychiatric disorders[(a,b)]		
occasionally employed	7	6.8	none	23	23.5
regularly employed	72	69.9	has one	51	52.0
other	4	3.9	has two or more	24	24.5
Financial condition of the family			Other medical conditions[(c)]		
poor	17	16.5	no	64	64.0
medium/mean	50	48.5	yes	36	36.0
good	36	35.0			
Area of living of the family					
rural	12	11.7			
suburban	13	12.6			
urban	78	75.7			

[a]n = 98

[b]most frequent co-occurring neurodevelopmental or neuropsychiatric conditions were: speech/language difficulties and aphasia (44.95%), ADHD (20.18%), epilepsy/EEG irregularities (12.84%)

[c]n = 100

psychopharmacological treatments. Considering the categorical data and the non-normal distribution (Kolmogorov-Smirnov test, $p < 0.001$), several non-parametric tests were employed for the inferential statistical analysis. These tests aimed to examine possible differences in the usage and perceived effectiveness of psychopharmacological treatments with regards to the parents'/families' and child's characteristics. The tests used included the Mann-Whitney U test, the Kruskal-Wallis H test, and the Spearman rank correlation test (as applicable). For analyses with ordinal data in the dependent variable, the Mann–Whitney U test was used (in cases of 2-groups independent variable, e.g., sex) or the Kruskal–Wallis H test (for analyses with more-than-2-groups independent variable, e.g., age, severity of ASD). The Spearman rank correlation testing was conducted only if both variables were ordinal (not conducted if data were nominal in at least one of the two variables). A difference or correlation was deemed statistically significant if $p < 0.05$. The statistical analysis was conducted using IBM SPSS Ver. 28.0.1.1(15) software.

3. Results

The socio-demographic characteristics of parents/families and the demographic and medical characteristics of children with ASD are presented in Table 1. We investigated the use and perceived effectiveness of psychopharmacological treatments and whether they differ among individuals with ASD, with regards to "sociodemographic characteristics of their parents and families" and "demographic and medical characteristics of the individuals with ASD" (Fig. 1).

3.1. Use and perceived effectiveness of psychopharmacological treatments

The sample consisted of a nearly equal division between individuals who did not use psychopharmacological treatments [54 (52.43%)] and those who did [49 (47.57%]. Interestingly, 15 (27.78%) of non-users' parents reported refusing such treatments for their children, despite them being prescribed by a physician. As a result, the overall number of individuals with autism spectrum disorder (ASD) who were prescribed these treatments, regardless of their usage, reached 64 (62.13%) (Table 2). The predominant types of psychopharmacological treatments used were antipsychotics and antiepileptics, as depicted in Fig. 2. Fig. 3 provides a quantitative summary of the information given to parents regarding the safety and effectiveness of various prescribed medications. Prior to examining the patterns of usage among these children, the number of children affected by ASD was determined. Fig. 4A illustrates the age distribution of ASD prevalence.

Among parents of children who utilize psychopharmacological treatments and provided an overall opinion on their effectiveness (n = 48), the majority [35 (72.92%)] consider them to be partially effective, while 10 (20.83%) find them to be fully effective. Only a small number, 3 (6.25%), perceive them as ineffective (Fig. 4B). In addition, parents were asked about the benefits and drawbacks of specific medications their children use to address ASD symptoms and deficits. However, due to a lack of clear indication regarding the source of perceived benefits or adverse effects (likely due to concurrent utilization of other treatments), it was not feasible to accurately analyze these responses statistically.
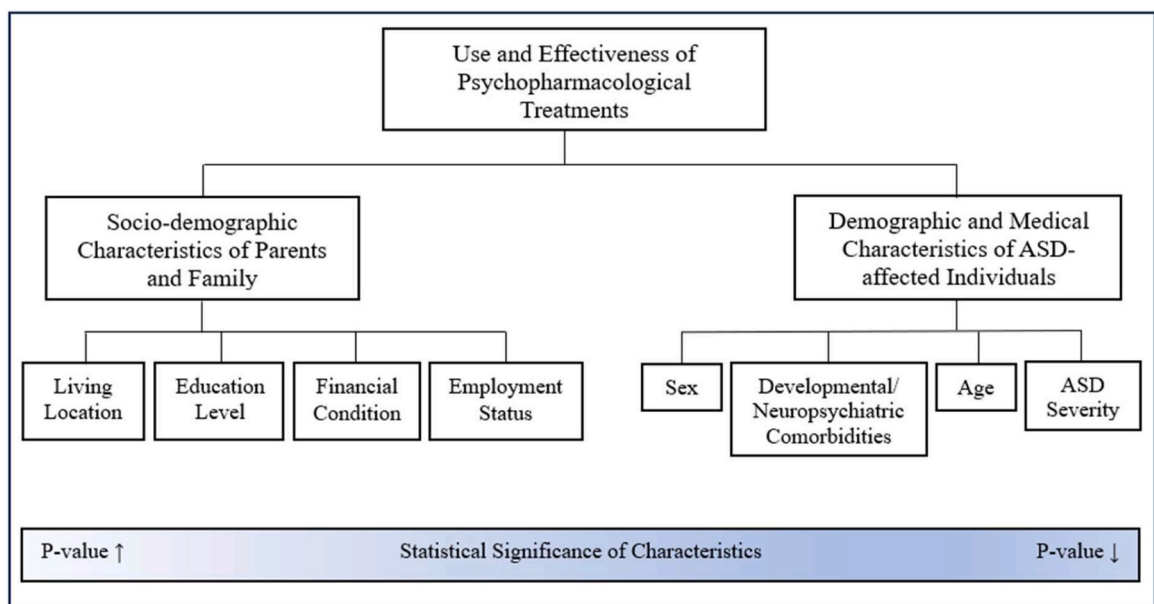

Fig. 1. This figure presents the socio-demographic characteristics of parents and families, and demographic and medical characteristics of individuals with ASD explored with regards to the use and effectiveness of psychopharmacological treatments. Characteristics are listed in ascending order of statistical significance.

Table 2
Prevalence of use of psychopharmacological treatments.

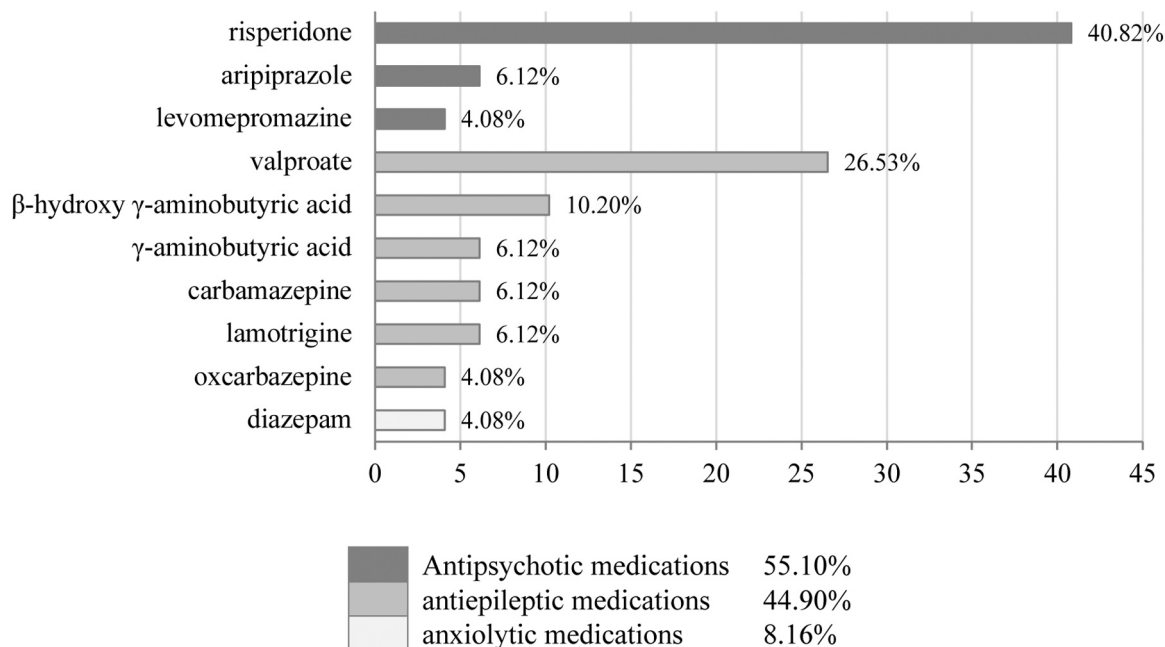| Use of psychopharmacological treatment		n	f (%)	
no	the physician considers it not needed	39	37.86	52.43
	although recommended by the physician, parents refuse to give it to their child	15	14.56	
yes	one medication	34	33.01	47.57
	more than one medication	15	14.56	

Fig. 2. The chart illustrates the prevalence of medication usage among individuals undergoing psychopharmacological treatment. It emphasizes the frequently utilized medications, while acknowledging that participants indicated sporadic use of other medications, each with a minimal occurrence rate ($\leq 2\%$). It is important to note that there was simultaneous utilization of multiple medications both within and between the groups.

3.2. Characteristics of parents, families and the individuals with ASD and the utilization and perceived effectiveness of psychopharmacological treatments

The results of the inferential statistical analysis are presented in Table 3.

3.2.1. Socio-demographic characteristics of parents and families and psychopharmacological treatment usage

The analysis revealed no statistically significant differences in the utilization of psychopharmacological treatments among children with parents of varying education levels and employment statuses, as well as financial conditions of the family and location of residence.

3.2.2. Demographic and medical characteristics of children with ASD and psychopharmacological treatment usage

The use of psychopharmacological treatments was not significantly different in individuals of opposite sex. Female and male individuals with ASD also did not differ significantly in terms of ASD severity ($p = 0.650$).

The ASD sample was divided into three age groups: below 8 years [32 (31.1%)], 8–14 years [40 (38.8%)], and 15 years and above [31 (30.1%)]. The utilization of psychopharmacological treatments showed variations among the age groups, with a marginal level of statistical significance ($H(2) = 5.683$, $p = 0.058$). The middle age group displayed the lowest usage of medications according to the Kruskal-Wallis H test. A post-hoc test revealed a significant difference between the oldest and middle age groups ($p = 0.022$). The middle age group (8–14 years) had the highest frequency of non-users [28 (70%)], while in the oldest and youngest groups, the frequency of users [19 (61.29%) and 18 (56.26%)] was higher than non-users (Fig. 4C). To determine if the higher usage in the youngest group was due to more severe ASD, we tested for a statistically significant difference in ASD severity among the three age groups. However, no significant difference was observed ($p = 0.076$).

The sample was divided into three groups based on parent-rated ASD severity: very mild/mild [38 (36,89%)], moderate [49 (47.57%)], and severe/very severe ASD [16 (15.53%)] (Fig. 4D). The usage of psychopharmacological treatments significantly differed
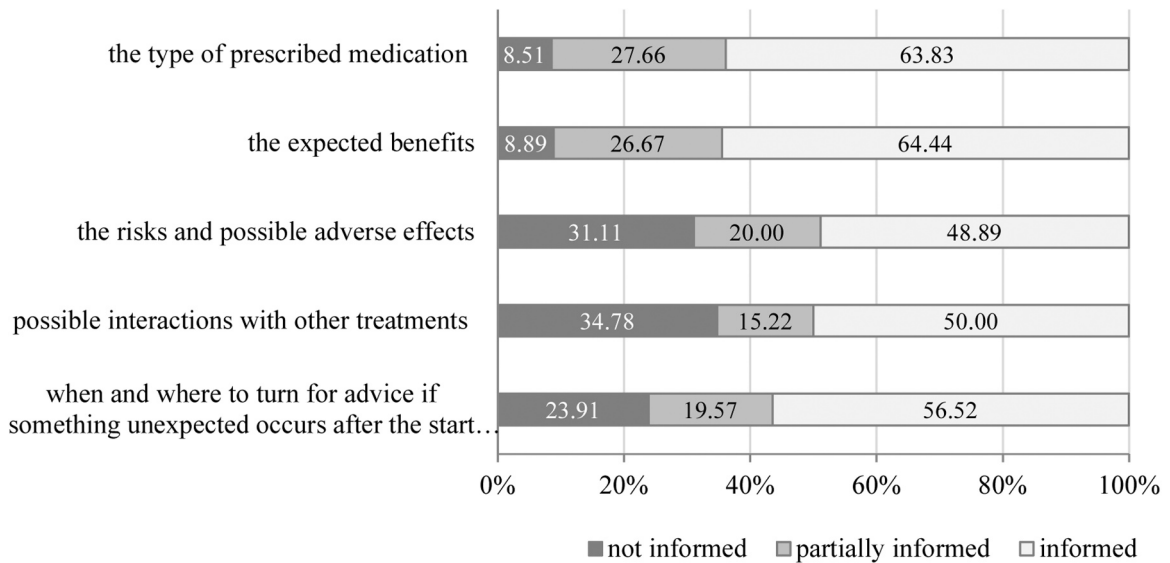
Fig. 3. Parents were asked whether they were informed regarding the effectiveness and safety of the psychopharmacological treatment by the prescriber. The chart provides comprehensive information about parents' information on the medication's effects, anticipated advantages, possible interactions with concurrent therapies, and the potential risks associated with adverse reactions.
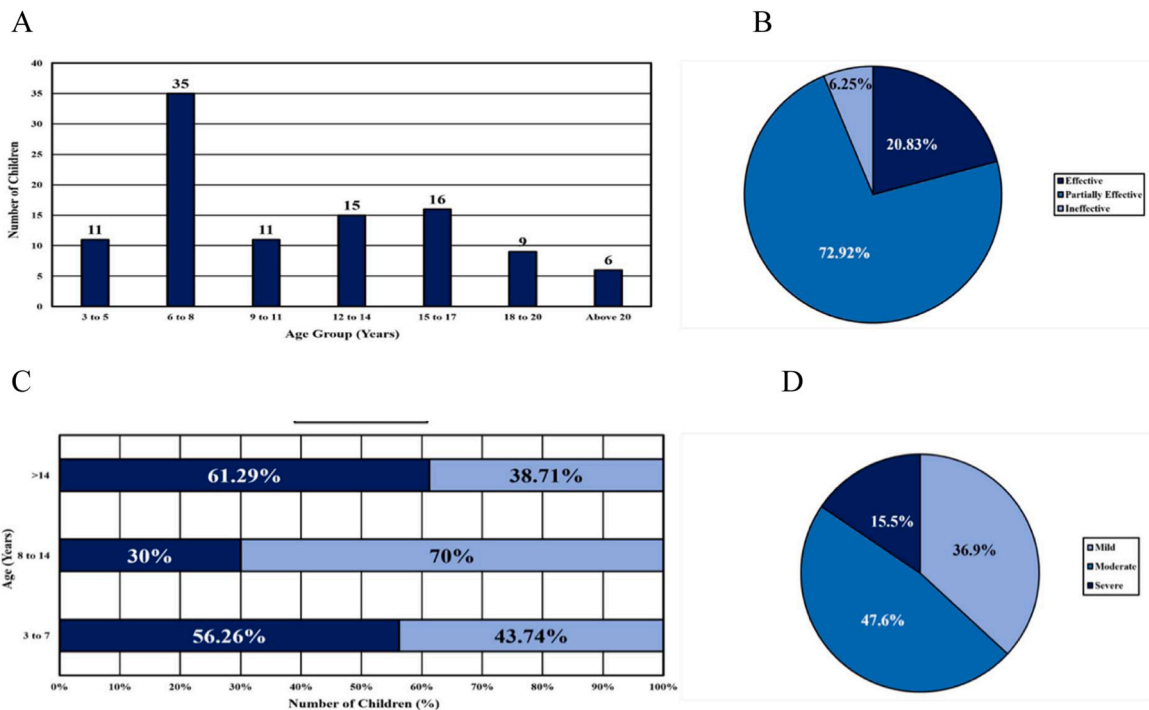

Fig. 4. Statistics on children impacted by Autism Spectrum Disorder (ASD): A. The age groups of children affected by autism spectrum disorder (ASD) B. Perception among parents regarding the effectiveness of psychopharmacological treatments. C. A comparison of psychopharmacological treatments usage trends among children affected by ASD, based on age groups, is examined. D. Severity of Autism Spectrum Disorder (ASD) as rated by parents.

among these groups (H(2) = 6.249, p = 0.044). Additionally, a significant positive correlation was found between the two variables (r = 0.247, p = 0.012).

Regarding the presence of other developmental or neuropsychiatric disorders, the ASD sample was divided into three groups: no other developmental or neuropsychiatric disorders, one, and more than one developmental or neuropsychiatric disorder. No

Table 3
The characteristics of parents, families and individuals with ASD and the use and effectiveness of psychopharmacological treatments.

	Use of psychopharmacological treatments		Effectiveness of psychopharmacological treatments	
	difference (p)	correlation (p)	difference (p)	correlation (p)
parents and families				
parental level of education	0.610 [a]	0.697 [c]		
parental employment status	0.244 [a]	/		
financial condition of the family	0.477 [a]	0.317 [c]		
living location	0.705 [a]	/		
individuals with ASD				
sex	0.201 [b]	/	0.955 [b]	/
age	0.058 (**0.022**)[1] [a]	0.517 [c]	0.797 [a]	0.634 [c]
severity of ASD	**0.044** [a]	**0.012** [c] (r = 0.247)	0.286 [a]	0.220 [c]
other neurodevelopmental or neuropsychiatric disorders	0.183 [a]	0.277 [c]	0.899 [a]	0.829 [c]

Notes:

p – significance. Significant results (p < 0.05) are in **bold**.

[1] between the age groups of "15 years and older" and "8-14 years"

[a] Kruskal–Wallis H test, [b] Mann–Whitney U test, [c] Spearman rank correlation test

"/" – correlation test not conducted (not applicable due to nominal data in at least one of two variables)

Gray-shaded table cells – statistical analyses not conducted (relationship considered not relevant)

significant differences were observed between the groups in terms of psychopharmacological treatment usage (H(2) = 3.396, p = 0.183).

3.2.3. Demographic and medical characteristics of children with ASD and the parental perceived overall effectiveness of psychopharmacological treatments

    The perceived effectiveness of used psychopharmacological treatments, as reported by parents, showed no significant difference with any of the four tested variables: sex, age, severity of ASD, and the presence of other developmental or neuropsychiatric disorders.

4. Discussion

    The existing literature on the utilization of psychopharmacological treatments in individuals with autism reveals notable inconsistencies. These inconsistencies predominantly arise from methodological disparities, encompassing study design (e.g., cross-sectional versus longitudinal), data sources (e.g., healthcare/insurance systems or institutions versus parents/caregivers), and participant selection (e.g., regional/national variances). Consequently, we approached the comparative analysis of our findings with cautiousness.

4.1. Use and perceived effectiveness of psychopharmacological treatments

    Studies that gather data from health care systems generally report higher rates of psychotropic medication use in individuals with autism spectrum disorder (ASD) compared to studies that rely on data obtained from caregivers. The former provides rates of recommended or prescribed medications, while the latter reflects the actual usage of medications. We observed a similar disparity between prescribed and utilized medications in our sample, with over a quarter of parents of medication non-users expressing their refusal to administer psychopharmacological treatments to their child, despite the physician's prescription. In our sample, the percentage of individuals prescribed such medications (62.13%) is higher than what has been reported in other research based on health care system data, such as the USA where it stands at 59.6% across a wide age range. (Feroe et al., 2021); Italy: 58.5% among adolescents and adults (Fusar-Poli et al., 2019); and the UK: only 32.3% among a wide age population (Houghton et al., 2018). As expected, the actual medication use in our sample (47.57%) is lower than prescribed. It is close to that from other studies based on parental surveys, such as those from the USA: 42.5% (Shurtz et al., 2023) and 48% (Becerra et al., 2017) both among children; Belgium: 42.6% among children (Heyde, Dhar, Hellemans, Schoentjes, & Van West, 2016); the Netherlands: 51.4% among children and adolescents (Jonkman et al., 2023); Serbia: 52.4% among children and adolescents (Pejovic-Milovancevic et al., 2018). As it is evident, the prescription rate of medications in our cohort is higher, while the actual usage rate appears to be comparable to recent studies involving participants of similar age (relatively young, like our sample). Among the medication users, the observed rate of

polypharmacy (the concurrent use of two or more psychotropic medications) was 30.61%, accounting for 14.56% of the entire sample. This falls within the range of the widely varied findings for psychotropic medication in ASD reported in two recent reviews, which spanned from 5.4% to 54%.(Jobski et al., 2017), 6.8–87% (Ritter et al., 2021).

High rates of prescribed or used psychotropic medications for ASD were found to be associated with unavailable or deficient behavioral and other rehabilitative and educational autism-related services (Wiggins et al., 2021), which could also be the case with our cohort. Indeed, recent analyses in the region of South-Eastern Europe (where our sample is located) have shown insufficient service options, challenging pathways to services utilization, lack of continuous support across the life span and insufficient parent support and training, as evidenced by Hansen et al. (2017) and Vasilevska Petrovska et al. (2021), resulting from decades' long paucity of substantial investment and interest from policy makers and no systematic approach to early intervention services (Trajkovski, 2017). A study from a developing country (Iran) also found overuse of psychotropic medications among children and adolescents with ASD, even among the youngest – 78.7% in children < 8 years of age (Memari et al., 2012).

Of the total number of participants, the majority in our sample use antipsychotic (26.21%) and/or antiepileptic (21.36%) medications. Likewise, within the group of users of psychotropic medication, antipsychotic (55.10%) and/or antiepileptic (44.90%) medications prevail, with risperidone and valproate being dominant (74.07% and 59.09% of antipsychotics and antiepileptics users). Antidepressants are not reported at all in the sample, similarly to psychostimulants and other ADHD drugs (despite the reported co-occurring ADHD in the sample in 20.18%) and anxiolytics (only 3.88%). For comparison, in the Becerra et al. (2017) study, the use of antipsychotics and antiepileptics is much lower (19.7% and 7.2%) compared to our sample, and the use of drugs for ADHD and antidepressants is much higher (31.4% and 20.4%). These rates are confirmed by Shurtz et al.(Shurtz et al., 2023) who also reported low rates of antipsychotics (17%) and antiepileptics (only 2%) and high rates of psychostimulants (38%), α-agonists (30%) and antidepressants (32%) among psychotropic medication users. The situation is very similar in the Belgian sample, where most of the children with ASD used medication for ADHD (31.6%) and much less antipsychotics (16.7%) (Heyde, et al., 2016), and in a sample from New Zealand, with predominant use of fluoxetine and methylphenidate (Thabrew et al., 2020). On the contrary (and similarly to our findings), Memari et al. (2012) found a higher-than-expected rate of antipsychotics use (57.4%) and much lesser frequency of antidepressants use among pupils with ASD from Iran, a developing country.

Considering the young median age (M=10) and the moderate severity of ASD in the sample, it is surprising to observe a high rate of antipsychotic use. The usage of antiepileptics is also relatively high, even though the prevalence of epilepsy/EEG irregularities in the sample is only 12.84%. However, this can be explained by the likelihood of these medications being prescribed for their mood stabilizing properties. These findings, along with the minimal use of anxiolytics, antidepressants, and ADHD medications, may suggest two possibilities: (a) specific prescribing preferences and habits among physicians in our region, relying on antipsychotics and mood stabilizers to address most behavioral and affective difficulties in ASD, or (b) a failure to recognize, identify, and treat co-occurring conditions that may be present. The literature has described the concept of "diagnostic overshadowing," which refers to attributing symptoms of a genuinely co-occurring condition to the diagnosis of autism. (Casanova et al., 2020; Lai et al., 2019). Further along, although anxiety is a frequent comorbid condition in ASD, anxiolytics and in particular, benzodiazepines are related to a common fear to prescribe, due to the risk of "paradoxical reactions" (behavioral activation with disinhibition, hyperactivity, and irritability (Persico et al., 2021) and of developing tolerance and dependence. High rates of behavioral activation, manifesting as an increased activity level, impulsivity, sleeplessness or disinhibition were also observed in studies of antidepressants in ASD (Vasa et al., 2016). Similarly, autistic children with ADHD tend to be less responsive to ADHD medications (e.g., methylphenidate) than ADHD without ASD and at a higher risk of experiencing adverse effects (Davico et al., 2023). Thus, the risk of worsening behaviors with these medications, might have also contributed to the low frequency of their use in our sample.

The rates of parents who were unfamiliar with the prescribed medication and its expected benefits were low, both below 10%. However, approximately one-third of parents were not provided with information about potential interactions with other treatments, and another one-third were not informed about the risks of adverse effects from the treatment. Furthermore, a quarter of parents had no guidance on when and where to seek advice if unexpected issues arose after starting the psychopharmacological treatment. These findings suggest that there may be a deficiency in communication between prescribing physicians, who serve as the primary source of information on prescription medications, and parents. Moreover, given the types of medications involved and the developmental stage of the individuals in the study, addressing this issue promptly is crucial for improving the quality of care for individuals with autism spectrum disorder (ASD).

Among the parents in our sample, the majority (72.92%) rated psychopharmacological treatments as partially effective, while 20.83% considered it fully effective. Interestingly, some parents reported paradoxical effects of the drugs. While antipsychotics were found to reduce irritability, hyperactivity, and improve sleep in most cases, there were instances where they actually increased irritability and self-injurious behavior. Additionally, some parents noted side effects such as drowsiness, impaired sleep, increased appetite and body weight, impaired glycemia regulation, as well as urinary and fecal incontinence. Experts have observed that individuals with autism spectrum disorder (ASD) tend to exhibit heightened sensitivity to the effects and side effects of psychotropic medications. Moreover, atypical responses, such as idiosyncratic reactions or paradoxical reactions, may be more prevalent in this population. (Aishworiya et al., 2022; Chun et al., 2016). The clear inconsistencies and variabilities in the effectiveness and tolerability observed within our sample highlight the importance of ongoing monitoring, treatment adjustments, and an individualized approach to therapy in general. This underscores the need for a more refined and personalized approach to ensure optimal outcomes. Similar to the general evaluation of the effectiveness of psychopharmacological treatments in our sample (mainly, rated as partially effective), the research by Coleman et al. (2019) within the framework of the US "National Survey on Treatment Effectiveness for Autism" (the effects of 26 neuropsychiatric drugs evaluated by 505 parents), showed that parents rated the benefit from pharmacological treatments only slightly higher than the adverse effects. Same as in our sample, high variability in individual evaluations of beneficial and

unwanted effects was seen, as an indication of significant variability in the clinical response to psychotropic medication.

&lev1;4.2Characteristics of parents, families and the individuals with ASD and the utilization and perceived effectiveness of psychopharmacological treatmentsOur study found no statistically significant differences in the utilization of psychopharmacological treatments among the individuals with ASD with regards to the four socio-demographic factors tested (parental level of education, employment status, financial condition, and living location of the family). Similarly, in the Memari et al. (2012)study, demographic characteristics such as educational level and income were not associated with the use of psychotropic medications.The difference in utilization of psychopharmacological treatments between individuals with ASD of the opposite sex in our study was insignificant. However, in contrast to our findings, a systematic review conducted by Ritter et al. (2021) revealed a correlation between male sex and a higher usage of psychotropic medications. The utilization of psychopharmacological treatments in our sample marginally differed by age (p = 0.058; p = 0.022 between the age groups 4.2. Characteristics of parents, families and the individuals with ASD and the utilization and perceived effectiveness of psychopharmacological treatments

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The difference in utilization of psychopharmacological treatments between individuals with ASD of the opposite sex in our study was insignificant. However, in contrast to our findings, a systematic review conducted by Ritter et al. (2021) revealed a correlation between male sex and a higher usage of psychotropic medications. The utilization of psychopharmacological treatments in our sample marginally differed by age (p = 0.058; p = 0.022 between the age groups "8–14 years" and "15 years and older"). Among the different age groups, the oldest group ($\geq$15 years) demonstrated the highest rate of psychopharmacological treatment, closely followed by the youngest group of subjects (<8 years). The prevalence of medication use among older individuals is anticipated (Ritter et al., 2021) likely stemming from parental fatigue and challenges in managing behavioral issues in an older child (or young adult). This could be attributed to the limited availability or absence of age-appropriate behavioral therapy options. In the study conducted by Spencer et al. (2013) it was found that older individuals had a significant association with both the use and polypharmacy of psychotropic medication. Interestingly, our research revealed a remarkably high prevalence of psychotropic medication usage among the youngest population (<8 years). This could potentially be attributed to the limited availability of non-medical alternatives, such as behavioral-educational therapy, which are typically recommended for this age group. Additionally, the study also demonstrated that children residing in regions with limited access to non-pharmacological treatment options were more likely to resort to psychotropic medication. These findings may reflect the prevailing pro-medication attitudes and practices among prescribing physicians. In an another study Shoumi Deb et al. (2023) also report that, although some physicians are successful and enthusiastic about rationalizing psychotropic medication (in particular, antipsychotic) prescribing, others still face barriers and challenges to achieving these goals.

There is a notable and meaningful distinction in the utilization of psychotropic medication among individuals with varying degrees of ASD severity (p = 0.044), exhibiting a positive correlation. These findings align with the anticipated outcomes and are consistent with the majority of similar research studies documented in the literature (Becerra et al., 2017; Coleman et al., 2019). In cases where behavioral symptomatology is severe and unresponsive to other intervention measures, it is often necessary to turn to drug therapy, which may include the use of multiple psychotropic medications. According to a study conducted by Logan et al. (2015) children exhibiting argumentative, aggressive, hyperactive/impulsive, or self-injurious behaviors were more likely to be prescribed a higher number of psychotropic medications. Interestingly, the occurrence of other neurodevelopmental or neuropsychiatric disorders within our sample did not have a significant impact on the utilization of psychotropic medications. Conversely, the study by Spencer et al. (2013) found that the presence of comorbid conditions, particularly epilepsy, ADHD, and anxiety, was consistently associated with the use of psychotropic medication and polypharmacy. Ritter et al. (2021) also reported higher rates of medication use among individuals with psychiatric comorbidities, self-injurious behavior, and physical aggression. However, it is important to acknowledge the potential under-diagnosis of co-occurring conditions in our sample (as discussed in Section 4.1), which may have led to an underestimation of the prevalence of these conditions and could have influenced the results. Conversely, the absence of a significant difference in medication use may indicate that psychotropic medications are prescribed to individuals with ASD in our sample irrespective of the presence of co-morbid conditions.

The effectiveness of psychopharmacological treatments was not perceived differently by parents of children of different sex, age, severity of ASD, and additionally present other developmental or neuropsychiatric disorders. This may be due to parental uncertainty when evaluating effectiveness, possibly caused by the simultaneous and overlapping effects of concomitant therapies. Nevertheless, this could suggest that the effectiveness of psychotropic medications is truly unrelated to the tested variables, but to other factors not considered in this study.

4.3. Limitations and advantages of the study

The study employed a quantitative approach, allowing for an objective evaluation of the established goals. Despite the relatively small sample size, this can be justified by the limited population of approximately 2 million from which participants were drawn. Moreover, the research covered a region and a middle-income country, both rarely represented in autism treatment studies. However, future investigations should aim to include a larger and more diverse pool of participants to ensure greater generalizability. It should be noted that the autism diagnoses of the participants were not officially confirmed. However, given that respondents were recruited

from relevant parental support associations, there is no doubt about their children's diagnosed ASD. The ASD severity was parent-rated, as this was the only measure of severity applicable for the type of study. The research relied on an online parental survey, which was retrospective in nature and relied on respondent memory. Consequently, this may have affected the accuracy of the responses to some extent. Additionally, the selection of variables pertaining to the use and effectiveness of psychotropic medications was limited to those that could be assessed through an online parental survey. While parental assessments of treatment effectiveness and adverse effects may be subject to bias, they provide unique insights into effects often overlooked in clinical trials.

5. Conclusions

The treating of autism spectrum disorder (ASD) with psychotropic medications varies widely across different regions and countries, reflecting local prescribing policies, preferences, and other factors. In our research conducted in a South-Eastern European middle-income country, we anticipated finding specific and distinct patterns of medication use, differing at least to some extent from findings in high-income countries. Our findings revealed a high utilization of psychotropic medications, particularly antipsychotics and antiepileptics. Notably, children below the age of 8 exhibited a remarkably high rate of medication use (56%), and both this age group and those $\geq$ 15 years showed a higher prevalence of psychotropic medication use. We also observed a positive correlation between the severity of ASD and the use of such medications. Parents were insufficiently informed by the medication prescribers about treatments they recommended, particularly about the risks of adverse effects and medication interactions.

Overall, the study provided a much-needed and comprehensive overview of the use of psychopharmacological treatments in ASD, specific for an underrepresented region and a middle-income country. The results demonstrated that prescribers need to provide parents with a broader information and advice concerning the psychopharmacological treatments that their children use. A more critical approach to prescribing such medications, especially in the youngest and mildly-to-moderately affected individuals should be endorsed, but also, supported through more available and accessible non-pharmacological treatments. The most important findings of this study – the extensive use of psychotropic medication, strikingly high in the youngest ASD population and the insufficient vital information on the prescribed medications provided to the parents should inform and help policy makers direct future steps in improving autism care.

Ethical standards

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2000.

Authorship contribution statement

The authors confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship but are not listed. We understand that the Corresponding Authors are the sole contact for the Editorial process. They are responsible for communicating with the other authors about progress, submissions of revisions and final approval of proofs.

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Trajkovski Vladimir: Writing – review & editing, Writing – original draft, Validation, Supervision, Project administration, Methodology, Conceptualization. **Syed Yasir Ahmed:** Writing – review & editing, Writing – original draft, Visualization, Supervision, Resources, Data curation. **Stojanovska Irena:** Writing – review & editing, Writing – original draft, Visualization, Validation, Methodology, Investigation, Formal analysis, Data curation. **Chatterjee Anirban:** Writing – original draft, Formal analysis.

Declaration of Competing Interest

The authors report no conflicts of interest.

Data availability

Data will be made available upon reasonable request.

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