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Prevalence and predictors of psychotropic medication use in adolescents and adults with autism spectrum disorder in Italy: A cross-sectional study

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ABSTRACT

Autism spectrum disorder (ASD) is a group of life-long neurodevelopmental conditions with a prevalence of 1.5% in developed countries. Beside core symptomatology, ASD people are frequently affected by psychiatric comorbidities and behavioral problems. To date, only risperidone and aripiprazole have been approved for the pharmacological treatment of ASD-associated irritability in children and adolescents, while no guidelines exist for adults. The present cross-sectional study examined the prevalence and predictors of psychotropic medication use in 195 autistic subjects, aged between 14 and 58, treated in two Italian tertiary care centers. 58.5% of the sample were taking at least one medication; one third of the sample were on polypharmacotherapy. Antipsychotics were prescribed to 40% of the sample. Nearly 30% of the sample were on anticonvulsants/mood stabilizers. Both antidepressants and benzodiazepines were prescribed to approximately 16% of the subjects. IQ, epilepsy and psychiatric comorbidities were regarded as independent predictors of both mono- and polypharmacotherapy, while severity of repetitive behaviors predicted only polypharmacotherapy. Our data highlighted that medications prescribed to adolescents and adults with ASD are heterogeneous and often rely only on clinicians' experience. Future research should investigate the effectiveness of psychotropic drugs in this specific population, to promote the development of appropriate treatment guidelines.

1. Introduction

Autism spectrum disorder (ASD) is a group of complex life-long neurodevelopmental conditions, characterized by impaired socio-communication skills and by the presence of restrictive and repetitive patterns of behaviors and interests (American Psychiatric Association, 2013). ASD prevalence has dramatically increased since its first description (Kanner, 1943), and it is now estimated that 1 every 59 children might be on the autism spectrum (Baio, 2018). Given the chronic nature of this condition, it could be argued that prevalence rates in adulthood are similar to those estimated in childhood (Brugha et al., 2011; Lyall et al., 2017), even if many autistic adults are probably still unrecognized (Lai and Baron-Cohen, 2015). In the near future, we could expect that adult psychiatrists will frequently have to treat individuals with ASD during their clinical practice (Muhle et al., 2018).

Currently, no efficacious pharmacological therapies are available for ASD core symptoms (Farmer et al., 2013; Howes et al., 2017). However, besides core features, a wide range of associated symptoms and psychiatric comorbidities frequently affects individuals with ASD. Subjects with average or above-average intelligence present higher rates of anxiety and mood disorders compared to non-autistic peers; on the other hand, individuals with intellectual disability (ID) display a higher prevalence of psychosis and behavioral problems, such as self- and/or other-directed aggressive behavior and irritability (Lai et al., 2014; Lever and Geurts, 2016). To date, only two atypical antipsychotics (i.e. risperidone and aripiprazole) have been approved by the U.S. Food and Drug Administration (FDA) for the treatment of ASD-related irritability in pediatric population (LeClerc and Easley, 2015). The strength of the evidence supporting the use of other pharmacological classes (for instance selective serotonin reuptake inhibitors or tricyclic antidepressants) is very low (Broadstock et al., 2007) and derives mostly from non-controlled, naturalistic studies or case reports (Bertelli et al., 2016; Doyle et al., 2014). Some researchers have hypothesized that the use of these medications might be associated with several adverse events, such as behavioral toxicity, social withdrawal and irritability (Hurwitz et al., 2012; Williams et al., 2013). Given the

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lack of evidence-based data regarding the efficacy, safety and tolerability of the most commonly used psychotropic drugs, to date no specific guidelines for the pharmacological treatment of psychiatric comorbidities and co-occurrent symptomatology in adults have been developed (Bertelli et al., 2016; Howes et al., 2017). In 2011, the Italian National Institute of Health (Istituto Superiore di Sanità, ISS) approved guidelines for the assessment and treatment of children and adolescents with ASD (Zappella and Bertelli, 2012). However, to date, recommendations for autistic adults still need to be developed, even if a specific committee has been recently instituted. Accordingly, clinicians in Italy usually follow international guidelines (Howes et al., 2017; Pilling et al., 2012).

Nonetheless, many psychotropic medications are prescribed off-label to ASD people, in everyday clinical practice (Broadstock et al., 2007; Farmer et al., 2013; Hsia et al., 2014; Murray et al., 2014). A recent systematic review (Jobski et al., 2017) has reported a median prevalence of psychiatric medication use of 45.7% (range between 3% and 80% according to different studies). Medication use tended to increase with age and with the presence of comorbidities (Jobski et al., 2017). However, almost all the studies included in the review were focused on children or adolescents: only two studies included patients with a mean age higher than 17 years. In fact, despite the high rate of prescription of psychopharmacological treatments in ASD, there are only sparse data on medication use in adulthood. In 2007, Tsakanikos and colleagues (Tsakanikos et al., 2007) reported that outpatients with ASD and ID were more likely to be prescribed antipsychotics compared to controls. Esbensen et al. (2009a) examined the longitudinal use of medications: they observed that the proportion of individuals taking psychotropic drugs as well as the number of prescribed medications increased over a period of 4.5 years (Esbensen et al., 2009a). In 2012, Lake and colleagues (Lake et al., 2012) found that 64% of ASD adults were on medication, and that the presence of polypharmacy was predicted by history of aggression, residence, and psychiatric support. More recently, Buck et al. (2014) have calculated that 59% of a sample of adults with ASD were taking at least one psychotropic medication. In a multinational study, Hsia et al. (2014) investigated pharmacological prescriptions in adults with ASD. Researchers found that risperidone, valproic acid, and haloperidol were the most frequently prescribed drugs in Italy. However, the aforementioned studies were generally focused on ASD with comorbid ID or unspecified cognitive abilities.

The present cross-sectional study was designed to partially fill this gap in literature, which contrasts with the growing prevalence of ASD among the general population and the urgent necessity to find effective treatments for its core and associated symptoms. We aimed to evaluate the prevalence and type of psychotropic medications used by a group of adolescents and adults with ASD who referred to two tertiary care centers in Italy. Second, we sought to identify potential differences between ASD people who were taking or not taking medications, and between individuals on monopharmacotherapy or polypharmacotherapy. Finally, we evaluated potential predictors of being on mono- and polypharmacotherapy.

2. Methods

2.1. Data collection

We conducted a cross-sectional study. In August 2018, we reviewed the clinical charts of individuals referring to two Italian outpatient services specifically dedicated to the diagnosis and treatment of adolescents and adults with ASD (Laboratorio Autismo, Department of Brain and Behavioral Sciences, University of Pavia; Outpatient service for ASD, Policlinico University Hospital, Catania). The services are tertiary care centers; therefore, patients are usually sent to these services after referral from professionals working in primary care (i.e. general practitioners) or secondary care centers (i.e. adult psychiatrists working in local health units or in the private sector).

In the present study, we included all the subjects who were in charge at these centers after June 2013, that is after the release of the Diagnostic and Statistical Manual of Mental Disorders 5th Edition (DSM-5; American Psychiatric Association, 2013), and were at least 14 years old at the moment of their last visit. All patients received a first formal diagnosis or a diagnostic re-evaluation according to DSM-5 criteria by a team of clinicians with expertise in ASD. Diagnoses of all participants were confirmed by the Autism Diagnostic Observation Schedule-2 (ADOS-2; Lord et al., 2012) and/or Autism Diagnostic Interview-Revised (ADI-R; Lord et al., 1994).

All subjects were evaluated by the medical personnel of the centers, during regular follow-up visits, for the prescription or modification of the pharmacological therapy and for the assessment of new onset psychiatric comorbidities. Follow-up periods were variable and usually established according to good clinical practice standard for severity levels and type of medication prescribed. In general, visits were less frequent (i.e. once every three months) for people who were not taking medications, while individuals who were taking psychotropic drugs were evaluated monthly.

Information collected from the medical records included the following variables:

1) Age;
2) Age at first ASD diagnosis, formally performed by a child or adult psychiatrist, retrieved by clinical documents provided by the patients or their caregivers; in case of no availability of past documents, subjects were asked to provide an approximate age at first ASD diagnosis.
3) Gender: male or female;
4) Intelligence quotient (IQ), measured by means of Raven's Matrices (Raven, 1938), Leiter-3 (Roid et al., 2013) or WAIS-R (Wechsler, 1981). When IQ was not evaluable due to the non-compliance of the subject, an IQ of 30 was computed;
5) Severity at criterion A and B: current severity levels for criterion A ("Persistent deficits in social communication and social interaction across multiple context") and B ("Restricted, repetitive patterns of behavior, interests, or activities") were specified for each subject, as recommended by DSM-5 (American Psychiatric Association, 2013). According to DSM-5, individuals with level 1 severity are considered as "Requiring support"; people with level 2 severity are labelled as "Requiring substantial support"; subjects with level 3 severity are categorized as "Requiring very substantial support";
6) Residence: with family or in a residential facility;
7) Current psychotropic medication, based on information collected during the last visit. Pharmacological prescriptions to the subjects included in our sample were generally done exclusively by the personnel of our centers, except for the prescriptions concerning organic comorbidities (i.e. seizures). Changes in medication use were recorded at each follow-up visit. Medications were classified into the following categories: antipsychotics (typical and atypical), antidepressants, benzodiazepines, mood stabilizers/anticonvulsants.
8) Diagnosis of epilepsy.
9) Psychiatric comorbidities (e.g. anxiety, depression, psychosis, obsessive-compulsive disorder, eating disorders, gender dysphoria, ADHD, substance use disorder, personality disorders, others). The onset of new psychiatric comorbidities was assessed at each follow-up visit by the psychiatrists of the two centers. Comorbidities were assessed through direct observation and clinical interviews during the visits. Specific diagnostic tools were administered only if required.

Patients referring to our centers (or their guardians) always signed a written informed consent during the first visit, allowing the use of their data for research purposes. Thus, a written informed consent was obtained for the inclusion in the present study. All the invited subjects accepted to participate. The protocol was approved by our internal

review board. The study was performed in accordance with the Declaration of Helsinki.

2.2. Statistical analysis

Demographic and clinical information of the sample were summarized as means and standard deviations for continuous variables and numbers and percentages for categorical variables. Chi-square test and *t*-test were used to evaluate differences between psychotropic medication users and non-users, as well as for differences between subjects on monopharmacotherapy and polypharmacotherapy. Additionally, we performed multinomial logistic regressions to evaluate potential predictors of the use of pharmacological therapy using three categories (no pharmacological therapy, monopharmacotherapy and polypharmacotherapy) as dependent variables. The reference category was "no pharmacological therapy". Given the lack of a priori hypotheses on the independent variables to insert in the regression model, gender, age at last prescription, age at diagnosis, IQ, severity at criteria A and B of DSM-5, place of residence, presence of psychiatric comorbidities and epilepsy were evaluated as potential predictors of the number of drugs in univariate multinomial logistic regressions. All predictors which reached the statistical significance at univariate regressions for either of the categories (mono- or polypharmacotherapy) were inserted in the multivariate model. All statistical tests were evaluated at the $\alpha = 0.05$ significance level. Statistical analysis was performed with SPSS Version 24.0.

3. Results

3.1. Characteristics of participants

We included 195 people in our analysis, of which 148 (75.9%) were males. Participants were on average 26.5 years old, with ages ranging from 14 to 58 years. Mean IQ was 80 and IQ ranged from 30 to 145; 44.1% of subjects had ID. Age at diagnosis varied from 3 to 55 years, with a mean age of 16.1 years at first formal diagnosis of ASD. Of note, almost 60% of the sample had been diagnosed after the age of 14. Severity levels were equally distributed for both criteria of DSM-5. Among psychiatric comorbidities, the most frequent diagnoses were anxiety (11.3% of the sample) and depression (6.7%). Obsessive-compulsive disorder, eating disorders or gender dysphoria were detected in 3 subjects each. Only one participant had a comorbid psychosis, while in 5.6% of the cases other psychiatric comorbidities were present (i.e. substance abuse, personality disorders). Subjects were mostly living at home with family or independently, while 12.8% were in a residential facility. 16.9% of the sample were also affected by seizures. Participants' characteristics are presented in Table 1.

Table 1
Characteristics of the sample.

Characteristics	Total (n = 195)
Gender	
Male (%)	148 (75.9)
Female (%)	47 (24.1)
Mean age (range)	26.5 ± 9.2 (14–58)
Age at diagnosis (range)	16.1 ± 11.6 (3–55)
Mean IQ (range)	80 ± 35.8 (30–145)
Severity, criterion A	
Level 1 (%)	61 (31.3)
Level 2 (%)	66 (33.8)
Level 3 (%)	68 (34.9)
Severity, criterion B	
Level 1 (%)	67 (34.4)
Level 2 (%)	61 (31.3)
Level 3 (%)	67 (34.4)
Comorbidities	
ID (%)	86 (44.1)
Secondary psychiatric diagnoses (%)	53 (27.2)
Anxiety	22 (11.3)
Depression	13 (6.7)
Obsessive-compulsive disorder	3 (1.5)
Eating disorders	3 (1.5)
Gender dysphoria	3 (1.5)
Psychosis	1 (0.5)
Other psychiatric comorbidities (%)	11 (5.6)
Seizures (%)	33 (16.9)
Residence	
Family (%)	170 (87.2)
Residential facility (%)	25 (12.8)

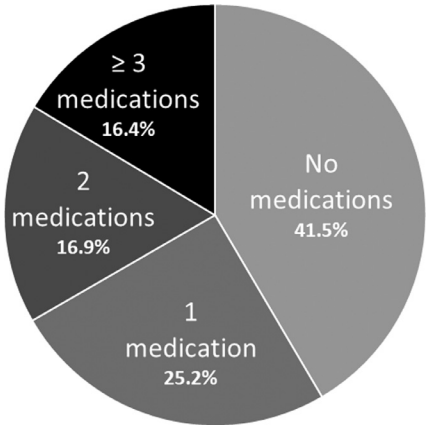

Fig. 1. Prevalence of psychotropic medication use in adolescents and adults with ASD.

3.2. Prevalence of current psychotropic medication use

As reported in Fig. 1, among 195 patients, 114 were taking at least one psychotropic medication (58.5%), and around one third of the entire sample were on polypharmacotherapy (≥2 medications). Overall, 44 different compounds were prescribed to the included subjects. A complete list of the medications prescribed as well as the number of subjects taking each drug have been reported in Supplementary Materials (Table s1).

The most frequently used drugs were antipsychotics, which were prescribed to 40% of the sample. Atypical antipsychotics were used by 68 subjects (34.9%). Of note, risperidone was prescribed to 27 patients, aripiprazole to 14 patients, and olanzapine to 12 people. First-generation antipsychotics were used by 10.3% of the sample (20 individuals). Precisely, haloperidol and zuclopenthixol were prescribed to 6 patients each. 29.2% of the sample were on anticonvulsants/mood stabilizers: valproate was prescribed to 33 people (16.9% of the sample), followed by carbamazepine (12) and gabapentin (7). Antidepressants were prescribed to 16.9% of the subjects, and benzodiazepines to 16.4% of the sample. Among benzodiazepines, clonazepam and lorazepam were taken by 7 subjects, as well as sertraline, that was the most frequently prescribed antidepressant.

Subjects on a single medication regimen used more frequently antipsychotics (n = 27), mood stabilizers (n = 11) or antidepressants (n = 11). None of the subjects were taking benzodiazepines in monotherapy. For people who were prescribed two or more medications, the most frequent combinations were antipsychotic associated with mood stabilizer (n = 18), antipsychotic associated with both mood stabilizer and benzodiazepines (n = 13), antidepressant plus mood stabilizer (n = 12), antipsychotic and antidepressant (n = 8), and benzodiazepines in addition to a mood stabilizer (n = 6). Other pharmacological combinations were adopted only in a small number of cases.

3.3. Differences between medication users and non-users

We did not find any significant differences neither in gender

Table 2
Differences between medication users and non-users.

Characteristics	Not taking medications (n = 81)	Taking medications (n = 114)	Statistics	p-value
Gender			χ^2 = 3.46	.06
Male (%)	56 (69.1)	92 (80.7)	φ = 0.13	
Female (%)	25 (30.9)	22 (19.3)		
Mean age	25.6 ± 9.6	27.1 ± 9	t = −1.09	.28
(range)	(14–57)	(16–58)	d = 0.16	
14–17 (%)	10 (12.3)	6 (5.3)	χ^2 = 3.45	.18
18–30 (%)	52 (64.2)	75 (65.8)	φ = 0.13	
>30 (%)	19 (23.5)	33 (28.9)		
Age at diagnosis	20.3 ± 11.3	13.1 ± 10.9	t = 4.45	<0.001*
(range)	(3–51)	(3–55)	d = 0.09	
Mean IQ	100.7 ± 28.3	65.2 ± 33.2	t = 7.8	<0.001*
(range)	(30–145)	(30–141)	d = 1.15	
Severity, criterion A			χ^2 = 38.25	<0.001*
Level 1 (%)	40 (49.4)	21 (18.4)	φ = 0.44	
Level 2 (%)	32 (39.5)	34 (29.8)		
Level 3 (%)	9 (11.1)	59 (51.8)		
Severity, criterion B			χ^2 = 47.52	<0.001*
Level 1 (%)	44 (54.3)	23 (20.2)	φ = 0.49	
Level 2 (%)	31 (38.3)	30 (26.3)		
Level 3 (%)	6 (7.4)	61 (53.5)		
Comorbidities				
ID (%)	13 (16)	73 (64)	χ^2 = 44.23	<0.001*
			φ = 0.48	
Other psychiatric diagnoses (%)	20 (24.3)	33 (28.9)	χ^2 = 0.43	.51
			φ = 0.05	
Seizures (%)	3 (3.7)	30 (26.3)	χ^2 = 17.22	<0.001*
			φ = 0.29	
Residence			χ^2 = 10.3	.001*
Family (%)	78 (96.3)	92 (80.7)	φ = 0.23	
Residential facility (%)	3 (3.7)	22 (19.3)		

(p = .06) nor age (p = .28) between medication users and non-users. Nevertheless, age at diagnosis was significantly different between the two groups (p < .001). Also, severity significantly influenced the use of psychotropic medications, both at criterion A (p < .001) and criterion B (p < .001). In fact, while half of medication-free individuals were collocated into severity level 1, half of the individuals who were taking psychotropic drugs were classified in severity level 3. Statistically significant differences were also found for people with comorbid ID (p < .001) and epilepsy (p < .001). Surprisingly, we did not find a significant association between medication use and the presence of comorbid psychiatric diagnoses (excluding ID) (p = .51). Differences between psychotropic medication users and non-users have been reported in Table 2.

3.4. Differences between patients on monopharmacotherapy and polypharmacotherapy

As reported in Table 3, we did not find any significant differences between patients on monopharmacotherapy and on polypharmacotherapy according to the following variables: gender (p = .83), age (p = .75), age at diagnosis (p = .36), severity at criterion A (p = .07) and presence of epilepsy (p = .09). On the contrary, significant differences were found in the level of severity at criterion B (p = .001) and the presence of ID (p = .001). Patients also showed significant differences according to the presence of comorbid psychiatric diagnoses, with psychiatric comorbidities more present in the monotherapy group (p = .001), and according to the place of residence (p = .03).

Table 3
Differences between individuals on monotherapy and on polytherapy.

Characteristics	Monotherapy (n = 49)	Polytherapy (n = 65)	Statistics	p-value
Gender			χ^2 = 0.05	.83
Male (%)	40 (81.6)	52 (80)	φ = −0.02	
Female (%)	9 (18.4)	13 (20)		
Mean age	26.6 ± 8.9	27.4 ± 9.1	t = −0.49	.75
(range)	(17–58)	(16–54)	d = 0.09	
14–17 (%)	2 (4.1)	4 (6.1)	χ^2 = 0.57	.75
18–30 (%)	34 (69.4)	41 (63.1)	φ = 0.07	
>30 (%)	13 (26.5)	20 (30.8)		
Age at diagnosis	14.2 ± 10.9	12.3 ± 11	t = 0.91	.36
(range)	(3–55)	(3–44)	d = 1.19	
Mean IQ	74.8 ± 35.6	58.1 ± 29.5	t = 2.75	.001*
(range)	(30–141)	(30–126)	d = 0.51	
Severity, criterion A			χ^2 = 5.28	.07
Level 1 (%)	13 (26.5)	8 (12.3)	φ = 0.21	
Level 2 (%)	16 (32.7)	18 (27.7)		
Level 3 (%)	20 (40.8)	39 (60)		
Severity, criterion B			χ^2 = 9.81	.001*
Level 1 (%)	14 (28.6)	9 (13.8)	φ = 0.29	
Level 2 (%)	17 (34.7)	13 (20)		
Level 3 (%)	18 (36.7)	43 (66.2)		
Comorbidities				
ID (%)	23 (46.9)	50 (76.9)	χ^2 = 10.91	.001*
			φ = 0.31	
Other psychiatric diagnoses (%)	22 (44.9)	11 (16.9)	χ^2 = 10.63	.001*
			φ = −0.31	
Seizures (%)	9 (18.4)	21 (32.3)	χ^2 = 2.8	.09
			φ = 0.16	
Residence			χ^2 = 4.56	.03*
Family (%)	44 (89.8)	48 (73.8)	φ = 0.2	
Residential facility (%)	5 (10.2)	17 (26.2)		

3.5. Predictors of mono- and polypharmacotherapy use in adolescents and adults with ASD

Predictors of medication use were assessed through multinomial logistic regressions. Results are shown in Table 4. Univariate regressions showed several significant predictors of mono- and polypharmacotherapy. Therefore, age at diagnosis, IQ, severity levels at criterion A and B, place of residence, presence of psychiatric comorbidities and epilepsy were inserted in the multivariate model. Cox and Snell pseudo R^2 for the model was 0.43, and the model was statistically significant (p < .001). The model revealed that IQ was a negative independent predictor of both monopharmacotherapy (β = .97, p = .007) and polypharmacotherapy (β = .96, p = .003): people with higher IQ were less likely to take psychotropic medications. Furthermore, the presence of psychiatric comorbidities positively predicted mono- (β = 12.5, p < .001) and polypharmacotherapy (β = 4.95, p = .007) compared to the “no medication” category. Epilepsy was another significant positive predictor of taking one (β = 5.45, p = .03) or more medications (β = 7.53, p = .008). Notably, severity at criterion B (restrictive interests and repetitive behaviors) was regarded as a significant independent predictor only for polypharmacy. In particular, people with level 1 (β = .03, p = .004) and level 2 autism (β = .04, p = .002) were less likely to be on polypharmacy than individuals with level 3.

4. Discussion

Despite the increasing prevalence of ASD, little is known about the efficacy of medications for ASD core and related symptoms in adolescence and adulthood. However, the prescription of psychotropic medications in this group of patients is frequent in clinical practice, partly due to the high rates of psychiatric comorbidities and behavioral

Table 4
Univariate and multivariate multinomial logistic regressions using no pharmacotherapy (reference category), mono- and polypharmacotherapy as dependant variables (Model $\chi^2 = 108.277$, $p < .001$, Cox and Snell Pseudo $R^2 = 0.426$).

		Univariate regressions			Multivariate regression model		
		B	β	*p*-value	B	β	*p*-value
Monopharmacotherpay	**Gender (Female)**	−0.68	.50	.12			
	Age	.01	1.01	.54			
	Age at diagnosis	−0.47	.95	.01*	−0.01	.99	.75
	IQ	−0.02	.98	<0.001*	−0.03	.97	.007*
	Severity A (Level 1)	−1.92	.15	<0.001*	−0.02	.97	.98
	Severity A (Level 2)	−1.49	.003	.22	−0.03	.97	.97
	Severity B (Level 1)	−2.24	.11	<0.001*	−1.29	.27	.27
	Severity B (Level 2)	−1.70	.18	.002*	−1.11	.33	.29
	Residence (Home)	−1.08	.34	.15	1.17	3.24	.25
	Psychiatric comorbidities	.91	2.48	.02*	2.53	12.5	<0.001*
	Epilepsy	1.77	5.85	.01*	1.70	5.45	.03*
Polypharmacotherapy	**Gender (Female)**	−0.58	.56	.14			
	Age	.02	1.02	.23			
	Age at diagnosis	−0.07	.94	<0.001*	.03	1.03	.27
	IQ	−0.04	.96	<0.001*	−0.04	.96	.003*
	Severity A (Level 1)	−3.08	.06	<0.001*	1.36	3.91	.26
	Severity A (Level 2)	−2.04	.13	<0.001*	1.67	5.33	.10
	Severity B (Level 1)	−3.56	.29	<0.001*	−3.41	.03	.004*
	Severity B (Level 2)	−2.84	.06	<0.001*	−3.25	.04	.002*
	Residence (Home)	−2.22	.11	.001*	.56	1.75	.55
	Psychiatric comorbidities	−0.48	.62	.26	1.6	4.95	.007*
	Epilepsy	2.52	12.41	<0.001*	2.02	7.53	.008*

problems in people with ASD. The present study examined the prevalence, type, and predictors of medication use in 195 subjects with ASD. Our data are in line with previous studies (Jobski et al., 2017), showing that 58.5% of the sample were taking at least one psychotropic medication. Our findings also confirm that the most frequently prescribed drugs are antipsychotics, particularly second-generation neuroleptics; this is consistent with FDA-approved medications for autism-associated irritability. Other reasons for the prescription of antipsychotics in this population are the presence of behavioral problems, such as aggressiveness, agitation, and self-injurious behaviors, which are frequent in autistic individuals, particularly those with comorbid ID (Park et al., 2016). Literature reported that aripiprazole has also shown some anti-depressant and anti-anxiety properties in this population (Kirino, 2012). Despite rates of depression and anxiety being usually higher among ASD people, antidepressants were used only by 16.9% of the sample. This could be due to the atypical responses of ASD people (Farmer et al., 2013) and to the limited evidence of the effectiveness of antidepressants in ASD (Williams et al., 2013). Nevertheless, clinicians may prescribe antidepressants to contrast the presence of repetitive behaviors (Hollander et al., 2012). Benzodiazepines were taken by a similar number of subjects, while mood stabilizers were used by nearly 30% of the sample. It is important to underline that many of the included subjects were also affected by epilepsy: in people with ASD and a comorbid epilepsy, drugs such as valproate or diazepam are often used to take advantage of both their anticonvulsant and stabilizing/sedative properties. Of note, it has been hypothesized that ASD may result from a disruption of the equilibrium between excitatory glutamatergic and inhibitory GABAergic pathways (Hussman, 2001). Additionally, attention has been brought to subclinical epileptiform abnormalities on the electroencephalogram (EEG), which have also been linked to cognitive, language and/or behavioral changes (Kagan-Kushnir et al., 2005). For this reason, GABA modulators, such as benzodiazepines and mood stabilizers, have been proposed as potential target therapies (Brondino et al., 2016). None of the subjects included in our sample had a comorbid diagnosis of attention deficit-hyperactivity disorder (ADHD) or were taking psychostimulants. On one hand, this is in contrast with previous findings reporting psychostimulants as a prominently-used medication category in ASD (Jobski et al., 2017). Our result could be partially justified by the inclusion of adolescents and adults, a population in which ADHD symptoms usually decrease (Mire et al., 2014). It is worth mentioning that most participants included in the present study had received a formal diagnosis of ASD for the first time in adulthood (Fusar-Poli et al., 2017b). On the other hand, our finding is in line with the multinational study conducted by Hsia et al. (2014), that reported no prescriptions of stimulants in Italian adults with ASD, in contrast with other countries. This could be explained by the restrictive Italian legislation about the prescription of stimulants for individuals older than 18 years of age (Brod et al., 2012).

In contrast with previous investigations, we did not find any significant differences in the prevalence of psychotropic drug prescription or in the number of psychotropic medications in relation to age groups. Literature reported age as a predictor of the use and number of medications (Jobski et al., 2017). Again, it is important to underline that the mean age of our sample is higher than previous studies; thus, our finding could be related to the stabilization of ASD symptomatology and co-occurring difficulties in adulthood, as reported by some authors (Esbensen et al., 2009b; Fusar-Poli et al., 2017a; Shattuck et al., 2007). Nonetheless, a significant association between age at diagnosis and psychotropic medication use was found in our sample: patients who were taking drugs had received a diagnosis of ASD nearly 13 years earlier than the comparison group (Table 1). Probably, this is related to the less pronounced symptomatology and the higher coping strategies of people who were diagnosed later in life (Lai and Baron-Cohen, 2015).

Our data revealed that people with ID were more likely to take medications than people without ID. This is not surprising since people with ID often present behavioral problems, such as aggressiveness, hyperactivity or irritability, which may lead to a significant worsening of quality of life of individuals with ASD and their families (Chiang and Wineman, 2014). Also, people with ID were more likely to be on polypharmacotherapy. Severity levels of criteria A and B were both associated with the use of medications. However, while severity at criterion B (repetitive and restrictive behaviors and interests) was a significant predictor of polytherapy, this was not observed for criterion A (socio-communication impairments). In fact, more than 66% of individuals who were taking two or more medications were classified into the severity level 3 of criterion B. A possible explanation could rely on the fact that repetitive behaviors and stereotypes are more difficult to manage, especially in people with a comorbid ID; this aspect could represent a significant treatment target for clinicians and families

(Gabriels et al., 2005).

Another surprising finding is that people on polypharmacotherapy were less likely to receive a comorbid psychiatric diagnosis (excluding ID) than those on monotherapy (44.9% vs 16.9%). A possible explanation is that individuals on polypharmacotherapy were more frequently affected by ID, a condition in which it could be challenging to diagnose specific psychiatric comorbidities, such as anxiety and depression (Aman, 1991). Moreover, these conditions are treated with single medications rather than with a polypharmacotherapy (Cascade et al., 2007). Notably, the presence of psychiatric comorbidities was regarded as a positive predictor of monopharmacotherapy, but not of polypharmacotherapy, in the univariate regression; however, after correcting for other factors in the multivariate model, psychiatric comorbidities predicted medication use also in the polypharmacy category. Finally, people living in a residential facility were more likely to take medications: this is in line with previous findings (Lake et al., 2012) and could also be explained by the fact that ID is highly prevalent in this population (100% in our sample). In fact, after correcting for IQ and the other variables, living in a residential facility did not predict polypharmacy use.

Our cross-sectional study was designed to provide a broad overview of the complex pharmacological pattern prescribed to people with ASD and was not meant to evaluate the efficacy of pharmacological treatments for ASD. Our research may partially fill the gap in literature regarding the use of psychotropic medications in adolescents and adults with ASD. The present paper has the main strength to report psychopharmacological prescriptions of patients who have been regularly followed-up by a team of psychiatrists with specific expertise in ASD. Conversely, some of the previous studies (i.e. Hsia et al., 2014; Murray et al., 2014) only reviewed registers or databases. However, we should carefully consider some limitations. The main limitation of the present paper is related to the cross-sectional design. Our analyses considered only medications taken or prescribed during each subject's last visit, which could have also occurred three months prior to data collection; moreover, we did not report changes in psychotropic medications over time (as in Esbensen et al., 2009a, for instance). This is a potentially relevant limitation since - given the absence of specific guidelines, and according to our clinical experience - changes in psychotropic prescriptions are frequent, either for the drugs' scarce efficacy or for the side effects experienced by patients. Additionally, we did not analyze the concomitant administration of nutraceuticals or non-psychotropic medications (e.g. melatonin) that according to literature are frequently used by ASD individuals (Brondino et al., 2015; Höfer et al., 2017), but do not need a medical prescription and were thus difficult to control.

Furthermore, specific tools for the evaluation of psychiatric comorbidities were administered only to a small part of our sample. Indeed, we relied mainly on direct observation or clinical interviews than on the administration of assessment scales. Nevertheless, it is worth mentioning that many diagnostic tools commonly used in mental health settings have not been specifically validated for autistic individuals. Therefore, they might not be reliable in this population, also considering the overlapping symptomatology between ASD and other conditions (e.g. anxiety, depression, etc.) (Cassidy et al., 2018). Importantly, since we included only patients referring to two tertiary care centers in Italy, we cannot extend the generalizability of our findings to the entire population of adolescents and adults with ASD. One reason is related to the drug prescription patterns in Italy which are slightly different from other countries and partially influenced by legislative restrictions, as already reported by multinational studies (Hsia et al., 2014). The complex prescriptive pattern could also be related to the absence of specific guidelines for autistic adults in this country (Zappella and Bertelli, 2012). In the future, involving more centers would be more informative as it is possible that medication prescribed by general practitioners and by psychiatrists working in local mental health services differ from those prescribed by clinicians with specific expertise in adults with ASD. Finally, many of the individuals included in our sample were diagnosed later in life. Therefore, we included also a part of the spectrum in which the symptomatology might have been covered by camouflaging or coping strategies (Lai and Baron-Cohen, 2015), or, conversely, in which has not been promptly recognized and appropriately treated with non-pharmacological therapies, such as educational therapies in childhood (Dawson et al., 2010; Peters-Scheffer et al., 2011).

Data reported in the present paper show that medications prescribed to adolescents and adults with ASD are heterogeneous and may be related to several factors. Moreover, given the lack of trials and specific guidelines focused on ASD adult population, pharmacological treatment is often related to clinicians' experience and not evidence-based. For this reason, psychiatrists should always consult and appropriately inform autistic patients and their families about the potential benefits and risks of psychotropic drug prescriptions. Randomized-controlled trials evaluating the efficacy of psychotropic medications on psychiatric comorbidities and associated symptoms in adolescents and adults with ASD are urgently needed. Side effects of psychopharmacological therapies also deserve to be studied in detail, since they might differ from neurotypical population. Given ASD high prevalence rates, it is plausible that many psychiatrists and general practitioners worldwide will soon have to manage the pharmacological therapy of adolescents and adults with ASD. An implementation of well-designed randomized-controlled trials may lay the ground for the development of consensus guidelines for this specific population.

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Conflict of interest

All authors declare that they have no conflict of interest.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.psychres.2019.04.013.

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