Characteristics associated with psychotropic medication use among children with autism in south Israel.

Authors: Gal Meiri1\*, Hen Azoulay1\*, Idan Menashe2,3

1. Pre-School Psychiatry Unit, Soroka University Medical Center, Beer Sheva, Israel
2. Public Health Department, Ben-Gurion University of the Negev, Beer Sheva, Israel
3. Zlotowski Center for Neuroscience, Ben-Gurion University of the Negev, Beer Sheva, Israel

\* Equal contribution

Corresponding author:

Idan Menashe, PhD

Department of Public Health

Faculty of Health Sciences

Ben-Gurion University of the Negev

Beer-Sheva, Israel

Email: idanmen@bgu.ac.il

Tel: +972-8-6477456; Fax: +972-8-6477638

**Abstract:**

**Background:** At present, there is no effective medication to treat the core symptoms of autism. However, people with autism use psychotropic drugs to treat other comorbidities associated with the disorder. Here we studied the prevalence and patterns of drug prescription and compliance among young children in south Israel.

**Methods**: We studied the characteristics associated with drugs prescription and compliance in a population-based sample of young children (ages 1-6 years) with autism between the years 2006-2013. Autism diagnosis was determined using DSM-IV and re-confirmed using DSM-V criteria. Data about drug prescription and compliance was acquired from the electronic records of these patients. Drug compliance was calculated as the percentage of purchased drugs out of total prescriptions, and was divided into three categories: 0-49% - no compliance; 50-74% - partial compliance; and 75-100% full compliance.

**Results**: Our sample included 211 children who received a total of 95 drugs prescriptions. Notably, one-third of these children received more than one type of medication during the study period. The most prevalent drugs that were prescribed were atypical antipsychotic drugs (49 children; 23.2%), followed by stimulants (28 children; 13.2%) and old generation antipsychotic drugs (16 children; 7.6%). Of the 75 children that received prescription to medications in our sample, almost half (45.3%) had full compliance, and only 18.7% did not comply at all with their drug prescriptions. Despite the high variability in compliance rate in our sample, it was not statistically associated with any of the variables in our study.

**Conclusions**: Our preliminary finding indicate that drug prescription and compliance among children with autism are associated with various clinical and demographic characteristics which should be considered by physicians.

**Introduction**

Autism is an increasingly prevalent neurodevelopmental disorder which at present has no cure [[1-7](#_ENREF_1)]. Common strategies directed to treat the core symptoms of autism are based on intensive educational-behavioral intervention such as applied behavior analysis (ABA [[8](#_ENREF_8)]), or the Early-Start-Denver-Model (ESDM [[9](#_ENREF_9)]). Other approaches such as the Developmental, Individual-differences, Relationship-based (DIR) model [[10](#_ENREF_10)] use spontaneous 'floor time' play sessions, to engage with the child’s interests, establish a foundation of shared attention, and lead him into the world of ideas and abstract thinking. These behavioral interventions are usually supported by complementary and alternative therapies such as speech, occupational and physical therapies [[11](#_ENREF_11)] that are designed to treat specific difficulties that are common among children with autism. In addition, the therapeutic market offers a range of dietary supplements such as vitamins, and minerals, or special diets [[12](#_ENREF_12)], as well as more invasive treatments, such as chelation [[13](#_ENREF_13)], hyperbaric oxygen treatments [[14](#_ENREF_14)] which claim to significantly improve the clinical condition of these children. However, robust evidence for the efficacy of these supplements in treating autism are lacking.

There are a range of psychoactive medications which are commonly prescribed for people with autism [[15-17](#_ENREF_15)]. These drugs are designed to alleviate associated symptoms such as irritability, hyperactivity, tantrums, aggression, sleep problems, and mood dysregulation and consequently improve the life quality of these people and their families. Of these, Risperidone and Aripiprazole are the only drugs which are approved by the FDA to treat specific maladaptive behaviors in children with autism [[18](#_ENREF_18)]. Risperidone is recommended for patients presenting irritability with aggression, tantrums or deliberate self-injury and is limited for age ≥5 years. The drug main adverse effects included weight gain, increased appetite, fatigue, drowsiness, dizziness, drooling, tremor, and constipation [[19](#_ENREF_19)]. Aripiprazole is approved for treating irritability in children aged 6 to 17 years. The main adverse effects associated with this drug included increased appetite, weight gain, elevated blood sugar secondary to insulin resistance, dyslipidemia, blood pressure changes, fatigue and drowsiness, dizziness and gynecomastia [[20](#_ENREF_20)].

Despite the uncertainty about the efficiency of the psycho-pharmacological treatment, the prevalence of drug treatment for children with autism increases [[21](#_ENREF_21), [22](#_ENREF_22)]. There are a range of studies which examined characteristics associated with medical drug utilization among people with autism (e.g. [[17](#_ENREF_17), [23](#_ENREF_23), [24](#_ENREF_24)]). However, these studies largely focused on drug prescription and have limited data regarding factors associated with the compliance with these prescriptions. To this end, we studied the sociodemographic and clinical characteristics of young children diagnosed with autism in south Israel, and evaluated the potential effects of these characteristics on drug prescription and compliance rates among these children.

**Materials and Methods**

Population

The population of south Israel, the Negev, contains ~ 700,000 citizen composed of ~60% Jewish and ~40% Bedouin Arabs, two ethnic groups that differ in their genetic background and lifestyle. About 75% of this population are members of Clalit health services and receive their medical services at the Soroka University Medical Center (SUMC), which is the only tertiary hospital in the Negev. A total of 318 children between the ages 1 to 6 years were referred to the Preschool Psychiatric Unit (PPU) at SUMC between the years 2006-2013. All of these children went through a rigorous clinical assessment that included a comprehensive intake interview regarding the clinical and socio-demographic background of the diagnosed child, and examination by a child psychiatrist which gave a diagnosis according to DSM-4 criteria [[25](#_ENREF_25)]. For the purpose of this study, the diagnoses of these children were reevaluated by the same child psychiatrist according to the new DSM-5 criteria [[26](#_ENREF_26)]. Consequently, a level of autism severity was assigned to each child in our sample according to the following DSM-V guidelines: 1) requiring support; 2) requiring substantial support; and 3) requiring very substantial support. This study was approved by the Helsinki committee responsible for human studies at SUMC.

Data collection

Clinical and sociodemographic data about individuals in our sample were retrieved from the PPU health records using the Clicks® software which is a clinic-based system linked to a clinic-resident management application which enables physicians and other medical staff to access their respective specialty-related application or designated dataset via a password-based routing strategy. Data about drug prescription and purchase frequency were retrieved from the OFEK virtual medical records [[27](#_ENREF_27)] which is an on-line information system that contains computerized medical records from all health services providers in Israel (i.e. hospitals and clinics, drug stores, medical labs, etc.). Medications were classified into the following four categories for standard use: 1) Atypical antipsychotic drugs (AA); 2) Old-generation antipsychotic drugs (OGA); 3) Stimulants (ST); 4) Sleep/tranquilizer (TRQ).

Compliance evaluation

The compliance rates (*CR*) for each patient *i* and each drug *j* were calculated as follow:

$$CR\_{i}=\sum\_{j=1}^{m}C\_{ij}/2 CR\_{j}=\sum\_{i=1}^{n}C\_{ij}/2$$

Where *m* is the total number of drugs per patient, *n* is the total number of patients per drug, and *Cij* is the compliance of a patient (*i*) with a prescribed drug (*j*) according to the following scales:

0 - recommendation was made by psychiatrist, but the drug was not purchased.

1 - drug was purchased inconsistently for only part of the prescribed period.

2 - drug was purchased consistently for the full period of the prescription.

We assumed that patients who bought the drugs, also used them according to the physician recommendation. Finally we classified the compliance rate to three categories: 0-49% - *no compliance*; 50-74% - *partial compliance*; and 75-100% *full compliance*.

Statistical analyses

We compared selected parameters between groups of patients divided according to patterns of drug prescription or drug compliance using independent t-test, or one-way ANOVA for continuous variables, and chi-square or Fisher-exact tests for nominal variables. We further used an unconditional logistic regression to assess the effect of multiple variables on drug prescription. All P values were two-sided, and statistical significance was defined as *P* < 0.05. Statistical analyses were conducted in SPSS 17th edition (SPSS Inc, Chicago, IL).

**Results**

Population characteristics

Of the 318 children who were referred to the PPU with suspected social communication difficulties and\or repetitive behaviors between the years 2006-2013, 235 (73.9%) had a positive diagnosis of autism. Of these, 24 children who’s their ethnicity was other than Jewish or Bedouin, and children who were not under medical surveillance at the PPU were excluded from the study. Consequently, 211 children with autism were included in this study.

Prevalence of drug prescription

Associations of basic demographic and clinical characteristics with drug prescription among the 211 children with autism in our sample are depicted in **Table 1**. A total of 95 prescriptions were made to these children as followed: 50 (23.7%) received a prescription for one type of drug, 19 (9.0%) received a prescription for two types of drugs, and six children (2.8%) received prescriptions to three or more drugs. Drug prescription was more prevalent among Bedouin than in Jewish children (46% vs. 31%; *P=0.036*). However, no significant differences were observed in the number of prescribed drugs between these two ethnic groups. Drug prescription was not associated with age at diagnosis or with the gender of the children in our sample.

Notably, drug prescription was significantly associated with autism severity as classified by the DSM-V (See methods) where children “requiring substantial support” and children “requiring very substantial support” were 7 time and 15 times more likely to have drug prescription than children “requiring support” respectively (Chi-square*; P<0.001*). Furthermore, autism severity was positively correlated with the number of drugs prescription (Spearman r = 0.34; *P<0.001*).

As expected, drug prescription was also associated with the types of autism comorbidities (**Figure 1A**). Specifically, children with autism and ADHD, intellectual disability (ID), or epilepsy were prescribed more drugs than other children with autism (*Bonferroni* corrected *P<0.05*). Remarkable differences were also seen in the prescription frequencies of different drugs (**Figure 1B**). The most prevalent prescription in our sample was to atypical antipsychotic drugs (49 children; 23.2%), followed by stimulants (28 children; 13.3%), old generation antipsychotic drugs (16 children; 7.6%), and tranquilizer drugs (8 children; 3.8%). Examination of the association between autism severity and the type of prescribed drugs revealed that both atypical and old-generation antipsychotic drugs are significantly associated with more severe autism (*Bonferroni* corrected *P<0.01;* **Figure 1B**).

Compliance to drugs.

Of the 75 children that received prescription to medications in our sample, 34 children (45.3%) had full compliance with their prescribed drugs, 27 children (36.0%) had partial compliance and 14 children (18.7%) did not comply at all with their drug prescriptions (**Table 2**). Compliance to drugs was not significantly associated with the age, sex and ethnic origin of the children in our sample, although there were fewer Bedouin children that did not comply with their drugs compared to Jewish children (**Table 2**). Children with severe autism had a slightly higher compliance to prescribed drugs than children with moderate and mild autism, but these differences were not statistically significant (**Table 2**). Similarly, there were minor but not significant differences in compliance rates between children with different comorbidities (**Figure 2A**). Finally, high compliance rates were observed for all drugs in our study tranquilizers (85.7%) having the highest compliance rate, followed by old generation antipsychotic drugs (78.1%), stimulants (76.0%), and atypical antipsychotic drugs (74.4%) (**Figure 2B**).

**Discussion**

Autism is a lifelong prevalent pervasive neurodevelopmental disorder that currently has no cure. Prescriptions of psychotropic medications in people with autism are mainly directed to treat specific comorbidities in these people [[28](#_ENREF_28)]. In our study we evaluated the rates of prescription and compliance of psychotropic medications among a sample of children with autism and assessed the effect of different child characteristic on these rates. The prevalence of drug prescription among children with autism in our sample (35.5%) was slightly lower than the reported >40% in other studies [[15-17](#_ENREF_15), [23](#_ENREF_23)]. However, this difference can be explained by the relatively young age of the children in our sample and the notable effect of age on drug prescription in children with autism [[17](#_ENREF_17)]. The most prevalent prescription in our sample was to atypical antipsychotic drugs followed by stimulants. These are also the two most frequently prescribed medications reported in most studies of children with autism (Jobski, 2016 #1546; Park, 2016 #1588}.

Drug prescription was significantly associated with autism severity in our sample. This association is not surprising as families of children with more severe autism are more likely to use health services and seek for treatments that will help them to cope with their symptoms. In addition, autism severity is also affected by the number and severity of associated comorbidities in these children [[29](#_ENREF_29), [30](#_ENREF_30)] of which some have effective treatments that may help reducing the clinical burden from these children (e.g. Melatonin to manage sleep disturbance [[31](#_ENREF_31), [32](#_ENREF_32)]). The effectiveness of different medications on specific symptoms among children with autism is also reflected in our observation that children with certain comorbidities tend to be prescribed more drugs (See Figure 1A). Similar findings were found in a study in North America where >80% of subjects with comorbid bipolar disorder, ADHD, OCD, or anxiety received medications on a regular basis [[33](#_ENREF_33)].

We observed a higher prevalence of drug recommendation among Bedouin children compared to Jewish children. However these ethnic differences are likely attributed to the differences in autism severity between these two populations. Indeed, when we included both ethnic origin and autism severity in the same logistic regression model that predicts drug prescription in our sample, the effect of child ethnicity completely disappeared (OR =1.02 95%, CI = 0.52-1.98, *P* = 0.96). The differences in autism severity between Jewish and Bedouin children in our sample likely stem from underdiagnoses of children with milder forms of autism in the Bedouin population [[34](#_ENREF_34), [35](#_ENREF_35)].

A unique aspect of our study was our ability to monitor the compliance with the prescribed medications in our sample. We observed remarkable differences in compliance rate related to the ethnicity, the autism severity, and the associated comorbidities of the children in our sample. However, none of these differences were statistically significant at the *P*<0.05 level due to the relative small size of our sample. Thus, studies of larger sample sizes will be needed to determine the effect of these characteristics on compliance to drugs among children with autism.

The ethnicity and severity level of children with autism were also associated with the compliance to the drug prescriptions. This may suggest that these medication have a better effect on children with more severe symptoms, however this hypothesis need to be tested in a well-designed clinical trial. Despite the remarkable differences in drug prescriptions that we saw between children with different comorbidities and between different types of medications, no such differences were seen in compliance to drugs among these groups. These results suggest that the severity of the symptoms and not their type and or their prescribed medication determine the compliance of the patient with the prescribed drug in our sample. Importantly, the compliance to the different drug types in our sample ranged between 74.4% (AA) to 85.7% (TRQ). These rates are significantly higher that the compliance rates (40%-52%) reported in another study of children with autism [[36](#_ENREF_36)] or the typical compliance rates for medications among people with other psychiatric conditions [[37](#_ENREF_37)].

Our study has several limitations including the relative small sample size that limits the statistical power to find small effects. In addition, we did not have consent to contact the patients and their families and thus we could evaluate the reasons for their incomplete compliance with the drug recommendation. We also did not have any information regarding non-pharmacological interventions in these children which may have influenced both prescription and compliance to these drugs.

**Conclusions**

Our study provides important information regarding the utilization and compliance rates of drugs that are commonly prescribed to children with autism, in an ethnically unique population. Future studies in larger populations are needed to confirm our finding and test the effect of additional clinical variables on prescription and compliance of medications among children with autism.

**Figure Legends**

**Figure 1:** Prevalence of drug prescription. **A**) Prevalence of drug prescription are depicted for groups of children with different comorbidities (ADHD; Developmental Delay [DD]; Intellectual disability [ID]; Epilepsy; Language impairments [Language]; and Other comorbidities [Others]). **B)** Prevalence of four classes of medications that were prescribed to children with autism in our sample. Atypical antipsychotic [AA] ; Old generation antipsychotic [OGA]; Sleep/tranquilizer [TRQ]; Stimulants [ST.

**Figure 2:** Prevalence of drug compliance. **A**) Levels of drug compliance are depicted for groups of children with different comorbidities in our sample (ADHD; Developmental Delay [DD]; Intellectual disability [ID]; Epilepsy; Language impairments [Language]; and Other comorbidities [Others]). **B)** Compliance rates for four types of drugs recommended to children with autism. Atypical antipsychotic [AA] ; Old generation antipsychotic [OGA]; Sleep/tranquilizer [ST]; Stimulants [S].

**Acknowledgements:**

**References:**

1. Christensen, D.L., et al., *Prevalence and Characteristics of Autism Spectrum Disorder Among Children Aged 8 Years--Autism and Developmental Disabilities Monitoring Network, 11 Sites, United States, 2012.* MMWR Surveill Summ, 2016. **65**(3): p. 1-23.

2. Taylor, B., H. Jick, and D. Maclaughlin, *Prevalence and incidence rates of autism in the UK: time trend from 2004-2010 in children aged 8 years.* BMJ Open, 2013. **3**(10): p. e003219.

3. Sun, X., et al., *Prevalence of autism in mainland China, Hong Kong and Taiwan: a systematic review and meta-analysis.* Mol Autism, 2013. **4**(1): p. 7.

4. Davidovitch, M., et al., *Prevalence and incidence of autism spectrum disorder in an Israeli population.* J Autism Dev Disord, 2013. **43**(4): p. 785-93.

5. Zeglam, A.M. and A.J. Maound, *Prevalence of autistic spectrum disorders in Tripoli, Libya: the need for more research and planned services.* East Mediterr Health J, 2012. **18**(2): p. 184-8.

6. Kuehn, B.M., *Data on autism prevalence, trajectories illuminate socioeconomic disparities.* Jama, 2012. **307**(20): p. 2137-8.

7. Elsabbagh, M., et al., *Global prevalence of autism and other pervasive developmental disorders.* Autism Res, 2012. **5**(3): p. 160-79.

8. Roane, H.S., W.W. Fisher, and J.E. Carr, *Applied Behavior Analysis as Treatment for Autism Spectrum Disorder.* J Pediatr, 2016.

9. Dawson, G., et al., *Randomized, controlled trial of an intervention for toddlers with autism: the Early Start Denver Model.* Pediatrics, 2010. **125**(1): p. e17-23.

10. Wieder, S. and S.I. Greenspan, *Climbing the symbolic ladder in the DIR model through floor time/interactive play.* Autism, 2003. **7**(4): p. 425-35.

11. Brondino, N., et al., *Complementary and Alternative Therapies for Autism Spectrum Disorder.* Evid Based Complement Alternat Med, 2015. **2015**: p. 258589.

12. Perrin, J.M., et al., *Complementary and alternative medicine use in a large pediatric autism sample.* Pediatrics, 2012. **130 Suppl 2**: p. S77-82.

13. Adams, J.B., et al., *Safety and efficacy of oral DMSA therapy for children with autism spectrum disorders: part B - behavioral results.* BMC Clin Pharmacol, 2009. **9**: p. 17.

14. Rossignol, D.A., *Hyperbaric oxygen therapy might improve certain pathophysiological findings in autism.* Med Hypotheses, 2007. **68**(6): p. 1208-27.

15. Jobski, K., et al., *Use of psychotropic drugs in patients with autism spectrum disorders: a systematic review.* Acta Psychiatr Scand, 2016.

16. Lake, J.K., et al., *Psychotropic medication use among adolescents and young adults with an autism spectrum disorder: parent views about medication use and healthcare services.* J Child Adolesc Psychopharmacol, 2015. **25**(3): p. 260-8.

17. Madden, J.M., et al., *Psychotropic Medication Use among Insured Children with Autism Spectrum Disorder.* J Autism Dev Disord, 2016.

18. (FDA), U.F.D.A., *Approved product information.* , 2014: US National Library of Medicine.

19. McCracken, J.T., et al., *Risperidone in children with autism and serious behavioral problems.* N Engl J Med, 2002. **347**(5): p. 314-21.

20. Farmer, C.A. and M.G. Aman, *Aripiprazole for the treatment of irritability associated with autism.* Expert Opin Pharmacother, 2011. **12**(4): p. 635-40.

21. Aman, M.G., K.S. Lam, and M.E. Van Bourgondien, *Medication patterns in patients with autism: temporal, regional, and demographic influences.* J Child Adolesc Psychopharmacol, 2005. **15**(1): p. 116-26.

22. Frazier, T.W., et al., *Prevalence and correlates of psychotropic medication use in adolescents with an autism spectrum disorder with and without caregiver-reported attention-deficit/hyperactivity disorder.* J Child Adolesc Psychopharmacol, 2011. **21**(6): p. 571-9.

23. Mire, S.S., et al., *Psychotropic medication use among children with autism spectrum disorders within the Simons Simplex Collection: are core features of autism spectrum disorder related?* Autism, 2014. **18**(8): p. 933-42.

24. Schubart, J.R., F. Camacho, and D. Leslie, *Psychotropic medication trends among children and adolescents with autism spectrum disorder in the Medicaid program.* Autism, 2014. **18**(6): p. 631-7.

25. Association, A.P., *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)*. 2000, Arlington: American Psychiatric Publishing.

26. American Psychiatric, A., *Diagnostic and Statistical Manual of Mental Disorders:: DSM-5*. 2003: ManMag.

27. Nirel, N., et al., *[OFEK virtual medical records: an evaluation of an integrated hospital-community system].* Harefuah, 2011. **150**(2): p. 72-8, 209.

28. Gerhard, T., et al., *National patterns in the outpatient pharmacological management of children and adolescents with autism spectrum disorder.* J Clin Psychopharmacol, 2009. **29**(3): p. 307-10.

29. Adams, J.B., et al., *Toxicological status of children with autism vs. neurotypical children and the association with autism severity.* Biol Trace Elem Res, 2013. **151**(2): p. 171-80.

30. Tureck, K., et al., *Autism severity as a predictor of inattention and impulsivity in toddlers.* Dev Neurorehabil, 2015. **18**(5): p. 285-9.

31. Leu, R.M., et al., *Relation of melatonin to sleep architecture in children with autism.* J Autism Dev Disord, 2011. **41**(4): p. 427-33.

32. Rossignol, D.A. and R.E. Frye, *Melatonin in autism spectrum disorders: a systematic review and meta-analysis.* Dev Med Child Neurol, 2011. **53**(9): p. 783-92.

33. Coury, D.L., et al., *Use of psychotropic medication in children and adolescents with autism spectrum disorders.* Pediatrics, 2012. **130 Suppl 2**: p. S69-76.

34. Mahajnah, M., et al., *Clinical characteristics of autism spectrum disorder in Israel: impact of ethnic and social diversities.* Biomed Res Int, 2015. **2015**: p. 962093.

35. Raz, R., et al., *Differences in Autism Spectrum Disorders Incidence by Sub-Populations in Israel 1992-2009: A Total Population Study.* J Autism Dev Disord, 2014.

36. Logan, S.L., et al., *Rates and predictors of adherence to psychotropic medications in children with autism spectrum disorders.* J Autism Dev Disord, 2014. **44**(11): p. 2931-48.

37. Osterberg, L. and T. Blaschke, *Adherence to medication.* N Engl J Med, 2005. **353**(5): p. 487-97.