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

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**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. In this study we examined the prevalence and patterns of drug prescription and compliance among young children with autism in south Israel.

**Methods**: We studied the patterns associated with drug prescription and compliance in a population-based sample of young children (ages 1-6 years) with autism, for 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. 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 older antipsychotic drugs (16 children; 7.6%). Of the 75 children in our sample who received prescriptions for medications, almost half (45.3%) had full compliance, and only 18.7% did not comply at all with their drug prescription. 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 findings indicate that prescription of drugs 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, or the 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 or her into the world of ideas and abstract thinking. These behavioral interventions are usually supported by complementary and alternative therapies such as speech, occupational, or 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)] or hyperbaric oxygen treatments [[14](#_ENREF_14)]. Their proponents claim that these treatments significantly improve the clinical condition of these children. However, robust evidence is lacking for the efficacy of these supplements in treating autism.

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 quality of life 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 to those whose age ≥5 years. The main adverse effects include 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 include 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 efficacy of the psycho-pharmacological treatment, the prevalence of drug treatment for children with autism has been increasing [[21](#_ENREF_21), [22](#_ENREF_22)]. A number of studies have 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 prescription of drugs and have limited data regarding factors associated with the compliance with these prescriptions. For this reason, 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 prescription of drugs and compliance rates among these children.

**Materials and Methods**

Population

About 700,000 people are found in the Negev region in the south of Israel. About 60% of the population is 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 who provided 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)]. 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 medical staff to access their respective application or designated dataset. Data about drug prescription and purchase frequency were retrieved from the OFEK electronic medical records system, [[27](#_ENREF_27)] which is an on-line information system that contains electronic medical records from all health service providers in Israel (i.e. hospitals and clinics, drugstores, medical labs, etc.). Medications were classified into the following four categories: 1) Atypical antipsychotic drugs (AA); 2) Older antipsychotic drugs (OGA); 3) Stimulants (ST); 4) Sleep/tranquilizer (TRQ).

Compliance rates

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 as one of 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 with 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 were neither Jewish nor 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

Association between basic demographic and clinical characteristics with prescription of drugs among the children with autism in our sample are depicted in **Table 1**. A total of 95 prescriptions were made for these children as follows: 50 children (23.7%) received a prescription for one type of drug, 19 (9.0%) received a prescription for two types of drugs, and six (2.8%) received prescriptions for 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 or gender of the children in our sample.

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

As could be 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 atypical antipsychotic drugs (49 children; 23.2%), followed by stimulants (28 children; 13.3%), older antipsychotic drugs (16 children; 7.6%), and tranquilizers(8 children; 3.8%). Examination of the association between autism severity and the type of prescribed drugs revealed that both atypical and older antipsychotic drugs are significantly associated with more severe autism (*Bonferroni* corrected *P<0.01;* **Figure 1B**).

Prescription compliance.

Of the 75 children who received prescriptions in our sample, 34 children (45.3%) had full compliance with their prescribed drugs, 27 (36.0%) had partial compliance and 14 (18.7%) did not comply at all with their prescription of drugs (**Table 2**). Prescription compliance was not significantly associated with age, sex, or ethnic origin of the children in our sample, although there were fewer Bedouin children that did not comply with their prescriptions compared to Jewish children (**Table 2**). Children with severe autism had a slightly higher compliance 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%) had the highest compliance rate, followed by older antipsychotic drugs (78.1%), stimulants (76.0%), and atypical antipsychotic drugs (74.4%) (**Figure 2B**).

**Discussion**

Autism is a lifelong, 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 characteristics on these rates. The prevalence of drug prescription among children with autism in our sample (35.5%) was slightly lower than the reported 40% or more 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 highest rate of prescription in our sample was for 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 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)]. Some of these comorbidities have effective treatments that may help reduce the clinical burden for 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 more than 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 prescriptions 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 the monitoring of the compliance with the prescribed medications in our sample. We observed remarkable differences in compliance rate related to ethnicity, autism severity, and the comorbidities of the children in our sample. However, none of these differences were statistically significant at the *P*<0.05 level due to the relatively small size of our sample. Thus, studies with larger sample sizes will be needed to determine the effect of these characteristics on compliance with prescription of drugs among children with autism.

The ethnicity and severity of autism were also associated with the compliance with the drug prescriptions. This may suggest that these medications have a greater effect on children with more severe symptoms, however this hypothesis needs 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 with compliance among these groups. These results suggest that the severity of the symptoms and not their type or the medication prescribed determine the compliance of the patient with the prescribed drug. It is worth noting that the compliance for the different drug types in our sample ranged between 74.4% (AA) to 85.7% (TRQ). These rates are significantly higher than the compliance rates (40%-52%) reported in another study of children with autism [[36](#_ENREF_36)] or the typical compliance rates for medication among people with other psychiatric conditions [[37](#_ENREF_37)].

Our study has several limitations including the relatively 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 not investigate 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 with these drugs.

**Conclusions**

Our study provides important information regarding the utilization and compliance rates of drugs that are commonly prescribed for children with autism, in an ethnically unique population. Future studies in larger populations are needed to confirm our findings and test the effects of additional clinical variables on prescription and medication compliance 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] ; Older 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] ; Older antipsychotic [OGA]; Sleep/tranquilizer [ST]; Stimulants [S].

**Acknowledgements:**

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