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S.I. : AUTISM INPATIENT COLLECTION - STUDYING THE SEVERELY AFFECTED

Characterization of Medication Use in a Multicenter Sample of Pediatric Inpatients with Autism Spectrum Disorder

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Abstract Nearly 11% of youth with Autism Spectrum Disorder (ASD) undergo psychiatric hospitalization, and 65% are treated with psychotropic medication. Here we characterize psychotropic medication usage in subjects enrolled in the Autism Inpatient Collection. Participant psychotropic medication usage rates topped 90% at admission and discharge, though there was a decline at 2-month follow-up. Antipsychotics, ADHD medications, and sleep aids were the most commonly reported classes of medications. The impact of age, gender, and non-verbal IQ on medication usage rates was minimal, though age and IQ may play a role in prescribing practices. Future work is indicated to explore medication usage trends, the impact of clinical factors on medication use rates, and the safety of psychotropic medications in youth with ASD.

Keywords Autism · Autism Spectrum Disorder · Medication · Antipsychotics · Psychiatric hospitalization

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Introduction

Youth with Autism Spectrum Disorder (ASD) are admitted to psychiatric hospitals at startlingly high rates, with recent research reporting nearly 11% of youth with ASD hospitalized before reaching 21 years of age (Mandell 2008). The primary predictors of psychiatric hospitalization in youth with ASD are aggressive and self-injurious behavior, inadequate social supports (i.e. single-parent homes), and psychiatric co-morbidities (Siegel and Gabriels 2014). For patients with ASD that suffer from severe behavioral symptoms including hyperactivity, impulsivity, mood lability, and irritability (defined as aggression, self-injury, and severe tantrums), psychotropic medication treatment is evidence-based and often initiated. Two second generation antipsychotic medications, risperidone and aripiprazole, have been approved by the United States Food and Drug Administration for the treatment of irritability in youth with ASD following several large placebo-controlled trials (Marcus et al. 2009; McCracken et al. 2002; Owen et al. 2009). There is also strong evidence supporting the use of stimulant medications for treatment of hyperactivity, inattention, and impulsivity in this population (Research Units on Pediatric Psychopharmacology Autism 2005). Furthermore, antidepressants, mood stabilizers, anticonvulsants, and alpha-2 agonists are frequently employed to treat psychiatric co-morbidities and behavioral concerns in this patient population (Erickson et al. 2007; Politte et al. 2014; Wink et al. 2010).

Psychotropic drug usage rates in youth with ASD are climbing. Recent analyses of data from Medicaid and United States commercial healthcare claims databases demonstrate that nearly 65% of outpatient youth with ASD are prescribed at least one psychotropic medication, with antipsychotics being the most frequently prescribed drug class (Schubart et al. 2014; Spencer et al. 2013). Park et al. recently published a meta-analysis of antipsychotic use in over 350,000 youth, and identified that nearly 1 in 10 antipsychotic treated youth were diagnosed with ASD and/or intellectual disability (Park et al. 2016). Antipsychotic polypharmacy rates (use of more than one antipsychotic concomitantly) in youth with ASD also appear to be climbing, with Schubart et al. reporting frequencies of 6.2% in 2000 and 8.7% in 2003 (Schubart et al. 2014). A 2014 study by Saldana et al., which reviewed data on antipsychotic prescribing practices at discharge from pediatric inpatient psychiatric hospitalization, reported that diagnoses of intellectual or developmental disorders (including ASD) correlated with higher rates of antipsychotic polypharmacy (Saldana et al. 2014). Despite the prevalence of psychiatric hospitalization and psychotropic medication, to date we have minimal specific information on inpatient psychotropic usage in youth with ASD.

In this report we undertake preliminary characterization of psychotropic medication use in subjects enrolled in the Autism Inpatient Collection (AIC). The climbing rate of ASD diagnoses (Christensen 2016), relative high frequency of psychiatric hospitalization in this population (Mandell 2008), and growing use of pharmacologic treatment (Schubart et al. 2014), make this data imperative to future work focused on improving efficacy of treatment and reducing burden of care in ASD. Based on our clinical experience with this severely affected patient population, we hypothesized that the vast majority of enrolled study participants would be treated with at least one psychotropic medication and that antipsychotics would be the most frequently employed class. Furthermore, we hypothesized that, with the experience and expertise in both behavioral and psychopharmacologic interventions provided by these specialized inpatient psychiatric units, psychotropic medication rates would decrease from admission to discharge and medication usage rates would remain stable at 2-month post-hospitalization follow-up. Finally, we anticipated that gender, age, and non-verbal intellectual functioning (IQ) of enrolled participants would potentially serve as meaningful moderators of medication usage.

Methods

Participants and Procedures

The AIC is a multi-site study enrolling youth ages 4–20 years admitted to one of six specialized psychiatric hospital units for youth with autism and other developmental disorders. The sites employ an interdisciplinary treatment plan that includes intensive behavioral training, parent education, and medication evaluation (McGuire et al. 2015). Enrollment in the AIC began in March of 2014 and continues at a rate of over 400 subjects per year. The methods for this ongoing study have been previously described (Siegel et al. 2015). Briefly, youth with a score of ≥12 on the Social Communication Questionnaire (Rutter et al. 2003) or referral by the inpatient team due to suspicion of ASD were eligible for study enrollment. ASD diagnosis was confirmed by research-reliable administration of the Autism Diagnostic Observation Schedule, Second Edition (ADOS-2) (Lord et al. 2012). The overall research goal of the AIC focuses on phenotypic and genetic description of enrolled subjects including adaptive and cognitive functioning, measures of externalizing behaviors and emotion regulation, description of psychiatric and medical co-morbidities, and measures of parental stress. Biologic samples from enrolled subjects and their biological parents are banked and processed for later genomic study. Ultimately, the full AIC dataset and bio-samples will be made available

to approved investigators through the Simons Foundation (http://www.sfari.org).

Data Collection and Measures

In the present report we analyzed medication usage data drawn from AIC participants enrolled through January 15, 2016. All subjects in this subset were recruited and met admission criteria per the AIC protocol. Demographic and behavioral data was collected from all participants per study protocol including ASD diagnostic confirmation via the ADOS-2 (Lord et al. 2012), intellectual functioning assessment via the Leiter International Performance Scale, Third Edition (Leiter-3) (Roid et al. 2013), adaptive functioning assessment via the Vineland Adaptive Behavior Scales, Second Edition (VABS-II) (Sparrow et al. 2008), and behavioral assessment via the Aberrant Behavior Checklist (Aman et al. 1985). To capture medication usage patterns in this patient population, a detailed review of all medications reported at time of admission, those prescribed at discharge, and all medications reported at 2-months post-hospitalization was completed for each enrolled subject. Medications were coded and classified into 6 psychotropic drug classes (see Online appendix for a comprehensive list of reported medications and classifications). Additionally, due to common gastrointestinal (GI) co-morbidities in ASD (i.e. constipation or dyspepsia) (McElhanon et al. 2014; Molloy and Manning-Courtney 2003), and the metabolic and GI impact of certain psychotropic medications, we chose to include data on metformin and GI drugs to further explore this relationship. Information on prescribed medications that did not fall into one of the defined psychotropic, GI, or metformin classes was excluded from this analysis (see Online appendix for full list of "other" excluded medications).

Statistical Analysis

Descriptive statistics were calculated using means and standard deviations for continuous variables and numbers and proportions for categorical variables. We examined medication usage trends in study participants in two ways. First we examined the total number of psychotropic medications prescribed for each individual (i.e. the sum of all psychotropic medications reported across the defined categories) at each time period. Second, to examine medication class data, we calculated, for each of the categories of medications (including GI medications and metformin), a yes (i.e. reported taking at least one medication from that category) /no (i.e. did not report taking any medications from that category) separately for each time period. To examine the main study questions, we tested changes in the frequency of use for both total number of medications and by drug class from admission to discharge (during hospitalization) and change from discharge to 2-month follow-up (post-hospitalization) using paired sample *t* tests (total number of medications) and McNemar Chi square tests (drug category). Finally we reviewed the impact of age, sex, and non-verbal IQ on frequency of medications reported at each time point (both in total and by drug class) using *t* tests and Chi square analyses. All analyses were conducted using SPSS version 24.0 with statistical significance determined at $p \leq 0.05$, two-tailed tests. This work was approved by the Institutional Review Boards at each of the ADDIRC sites participating in the AIC.

Results

Data on 350 participants was available and included in the final analysis. The mean age of study participants was 12.9 years (SD = 3.3, range 4–21 years), 79% of the sample was male, and the population was 79% Caucasian (demographic detail and baseline behavioral assessments detailed in Table 1). The mean non-verbal IQ of participants as measured by the Leiter-3 was 74.9 (n = 274, SD = 28.2, range 30–145). Study participants had significantly impaired expressive language skills, with scores on the expressive communication subscale of the VABS-II in the very low range (mean score 7.1, n = 256, SD 4.5, range 1–24). Participants additionally scored in the very low range on the adaptive behavior composite of the VABS-II which evaluates communication, daily living skills, socialization, and motor skills (mean score 57.5, n = 220, SD 15.1, range 25–118). The mean Aberrant Behavior Checklist – Irritability (ABC-I) subscale score at admission was 27.4 (n = 307, SD = 9.4, range = 2–45) which was well above the typical entry criteria score of 16 for treatment studies targeting externalizing problem behaviors such as irritability and hyperactivity. The average length of hospital stay was 25.6 days (SD = 23.8, range 3–163 days).

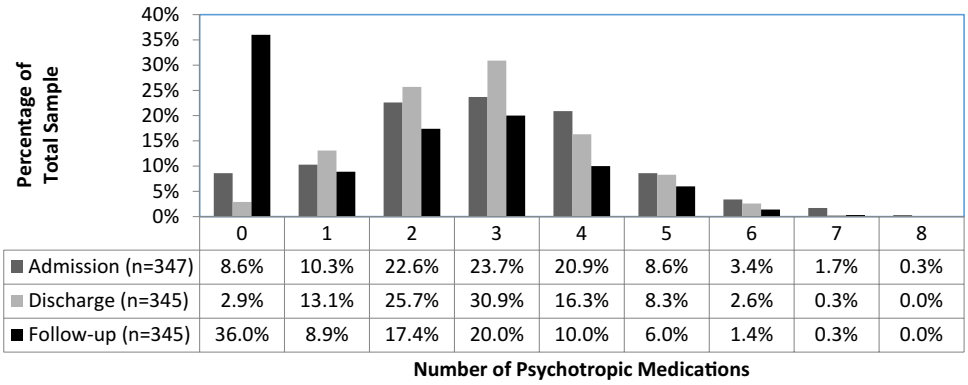
At admission 91.4% of participants were taking one or more medications from the 6 psychotropic drug classes (n = 347, M = 2.88, SD = 1.6, Fig. 1). Antipsychotics were the most frequently employed class of medication at admission (63.7%), followed by ADHD medications (45.7%), and sleep aids (43.4%, Fig. 2). At discharge, 97.1% of participants were taking one or more medications from the 6 psychotropic classes (n = 345, M = 2.81, SD = 1.3), with antipsychotics being the most employed class of medications (67.4%), followed by sleep aids (46.0%), and ADHD medications (44.3%). Just over 10% of participants were taking one or more GI medications at admission, and this increased to 16.0% at discharge. Metformin use remained stable from admission to discharge at just under 5% of study participants. Two-months post-hospitalization, only

Table 1 Demographic data

	Overall sample (N = 350)		Males (N = 275, 79%)		Females (N = 75, 21%)		p value
Age (years) (M(SD), range)	12.9 (3.3)	4–21	12.9 (3.4)	4–21	12.8 (2.9)	6–18	0.76
Ethnicity (N = 314) (Non-Hispanic/Latino) (N/%)	292 (93%)		228 (92%)		64 (96%)		0.36
Race (Caucasian) (N/%)	276 (79%)		217 (79%)		59 (79%)		0.96
Length of hospital stay (M(SD), range)	25.6 (23.8)	3-163	25.9 (22.2)	3-130	24.7 (29.0)	4-163	0.69
Non-verbal IQ (N = 287) (M(SD), range)	76.4 (28.9)	30–145	75.5 (28.8)	30–145	73.2 (29.4)	30–141	0.60
Intellectual disability (NVIQ ≤ 70) (N/%)	116 (42%)		94 (44%)		22 (38%)		0.44
Expressive communication subscale (Vineland-2) (N = 256) (M(SD), range)	7.1 (4.5)	1–24	7.2 (4.7)	1–24	6.9 (3.7)	1–17	0.67
Adaptive behavior composite (Vineland-2) (N = 220) (M(SD), range)	57.5 (15.1)	25–118	57.8 (15.3)	25–118	56.1 (14.4)	28–87	0.49
ADOS-2 module administered (N = 346) (N/%)							
1	127 (36%)		101 (37%)		26 (35%)		0.84
2	42 (12%)		31 (11%)		11 (15%)		
3	144 (42%)		113 (42%)		31 (42%)		
4	33 (10%)		27 (10%)		6 (8%)		
Aberrant behavior checklist (ABC) subscale scores (N = 307)							
Admission (N = 307) (M(SD), range)							
Irritability	27.4 (9.4)	2–45	26.8 (9.3)	2–45	29.7 (9.6)	5–45	0.03*
Lethargy	15.3 (8.4)	0–44	15.1 (8.5)	0–44	15.9 (8.1)	1–39	0.51
Stereotypy	7.9 (5.6)	0–20	7.8 (5.5)	0–20	8.6 (5.7)	0–20	0.31
Hyperactivity	28.6 (10.6)	0–47	28.7 (10.6)	0–47	28.2 (10.4)	4–47	0.73
Inappropriate speech	5.3 (3.6)	0–12	5.0 (3.6)	0–12	6.2 (3.7)	0–12	0.03*
Discharge (N = 251) (M(SD), range)							
Irritability	15.7 (10.4)	0–43	15.9 (10.4)	0–43	15.0 (10.3)	0–40	0.58
Hyperactivity	18.1 (12.3)	0–46	18.6 (12.4)	0–46	16.3 (11.5)	0–45	0.21
2-month follow-up (N = 223) (M(SD), range)							
Irritability	19.5 (10.4)	0–44	19.5 (10.5)	0–44	19.3 (10.2)	1–42	0.92
Hyperactivity	22.4 (11.1)	0–46	22.8 (11.0)	1–46	20.8 (11.5)	0–46	0.28
Self-injurious behavior (SIB) present (N = 76) (N/%)	76 (22%)		58 (21%)		20 (27%)		0.40
Repetitive behavior scale revised (RBS-R) self-injury subscale score for subjects with sib present (N = 76) (M(SD), range)	11.5 (4.8)	0–23	11.0 (4.8)	0–23	12.8 (4.8)	6–22	0.16

64% of participants reported taking one or more medications from the 6 psychotropic classes (n = 345, M = 1.84, SD = 1.7), though antipsychotics remained the most frequently employed class of medication at this time point (46.6%), followed by ADHD medications (30.0%) and sleep aids (27.7%). Use of GI medication decreased by nearly half (down to 7.4%) at 2-month follow-up, and metformin usage remained fairly stable (4.0%). Figure 1 suggests a trend toward decreasing frequency of psychotropic medication usage from discharge to 2-month follow-up due to an increase in the number of participants taking no medications from the defined classes.

Psychotropic polypharmacy (use of more than one concomitant psychotropic medication) was found across all three time points (admission M = 2.88, SD = 1.6; discharge M = 2.81, SD = 1.3; 2-month follow-up M = 1.84, SD = 1.7). More than half of all youth were taking more than one psychotropic medication at all timepoints (see Fig. 1). The mean frequency of reported psychotropic medications per study participant remained stable from



	0	1	2	3	4	5	6	7	8
Admission (n=347)	8.6%	10.3%	22.6%	23.7%	20.9%	8.6%	3.4%	1.7%	0.3%
Discharge (n=345)	2.9%	13.1%	25.7%	30.9%	16.3%	8.3%	2.6%	0.3%	0.0%
Follow-up (n=345)	36.0%	8.9%	17.4%	20.0%	10.0%	6.0%	1.4%	0.3%	0.0%

Fig. 1 Frequency of psychotropic medication usage for the total sample at admission, discharge, and 2-month follow-up

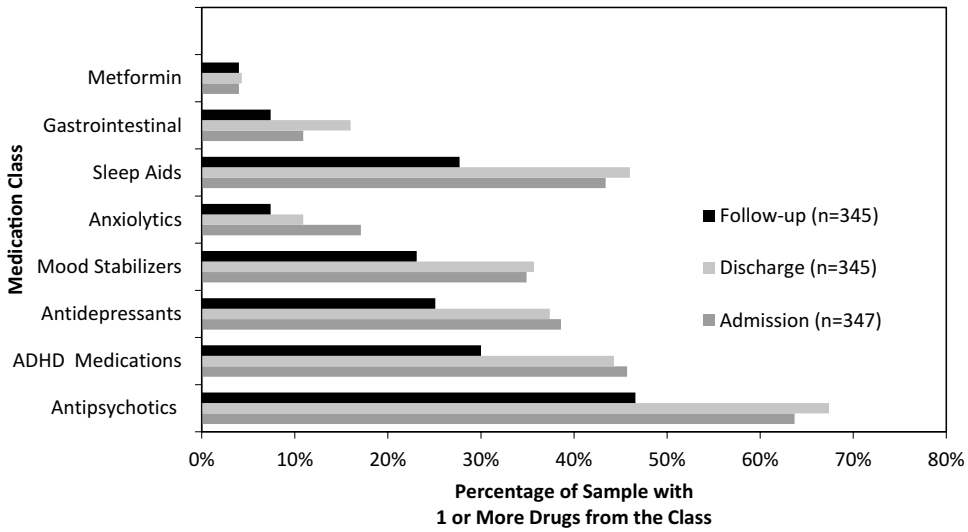


Fig. 2 Frequency of taking at least one drug from each drug category at admission, discharge, and two-month follow-up

Table 2 Change from admission to discharge in taking at least one drug from each medication class

	Percent of total sample ($n=345$)				McNemar test
	Never	Started	Stopped	Stable	
Antipsychotics	21.4	14.9	11.1	52.6	1.86
ADHD medications	46.0	8.3	9.7	36.0	0.40
Antidepressants	50.6	10.9	12.0	26.5	0.20
Mood stabilizers	56.3	8.9	8.0	26.8	0.15
Anxiolytics	80.6	2.3	8.6	8.6	12.74***ˇ
Sleep aids	47.1	9.4	6.9	36.6	1.42
Gastrointestinal	82.6	6.6	1.4	9.4	11.57***^
Metformin	94.6	1.4	1.1	2.9	0.11

Never = no drug during admission or discharge, Started = no drug during admission and taking drug at discharge, Stopped = taking drug at admission and no drug at discharge, Stable = taking drug at admission and discharge

*$p<0.05$; **$p<0.01$; ***$p<0.001$

ˇSignificantly more likely to be stopped

^Significantly more likely to be started

admission to discharge (t (343) = 0.94, p > 0.34). However, there was a significant reduction in the mean total number of psychotropic medications reported per patient between discharge and 2-months post-hospitalization (t (343) = 10.85, p < 0.001).

To further understand the trends in medication usage, we calculated frequencies of participants who *never* reported taking a medication, *started* taking a medication, *stopped* taking a medication, or were *stable* on a medication for each medication class during two distinct time periods: during hospitalization (from admission to discharge), and post-hospitalization (from discharge to 2-month follow-up, Tables 2, 3). During hospitalization, 52.6% of participants were stably treated with an antipsychotic, and nearly half of the sample did not take a medication from any of the other medication classes. Antipsychotics were the most frequently started drugs during hospitalization (14.9%), but antipsychotics were also often stopped during the same time period (11%). Antidepressants were the second most frequently started medication class during hospitalization (10.9%), but

Table 3 Change from discharge to 2-month follow-up in taking at least one drug from each medication class

	Percent of total sample ($n=345$)				McNemar Test
	Never	Started	Stopped	Stable	
Antipsychotics	29.7	2.9	23.7	43.7	57.30***ˇ
ADHD medications	52.6	3.1	17.4	26.9	34.72***ˇ
Antidepressants	59.4	3.2	15.4	22.0	28.45***ˇ
Mood stabilizers	62.6	1.7	14.3	21.4	34.57***ˇ
Anxiolytics	87.1	2.0	5.4	5.4	5.53*ˇ
Sleep aids	50.6	3.4	21.7	24.3	46.54***ˇ
Gastrointestinal	83.4	0.6	9.1	6.9	26.47***ˇ
Metformin	94.6	1.1	1.4	2.9	0.11

Never = no drug during discharge or follow-up, Started = no drug during discharge and taking drug at follow-up, Stopped = taking drug at discharge and no drug at follow-up, Stable = taking drug at discharge and follow-up

*$p<0.05$; **$p<0.01$; ***$p<0.001$

ˇSignificantly more likely to be stopped

also the most frequently stopped medication class during this time period (12.0%). There was a significant change noted via McNemar Chi square analysis of change for anxiolytic usage (more likely to be stopped; McNemar Chi square = 12.74, $p<0.001$) and GI medication usage (more likely to be started; McNemar Chi square = 11.57, $p<0.001$) during hospitalization. Post-hospitalization, there was a noted global reduction in psychotropic medication use, with antipsychotics being the most frequently discontinued class of medication (23.7%) followed by sleep aids (21.7%) and ADHD medications (17.4%). Few medications from any class were started post-hospitalization, and all drug classes (with the exception of metformin) were significantly likely to be stopped during this time period.

Finally, we analyzed the impact of age, nonverbal IQ (NVIQ), and gender on medication usage in the study population. Overall, the total number of medications at each time point did not correlate with any of the three demographic factors (AGE: all rs <0.11, ps >0.06; NVIQ: all rs <0.03, ps >0.57; GENDER: all t values <0.58, ps >0.56). Of interest, however, age and NVIQ impacted medication usage at certain time points. On average, the cohort taking ADHD medications were younger that those not taking this class of medication (discharge $t=2.33$, $p<0.05$ and at 2-months $t=2.28$, $p<0.05$). Participants taking antidepressants (admission $t=2.62$, $p<0.01$ and discharge $t=2.13$, $p<0.05$), mood stabilizers (admission $t=3.56$, $p<0.001$, discharge $t=2.61$, $p<0.01$, and 2-months $t=2.65$, $p<0.01$.), anxiolytics (admission $t=4.21$, $p<0.001$, follow-up $t=3.61$, $p<0.001$), and metformin (discharge $t=2.39$, $p<0.05$, 2-months $t=2.37$, $p<0.05$) were older than those not taking medications from these classes. In addition, the mean NVIQ of those taking ADHD medication and antidepressants was higher than those not taking a medication from these two classes (ADHD medication: admission $t=2.70$, $p<0.01$, discharge $t=2.62$, $p<0.01$, 2-months $t=2.10$, $p<0.05$, antidepressants: admission $t=2.36$, $p<0.05$, discharge $t=3.81$, $p<0.001$, and 2-months $t=2.27$, $p<0.05$). No difference in gender was identified between those who did and did not report taking a medication from each medication class at any of the three time points (all Chi-squares <2.91, ps >0.09).

Discussion

This is the first study to prospectively capture psychotropic medication usage data for a large number of youth with ASD admitted to inpatient psychiatric facilities. The overall goal of this multi-site, characterization study was to better understand usage patterns of psychotropic medication in this severely affected patient population and provide future hypotheses for investigation. As expected, we observed that the vast majority (91.7%) of participants were treated with a least one psychotropic medication during the course of the study, much higher than the 65% rate of psychotropic use described in outpatient reports. Antipsychotics were the most frequently employed class of medication throughout our study, which is not surprising given that the acute behavioral crises that precipitate inpatient admission often involve symptoms of irritability, as well as the magnitude of research demonstrating the ability of antipsychotics to mitigate these behaviors (Fitzpatrick et al. 2016; McCracken et al. 2002). Furthermore, the relatively high usage rates of antidepressants, ADHD medications, and sleep aids in this cohort is consistent with the known psychiatric co-morbidities that impact many individuals with ASD (Research Units on Pediatric Psychopharmacology Autism 2005; Vasa et al. 2014). Finally, psychotropic polypharmacy was highly prevalent, with over half of study participants taking more than one psychotropic medication at all study time points. This high psychotropic polypharmacy rate coupled with the elevated ABC – I ratings at admission, indicates that this study captured a highly treatment refractory population.

We expected that the behavioral treatment and expert psychopharmacology provided at our specialized psychiatric inpatient facilities would result in reduction in total psychotropic medication usage in participants from admission to discharge. However, this was not this case in our analysis. Participants remained on relatively stable numbers of psychotropic medications from admission to discharge, with 52.6% of participants continuing an antipsychotic

throughout the study. The specific reasons for this lack of change were not elicited in this study, but may underscore the severity of behavior, psychiatric co-morbidities, functional impairment, and treatment refractory nature of youth with ASD requiring psychiatric hospitalization. We also did not collect data on dosage, which may have changed across time points. The reduction in medication use across our 8 categories from discharge to 2-month follow-up was surprising, particularly that 23% of participants discontinued antipsychotics during this time period. This may indicate improved behavioral patterns post-discharge (including potentially effective implementation of new behavioral plans), differing prescribing practices between inpatient and outpatient psychiatric prescribers, adverse effects noted post-discharge, completion of medication tapers initiated during admission, or parent/caregiver preference (including non-compliance or self-discontinuation). Additionally, the reduction in sleep aids and GI medications post-discharge may indicate a return to normal sleep and bowel function that had temporarily been disrupted by hospitalization. While the etiology of the mean decrease in medication usage in the 2 months post-discharge is unclear, the appearance of a decrease rather than a substitution of new medications, may indicate that the reduction is partially due to overall improvement in symptomatology. This change in medication management post-discharge is striking and an area that needs further exploration, as it is a public health priority to reduce medication burden and increase effective treatment in ASD.

The impact of age, gender, and NVIQ on medication usage rates was minimal in our patient population with no impact on mean medication frequency usage across the time points. However, we must note that we were unable to collect NVIQ data on some participants (n = 63), and this may have impacted the results of this analysis. Additionally, our study suggests that age may play a role in prescribing practices, as antidepressants, mood stabilizers, anxiolytics, and metformin were more frequently reported in older participants, and ADHD medication usage more common in younger. This is consistent with clinical experience, as inattention and hyperactivity are often more significant concerns in younger children, while mood, anxiety, and weight gain tend to become greater issues as children age. Additionally in this study, participants with higher non-verbal IQs appeared more likely to be treated with ADHD medications and antidepressants. Again this is consistent with clinical experience as identifying and treating these symptoms is more straight forward in youth who can communicate their internal experience. Furthermore, the documented risk of irritability with these medication classes in youth with ASD may make prescribers hesitant to use these medications in youth whose symptomatology is more unclear (King et al. 2009; Research Units on Pediatric Psychopharmacology Autism 2005). Unfortunately in this study, the effects of gender, age, and non-verbal IQ on changes in medication use within each drug class (i.e., changes in use from admission and discharge and changes from discharge to follow-up) could not be tested due to small cell sizes, which is an area for further exploration in future studies. Future exploration of behavioral factors such as irritability and hyperactivity levels as captured on the ABC subscales, as well as duration of hospitalization, as potential moderators of psychotropic medication use will be important in guiding future treatment trials for those with treatment refractory presentations.

In this preliminary analysis, treatment with GI medications in 10–15% of study participants highlights the significance of GI concerns in this patient population. The trends toward increasing use of GI medications during hospitalization and subsequent reduction post-discharge are interesting and suggest the need for further exploration. These trends may suggest that GI concerns are more aggressively addressed by hospital prescribers or that the needs of participants change as they transition back to their home environments. These trends also may suggest increasing need for treatment of GI concerns (constipation) with increasing frequency of antipsychotic use, and reduction of GI symptoms with decreased frequency of this drug class post-discharge. The use of metformin in 4–5% of our study population is also striking, and would benefit from further exploration. Examination of why subjects are prescribed this medication, analysis of its efficacy and tolerability in this patient population, measuring the impact of metformin on body mass index, and investigating its relationship to antipsychotic drug use are paths of future exploration. Future work capturing details of medication-related adverse effects, both type and frequency, in this severely affected and treatment refractory patient population also will be meaningful in guiding both clinical treatment and future research.

Interpretation of our study results must be completed in the context of the study's limitations. First, the results of this study represent youth inpatient care within a specialized setting and attended by clinicians who are familiar with ASD, and therefore may not generalize to more conventional psychiatric inpatient facilities. Second, though we have rigorously captured medication names and classifications, there was variability in how and when this information was obtained between sites (i.e. one site used parent report at admission, while the others captured admission medications as prescribed by the attending psychiatrist). Additionally, we had to make hard choices in categorizing medications, which due to sample size resulted in imperfect lumping of some medications by drug type (antipsychotics) and others by symptom target (ADHD medications/

sleep aids). Future studies with larger sample sizes may better be able to examine medication usage more specifically via categorization by mechanism of action (i.e. typical antipsychotics, atypical antipsychotics, stimulants, alpha-2 agonists, benzodiazepines, lithium, anti-epileptics, valproic acid, etc.). We were also unable to reliably obtain dosing information, and our study does not adequately capture medication changes made within drug classes. These factors may have impacted study results and should be addressed in future endeavors.

Conclusion

The high rates of psychotropic medication usage coupled with elevated psychometrics indicating severe behavior noted in this study underscore the high burden of disease within our patient population. Despite intensive and expert behavioral intervention and training at all AIC sites, for the majority of individuals, the frequency of medication use remained fairly constant from admission to discharge, and declined 2 months post-discharge. Thus, we can say with some certainty that medication treatment remains a central aspect of inpatient psychiatric care in this population, and hospitalization in the participating programs is associated with decreased medication use 2 months after discharge. The current study design and results provide descriptive data regarding medication use, but are limited in their ability to address the causal impact of medication changes on behavioral metrics. Nevertheless, we found valuable trends in medication usage, particularly the striking decrease in medication usage reported post-hospitalization, which will help guide future studies.

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Author Contributions LW participated in acquisition of the data, drafting and revision of the manuscript, and approval of the final draft. EP, CE, EM, and DK participated in acquisition of the data, revision of the manuscript, and approval of the final draft. RA and KP completed statistical analysis of the data, participated in drafting and revision of the manuscript, and approved the final draft. MS participated in conception and design of the study, revision of the manuscript, and approval of the final draft.

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Compliance with Ethical Standards

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Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This project was approved by the Institutional Review Boards at each of the ADDIRC sites participating in the AIC.

Informed Consent Guardians of all participants provided written informed consent prior to enrolling in the project.

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