HHS Public Access
Author manuscript
Pediatr Res. Author manuscript; available in PMC 2019 July 19.

Published in final edited form as:
Pediatr Res. 2019 April ; 85(5): 602–606. doi:10.1038/s41390-019-0305-z.

CYP2D6 genotype and adverse events to risperidone in children and adolescents

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Abstract

Background: There are few and conflicting data on the role of cytochrome P450 2D6 *(CYP2D6)* polymorphisms in relation to risperidone adverse events (AEs) in children. This study assessed the association between CYP2D6 metabolizer status and risk for risperidone AEs in children.

Methods: Children ≤18 years with at least four weeks of risperidone exposure were identified using BioVU, a de-identified DNA biobank linked to electronic health record data. The primary outcome of this study was AEs. After DNA sequencing, individuals were classified as CYP2D6 poor, intermediate, normal, or ultrarapid CYP2D6 metabolizers.

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Dr. Oshikoya conceptualized and designed the study, designed the data collection instruments, collected the data, interpreted the data, and revised the manuscript.
Dr. Neely analyzed and interpreted the data, drafted the initial manuscript, and revised the manuscript.
Dr. Carroll collected the data and revised the manuscript.
Ms. Aka analyzed the data and revised the manuscript.
Dr. Maxwell-Horn revised the manuscript.
Dr. Roden designed the study and revised the manuscript.
Dr. Van Driest conceptualized and designed the study, reviewed the data collection instruments, coordinated and supervised data collection and revised the manuscript
All authors gave final approval of this version of the article.

Disclosures: Dr. Van Driest has been an invited speaker to Merck. Dr. Oshikoya, Dr. Neely, Dr. Carroll, Ms. Aka, Dr. Maxwell-Horn, and Dr. Roden declare no conflicts of interest.

Study Category: Population Study

Results: For analysis, the 257 individuals were grouped as poor/intermediate metabolizers (*n*=33, 13%) and normal/ultrarapid metabolizers (*n*=224, 87%). AEs were more common in poor/intermediate versus normal/ultrarapid metabolizers (15/33, 46% vs. 61/224, 27%, *P*=0.04). In multivariate analysis adjusting for age, sex, race, and initial dose, poor/intermediate metabolizers had increased AE risk (adjusted odds ratio 2.4, 95% confidence interval 1.1-5.1, *P*=0.03).

Conclusion: Children with CYP2D6 poor or intermediate metabolizer phenotypes are at greater risk for risperidone AEs. Pre-prescription genotyping could identify this high-risk subset for an alternate therapy, risperidone dose reduction, and/or increased monitoring for AEs.

INTRODUCTION

Risperidone is an atypical antipsychotic and a serotonin-dopamine antagonist (1) with FDA approval for some pediatric diagnoses including schizophrenia in adolescents aged 13-17, bipolar 1 disorder in children aged 10-17, and irritability associated with autism in children aged 5-16 years (2). However, atypical antipsychotics are most commonly prescribed in pediatric patients for off label uses including depression, obsessive-compulsive disorder (OCD), Tourette Syndrome, post-traumatic stress disorder (PTSD), and attention deficit hyperactivity disorder (ADHD) (3–5). Atypical antipsychotic use in children peaked in the mid-2000s and was associated with a trend in initiating prescriptions at a younger age, although antipsychotic use has continued to rise in adolescents since that time (3,6).

Multiple adverse events (AEs) associated with risperidone have been established in adults, including weight gain, sedation, prolongation of the corrected QT interval (long QTc), tardive and withdrawal dyskinesia, diabetes mellitus, and hyperlipidemia (2,7,8). There are fewer data on the side effect profile and long term effects of atypical antipsychotics in pediatric patients (3). Children are at higher risk than adults for AEs following antipsychotic exposure, and emerging evidence indicates that children and adolescents are at higher risk for hyperprolactinemia, weight gain, and metabolic abnormalities compared to adults (3,5).

Risperidone is primarily metabolized by the cytochrome P450 (CYP) 2D6 enzyme while other enzymes such as CYP3A4 contribute less to the metabolism (9). The *CYP2D6* gene is highly polymorphic (10). Common polymorphisms lead to loss of function, gene deletion, or gene duplication, leading to a spectrum of CYP2D6 activity from complete lack of function in poor metabolizers to excessive function in ultrarapid metabolizers (11). In the Caucasian population, 1-2% of individuals are CYP2D6 ultrarapid metabolizers; 77-92% are normal metabolizers; 2-11% are intermediate metabolizers; and 5-10% are poor metabolizers (12). Recent studies have shown that CYP2D6 status may affect the risk of AEs in individuals exposed to risperidone (13). Some studies in adults suggest a significant association between *CYP2D6* genotypes and pharmacokinetics, efficacy, or adverse effects of risperidone, while others have found no association (14–17). There are few studies examining the relationship of CYP2D6 status to drug levels, drug efficacy, or AEs in children; the small number of studies published to date have conflicting results (4,18–21). There are no specific national or international guidelines for prescribing risperidone based on the *CYP2D6* genotype of individual patients (4).

This retrospective cohort study assessed the association between CYP2D6 status and the risk for AEs in pediatric patients exposed to risperidone for at least 4 weeks. Our hypothesis was that individuals with reduced CYP2D6 enzyme activity have increased AEs compared to individuals who are normal metabolizers.

METHODS

Study Design and Cohort

Data for this study were obtained from BioVU, the Vanderbilt University Medical Center (VUMC) biobank linking DNA to de-identified electronic health records (EHR) (22–24). This study was reviewed by the Vanderbilt Institutional Review Board and determined to be non-human subjects research. Previous studies documenting most AEs in specific subgroups of pediatric patients were limited to ≤8 weeks (25–27). Therefore, we performed a preliminary search of children exposed to risperidone for ≤8 weeks. No patient exposed to risperidone for <4 weeks had any form of AEs. Hence, our study inclusion criteria were limited to use of risperidone for ≥4 weeks; age ≤18 years at the time of initial dose of risperidone; and non-compromised DNA sample available in BioVU. Exclusion criteria were management of patients on risperidone by non-VUMC providers and insufficient follow up data, such as lack of records of prescribed dose of risperidone or unclear data on presence or absence of AEs. Individuals whose CYP2D6 status was ambiguous based on genetic results excluded from analysis after genotyping was performed.

Primary Outcome and Identification

The primary outcome of this study was AEs in individuals taking risperidone. AEs were defined as any untoward event identified by the patient or their parent/guardian, observed by a physician, or detected following a change in laboratory investigation (e.g. increase in fasting blood glucose level just before the AE compared to baseline level at the commencement of risperidone) that was documented in the EHR and attributed to risperidone. As a retrospective study, no causality assessment was performed to establish the relationship between the AEs and risperidone. The presence or absence of AEs was identified through manual review of the EHR for each individual, blinded to CYP2D6 status.

Data Abstraction

Data for this study were collected and stored in REDCap, an electronic data management tool hosted by VUMC. The following data were extracted for each individual in the study cohort: demographic data (sex, race, ethnicity, and age at time of risperidone start), pertinent clinical information (indication for risperidone, mental health diagnoses, and medical comorbidities), medication data (risperidone dosage amount, risperidone dosing schedule, risperidone duration, and number and type of concomitant drugs including strength and number of any CYP2D6 inhibitors) (28), and presence or absence of AEs. Specific risperidone dosage modifications (increase, decrease or discontinuation) were noted. If AEs were documented in the EHR data, specific details surrounding the event were recorded, including the type of AE, timing of AE in relation to risperidone start date, dose of risperidone at the time of AE, further management steps taken by the prescriber, and any subsequent use of antipsychotic medications.

DNA Analysis

DNA from each individual was analyzed in order to determine their CYP2D6 functional status. *CYP2D6* analysis was performed using the Kailos TargetRich™ PGx Panel Next Generation sequencing assay (Kailos Genetics, Inc, Huntsville, AL) performed by the Vanderbilt Technologies for Advanced Genomics (VANTAGE) laboratory using reagents and protocols as specified by the manufacturer. Processing steps include restriction digestion, patch ligation, enzymatic clean up, on-bead purification, universal PCR amplification, library quality control, and sequencing of the pooled and normalized libraries using a MiSeq instrument (Illumina, San Diego, CA). An additional long-range PCR to determine *CYP2D6* deletions or duplications was performed using the primers specified in Supplemental Table S1 (online). Genotypes were assigned to known *CYP2D6* star alleles per Supplemental Table S2 (online), and then individuals were characterized as poor metabolizers, intermediate metabolizers, normal metabolizers, or ultrarapid metabolizers based on predicted CYP2D6 function as shown in Supplemental Table S3 (online) (29,30). In cases of duplication with heterozygosity, allelic balance of the specific variants identified was used to determine which allele was duplicated. All variants defining an allele were required to have at least 55% of the reads in favor of one allele and less than 45% in favor of the other to support duplication of the allele. If the allelic balance was unable to identify the duplicated allele, possible metabolic statuses were considered. In instances of unambiguous metabolic status (e.g. *1×N/*2 and *1/*2×N are both ultrarapid), the first allele was selected as duplicated. In some instances, the metabolic status was ambiguous (e.g. *1×N/*10 and *1/*10×N are ultrarapid and normal, respectively), in which case the individual was excluded from analysis.

Statistical Analysis

Patients with poor and intermediate metabolizer statuses were combined and analyzed as poor/intermediate metabolizers. Patients with normal and ultrarapid metabolizer status were combined and analyzed as normal/ultrarapid metabolizers. All demographics, clinical variables, and medication outcomes were calculated as frequencies and percentages for categorical variables or medians and interquartile ranges (IQR) for continuous variables. Characteristics of poor/intermediate metabolizers were compared to those of normal/ultrarapid metabolizers using Fisher's exact test or Kruskal-Wallis test, as appropriate. Multivariate logistic regression was performed with AEs as the primary outcome, adjusting for age, sex, race, and risperidone dose. We also tested for associations of concomitant use of strong CYP2D6 inhibitors with AEs in normal/ultrarapid metabolizers using Fisher's exact test and multivariate logistic regression with AEs as the primary outcome, adjusting for age, sex, race, and risperidone dose. Data analysis was performed using STATA v15.1 (StataCorp, College Station, TX). All statistical tests were 2-sided and any P value < 0.05 was considered statistically significant.

RESULTS

Study Cohort and *CYP2D6* Analysis

Of 520 individuals initially identified in a search for risperidone exposed children and adolescents in BioVU, 270 (52%) met inclusion criteria. Due to the highly polymorphic nature of *CYP2D6* and the added complexity of copy number variants, definitive resolution of specific alleles is not always possible during sequencing which can lead to ambiguity of metabolizer status for some individuals. In our study, of those who met the inclusion criteria, 13 individuals were excluded from the cohort due to ambiguous CYP2D6 status (7 unknown metabolizer status, 1 normal versus ultrarapid metabolizer, and 5 intermediate versus normal metabolizers). The remaining 257 individuals were predominantly male (188; 73%), white (217; 84%), and non-Hispanic (246; 96%), with a median age of 8.3 (IQR 6.3-10.5) years at initiation of therapy (Table 1). *CYP2D6* genotyping indicated that 15 (6%) were poor metabolizers, 18 (7%) were intermediate metabolizers, 218 (85%) were normal metabolizers, and 6 (2%) were ultrarapid metabolizers (Table 1). A complete list of *CYP2D6* diplotypes identified is included in Supplemental Table S3 (online). The demographics, comorbid conditions, indication for risperidone, and its dosing regimen for poor/intermediate and normal/ultrarapid metabolizers did not show any statistically significant differences (Table 2).

Adverse Events

In all, 76 individuals (30%) experienced 20 different types of AEs and a total of 104 AEs. The most common AEs were weight change (9%), sedation (6%), and extrapyramidal symptoms (6%). In total 5/15 (33%) poor, 10/18 (56%) intermediate, 58/218 (27%) normal, and 3/6 (50%) ultrarapid metabolizers experienced AEs. All AEs documented in this cohort with the frequency of each AE by metabolizer status are listed in Supplemental Table S4 (online). In univariate analysis, AEs were more common among poor/intermediate metabolizers than normal/ultrarapid metabolizers (15/33, 46% vs. 61/224, 27%, P=0.04) (Table 2). No demographic or baseline characteristics were associated with CYP2D6 status, but race (P=0.04) and presence of aggression (P=0.03) or self-injurious behaviors (P <0.001) were associated with AEs (Supplemental Table S5 (online)). In multivariate analysis, the risk for AEs, after adjustment for age, sex, race, and initial risperidone dose was higher for poor/intermediate metabolizers compared to normal/ultrarapid metabolizers (adjusted odds ratio (OR) 2.4, 95% confidence intervals (CI) 1.1-5.1, P=0.03), (Figure 1).

Of the 224 normal/ultrarapid metabolizers, 20 (9%) were taking one or more concomitant drugs that are known strong inhibitors of CYP2D6. The frequency of AEs was not different among those with a strong concomitant CYP2D6 inhibitor (6/20, 30%) versus those without (55/204, 27%, P=0.8). In multivariate analysis adjusting for risperidone dose, age, sex, and race, the adjusted odds ratio for AEs with concomitant strong CYP2D6 inhibitor use in normal/ultrarapid metabolizers was 1.2, 95% CI 0.4-3.3, P=0.7.

DISCUSSION

This study demonstrates that children who are CYP2D6 poor or intermediate metabolizers have increased incidence of AEs during risperidone treatment, with consistent results in both univariate and multivariate analyses. In total, almost one third of the children treated with risperidone experienced an AE. The high AE rate merits close monitoring in children treated with risperidone and consideration of alternate therapies, as the therapeutic risk may exceed the potential benefit, particularly for those with impaired CYP2D6 function and potentially for those with ultrarapid CYP2D6 function.

The increased incidence of AEs in pediatric patients during risperidone exposure with decreased or no CYP2D6 activity in our study is consistent with findings reported by other pediatric studies. Youngster, *et al.* performed an observational study of 40 pediatric patients with autism spectrum disorder and risperidone exposure which showed a trend of increased AEs such as weight gain and tardive dyskinesia in 2 CYP2D6 poor metabolizers but no AEs in the 2 ultrarapid metabolizers (20). Two prior studies, including 81 and 120 individuals up to 20 years of age, have shown an increased risk for weight gain in those with reduced CYP2D6 activity, although one of these studies included multiple other atypical antipsychotics in addition to risperidone (31,32). Another study showed a correlation between serum prolactin levels and CYP2D6 status in 25 children, although there was no association with AEs (19). A study of 45 pediatric patients with autism spectrum disorder showed reduced weight gain in 8 ultrarapid CYP2D6 metabolizers, although 1 poor and 36 normal metabolizers had similar outcomes (18). Across all of these studies, potential reasons for the differences in results include variable definitions of AEs, different indications for risperidone, differences in alleles genotyped, and small sample size of some metabolizer subgroups. However, taken together, these studies do suggest an increased rate of risperidone AEs, particularly for increased frequency of weight gain, in pediatric patients with decreased or no CYP2D6 activity.

Risperidone is metabolized to paliperidone by CYP2D6, and paliperidone is an active metabolite (13). Some studies suggest that the ratio of risperidone to paliperidone, as determined by CYP2D6 phenotype, may affect the type of AEs that an individual is at risk to develop (1). For example, prolactin levels correlate with paliperidone levels, so ultrarapid metabolizers may be at increased risk for hyperprolactinemia (19). In our cohort, 3 ultrarapid metabolizers experienced 4 different adverse events, and no ultrarapid metabolizers experienced hyperprolactinemia or gynecomastia. Due to the small number of ultrarapid metabolizers in our cohort, we are not able to make definitive conclusions regarding specific AEs among this subset (Supplemental Table S4 (online)).

Clinical *CYP2D6* testing is available from a variety of commercial and academic laboratories, and there are resources available to assist in assigning metabolizer status based on the genetic variants identified (33,34). For risperidone, there are no formal guidelines recommending changes in dosing or use of an alternative drug based on *CYP2D6* genotype (4). It may be particularly difficult to provide automated genotype-guided prescribing advice for this drug due to the wide range of indications for which risperidone is used. The potential risks and benefits for each patient must be weighed, and CYP2D6 status can be taken into consideration. Based on our evidence and that which has been previously reported, if a patient already has *CYP2D6* test results available, clinicians should consider alternative antipsychotic or mood stabilization therapy in poor and intermediate metabolizers. If risperidone is initiated in poor or intermediate CYP2D6 metabolizers, clinicians should consider to lower the initiation dose and slowly titrate dose thereafter. Also, counseling on the increased risk of AEs should be stressed as well as the importance of routine monitoring for metabolic and movement abnormalities (35). Increased vigilance is also warranted in ultrarapid metabolizers as they may also be at increased AE risk. As a corollary, for those patients already at high risk for risperidone AEs or for whom risperidone AEs will be particularly problematic (e.g. overweight or obese patients, patients with underlying neurological disorder), pre-prescription *CYP2D6* testing to assess the potential risks and benefits may be beneficial.

CYP2D6 status is not the only risk factor for AEs in children treated for risperidone. In this cohort, an indication of self-injurious behaviors or aggression was associated with higher AEs. Race was also associated with AEs in univariate analysis, though was not significantly associated in the multivariable analysis including metabolizer status. In one prior study, younger age and higher dose at risperidone initiation were associated with increased weight gain (36). Another small study showed no association between AE risk and indication, age, BMI, gender, dose, or therapy duration (37). However, robust investigations of the risk factors for risperidone AEs are lacking. Further work in this area is needed in order to provide an evidence basis for safe use of this drug in young patients.

In this cohort, concomitant use of strong CYP2D6 inhibitors was not associated with risperidone AEs. There are few pediatric studies examining the use of CYP2D6 inhibitors and risperidone metabolism, and there is uncertainty surrounding their clinical effect on AEs (38). Although some resources include consideration of drug-drug interactions of risperidone with CYP2D6 inhibitors (39), our data suggest that genotype is a stronger predictor of risk.

We recognize several limitations of this study. Data from this study are from a single center and may not be generalizable to other pediatric populations. AEs were identified retrospectively via EHR, and thus may be affected by inaccurate or insufficient documentation. Many individuals of this study were taking concomitant medications, and although there was no statistical evidence of this variable as a confounder, caution should be used when contributing the association of AEs to risperidone. In spite of our relatively large sample size, ultrarapid, intermediate, and poor metabolizer subgroups were small. Thus, we were unable to assess all phenotype classes individually or identify a trend across all classes due to inadequate power in these smaller phenotype groups. The ultrarapid metabolizer group is of particular interest as it remains unclear if they are at increased risk for AEs, and with 6 ultrarapid metabolizers in this cohort analysis of this group was not possible.

We did not perform causality assessment between the AEs and risperidone to exclude concomitant medications as the likely cause of the AEs or exclude erroneous documentation of AEs that are unlikely to be related to risperidone exposure. Such erroneous AEs include subjective weight gain without using specific indices to assess age-based weight gain, and the rare AEs (e.g. bruising) that have not been established to be risperidone-related. However, our findings are within the scope of AE definition, which refers to any problem occurring at the time a medicine is used, whether or not it is identified as a cause of the problem (40). It is hoped that larger prospective studies would address this problems in the future.

In summary, our results indicate that children with CYP2D6 poor or intermediate metabolizer phenotype are at increased risk of risperidone related AEs. This study along with others suggests clinical relevance of this enzyme, with increased pediatric AE rates associated with decreased or no CYP2D6 enzyme activity with risperidone exposure (18,20,31,32). Thus, if a child or adolescent is known to have CYP2D6 poor or intermediate metabolism, clinicians should consider alternate therapy or a reduced dosing regimen while emphasizing counseling on risks of AEs as well as the importance of routine monitoring to identify AEs during treatment.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements:

Data extraction and formatting was performed by Christian Shaffer, Vanderbilt University Medical Center.

Financial Support: This work used a dataset from Vanderbilt University Medical Center's BioVU which is supported by institutional funding and by the CTSA grant UL1 TR000445 from NIH/NCATS. This work was also supported by NIH/NCATS KL2 TR000446 (SLV), Burroughs Wellcome Fund IRSA 1015006 (SLV), and the NIH/NIGMS Clinical Pharmacology Training Program 5T32 GM007569 (KAO and KMN).

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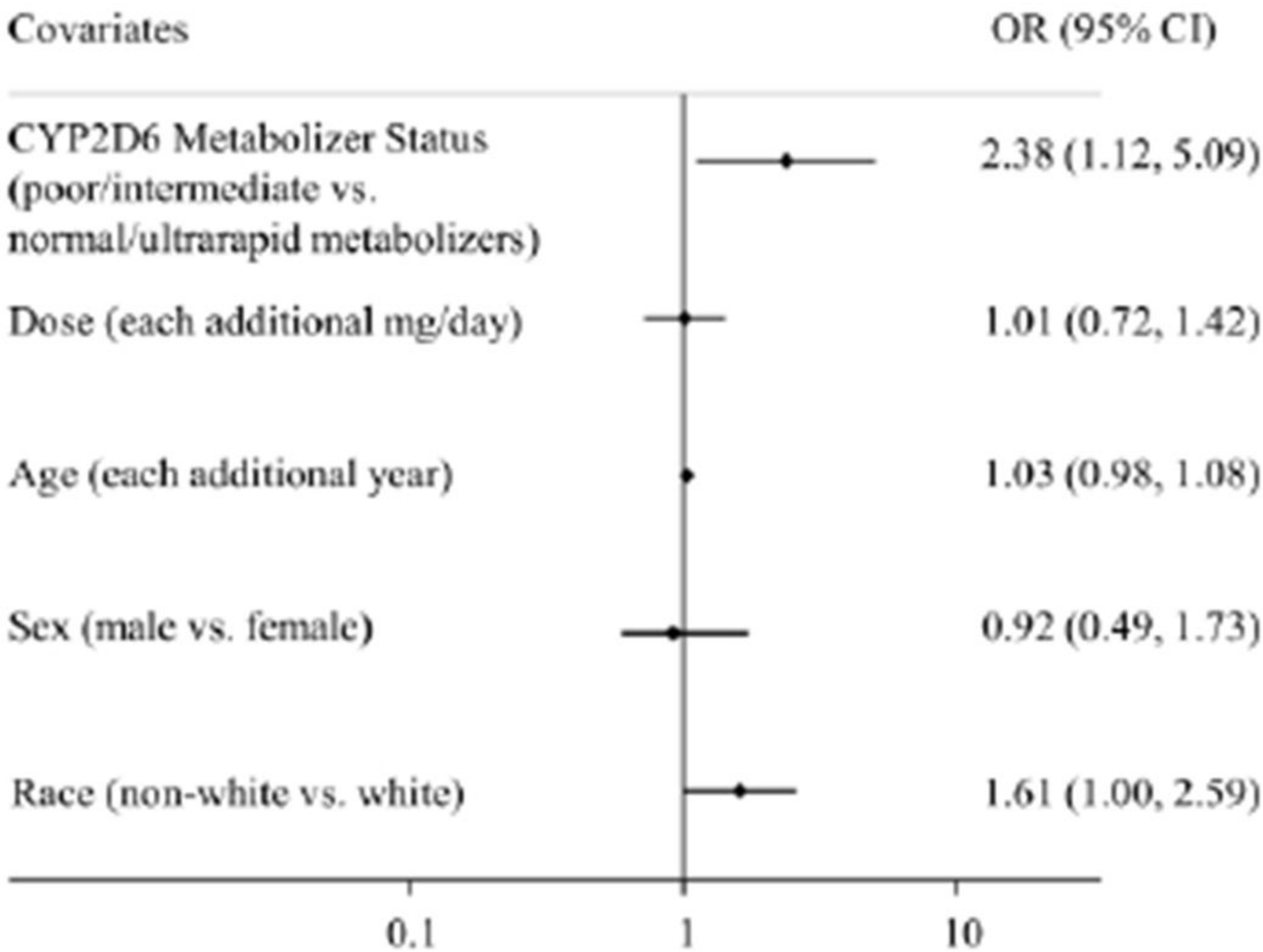

Figure 1:

Logistic regression of adverse events during risperidone treatment in children. Shown are the adjusted odds ratios (ORs) and 95% confidence intervals (CIs) for CYP2D6 poor/intermediate vs. normal/ultrarapid metabolizers, adjusted by risperidone dose, age at start of risperidone, sex, and race

Table 1:

Demographics, metabolizer status, and risperidone exposures in study cohort

	***N*=257**
	***n*(%)**
Age at commencement of risperidone (years), median (IQR)	8.3 (6.3-10.5)
Sex	
Male	188 (73.2)
Female	69 (26.8)
Race	
White	217 (84.4)
African-American	29 (11.3)
Asian/Pacific islander	5 (1.9)
Unknown	5 (1.9)
Native American	1 (0.4)
Ethnicity	
Hispanic	6 (2.3)
Non-Hispanic	246 (95.7)
Unknown	5 (1.9)
Risperidone baseline dose in mg/day, median (IQR)	0.5 (0.5-1)
CYP2D6 metabolizer phenotype	
Poor metabolizer	15 (5.8)
Intermediate metabolizer	18 (7)
Normal metabolizer	218 (84.8)
Ultrarapid metabolizer	6 (2.3)

IQR – Interquartile Range

Table 2:

Comparison of demographic and baseline characteristics among metabolizer groups

	Poor or Intermediate Metabolizers (*n*=33)	Normal or Ultrarapid Metabolizers (*n*= 224)	*P** value
	Frequency (%) or median (IQR)		
Age at risperidone commencement (years)	8.9 (6.2-10.6)	8.3 (6.3-10.5)	0.9
Male Sex	25 (75.8)	163 (72.8)	0.8
Race			0.5
African-American	5 (15.2)	24 (10.7)	
Asian/Pacific islander	1 (3)	4 (1.8)	
Caucasian	26 (78.8)	191 (85.3)	
Unknown	1 (3)	4 (1.8)	
Native American	0	1 (0.5)	
Ethnicity			0.4
Hispanic	1 (3)	5 (2.2)	
Non-Hispanic	31 (93.9)	215 (96)	
Unknown	1 (3)	4 (1.8)	
Presence of comorbid conditions			0.8
No	21 (63.6)	146 (65.2)	
Yes	12 (36.4)	78 (34.8)	
Specific comorbidities			
Seizure disorder	8 (24.2)	31 (13.8)	0.1
Asthma	2 (6.1)	21 (9.4)	0.7
Attention deficit hyperactivity disorder	13 (39.4)	101 (45)	0.6
Autism	10 (30.3)	61 (27.2)	0.7
Specific indication for risperidone			
Aggression	18 (54.5)	107 (47.8)	0.6
Behavioral problems	13 (39.4)	66 (29.5)	0.3
Agitation	4 (12.1)	38 (17)	0.6
Irritability	5 (15.2)	58 (25.9)	0.2
Self-injurious behaviors	6 (18.2)	39 (17.4)	0.5
Baseline dosing regimen of risperidone (mg/day)	0.8 (0.3-1)	0.5 (0.5-1)	0.9
Dose modification			0.4
Yes	13 (39.4)	109 (48.7)	
No	20 (60.6)	115 (51.3)	
Adverse Events	15 (45.5)	61 (27.2)	**0.04**

* *P* values for slow versus extensive metabolizers from Kruskal-Wallis test for continuous variables and Fisher’s exact for categorical variables. IQR – Interquartile Range