Pharmacogenetic factors influence escitalopram-induced side effects and self-injury in youth at high-risk for developing bipolar disorder

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Objective

Evaluate the influence of genetic factors on escitalopram pharmacokinetics and adverse events in youth with (1) a first-degree relative with bipolar I and (2) clinically significant depression or anxiety

Introduction[1]

- Escitalopram (ESC) is a selective serotonin reuptake inhibitor prescribed to treat symptoms of anxiety and depression in children and adolescents.
- The highly polymorphic enzymes cytochrome P450 2C19 and 2D6 (CYP2C19, CYP2D6) are primarily responsible for ESC metabolism and might explain some variability in ESC pharmacokinetics and side effects.
- The "short" (S) allele of SLC6A4 may diminish the efficacy of antidepressants and increase risk of hyperarousal relative to the "long" (L) allele; a SNP near the HTR2A gene (rs6311 (-1438G>A)) may increase the risk of antidepressant-related adverse events.

Methods[1]

- Blood samples were obtained from adolescents of parents with bipolar disorder aged 12 to 18 treated with ESC (n=48) and plasma ESC concentrations were measured via LC-MS-MS.
- Rating scales (TEASAP) were administered at baseline and throughout study to assess side effects and adverse events.
- Buccal swabs for genotyping were collected (n=66 in ESC group) during outpatient visits and genotyped for CYP2C19 no-function alleles and the increased function allele; CYP2C19 & CYP2D6 phenotypes are based on CPIC Guidelines[2].
- A one-compartment pharmacokinetic model with CYP2C19 phenotypes as a covariate accounting for differences in clearance was developed using MwPharm (Mediware; **Figure 1A**).
- Each patient's ESC concentration was modeled to account for dose timing, doses missed, and blood sample collection time to estimate half-life ($t_{1/2}$) and clearance (CL), then normalized to 20 mg/day to estimate 24-hour area under the curve (AUC_{24}), and maximum (C_{max}) and trough concentrations (C_{trough}).
- Data were analyzed using ANOVA test for linear trend if there were 3 or more groups, and t-tests if there were two groups.

Results

- CYP2C19 phenotype significantly predicts ESC AUC_{24} (p=0.03; **Figure 1B**), C_{trough} (p=0.01), $t_{1/2}$ (p<0.001), but not C_{max} (p=0.057), CL (p=0.22) or TEASAP Self-injury score (p=0.09; **Figure 3A**).
- Slower CYP2D6 phenotype correlates with greater increase in disinhibition (p=0.02) and akathisia (p=0.01; **Figure 2**), but not other TEASAP outcomes.
- High-risk youth with *HTR2A* SNP rs6311 (genotypes A/G and A/A) had a significantly greater increase in self-injury compared to wild-type (G/G; p=0.02; t-test; **Figure 3B**); *SLC6A4* genotype did not have a significant effect on TEASAP outcomes.

References

1. Honeycutt DC, et al. A Double-Blind Randomized Trial to Investigate Mechanisms of Antidepressant-Related Dysfunctional Arousal in Depressed or Anxious Youth at Familial Risk for Bipolar Disorder. J Pers Med. 2022 Jun 20;12(6):1006.

2. Hicks JK, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for CYP2D6 and CYP2C19 Genotypes and Dosing of Selective Serotonin Reuptake Inhibitors. Clin Pharmacol Ther. 2015 Aug;98(2):127-34.

Pharmacokinetic modeling based on CYP2C19

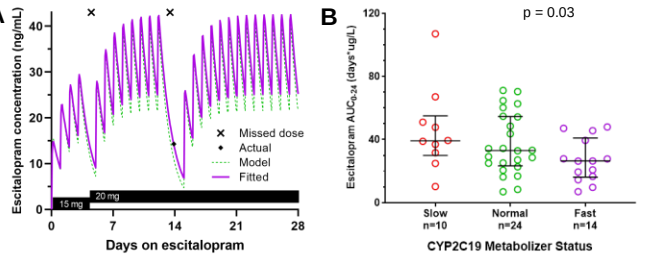

Figure 1. (A) Sample curve from CYP2C19 normal metabolizer including initial model curve based on dose data and fitted curve adjusted for serum escitalopram concentration ("Actual") **(B)** Slow & normal CYP2C19 metabolizers had higher AUC_{24} relative to fast metabolizers.

Genetic influences on Self-injury score

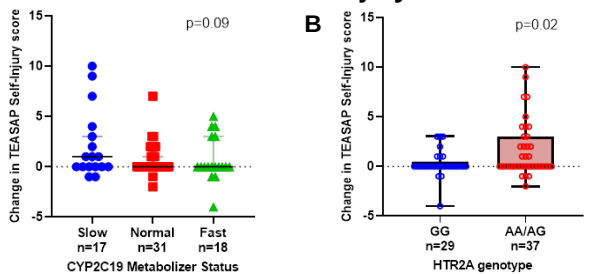

Figure 3. (A) CYP2C19 metabolizer status did not significantly predict participants' increase in self-injury, though slower metabolizers tended to show greater increases in TEASAP "Self-injury, Suicidality, and Harm to Others" score (i.e., Self-injury score). **(B)** Participants with SNP rs6311 (-1438G>A) had a significantly greater increase in Self-injury score compared to those with wild-type alleles.

Side effects and CYP2D6

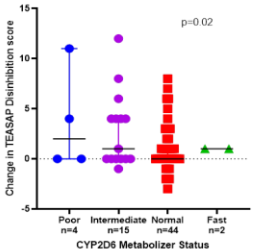

Figure 2. Slower CYP2D6 metabolism was correlated with greater increases in disinhibition (p=0.02) and akathisia (p=0.01).

Discussion

1. Gene-drug interactions may contribute to greater rates of adverse events in high-risk youth treated with escitalopram.
2. Youth with a family history of bipolar disorder warrant careful consideration to avoid iatrogenic precipitation of self-injurious or manic behavior.
3. Genetic testing may improve the safety of antidepressants in high-risk youth.

Future Analysis

- Refine pharmacokinetic modeling to include CYP2D6 status and estimate relative contribution of CYP2C19 vs. CYP2D6 to ESC exposure.
- Correlate clinical outcomes to ESC exposure rather than individual enzyme metabolizer phenotypes.
- Determine whether combinations of genetic risk factors predict ESC-induced adverse events in youth at high risk of developing bipolar disorder.

Methods Paper Link

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Table 1. Cohort Demographics

Pharmacokinetic Analysis (n=48)	
Age (yrs), mean±SD	14.9±1.7
Sex (%female)	56.3
Race & Ethnicity	n (%)
African	6 (12.5)
Hispanic Caucasian	6 (12.5)
Non-Hispanic Caucasian	30 (62.5)
Other & Mixed	6 (12.5)

Genetic Analysis (n=66)	
Age (yrs), mean±SD	14.8±1.7
Sex (%female)	51.5
Race & Ethnicity	n (%)
African	7 (10.6)
Hispanic Caucasian	7 (10.6)
Non-Hispanic Caucasian	44 (66.7)
Other & Mixed	8 (12.1)

Contact Information & Acknowledgements

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