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

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Objectives

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

- 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 hyper arousal relative to the "long" (L) allele; SNPs near the HTR2A gene (rs6311; 1438G>A) may increase the risk of antidepressant-related adverse events.

Methods

- Blood samples were obtained from adolescent patients with bipolar disorder aged 12 to 18 treated with ESC (n=48) and plasma ESC concentrations were measured via LC-MS-MS.
- Raising 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).
- Each patient’s ESC concentration was modeled to account for dose timing, doses missed, and blood sample collection time to estimate half-life (t1/2) and clearance (CL) then normalized to 20 mg/day to estimate 24-hour area under the curve (AUC24) and maximum concentration (Cmax) and trough concentrations (Cmin).
- 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 AUC24 (p=0.03; Figure 1B, CYP2C19 Normal metabolizer status did not significantly predict participants’ increase in self-injury, though slower metabolizers had higher AUC24 relative to fast metabolizers.
- Slower CYP2D6 metabolism was correlated with greater increase in TEASAP "Self-Injury, Suicidality, and Harm to Others" score (i.e., Self-injury score) (p=0.03; Figure 2), but not other TEASAP outcomes.
- High-risk youth with HTR2A A/G or A/A genotypes had a significantly greater increase in self-injury compared to wild-type (GG) (p=0.02; Figure 3B). SLC6A4 genotype did not have a significant effect on TEASAP outcomes.

Discussion

1. Gene-drug interactions may contribute to greater rates of adverse events in high-risk youth treated with escitalopram.
2. Youths 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.

Contact Information & Acknowledgements

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References

3. Table 1. Cohort Demographics

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Table: Cohort Demographics

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<thead>
<tr>
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<td>Pharmacokinetic Analysis (n=48)</td>
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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 relative to fast metabolizers.

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