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Abstract Title

Pharmacogenetic Associations of CYP3A4, CYP3A5, and ABCB1 with guanfacine treatment outcomes among children and young adults

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Background

Guanfacine, an alpha-2-agonist, is used as an adjunctive treatment for mental disorders, including attention-deficit/hyperactivity disorder (ADHD). It is primarily metabolized by CYP3A4 and CYP3A5 and is a putative substrate of ABCB1. However, the influence of variation in the genes encoding these enzymes and transporter on guanfacine efficacy and tolerability remains poorly understood.

Objective

To evaluate associations between CYP3A4, CYP3A5, and ABCB1 genetic variations and guanfacine treatment outcomes.

Methods

Youth (6-24 years) enrolled in the Pharmacogenomics-Supported Prescribing in Kids (PGx-SPark) study with a history of guanfacine use were genotyped for CYP3A4 (*20, *22), CYP3A5 (*3, *6, *7), and ABCB1 (C3435T). Reported outcomes included symptom improvements, side effects, and medication adherence. Binomial and ordinal regression models were used to evaluate associations between the genotype-predicted phenotypes and guanfacine outcomes, adjusting for covariates.

Results

Among the 189 participants (mean age 11.5 ± 3.1 years; 68.3% male; 68.3% European), the mean guanfacine dose was 3.13 ± 1.5 mg/day. Most participants were CYP3A4 normal metabolizers (86.8%) and CYP3A5 non-expressers (81.5%), while 46.6% were predicted to have intermediate ABCB1 transporter activity. Approximately half (50.3%) were concurrently taking stimulants. A significant interaction between CYP3A4 genotype-predicted metabolizer phenotype and guanfacine dose was observed (OR = 3.59, 95% CI 1.21–10.64, $p = 0.021$), with the predicted probability of reporting side effects increasing with dose among participants with reduced genotype-predicted phenotype. In a subgroup analysis, among participants taking concomitant stimulants ($n = 95$), CYP3A5 genotype-predicted expresser phenotype had significantly lower odds of reporting side effects than non-expressers (OR = 0.25, 95% CI 0.07–0.93, $p = 0.038$).

Conclusion

Our findings suggest that the pharmacogenetic contributions to guanfacine treatment outcomes may extend beyond the effects of individual genetic variants. CYP3A4 phenotype-by-dose interaction and the CYP3A5 finding in participants taking stimulants suggest genetic variation may influence guanfacine treatment response. Larger replication studies are needed to validate these findings.