Fluoxetine Response Associated with Enantiomer Abundance in Adolescents

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Introduction. Only 3-in-5 adolescents respond to antidepressants the first time. Identifying individual factors that influence response can guide treatment and expedite recovery. FLX is administered in racemic form (S and R). The S-enantiomer of norFLX is 20 times more active than R-enantiomer and thought to contribute meaningfully to drug response.

Methods. Youth (12-21yr) on FLX at steady state had plasma FLX and norFLX S/R measured by UPLC-MSMS and CYP2D6 genotyped by Illumina array with ddPCR copy number confirmation. Participant PHQ9 scores ≥11 or Promis Anxiety t-scores ≥60 were considered non-responders.

Results. In 56 youth (16±1.9yr (12-21yr), 70% female), average norFLX S/R was higher in responders compared to non-responders (depression: 1.34±0.84 vs 0.84±0.45, p = 0.001, Cohen's d = 0.73; anxiety: 1.56±0.98 vs 0.97±0.55, p = 0.006, Cohen's d = 0.74). Participant symptom scores were negatively correlated with norFLX S/R (depression r_s = -0.28; anxiety r_s = -0.34), while FLX S/R was not associated with depression or anxiety response. Mean norFLX S/R was similar across CYP2D6 phenotypes (PM n = 2, IM n = 11, NM n = 36, UM n = 3).

Conclusions. In adolescents on FLX, norFLX S/R was significantly higher in responders compared to non-responders. No difference was detected in norFLX S/R across CYP2D6 phenotypes, a finding limited by small sample size and likely related to autoinhibition of CYP2D6 activity resulting in FLX-associated phenoconversion to poor metabolizer status in all participants. Further research is needed to evaluate the role of norFLX S/R as a predictor of FLX response.

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