ABSTRACT

Background
Aim: To assess whether pharmacogenetic polymorphisms are associated with increased adverse effects or non-response with certain antidepressants whose metabolism is highly dependent on specific CYP450 isoenzymes This is interim analysis of an ongoing study

METHODS
We used a Case-Control design comparing patients with major depressive disorder or generalized anxiety disorder who had high adverse events from specific antidepressants (Cases) to patients who were poor responders to an antidepressant but without significant adverse effects (Controls). Genospect Assay™ (Battery of pharmacogenetic tests relevant to psychiatry) was obtained using saliva or cheek swab

RESULTS
Importantly, 57.1% of Cases were poor or intermediate metabolizers on the concerned isoenzyme compared to 24.3% of those who did not. This difference showed a trend towards statistical significance (p = .064).

CONCLUSIONS
Patients on selected commonly used antidepressants who had increased adverse effects were very likely to be poor or intermediate metabolizers on the relevant CYP450 isoenzyme. Pharmacogenetic testing should routinely be considered in these patients and definitely in those who have had more than one severe adverse effect before prescribing one of these antidepressants may potentially reduce significant adverse effects/lack of response.

Hypotheses: that Cases would be more likely to be:
1. Poor metabolizers (PM) or intermediate metabolizers (IM) on the CYP2C19 gene mainly responsible for metabolizing that antidepressant
2. Homozygous for the T/T allele of the CYP2D6 polymorphism of MTHFR
3. Homozygous for the short allele of SLCOA4
4. That Controls would be more likely to be ultrarapid metabolizers (UM) on the CYP1A2 gene mainly responsible for metabolizing that antidepressant
5. That Cases would have higher scores on trait anxiety, since anxious subjects are believed to report more adverse effects (Fava et al., 2008).

For each index antidepressant, one CYP450 isoenzyme was considered to be the key main isoenzyme as follows: CYP2C19 (Paroxetine), CYP2D6 (Venlafaxine), CYP2C9 (Clarithromycin), CYP2C9/3A4 (Escitalopram), CYP2D6 (Paroxetine).

Table 3: Pharmacogenetic polymorphisms and increased adverse effects/lack of response

Table 4: Pharmacogenetic polymorphisms and one or more severe adverse effects

CONCLUSIONS

• Patients on selected commonly used antidepressants who had increased adverse effects were quite likely to be PM or IM on the CYP450 isoenzyme mainly responsible for metabolizing that antidepressant
• Pharmacogenetic testing should routinely be considered in these patients and definitely in those who have had more than one severe adverse effect before prescribing one of these antidepressants may potentially reduce significant adverse effects/lack of response.
• Anxiety believed to be related to reporting more adverse effects. Trait anxiety was not associated with increased adverse effects in this sample. Being retrospective, this study could not assess state anxiety at the time of the increased adverse effects
• Proportion of UM numerically greater in Controls but not statistically significant. Should be evaluated in larger samples
• Contrary to prior reports, no associations found between Cases or Control in short/short form of the serotonin transporter promoter region allele

Table 1: Sample characteristics (n=50)

Table 2: Predicted phenotype for cytochrome P450 isoenzymes (n=50)

Table 3: Pharmacogenetic polymorphisms and increased adverse effects/lack of response

**Fisher’s Exact test**

• Importantly, 57.1% of Cases were PM or IM on the concerned isoenzyme vs. 17.2% of Controls (p = .006)

**Statistically significant differences in proportions of Cases vs. Controls who were homozygous (TT) for methylene tetrahydrofolate reductase (MTHFR) C677T polymorphism, or for the Short/Short form of the serotonin transporter promoter region allele**

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**Patients on selected commonly used antidepressants who had increased adverse effects were likely to be poor or intermediate metabolizers on the relevant CYP450 isoenzyme. Pharmacogenetic testing should routinely be considered in these patients and definitely in those who have had more than one severe adverse effect before prescribing one of these antidepressants may potentially reduce significant adverse effects/lack of response.**