Genetic Polymorphisms and Antidepressant Adverse Effects

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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 had increased adverse effects from specified antidepressants (Cases) to patients who were poor responders to an antidepressant but without significant adverse effects (Controls)

Genecept 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 vs. 17.2% of Controls (p= .006)

52.9% of subjects who had at least one severe adverse effect were found to be poor or intermediate metabolizers on the concerned isoenzyme compared to 24.2% of those who did not. This difference showed a trend towards statistical significance (p= .061)

69.2% of subjects who had *more than one* severe adverse effect were found to be poor or intermediate metabolizers on the concerned isoenzyme compared to 21.6% of those who did not (p= .005)

27.6% of Controls were ultrarapid metabolizers on the concerned isoenzyme vs. 14.3% of Cases (p= .221)

No statistically significant differences in the proportions of Cases vs. Controls who were homozygous (TT) for methylenetetrahydrofolate reductase (MTHFR) C677T polymorphism, or for the Short/Short form of the serotonin transporter promoter region allele.

Conclusions

Patients on certain 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

BACKGROUND

- Paucity of clinically useful predictors of increased susceptibility to adverse effects of antidepressants
- Aim: to assess whether pharmacogenetic polymorphisms are associated with increased adverse effects with certain antidepressants whose metabolism is highly dependent on specific CYP450 isoenzymes
- CYP450 polymorphisms affect metabolism/drug levels of antidepressants; may cause increased adverse effects or lack of response
- Data on association of short/short allele of the serotonin transporter promotor region (SLC6A4) with poor response to serotonergic antidepressants is inconsistent, but it has been associated with increased adverse effects (Hu et al., 2007)
- T/T allele of the C677T polymorphism of the methylenetetrahyrofolate (MTHFR) gene has been associated with poor response to an antidepressant (Lanctôt et al., 2010)

METHODS

- Case Control design comparing patients with major depressive disorder or generalized anxiety disorder who:
  1. Had had increased adverse effects from specified antidepressants (Cases)
  2. Patients who were poor responders to an antidepressant but without significant adverse effects (Controls)
- Increased adverse effects (Cases) was operationalized as having had either > 3 moderate/severe adverse effects OR > 5 mild effects on a usual dose
- Poor response (Controls) was operationalized as having had < 30% reduction in depression and with minimal/no adverse effects
- Genecept Assay™ (battery of pharmacogenetic tests relevant to psychiatry) was obtained using saliva or cheek swab

Supported in part by a grant from Genomind, LLC

- **Hypotheses**: that Cases would be more likely to be:
  1. Poor metabolizers (PM) or intermediate metabolizers (IM) on the CYP450 enzyme mainly responsible for metabolizing that antidepressant
  2. Homozygous for the T/T allele of the C677T polymorphism of MTHFR
  3. Homozygous for the short allele of SLC6A4
  4. That Controls would be more likely to be ultrarapid metabolizers (UM) on the CYP450 enzyme 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: citalopram (2C19), duloxetine (2D6), escitalopram (2C19), paroxetine (2D6), venlafaxine (2D6)

RESULTS

Table 1. Sample characteristics (n=50)

	Median	Range
Age	48.0	21 - 69
	N	**%**
Female	40	80.0
Race		
Caucasian	40	80.0
Asian	4	8.0
African American	4	8.0
Other/ Mixed	4	8.0
Lack of response	29	58.0
Increased AEs	21	42.0
Antidepressant		
Escitalopram	16	32.0
Venlafaxine	12	24.0
Duloxetine	9	18.0
Citalopram	9	18.0
Paroxetine	4	8.0

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

		Poor metabolizer		Intermediate metabolizer		Extensive metabolizer		Ultrarapid metabolizer	
		N	**%**	**N**	**%**	**N**	**%**	**N**	**%**
CYP450 2C19	**Increased AEs**	2	9.5	5	23.8	9	42.9	5	23.8
	Non-responders	0	0	6	20.7	15	51.7	8	27.6
	Total	2	4.2	10	20.8	23	47.9	13	27.1
CYP450 2D6	**Increased AEs**	1	4.8	11	52.4	7	33.3	2	9.5
	Non-responders	1	3.4	8	27.6	17	58.6	3	10.3
	Total	2	4.2	19	39.6	23	47.9	4	8.3
CYP450 3A4/5*	**Increased AEs**	12	63.2	4	21.1	3	15.8	0	-
	Non-responders	23	79.3	4	13.8	2	6.9	0	-
	Total	35	72.9	8	16.7	4	8.3	0	-

*EM is the normal phenotype for CYP450 2C19 and 2D6

** ~90% of Caucasian, ~70% of Asian and ~25% of African ancestry populations are classified as the CYP3A4/5 PM phenotype, and therefore PM is considered "Baseline"

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

		Cases (increased AEs) n=21		Controls (lack of response) n=29		p value**
		N	**%**	**N**	**%**	
Predicted phenotype*	**Poor/intermediate metabolizer**	12/21	**57.1**	5/29	**17.2**	**.006**
	Ultrarapid metabolizer	3/21	14.3	8/29	27.6	.221
MTHFR	**T/T**	2/21	9.5	5/29	17.2	.684
	C/C	13/21	61.9	13/29	44.8	.265
SLC6A4	**S/S**	3/21	14.3	6/29	20.7	.716
	L/L	6/21	28.6	10/29	34.5	.673
	L(A)/L(A)	6/21	28.6	8/29	27.6	1.00

*Predicted phenotype for the isoenzyme mainly responsible for metabolizing that antidepressant

**Fisher's Exact test

- Importantly, 57.1% of Cases were PM or IM on the concerned isoenzyme vs. 17.2% of Controls (p= .006)
- 27.6% of Controls were UM on the concerned isoenzyme vs. 14.3% of Cases, but not statistically significant

No statistically significant differences in proportions of Cases vs. Controls who were homozygous (TT) for MTHFR C677T polymorphism, or for the Short/Short form of the serotonin transporter promoter region allele

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

	At least one severe adverse effect			More than one severe adverse effect		
	Yes (n=17)	**No (n=33)**	**p****	**Yes (n=13)**	**No (n=37)**	**p****
	n (%)	**n (%)**		**n (%)**		
Poor/ intermediate metabolizer	9/17 (**52.9**)	8/33 (**24.2**)	**.061**	9/13 (**69.2**)	8/37 (**21.6**)	**.005**
Ultrarapid metabolizer	3/17 (17.6)	8/33 (24.2)	.728	2/13 (15.4)	9/37 (24.3)	.704

- 52.9% of subjects who had at least one severe adverse effect were found to be PM or IM on the concerned isoenzyme vs. 24.2% of those who did not, with trend towards statistical significance (p= .061)
- 69.2% of subjects who had *more than one* severe adverse effect were PM or IM on the concerned isoenzyme vs. 21.6% of those who did not (p=.005)
- Cases did not have higher levels of trait anxiety on the State-Trait Anxiety Inventory than Controls (Mann-Whitney U test, p = .745)

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
- 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 allele of the serotonin transporter promoter region or in MTHFR T/T polymorphism
- Pharmacogenetic testing *before* prescribing one of these antidepressants may potentially reduce significant adverse effects and drop outs from treatment