The Association Between COMT Genotype and Bupropion Treatment Response in Outpatients with Major Depressive Disorder

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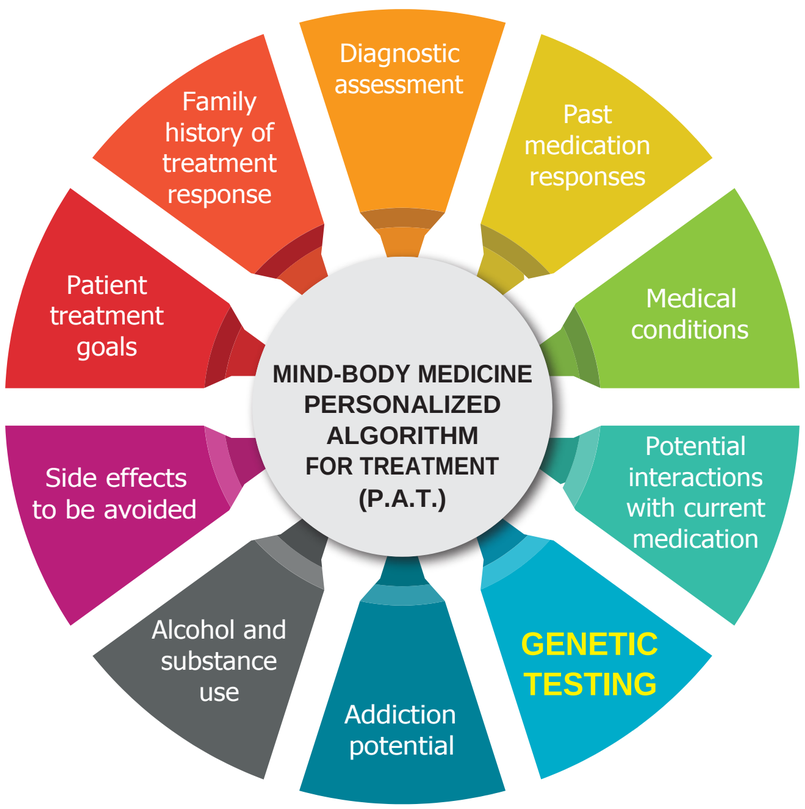
Background:

Studies examining treatment responses to anti-depressants based on genotype have produced inconsistent findings. Although catechol-O-methyl-transferase (COMT) metabolizes catecholamines, the association of COMT genotypes in treating major depressive disorder (MDD) has limited study. A valine (Val) to methionine (Met) substitution at position 158 results in reduced capacity of the enzyme to degrade dopamine, which results in increased dopamine activity. This naturalistic study of outpatients with MDD examined the relationship between COMT genotypes and treatment responses to bupropion, a pro-dopaminergic antidepressant extensively utilized for the past 3 decades.

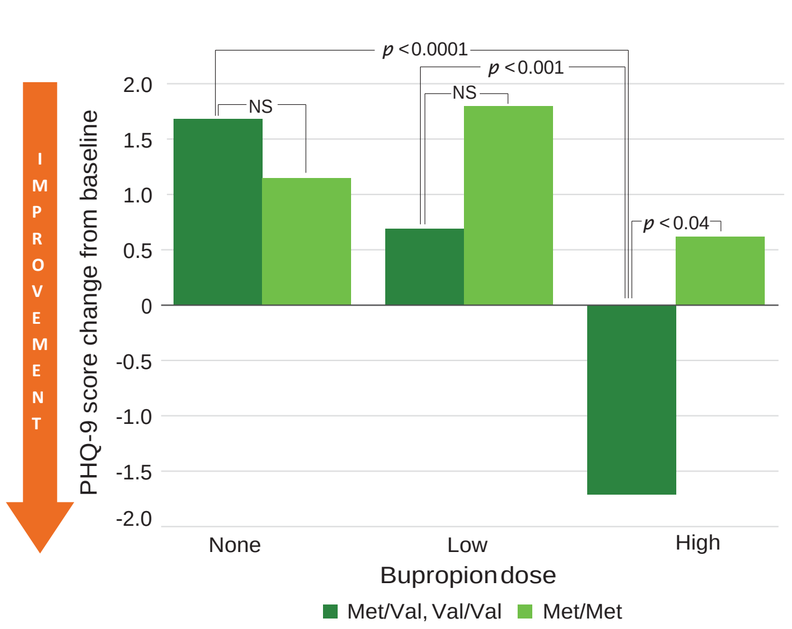
Study Aims:

1. Create a patient registry that contains key data elements for patients of PPG – Mind-Body Medicine with primary diagnoses of MDD who have participated in Genomind genetic testing to identify the pharmacodynamic correlation between genetic markers and the efficacy of bupropion.
2. Determine a probability of response to bupropion for patients diagnosed with MDD based upon pharmacodynamic genetic markers obtained by utilizing the Genecept 2.0 Assay.
3. Determine the role of genetic testing as a dimension within a systematic personalized treatment algorithm to personalize antidepressant treatment options.



Methods:

Participants were 241 adult outpatients with various levels of prior treatment at one Midwestern psycho-pharmacology clinic who met the DSM-5 criteria for MDD without significant psychiatric or medical comorbidities, had available genetic testing results (Genomind's Genecept Assay 2.0) between February 2016 and January 2017, and adhered to pharmaco-therapy recommendations based upon genetic testing results for > 2 months. We used retrospective chart reviews to gather 1) demographic data, 2) COMT variant (dichotomized as Met/Val, Val/Val, or Met/Met), 3) Patient Health Questionnaire (PHQ-9) scores obtained at each clinic visit (M = 3.8 visits, SD = 1.5, range = 1 – 10), and 4) bupropion doses (no bupropion, <200 mg [low dose], or ≥200 mg [high dose]). The sample was 63.9% female, 85.9% Caucasian with an average age of 44.5 years (SD=17.9, range 18 – 86). At the time of genetic testing, 24.1% (n=53) were currently taking bupropion. Over the course of the observation period, 16.7% (n=10) Met/Met, 22.5% (n=29) Val/Met, and 26.9% (n=14) Val/Val cases started a new prescription for bupropion.



Results:

75% of the cohort carried at least one Val allele; 24.9% displayed Met/Met genotype. At baseline, the likelihood of being prescribed bupropion was unrelated to Val allele carrier status. Tests for response differences by bupropion dose demonstrated:

- For Val carriers, high dose bupropion resulted in significantly greater declines in PHQ-9 scores than:
  - no bupropion, (p< 0.0001) or
  - low dose bupropion, (p= 0.001)
- Val carriers differed significantly compared to Met/Met patients in response to high dose bupropion (p = 0.04)
- Val carriers did not differ significantly compared to Met/Met patients in response to low dose bupropion

Case study:

A middle-aged married female had been treated at a psychiatric clinic for 18 years and prescribed sertraline 100 mg for MDD with partial efficacy.

4 months prior to baseline	• Due to her increasing depression, bupropion XL (up to 300 mg) was added to sertraline and the patient was sampled for genetic testing
2 months prior to baseline	• Due to her worsening anxiety and insomnia, alprazolam and zolpidem were added. • Bupropion XL 300 mg and sertraline 100 mg were continued • Her genetic testing results were not addressed
Baseline visit	• Patient continued feeling increasingly irritable, depressed and impatient so she had her first appointment with Mind-Body Medicine where her genetic testing results were discussed • Genetic testing guided treatment was initiated based upon the following genotypes: – COMT Met/Met: Bupropion was tapered and discontinued – SLC6A4 L(A)/S: Sertraline was tapered and discontinued; and duloxetine 30 mg was initiated – Compound heterozygous MTHFR mutation: L-methylfolate 10 mg daily was initiated • Within 1 week, zolpidem and alprazolam were discontinued

	PHQ-9 Total Score	GAD-7 Total Score
Baseline Visit	15	16
2nd Visit 15 days later	2	3
3rd Visit 34 days later	1	2

Conclusions:

High dose bupropion (≥200 mg daily) was beneficial for MDD patients with Val carrier COMT genotypes, but not for patients with a Met/Met genotype. Based upon COMT genotypes, Val carriers should be prescribed bupropion at doses ≥200mg. Met/Met individuals should avoid, or cautiously use, bupropion for MDD. Prospective studies are necessary to replicate this pharmacodynamic relationship between bupropion and COMT genotypes and explore economic and clinical outcomes.

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