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Clinical utility of pharmacogenetics-guided treatment of depression and anxiety

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ABSTRACT

Major depressive disorder (MDD) and generalized anxiety disorder (GAD) are associated with significant morbidity/mortality risk. Prolonged episodes increase impact on quality of life, risk for suicide, and harbor greater societal costs. Current management is inadequate as half of individuals do not respond to first-line therapies. Identification of an optimal treatment may hinge on exploiting interindividual genetic variability, which—in combination with other extraneous factors—is associated with heterogeneous antidepressant response. We evaluated the use of Genecept testing in an open-label trial of 468 patients, focusing on the methylenetetrahydrofolate reductase (*MTHFR*) and serotonin transporter (*SLC6A4*) genes and evaluating their plausibility as putative predictors of MDD/GAD treatment outcome. After receiving genotyping, 50.6% of clinicians made assay-congruent changes to treatment. This yielded a selective serotonin reuptake inhibitor (SSRI) discontinuation rate of 19.0% in patients with a risk *SLC6A4* genotype, and, an acute folate derivative addition rate of 41.8% in *MTHFR* risk allele carriers. After 8 weeks of treatment, patients with a risk *MTHFR* genotype that were treated with assay-guided treatment regimens—as compared to those that were not—demonstrated a greater reduction in Quick Inventory of Depressive Symptoms (QIDS-SR) and Undersøgelser (UKU) scores, and an increased quality of life score (Q-LES-Q-SF). *SLC6A4* risk patients who adhered to assay-guided treatment achieved a greater reduction in QIDS-SR and UKU scores and a statistically significant increase in Q-LES-SF scores, *versus* those that did not. Results support the utility of genotyping in the treatment of MDD/GAD and propose *SLC6A4* and *MTHFR* as biological predictors of treatment outcome.

Introduction

Varied drug response has long been recognized in the treatment of major depressive disorder (MDD) and generalized anxiety disorder (GAD). Of the approximately 3–7% of patients in the United States affected, nearly 50% fail to respond to first-line treatment regimens [1–3]. Influences such as environmental exposures, nutritional status, co-morbidities, severity of disease, and concomitant medications help to explain some unpredictable drug responses. However, genome wide association studies (GWAS) propose that genetic variation alone accounts for 42% of varied antidepressant response [4–9]. This presents an auspicious principle on which to base the delivery of personalized medicine.

Several classes of antidepressant medication have been shown to benefit individuals with MDD–selective serotonin reuptake inhibitors (SSRIs), selective norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), and monoamine oxidase inhibitors (MAOIs) are among the most widely used and well-studied [10]. SSRIs are currently the most commonly prescribed drug class for MDD treatment, though even within-class response to treatment varies considerably between patients and identification of the most appropriate medication is a continued challenge [11,12]. Antidepressant response does not show a classic Mendelian model of inheritance, but instead, a moderate number of loci—each with a small effect size—are proposed to be involved in response [13]. Pharmacogenetics research is actively attempting to link antidepressant treatment response to a portfolio of polymorphisms that correspond to brain circuitry/plasticity [14]. Theoretically, this will allow the personalization of MDD/GAD treatment by minimizing the use of 'trial-and-error' treatment. It is important to note that MDD and GAD likely have an overlapping genetic etiology [15]. This, in combination with high rates of comorbidity and ambiguity of onset, provide a strong case for treating MDD and GAD in the same manner [16–18].

Much research has focused on pharmacokinetic factors, specifically

Abbreviations: MDD, major depressive disorder; GAD, generalized anxiety disorder; QIDS-SR, Quick Inventory of Depressive Symptoms; Q-LES-Q-SF, Quality of Life Enjoyment and Satisfaction Questionnaire Short Form; UKU, Udvalg for Kliniske Undersøgelser Side Effect Rating Scale

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the liver metabolizing Cytochrome P450 (CYP450) superfamily of enzymes that is responsible for the oxidation of antidepressant medication. The *CYP450* genes mainly involved in antidepressant metabolism encode isoforms in the CYP2D6, CYP2C19, CYP2C9, and CYP3A4/5 enzymes. These genes are highly polymorphic and result in normal (EM-extensive metabolizer), abnormal (IM-intermediate, UM-ultrarapid, and PM-poor metabolizer), or aberrant metabolizer phenotypes [19]. Metabolizer status was demonstrated to be associated with antidepressant pharmacokinetics in a number of studies and variable rates of metabolism have been shown to increase the potential for adverse drug effects and reduce rates of compliance in patients taking antidepressants [20]. Despite the fact that the Food and Drug Administration (FDA) has incorporated genetic testing information into the labeling of nineteen antidepressants, pharmacogenetics testing has not been incorporated into treatment guidelines because of a gap in consistent evidence linking testing to clinical outcomes, i.e. clinical utility [21,22].

More recently, candidate gene studies aimed to detect an association between antidepressant response and catecholaminergic genes. The serotonin transporter gene (*SLC6A4*) is an obvious candidate as the serotonin transporter is the primary site of SSRI action [20]. A common 44-bp insertion/deletion polymorphism—referred to as the long (L_A) or short (S) forms of *SLC6A4*, respectively—was shown to impact transcription and ultimately levels of the serotonin transporter [23]. In addition to the S allele, a variant of the L allele in which the adenine (L_A) has been replaced with guanine (L_G), is also associated with reduced serotonin transporter levels and is functionally comparable to the S allele [24,25]. Patients with variant transporter translation exhibit lower remission rates, increased side effects, and intolerance to SSRIs [26]. Further, the S and L_G alleles of *SLC6A4* have been correlated with depression and anxiety-related symptomology and antidepressant response in numerous studies [23,27–31]. For example, a study of 36 patients suggested an association between fluoxetine response and *SLC6A4* genotype and identified S allele carriers as being at risk for developing insomnia and agitation with treatment [32]. Poor response to citalopram was associated with S/S genotypes [33]. Finally, a recent meta-analysis reported an associative model between SSRI response (OR: 1.58; 95% CI: 1.16–2.16, p = .004) and remission (OR: 1.53; 95% CI: 1.14–2.04, p = .004) in Caucasian *SLC6A4* L_A allele carriers [34].

Methylenetetrahydrofolate reductase (MTHFR) is a rate limiting enzyme in the production of L-methylfolate; L-methylfolate is a critical regulatory molecule in the synthesis of monoamine neurotransmitters associated with mood regulation (i.e. dopamine, norepinephrine, and serotonin) [35]. Although the *MTHFR* gene has not been directly linked to antidepressant response, numerous studies have identified a modest association with depression symptomology and disease [36–39]. Two *MTHFR* polymorphisms, C677T and A1298C, result in diminished enzyme activity, and moreover the T allele of C677T has been associated with decreased L-methylfolate levels [40]. As MDD has an established association with low serum folate levels [38,40], folate augmentation in patients unresponsive to SSRI/SNRI treatment improved patient adherence [41,42]. Further, a meta-analysis of 15,315 participants reported a significant relationship between folate status and depression (OR: 1.55; 95% CI: 1.26–1.91; p < .05) [38]. L-Methylfolate has been efficaciously used as an adjunctive therapy for patients with inadequate or poor SSRI response and was shown to improve adherence and decrease cost of care [41,42]. Therefore, an indirect link to *MTHFR* polymorphisms and antidepressant treatment outcome is likely.

Pharmacogenetic testing has the potential to reduce antidepressant discontinuation due to adverse events and increase overall efficacy. Ideally, pharmacogenetics would inform individualized decisions by identifying DNA variants that predict outcomes. Promising evidence, including increased quality of life and reduced depression/anxiety scores, were reported with assay-guided treatment of MDD patients [43]. To date, only two randomized controlled trials (RCTs) have been conducted to investigate the impact of pharmacogenetics testing on antidepressant outcome [44,45]; one reported a two-fold increase in depression symptom relief while the other reported a greater chance of disease remission with pharmacogenetics testing usage (2.52-fold; 95% CI: 1.71–3.73; Z: 4.66, p < .0001). Despite these promising results, a systematic review of guided-treatment *versus* usual care deemed current evidence inconclusive and condemns the widespread use of pharmacogenetics testing at the onset of MDD treatment [46].

The utility of pharmacogenetics testing remains unclear though—in part because of a relative lack of RCTs and an abundance of small cohort, statistically under powered studies—because the method by which pharmacogenetic testing influences clinical treatment is not well-established [47,48]. We therefore examined data from a naturalistic study of a commercial pharmacogenetic test to characterize how likely clinicians were to make test-concordant medication changes, and whether outcomes improved when assay-congruent medication regimens were implemented. As a means to thoroughly address this gap in the literature and realistically assess the utility of pharmacogenetics testing in the treatment of MDD/GAD, we aimed to (i) determine if pharmacogenetics testing influenced clinician decision-making and prescribing patterns, and, (ii) identify putative genetic predictors of treatment outcome.

Materials and methods

Patient cohort

A post-hoc analysis was performed on genotyping and outcomes data from a previously conducted clinical trial (ClinicalTrails.gov: NCT01507155) [43]. Original study design stipulated that adult patients must be diagnosed with a psychiatric disorder by a mental health care specialist who, for the purpose of this trial, ordered Genecept pharmacogenetic testing (n = 1024). Study participants were required to have the ability to complete electronic informed consents and be able to comprehend/complete online questionnaires. For the present study, primary diagnoses other than MDD (n = 297) or GAD (n = 171) were excluded. There were 468 patients in total evaluated in this analysis. Each of the 468 patients were evaluated by the clinician-reported outcome scales, but just 86 (18.4%) patients completed all of the patient-reported outcome questionnaires at each time point. Only patients that had full and complete data sets were included in this study (observed cases analysis). Clinicians were defined as mental health care professionals with the ability to prescribe medication and order a pharmacogenetics test, i.e. possession of a valid national provider identifier (NPI) number and prescribing privileges.

Genecept reporting

All clinicians were given information about trial design and goals and were willing clinicial participants. Clinicians were provided with a Genecept Report (Genomind King of Prussia, PA, USA) for each study participant at a one-month follow-up visit (to baseline visit). The report included genotyping results for ten genes (*SLC6A4*, *MTHFR*, 5HT2C, *COMT*, *CACNA1C*, *DRD2*, *ANK3*, *CYP2D6*, *CYP2C19*, *CYP3A4*) and details the implications of each genetic result on the use of a variety of FDA approved medications in the following classes: antidepressants, mood stabilizers/anticonvulsants, typical antipsychotics, atypical antipsychotics, anxiolytics, stimulants, nonsteroidal anti-inflammatory drugs (NSAIDs) and analgesics.

Genotypic processing

Of the ten genes that the Genecept Assay addressed, *SLC6A4* and *MTHFR* were the genes directly associated with antidepressant treatment. As the assay was designed to assess how one would respond to a variety of drug classes, limiting the evaluation to just genes that effect response to antidepressants was adequate for the purposes of this