Pharmacogenomics and Biomarkers of Depression

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Abstract

The standard of care for antidepressant treatment in major depressive disorder (MDD) is a trial-and-error approach. Patients often have to undergo multiple medication trials for weeks to months before finding an effective treatment. Clinical factors such as severity of baseline symptoms and the presence of specific individual (anhedonia or insomnia) or cluster (atypical, melancholic, or anxious) of symptoms are commonly used without any evidence of their utility in selecting among currently available antidepressants. Genomic and proteomic biomarker have gained recent attention for their potential in informing antidepressant medication selection. In this report, we have reviewed some of the major pharmacogenomics studies along with individual genetic and proteomic biomarker of antidepressant response. Additionally, we have reviewed the blood-based protein biomarkers that can inform selection of one antidepressant over another. Among all currently available biomarkers, C-reactive protein (CRP) appears to be the most promising and pragmatic choice. Low CRP (<1 mg/L) in patients with MDD predicts better response to escitalopram while higher levels are associated with better response to noradrenergic/dopaminergic antidepressants. Future studies

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are needed to demonstrate the superiority of a CRP-based treatment assignment over high-quality measurement-based care in real-world clinical practices.

Keywords
Antidepressant treatment selection biomarkers · C-reactive protein · Inflammation · Major depressive disorder · Pharmacogenomics

1 Introduction

Biological markers (or biomarkers) are objective measures of biological function that can be measured externally (Strimbu and Tavel 2010). As the name suggests, pharmacogenomics combines pharmacology (the study of medications) and genomics to evaluate the role of genetics in an individual patients' response to medications. The interest in pharmacogenomics and biomarkers of depression has been driven by the limited utility of clinical markers in improving treatment outcomes of patients with major depressive disorder (MDD). Despite lacking supportive evidence, the standard of care for antidepressant prescription in clinical practice is based on subjective factors such as anticipated side effect profile of medications, patient or provider preference, cost, and availability on insurer's approved drug lists (Gelenberg et al. 2010). Comparison of antidepressant medications in head-to-head trials has failed to find any significant difference (Gartlehner et al. 2011). Previous studies that have evaluated clinical factors such as baseline depression severity (Friedman et al. 2012), early age of onset (Sung et al. 2013), chronic depression (Sung et al. 2012), presence of insomnia (Sung et al. 2015), or presence of atypical, melancholic, or anxious features (Bobo et al. 2011; Arnow et al. 2015) have failed to find any significant difference in treatment outcomes among currently available antidepressant medications. Thus, a biomarker-driven approach is advocated to individualize selection of antidepressant treatments in order to enhance recovery and treatment adherence and minimize the likelihood of adverse events and attrition from care (Trivedi 2016; Gadad et al. 2018a). Due to the broad scope, we will restrict the discussion to biomarkers that can be assayed from blood and predict response to antidepressant medications in patients with major depressive disorder (MDD).

2 Major Pharmacogenomic Studies of Antidepressant Response

1. *Sequenced Treatment Alternatives to Relieve Depression (STAR*D):* The STAR*D study enrolled treatment seeking outpatients from primary care and psychiatric outpatient clinics who were enrolled in open-label monotherapy with citalopram during the first level. A large proportion of STAR*D participants ($n = 1914$) provided samples for genetic analyses that were used to predict improvement and adverse events with antidepressant treatment (Laje et al. 2009). Laje et al. reviewed the strengths and limitations of STAR*D sample

along with the findings of pharmacogenomic results until 2009 in an exhaustive report (Laje et al. 2009). Briefly, novel variants in serotonin receptor (HTR2A), glutamate receptor (GRIK4), and potassium channel (KCNK2) predicted improvement with citalopram. Notably, association of improvement with polymorphisms in pharmacokinetic genes was not significant. Treatment-emergent suicidal ideations and sexual dysfunction were associated with polymorphisms in genes coding for glutamate receptor and immune regulatory pathways (Laje et al. 2009). In the last few years, STAR*D data has also been used to replicate findings from other studies, as described below.

2. *Munich Antidepressant Response Signature (MARS):* The MARS project enrolled patients ($n = 842$) with MDD or bipolar disorder who were admitted to a psychiatric hospital for an ongoing major depressive episode in order to understand the biological mechanisms (genetic and hormonal markers) of response to antidepressant treatment (Hennings et al. 2009). Among genetic markers, the MARS project focused on both pharmacokinetic (related to drug efflux) and pharmacodynamic (related to regulation of glucocorticoid receptor) genetic markers (Holsboer 2001). Among hormonal markers, the MARS project focused on the release of cortisol using the dexamethasone suppression/corticotropin-releasing hormone (CRH) stimulation test. More recent reports from the MARS project have identified polymorphisms in brain-derived neurotrophic factor (BDNF) and its receptor as predictive of antidepressant response (Hennings et al. 2013).
3. *Genome-Based Therapeutic Drugs for Depression (GENDEP):* This open-label study enrolled patients with MDD for treatment with flexible doses of either escitalopram or nortriptyline (Uher et al. 2009). The initial report ($n = 760$) from the GENDEP study utilized a candidate gene approach evaluating 116 single-nucleotide polymorphisms (SNPs) from 10 candidate genes and found and association of serotonin receptor genes (HTR2A) with response to escitalopram and an association of the norepinephrine transporter (SLC6A2) with response to nortriptyline (Uher et al. 2009). In a subsequent study ($n = 796$) that utilized a candidate gene approach for treatment-emergent suicidal ideation, there was a significant association of polymorphism in BDNF (rs962369) and its receptor (Perroud et al. 2009).
4. *Pharmacogenomics Research Network Antidepressant Medication Pharmacogenomic Study (PGRN-AMPS):* This study enrolled patients ($n = 529$) with nonpsychotic MDD for an 8-week trial of either citalopram or escitalopram (Mrazek et al. 2014). Reports from this study have focused on the role of pharmacokinetic genes on levels of antidepressant medications. Specific SNPs were associated with levels of escitalopram (s-enantiomer of citalopram) and its metabolite in or near cytochrome p450 2C19 and 2D6 genes (Ji et al. 2014). Investigators from this study also informed the development of commercially available combinatorial genetic testing to prescribe antidepressant treatment (Mrazek et al. 2014; Altar et al. 2013). In a recent report, such a combinatorial approach was shown to be superior in efficacy rates as compared to a treatment as usual approach (Altar et al. 2015).

5. *International Study to Predict Optimized Treatment in Depression (iSPOT-D):* In this large multi-site study conducted in five countries, genetic information from patients with MDD ($n = 683$) was analyzed to predict differential rates of improvement and adverse events to escitalopram, sertraline, or venlafaxine (Schatzberg et al. 2015). The genetic analyses, described below, have focused on SNPs in genes regulating drug efflux across the blood-brain barrier and hypothalamic-pituitary-adrenal (HPA) axis (Schatzberg et al. 2015; O'Connell et al. 2018b).
6. *International SSRI Pharmacogenomics Consortium (ISPC):* This consortium focused predominantly on genes involved with response to selective serotonin reuptake inhibitors (SSRIs) and enrolled patient with MDD at seven sites from five different countries including those in North America, Europe, and Asia (Biernacka et al. 2015). In a large sample of patients ($n = 865$), there was no SNP that attained genome-wide level of significance (Biernacka et al. 2015).
7. *Combining Medications to Enhance Depression Outcomes (CO-MED) trial:* In this large single-blind study of outpatients with MDD comparing escitalopram monotherapy with combinations of escitalopram and bupropion and of venlafaxine and mirtazapine, blood samples were obtained from a subgroup of participants ($n = 459$) for genetic analyses. In a recent genome-wide association study (GWAS) of the three treatment arms, a SNP (rs10769025) in the ALX4 gene on chromosome 11 was significantly associated with response ($\geq$50% reduction in symptoms) at week 6 with escitalopram but not with the other two antidepressant combinations (Gadad et al. 2018b).
8. *Genome-wide association studies (GWAS) meta-analyses:* Multiple reports have now combined samples from the above-described studies to conduct GWAS meta-analyses to identify differences using a larger sample size. In a GWAS analyses of 1.2 million SNPs in individuals of northern European ancestry ($n = 2{,}256$) from the GENDEP, MARS, and STAR*D studies, there was no SNP that met the threshold for genome-wide association with symptom improvement over a 12-week period (Investigators et al. 2013). Additionally, a polygenic risk score derived from the GENDEP and MARS studies accounted for only 1.2% variance in outcomes in the STAR*D study (Investigators et al. 2013). Similarly, a meta-analysis of ISPC, STAR*D, and PGRN-AMPS failed to find any SNP with genome-wide significance for predicting response to SSRI antidepressants (Biernacka et al. 2015).

3 Genetic Biomarkers of Antidepressant Response

1. *Drug Efflux:* Genetic polymorphisms also known as ABCB1 have been investigated for predicting response to antidepressant medications. Polymorphisms in MDR1/ABCB1 genes that code for P-glycoprotein (P-gp), an efflux pump at the blood-brain barrier that regulates the level of antidepressants such as citalopram and venlafaxine that are substrates of P-gp (Uhr et al. 2008), have been widely studied for predicting antidepressant response. While there are multiple studies showing an association of MDR1/ABCB1 SNPs with response

to antidepressant medications that are P-gp substrates (Uhr et al. 2008; Gex-Fabry et al. 2008; Kato et al. 2008; Nikisch et al. 2008; Dong et al. 2009), others have failed to find any significant association of these SNPs with either response or adverse events (Laika et al. 2006; Peles et al. 2008; Peters et al. 2008). In a recent report, Schatzberg et al. tested for ten SNPs in or near the ABCB1 location for their association with either improvement (remission of depressive symptoms) or side effect severity (Schatzberg et al. 2015). Of the nine SNPs investigated, they found that one (rs10245483, a functional SNP upstream of ABCB1) was differentially associated with improvement and side effect severity. The major G allele and minor T allele of this SNP predicted differential outcomes with SSRIs (escitalopram or sertraline) and venlafaxine [serotonin and norepinephrine reuptake inhibitor (SNRI)]. Remission rates were higher with SSRIs than venlafaxine in G/G homozygotes for this SNP. Conversely, in T/T homozygotes, remission rates were significantly higher with venlafaxine than SSRIs (Schatzberg et al. 2015).

2. *Neurotransmitter Transport and Transmission*
   (a) *Serotonin transporter:* Polymorphisms in the serotonin transporter linked polymorphic region (5-HTTLPR) of the SLC6A4 gene influence serotonin reuptake and have been investigated widely for antidepressant response. In the STAR*D study, while an initial report suggested no significant association (Kraft et al. 2007), a follow-up study showed differential treatment outcomes with citalopram only in non-Hispanic white subjects and not in Hispanic white and black subjects (Mrazek et al. 2009). In a systematic meta-analysis, Procelli et al. found a strong association between polymorphism in 5-HTTLPR and treatment outcomes with selective serotonin reuptake inhibitors (SSRIs) in Caucasians but not in Asians (Porcelli et al. 2012). Notably, several studies have failed to find association of 5-HTTLPR polymorphism with antidepressant outcomes (Maron et al. 2009; Perlis et al. 2010).
   (b) *Serotonin receptor:* A specific SNP (rs7997012) of the serotonin receptor 2A (HTR2A) gene was significantly associated with antidepressant response in both STAR*D and the MARS studies (McMahon et al. 2006; Peters et al. 2009; Lucae et al. 2010). However, other studies failed to replicate this association but found associations with other SNPs of HTR2A and antidepressant treatment outcomes (Uher et al. 2009; Horstmann et al. 2010). Adding to the variability of these findings, other studies did not find an association of HTR2A SNPs with outcomes but implicated other serotonin receptors (HTR1A) (Hong et al. 2006).
   (c) *Dopamine metabolism:* The catechol-O-methyltransferase (COMT) val/met polymorphism (rs4680) has been associated with response to antidepressant medications. The val/val genotype is associated with higher activity of the COMT enzyme than the val/met and met/met genotypes (Chen et al. 2004). In a study of Caucasian patients with MDD ($n = 256$), the val/val genotype was associated with significantly less likelihood of response from weeks 4 to 6 (Baune et al. 2007). Interestingly, in MDD patients who have failed to respond to multiple antidepressant treatments, those with the val/val

genotype had a much higher chance of responding with electroconvulsive therapy (Anttila et al. 2008). These findings were partially replicated in a separate sample of treatment-resistant depressed patients where the association of val/val genotype was associated with greater improvement only in females but not males (Katharina et al. 2010).

(d) *Glutamate:* Association of response to antidepressant treatment with polymorphisms in ionotropic glutamate receptors (GRIK4) has been reported in STAR*D, MARS, and other studies (Horstmann et al. 2010; Paddock et al. 2007; Pu et al. 2013). However, these findings were not replicated in studies by Perlis et al. (2010) and Serretti et al. (2012) who failed to replicate these associations.

(e) *Monoamine* metabolism: While variations in genes coding for the type A monoamine oxidase A (MAO-A) enzyme exist, the principal catabolic enzyme of monoamine neurotransmitters has been associated with response to mirtazapine in female patients with MDD (Tadić et al. 2007). Studies of bupropion (Tiwari et al. 2013) and fluoxetine (Peters et al. 2004) failed to replicate these findings.

3. *Liver Enzymes:* Tests for common polymorphisms in genes encoding for cytochrome P450 (CYP) enzymes, which can affect the metabolism of antidepressant medications, are included in commercially available kits (O'Connell et al. 2018b) and may be used to classify patients on the basis of their metabolism of individual drugs (extensive, intermediate, poor, or ultrarapid metabolizers) (Porcelli et al. 2011). The utility of these polymorphisms is mainly restricted to predicting adverse events (Porcelli et al. 2011). The association of CYP SNPs with response to antidepressant medications was negative in the STAR*D and GENDEP studies (Peters et al. 2008; Hodgson et al. 2015). Consistent with these reports, a recent review of combinatorial pharmacogenetic tests found that the clinical utility of these tests is limited and may be informative in predicting adverse events with antidepressants (Zeier et al. 2018).
4. *Hypothalamic-Pituitary-Adrenal (HPA) Axis*

(a) *FK506-binding protein 5 (FKBP5)*: Variants in gene coding for FKBP5, a protein regulating glucocorticoid receptor, were initially identified by Binder et al. to show strong association with response to antidepressant medication and risk of recurrence using sample from MARS study ($n = 233$) and replicated in an independent sample of patients ($n = 85$) (Binder et al. 2004). Interestingly, they found an association of these polymorphisms with levels of FKBP5 protein but not with mRNA (Binder et al. 2004). The levels of FKBP5 protein, in turn, were associated with levels of cortisol after dexamethasone suppression/CRH stimulation. The association of functional genetic variants of FKBP5 with antidepressant response was replicated in independent samples using STAR*D and PGRN-AMPS studies (Ellsworth et al. 2013). However, Uher et al. failed to find any association of FKBP5 polymorphisms with antidepressant response in GENDEP (Uher et al. 2009).

(b) *Corticotropin-releasing hormone (CRH)*: A recent report evaluated 16 candidate polymorphisms in 5 CRH and cortisol-associated genes and found 1 (rs28365143) that was differentially associated with treatment response in the iSPOT-D study (O'Connell et al. 2018a). Participants of iSPOT-D who

were homozygotes for the G allele and were treated with SSRIs (escitalopram or sertraline) had significantly higher response and remission rates than those who carried A alleles (A/G and A/A) (O'Connell et al. 2018a). This pattern of association was replicated in a separate sample of depressed outpatients (O'Connell et al. 2018a).

4 Protein Treatment Selection Biomarkers (Moderators)

In contrast to clinical markers which have failed to guide antidepressant treatment selection, several biomarkers have shown potential in guiding antidepressant treatment selection in recent reports. Most of these are related to immune dysfunction or inflammation. Notable in this regard is the role of obesity, which has been shown to partly account for elevated inflammatory markers in patients with MDD (Shelton et al. 2015). Two recent reports suggest that body mass index (BMI), a commonly used measure of obesity, can guide selection of antidepressant medications. While depressed patients with normal BMI respond better to SSRIs, those with BMI >35 respond better to either venlafaxine monotherapy or a combination of SSRI's and bupropion (Jha et al. 2018a; Green et al. 2017). A variety of protein biomarkers have been shown to differentially predict antidepressant response (Jha and Trivedi 2018).

1. *C-reactive protein (CRP):* CRP is a plasma protein which is synthesized mainly by the liver and increases markedly in response to acute infection or injury and thus is also labelled as an acute-phase reactant. Levels of CRP below 1 mg/L have been associated with low likelihood of cardiovascular mortality than those about CRP >3 mg/L. In a recent report, CRP in plasma was shown to have very high correlation (coefficient = 0.855) with CRP in cerebrospinal fluid suggesting the utility of CRP in blood as a marker of central nervous system inflammation. In the GENDEP study, Uher et al. studied differential treatment outcomes with escitalopram vs. nortriptyline at three thresholds of CRP (<1 mg/L, 1–3 mg/L and >3 mg/L). They found that escitalopram was significantly superior to nortriptyline in MDD patients with CRP <1 mg/L. Conversely, among those with CRP ≥1 mg/L, nortriptyline was superior to escitalopram (Uher et al. 2014). These findings were partly replicated in the CO-MED trial where the combination of bupropion-escitalopram was considered analogous to nortriptyline in pharmacological profile. In the CO-MED trial, patients with CRP <1 mg/L had significantly higher remission rates with escitalopram monotherapy (57.1%) than bupropion-escitalopram combination (33.3%). Conversely, among those with CRP ≥1 mg/L, remission rates were significantly higher with bupropion-escitalopram combination (51.4%) than escitalopram monotherapy (29.7%) (Jha et al. 2017a). Taken together, these findings support the utility of CRP in blood as treatment selection biomarker (Miller et al. 2017).
2. *Interleukin 17 (IL-17):* Recent reports suggest the role of IL-17-mediated immune response in pathophysiology of depression (Beurel et al. 2013). Elevated levels of IL-17 have also been associated with greater severity of anhedonia in male

patients with MDD (Jha et al. 2018b). Hence, a recent report from CO-MED trial explored a panel of cytokines containing IL-17, Th1- (interferon gamma and tumor necrosis factor alpha), Th2- (IL-4, IL-5, IL-9, and IL-13), and non-T-cell-related (IL-1β, IL-1 receptor antagonist, IL-6, IL-8, and macrophage inflammatory protein (MIP) 1 α and β) markers as moderators of antidepressant treatment outcomes. In this report, only IL-17 was associated with differential treatment outcomes. Elevated IL-17 levels were associated with greater reduction in depression severity with the bupropion-escitalopram combination only. There was no such association with either escitalopram monotherapy or venlafaxine-mirtazapine combination (Jha et al. 2017b).

3. *Biomarkers of blood-brain barrier (BBB) dysfunction:* Disruption of the blood-brain barrier has gained recent attention for its role in pathogenesis of depressive symptoms (Cheng et al. 2018). In response to BBB disruption, pericytes can be recruited to breach the disruption. Platelet-derived growth factor (PDGF) has been shown to be critical in the activity of pericytes and increase in response to BBB disruption. Additionally, BBB disruption can also lead to increase in levels of astrocytic markers such as S-100 calcium binding protein B (S100B) as they escape out of CNS into peripheral circulation. The hypotheses of BBB dysfunction in predicting antidepressant response were tested in two different reports in the CO-MED trial. Elevated levels of PDGF were associated with greater reduction in overall depression severity and anhedonia with bupropion-escitalopram combination with no similar association seen for escitalopram monotherapy or venlafaxine-mirtazapine combination (Jha et al. 2017c). Interestingly, improvement in anhedonia completely accounted for the change in depressive symptom severity suggesting that these differences were driven by changes in severity of anhedonia. In a separate report, pre-treatment levels of S100B were differentially associated with changes in anhedonia severity. Among those treated with escitalopram monotherapy, low S100B (reflecting greater BBB integrity) was associated with better outcomes (Jha et al. 2018c). Among those treated with bupropion-escitalopram or venlafaxine-mirtazapine combinations, there was no similar association.

5 Conclusions and Recommendations

The last few decades have seen tremendous advances in our understanding of the biological underpinnings of depression. However, these findings have not translated in improved outcomes for patients with MDD. Pharmacogenomic tools, while in wide use, have proven to be of little benefit in predicting improved treatment outcomes. In this regard, CRP seems to be the most promising and pragmatic biomarker. It is readily available through commercial laboratories, is stable in biospecimens under varying conditions of storage and processing, and can even be measured with point-of-care finger-stick devices. However, future trials are needed to test if implementing a CRP-based treatment assignment in real-world clinical practices will result in higher rates of remission as compared to high-quality care delivered by clinicians.

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