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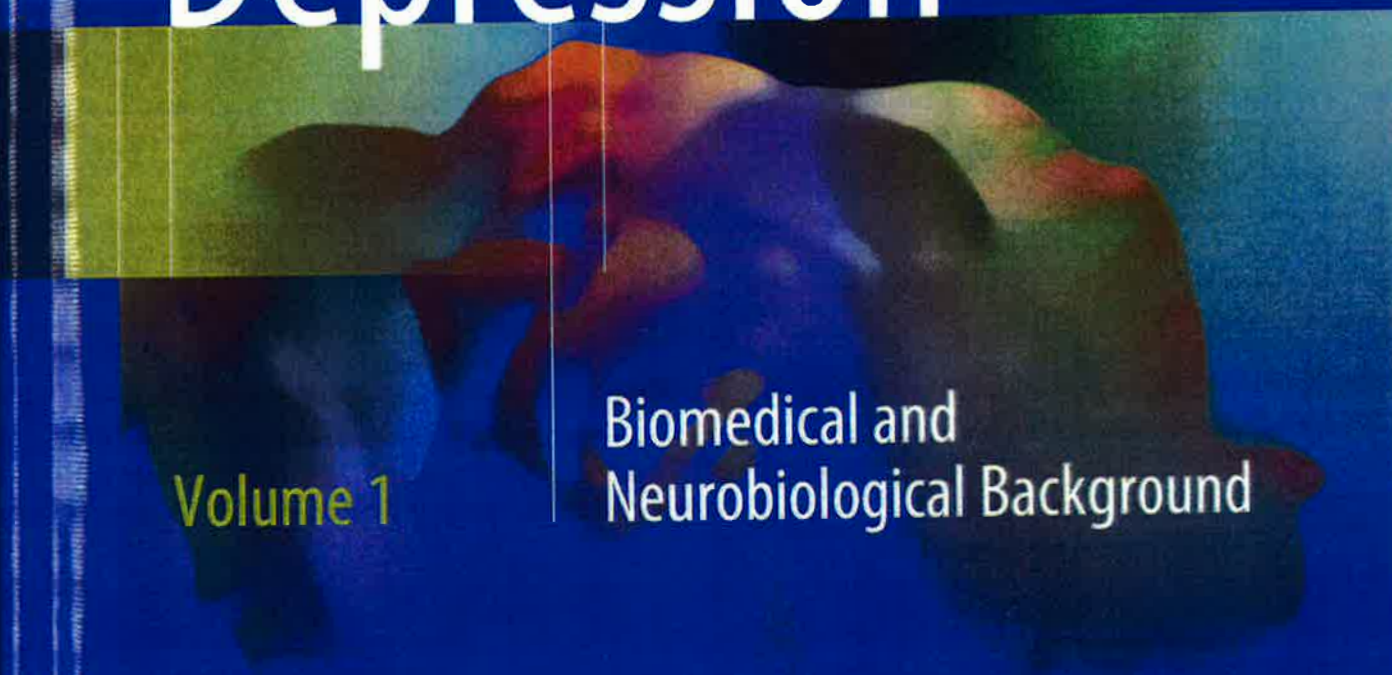
Editor

Understanding Depression



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Precision Psychiatry: Personalized Clinical Approach to Depression

21

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21.1 Personalized Medicine in Major Depressive Disorder

Personalized medicine is a valuable approach to disease prevention and treatment. It proposes tailoring health care by integrating genetics and epigenetic factors, brain imaging findings, clinical aspects, and environmental factors (Perna and Nemeroff 2017). The aim of personalized medicine in major depressive disorder (MDD) is to predict more accurately disease susceptibility and to tailor the most effective treatment for each individual (Prendes-Alvarez and Nemeroff 2016).

This strategy is important in the treatment of patients with MDD, one of the most prevalent and severe of the major psychiatric disorders. Indeed, MDD affects more than one hundred million people worldwide and increases the risk of suicide by 20 times (Korte et al. 2015). It is among the leading causes of disability, lost workdays, and income.

Although some patients with MDD only suffer from a single depressive episode, many, if not most, experience multiple episodes and, for others, a progressive and chronic illness. As initially observed by Kraepelin (Jablensky 1999), clinical features suggestive of progression include reduced inter-episode duration as a function of increasing number and length of episodes over time. Clinical, neurochemical, and structural and functional neuroimaging studies support the idea that the progressive course of MDD is related to a pathological reorganization of the central nervous system (CNS) during the course of the illness, defined as "neuroprogression" (Moylan et al. 2013). This reorganization is characterized by structural and functional brain abnormalities posited to be due to neural apoptosis, neurodegeneration, and decreased neuroplasticity. Such neuroprogression may arise from several sources including the activation of immuno-inflammatory and oxidative and nitrosative stress pathways as well as hypercortisolism.

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A myriad of studies have revealed that substantially fewer than 50% of patients with MDD achieve remission following treatment with antidepressants and/or psychotherapy. This may be explained by, in part, the heterogeneity of depression. Indeed, depression is now conceptualized as a systemic disease influencing several biological processes, such as inflammation, neuroendocrine function, platelet activity, autonomic nervous system activity, and cardiovascular and bone metabolism (Sotelo and Nemeroff 2017). As an example, remission of clinical depression has been reported to be accompanied by a normalization of inflammatory markers; in contrast lack of response is associated with persistently elevated levels of pro-inflammatory cytokines (Eller et al. 2008), a factor that may contribute to neuroprogression and to a negative clinical outcome. Similarly, child maltreatment, a documented vulnerability factor for adult MDD, is associated with increased levels of C-reactive protein (CRP), an inflammatory biomarker that is indicative of systemic inflammation (Coelho et al. 2014). The personalized medicine approach, which is able to integrate biological and environmental factors, can likely contribute not only to improved remission rates but also to ameliorate the longitudinal course of the illness.

The present chapter summarizes different factors that may serve as possible indicators of susceptibility to MDD and predictors of treatment response.

21.2 Major Depressive Disorder and Symptom-Based Subtypes

The fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) (American Psychiatric Association 2013) describes MDD as a condition characterized by at least 2 weeks of depressed mood (i.e., hopeless, feeling sad or empty) and/or loss of interest and pleasure (anhedonia) accompanied by at least four additional depressive symptoms, present almost every day and for most of the day. Additional symptoms include increased or decreased appetite and/or significant changes in body weight, insomnia or hypersomnia, psychomotor agitation or retardation, loss of energy (fatigue), feelings of guilt or worthlessness, impaired concentration or indecisiveness, recurrent thoughts of death, and suicidal ideation or any attempt. Different specifiers are given to diagnose symptom-based subcategories of MDD, in particular MDD with melancholic features, MDD with atypical features, and, newly introduced by DSM-5, MDD with anxious distress, characterized by additional anxiety symptoms (American Psychiatric Association 2013).

Some of the symptoms listed in the DSM-5 description, in particular those relating to appetite/body weight, sleep, and psychomotor activation, differ in the various subtypes of MDD (Lamers et al. 2010; Korte et al. 2015). Patients with melancholic features experience loss of appetite and weight loss, insomnia, and psychomotor agitation whereas atypical depression is associated with increased appetite/weight gain, fatigue, hypersomnia, and psychomotor retardation (Baldwin and Papakostas 2006). Contrasts emerge from neuro-immuno-neuroendocrinological findings. In melancholic depression, there is a hyperactivity of the corticotropin-releasing hormone (CRH) system and the hypothalamic-pituitary-adrenal (HPA) axis (Stewart et al. 2005; Wong et al. 2000), whereas in atypical depression a CRH deficiency and a reduction of HPA axis activity have been reported (Lamers et al. 2010). Although MDD with melancholic features and with atypical features are different in several clinical and biological aspects, the International Study to Predict Optimized Treatment in Depression (iSPOT-D) showed that remission rates and symptom reduction did not differ among the melancholic, atypical, and anxiety subtypes at least not in the first 1000 subjects (Arnow et al. 2015). The three depression subtypes did not differ in response to three frequently used antidepressants: escitalopram, sertraline, and venlafaxine extended release. More than one third of the participants with MDD met the criteria for two or more subtypes, with no evidence that the mixed subtypes selectively predicted outcome (Uher et al. 2011). These results are consistent with data from the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) (Trivedi et al. 2006), the largest trial

enrolling patients with MDD seeking routine medical or psychiatric care. Overall, these findings do not currently support the clinical utility of symptom-based subtypes of MDD in selecting the best antidepressant treatment for each patient. One clear exception is MDD with psychotic features, which absolutely requires treatment with combination antidepressant-antipsychotic medications or electroconvulsive therapy (American Psychiatric Association (APA) 2010).

In order to improve the management of patients with MDD, clinical symptoms will likely need to be integrated with other factors contributing to each patient's profile, such as genetic, epigenetic, endophenotypes/biomarkers, and environmental influences.

21.3 Endophenotypes/ Biomarkers

Because psychiatric disorders are currently primarily defined on the basis of sign and symptoms, often shared by several disorders, one major goal of psychiatric research is to identify more defined and quantifiable endophenotypes with associated biomarkers.

Criteria defining endophenotypes include being heritable and more prevalent in affected families than in unaffected ones, segregating with the illness in the population and co-segregating with the illness within families, not depending on whether the illness is clinically manifested, being specific to the illness, and being reliably measurable (Gottesman and Gould 2003). Biomarkers are measurable characteristics reflecting biological function or dysfunction, response to therapeutic interventions, and natural progression of the illness (Biomarker Definition Working Group 2001; Ozomaro et al. 2013). The distinctions between endophenotypes and biomarkers are subtle with a partial overlap between these two concepts. Endophenotypes are trait markers, whereas biomarkers may be either state or trait markers.

The identification of endophenotypes/biomarkers would help to identify individuals at risk of developing a disease, and more likely to predict the response to treatments in a less heterogeneous disease population (Alhajji and Nemeroff 2015). To date, available data do not allow the identification of clear endophenotypes/biomarkers able to predict the development of subsequent MDD in at-risk populations and the prediction of antidepressant treatment outcomes. However, there are several promising candidates that need to be tested in longitudinal studies.

21.3.1 Prediction of Disease Vulnerability

21.3.1.1 Clinical Features

Negative mood and anhedonia have been proposed as endophenotypes.

The relationship between daily life negative mood bias and the lifetime diagnosis of MDD was investigated in a population of 259 female twin pairs. Probands with co-twins meeting a diagnosis for lifetime depression exhibited greater negative affect responsiveness to daily life stressors, after controlling for past or current depression in probands (Wichers et al. 2007).

Anhedonia often precedes the onset of MDD and is associated with a family history of depression in unaffected relatives (Hecht et al. 1998). It predicts depression 2 years later (Wardenaar et al. 2012), poor outcomes (McMakin et al. 2012), and chronic course of depression over a 10-year period.

Functional magnetic resonance imaging (fMRI) was used to evaluate whether deficits in brain reward systems, which are posited to be the neural basis of anhedonia, are present in those at risk for developing MDD. Compared with healthy controls, recovered MDD patients showed a decreased neural response in the ventral striatum to pleasant stimuli and an increased response in the caudate nucleus to aversive stimuli, suggesting that even MDD remitted patients may have deficits in the neural basis of reward (McCabe et al. 2009).

21.3.1.2 Blood-Based and Cerebrospinal Fluid Biomarkers

Studies of monoaminergic biomarkers such as peripheral and cerebrospinal fluid (CSF) concentrations of serotonin, dopamine, and noradrenaline

and their metabolites reported inconsistent results (Kunugi et al. 2015), though there is general agreement that reduced CSF 5-hydroxyindoleacetic acid (5-HIAA) concentrations are associated with increased suicidality.

A meta-analysis of longitudinal studies (Valkanova et al. 2013) revealed that an increase in the inflammatory markers C-reactive protein (CRP) and interleukin (IL)-6 has a small but significant association with the subsequent development of depressive symptoms, supporting the hypothesis of a causal pathway from inflammation to depression. Different inflammatory markers in MDD patients appear to be linked to different depression subtypes. Two studies (Lamers et al. 2013; Rudolf et al. 2014) found that increased inflammatory marker levels, in particular IL-6, were associated with atypical depression as compared to typical or melancholic depression.

Lipids, which have a central role in neuronal function, have been proposed as a potential family of peripheral biomarkers (Van Heesch et al. 2014). The main finding, when comparing MDD patients with controls, is an altered lipid profile. In particular an increase of low-density lipoproteins (LDL) and omega-6 levels and a decrease of high-density lipoproteins (HDL) and omega-3 levels have been reported (Parekh et al. 2017).

Brain-derived neurotrophic factor (BDNF) is the most common neurotrophin in the human brain and shows promising features as a MDD biomarker. In line with the neurotrophin hypothesis of depression, which posits that a scarcity of BDNF contributes to the pathophysiology of depression by decreasing neuronal plasticity, low BDNF blood levels have been consistently reported in patients with MDD (Neto et al. 2011). The relationship of blood to CNS levels of BDNF remains obscure.

21.3.1.3 Neuroimaging

Both structural and functional neuroimaging are potentially useful methods to identify phenotypes indicative of vulnerability to MDD. Patients with MDD showed significantly smaller hippocampal volumes, though it remains unclear whether this is a consequence of the disorder, a consequence of early life trauma (Rao et al. 2010), or if it precedes the onset of the disease (Rao et al. 2010; Schmaal et al. 2016). Decades of task-based fMRI have identified brain circuits with altered functional activity, e.g., the increased amygdala reactivity in patients with MDD while processing negative stimuli (Siegle et al. 2002). More recently, resting-state fMRI, which allows the identification of spontaneous activity of brain networks, i.e., brain areas that increase or decrease their activity synchronically, has been investigated in MDD. The hyperactivity of the default mode network (DMN), which is active during internally directed mental states, such as introspective states, has been reported in MDD patients (Sheline et al. 2010).

21.3.2 Prediction of Antidepressant Treatment Outcome

21.3.2.1 Blood or Other Peripheral Measures

Efforts in the identification of predictors of differential antidepressants treatment response based on blood or other peripheral measures date back several decades.

Evidence of HPA axis hyperactivity, including but not limited to increased blood/CSF/urinary cortisol levels and CSF concentrations of CRH (Nemeroff et al. 1984), non-suppression of cortisol in the dexamethasone suppression test (DST), and the dexamethasone-CRH (DEX/CRH) test, have been observed in up to than 70% of patients with MDD (Vreeburg et al. 2009) especially in severe/melancholic MDD. Several studies have reported that SSRIs decrease HPA axis hyperactivity (Nikisch et al. 2005), though contradictory findings exist (Deuschle et al. 2003). Because effects of antidepressants on the HPA axis seem to occur mainly in MDD patients responsive to treatment (Deuschle et al. 2003; Nikisch et al. 2005), it has been suggested that resolving HPA axis abnormalities during MDD treatment is indicative of SSRI response.

Changes in response to the DST in MDD patients receiving antidepressants might represent a laboratory marker of treatment outcome. Most non-suppressors had progressive normalization of DST responses in conjunction with

clinical improvement, and failure to normalize was often associated with poorer clinical outcome (Greden et al. 1983).

After CRH became available for clinical studies, the DST was combined with CRH administration and the resulting combined DEX/CRH test proved to be more sensitive in detecting HPA system changes than the original DST. Elevated cortisol release after the DEX/CRH test has been consistently observed in patients in an acute major depressive episode, and normalization of the DEX/CRH test was shown to precede or parallel response to antidepressant treatment. Sustained non-suppression of the HPA axis in MDD patients undergoing the DEX/CRH test predicts a poorer outcome of treatment response (Binder et al. 2009) and may be associated with depressive relapse (Aubry et al. 2007).

There is evidence of an interaction between inflammatory processes and antidepressant response (Miller and Raison 2016). MDD is characterized by low-grade inflammation, revealed by higher concentrations of inflammatory biomarkers such as C-reactive protein (CRP), tumor necrosis factor (TNFα), and interleukin 6 (IL-6) (Howren et al. 2009). A meta-analysis (Strawbridge et al. 2015) supports the view that heightened levels of inflammation may contribute to treatment refractoriness. Non-steroidal anti-inflammatory drugs might be beneficial as adjunctive treatments in unipolar (Akhondzadeh et al. 2009) and bipolar (Nery et al. 2008) depressed patients. Although the levels of IL-6 decreased with antidepressant treatment regardless of outcome, persistently elevated levels of TNFα were associated with prospectively determined treatment resistance (Strawbridge et al. 2015). This last result is strengthened by the findings that a TNFα antagonist, infliximab, can improve depression in treatment-resistant patients with higher basal levels of inflammation as defined by elevations in CRP (Raison et al. 2013).

The putative role of IL-6 plasma concentrations as a reliable marker of antidepressant response is still highly debated. Higher serum levels of IL-6 predicted response to ketamine, an *N*-methyl-D-aspartate receptor antagonist that produces a rapid antidepressant effect in patients with treatment-resistant MDD (Yang et al. 2015).

CRP levels have been used to differentially evaluate treatment efficacy in response to antidepressants and the results are discordant. A recent meta-analysis (Strawbridge et al. 2015) and a study by Schmidt et al. (2016) did not find an association between baseline CRP levels and response to antidepressants; in contrast others reported a positive association (Uher et al. 2014; Jha et al. 2017; Mocling et al. 2017).

The role of peripheral BDNF concentrations in the prediction of antidepressant efficacy is also unclear. Higher baseline serum BDNF levels were reported to predict antidepressant treatment response (Mikoteit et al. 2014), but low baseline levels were as well (Nase et al. 2016). Clinical response has also been reported in the absence of a BDNF increase (Başterzi et al. 2009). A recent meta-analysis (Polyakova et al. 2015) concluded that antidepressant treatment increases serum BDNF levels in MDD in responders and remitters significantly more than in non-responders.

21.3.2.2 Electroencephalogram

A number of different electroencephalography (EEG)-derived biomarkers, mainly change in frequency band (alpha and theta) measures, antidepressant treatment response index (ATR), and event-related potentials (ERPs), have been the focus of investigations as potential biomarkers of antidepressant response in MDD.

Early studies reported that pretreatment changes in the alpha band differentiate responders from non-responders to the tricyclic antidepressant imipramine and the SSRIs (Knott et al. 1996; Knott et al. 2000; Bruder et al. 2008). However, data derived from iSPOT-D, a multicenter, randomized, prospective trial, in which 1008 MDD participants were randomized to escitalopram, sertraline, or venlafaxine-XR, concluded that alpha in the occipital and frontal cortex was not associated with treatment outcome (Arns et al. 2016).

Early studies investigating pretreatment changes in the theta band reported conflicting results. When a more sensitive method to localize cerebral sources from where EEG signals generate, the low-resolution electromagnetic tomo-

graphic analysis (LORETA), was applied, studies found more consistently an association between elevated pretreatment theta current density in rostral anterior cingulate cortex (rACC) and response to a variety of antidepressants in MDD (Pizzagalli 2011; Koo et al. 2017). More recently, however, iSPOT-D data was unable to replicate the high frontal and rACC theta association with treatment response (Arns et al. 2015).

In quantitative EEG (QEEG), electrical signals from the brain are converted to digital form, which allows patterns undetectable by the naked eye to be revealed. The antidepressant treatment response index (ATR) is a QEEG measure that integrates frontal alpha and theta power extracted at pretreatment baseline and at 1-week posttreatment. In the biomarkers for rapid identification of treatment effectiveness in major depression study (BRITE-MD) (Leuchter et al. 2009), patients with ATR values above the threshold value were 2.4 times more likely to respond to escitalopram than those with ATR values below threshold.

ERPs are a measure of change in voltage, which represent brain activity elicited in response to visual or auditory stimulation. Among them, loudness dependence of auditory evoked potential (LDAEP), a measure of the ERP component N1/P2, taken 100–200 ms after presentation of an auditory stimulus, is a promising biomarker of response to antidepressants. A larger slope of the P2 amplitude in response to stimulus intensity (strong LDAEP) at baseline was associated with response to SSRIs, such as fluoxetine, paroxetine, and citalopram, while weak LDAEP (lower slope) was found to be associated with response to the norepinephrine reuptake inhibitor (NRI) reboxetine (Juckel et al. 2007; Lee et al. 2015).

Some recent methodological advances in analysis of EEG data seem to be promising. Analysis of a list of discriminating EEG features with a machine learning methodology has allowed an overall prediction accuracy of 87.9% of response to treatment with selective serotonin reuptake inhibitor (SSRI) antidepressants in subjects with MDD (Khodayari-Rostamabad et al. 2013). Moreover, significant wavelet coefficients extracted from frontal and temporal pretreatment EEG data were able to predict antidepressant treatment outcomes (Mumtaz et al. 2017).

Overall, the possibility to predict treatment response using EEG markers need further studies because the extant data are not yet consistent and their clinical relevance still questionable.

21.3.2.3 Neuroimaging

Resting state fMRI studies suggest an association between response to antidepressant medications and increased connectivity between frontal and limbic brain regions, possibly resulting in greater inhibitory control over neural circuits that process emotions (Dichter et al. 2014). The subcallosal cingulate cortex (SCC) connectivity appeared to predict the response to antidepressants and, more consistently, to repetitive transcranial magnetic stimulation (rTMS) in patients with MDD. The resting-state functional connectivity of three regions with the SCC (the left anterior ventrolateral prefrontal cortex/insula, the dorsal midbrain, and the left ventromedial prefrontal cortex) was differentially associated with outcomes of remission and treatment failure to CBT and antidepressant treatment in never treated MDD patients (Dunlop et al. 2017).

Measures of cerebral glucose metabolism by brain PET scan at baseline and after treatment found that hypometabolism in the insula is correlated with a good response to CBT and poor response to escitalopram, while hypermetabolism is associated with a better therapeutic response to escitalopram compared to CBT (McGrath et al. 2013).

21.4 Genetics

The pathophysiology of MDD and the mechanism of action of the antidepressant treatments remain largely obscure. Family, twin and, to a lesser extent, adoption studies provide evidence that genetic factors are involved both in susceptibility to MDD and in response to ADs.

21.4.1 Prediction of Disease Vulnerability

Studies estimate that the genetic risk for developing MDD is approximately 40% (Prendes-Alvarez and Nemeroff 2016). In the past few decades, genetic research on the susceptibility to

MDD has uncovered several so-called candidate genes, primarily chosen on the basis of their role in presumed pathophysiologic mechanisms.

The serotonin transporter (SERT or SLC6A4), through removal of serotonin at the synapse, plays an important role in determining the extent and duration of serotonergic signaling. A polymorphism in the SERT gene promoter region (5-HTTLPR) produces a variation in SERT gene transcription rates such that the short (S) allele, both the homozygote and heterozygote, is less transcriptionally efficient than the homozygotes long (LL) genotype.

In a pioneering study, Caspi and coworkers (2003) reported S-allele-carriers were more likely to develop depression in relation to stressful early life events than the LL-homozygotes. Recently, a meta-analysis confirmed a link between the short (S) form of 5-HTTLPR and stressful life events, resulting in depression (Sharpley et al. 2014). However, approximately 35% of the studies included in the meta-analysis failed to show any significant association or found contrasting results.

Tryptophan hydroxylase (TPH), the rate-limiting step in serotonin synthesis, has been implicated in susceptibility for MDD in a number of reports, with mixed results (Gao et al. 2012). Although TPH1 is primarily found in peripheral tissues, a study identified an association between six haplotypes of this gene and MDD (Gizatullin et al. 2006). In contrast, TPH2 is expressed in CNS and is considered to exert effects on sleep, aggression, food intake, and mood. The identification of single nucleotide polymorphisms (SNPs) (Zill et al. 2004) and loss of function mutations for this gene (Zhang et al. 2005) have been reported to be more common in patients with MDD than controls, suggesting that defects in brain serotonin synthesis can be an important contributor to MDD susceptibility (Zhang et al. 2005).

As noted above, hyperactivity of the HPA axis has been frequently reported in individuals with MDD (Ozomaro et al. 2013). Several gene codings for components of this system have been scrutinized, in particular the FK506 binding protein 5 (FKBP5) and the corticotropin-releasing hormone receptor 1 (CRHR1) genes (Myers and Nemeroff 2010). FKBP5 codes for a co-chaperone protein that modulates the glucocorticoid receptor. Individuals homozygous for the minor alleles of the FKBP5 SNPs were more likely to express depression after trauma exposure (Zimmermann et al. 2011). FKBP5 polymorphisms were associated with an increased recurrence of MDD episodes, poor antidepressant response (Binder et al. 2004), and with suicidal events (Brent et al. 2010). The CRH type 1 receptor mediates the majority of the CNS effects of CRH. Findings of increased concentrations of CRH both in specific brain areas and in cerebrospinal fluid have been consistently replicated in MDD, as well as in suicide victims (Aratò et al. 1989; Nemeroff et al. 1984), and a corresponding downregulation of CRHR1 mRNA expression and binding. Genetic variations in the CRHR1 gene have been associated with increased susceptibility to MDD in a Chinese population (Liu et al. 2006) and moderate the effect of child abuse on the risk for adult MDD (Bradley et al. 2008) as well as suicide risk (Roy et al. 2012).

Genome-wide association studies (GWAS), a powerful tool to probe a molecular phenotype of a disease without requiring an a priori hypothesis, have had only limited success in identifying genetic variants that predispose or protect from MDD, even with relatively large samples (García-González et al. 2017).

21.4.2 Prediction of Antidepressant Treatment Outcome

Approximately 60% of patients with MDD exhibit only a partial response to antidepressants and up to 30% do not respond at all. It is likely that genetic factors and polymorphism contribute to the variability in antidepressant response (Kato and Serretti 2010). In this regard, the definition of biological predictors of treatment response, i.e., "treatment biomarkers," would contribute to the personalized approach driving the selection of the most suitable medication for each individual patient with MDD. One relatively new approach is the microarray analysis of peripheral gene expression in blood cells. The gene expression level in blood has been reported to be comparable to prefrontal cortex (Sullivan et al. 2006) and has been associated with antidepressant response (Labermaier et al. 2013).

A set of candidate genes has been widely investigated as predictors of antidepressant response. The most studied genetic variant is the serotonin transporter (SERT) gene in its promoter region (5-HTTLPR). There is evidence (Porcelli et al. 2012) pointing to a better SSRI response in Caucasian patients carrying the 5-HTTLPR L-allele, though negative findings have been reported as well. Investigations of the relationship between norepinephrine and dopamine transporter genetic polymorphisms and response to antidepressant treatments in MDD have not yielded unequivocal results.

It has been suggested that the HPA axis plays some role in the mechanism of action of antidepressant drugs, because a normalization of HPA axis activity has been reported after successful antidepressant treatment. Polymorphisms of the CRH type 1 receptor (CRHR1) gene, which plays a key role in mediating the CRH effects in depression and anxiety, were found to be associated with response to both fluoxetine (Liu et al. 2006) and citalopram (Lekman et al. 2008). Allele G carriers of rs2270007 of the CRHR2 gene showed a poorer response to citalopram with a threefold increased risk for non-responding after 4 weeks of treatment (Papiol et al. 2007). One single nucleotide polymorphism (SNP) (rs10473984) within the CRHBP gene encoding the CRH-binding protein, which binds CRH with subnanomolar affinity to modulate CRH receptor activity, affects response to citalopram in African American and Hispanic patients (Binder et al. 2010). As noted above, polymorphisms in FKBP5 are associated with rapid response to AD treatment (Binder et al. 2004) and also with remission over 14 weeks of citalopram treatment (Lekman et al. 2008).

Studies on the influence of BDNF polymorphisms in antidepressant response resulted in mixed results with some studies reporting the Met allele polymorphism associated with better response (Licinio et al. 2009) and others showing the Val/Val genotype to have a better outcome (Zou et al. 2010).

Genome-wide association studies (GWAS), performed to identify SNPs associated with antidepressant response, have reported several findings, but most of them have been inconclusive and remain not replicated. In a recent study, 32 differentially expressed probe sets were associated with response to citalopram treatment in MDD (Mamdani et al. 2011). Another study revealed the association of four mRNAs and two microRNAs (miRNAs) with antidepressant treatment response in MDD (Belzeaux et al. 2012). Another microarray study aiming to identify peripheral gene expression profiles reported how responders and treatment-resistant patients with MDD to the SSRI escitalopram could be predicted at the beginning of treatment by expression levels of NLGN2 gene (Pettai et al. 2016).

One possible explanation is that antidepressant response is polygenic and each individual SNP is only responsible for a small fraction of heritability hardly detectable in statistical analyses. However, a polygenic approach (differently from GWAS analysis where a single SNP can reach significance level) that captured the additive effect of multiple SNP alleles across the genome failed to predict antidepressant response analyzing results of two large pharmacogenetic trials (GENDEP, MARS, STAR*D) (García-González et al. 2017; GENDEP Investigators, MARS Investigators, STAR*D Investigators 2013; Lekman et al. 2008).

21.4.3 Pharmacogenetic-Based Decision Support Tools

Genetic variants explain about 50% of individual differences in antidepressant response and adverse effects (Crisafulli et al. 2011). To optimize the individual patient's responses to a prescribed antidepressant, one emerging strategy is to consider the patient's pharmacokinetic and pharmacodynamic genetic profile. Currently, several second-generation tools that offer combinatorial polygenic testing are commercially available. They analyze polymorphisms in genes for cytochrome P450 (CYP) liver enzymes that metabolize antidepressant drugs in addition to genes which encode brain response proteins that purportedly contribute to their efficacy and/or side effects. Moreover, combinatorial pharmacogenomics is able to identify synergies

between genes and provide drug-drug interaction information.

Less than 20% of current available pharmacogenetic tools have been empirically evaluated, and it is not clear if these tools can, indeed, shorten the time to remission, sustain the duration of remission, and improve adherence to antidepressant treatment (Bousman and Hopwood 2016). In treatment-resistant depressed patients, three prospective studies have evaluated the clinical validity and utility of a combinatorial pharmacogenomic test (GeneSight test) compared to a treatment as usual (TAU). The analysis of data from these combined studies demonstrates that GeneSight-guided treatment is associated with a greater reduction in overall depression symptoms and increases in response rates compared to TAU (Altar et al. 2015). However, there are serious methodological concerns in these studies including lack of blindness and very small sample sizes. Pharmacogenetic testing is potentially useful in particular clinical situations but the widespread adoption of these tools in practice is premature relative to the extant data. In the next several years, data derived from ongoing randomized clinical trials in the USA and Canada will allow a better understanding of the role of antidepressant pharmacogenetic tools in real-world practice.

21.5 Epigenetics in MDD

Epigenetics may play an important role in the etiology of complex diseases such as MDD. The term "epigenetics" refers to potentially heritable and functionally relevant changes in gene expression obtained without modification of nucleotide sequence. DNA methylation is one of the major forms of epigenetic modifications. It consists of the addition of a methyl group to cytosine at cytosine-phosphate-guanine dinucleotides (CpG) sites which results in a reduced access of transcription factors into regulatory elements, with consequent reduction in transcription. A second epigenetic mechanism involves histone modification with change of the DNA-histone interaction. Enzymes known as histone deacetylases (HDACs) remove the acetyl group from the histone tail, cause chromatin condensation, and prevent transcription factors access to DNA resulting in a decreased gene expression. Epigenetic modifications in response to early life traumatic experiences have provided new insight into pathophysiology of MDD and may yield novel biomarkers for diagnosis and treatment response.

21.5.1 Prediction of Disease Vulnerability

The role of epigenetic modifications in personalized medicine of MDD has been hypothesized to impact illness vulnerability.

In the first genome-wide DNA methylation scan in MDD, the comparison of 39 postmortem frontal cortex samples of patients with 26 controls identified 224 candidate regions having DNA methylation differences >10% (Sabunciyan et al. 2012). Several other studies have explored these findings and overall support the idea that SLC6A4 methylation and demethylation of CpGs in the functional glucocorticoid response elements in intron 7 of the FKBP5 gene may be related to childhood maltreatment and thus might be a useful marker of MDD susceptibility. Higher methylation status of the BDNF promoter, repeatedly associated with MDD, might also represent another epigenetic marker of disease vulnerability (Fabbri et al. 2017).

Although brain tissue is an ideal sample for DNA methylation analyses, it is restricted to postmortem tissue sampling. Fortunately, peripheral blood samples have provided a noninvasive model for DNA methylation status, and the results are correlated in some studies to those observed in postmortem brain tissue, as, for example, the Stenz et al. (2015) study, in which the promoter methylation of the BDNF gene was measured both in blood and postmortem brain tissue from depressed patients. Januar et al. (2015) proposed the detection of BDNF hypermethylation in oral tissue as a potential biomarker of depression. Finally, two studies (Hobara et al. 2010; Iga et al. 2007) evaluated gene expression of the histone deacetylases (HDACs) in peripheral blood cells of depressed patients as potential

biomarkers and found that HDAC2 and HDAC5 expression were significantly increased in MDD patients compared to healthy controls.

21.5.2 Prediction of Antidepressant Treatment Outcome

The most studied epigenetic modification, DNA methylation, has been evaluated in the context of AD treatment response.

Investigations focused on baseline levels of DNA methylation of specific genes, in particular SERT (SLC6A4), BDNF, and interleukin-11 (IL-11) genes in the prediction of antidepressant response with some promising results (Lisoway et al. 2017).

Domschke et al. (2014) reported that DNA hypomethylation of the SERT region was associated with impaired antidepressant treatment response to escitalopram in a Caucasian population. Okada et al. (2014) reported that higher pretreatment methylation rate of SLC6A4 is associated with better therapeutic responses to antidepressants in a Japanese population sample. Kang et al. (2013), however, did not confirm this finding using a series of different antidepressants. Lower baseline methylation status of the BDNF promoter region predicted non-response to antidepressant medication (Tadić et al. 2014). Higher levels of DNA methylation at IL-11CpG unit 4 were associated with better response in individuals treated with escitalopram, but with worse response in those treated with nortriptyline (Powell et al. 2013).

21.6 Childhood Adversity

21.6.1 Prediction of Disease Vulnerability

A large body of evidence has confirmed and extended the finding that childhood adversities, such as sexual, physical or emotional abuse, emotional or physical neglect, or parental loss, are significant contributors to the subsequent development of MDD and predict a more severe course of illness and greater chronicity (Nemeroff 2016). Physically abused (odds ratio, OR = 1.54), emotionally abused (OR = 3.06), and neglected (OR = 2.11) individuals were found to have a higher risk of developing depressive disorders than non-abused individuals (Norman et al. 2012). A meta-analysis of 16 epidemiological studies (more than 20,000 participants) suggested that childhood maltreatment was associated with an elevated risk of developing recurrent and persistent depressive episodes (OR = 2.27) (Nanni et al. 2012).

21.6.2 Prediction of Antidepressant Treatment Outcome

Several studies suggest that a history of early life childhood trauma predicts poorer response to antidepressant and psychotherapy. A meta-analysis of ten clinical trials (more than 3000 participants) concluded that childhood maltreatment was associated with lack of response/remission to treatments for depression (OR = 1.43) (Nanni et al. 2012).

Patients with chronic depression without a history of childhood trauma had an equivalent response to nefazodone, when compared with a form of CBT designed for chronic depression, Cognitive Behavioral Analysis System of Psychotherapy (CBASP), and a better response to the combination of treatments (Keller et al. 2000). Among patients with a history of early childhood trauma, CBASP alone was superior to antidepressant monotherapy, and the combination of psychotherapy and pharmacotherapy was only slightly superior to CBASP alone (Nemeroff et al. 2003).

Lewis et al. (2010) compared the efficacy of a 12-week treatment with fluoxetine, CBT, their combination, and placebo in 427 adolescents with MDD. The no-trauma group responded to fluoxetine, while CBT was not superior to placebo. In individuals with a history of trauma or physical abuse, no treatment was more effective than placebo. In sexually abused patients, placebo was more effective than CBT (Lewis et al. 2010).

In patients with MDD in the iSPOT trial, the incidence of childhood abuse was fourfold higher than in their healthy peers. Abuse occurring before the age of 7 years predicted poorer

response and remission following treatment with escitalopram, sertraline, or venlafaxine extended release (XR) (Williams et al. 2016). Finally, childhood abuse was associated with poorer treatment response to "low serotonin affinity" medications than to "high serotonin affinity" ones (Quilty et al. 2017).

Conclusions

The personalized or precision medicine approach to MDD is a very active avenue of investigation. This approach is relatively novel yet there are several promising findings that need to be explored further with studies of large samples before being considered for translation in clinical practice.

Genetic and epigenetic factors clearly play a role both in the prediction of disease vulnerability and treatment outcome. However, in studies that evaluated the association of candidate genes with MDD and responses to treatment, candidate genes were selected on the basis of existing knowledge on MDD and the supposed mechanisms of action of antidepressants. Because the gene selection is done a priori, this approach rarely opens new fields of investigation. Until now, candidate gene studies have failed to find a strong genetic impact on MDD, but rather they have confirmed or denied the influence of the selected genes. It was expected that a GWAS strategy, which evaluates all known genes without any a priori hypotheses, could identify genetic variants associated with MDD and treatment response. Despite this great technical advancement, genes or biomarkers predictive of susceptibility to MDD or of response to antidepressant have not yet been reliably identified. Because studies have revealed that common genetic variants and biomarkers are unlikely to have widespread predictive value as single predictors, a strategy that integrates several types of genetic clinical and neurobiological markers should be considered. Polygenic risk factor scores represent one promising new direction. In the near future, multi-omics including transcriptomics, metabolomics, and proteomics will also surely be scrutinized as potential markers as well. The development of biosignatures profiling clinical phenotypes, neuroimaging and EEG data, a diverse array of peripheral/serum growth factors, cytokines, hormones and metabolic markers, genetic makeup, and environmental factors (e.g., childhood early experiences) is clearly an alternative to the single-biomarker approach. Personality features in patients with depression might disentangle depression heterogeneity and help to tailor treatments (Berg et al. 2017). Moreover, there is some evidence that pretreatment information on sex, height, weight, and BMI may help medication selection in depressed patients. Venlafaxine XR was more effective than escitalopram in patients with comorbid obesity and MDD, and the association between adiposity and remission was greater in females than in males (Green et al. 2017). Finally, it has been observed that socioeconomic measures, including education, income, and employment status, were better predictors of treatment response than clinical factors, such as past medication response, severity of MDD, and comorbid psychiatric diagnoses (Jakubovski and Bloch 2014). More studies are needed to foster the development of new methodological and statistical means to better capture the complex world of depression and to allow a concrete move from the hope of a personalized approach toward the reality of widespread clinical practice.

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References

Akhondzadeh S, Jafari S, Raisi F, Nasehi AA, Ghoreishi A, Salehi B, Mohebbi-Rasa S, Raznahan M, Kamalipour A. Clinical trial of adjunctive celecoxib treatment in patients with major depression: a double blind and placebo controlled trial. Depress Anxiety. 2009;26:607–11.

Alhajji L, Nemeroff CB. Personalized Medicine and Mood Disorders. Psychiatr Clin North Am. 2015;38(3): 395–403.

Altar CA, Carhart J, Allen JD, Hall-Flavin D, Winner J, Dechairo B. Clinical utility of combinatorial pharmacogenomics-guided antidepressant therapy: evidence from three clinical studies. Mol Neuropsychiatry. 2015;1(3):145–55.

American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 5th ed. Arlington: American Psychiatric Publishing; 2013.

American Psychiatric Association (APA) (2010) Practice guideline for the treatment of patients with major depressive disorder. https://psychiatryonline.org/pb/assets/raw/sitewide/practice_guidelines/guidelines/mdd.pdf. Accessed May 2017.

Aratò M, Bankl CM, Bissette G, Nemeroff CB. Elevated CSF CRF in suicide victims. Biol Psychiatry. 1989;25(3):355–9.

Arnow BA, Blasey C, Williams LM, Palmer DM, Rekshan W, Schatzberg AF, Etkin A, Kulkarni J, Luther JF, Rush AJ. Depression subtypes in predicting antidepressant response: a report from the iSPOT-D trial. Am J Psychiatry. 2015;172(8):743–50.

Arns M, Etkin A, Hegerl U, Williams LM, DeBattista C, Palmer DM, Fitzgerald PB, Harris A, deBeuss R, Gordon E. Frontal and rostral anterior cingulate (rACC) theta EEG in depression: implications for treatment outcome? Eur Neuropsychopharmacol. 2015;25(8):1190–200.

Arns M, Bruder G, Hegerl U, Spooner C, Palmer DM, Etkin A, Fallahpour K, Gatt JM, Hirshberg L, Gordon E. EEG alpha asymmetry as a gender-specific predictor of outcome to acute treatment with different antidepressant medications in the randomized iSPOT-D study. Clin Neurophysiol. 2016;127(1):509–19.

Aubry JM, Gervasoni N, Osiek C, Perret G, Rossier MF, Bertschy G, Bondolfi G. The DEX/CRH neuroendocrine test and the prediction of depressive relapse in remitted depressed outpatients. J Psychiatr Res. 2007;41:290–4.

Baldwin DS, Papakostas GI. Symptoms of fatigue and sleepiness in major depressive disorder. J Clin Psychiatry. 2006;67(Suppl 6):9–15.

Başterzi AD, Yazici K, Aslan E, Delialioğlu N, Taşdelen B, Tot Acar S, Yazici A. Effects of fluoxetine and venlafaxine on serum brain derived neurotrophic factor levels in depressed patients. Prog Neuro-Psychopharmacol Biol Psychiatry. 2009;33(2):281–5.

Belzeaux R, Bergon A, Jeanjean V, Loriod B, Formisano-Tréziny C, Verrier L, Loundou A, Baumstarck-Barrau K, Boyer L, Gall V, Gabert J, Nguyen C, Azorin JM, Naudin J, Ibrahim EC. Responder and nonresponder patients exhibit different peripheral transcriptional signatures during major depressive episode. Transl Psychiatry. 2012;13(2):e185.

Berg JM, Kennedy JC, Dunlop BW, Ramirez CL, Stewart LM, Nemeroff CB, Mayberg HS, Craighead WE. The structure of personality disorders within a depressed sample: implications for personalizing treatment. Pers Med Psychiatr. 2017;1–2:59–64.

Binder EB, Salyakina D, Lichtner P, Wochnik GM, Ising M, Pütz B, Papiol S, Seaman S, Lucae S, Kohli MA, Nickel T, Künzel HE, Fuchs B, Majer M, Pfennig A, Kern N, Brunner J, Modell S, Baghai T, Deiml T, Zill P, Bondy B, Rupprecht R, Messer T, Köhnlein O, Dabitz H, Brückl T, Müller N, Pfister H, Lieb R, Mueller JC, Lõhmussaar E, Strom TM, Bettecken T, Meitinger T, Uhr M, Rein T, Holsboer F, Muller-Myhsok B. Polymorphisms in FKBP5 are associated with increased recurrence of depressive episodes and rapid response to antidepressant treatment. Nat Genet. 2004;36(12):1319–25.

Binder EB, Kunzel HE, Nickel T, Kern N, Pfennig A, Majer M, Uhr M, Ising M, Holsboer F. HPA axis regulation at in-patient admission is associated with antidepressant therapy outcome in male but not in female depressed patients. Psychoneuroendocrinology. 2009;34:99–109.

Binder EB, Owens MJ, Liu W, Deveau TC, Rush AJ, Trivedi MH, Fava M, Bradley B, Ressler KJ, Nemeroff CB. Association of polymorphisms in genes regulating the corticotropin-releasing factor system with antidepressant treatment response. Arch Gen Psychiatry. 2010;67(4):369–79.

Biomarker Definition Working Group. Biomarkers and surrogate endpoints: preferred definition and conceptual framework. Clin Pharmacol Ther. 2001;69(3):89–95.

Bousman CA, Hopwood M. Commercial pharmacogenetic-based decision-support tools in psychiatry. Lancet Psychiatry. 2016;3(6):585–90.

Bradley RG, Binder EB, Epstein MP, Tang Y, Nair HP, Liu W, Gillespie CF, Berg T, Evces M, Newport DJ, Stowe ZN, Heim CM, Nemeroff CB, Schwartz A, Cubells JF, Ressler KJ. Influence of child abuse on adult depression: moderation of corticotropin-releasing hormone receptor gene. JAMA Psychiatry. 2008;65(2):190–200.

Brent D, Melhem N, Ferrell R, Emslie G, Wagner KD, Ryan N, Vitiello B, Birmaher B, Mayes T, Zelazny J, Onorato M, Devlin B, Clarke G, DeBar L, Keller M. Association of FKBP5 polymorphisms with suicidal events in the treatment of resistant depression in adolescents (TORDIA) study. Am J Psychiatry. 2010;167(2):190–7.

Bruder GE, Sedoruk JP, Stewart JW, McGrath PJ, Quitkin FM, Tenke CE. Electroencephalographic alpha measures predict therapeutic response to a selective serotonin reuptake inhibitor antidepressant: pre- and post-treatment findings. Biol Psychiatry. 2008;63:1171–7.

Caspi A, Sugden K, Moffitt TE, Taylor A, Craig IW, Harrington H, McClay J, Mill J, Martin J, Braithwaite A, Poulton R. Influence of life stress on depression: moderation by polymorphism in the 5-HTT gene. Science. 2003;301(5631):386–9.

Coelho R, Viola TW, Walss-Bass C, Brietzke E, Grassi-Oliveira R. Childhood maltreatment and inflammatory markers: a systematic review. Acta Psychiatr Scand. 2014;129(3):180–92.

Crisafulli C, Fabbri C, Porcelli S, Drago A, Spina E, De Ronchi D, Serretti A. Pharmacogenetics of antidepressants. Front Pharmacol. 2011;2:6.

Deuschle M, Hamann B, Meichel C, Krumm B, Lederbogen F, Kniest A, Colla M, ' Heuser I. Antidepressive treatment with amitriptyline and paroxetine: effects on saliva cortisol concentrations. J Clin Psychopharmacol. 2003;23(2):201–5.

Dichter GS, Gibbs D, Smoski MJ. A systematic review of relations between resting state functional-MRI and treatment response in major depressive disorder. J Affect Disord. 2014;172:8–17.

Domschke K, Tidow N, Schwarte K, Deckert J, Lesch KP, Arolt V, Zwanzger P, Baune BT. Serotonin transporter gene hypomethylation predicts impaired antidepressant treatment response. Int J Neuropsychopharmacol. 2014;17(8):1167–76.

Dunlop BW, Rajendra JK, Craighead WE, Kelley ME, McGrath CL, Choi KS, Kinkead B, Nemeroff CB, Mayberg HS. Functional connectivity of the subcallosal cingulate cortex and differential outcomes to treatment with cognitive-behavioral therapy or antidepressant medication for major depressive disorder. Am J Psychiatry. 2017;174(6):533–45.

Eller T, Vasar V, Shlik J, Maron E. Pro-inflammatory cytokines and treatment response to escitalopram in major depressive disorder. Prog Neuro-Psychopharmacol Biol Psychiatry. 2008;32(2):445–50.

Fabbri C, Hosak L, Mössner R, Giegling I, Mandelli L, Bellivier F, Claes S, Collier DA, Corrales A, Delisi LE, Gallo C, Gill M, Kennedy JL, Leboyer M, Lisoway A, Maier W, Marquez M, Massat I, Mors O, Muglia P, Nöthen MM, O'Donovan MC, Ospina-Duque J, Propping P, Shi Y, St Clair D, Thibaut F, Cichon S, Mendlewicz J, Rujescu D, Serretti A. Consensus paper of the WFSBP Task Force on Genetics: eenetics, epigenetics and gene expression markers of major depressive disorder and antidepressant response. World J Biol Psychiatry. 2017;18(1):5–28.

Gao J, Pan Z, Jiao Z, Li F, Zhao G, Wei Q, Pan F, Evangelou E. TPH2 gene polymorphisms and major depression - a metaanalysis. PLoS One. 2012;7(5):e367271.

García-González J, Tansey KE, Hauser J, Henigsberg N, Maier W, Mors O, Placentino A, Rietschel M, Souery D, Žagar T, Czerski PM, Jerman B, Buttenschøn HN, Schulze TG, Zobel A, Farmer A, Aitchison KJ, Craig I, McGuffin P, Giupponi M, Perroud N, Bondolfi G, Evans D, O'Donovan M, Peters TJ, Wendland JR, Lewis G, Kapur S, Perlis R, Arolt V, Domschke K, Breen G, Curtis C, Sang-Hyuk L, Kan C, Newhouse S, Patel H, Baune BT, Uher R, Lewis CM, Fabbri C, Major Depressive Disorder Working Group of the Psychiatric Genomic Consortium. Pharmacogenetics of antidepressant response: a polygenic approach. Prog Neuro-Psychopharmacol Biol Psychiatry. 2017;75:128–34.

GENDEP Investigators, MARS Investigators, STAR*D Investigators. Common genetic variation and antidepressant efficacy in major depressive disorder: a meta-analysis of three genome-wide pharmacogenetics studies. Am J Psychiatry. 2013;170(2):207–21.

Gizatullin R, Zaboli G, Jonsson EG, Asberg M, Leopardi R. Haplotype analysis reveals tryptophan hydroxylase (TPH) 1 gene variants associated with major depression. Biol Psychiatry. 2006;59(4):295–300.

Gottesman II, Gould TD. The endophenotype concept in psychiatry: etymology and strategic intentions. Am J Psychiatry. 2003;160(4):636–45.

Greden F, Gardner R, King D, Grunhaus L, Carroll J, Kronfol Z. Dexamethasone suppression test in antidepressant treatment of melancholia. Arch Gen Psychiatry. 1983;40:493–500.

Green E, Goldstein-Piekarski AN, Schatzberg AF, Rush AJ, Ma J, Williams L. Personalizing antidepressant choice by sex, body mass index, and symptom profile: an iSPOT-D report. Pers Med Psychiatr. 2017;1–2:65–73.

Hecht H, van Calker D, Berger M, von Zerssen D. Personality in patients with affective disorders and their relatives. J Affect Disord. 1998;5(1):33–43.

Hobara T, Uchida S, Otsuki K, Matsubara T, Funato H, Matsuo K, Suetsugi M, Watanabe Y. Altered gene expression of histone deacetylases in mood disorder patients. J Psychiatr Res. 2010;44(5):263–70.

Howren MB, Lamkin DM, Suls J. Associations of depression with C-reactive protein, IL-1, and IL-6: a meta-analysis. Psychosom Med. 2009;71(2):171–86.

Iga J, Ueno S, Yamauchi K, Numata S, Kinouchi S, Tayoshi-Shibuya S, Song H, Ohmori T. Altered HDAC5 and CREB mRNA expressions in the peripheral leukocytes of major depression. Prog Neuro-Psychopharmacol Biol Psychiatry. 2007;31(3):628–32.

Jablensky A. The conflict of the nosologists: views on schizophrenia and manic-depressive illness in the early part of the 20th century. Schizophr Res. 1999;39:95–100.

Jakubovski E, Bloch MH. Prognostic subgroups for citalopram response in the STAR*D trial. J Clin Psychiatry. 2014;75(7):738–47.

Januar V, Ancelin ML, Ritchie K, Saffery R, Ryan J. BDNF promoter methylation and genetic variation in late-life depression. Transl Psychiatry. 2015;5:e619.

Jha MK, Minhajuddin A, Gadad BS, Greer T, Grannemann B, Soyombo A, Mayes TL, Rush AJ, Trivedi MH. Can C-reactive protein inform antidepressant medication selection in depressed outpatients? Findings from the CO-MED trial. Psychoneuroendocrinology. 2017;78:105–13.

Juckel G, Pogarell O, Augustin H, Mulert C, Müller-Siecheneder F, Frodl T, Mavrogiorgou P, Hegerl U. Differential prediction of first clinical response to sertonergic and noadrenergic antidepressants using the loudness dependence of auditory evoked potentials in patients with major depressive disorder. J Clin Psychiatry. 2007;68:1206–12.

Kang HJ, Kim JM, Stewart R, Kim SY, Bae KY, Kim SW, Shin IS, Shin MG, Yoon JS. Association of SLC6A4 methylation with early adversity, characteristics and outcomes in depression. Prog Neuro-Psychopharmacol Biol Psychiatry. 2013;44:23–8.

Kato M, Serretti A. Review and meta-analysis of antidepressant pharmacogenetic findings in major depressive disorder. Mol Psychiatry. 2010;15(5):473–500.

Keller MB, McCullough JP, Klein DN, Arnow B, Dunner DL, Gelenberg AJ, Markowitz JC, Nemeroff CB, Russell JM, Thase ME, Trivedi MH, Zajecka J. A comparison of nefazodone, the cognitive behavioral-analysis system of psychotherapy, and their combination for the treatment of chronic depression. N Engl J Med. 2000;342(20):1462–70.

Khodayari-Rostamabad A, Reilly JP, Hasey GM, de Bruin H, Maccrimmon DJ. A machine learning approach using EEG data to predict response to SSRI treatment for major depressive disorder. Clin Neurophysiol. 2013;124(10):1975–85.

Knott VJ, Telner JI, Lapierre YD, Browne M, Horn ER. Quantitative EEG in the prediction of antidepressant response to imipramine. J Affect Disord. 1996;39:175–84.

Knott V, Mahoney C, Kennedy S, Evans K. Pre-treatment EEG and its relationship to depression severity and paroxetine treatment outcome. Pharmacopsychiatry. 2000;22:201–5.

Koo PC, Thome J, Berger C, Foley P, Hoeppner J. Current source density analysis of resting state EEG in depression: a review. J Neural Transm. 2017; 124(1):109–18.

Korte SM, Prins J, Krajnc AM, Hendriksen H, Oosting RS, Westphal KG, Korte-Bouws GAH, Olivier B. The many different faces of major depression: it is time for personalized medicine. Eur J Pharmacol. 2015;753:88–104.

Kunugi H, Hori H, Ogawa S. Biochemical markers subtyping major depressive disorder. Psychiatry Clin Neurosci. 2015;69(10):597–608.

Labermaier C, Masana M, Müller MB. Biomarkers predicting antidepressant treatment response: how can we advance the field? Dis Markers. 2013;35(1):23–31.

Lamers F, de Jonge P, Nolen WA, Smith JH, Zitman FG, Beekman AT, Penninx BW. Identifying depressive subtypes in a large cohort study: results from the Netherlands study of depression and anxiety (NESDA). J Clin Psychiatry. 2010;71(12):1582–9.

Lamers F, Vogelzangs N, Merikangas KR, de Jonge P, Beekman AT, Penninx BW. Evidence for a differential role of HPA axis function, inflammation and metabolic syndrome in melancholic versus atypical depression. Mol Psychiatry. 2013;18(6):692–9.

Lee BH, Park YM, Lee SH, Shim M. Prediction of long-term treatment response to selective serotonin reuptake inhibitors (SSRIs) using scalp and source loudness dependence of auditory evoked potentials (LDAEP) analysis in patients with major depressive disorder. Int J Mol. 2015;16(3):6251–65.

Lekman M, Laje G, Charney D, Rush AJ, Wilson AF, Sorant AJM, Lipsky R, Wisniewski SR, Manji H, McMahon FJ, Paddock S. The FKBP5-gene in depression and treatment response - an action study in the sequenced treatment alternatives to relieve depression (STAR*D) cohort. Biol Psychiatry. 2008;63(12):1103–10.

Leuchter AF, Cook IA, Marangell LB, Gilmer WS, Burgoyne KS, Howland RH, Trivedi MH, Zisook S, Jain R, McCracken JT, Fava M, Iosifescu D, Greenwald S. Comparative effectiveness of biomarkers and clinical indicators for predicting outcomes of SSRI treatment in major depressive disorder: results of the BRITE-MD study. Psychiatry Res. 2009;169:124–31.

Lewis CC, Simons AD, Nguyen LJ, Murakami JL, Reid MW, Silva SG, et al. Impact of childhood trauma on treatment outcome in the treatment for adolescents with depression study (TADS). J Am Acad Child Adolesc Psychiatry. 2010;49(2):132–40.

Licinio J, Dong C, Wong ML. Novel sequence variations in the brain-derived neurotrophic factor gene and association with major depression and antidepressant treatment response. Arch Gen Psychiatry. 2009;66(5):488–97.

Lisoway AJ, Zai CC, Tiwari AK, Kennedy JL. DNA methylation and clinical response to antidepressant medication in major depressive disorder: a review and recommendations. Neurosci Lett. 2017. Jan [Epub ahead of print].

Liu Z, Zhu F, Wang G, Xiao Z, Wang H, Tang J, Wang X, Qiu D, Liu W, Cao Z, Li W. Association of corticotropin releasing hormone receptor 1 gene SNP and haplotype with major depression. Neurosci Lett. 2006;404(3):358–62.

Mamdani F, Berlim MT, Beaulieu MM, Labbe A, Merette C, Turecki G. Gene expression biomarkers of response to citalopram treatment in major depressive disorder. Transl Psychiatry. 2011;21(1):e13.

McCabe C, Cowen PJ, Harmer CJ. Neural representation of reward in recovered depresses patients. Psychopharmachology. 2009;205(4):667–77.

McGrath CL, Kelley ME, Holtzheimer PE, Dunlop BW, Craighead WE, Franco AR, Craddock RC, Mayberg HS. Toward a neuroimaging treatment selection biomarker for major depressive disorder. JAMA Psychiatry. 2013;70(8):521–9.

McMakin DL, Olino TM, Porta G, Dietz LJ, Emslie G, Clarke G, Wagner KD, Asarnow JR, Ryan ND, Birmaher B, Shamseddeen W, Mayes T, Kennard B, Spirito A, Keller M, Lynch FL, Dickerson JF, Brent DA. Anhedonia predicts poorer recovery among youth with selective serotonin reuptake inhibitor treatment-resistant depression. J Am Acad Child Adolesc Psychiatry. 2012;51(4):404–11.

Mikoteit T, Beck J, Eckert A, Hemmeter U, Brand S, Bischof R, Holsboer-Trachsler E, Delini-Stula A. High baseline BDNF serum levels and early psychopathological improvement are predictive of treatment outcome in major depression. Psychopharmacology. 2014;231(15):2955–65.

Miller AH, Raison CL. The role of inflammation in depression: from evolutionary imperative to modern treatment target. Nat Rev Immunol. 2016;16(1):22–34.

Mocling RJT, Nap TS, Westerink AM, Assies J, Vaz FM, Koeter MWJ, Ruhe HG, Schene AH. Biological profiling of prospective antidepressant response in major depressive disorder: association with (neuro)inflammation, fatty acid metabolism and amygdala reactivity. Psychoneuroendocrinology. 2017;79:84–92.

Moylan S, Maes M, Wray NR, Berk M. The neuroprogressive nature of major depressive disorder: pathways to disease evolution and resistance, and therapeutic implications. Mol Psychiatry. 2013;18(5):595–606.

Mumtaz W, Xia L, Mohd Yasin MA, Azhar Ali SS, Malik AS. A wavelet-based technique to predict treatment outcome for major depressive disorder. PLoS One. 2017;12(2):e0171409.

Myers AJ, Nemeroff CB. New vistas in the management of treatment-refractory psychiatric disorders: genomics and personalized medicine. Focus. 2010; 8(4):525–35.

Nanni V, Uher R, Danese A. Childhood maltreatment predicts unfavorable course of illness and treatment outcome in depression: a meta-analysis. Am J Psychiatry. 2012;169(2):141–51.

Nase S, Köhler S, Jennebach J, Eckert A, Schweinfurth N, Gallinat J, Lang UE, Kühn S. Role of serum brain derived neurotrophic factor and central N-acetylaspartate for clinical response under antidepressive pharmacotherapy. Neurosignals. 2016;24(1): 1–14.

Nemeroff CB. Paradise lost: the neurobiological and clinical consequences of child abuse and neglect. Neuron. 2016;89(5):892–909.

Nemeroff CB, Widerlov E, Bissette G, Walleus H, Karlsson J, Eklund K, Kilts CD, Loosen PT, Vale W. Elevated concentration of CSF corticotropin releasing factor-like immunoreactivity in depressed patients. Science. 1984;226(4680):1342–4.

Nemeroff CB, Heim CM, Thase ME, Klein DN, Shatzberg AF, Ninan PT, McCollough JP, Weiss PM, Dunner DL, Rothbaum BO, Kornstein S, Keitner G, Keller MB. Differential responses to psychotherapy versus pharmacotherapy in patients with chronic forms of major depressive disorder and childhood trauma. Proc Natl Acad Sci U S A. 2003;100(24): 14293–6.

Nery FG, Monkul ES, Hatch JP, Fonseca M, Zunta-Soares GB, Frey BN, Bowden CL, Soares JC. Celecoxib as an adjunct in the treatment of depressive or mixed episodes of bipolar disorder: a double-blind, randomized, placebocontrolled study. Hum Psychopharmacol. 2008;23:87–94.

Neto FL, Borges G, Torres-Sanchez S, Mico JA, Berrocoso E. Neurotrophins role in depression neurobiology: a review of basic and clinical evidence. Curr Neuropharmacol. 2011;9(4):530–52.

Nikisch G, Mathé AA, Czernik A, Thiele J, Bohner J, Eap CB, Agren H, Baumann P. Long-term citalopram administration reduces responsiveness of HPA axis in patients with major depression: relationship with S-citalopram concentrations in plasma and cerebrospinal fluid (CSF) and clinical response. Psychopharmacology. 2005;181(4): 751–60.

Norman RE, Byambaa M, De R, Butchart A, Scott J, Vos T. The long-term health consequences of child physical abuse, emotional abuse, and neglect: a systematic review and meta-analysis. PLoS Med. 2012;9(11):e1001349.

Okada S, Morinobu S, Fuchikami M, Segawa M, Yokomaku K, Kataoka T, Okamoto Y, Yamawaki S, Inoue T, Kusumi I, Koyama T, Tsuchiyama K, Terao T, Kokubo Y, Mimura M. The potential of SLC6A4 gene methylation analysis for the diagnosis and treatment of major depression. J Psychiatr Res. 2014;53(43): 47–53.

Ozomaro U, Wahlestedt C, Nemeroff CB. Personalized medicine in psychiatry: problems and promises. BMC Med. 2013;11:132.

Papiol S, Arias B, Gastò C, Gutierrez B, Catalan R, Fananas L. Genetic variability at HPA axis in major

depression and clinical response to antidepressant treatment. J Affect Disord. 2007;104(1–3):83–90.

Parekh A, Smeeth D, Milner Y, Thure S. The role of lipid biomarkers in major depression. Healthcare. 2017;5(1):E5.

Perna G, Nemeroff CB. Personalized medicine in psychiatry: back to the future. Pers Med Psychiatr. 2017;1–2:1.

Pettai K, Milani L, Tammiste A, Võsa U, Kolde R, Eller T, Nutt D, Metspalu A, Maron E. Whole-genome expression analysis reveals genes associated with treatment response to escitalopram in major depression. Eur Neuropsychopharmacol. 2016;26(9):1475–83.

Pizzagalli DA. Frontocingulate dysfunction in depression: toward biomarkers of treatment response. Neuropsychopharmacol Rev. 2011;36:183–206.

Polyakova M, Stuke K, Schuemberg K, Mueller K, Schoenknecht P, Schroeter ML. BDNF as a biomarker for successful treatment of mood disorders: a systematic & quantitative meta-analysis. J Affect Disord. 2015;174:432–40.

Porcelli S, Fabbri C, Serretti A. Meta-analysis of serotonin transporter gene promoter polymorphism (5-HTTLPR) association with antidepressant efficacy. Eur Neuropsychopharmacol J Eur Coll Neuropsychopharmacol. 2012;22(4):239–58.

Powell TR, Smith RG, Hackinger S, Schalkwyk LC, Uher R, McGuffin P, Mill PJ, Tansey KE. DNA methylation in interleukin-11 predicts clinical response to antidepressants in GENDEP. Transl Psychiatry. 2013;3:e300.

Prendes-Alvarez S, Nemeroff CB. Personalized medicine: prediction of disease vulnerability in mood disorders. Neurosci Lett. 2016. Oct [Epub ahead of print].

Quilty LC, Marshe V, Lobo DS, Harkness KL, Müller DJ, Bagby RM. Childhood abuse history in depression predicts better response to antidepressants with higher serotonin transporter affinity: a pilot investigation. Neuropsychobiology. 2017;74(2):78–83.

Raison CL, Rutherford RE, Woolwine BJ, Shuo C, Schettler P, Drake DF, Haroon E, Miller AH. A randomized controlled trial of the tumor necrosis factor antagonist infliximab for treatment-resistant depression: the role of baseline inflammatory biomarkers. JAMA Psychiatry. 2013;70(1):31–41.

Rao U, Chen LA, Bidesi AS, Shad MU, Thomas MA, Hammen CL. Hippocampal changes associated with early-life adversity and vulnerability to depression. Biol Psychiatry. 2010;67(4):357–64.

Roy A, Hodgkinson CA, DeLuca V, Goldman D, Enoch MA. Two HPA axis genes, CRHBP and FKBP5, interact with childhood trauma to increase the risk for suicidal behavior. J Psychiatry Res. 2012;46(1):72–9.

Rudolf S, Greggersen W, Kahl KG, Hüppe M, Schweiger U. Elevated IL-6 levels in patients with atypical depression but not in patients with typical depression. Psychiatry Res. 2014;217(1–2):34–8.

Sabunciyan S, Aryee MJ, Irizarry RA, Rongione M, Webster MJ, Kaufman WE, Murakami P, Lessard A, Yolken RH, Feinberg AP, Potash JB, GenRED Consortium. Genome-wide DNA methylation scan in major depressive disorder. PLoS ONE. 2012;7(4):e34451.

Schmaal L, Veltman DJ, Van Erp TGM, Samann PG, Frodl T, Jahanshad N, Loehrer E, Tiemeier H, Hofman A, Niessen WJ, Vernooij MW, Ikram MA, Wittfeld K, Grabe HJ, Block A, Hegenscheid K, Völzke H, Hoehn D, Czisch M, Lagopoulos J, Hatton SN, Hickie IB, Goya-Maldonado R, Krämer B, Gruber O, Couvy-Duchesne B, Rentería ME, Strike LT, Mills NT, de Zubicaray GI, McMahon KL, Medland SE, Martin NG, Gillespie NA, Wright MJ, Hall GB, MacQueen GM, Frey EM, Carballedo A, van Velzen LS, van Tol MJ, van der Wee NJ, Veer IM, Walter H, Schnell K, Schramm E, Normann C, Schoepf D, Konrad C, Zurowski B, Nickson T, McIntosh AM, Papmeyer M, Whalley HC, Sussmann JE, Godlewska BR, Cowen PJ, Fischer FH, Rose M, Penninx BW, Thompson PM, Hibar DP. Subcortical brain alterations in major depressive disorder: findings from the ENIGMA major depressive disorder working group. Mol Psychiatry. 2016;21(6):806–12.

Schmidt FM, Schroder T, Kirkby KC, Sander C, Suslow T, Holdt LM, Teupser D, Hegerl U, Himmerich H. Pro- and anti-inflammatory cutokines, but not CRP, are inversely correlated with severity and symptoms of major depression. Psychiatry Res. 2016;239:85–91.

Sharpley CF, Palanisamy SK, Glyde NS, Dillingham PW, Agnew LL. An update on the interaction between the serotonin transporter promoter variant (5-HTTLPR), stress and depression, plus an exploration of non-confirming findings. Behav Brain Res. 2014;273:89–105.

Sheline YI, Price JL, Yan Z, Mintun MA. Resting-state functional MRI in depression unmasks increased connectivity between networks via the dorsal nexus. Proc Natl Acad Sci U S A. 2010;107(24):11020–5.

Siegle GJ, Steinhauer SR, Thase ME, Stenger VA, Carter CS. Can't shake that feeling: event-related fMRI assessment of sustained amygdala activity in response to emotional information in depressed individuals. Biol Psychiatry. 2002;51(9):693–1007.

Sotelo JL, Nemeroff CB. Depression as a systemic disease. Pers Med Psychiatr. 2017;1–2:11–25.

Stenz L, Zewdie S, Laforge-Escarra T, Prados J, La Harpe R, Dayer A, Paoloni-Giacobino A, Perroud N, Aubry JM. BDNF promoter I methylation correlates between post-mortem human peripheral and brain tissues. Neurosci Res. 2015;91:1–7.

Stewart JW, Quitkin FM, McGrath PJ, Klein DF. Defining the boundaries of atypical depression: evidence from the HPA axis supports course of illness distinctions. J Affect Disord. 2005;86(2–3):161–7.

Strawbridge R, Arnone D, Danese A, Papadopoulos A, Herane Vives A, Cleare AJ. Inflammation and clinical response to treatment in depression: a meta-analysis. Eur Neuropsychopharmacol. 2015;25:1532–43.

Sullivan PF, Fan C, Perou CM. Evaluating the comparability of gene expression in blood and brain. Am J Med Genet B Neuropsychiatr Genet. 2006;141B(3):261–8.

Tadić A, Müller-Engling L, Schlicht KF, Kotsiari A, Dreimüller N, Kleimann A, Bleich S, Lieb K, Frieling H. Methylation of the promoter of brain-derived neurotrophic factor exon IV and antidepressant response in major depression. Mol Psychiatry. 2014;19(3):281–3.

Trivedi MH, Rush AJ, Wisniewski SR, Nierenberg AA, Warden D, Ritz L, Norquist G, Howland RH, Lebowitz B, McGrath PJ, Shores-Wilson K, Biggs MM, Balasubramani GK, Fava M. STAR*D Study Team: evaluation of outcomes with citalopram for depression using measurement-based care in STAR*D; implications for clinical practice. Am J Psychiatry. 2006;163(1):28–40.

Uher R, Dernovsek MZ, Mors O, Hauser J, Souery D, Zobel A, Maier W, Henigsberg N, Kalember P, Rietschel M, Placentino A, Mendlewicz J, Aitchison KJ, McGuffin P, Farmer A. Melancholic, atypical, and anxious depression subtypes and outcome of treatment with escitalopram and nortriptyline. J Affect Disord. 2011;132:112–20.

Uher R, Tansey KE, Dew T, Maier W, Mors O, Hauser J, Dernovsek MZ, Henigsberg N, Souery D, Farmer A, McGuffin P. An inflammatory biomarker as a differential predictor of outcome of depression treatment with escitalopram and nortriptyline. Am J Psychiatry. 2014;171(12):1278–86.

Valkanova V, Ebmeier KP, Allan CL. CRP, IL-6 and depression: a systematic review and meta-analysis of longitudinal studies. J Affect Disord. 2013;150(3):736–44.

Van Heesch F, Prins J, Konsman JP, Korte-Bouws GA, Westphal KG, Rybka J, Olivier B, Kraneveld AD, Korte SM. Lipopolysaccharide increases degradation of central monoamines: an in vivo microdialysis study in the nucleus accumbens and medial prefrontal cortex of mice. Eur J Pharmacol. 2014;725:55–63.

Vreeburg SA, Hoogendijk WJ, van Pelt J, Derijk RH, Verhagen JC, van Dyck R, Smit JH, Zitman FG, Penninx BW. Major depressive disorder and hypothalamic-pituitary-adrenal axis activity: results from a large cohort study. Arch Gen Psychiatry. 2009;66(6):617–26.

Wardenaar KJ, Giltay EJ, van Veen T, Zitman FG, Penninx BW. Symptom dimensions as predictors of the two-year course of depressive and anxiety disorders. J Affect Disord. 2012;136(3):1198–203.

Wichers M, Myin-Germeys I, Jacobs N, Peeters F, Kenis G, Derom C, Vlietinck R, Delespaul P, Van Os J. Genetic risk of depression and stress-induced negative affect in daily life. Br J Psychiatry. 2007;191:218–23.

Williams LM, Debattista C, Duchemin AM, Schatzberg AF, Nemeroff CB. Childhood trauma predicts antidepressant response in adults with major depression: data from the randomized international study to predict optimized treatment for depression. Transl Psychiatry. 2016;6:e799.

Wong ML, Kling MA, Munson PJ, Listwak S, Licinio J, Prolo P, Karp B, McCutcheon JE, Geracioti TD Jr, DeBellis MD, Rice KC, Goldstein DS, Veldhuis JD, Chrousos GP, Oldfield EH, McCann SM, Gold PW. Pronounced and sustained central hypernoradrenergic function in major depression with melancholic features: relation to Hypercortisolism and corticotropin-releasing hormone. Proc Natl Acad Sci U S A. 2000;97:325–30.

Yang JJ, Wang N, Yang C, Shi JY, HY Y, Hashimoto K. Serum interleukin-6 is a predictive biomarker for ketamine's antidepressant effect in treatment-resistant patients with major depression. Biol Psychiatry. 2015;77(3):e19–20.

Zhang X, Gainetdinov RR, Beaulieu JM, Sotnikova TD, Burch LH, Williams RB, Schwarz DA, Krishnan KRR, Caron MG. Loss-of-function mutation in tryptophan hydroxilase-2 identified in unipolar depression. Neuron. 2005;45:11–6.

Zill P, Baghai TC, Zwanzger P, Schule C, Eser D, Rupprecht R, Moller HJ, Bondy B, Ackenheil M. SNP and haplotype analysis of a novel tryptophan hydrolase isoform (TPH2) gene provide evidence for association with major depression. Mol Psychiatry. 2004;9:1030–6.

Zimmermann P, Brückl T, Nocon A, Pfister H, Binder EB, Uhr M, Lieb R, Moffitt TE, Caspi A, Holsboer F, Ising M. Interaction of FKBP5 gene variants and life events in predicting depression onset: results from a 10-years prospective community study. Am J Psychiatry. 2011;168(10):1107–16.

Zou YF, Ye DQ, Feng XL, Su H, Pan FM, Liao FF. Meta-analysis of BDNF Val66Met polymorphism association with treatment response in patients with major depressive disorder. Eur Neuropsychopharmacol. 2010;20(8):535–44.