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Review Article

A Review on Biomarkers for Treatment Response in Major Depressive Disorder

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Abstract: Despite the significance of major depressive disorder, objective procedures for selecting optimal treatments are lacking, there is a need for reliable and objective measures capable of differentiating between those who may or may not respond to specific treatments. Studies using neuroimaging, neurocognitive, and electrophysiologic measures have found that pre-treatment differences among depressed patients are related to subsequent clinical response to antidepressant drugs. Besides some clinical features and biological markers, the modern methods of brain imaging and quantitative electroencephalogram might be useful in prediction of treatment response.
Keywords: Biomarker, major depressive disorder, antidepressant, treatment response

INTRODUCTION

In industrialized countries, mental illnesses may account for about 16% of total health care costs and 30% of disability claims [1]. A tool capable of differentiating between those who may or may not respond to specific treatments is needed. Such a measure should be reliable, objective, and readily available.

Antidepressant medication is the first line of treatment for major depressive disorder (MDD). However, given the multifactorial nature of depression not all patients will benefit from the same treatment. Identification of patient subgroups based on objective biomarkers may contribute to a more effective treatment prescription.

Despite the significance of MDD, there is a lack of objective procedures for selecting optimal treatments. Typically, 60 to 70% of subjects do not go into remission after the first antidepressant medication trial [2]. Although 67% of those treated for major depression will eventually reach remission, up to 4 different antidepressant medication treatments may be required [2]. Non-response to the first medication treatment puts an enormous amount of distress on the depressed patient and may even increase the risk of suicide. A prediction of the individual response to an antidepressant treatment could avoid the mentioned disadvantages and could achieve faster treatment results. A methodology that can utilize pre-treatment measures to predict the response to a treatment would eliminate the inefficient trial-error process that often characterizes the management of major depression.

Electrophysiological and neurocognitive measures

Studies using neuroimaging, neurocognitive, and electrophysiological measures have found that certain pre-treatment differences among depressed patients may be related to subsequent clinical response to antidepressant drugs.

P300 studies of depression gave conflicting results as to whether patients display reduced P300 latency. Event-related potential (ERP) research has shown a relationship between the (loudness dependence of the auditory evoked potential and serotonergic treatment outcome [3]. A strong loudness dependence of the auditory evoked potential has with a better response to selective serotonin reuptake inhibitors [3, 4]. Another finding from ERP studies is that smaller P300 amplitudes in a perceptual asymmetry task are associated with poor treatment outcome [5]. Delayed P300 latency is associated with poor response to antidepressants [6, 7]. Non-responders had smaller baseline P300 [8]. It has that prolonged P300 latency may be a state marker for major depression [9]. The P300 evoked response was used as an electrophysiological index of prefrontal dysfunction. The P300 electrical wave is generated during tasks of sustained attention, in response to an unanticipated auditory stimulus, and requires integrity of the prefrontal system and its limbic and temporal connections [10]. Long P300 latency is associated with poor or delayed response to antidepressant treatment [11].

Neuropsychological studies find that generally better cognitive performance is predictive of better treatment response to antidepressants [12, 13]. Previous studies have proposed working memory, executive and psychomotor functioning as predictors [14, 15].

Genetic studies

From a genetic perspective, catechol-O-methyltransferase (COMT) and 5-HT (serotonin)

related polymorphisms are currently the most promising candidates in antidepressant treatment prediction [16]. However results to date have not yet been consistent; various combinations of carriers resulting in different associations with antidepressant treatment outcome. Numerous gene combinations result in various antidepressant treatment results [17, 18, 19]

In genetic studies the catechol-O-methyltransferase, the 'Met/Met' group, was found to have the strongest relationship to treatment outcome [20]. This result is in accordance with SSRI treatment outcome studies. Most of the studies demonstrated a favorable association with the treatment outcome for carriers of the Met/Met genotype. In contradiction, others have found a negative effect of the Met Catechol-O-methyltransferase variant to antidepressant response to a TCA and SSRI [21, 22].

Brain and body metabolism

The mood-improving effect of sleep deprivation is well known. Several brain imaging studies have tried to correlate the sleep deprivation response with metabolic states of certain brain areas. Two early studies using single photon emission computed tomography and positron emission tomography [23, 24], found higher metabolic rates in limbic areas of antidepressant treatment responders. Subjects with higher metabolic rates in several areas respond better to sleep deprivation as well as paroxetine [25] and venlafaxine [26]. For paroxetine, on pre-treatment scans, lower metabolism in the left ventral anterior cingulate gyrus was associated with better treatment response [25]. In depression treatment, response to both venlafaxine and cognitive behavioral were associated with decreased glucose metabolism bilaterally in the orbitofrontal cortex and left medial prefrontal cortex [26].

In another study to determine whether the baseline metabolic profile (metabotype) of a patient with major depressive disorder would define how an individual will respond to treatment patients showing a good response to sertraline found to have higher pretreatment levels of 5-methoxytryptamine (5-MTPM), greater reduction in 5-MTPM levels after treatment, and an increase in 5-methoxytryptophol and melatonin levels [27].

BDNF

Many clinical studies on MDD have shown that blood brain-derived neurotrophic factor (BDNF) is with depression response. Pre-treatment serum BDNF levels also tested to predict antidepressant response. Wolkowitz *et al.* found low serum BDNF levels in unmedicated depressed subjects and antidepressant-induced increases in BDNF levels. Changes in BDNF levels were not significantly correlated with changes in depression ratings. However, pre-treatment BDNF levels were directly correlated with antidepressant responses [28]. In another study, baseline plasma BDNF levels did not significantly differentiate responders vs. non-responders to SSRI or SNRI medications [29].

EEG and Quantitative EEG

There are several studies that have pointed to a link between depression and alterations in different electroencephalography (EEG) spectral power bands which may provide useful information for the evaluation of depression. When the subject is in a relaxed and wakeful state, posteriorly recorded 8Hz to 13Hz wave is the alpha wave, which may be blocked when the subject is alert or opens his eyes. Several research groups have used alpha power in depression, and interhemispheric alpha asymmetries have been reported by several authors [30, 31]. EEG alpha has found extensive use as an index of relative cortical deactivation (i.e., greater alpha, less activation) in studies of depressive disorders. However, the validity potential of frontal alpha asymmetry as a clinical measure for depression still remains unclear [32].

Decreases in the slow activity of the delta-theta bands and increases in the beta activity in depressed patients have also been shown [33, 34]. Increases in current power densities in the alpha and the theta EEG bands have been shown, and this finding is which was consistent with a hypoactivation hypothesis [35, 36]. Abnormal regional hemispheric asymmetries have been found in QEEG studies of depressed patients, which have hypothesized to be vulnerability markers of depression. These studies show that left frontal hypoactivation is more in depressed patients than healthy subjects [37].

Several studies have analyzed resting EEG data for predicting treatment outcome in depressed subjects [38, 39]. In quantitative EEG (QEEG) research, several pretreatment differences in QEEG measurement results have been reported to be associated with improved antidepressant treatment outcomes [40]. For example, lower pretreatment theta power, decreased theta cordance 48 h to 2 week after the start of medication, decreased beta power, slower beta frequencies, greater interhemispheric beta coherences, greater alpha power, increased theta in the rostral anterior cingulate and greater alpha power over the right hemisphere were all noted as predictors of good response.

Bruder *et al.* found that patients who had responded to fluoxetine had greater alpha power than non-responders or healthy controls before and after 12 weeks of treatment [41]. The largest differences were at occipital sites, consistent with the classical alpha rhythm which is an evidence of reduced cortical activity in antidepressant responsive depressed patients in posterior areas. Regarding the alpha asymmetry, fluoxetine responders showed relatively greater alpha

over right posterior regions than the left before and after the treatment. The finding that alpha power and asymmetry differences were stable in either responders or non-responders are consistent with the suggestion that alpha may be a trait marker. In contrast, increased theta and delta power have been associated with poor treatment response [42].

Cordance measures

QEEG cordance is one of the promising tools for the prediction of response which has created research interest. Cordance is a QEEG method which combines complementary information from absolute (amount of power in a frequency band at a given electrode) and relative power (the percentage of power contained in a frequency band relative to the total spectrum) of EEG spectra [43].

Cordance values are correlated with regional cerebral blood flow. Previous studies demonstrated an abnormal pattern of metabolism or perfusion in the prefrontal cortex. Previous research has linked higher pretreatment theta activity of the anterior cingulate with clinical response to nortriptyline [44] and citalopram [45]. Cook et al. did not find pretreatment differences between antidepressant responders and nonresponders in theta power over time but did find group differences in "cordance." [46].

Several studies have demonstrated that a reduction of prefrontal QEEG theta cordance value after 1 or 2 weeks of treatment with antidepressants can predict clinical response to 8-week treatment in non-resistant patients or non-responders. These changes were different from those observed in placebo responders [47]. In a bupropion treatment study, the result was that the reduction of prefrontal QEEG cordance value in theta frequency band after one week of bupropion treatment predicted clinical response to 4-week treatment [48]. These findings suggest that pretreatment alpha or theta measures might be of value as predictors of clinical response to SSRI or other antidepressant drugs.

CONCLUSION

To date, various predictors have been proposed, but the results are both limited and heterogeneous. In addition, none of the findings have resulted in clinically meaningful applications. There is a need to continue to search for objective biomarkers and combination of markers in order to proceed to a faster and more efficacious treatment of depression. None of the biomarkers in each of these modalities has shown to be robust and specific enough to be used in current practice.

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