Prediction of Antidepressant Outcomes

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Abstract
Major depressive disorder (MDD) is the most common mental illness. It is a frequent and disabling disorder with prevalence rates of about 16%**.** It is not surprising that, under the current treatment paradigm, most patients face a long and frustrating course of treatment. The Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study, the largest study of MDD conducted in the United States, showed that even with enriched resources devoted to treatment, recovery with the first selected SSRI occurred only about 30% of the time, more than 40% of patients with MDD did not achieve remission even after two optimally delivered trials of antidepressant medications**.** This low recovery rate is not simply a matter of needing more or better medications. There are more than 20 treatments for MDD approved as effective by the Food and Drug Administration (FDA). but they do not go on to address specific choices of antidepressants depending on clinical symptoms**.** The current treatment guidelines for MDD of the American Psychiatric Association support a "watchful waiting" approach to determine if a particular medication will be useful for an individual patient. The challenge is choosing the best treatment for each patient.
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Introduction:

A major gap in the field is tailoring the right treatment for the individual MDD patient (i.e., personalized medicine) **(1).** The challenge of predicting which MDD patient will respond to which treatment often results in delayed treatment response, personal suffering, extended disability, higher risk of suicide, and high medical expense **(2).**

Factors influencing an individual's drug response in depressive disorder may include a number of clinical variables (such as number and types of previous treatments, severity of illness, concomitant anxiety etc) as well demographics (for instance, age, weight, social support and family history) (3).

Among systematic reviews, These factors are most associated with treatment response: symptom profile, early response to treatment, psychiatric comorbidities, electrophysiological

markers, imaging test results, other biological and peripheral markers, which can be found in saliva, urine, spinal fluid, blood and lymph circulation and genetic predictors (4).

Symptom profile:

Major depressive disorder (MDD) is a complex disease comprising several symptoms related to mood, capacity to derive pleasure, physical status, and cognitive functioning (5). Despite variable efficacy rate, antidepressants are the most-commonly used treatments for MDD (6).

The onset of a depressive episode at a young age is a significant marker associated with high treatment resistance (7). MDD is one of the most common mental disorders among young adolescents aged 12- 18 years, with a lifetime prevalence of up to 12% (8).

The more severe form of major depression also significantly determines the risk of relapse, which is observed in 50-70% of successfully treated patients 1 year after treatment. Therefore, the more severe the major depressive episode is, when the symptoms are fewer but more severe, it is more unlikely that the patient will respond to the treatment (7).

The Canadian Network for Mood and Anxiety Treatments clinical guidelines refer to specific drug recommendations for some symptoms, including vortioxetine, bupropion, duloxetine, and SSRIs for cognitive dysfunction; agomelatine, mirtazapine, and trazodone for sleep disturbance; and bupropion and SSRIs for fatigue (9).

Chekroud et al. reported that duloxetine outperformed escitalopram for core emotional symptoms, fluoxetine for sleep symptoms, and escitalopram, paroxetine, fluoxetine, and low-dose duloxetine for atypical symptoms (10).

Early response to treatment

If individuals respond to the therapy within 2 weeks after initiation of treatment, it is generally observed that they do much better in the longer term and achieve a higher rate of symptom relief. (11)

Psychiatric comorbidities

Co-existing psychiatric comorbidities are a very common feature of a major depressive episode, sometimes with diagnostic value, and can have a significant impact on the outcome of treatment. These effects have proven replicable in case of anxiety disorders and substance use disorders. (4) Co-existing comorbid anxiety disorders therefore have a major impact on remission and increase treatment resistance, increasing the risk of relapse. Their prevention, accurate diagnosis and appropriate treatment strategy are key to the treatment of major depression (12).

Electrophysiological markers

One group of measurable markers that has been evaluated for objective prediction of pharmacological treatment is the brain's electrophysiological parameters. Electroencephalography (EEG) is essentially a method and technique for measuring electrical activity that is non-invasive,

easy to access, and at the same time helps to determine the therapeutic response to the antidepressants **(13).**

Although there are a few inconsistent results as well, the most significant finding was an increase in theta (slow-wave phase) activity in the frontal cortex before treatment, which was associated with a positive therapeutic outcome **(Voegeli *et al.*, 2017).**

Neuroimaging markers

Functional magnetic resonance imaging (fMRI) is the first choice for the assessment of functional disorders, which assesses changes in neural activity based on the blood-oxygen level-dependent (BOLD) signal **(4).** Within the cortico-limbic brain regions, the anterior cingulate cortex (ACC), as well as the hippocampal area, showed replicable effects of sufficient magnitude **(14).**

Peripheral markers

As it is well known, a large group of biomarkers can be detected in urine, saliva, blood and cerebrospinal fluid (CSF), so they are among the variables that can be measured and collected relatively quickly and efficiently. Most of the results are closely related to immune function, as a correlation between the pathophysiology of MDD and the background of immune dysfunction is hypothesised. The role of BDNF in serum is to promote cell differentiation. Therefore, elevated levels in the early treatment phase are a good predictor of the subsequent therapeutic response **(4).**

Genetic markers

For over a decade, studies investigated the predictive value of single polymorphisms for antidepressant response and a breakthrough was not happening. Thus, a next step was to look at interactive effects of such single-nucleotide polymorphisms (SNPs) **(15).**

Lopez *et al.* showed that baseline expression of microRNA (miRNA) miR-1202 was lower in patients with depression who subsequently responded to an 8-week regimen of the SSRI citalopram **(16).**

Side effects of treatment

The possibly of more frequent adverse events should be considered when making a treatment decision. Sertraline and escitalopram were also considered first-line treatments, which is compatible with previous reviews and expert consensus guidelines that endorsed SSRIs as the first-line treatment for older patients **(17,18).**

Previous medication

Recommendations differed regarding regimen change, depending on previous medications and treatment response. While the first-line treatment for non-response to an SSRI was switching to an SNRI or mirtazapine, the treatment for non-response to an SNRI was switching to

mirtazapine and vice versa. Augmentation with aripiprazole, olanzapine, or quetiapine was generally considered reasonable in the case of non-response based on clinical trial data **(19).**

Previous response

The sole reliable predictor of improvement in sequential treatment is that improvement at one step is associated with further improvement at the next step, whereas failure to improve indicates a poor prognosis for improvement during future treatments **(20).**

Intra individual factors

Many such intra individual factors are psychological, including patient expectations, cognitions, or conditioned responses. Data from subjects enrolled in clinical trials has shown that patients with high expectations of the effectiveness of their treatment are more likely to benefit from their treatment **(21).**

Machine learning

Due to cost and resource constraints, only those markers that prove to be the most cost effective can be introduced into clinical practice. Drugs are also primarily targeted at patients who are most likely to benefit from the effectiveness of the therapy. In the future, the best solution would be to set up a predictive model that considers the patient's predominant symptoms, medical history and available biomarkers that influence his or her therapy. The predictive value would consist of a combination of several aspects, with each factor being weighted according to its effect size **(4).**

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