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Review article

Peripheral biomarkers of major depression and antidepressant treatment response: Current knowledge and future outlooks

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ABSTRACT

Background: In recent years, we have accomplished a deeper understanding about the pathophysiology of major depressive disorder (MDD). Nevertheless, this improved comprehension has not translated to improved treatment outcome, as identification of specific biologic markers of disease may still be crucial to facilitate a more rapid, successful treatment. Ongoing research explores the importance of screening biomarkers using neuroimaging, neurophysiology, genomics, proteomics, and metabolomics measures.

Results: In the present review, we highlight the biomarkers that are differentially expressed in MDD and treatment response and place a particular emphasis on the most recent progress in advancing technology which will continue the search for blood-based biomarkers.

Limitations: Due to space constraints, we are unable to detail all biomarker platforms, such as neurophysiological and neuroimaging markers, although their contributions are certainly applicable to a biomarker review and valuable to the field.

Conclusions: Although the search for reliable biomarkers of depression and/or treatment outcome is ongoing, the rapidly-expanding field of research along with promising new technologies may provide the foundation for identifying key factors which will ultimately help direct patients toward a quicker and more effective treatment for MDD.

1. Introduction

Major depressive disorder (MDD) is a prevalent psychiatric disorder associated with varied prognosis, chronic course, and duration of illness with reduced quality of life (Beck et al., 1961; Burton et al., 2015; Daly EJ, 2010). Most MDD patients stay on ineffective medications for too long, switch treatments too early, or simply drop out of care (Burton et al., 2015; Rush et al., 2008; Warden et al., 2007b). Compared to treatment of several other somatic diseases, antidepressant response rates are low, duration to attain therapeutic benefit is long, and treatment-emergent side effect burden is significant (Rush et al., 2011; Trivedi et al., 2006b; Warden et al., 2007a). Furthermore, treatments are selected not based on efficacy, but instead on patient or provider preferences. The factors that ultimately drive these decisions include cost, side effects, tolerability, and/or response during previous episode (s) (Meron et al., 2015). Unlike other specialty fields of medicine, such as breast cancer (Dowsett and Dunbier, 2008), asthma (Lima et al., 2009), macular degeneration (Lee et al., 2009), and multiple sclerosis (Vosslamber et al., 2009), there are no validated biomarkers for depression, thereby stalling the goal of offering precise, targeted treatment for this devastating disorder. Indeed, personalized treatment has the capacity to maximize the likelihood of treatment response or remission, while simultaneously minimizing detrimental side effects (Kessler et al., 2003; Murray et al., 2013).

The search for biomarkers is hindered by the heterogeneity of MDD (Hasler et al., 2004) and the limitation of its current diagnostic categories such as self-reports, measurement based scales, with a lack of understanding of the molecular blood testing compared to other diseases (Insel et al., 2010a). In clinical practice, efforts are made to understand the demographic features, (e.g., gender (Young et al., 2009), race (Friedman et al., 2009), employment status (Warden et al., 2007a)), illness characteristics (e.g., baseline severity of depression (Friedman et al., 2012), duration of illness (Rush et al., 2012), number of previous episodes (Trivedi et al., 2005), age of onset (Zisook et al., 2007), family history of mood disorders (Trivedi et al., 2005), presence of anxious features (Fava et al., 2008), depression symptoms and its subtypes (Friedman et al., 2009), co-morbid psychiatric disorders (Friedman et al., 2009), psychosocial functioning (Vittengl et al., 2009),

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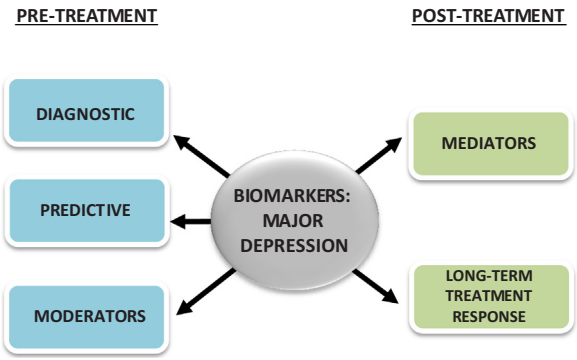

Fig. 1. *Biomarkers of major depression.* Biomarkers identified before treatment initiation are classified as diagnostic, predictive, or moderators. Diagnostic markers classify an MDD patient, predictive markers determine overall likelihood of response/remission, and moderators determine likelihood of response/remission with a particular treatment. Mediators are biomarkers collected soon after treatment initiation and help predict overall likelihood of response/remission. Long-term treatment response may also be indicative of ultimate outcome.

and social factors (e.g., marital status (Trivedi et al., 2005), level of social support (Lesser et al., 2008), social status (Lesser et al., 2008)). Unfortunately, these have proven to be of limited utility due to the knowledge gap regarding cellular and molecular pathophysiology, blood tests, and events that occur during brain development and maturation in MDD. (Arnow et al., 2015; Bobo et al., 2011; Chan et al., 2012; Sung et al., 2012, 2013, 2015). The underlying biological factors that drive MDD may be better suited to serve as biomarkers for guiding personalized medicine, as they are objective and can be measured externally (Biomarkers Definitions Working Group, 2001; Strimbu and Tavel, 2010). The heterogeneity of MDD necessitates and/or allows for numerous biomarker classifications, as shown in Fig. 1. Diagnostic biomarkers indicate presence and/or future development of disease. Most of the currently-identified biomarkers, described below, are predictive, such that baseline levels will provide insight as to whether or not a patient will respond to treatment. Moderators are also characterized at baseline, though provide more detailed information, such that clinicians can predict how a patient will respond to a particular treatment. Mediators define markers that change following treatment initiation and may predict future performance with the same or alternative treatment methodology. To maximize the chances of success, we may also need to go beyond individual biomarkers and venture towards generating multidimensional biomarkers (i.e., biosignatures) by systematically evaluating combinations of both clinical and biological markers.

In this report, we briefly review currently available treatment options for depression, though emphasize the necessity for biomarker identification to discriminate depression subtypes and work toward personalized medicine. We present the tools available for biomarker discovery and discuss what these technologies have identified as hits to date. In addition, we discuss our own clinical trial study, EMBARC (Establishing Moderators and Biosignatures of Antidepressant Response for Clinical Care), which is exclusively designed to screen numerous putative biomarkers with the aim to identify biosignatures for depression response.

2. Antidepressant treatment strategies

Numerous modalities are available to treat individuals with depression. Unfortunately, no treatment is universally effective, although different molecules and neural circuits are targeted, promoting distinct physiological changes. Pharmacological medications continue to be the most commonly-recommended first-line treatment for MDD (Olfson and Marcus, 2009). While there are several ADM classes like selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs), and others (bupropion and mirtazapine), all similarly target monoamine neurotransmission (Ball et al., 2014; Feighner, 1999; Lin et al., 2011; Saragoussi et al., 2012). Despite the variety of molecular targets, two thirds of MDD patients fail to achieve remission after initial treatment, and almost one third fail to achieve remission even after four consecutive treatment trials (McGrath et al., 2006; Rush et al., 2006a, 2006b; Trivedi et al., 2006a; Warden et al., 2007a).

Outside of the widely-prescribed pharmacological therapies, alternative treatment strategies instead employ indirect mechanisms which may still affect brain physiology, such as psychotherapy, exercise, and somatic treatments. Although their central mechanism(s) of action remain largely unknown, each has demonstrated efficacy in clinical populations. For example, individual or group psychotherapy sessions (e.g., including cognitive-behavioral therapy (CBT), interpersonal therapy (IPT), and behavioral activation) show efficacy in treating depression (Craighead and Dunlop, 2014). Physical activity, including aerobic, anaerobic, and mindfulness ameliorates depressive symptomatology following both acute and chronic sessions. This is demonstrated in numerous studies, although it is important to point out that results are not always consistent, likely due to the heterogeneity of participants and treatment design (Blumenthal et al., 2012; Bridle et al., 2012; Rethorst and Trivedi, 2013; Silveira et al., 2013). Lastly, somatic treatments, including electroconvulsive therapy (ECT), repetitive transcranial magnetic stimulation (rTMS), and vagus nerve stimulation (VNS) have evidence of some efficacy, though its use is often restricted to patients with treatment-resistant or moderate-to-severe depression (Meron et al., 2015).

In each case, these treatment options have demonstrated benefit alone or as an augmentation therapy to previously-described ADMs. The problem persists, however, that even by combining medications or treatment strategies, depressed patients frequently do not achieve response or remission. Discovery of biomarkers will help identify a personalized treatment strategy for each patient and thereby assist with quick and efficacious responsiveness.

3. Biomarker discovery—Tools and application

Technological advances over the last few decades has fueled the search for biomarkers which may predict individual response to particular antidepressant treatment strategies. In this section we detail the advanced methodologies with a particular focus on the strategies which enable screening of “Omics” biomarkers. Fig. 2 denotes the cascade of events necessary for identifying a biomarker, including discovery and validation processing using high- and low-throughput methodology, respectively. These approaches hold promise, as they enable study of a wide variety of biological processing, ranging from genetic composition to protein breakdown, and any biological entity in between. Below we will review the methodological design and tools for pharmacogenomics, epigenomics, transcriptomics, proteomics, and metabolomics and provide examples of their employment thus far:

3.1. Pharmacogenomics, epigenomics and transcriptomics

Genomics enables the identification of one's genetic makeup and post-translational modifications, ultimately providing insight regarding a target's structure and function. Standard large scale genome-wide association studies (GWAS) as well as newer, next-generation technologies will serve at the forefront of identifying genetic biomarkers. Large clinical trials [e.g., STAR*D (n = 1953) (Garriock et al., 2010), MARS (n = 339) (Ising et al., 2009), GENDEP (n = 706) (Uher et al., 2010), and PGRN-AMPS (n = 529) (Ji et al., 2013)] are harnessing the power of pharmacogenomics to help identify predictors of depression and/or treatment response.

To date, single nucleotide polymorphism (SNP) identification