Review
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Clinical Utility of Fluid Biomarker in Depressive Disorder

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Major depressive disorders are ranked as the single largest contributor to non-fatal health loss and biomarkers could largely improve our routine clinical activity by predicting disease course and guiding treatment. However there is still a dearth of valid biomarkers in the field of psychiatry. The initial assumption that a single biomarker can capture the myriad of complex processes proved to be naive. The purpose of this paper is to critically review the field and to illustrate the possible practical application for routine clinical care. Biomarkers derived from DNA analysis are the ones that have received the most attention. Other potential candidates include circulating transcription products, proteins, and inflammatory markers. DNA polygenic risk scores proved to be useful in other fields of medicine and preliminary results suggest that they could be useful both as risk and diagnostic biomarkers also in depression and for the choice of treatment. A number of other possible fluid biomarkers are currently under investigation for diagnosis, outcome prediction, staging, and stratification of interventions, however research is still needed before they can be used for routine clinical care. When available, clinicians may be able to receive a lab report with detailed information about disease risk, outcome prediction, and specific indications about preferred treatments.

KEY WORDS: Major depressive disorder; Antidepressive agents; Biomarkers; Therapeutics; Body fluids.

INTRODUCTION

There are 322 million people in the world who suffer from major depressive disorder, and there is a significant trend toward the disorder becoming more prevalent as the average age of people in many countries continues to rise. Not only depressive disorders are extremely common, but they also frequently recur, have a severe impact on a person's ability to function in their social and professional lives, call for a significant amount of support from the healthcare system, and frequently patients do not respond to treatments; even when they do respond, it takes at least 2 or 3 weeks. According to the World Health Organization, depressive disorders are therefore ranked as the single largest contributor to non-fatal health loss and are a major contributor to suicidal behaviors [1].

Therefore, it is clear that in order to better manage depressive disorders, we need reliable biomarkers to predict their course and response to treatments.

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DEFINITION OF BIOMARKERS

Biomarkers are defined as biological measures that can be helpful for defining the presence or absence of a pathogenic process or for evaluating the clinical response to a pharmacological treatment. There are many different classifications for biomarkers.

Biomarkers of risk are indicators of the likelihood of developing a disease that an individual does not already have. They are most frequently used in the process of formulating preventive measures for individuals who are at high risk of becoming ill. An illustration of this would be cystic fibrosis.

Diagnostic biomarkers can be utilized to either detect or confirm the presence of a disease, as well as to identify individuals who are affected by a particular disease subtype. Glomerular filtration rate is an excellent example of this for renal disease.

When a patient is ill, diagnostic biomarkers can be used to determine the likelihood of a clinical event, a recurrence of illness, or the illness's progression. They are usu-

ally defined as prognostic biomarkers.

Biomarkers of treatment response may be extremely useful for predicting response and tolerability to a specific drug or psychological treatment, as well as to treatment in general. Other biomarkers may show early signs of response, even when there is no clinical observable benefit yet, thereby guiding the treatment before it may be clinically evident that the response has occurred.

Ideally, biomarkers should be simple to dose, relatively noninvasive, inexpensive, and reliably reproducible across centers. Moreover, their specificity and sensitivity should be clinically relevant. Sensitivity is the ability of a test to detect a condition of interest when it is truly present and specificity is the ability of a test to exclude the condition of interest in patients who do not have the disease. Clinical relevance refers to the ability of the test to explain a relevant proportion of the outcome, either a diagnosis or a prognosis. As an example, if a test may explain about 1% of the disease variance, as it is the case of many polygenic risk scores analyses, may not have a relevant clinical use.

Regrettably, there is still a dearth of valid biomarkers in the field of psychiatry [2].

BIOMARKERS IN PSYCHIATRY

The initial assumption that a single biomarker can capture the myriad of complex processes that lie at the root of a psychiatric disease is now viewed as naive. In fact, if one views the disease through the lens of systems biology, as dysfunctional regulatory networks, it is immediately apparent that a multi-parameter analysis, also known as a panel of markers, is necessary. It may provide a better insight into the disease diagnosis, prognosis, and treatment response. However, the combination of a number of biomarkers may raise other issues, such as the possible collinearity across biomarkers and the stability and reproducibility of the same set of biomarkers in independent samples. In particular when they belong to different ethnicities [3].

A large international effort promoted by the National Institute of Health of the United States was launched over a decade ago with the aim of redefining biologic research in psychiatric disorders, including biomarkers. The Research Domain Criteria initiative (RDoC) aimed at combining dimensional clinical assessments with valid biological mechanisms of disease pathophysiology [4], however over a decade after its official presentation, concerns have been raised about the potential to identify a reliable framework for psychiatric disorders [5,6]. A relevant issue is that probably the biological complexity of psychiatric disorders may not be reduced to the RDoC dimensions only.

Many potential biomarkers in psychiatry have been the subject of research that has spanned decades. Biomarkers derived from DNA analysis are the ones that have received the most attention, but other potential candidates include circulating transcription products, proteins, and brain imaging features, to name a few. As a consequence, there are a large number of results, and the purpose of this paper is not to provide an exhaustive summary, which was reviewed elsewhere [7-10]. The current narrative review will therefore conduct a survey of the current status of research on fluid biomarkers focusing on depression with a critical perspective, and it will illustrate the possible practical applications in routine clinical care.

BIOMARKERS IN MAJOR DEPRESSIVE DISORDERS

Unfortunately, if a comprehensive assessment of biomarkers in psychiatry is scarce [7-10], a specific focus on depression is even less common [11,12], as also reported in the recent consensus paper of the World Federation of Societies of Biological Psychiatry Task Force on Genetics [13]. Biomarker investigations spanned across a large range of possible targets. Peripheral biomarkers, which is mainly the topic of the present paper, mainly include analyses on blood samples, such as DNA variants and Polygenic Risk Scores, gene expression, mRNA, non coding RNA, DNA methylation, proteins/peptides (e.g., immunological and metabolic factors), but we should also mention analyses not on body fluids such as post mortem tissues, imaging, electroencephalogram, cognitive, neuropsychological and clinical features [11,14-20]. Those are not discussed in the present review but will probably be used in combination with peripheral biomarkers, as will be shown later.

Early biomarker studies focused on neurotransmitter metabolites which are detectable in blood. Specifically, the serotonergic system was much investigated because of its involvement in depressive disorders, as suggested by the clinical benefit of serotonin reuptake inhibitors, and

therefore initial biomarker studies focused on measuring the levels of serotonin and its major metabolite, known as 5-hydroxyindoleacetic acid [8]. Another relevant potential biomarker during the seventies and eighties was the dexamethasone cortisol suppression test, which was suggested as a very promising tool [21]. However much of the early peripheral biomarker studies received few or no replication in the following decades, and therefore at present there is no indication to use them in clinical practice.

The use of DNA variants for predicting antidepressant outcomes has been recently reviewed in this journal [22]. In summary, we already have a valid prediction available for routine clinical use coming from pharmacokinetic gene variants, which can guide medication and dose choice by the treating clinician. About 20% of patients are rapid or poor metabolizers and may benefit from dose adjustments. Future perspectives include the increase of the variants validated for clinical use, which may be extended to variants in pharmacodynamic genes, and provide more precise information on the recommended drugs or drug combinations. Variants in pharmacodynamic genes are under investigation and may potentially inform in the future on the most suitable drug for each patient on the basis of each individual specific brain physiology. Similar, for disease risk prediction, a small percentage of subjects with a relevant genetic risk for depressive disorders may be identified prior to disease onset [23], though this hypothesis is also still under investigation. A promising recent approach is the use of polygenic risk scores. This is a single number for each individual which informs on the cumulative genetic risk of a complex disorder such as depression. Genetic risk is in fact the result of hundreds or more genetic variants, which may modulate not only the risk of developing the disorder, but also the probability of having a specific subtype of the disorder and predict treatment outcome. This cumulative genetic risk is estimated using the so-called polygenic risk scores. Polygenic risk scores may therefore be biomarkers of disease risk, but also be useful for diagnostic stratification and prognosis formulation. Polygenic risk scores proved to be useful in other fields of medicine [24], to the point that are suggested for use in clinical practice, to guide diagnosis and treatments, with a clinical relevance that is similar to the ones of clinical risk factors. In psychiatry, and specifically in regard to depression, they are still under investigation, however preliminary results suggest that they could be useful both as risk and diagnostic biomarkers [25,26], but also for the choice of the treatment [27,28]. In any case research is still needed before a routine clinical care use.

It may be argued that DNA variants do not capture completely the complex biology of depression, therefore transcriptomic biomarkers have also been extensively investigated, by our group and others [29-31]. Many results were reported, also focusing on specific clinical aspects such as suicidal behaviors, but unequivocal confirmation is still lacking [32-34]. Similarly, transcriptional biomarkers of response to pharmacological treatments have also been investigated, still with not unequivocal results yet. A recent review covers this issue [35].

A step further in the study of the pathophysiology of depression is proteomics, that focuses on the final product of genes, avoiding potential confounders coming from intermediate transcriptional modifications. Proteomic investigations were recently very productive, also in the study of bipolar disorder [36], to the point of suggesting also a phase specific profile [37] and differentiating between bipolar and major depressive disorder [38]. For example, the brain-derived neurotrophic factor has been widely investigated, with promising results, as it shows normalization after treatment [39,40]. However, evidence referring to single biomarkers should be interpreted very cautiously, as results are usually not univocal, and the variance explained is limited, because of the discussed complexity of psychiatric disorders. The combination of transcriptomics and proteomics has been also suggested, in order to provide complementary and potentially more relevant information [41]. The combination with other types of omics, e.g., metabolomics, has support of being a promising strategy [42,43].

Inflammatory biomarkers are an interesting area of investigation, given the known involvement of inflammation factors in the pathophysiology of depression [44], and a number of possible biomarkers are currently under investigation for diagnosis, outcome prediction, staging, and stratification of interventions [45-48]. However, at present there are no approved inflammatory biomarkers for use in routine clinical practice.

In the meantime, research in the field of biomarkers is ongoing, with a number of efforts. The Biomarkers Consortium is an example of a combination of public and pri-

vate contributors aiming to detect clinically relevant biomarkers [49]. Given the raising importance of microbiome in mental health, also nutritional biomarkers have been suggested [50], also on the basis of possible abnormalities in serum ghrelin and leptin levels in patients with depression and after treatment [51].

More recent approaches summarize lessons from previous studies and investigate blood diagnostic and prognostic biomarkers with a longitudinal perspective in order to avoid state dependent biases, replicate across samples to support validity and investigate the potential for drug repurposing [19,52]. However, a validated and reliable biomarker panel has not yet been defined.

POTENTIAL LIMITATIONS OF BIOMARKERS

We are only able to analyze fluid biomarkers in blood or other fluids; we cannot do so directly in the brain. This is a significant limitation. It has been debated for a long time whether or not peripheral markers are representative of the pathophysiological mechanisms that occur in the brain.

As an example, Cai *et al.* [53] compared three human brain expression data sets (from cortex, cerebellum and caudate nucleus) to two large human blood expression data sets and found protein expression levels weakly correlated (0.24–0.32). Nevertheless, a subset of preserved co-expression relationships were identified, particularly for proteins coded by genes whose expression levels tend to be more heritable and, in particular, involved in infection mechanisms, post-transcriptional and post-translational modifications and other basic processes. Other studies have demonstrated that, in some cases, measures in blood are very similar to those at the level of the central nervous system [54]. As an example, blood miRNA levels were shown to largely correlate with brain expression [55]. Indeed, miRNA circulating levels are a promising field of investigation [56-60]. Access to cerebrospinal fluid could reduce this bias [61,62], however feasibility is obviously a strong limitation.

Since the interest for peripheral biological markers in humans *in vivo* is relatively recent, for the large part of candidate markers we do not have sufficient information about their ability to accurately reflect processes occurring in the brain.

BIOMARKERS AND FUTURE POTENTIAL CLINICAL ROUTINE USE

In the previous sections, available data on depression biomarkers were critically reviewed. A number of promising findings are reported, at different levels of blood analyses. Unfortunately, at present none of them is approved by regulatory agencies or international guidelines. However it is likely that soon they will start to receive recommendations for clinical use.

This may have a relevant impact for routine clinical practice, an example has been recently reported [19]. Clinicians may receive a report from the lab with information about: overall depression risk, risk for future depressive episodes and switch to bipolar disorder, a list of existing suggested medications best fitting with the patient, possible non psychiatric medications that may be of benefit and suggestions for potentially useful combinations of medications. If valid, all these indications will be

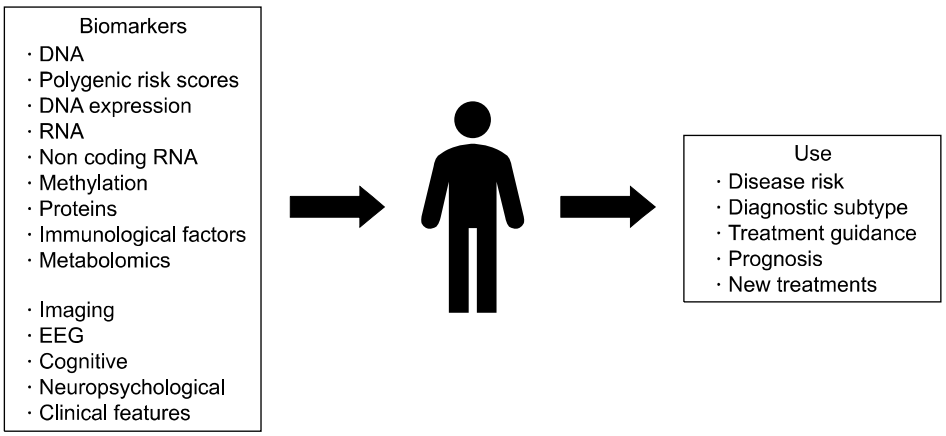

Fig. 1. Potential fluid and clinical biomarkers and their possible clinical use.
EEG, electroencephalogram.

of great benefit for routine clinical care, avoiding unnecessary long, ineffective or poorly tolerated treatments, as well as for predicting disease risk, course and long term prognosis.

In conclusion, peripheral fluid biomarkers are a very promising field of investigation which soon will add relevant information for routine clinical care (Fig. 1). Personalization of treatment will be the final outcome, the same personalization that at present is achieved only after many months or years of trials and error solely based on clinical data.

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