METABOLISM CLINICAL AND EXPERIMENTAL 64 (2015) S 11–S15

Available online at www.sciencedirect.com

Metabolism

www.metabolismjournal.com

Biomarkers of psychiatric diseases: Current status and future prospects

Madhu Kalia [a,*], Jorge Costa e Silva [b]

[a] Thomas Jefferson University, Philadelphia, PA 19107
[b] Brazilian Brain Institute, 22461-210 Rio de Janeiro, Brazil

ARTICLE INFO

Keywords:
Depression
Schizophrenia
Bipolar disorder
Suicidality

ABSTRACT

Abnormal behavior and disturbed cognition, often assumed to represent psychiatric illness, may actually result from some form of occult organic brain disease that can be detected by means of one or more biomarkers. This truth was discovered more than a century ago by Aloysius Alzheimer, a German psychiatrist and neuropathologist. As a psychiatrist, he described the behavioral manifestations of "senile dementia" in a 51-year-old female; as a neuropathologist, he was the first to recognize the significance of the senile plaques and neurofibrillary tangles found in her brain after her death at age 55 years. It was Alzheimer who made the connection between these "biomarkers" and the symptoms of the increasingly prevalent disease that now bears his name. In recent years, the search for psychiatry-relevant biomarkers of major depression, schizophrenia, bipolar disease, and other important psychiatric/neuropsychiatric disorders has intensified. Biomarkers in psychiatry and neuropsychiatry have the potential of clarifying the etiology of an ambiguous clinical presentation—making it possible, for example, to detect underlying differences between psychological maladies that have confusingly similar symptoms. In addition, attempts are now being made to classify mental disorders on the basis of biomarkers. Biomarkers may also disclose the presence of a previously unsuspected physical explanation for behavior(s) originally presumed to be "psychiatric" in origin. Although clinically usable biomarkers in the diagnosis and treatment of mental illness await validation, candidate genomic biomarkers and protein profiling of candidate biomarkers in psychiatry are rapidly gaining ground as areas of interest, with considerable future potential. This review considers biomarker-related issues germane to psychiatry and neuropsychiatry in the context of new data that can be used to tailor therapies to the individual psychiatric patient.

1. Biomarker-related issues pertinent to psychiatry

Over 100 years ago, Aloysius Alzheimer observed plaques and neurofibrillary tangles in the brains of two demented patients post-mortem. One of them, Auguste Deter exhibited bizarre behavioral symptoms at the early age of 51 years, together with a marked loss of short-term memory. She died in 1906 at age 55 and, in a lecture later that year, Alzheimer presented her "psychiatric" picture—described as "presenile dementia"—in juxtaposition with the neuropathologic findings. This syndrome, first reported 108 years ago and now alarmingly prevalent, has been widely known as Alzheimer's disease since 1911 [1–3].

* *Corresponding author at:* Thomas Jefferson University, Suite 520, 1020 Walnut Street, Philadelphia, PA 19107. Tel.: +1 215 920 5134.
E-mail addresses: madhu.kalia@jefferson.edu, mkalia@msn.com (M. Kalia).

http://dx.doi.org/10.1016/j.metabol.2014.10.026
0026-0495/

In recent years, increasing efforts have been made to classify mental disorders on the basis of objective biological markers (biomarkers), and to include this exercise in the standard diagnostic process [4–6]. Biomarkers have been defined as: *Measurable characteristics that reflect biological function or dysfunction, response to a therapeutic measure, or indication of the natural progression of disease* (Biomarkers Definitions Working Group 2001) [7]. Biomarkers in the field of psychiatry have the potential of being particularly significant because they could clarify the etiology of psychiatric problems, confirm the diagnosis of disorders with similar symptoms, and predict the course of the disorder and determine how to treat [8]. This is important because, in psychiatry, the close association between symptoms and pathology is tenuous and varied and "…the majority of psychiatric symptoms are best regarded as features, which can arise in a multitude of settings and which reflect a variety of underlying causes.… Consequently, in the absence of any definitive neurobiological underpinning for neuropsychiatric diseases, psychiatric classification remains dependent on eliciting signs and symptoms of mental illness. This is the central problem from which many other difficulties in psychiatry arise" [9].

At present, diagnosis of psychiatric disorders relies primarily on a personal psychiatric interview and evaluation based on international guidelines (ICD-10, World Health Organization 2014) [10], and the recently updated classification system of mental disorders (DSM-5) [11,12]. The updated DSM-5 of diagnostic criteria and classification guidelines was published on May 19, 2013 after a 14-year revision process that included consultation with expert workgroups (clinicians and researchers). DSM-5 was designed as a "diagnostic tool" that considers different disorders as distinct entities. However, the boundaries between disorders have not been strictly defined in these guidelines, which makes it difficult to distinguish among fundamentally different disorders with similar symptoms [10].

Since the traditional differentiation of psychiatric phenotypes has been almost entirely based on clinical symptoms, without taking biological differences into account, patient subgroups are difficult to discriminate [13]. The NIMH has attempted to correct this deficiency of the DSM-5 by launching an alternative framework based on pathophysiology, especially as disclosed by genomics and neuroscience. The NIMH has introduced its Domain Criteria (RDoC) project, in which each of five "domains" reflects a brain system whose functioning is impaired to different degrees in different psychiatric conditions [10,14]. Such an approach is intended to improve therapeutic intervention that could reduce the relapse rates of psychiatry patients. For this reason, a major research goal in psychiatry is to develop and use biomarkers to identify "at risk" individuals and to objectively diagnose and/or determine the severity of mental illness [15]. It is hoped that RDoC domain criteria will facilitate reliable and valid diagnoses, identify new targets for treatment development, detect subgroups for treatment selection, and provide a better match between research findings and clinical decision making [14].

Expanded knowledge of molecular signatures, including protein expression levels, could enhance our understanding of the molecular pathways that underlie the clinical manifestation and disease course of mental disorders [16]. As evidence of this recent interest in putative potential biomarkers in psychiatry, there have been over 302 articles published on this topic – which includes gene expression levels (Ovid MEDLINE: key words psychiatry and biomarkers), with 103 articles published between 2012 and 2014, as compared to 24 published between 2002 and 2004.

In this review we will discuss recent concepts related to biomarkers in psychiatry, provide an update on how biomarkers are currently being used in the practice of psychiatry and in clinical trials in psychiatry, and examine future trends. The focus will be on published data on biomarkers that can be used in tailoring therapies to the individual psychiatric patient. However, it should be pointed out that, despite numerous recent advances in neuroscience and genetic research, the diagnosis of major classes of psychiatric disorders has not yet been correlated with clinically usable (or validated) biomarkers [15], nor are there many genetic and other biomarkers available that can reliably guide the diagnosis of psychiatric disorders [10]. Nevertheless, candidate genomic biomarkers and protein profiling of serum candidate biomarkers in psychiatry constitute an area of growing interest and can be expected to have considerable future potential [17–21].

2. Mood disorders

2.1. *Major depressive disorder (MDD)*

Recent biomarker research in psychiatry has involved use of multimodal approaches, such as neuroimaging, genetics, proteomics, metabolomics, to explore potential predictor and mediator biomarkers of the rapidly acting antidepressants ketamine and scopolamine. The goal, as described by Niciu, et al. [22] is "… to improve pathophysiological understanding, personalize treatment selection, and expand our armamentarium of novel therapeutics." Treatment of depression (antidepressant medication and electroconvulsive therapy) has been shown to influence oxidative stress and inflammatory markers [23]. In most of these studies the relationship between variations in levels of biomarkers and changes in depressive symptoms has not been studied thoroughly enough to permit conclusions about the usefulness of biomarkers as indicators of the effectiveness of treatment of depression [23].

Although assessment of pre-treatment biomarkers has the potential to enhance clinical decision making in psychiatry, the usefulness of candidate biomarkers in evaluation of treatment efficacy needs to be more firmly established. A number of studies have attempted to measure treatment progress over time by means of treatment-response biomarkers. Validation of these treatment-response biomarkers and the careful monitoring of their changes can be expected to provide useful information about treatment efficacy in the future [23]. Examples of depression-related biomarkers follow:

(a) C-reactive protein (CRP). The potential of biomarkers to predict the onset of depression: In a prospective study, increased CRP levels were associated with an increased risk for hospitalization with depression [24]. Higher CRP levels have also been identified as an independent risk factor for de novo depression in women [23,25], and a