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Proposing an integrative use of biomarkers for antidepressant treatment outcome bridging the gap from blockbuster medicine to personalized treatment.

Are there meaningful biomarkers of treatment response for depression?

Barbara Breitenstein[1,2,3], **Sandra Scheuer**[2,3] and **Florian Holsboer**[1,2]

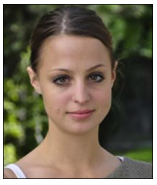
[1] HolsboerMaschmeyerNeuroChemie, Munich, Germany
[2] Max Planck Institute of Psychiatry, Munich, Germany

During the past decades, the prevalence of affective disorders has been on the rise globally, with only one out of three patients achieving remission in acute treatment with antidepressants. The identification of physiological markers that predict treatment course proves useful in increasing therapeutic success. On the basis of well-documented, recent findings in depression research, we highlight and discuss the most promising biomarkers for antidepressant therapy response. These include genetic variants and gene expression profiles, proteomic and metabolomic markers, neuroendocrine function tests, electrophysiology and imaging techniques. Ultimately, this review proposes an integrative use of biomarkers for antidepressant treatment outcome.

Introduction

According to current estimates, around one in ten individuals will at least once in life suffer from a depression that is severe enough to require medical treatment [1]. Major depression (MD) is a potentially lethal disease, every year one million people die from suicide worldwide [2]. MD increases our vulnerability to other common complex diseases such as dementia [3], cardiovascular disease [4] and type II diabetes [5]. Symptoms of MD include depressed mood, anxiety, anhedonia, disturbed sleep, cognitive impairment, suicidal ideation and, in extreme cases, psychotic symptoms. First manifestations of MD usually occur in early adulthood, where onset is frequently triggered by stressful life events [6]. Late-onset depression at the age of >60 years often develops in conjunction with other clinical conditions such as hormonal changes, neurodegeneration or vascular disorders, to name just a few [7]. The disease is characterized by recurrent episodes with changing clinical phenotype, sometimes chronicity and a trend to develop manic episodes of a conversion rate of ~1% per year throughout the lifespan [8]. Affective disorders are associated with substantial impairments in quality of life and functioning comparable to those observed with chronically physically ill patients [9]. In the light of the considerable socioeconomic impact of MD, the fragmentary nature of our knowledge about the underlying pathophysiology is sobering. Depression frequently runs in families, pointing toward genetic

Corresponding author: Holsboer, F. (holsboer@mpipsykl.mpg.de)
[3] Authors contributed equally to this work.



Barbara Breitenstein studied psychology at the Humboldt University in Berlin, Germany, and the University of California, San Diego, USA. She received her diploma degree of psychology in 2011 and has since been working as a PhD student at the Max Planck Institute of Psychiatry in Munich, Germany. Her research interests include biomarkers for antidepressant response with a focus on drug delivery across the blood–brain barrier and sleep research. She is an employee of HMNC where she is actively involved in the development of laboratory tests and personalized treatment strategies in major depression

Sandra Scheuer studied psychology at the Faculty of Nature Sciences at the Paris Lodron University of Salzburg, Austria. After receiving her diploma in 2011, she moved to the Max Planck Institute of Psychiatry (Munich, Germany), where she is currently a PhD student. She is working on a naturalistic clinical study that aims to detect genetic factors for predicting treatment response in depression.

Professor Florian Holsboer, MD, PhD, studied chemistry (PhD) and medicine in Munich, Germany. Since 1989 he is director at the Max Planck Institute of Psychiatry, a research institute with over 600 employees in ten clinical and 15 basic research groups including clinical and molecular psychopharmacology, human and mouse genomics, proteomics and sleep research. The institute has 120 research beds and a day-care clinic. Dr Holsboer has published more than 950 scientific articles and is among the 100 most-cited neuroscientists worldwide, his h-factor is 101. His work has been recognized by numerous prizes, most recently the Robert Pfleger Prize 2012 and in 2013 the WFSBP Lifetime Achievement Award in Biological Psychiatry. In 2008 he received the Doctor Honoris Causa from the University of Leiden, The Netherlands; and in 2013 received the same honor from the Medical Faculty of the University of Zürich, Switzerland.

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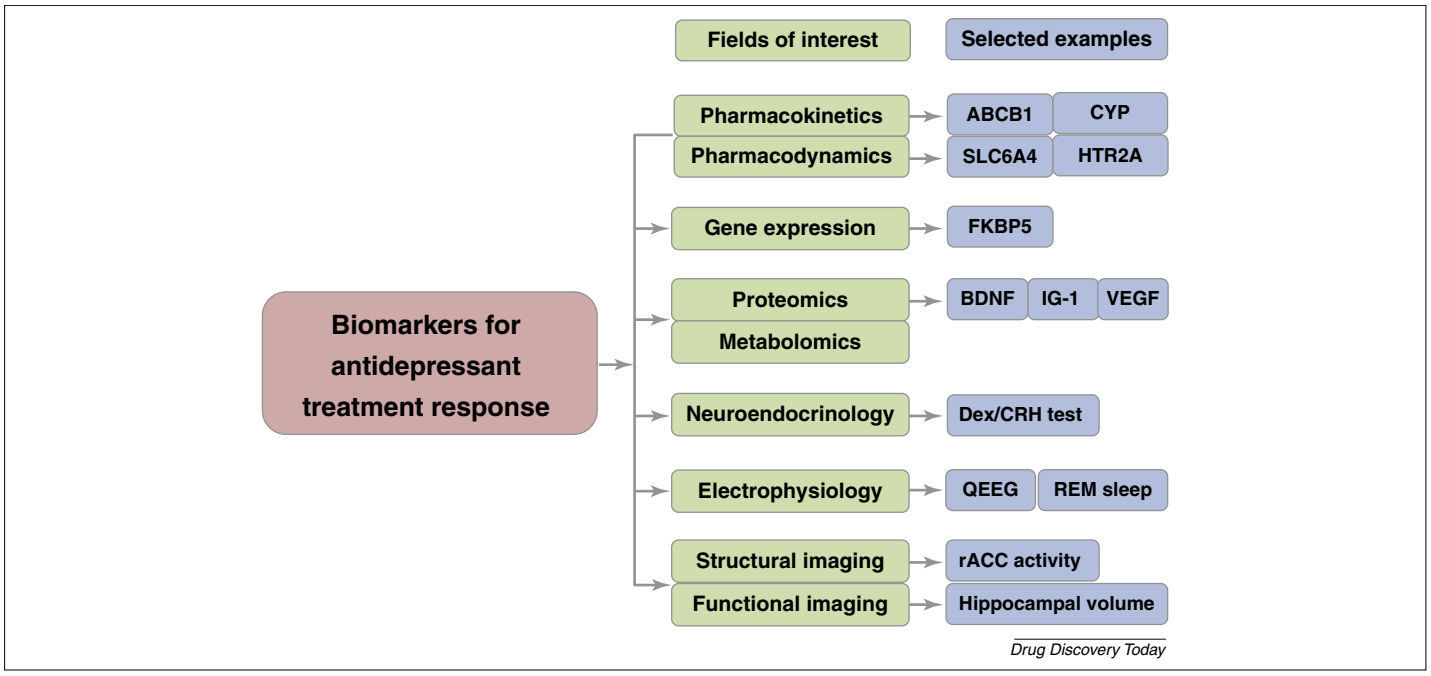

FIGURE 1

Overview: biomarkers of antidepressant treatment response. *Abbreviations*: CRH, corticotropin-releasing hormone; CYP, cytochrome P450; Dex, dexamethasone; FKBP5, FK506-binding protein 5; IGF-1, insulin-like growth-factor-1; QEEG, quantitative electroencephalographic; rACC, rostral anterior cingulate cortex; REM, rapid eye movement; VEGF, vascular endothelial growth factor.

predisposition that interacts with environmental risk factors such as endured exposure to severe stressors. Genetic factors do not need to be inherited; they can also be a result of spontaneous mutations as is indicated by the constant prevalence despite a reduced fertility among patients with MD. The disposition can also be acquired and traumatizing experiences in early childhood can render an individual at risk for MD in later life [10]. Those early adversities often interact with genetic factors amplifying an individual's risk to succumb to MD even at a young age [11]. In comparison to all major complex disorders, the diagnosis of MD relies entirely on verbal communication and other subjective measures such as interpretation of body language, physiognomy or fluidity of speech. Thus, any objective measure or biological marker to ensure the diagnosis of MD would be highly desired. A biomarker can be defined as: 'a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, or pharmacologic responses to a therapeutic intervention' [12].

The past three decades have seen many attempts to confirm diagnostic categories by laboratory measures, mainly derived from endocrinology and neurophysiology. Examples are attempts to differentiate so-called endogenous depression from neurotic depression by measuring plasma growth hormone concentrations following several stimuli that included insulin, clonidine (an α_2 adrenoceptor agonist) or other agents. Still, the most robust finding in MD is the overactivity of stress hormones resulting in higher plasma cortisol levels, which can only be incompletely suppressed by the synthetic corticosteroid dexamethasone [13]. The so-called dexamethasone suppression test (DST) was strongly advocated as a tool that allows differentiation between neurotic and endogenous depression, a finding that turned out to be meaningless once the distinction between these subtypes was dropped and new depression categories were defined. This raises the pertinent question: what is a biomarker going to mark if diagnostic categories are coming and going? A much more fruitful application of laboratory abnormalities is to use them as biomarkers that predict treatment course and assist discovery of new antidepressant drugs. Patients suffering from MD often face long therapy courses failing to meet remission criteria even after several consecutive treatment trials [14]. The incorporation of biomarkers in the treatment of MD could help improve the efficiency of treatment trials and ultimately speed remission. In this article we will review biomarkers for treatment response in MD. We follow the definition of biomarkers as objective indicators of pharmacologic responses to therapeutic interventions and include findings from the fields of DNA-sequence variations, gene expression, proteomics, metabolomics, neuroendocrinology, electrophysiology and brain imaging (Fig. 1).

Genetic variants

Pharmacogenetics aims to detect genetic variations that affect individual responses to drugs, leading to a better prediction of treatment outcome. This emerging field is often subdivided into genetics of drug pharmacokinetics and pharmacodynamics. The term pharmacokinetics refers to the way in which drugs move through the body during absorption, distribution, metabolism and excretion, influencing the delivery of an antidepressant to its target [15]. Here we highlight recent findings on how variations in the *ABCB1* gene and the cytochrome P450 (CYP) family influence antidepressant treatment outcome.

The ABCB1 *gene*

Drug delivery to the central nervous system (CNS), and in particular transport across the blood–brain barrier (BBB), is a major

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