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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?

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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

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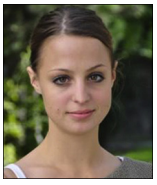

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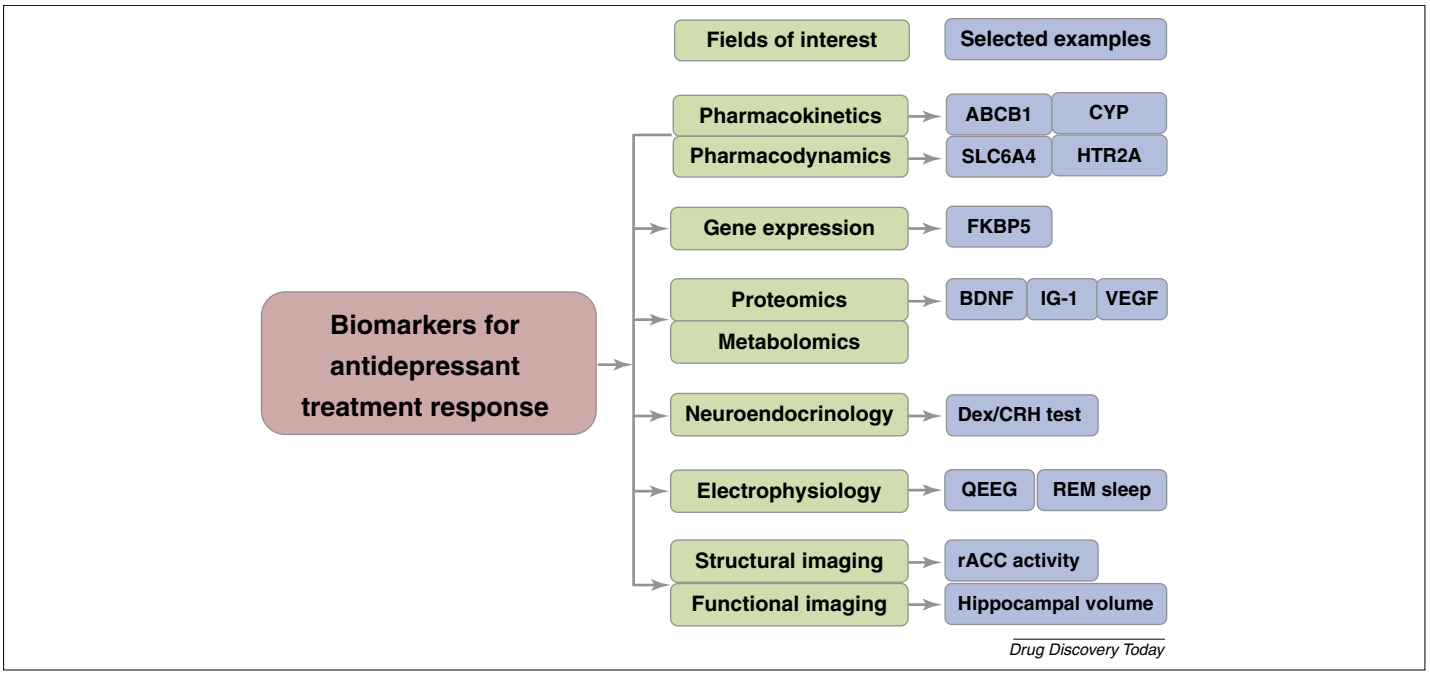

FIGURE 1

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

hurdle limiting the efficacy of antidepressant medication. During the past five years, much attention has been given to the influence of genetic traits on the permeability of the BBB. An important gene that has been studied in this context is *ABCB1*, also known as the multidrug-resistance gene *MDR1* located on chromosome 7. The gene product of *ABCB1*, P-glycoprotein (P-gp), is a custodian molecule mainly expressed at the luminal membrane of brain capillary endothelial cells forming the BBB. P-gp can bind a variety of endogenous and exogenous substances, including several antidepressants. Substrates of P-gp have a reduced ability to penetrate P-gp-expressing membranes and thus enter the brain. A growing body of research supports the hypothesis that therapeutic outcome under antidepressants with P-gp substrate properties can be predicted by genetic polymorphisms in *ABCB1* [16–25]. The first evidence came from Uhr *et al.* [16] who demonstrated that patients carrying the minor allele at several common intronic single nucleotide polymorphisms (SNPs) had a 7.7-fold higher likelihood to remit when treated with P-gp substrates (i.e. citalopram, venlafaxine or paroxetine) compared with patients carrying two copies of the major allele at the respective SNPs. However, other studies yielded conflicting results finding no association of genetic variants within *ABCB1* and antidepressant treatment outcome [26–31]. This could be partly caused by the lack of consistency regarding the study samples, the studied *ABCB1* SNPs and the study medication. For instance, Perlis *et al.* [31] found no influence of variants in *ABCB1* on duloxetine response. Duloxetine, however, is a serotonin norepinephrine reuptake inhibitor (SNRI) with no proven substrate properties for P-gp, for example see Ref. [32]. Its transport across the BBB is therefore likely to be mediated by mechanisms other than via the P-gp efflux pump. A previous meta-analysis solely considered two exonic SNPs of the *ABCB1* gene (rs1045642 and rs2032582) and found a weak association between antidepressant response and SNP rs2032582 [33]. In a small pilot study, we evaluated the application of *ABCB1* genotyping in a clinical setting and suggested that the implementation of *ABCB1* testing as a diagnostic tool could influence clinical decisions leading to an improvement of treatment outcome [25]. However, additional replications and prospective clinical trials are needed to determine the clinical relevance of *ABCB1* genotyping.

Cytochrome P450

Enzymes from the CYP family are predominantly expressed in the liver and alter the bioavailability of various drugs by regulating their oxidation and degradation. Polymorphisms in the genes encoding the CYP enzymes are associated with differences in enzyme activity according to which individuals can be classified into extensive metabolizers (EMs), intermediate metabolizers (IMs) or poor metabolizers (PMs), as well as, in the case of *CYP2D6*, ultrarapid metabolizers (UMs) [34]. These phenotype distributions vary widely across ethnicities. It has been suggested that genotyping of CYP enzymes could improve the efficacy of antidepressant drugs by matching a patient's metabolizer status with the prescribed dose [35]. Among the high number of known isoenzymes, *CYP2D6*, *CYP2C19*, *CYP2C9* and *CYP2B6* are the most studied [34]. The effects of CYP enzymes on drug metabolism under treatment with CYP substrates have been studied and reviewed extensively, for example see Refs. [34,36], and have proven useful mainly in terms of avoidance of adverse effects. However, only a limited number of studies with controversial results have assessed the relationship between CYP genotypes or phenotypes and clinically meaningful differences in antidepressant treatment response. Three small studies [37–39] and one re-analysis of four studies of larger sample size [40] reported an association between *CYP2D6* metabolizer status with SNRI concentrations and antidepressant efficacy, but others failed to do so [41,42]. Tsai *et al.* [43] evaluated the impact of *CYP2D6*, *CYP2C19* and *CYP3A4* genetic polymorphisms on treatment response under the selective serotonergic reuptake inhibitor (SSRI) escitalopram and found that specific *CYP2D6* polymorphisms could improve the prediction of treatment outcomes. However, Serretti *et al.* [44] studied 278 patients with MD treated with various classes of antidepressants and reported no association of *CYP1A2*, *CYP2C9*, *CYP2C19* and *CYP2D6* polymorphisms with therapeutic response or remission. Moreover, there was no association of *CYP2D6* or *CYP2C19* metabolizer status with SSRI response in the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) sample [27,45] and with SSRI/tricyclic antidepressant (TCA) response in the Genome-based Therapeutic Drugs for Depression (GENDEP) sample [46]. These results suggest that there is no clear relationship of CYP genotype and antidepressant treatment response, therefore questioning the usefulness of the clinical implementation of CYP testing.

Pharmacodynamics can be described as the effect of a drug on the body. This effect is determined by the drug binding with receptors, transporters and downstream targets [47]. Several candidate genes related to different hypotheses about the pathogenesis of depression have been proposed as predictors for antidepressant response. Most research in this context has focused on genes related to monoamine function (in particular genes involved in serotonin neurotransmission), the glutamatergic system, neurotrophic activity and hypothalamic–pituitary–adrenocortical (HPA) axis activation. For more-detailed information on pharmacodynamic genes associated with antidepressant response we refer to some excellent reviews [15,47–49].

Serotonin system

The serotonin transporter 5-HTTLPR and the serotonin receptor *HTR2A* are two main candidate structures that have been the source of considerable research interest over the past ten years. Within the serotonin system, the *SLC6A4* gene encoding for the serotonin transporter 5-HTTLPR has received much attention. Because it contains various polymorphic loci that affect the number and function of the gene product, genetic variants in *SLC6A4* can influence serotonin reuptake in a similar way to antidepressants. A genetic decrease of function would intuitively agree with inherent enhancement of serotonergic neurotransmission – a mechanism believed to be crucial for antidepressant drug action. Lesch *et al.* [50] discovered an insertion/deletion polymorphism located in the regulatory sequence of *SLC6A4* with two alleles of different length. The long allele results in higher *SLC6A4* gene activity compared with the short one. Because of these transcription differences and the resulting 5-HTT endowment, many studies were conducted to explore whether promoter variants are associated with response to SSRI treatment. The original finding by Smeraldi *et al.* [51] indicated that depressive patients with Caucasian ethnicity responded favorably to SSRIs if they were carriers of

the long allele. However, not all studies were able to confirm this finding. Therefore, a large number of pharmacogenetic studies were conducted confirming that the 5-HT gene promoter polymorphism could be a predictor of antidepressant response and remission [52]. One important limitation of this finding that could partly account for the high variability of findings is the influence of ethnicity: the L-allele is present in 29–43% of Caucasians but only in 1–12% of Asians [53], whereas the S-allele is present in 42% of Caucasians and 79% of Asians [54]. Similar ethnic differences were also obtained in the STAR*D sample. It was found that patients with the LL genotype had higher remission rates compared with the other genotypes [55]. This effect was restricted to the white non-Hispanic group, whereas no association between remission and genotype was found in the Black and in the White Hispanic group. The most recent studies investigating the association of *SLC6A4* and antidepressant response are summarized in Table 1.

Results from large cohort studies provide a substantial amount of data supporting the role of the serotonin receptor 2A (*HTR2A*) gene in influencing antidepressant response. In the STAR*D sample, for instance, the SNP rs7997012 was significantly associated with response to the SSRI citalopram [99]. Further evidence for the influence of rs7997012 on antidepressant treatment outcome comes from the Munich Antidepressant Response Signature (MARS) project [100,101]. In another large sample the *HTR2A* marker rs9316233 predicted the response to escitalopram treatment [102]. Together, several studies exhibited specific SNPs of the *HTR2A* gene predicting the response primarily to SSRIs. The most recent studies investigating the association of *HTR2A* and antidepressant response are summarized in Table 2.

Monoamine metabolic enzymes

Three monoamine metabolic enzymes: tryptophan hydroxylase (TPH), monoamine oxidase A (MAO-A) and catechol-*O*-methyl transferase (COMT), have attracted considerable interest with respect to antidepressant treatment outcome prediction. TPH is an essential mechanism in serotonin biosynthesis. It comprises two isoforms: *TPH1* and *TPH2* both linked to pharmacodynamics of antidepressant drugs. Most attention has been given to a functional SNP within *TPH1*: rs1800532. Although a few studies reported that patients carrying the A allele had a poor response to SSRIs [113–115], most of the studies to date found no association with rs1800532 and treatment response [89,95,96,102,107,108,116–118]. Regarding genetic variation in the *TPH2* gene, some studies revealed an association between various SNPs and response to antidepressants [94,119,120]. However, results from a large cohort study showed no significant associations between *TPH2* gene variants and treatment response [102]. The most recent studies investigating the association of *TPH1/TPH2* and antidepressant response are summarized in Table 3.

MAO-A is an enzyme encoded by the *MAO-A* gene. It functions as a degrading enzyme in the monoaminergic neurotransmitters dopamine, serotonin and norepinephrine. In the promoter region of *MAO-A* there is a variable number of tandem repeats (VNTR) that have been reported to influence the transcription activity of *MAO-A* [122]. It is known that longer alleles (3.5 or 4 copies of the repeat sequence) are transcribed two to ten times more efficiently than shorter alleles (3 or 5 copies of the repeat) [122]. Owing to its functional role, the VNTR polymorphism is assumed to be a potential genetic marker regarding antidepressant outcome. One study showed that patients carrying the short form of VNTR responded better to the treatment with mirtazapine than patients carrying the long form [123]. Two studies also reported a positive association, although effects were restricted to female patients [124,125]. However, other studies found no association between *MAO-A* and treatment response [94,95]. Regarding other polymorphisms within *MAO-A*, results also conflict with some studies reporting no association [107,126], and others report associations among subgroups [127] or response subtypes [94]. In a recently published study, the effect of *MAO-A* was restricted to placebo-treated patients [104]. A relatively common finding of the studies is the failure to detect *MAO-A*-specific effects in male patients. This could be because *MAO-A* is located on the X chromosome, which makes it difficult to draw general conclusions for male and female patients. The most recent studies investigating the association of *MAO-A* and antidepressant response are summarized in Table 4.

Further possible evidence for an association with antidepressant response is available for the *COMT* gene, the gene product of which determines intrasynaptic deactivation of norepinephrine and dopamine. Szegedi *et al.* [128] were the first to report an association with treatment outcome in MD. They showed that mirtazapine-treated patients carrying the val allele at rs4690 had faster decreases in Hamilton Rating Scale for depression (HAM-D) scores than patients with the met/met genotype. Arias *et al.* [129] found a similar genotype effect for citalopram-treated patients, but not for patients who were treated with fluvoxamine or paroxetine. Several other studies revealed contradictory results with better treatment outcomes for the met/met genotype [130–135]. Studies that investigated other SNPs within the *COMT* gene found various SNPs and some haplotypes to be associated with antidepressant response [109,136,137]. Conflicting results come from Leuchter *et al.* [126] and Serretti *et al.* [103]. Most of the above-reported studies point toward an association between *COMT* and treatment outcome, although often restricted to subgroups of antidepressants. The most recent studies investigating the association of *COMT* and antidepressant response are summarized in Table 5.

Glutamatergic system

Considering the glutamatergic system, several glutamate receptor genes have been of particular interest in antidepressant treatment prediction. Here, we highlight the most commonly studied glutamate ionotropic kainite 4 (*GRIK 4*) receptor gene. The influence of *GRIK4* variants on antidepressant treatment outcome has been studied extensively with a total sample size of more than 2000 patients. Paddock *et al.* [138] were the first to detect associations of *GRIK4* with response to citalopram. Analyzing the STAR*D sample, they showed that carriers of the C allele on rs1954787 had a reduced risk of nonresponse. This result could be replicated within the MARS sample [100], although the previous reported SNP rs1954787 showed only a nominally significant association with treatment outcome. In this sample, the most predictive value in the *GRIK4* gene was obtained for the SNP rs12800734. Within this variant, the GG genotype was favorable for treatment outcome, whereas the unfavorable genotype AG showed impaired treatment response. Although these studies propose strong evidence for an influence of *GRIK4* on treatment response, Serretti *et al.* recently

TABLE 1

Association studies of *SLC6A4* with antidepressant response, published within the past ten years

Authors and year published	*n*	Ethnicity	Type of AD	Variant(s) examined	Association with favorable treatment outcome
Staeker *et al.* (2014) [56]	273	Caucasian	SSRI, SSNRI, SNRI, TCA	5-HTT VNTR, 5-HTTLPR rs25531 A/G	5-HTTLPR rs25531 L_A allele[a]
Sahraian *et al.* (2013) [57]	104	Persian	Citalopram	5-HTTLPR	5-HTTLPR L allele[b]
Poland *et al.* (2013) [58]	201	African-American (50%) and Caucasian (50%)	Citalopram	5-HTTLPR	No association
Kato *et al.* (2013) [59]	81	Asian	Paroxetine, fluvoxamine	5-HTTLPR rs25531 A/G	5-HTTLPR rs25531 L allele[c]
Myung *et al.* (2013) [60]	88	Asian	Fluoxetine, sertraline	5-HTTLPR	5-HTTLPR S allele
Dreimüller *et al.* (2012) [61]	49	Caucasian	SSRIs	5-HTTLPR rs25531 A/G	No association[d]
Won *et al.* (2012) [62]	74	Asian	Escitalopram	5-HTTLPR	5-HTTLPR S allele
Lewis *et al.* (2011) [63]	520	Caucasian	Citalopram, reboxetine	5-HTTLPR	No association
Rundell *et al.* (2011) [64]	205	Caucasian	Various ADs	5-HTTLPR	5-HTTLPR LL genotype
Muhonen *et al.* (2011) [65]	48	Caucasian	Memantine, escitalopram	5-HTTLPR	5-HTTLPR LL genotype[e]
Umene-Nakano *et al.* (2010) [66]	59	Asian	Sertraline	5-HTTLPR	5-HTTLPR S allele
Lee *et al.* (2010) [67]	84	Asian	Venlafaxine	5-HTTLPR, 5-HTT VNTR	5-HTTLPR L allele
Reimherr *et al.* (2010) [68]	• 261 • 138	Mainly Caucasian (78%)	• Sertraline (monotherapy) • Sert + atomoxetine/Sert + - placebo	5-HTTLPR	• No association • 5-HTTLPR SS genotype (augm.)
Baffa *et al.* (2010) [69]	252	Caucasian	Various ADs	5-HTTLPR, rs25531	5-HTTLPR LL genotype, rs25531 L_AL_A[f]
Yoshimura *et al.* (2009) [70]	60	Asian	Paroxetine	5-HTTLPR	No association
Gressier *et al.* (2009) [71]	103	Caucasian	SSRI, SNRI, TCA and others	5-HTTLPR	5-HTTLPR L allele[g]
Min *et al.* (2009) [72]	567	Asian	SSRI, SNRI	5-HTTLPR, 5-HTT VNTR	5-HTTLPR LL genotype, 5-HTT VNTR 12/12[h]
Huezo-Diaz *et al.* (2009) [73]	795	Caucasian	Escitalopram, nortriptyline	5-HTTLPR and 13 additional markers within SLC6A4	5-HTTLPR L allele[i]
Maron *et al.* (2009) [74]	135	Caucasian	Escitalopram	5-HTTLPR, rs25531	No association
Mrazek *et al.* (2009) [55]	1503	White non-Hispanic (71.4%), white Hispanic (13%), black (15.6%)	Citalopram	5-HTTLPR, 5-HTT VNTR, rs25531 and 18 tag SNPs within *SLC6A4*	5-HTTLPR LL genotype, 5-HTT VNTR 9/12, 3 SNP haplotype[j]
Wilkie *et al.* (2009) [75]	163	Caucasian	Paroxetine	5-HTTLPR, 5-HTT VNTR	5-HTTLPR SS genotype, 5-HTT VNTR 12/10
Smits *et al.* (2008) [76]	214	Caucasian	SSRIs (5 various)	5-HTTLPR, 5-HTT VNTR	5-HTTLPR LL genotype[k]
Dogan *et al.* (2008) [77]	64	Caucasian	Sertraline	5-HTTLPR, 5-HTT VNTR	No association
Lotrich *et al.* (2008) [78]	110	Caucasian (90%), African American (10%)	Paroxetine	5-HTTLPR	5-HTTLPR LL genotype
Bozina *et al.* (2008) [79]	130	Caucasian	Paroxetine	5-HTTLPR, 5-HTT VNTR	5-HTTLPR L allele, 5-HTT VNTR 9 or 10 copies allele

TABLE 1 (*Continued*)

Authors and year published	*n*	Ethnicity	Type of AD	Variant(s) examined	Association with favorable treatment outcome
Kronenberg *et al.* (2007) [80]	74	Israelian children (Jewish descent)	Citalopram	5-HTTLPR	5-HTTLPR L allele
Kang *et al.* (2007) [81]	101	Asian	Mirtazapine	5-HTTLPR	5-HTTLPR SS genotype
Hu *et al.* (2007) [82]	1131	White non-Hispanic	Citalopram	5-HTTLPR rs25531 A/G	No association
Kraft *et al.* (2007) [83]	1914	Mainly Caucasian (78%)	Citalopram	5-HTTLPR and 10 SNPs within *SLC6A4*	No association
Kirchheiner *et al.* (2007) [84]	190	Caucasian	Various ADs	5-HTTLPR	No association
Kim *et al.* (2006) [85]	208	Asian	SSRIs (fluoxetine, sertraline), nortriptyline	5-HTTLPR, 5-HTT VNTR	5-HTTLPR SS genotype, 5-HTT VNTR 12/12[l]
Smeraldi *et al.* (2006) [86]	228	Caucasian	Fluvoxamine	5-HTTLPR	5-HTTLPR L allele, 16D *L allele
Ng *et al.* (2006) [87]	35	Caucasian (30%) and Asian (70%)	Sertraline	5-HTTLPR	No association
Kato *et al.* (2006) [88]	80	Asian	Paroxetine, fluvoxamine	5-HTTLPR	5-HTTLPR L allele
Hong *et al.* (2006) [89]	224	Asian	Fluoxetine	5-HTTLPR, 5-HTT VNTR	5-HTTLPR LL genotype
Kraft *et al.* (2005) [90]	96	Mainly Caucasian	Fluoxetine	5-HTTLPR, 5-HTT VNTR and 25 SNPs within *SLC6A4*	A/14-repeat/T allele haplotype of rs25531/HTTLPR/rs25533
Kato *et al.* (2005) [91]	64	Asian	Paroxetine, fluvoxamine	5-HTTLPR	5-HTTLPR L allele
Murphy *et al.* (2004) [92]	246	Mainly Caucasian	Mirtazapine, paroxetine	5-HTTLPR	5-HTTLPR L allele
Yoshida *et al.* (2004) [93]	80	Asian	Milnacipran	5-HTTLPR, 5-HTT VNTR	No association
Peters *et al.* (2004) [94]	96	Mainly Caucasian	Fluoxetine	5-HTTLPR, 5-HTT VNTR, intron 7, 17 other SNPs	rs25533 TT genotype
Serretti *et al.* (2004) [95]	185	Caucasian	Paroxetine, fluvoxamine	5-HTTLPR	No association
Serretti *et al.* (2004) [96]	220	Caucasian	Paroxetine, fluvoxamine	5-HTTLPR	5-HTTLPR L allele
Durham *et al.* (2004) [97]	206	Mainly Caucasian	Sertraline	5-HTTLPR	5-HTTLPR L allele
Lee *et al.* (2004) [98]	97	Asian	Various ADs	5-HTTLPR	5-HTTLPR L allele

[a] Genotype-dependent favorable outcome was restricted to patients treated with SSRIs ($n = 100$), the whole group analysis revealed no effect of treatment response.
[b] Genotype-dependent effect was restricted to male patients.
[c] L allele carriers had a better response than S homozygotes (s and L_G) only for the treatment with fluvoxamine; no genotype-dependent difference for paroxetine.
[d] Interaction with serum concentration: L_A allele carriers had a favorable treatment outcome if serum concentration was high; this effect was absent in S/L_G allele carriers.
[e] Genotype-dependent effect only found for patients treated with escitalopram ($n = 27$).
[f] These genotypes only showed association with treatment response after classification into subgroups of depression (anxious versus nonanxious depression).
[g] Effect restricted to female patients.
[h] Genotype-dependent effects only for patients treated with SSRIs ($n = 362$).
[i] Genotype-dependent effect was restricted to male patients treated with escitalopram ($n = 172$).
[j] Genotype-dependent effect was found among white non-Hispanic patients ($n = 1074$), but not in the black or the white Hispanic group; a haplotype block (5-HTTLPR, rs25531, 5-HTT VNTR) was associated with remission: noncarriers of the *S-a-12* haplotype had a higher probability of remission.
[k] Genotype-dependent effect restricted to female patients.
[l] The 5-HTTLPR SS genotype showed better response to SSRIs and nortriptyline; the 5-HTT VNTR 12/12 genotype showed better response to SSRIs ($n = 119$).

TABLE 2

Association studies of HTR2A with antidepressant response, published within the past ten years

Authors and year published	*n*	Ethnicity	Type of AD	Variant(s) examined	Association with favorable treatment outcome
Staeker *et al.* (2013) [56]	60	Caucasian	SSRI, SSNRI, SNRI, TCA	rs7997012	No association
Serretti *et al.* (2013) [103]	102	Caucasian	SSRI, SNRI, other ADs	rs7997012, rs2224721	No association
Tiwari *et al.* (2013) [104]	319	European, African, Mexican	Bupropion	44 SNPs within HTR2A	rs2770296 GG genotype
Xu *et al.* (2012) [105]	308	Asian	SSRI, SNRI, NaSSa, TCA	rs6313	No association
Kishi *et al.* (2010) [106]	265	Asian	Fluvoxamine, sertraline, paroxetine	rs6311, rs6313, rs7997012, rs1928040	Various haplotypes[a]
Lucae *et al.* (2010) [101]	637	Caucasian	Various ADs	rs7997012, rs1928040	rs7997012 G allele
Uher *et al.* (2009) [102]	424	Caucasian	Escitalopram	36 SNPs within serotonergic genes	rs9316233 G allele, rs2224721 A allele
Peters *et al.* (2009) [107]	1631	Mainly Caucasian (78%)	Citalopram	15 SNPs within *HTR2A*	rs7997012 A allele, rs1923884 CC genotype
Wilkie *et al.* (2009) [75]	163	Caucasian	Paroxetine	rs6313, rs6314	rs6314 CT genotype
Illi *et al.* (2009) [108]	86	Caucasian	Citalopram, fluoxetine, Paroxetine	rs6313, rs6311, rs7997012	No association
Perlis *et al.* (2009) [109]	250	Caucasian	Duloxetine	41 SNPs within *HTR2A*	rs9534505, rs1923884, rs2760351[b]
Horstmann *et al.* (2008) [110]	300	Caucasian	Various ADs	38 SNPs within *HTR2A*	rs7997012 G allele
Kang *et al.* (2007) [111]	101	Asian	Mirtazapine	rs6311	No association
Hong *et al.* (2006) [89]	224	Asian	Fluoxetine	rs6311 (T102C)	No association
Kato *et al.* (2006) [88]	80	Asian	Paroxetine, fluvoxamine	rs6311	rs6311 GG genotype
McMahon *et al.* (2006) [99]	1953	Mixed[c]	Citalopram	768 markers covering 68 candidate genes	rs7997012
Choi *et al.* (2005) [112]	71	Asian	Citalopram	rs6311	rs6311 GG genotype
Yoshida *et al.* (2004) [93]	80	Asian	Milnacipran	G-1438A	No association
Peters *et al.* (2004) [94]	96	Mainly Caucasian (78%)	Fluoxetine	17 SNPs within *HTR2A*	rs1923882 CC genotype, rs6314 GG genotype, rs3125 GG genotype[d]

[a] All SNP haplotypes (rs6311, rs6313, rs1928040, rs7997012) were associated with response and remission to SSRIs; strongest association was found for a 3 SNP haplotype (rs6311, rs6313, rs1928040) with the G-C-T haplotype being more common in responder versus nonresponder.
[b] These SNPs were nominally the most significant SNPs within HTR2A; the analysis for the whole HTR2A gene (41 SNPs) revealed only gene-wise but no experiment-wise significance.
[c] White (78.2%), black (16%) and other and/or mixed (5.8%).
[d] These SNPs only showed association with treatment response after classification into subgroups of response.

failed to replicate this finding, possibly as a result of a general difficulty in the replication of candidate gene-association studies stemming from inconsistencies across study designs [139]. Recent findings on the association of *GRIK4* and antidepressant response are summarized in Table 6.

Neurotrophic activity

Brain-derived neurotrophic factor (*BDNF*) induces neurogenic activity and has extensively been studied with regard to antidepressant response prediction. The most commonly studied polymorphism within *BDNF* is the 66 Val/Met (rs6265) variant. Although several studies reported an association between rs6265 and antidepressant response [141–146], other research groups yielded conflicting results [147–151]. Regarding other polymorphisms within *BDNF*, one study found a SNP [152] to be associated with treatment response, whereas other studies found associations in SNPs and various haplotypes [153,154]. Domschke *et al.* [155] showed that rs7124442 could be linked to antidepressant treatment outcome but the authors could not replicate this finding within the STAR*D sample. Another large cohort study (GENDEP) also failed to detect an influence of BDNF polymorphisms on treatment response [102]. Considering the most recently published studies, results are mixed. Whereas Illi *et al.* [156] could not find any association, Murphy *et al.* [157] showed that four SNPs predicted the response to antidepressant treatment in geriatric depression. Hennings *et al.* [158] could identify seven single SNPs that were nominally associated with treatment outcome. Additionally, they found significant results for two haplotype blocks. In a large combined sample comprising their discovery and replication sample, Hennings *et al.* found one *BDNF* SNP to be associated with response to antidepressants. Studies published in the past ten years on the association of *BDNF* and antidepressant response are summarized in Table 7.

HPA axis activation

It is well known that dysregulation of the HPA axis plays an important part in development and maintenance of depressive symptoms [159]. As a major modulator of the HPA axis, most

TABLE 3

Association studies of *TPH1/TPH2* with antidepressant response, published within the past ten years

Authors and year published	*n*	Ethnicity	Type of AD	Variant(s) examined	Association with favorable treatment outcome
Wang *et al.* (2011) [118]	115	Asian	Fluoxetine, venlafaxine	*TPH1* 218A/C (rs1800532)	No association
Viikki *et al.* (2010) [121]	62	Caucasian	SSRI	*TPH1* 218A/C (rs1800532)	TPH1 218A/C A allele
Uher *et al.* (2009) [102]	424	Caucasian	Escitalopram	36 SNPs within serotonergic genes	No association
Illi *et al.* (2009) [108]	86	Caucasian	Fluoxetine, paroxetine, citalopram	*TPH1* (rs1800532) and *TPH2* (rs1386494)	No association
Tsai *et al.* (2009) [119]	187	Asian	SSRI (fluoxetine, citalopram)	5 SNPs within *THP2*	rs2171363 T/C genotype
Peters *et al.* (2009) [107]	1631	Mainly Caucasian (78%)	Citalopram	6 SNPs within *TPH1* and 9 SNPs within *TPH2*	No association
Tzvetkov *et al.* (2008) [120]	183	Caucasian	Various ADs	10 SNPs within *TPH2*	rs10897346 C allele, rs1487278 C allele
Kato *et al.* (2007) [117]	100	Asian	Paroxetine, fluvoxamine	*TPH1* 218A/C	No association
Ham *et al.* (2007) [115]	105	Asian	Citalopram	*TPH1* 218A/C	TPH1 218A/C CC genotype
Hong *et al.* (2006) [89]	224	Asian	Fluoxetine	*TPH1* 218A/C	No association
Ham *et al.* (2005) [116]	93	Asian	Various ADs	*TPH1* 218A/C	No association
Peters *et al.* (2004) [94]	96	Mainly Caucasian (78%)	Fluoxetine	19 SNPs within *TPH1* and 14 SNPs within *TPH2*	T-7180G, T-7065C, T-5806G (TPH1); rs1843809, rs1386492, rs1487276 (TPH2)
Serretti *et al.* (2004) [95]	185	Caucasian	Paroxetine, fluvoxamine	*TPH1* 218A/C	No association
Serretti *et al.* (2004) [96]	220	Caucasian	Paroxetine, fluvoxamine	*TPH1* 218A/C	No association

TABLE 4

Association studies of *MAO-A* with antidepressant response, published within the past ten years

Authors and year published	*n*	Ethnicity	Type of AD	Variant(s) examined	Association with favorable treatment outcome
Tiwari *et al.* (2013) [104]	319	Mixed (European, African, Mexican)	Bupropion	7 SNPs within *MAO-A*	No association[a]
Peters *et al.* (2009) [107]	1631	Mainly Caucasian (78%)	Citalopram	rs1465108	No association
Tzeng *et al.* (2009) [123]	58	Asian	Mirtazapine	*MAO-A* VNTR	VNTR short form
Leuchter *et al.* (2009) [126]	32	Unknown	Fluoxetine, venlafaxine, sertraline	rs6323	No association
Domschke *et al.* (2008) [124]	340	Caucasian	Various ADs	*MAO-A* VNTR	VNTR short form[b]
Tadić *et al.* (2007) [127]	102	Caucasian	Mirtazapine, paroxetine	rs1799835	rs1799835 TT genotype[c]
Yu *et al.* (2005) [125]	228	Asian	Fluoxetine	*MAO-A* VNTR	3R/3R genotype[d]
Serretti *et al.* (2004) [95]	185	Caucasian	Paroxetine, fluvoxamine	*MAO-A* VNTR	No association
Peters *et al.* (2004) [94]	96	Mainly Caucasian (78%)	Fluoxetine	8 SNPs within MAO-A and *MAO-A* VNTR	No association[e]

[a] MAO-A was only associated with placebo response: carriers of the G allele on rs6609257 had a better response compared to the other genotypes.
[b] Genotype-dependent effect was restricted to female patients ($n = 194$).
[c] Genotype-dependent effect was restricted to mirtazapine-treated females ($n = 41$).
[d] Genotype-dependent effect was restricted to female patients ($n = 133$).
[e] Association with response subtypes: by comparing specific response versus nonspecific response, rs1465108 GG genotype and rs6323 AA genotype had better response rates compared with the other genotypes.

attention has been given to *FKBP5* and its influence on treatment outcome. FK506-binding protein 5 (*FKBP5*) is a cochaperone of heat shock protein 90 (hsp90), which regulates the glucocorticoid receptor (GR) sensitivity [160–162]. Binder *et al.* [163] were the first to detect the association of certain *FKBP5* variants with treatment outcome in depression: three SNPs (rs1360780, rs3800373 and rs4713916) showed strong associations with treatment response and remission. There are numerous studies linking *FKBP5* polymorphisms with response to antidepressant treatment, for example [164–166], although sample sizes and therefore effect sizes were small. In the large STAR*D sample, Lekman *et al.* [167] reported a nominally significant association of the SNP rs4713916 with

TABLE 5

Association studies of *COMT* with antidepressant response, published within the past ten years

Authors and year published	*n*	Ethnicity	Type of AD	Variant(s) examined	Association with favorable treatment outcome
Serretti *et al.* (2013) [103]	102	Caucasian	SSRI, SNRI, other ADs	158 val/met (rs4680)	No association
Houston *et al.* (2011) [137]	225	Caucasian	Duloxetine	24 SNPs within COMT	rs165737 CC genotype, 2 SNP diplotype[a]
Spronk *et al.* (2011) [135]	31	Unknown	Various ADs	158 val/met (rs4680)	Met/met genotype
Benedetti *et al.* (2010) [134]	41	Caucasian	Fluvoxamine	158 val/met (rs4680)	Met allele
Kocabas *et al.* (2010) [136]	396	Caucasian	Various ADs	7 SNPs within *COMT*	rs2075507 GG genotype, 3 SNP haplotype[b]
Benedetti *et al.* (2009) [133]	55	Caucasian	Paroxetine	158 val/met (rs4680)	Met/met genotype
Leuchter *et al.* (2009) [126]	32	Unknown	Fluoxetine, venlafaxine, Sertraline	158 val/met (rs4680)	No association
Tsai *et al.* (2009) [132]	334	Asian	Fluoxetine	158 val/met (rs4680)	Met allele[c]
Perlis *et al.* (2009) [109]	250	Caucasian	Duloxetine	19 SNPs within *COMT*	rs165599 GG, rs165774 GG, rs174696 CC
Baune *et al.* (2008) [131]	256	Caucasian	Various AD	158 val/met (rs4680)	Met allele
Yoshida *et al.* (2008) [130]	81	Asian	Milnacipran	158 val/met (rs4680)	Met/met genotype
Arias *et al.* (2006) [129]	346	Caucasian	Fluvoxamine, Paroxetine, Citalopram	158 val/met (rs4680)	Val allele[d]
Szegedi *et al.* (2005) [128]	102	Caucasian	Mirtazapine, Paroxetine	158 val/met (rs4680)	Val allele[e]

[a] A 2 SNP diplotype (rs165599, rs165737) was associated with response; GC/GC genotype showed the strongest change in HAMD; this effect was restricted to male patients.
[b] A 3 SNP haplotype (rs4633, rs4818, rs4680) was associated with response; the C-C-A haplotype had a better treatment response than other haplotypes.
[c] Further analyses revealed a sex-specific effect as the met allele was associated with favorable treatment response only in male, but not in female, patients.
[d] Sample consisted of two populations: Italian ($n = 207$) and Spanish ($n = 139$); the Spanish sample was exclusively treated with citalopram; a genotype × time interaction was found for citalopram-treated patients only ($n = 139$).
[e] Genotype-dependent effect was restricted to patients treated with mirtazapine ($n = 53$).

TABLE 6

Association studies of *GRIK4* with antidepressant response, published within the past ten years

Authors and year published	*n*	Ethnicity	Type of AD	Variant(s) examined	Association with favorable treatment outcome
Pu *et al.* (2013) [140]	281	Asian	SSRIs (paroxetine, fluoxetine, sertraline, escitalopram) or SNRI (venlafaxine)	5 SNPs within *GRIK4*	rs1954787 G allele; 3 SNP haplotype with AGG (rs1954787–rs2230297–rs2298725)
Serretti *et al.* (2012) [139]	223	Caucasian	Various ADs	rs1954787	No association
Perlis *et al.* (2010) [31]	250	Caucasian	Duloxetine	rs1954787	No association
Horstmann *et al.* (2010) [100]	387	Caucasian	Various ADs	82 SNPs	rs12800734 GG genotype
Paddock *et al.* (2007) [138]	1816	Mixed[a]	Citalopram	768 markers covering 68 candidate genes	rs1954787 CC genotype

[a] White (78.2%), black (16%) and other and/or mixed (5.8%).

remission and response to antidepressant treatment. Despite this strong evidence, there are a few studies that found either no association between the previously reported SNPs and treatment outcome [165,168] or an effect in the other direction with the opposite allele showing association with response [166]. One explanation for the failure of these studies to find an association could be the limited sensitivity of scale-based assessment of antidepressant response as suggested by Zobel *et al.* [169]. The authors used the Dex (dexamethasone)/CRH (corticotropin-releasing hormone) test as a more objective measurement in addition to the HAM-D scale. In fact, Zobel *et al.* could show that the SNPs rs4713916 and rs3800373 were associated with reduction of cortisol secretion in the Dex/CRH test. This result was supported by the fact that the reduction of HPA hyperactivity appears to be a prerequisite for clinical response to antidepressant treatment [170]. Summarizing the results for *FKBP5* gene variation, a meta-analysis by Zou *et al.* [171] came to the conclusion that the SNP rs4713916 was associated with treatment response in patients with mood disorders, whereas the other abovementioned SNPs (rs1360780, rs3800373) seemed to have no effect. Recent findings on the association of *FKBP5* and antidepressant response are summarized in Table 8.

TABLE 7

Association studies of *BDNF* with antidepressant response, published within the past ten years

Authors and year published	*n*	Ethnicity	Type of AD	Variant(s) examined	Association with favorable treatment outcome
Hennings *et al.* (2013) [158]					
• MARS study	• 398	• Caucasian	• Various ADs	• 18 tagging SNPs within BDNF	• 7 BDNF SNPs and haplotypes[a]
• 2 replication samples	• 496	• Caucasian	• Various ADs	• 7 SNPs within *BDNF*	• rs11602246[b]
• Comined sample	• 894	• Caucasian	• Various ADs	• 7 SNPs within *BDNF*	• rs2049046 T allele
Murphy *et al.* (2013) [157]	216	Caucasian	Paroxetine, mirtazapine	13 SNPs within *BDNF*	rs11030086 AA genotype, rs6265 GG genotype, rs988712 CC genotype, rs988748 CC genotype
Illi *et al.* (2013) [156]	106	Caucasian	SSRIs	rs11030101, rs61888800	No association
Katsuki *et al.* (2012) [147]	64	Asian	Mirtazapine	66 val/met (rs6265)	No association
Xu *et al.* (2012) [141]	159	Asian	SSRIs, venlafaxine	66 val/met (rs6265)	Met/met genotype[c]
Yoshimura *et al.* (2011) [148]	132	Unknown	Paroxetine, sertraline	66 val/met (rs6265)	No association
Taylor *et al.* (2011) [142]	210	Caucasian	Various ADs	66 val/met (rs6265)	Met allele
Kocabas *et al.* (2011) [154]	206	Caucasian	Various ADs	8 tagging SNPs within *BDNF* (including 66 val/met)	rs10501087 C allele, rs6265 A allele, rs1491850 C allele, various haplotypes
Kang *et al.* (2010) [149]	243	Asian	Mirtazapine	66 val/met (rs6265)	No association
Chi *et al.* (2010) [143]	117	Asian	Fluoxetine, venlafaxine	66 val/met (rs6265)	Val/val genotype
Domschke *et al.* (2010) [155]					
• German sample	• 254	• Caucasian	• Various ADs	• 66 val/met (rs6265), rs7103411, rs7124442	• rs7124442 CC genotype[e]
• STAR*D (replication sample)	• 1953	• Mixed[d]	• Citalopram	• 10 SNPs within *BDNF*	• No association
Zou *et al.* (2010) [144]	295	Asian	Fluoxetine	66 val/met (rs6265)	Val/met genotype
Licinio *et al.* (2009) [152]	272	Mexican Americans	Fluoxetine, desipramine	130 SNPs within *BDNF*	rs61888800 GG genotype
Uher *et al.* (2009) [102]	760	Caucasian	Escitalopram, nortriptyline	57 SNPs in common pathway genes (including *BDNF*)	No association
Gratacòs *et al.* (2008) [153]	374	Caucasian	Various ADs	8 tagging SNPs within *BDNF* (including 66 val/met)	rs908867 A allele, TAT haplotype (rs12273363, rs908867, rs1491850)
Lin *et al.* (2008) [150]	72	Asian	Venlafaxine	66 val/met (rs6265)	No association
Yoshida *et al.* (2007) [145]	134	Asian	Milnacipran, fluvoxamine	G196A (rs6265)	G/A genotype
Wilkie *et al.* (2007) [151]	233	Caucasian	Various ADs	66 val/met (rs6265)	No association
Choi *et al.* (2006) [146]	83	Asian	Citalopram	66 val/met (rs6265)	Met allele

[a] Seven BDNF SNPs and two haplotype blocks were nominally associated with treatment outcome in the discovery sample ($n = 398$); the two haplotype blocks withstood correction for multiple testing.
[b] This SNP was nominally associated with treatment outcome in the MARS replication sample ($n = 249$) but not in the other replication sample ($n = 247$).
[c] Genotype-dependent effect was restricted to patients treated with SSRIs ($n = 104$).
[d] White (78.2%), black (16%) and other and/or mixed (5.8%).
[e] The other two investigated SNPs were associated with treatment response in the melancholic subtype of depression.

TABLE 8

Association studies of *FKBP5* with antidepressant response, published within the past ten years

Authors and year published	*n*	Ethnicity	Type of AD	Variant(s) examined	Association with favorable treatment outcome
Ellsworth *et al.* (2013) [172]					
• Mayo PGRN-AMPS[a]	• 512	• White non-Hispanic	• Citalopram, escitalopram	• 481 SNPs: 127 *FKBP5* SNPs and 354 FKBP5 eQTL[b] SNPs	• 24 FKBP5 SNPs, 21 FKBP5 eQTL SNPs
• STAR*D s (replication)	• 960	• White non-Hispanic	• Citalopram	• 6 SNPs: 3 *FKBP5* SNPs and 3 *FKBP5* eQTL SNPs	• rs352428 GG genotype
Zobel *et al.* (2010) [169]	110	Caucasian	Citalopram	rs1360780, rs3800373, rs755658, rs1334894, rs4713916	No association
Sarginson *et al.* (2010) [168]	246	Caucasian (92%), remainder is mixed	Paroxetine, mirtazapine	rs1360780, rs3800373	No association
Uher *et al.* (2009) [102]	760	Caucasian	Escitalopram, nortriptyline	57 SNPs within common pathway genes	No association
Perlis *et al.* (2009) [109]	250	Caucasian	Duloxetine	4 SNPs within *FKBP5*	No association
Kirchheiner *et al.* (2008) [164]	179	Caucasian	Various ADs	rs1360780, rs3800373	rs1360780 T allele, rs3800373 C allele
Lekman *et al.* (2008) [167]	1370	White non-Hispanic (82%), remainder black	Citalopram	rs1360780, rs4713916, rs3800373	rs4713916 A allele
Tsai *et al.* (2007) [165]	125	Asian (Chinese)	Fluoxetine	rs1360780	No association
Papiol *et al.* (2007) [166]	159	Caucasian (Spanish)	Citalopram	rs1360780	No association
Binder *et al.* (2004) [163]	294	Caucasian	Various ADs	21 SNPs within *FKBP5*	rs1360780 TT genotype, rs4713916 AA genotype, rs3800373 CC genotype

[a] Mayo PGRN-AMPS: Mayo Clinic Pharmacogenomics Research Network – Antidepressant Medication Pharmacogenomic Study.
[b] FKBP5 eQTL: FKBP5 expression Quantitative Trait Locus analysis: search for genome-wide SNPs that are associated.

To date, the prediction of treatment response via genetic variants has had limited success. The major mechanisms of drug pharmacokinetics are relatively well understood and research in this field has developed significantly throughout the past decade, with an important focus on drug delivery across the BBB. In pharmacodynamics several findings of genetic loci have led to a better understanding of the way antidepressants work but are still far from being uncovered. Up until today, the strength of the associations of pharmacodynamic candidate genes with treatment outcome is too weak to provide actual value for a clinical application.

Gene expression profiling

Measuring gene activity allows analysis of inherited or acquired changes of gene regulation in a tissue-specific way that also provides neuroanatomical resolution. This approach proved successful in directly accessible pathological tissues such as cancer [173]. In psychiatric disorders, brain samples would be the optimal choice; however, tissue collection is limited to postmortem samples from which some important insights into depression genomics emerged [174,175]. Such analyses are burdened with several technical problems that arise from gene expression changes accompanying death (pH, temperature, length of agonal state) and the difficulty of psychological autopsies as a result of its retrospective nature [176]. Moreover, depression and other stress-related diseases are caused by impaired signaling cascades across neurocircuits rather than by changes in specific neuroanatomical locations. That limits any approach to study certain brain regions or subpopulations of brain cells collected from these patients [177].

Biomarkers used as a diagnostic approach or for prediction of treatment response and monitoring issues have to be readily accessible; therefore peripheral blood cells represent an attractive tissue source [178,179]. However, the question arises if the transcriptome of peripheral blood cells reflects profiles of neuronal cell populations. At least there is a considerable overlap between gene activity measures in brain and peripheral blood [180,181]. Recent research efforts have shown that the firmly established links between endocrine and immune systems and the CNS in depression would favor the use of lymphocytes [163].

Gene expression profiles have been investigated in the search for biomarkers of post-traumatic stress disorder [182–184], bipolar disorder [185,186], schizophrenia [187] and MD [188–190] using peripheral blood cells. Aiming at biomarkers for treatment response, a recent study used a transcriptome-based genome-wide approach in lymphoblastoid cell lines of healthy adults to compare profiles of subjects displaying high versus low paroxetine sensitivity. One of the top hits was a gene implicated in neuronal cell adhesion and thalamocortical circuitry [191].

During a depressive episode, stress hormone dysregulation is frequently observed, which is caused by impaired GR signaling [159]. In fact, this GR signaling disturbance precedes the onset of the disease episode and its normalization predicts beneficial drug response. This time connection supports the notion that HPA function is closely related to causality of depression in many patients [170,192]. Most studies using HPA measures as biomarkers confirm relative GR resistance during depressive episodes [193,194]. For example, DNA-sequence variations in *FKBP5* are associated with increased FKBP5 concentration in lymphocytes.

Notably, these polymorphisms are associated with changes in the HPA regulation and predict antidepressant treatment response. Ligand-activated GR is a transcription factor acting at many hormone-regulated genes, in particular those carrying in their DNA so-called glucocorticoid response elements to which ligand-activated GR can bind. Because studies using baseline gene expression profiles provided mixed results, a recent study investigated GR-mediated changes in gene expression in whole blood between depressed patients and healthy controls [190]. Using microarrays in combination with quantitative real-time PCR this study documented that *in vivo* GR-stimulated gene expression by dexamethasone uncovered a GR resistance in depressed patients and proved to be superior to default endocrine measurements like the DST. Inherited changes of GR function are found to convey susceptibility for depression and treatment response [195]. Also the fact that *FKBP5* was among the best classifiers in the study by Menke *et al.* [190] supports the functional relevance of the observed changes in gene expression profiles: DNA-sequence variations in the *FKPB5* encoding gene predict antidepressant treatment response. In essence, whole-blood expression profiles have potential to become important genomic biomarkers informing the clinician about specific treatment options such as GR-modifying medicines. Future diagnostic algorithms will benefit if reliable biomarkers identifying clinical subgroups are integrated. Whether gene expression profiles help to achieve this goal will be further clarified. In particular, some technical difficulties need to be overcome.

Proteomics

Proteins are the main actors within cells, building blocks of all organs and targets of most drugs. Thus, the total complement of proteins within cells, called the proteome, determines the development and course of any given disease. Therefore, studying proteins as potential disease or treatment biomarkers seems to be a straightforward approach, particularly in light of considerable bioanalytical progress.

One pragmatic approach is to study proteins with immunochemical techniques, mostly based on ELISA. Growth factors including BDNF, insulin-like growth-factor-1 (IGF-1) and vascular endothelial growth factor (VEGF) are currently of the main interest. Most emphasis was put on BDNF, which is reduced in hippocampi of stressed animals and probably in humans with depression [30,196]. This is most probably mediated by enhanced corticosteroid levels because the *BDNF* gene is negatively regulated by ligand-activated GR [197]. Long-term treatment with antidepressants is known to reinstate excessive HPA activity and reverse BDNF suppression and associated depressive-like behavior in animals [198]. Blood BDNF concentrations have the potential to be used as a treatment biomarker because plasma BDNF levels are also decreased in depression and normalized following antidepressant treatment. Although the hippocampus is the main source for central BDNF, it is unlikely that peripherally measured changes reflect central BDNF levels, because nearly all peripheral tissues produce this growth factor. It is also unclear whether increased peripheral BDNF, irrespective of source, can enter the brain to induce behavioral effects. Because BDNF has been implicated in neuronal survival and even neurogenesis, which might be a possible contributor to mechanism of antidepressant effects, the observed changes during drug treatment also seem to have some functional implications [199].

Similarly, IGF-1, also involved in hippocampal neurogenesis, and VEGF, an endothelial cell mitogen and regulator of vascular function, show decreased levels in the hippocampus of stressed mice. Treatment with antidepressants in turn increases the levels of these growth factors. Because clinical studies of peripheral IGF-1 and VEGF are limited, their potential as treatment biomarkers is as yet impossible to judge [200,201].

There is good evidence available suggesting that neuroimmune systems and CNS function are closely intertwined [202]. Therefore, it is of interest that several clinical studies support a depressiogenic effect of proinflammatory cytokines. In line with this notion is the observation of improved response to antidepressants in depressed patients where inflammation is suppressed, for example by administration of cyclooxygenase (Cox)2 inhibitors [203]. The role of cytokines in mediating depression and associated symptoms is also supported by studies that show cytokine-induced elevation of HPA activity [204] and antidepressant-induced normalization of interleukin 1 elevations in depressives [205]. This has been corroborated in a meta-analysis by Hannestad *et al.* [206] that found association of beneficial response to antidepressants with normalization of circulating inflammatory cytokines. It seems fair to say that several immune and growth factors are interesting candidates for subgrouping depressed patients regarding which specific treatments might be indicated. At this point it would be premature to judge whether such a biased approach will ultimately be fruitful.

Unbiased proteomic approaches with human specimens aiming at predictive treatment biomarkers are sparse, despite several studies showing differentially regulated proteins in depression. One of the first studies of this kind compared depressed unmedicated suicide attempters with depressed nonattempters and found different protein regulation [207] pointing to the possibility that proteins involved in medication of impulsive and aggressive behavior could be identified. In the meantime several new proteins likely to be associated with mechanisms of causality were observed. For example Ditzen *et al.* [208] used two-dimensional polyacrylamide gel electrophoresis and time-of-flight (TOF) mass spectrometry (MS) peptide profiling and subsequent protein identification with matrix-assisted laser desorption/ionization (MALDI)-TOF-MS. In the cerebral spinal fluid (CSF) specimens, 11 proteins and 144 peptide features, were found that differed significantly between patients with MD and controls. Most importantly, a substantial number of proteins found to be expressed differentially have been directly implicated in depression-related CNS abnormalities. Upcoming studies from this laboratory will show which of these biomarkers will help to inform the clinician about choice of drug treatment and outcome.

Proteomics also has the potential to identify targets of antidepressants beyond monoaminergic signaling. Piubelli *et al.* [209] found that escitalopram modulates proteins involved in cytoskeleton organization, neuronal development, vesicle-medicated transport and synaptic plasticity. All these factors are entirely plausible as contributors of antidepressant efficacy.

A recent study by Filiou *et al.* [210] took an entirely different approach and measured cingulate cortex synaptosome proteomes of mice that were selectively bred for high or low anxiety-like behavior up to 40 generations. A large number of proteins were

found to differentiate both groups and careful interrogation of the data pointed toward an important role of energy metabolism and mitochondria. Importantly, these proteomic data were complemented by an analysis of metabolite networks highlighting the importance of combining different levels of observation. Similarly, combining analysis of DNA-sequence variations with proteomics proved useful: the abovementioned two mouse lines with extremes in their anxiety-like behavior expressed different forms of enolase phosphatase (EP). This enzyme is involved in the methionine salvage pathway where *S*-adenosyl-L-methionine (SAM) is synthesized. It was also observed that these two protein isoforms of EP differ in gel mobility and enzymatic activity because they are carrying different nonsynonymous gene variants. This finding is of particular interest because SAM has frequently been implicated in antidepressant mechanisms of action and is a substrate for DNA-methyltransferases that bind SAM-donated methyl groups covalently to specialized DNA sequences where they can inhibit or enhance gene activity. The latter effect is a key mechanism of epigenetics, a growing field from which novel targets of interest for the pharmaceutical industry will emerge.

Taken together, proteomics represents a high-potential field for the discovery of biomarkers for companion tests of novel drugs acting on unprecedented targets. However, among all omic technologies, proteomics represents the most daunting task because we are dealing with around one million proteins stemming from less than 25,000 genes. These proteins are permanently changing their tissue concentrations and many of their functions are related to features other than their amino acid sequences (e.g. folding). Presently, no biomarker established within the field of proteomics has reached clinical relevance but, once several levels of analysis are integrated, a map from genomics, proteomics and metabolomics will emerge and help to inform the clinician treating patients and the scientist involved in drug discovery and development [211].

Metabolomics

Metabolomics is the term for an integrated study of small molecules mostly stemming from carbohydrate and lipid metabolism that add to the toolbox for biomarker-driven drug discovery and development. The objective is the identification of metabolite profiles that are different in healthy controls and clinical conditions. Metabolomic studies also have the potential to indicate a disease-causing process before clinical symptoms emerge. Permanent elevations of blood glucose concentrations as an indicator of diabetes mellitus type 2 are one obvious example. Along this track are expectations that a metabolite map can predict whether an organism is in a biochemical state where drug response is likely or not. Metabolomics is also attractive under another more pragmatic aspect: there are ~20,000–25,000 genes yielding roughly 100,000 transcripts and one million proteins. The human metabolome, however, consists of 2500 detectable metabolites, which in light of current technological advances makes metabolite profiling a feasible approach, particularly for diagnostic applications [212]. Further, the metabolome is an 'integral' of multiple gene, protein and environmental interactions. Small molecular changes on the protein or gene level, such as post-translational modifications or SNPs can be extrapolated into a multiplicative change on the metabolite level [213]. Thus, metabolomics could become a powerful tool to generate quantitative molecular phenotypes yielding higher odds ratios than approaches so far. The key technologies to identify profiles of metabolites are gas or liquid chromatography combined with MS or NMR spectroscopy and subsequent principal components analysis (PCA).

Kaddurah-Daouk *et al.* [214] interrogated whether baseline metabolite profiles would enable prediction of which patients would respond to the antidepressant sertraline, which to placebo and which to both treatments. The authors used a liquid chromatography electrochemical array (LCEA) platform and found that metabolic profiles before treatment enabled differentiation of responders from nonresponders to active treatment and also separation of placebo responders from nonresponders. Although promising, these results do not allow for far-reaching conclusions. The dataset supports the notion that 'metabotyping' has the potential to identify a metabolic signature with predictive value. Future studies will show whether such signatures are helpful in guiding antidepressant treatment. It can also be envisaged that, in drug discovery and development, metabolic profiles can be used as surrogate endpoints to judge the effect of a new drug candidate. There are preliminary data pointing toward altered metabolism of lipids, carbohydrates and even neurotransmitters that will help to define the metabotype-based subgroups that respond differently to existing and upcoming antidepressants [215]. In light of the paucity of studies such cautiously optimistic assessment seems justified.

Neuroendocrinology

An almost overall and well-documented endocrinologic finding in depressed patients is an increased secretion of the stress hormone cortisol [216]. This result is in line with findings of elevated levels of CRH in the cerebrospinal fluid [217]. This finding is in turn supported by Raadsheer *et al.* [218] who found a higher amount of CRH-expressing neurons in limbic brain regions of depressed patients. On the basis of the prior finding of a hypersecretion of CRH, Nemeroff *et al.* [219] could further demonstrate a reduced number of CRH-binding sites in the frontal cortex of suicide victims. Taken together, all these single studies provide evidence for an impaired regulation of the HPA axis in depression [159]. In general, stressful situations activate the stress hormone system by stimulating the parvocellular neurons of the hypothalamus to secrete vasopressin and CRH. These two neuropeptides induce the secretion of adrenocorticotropic hormone (ACTH), also known as corticotropin, from the anterior pituitary. ACTH subsequently leads to the secretion of glucocorticoids, especially cortisol in humans, via activation of the adrenal cortex. These glucocorticoid hormones in turn influence the hypothalamus and pituitary by way of a negative feedback loop [13]. In depressed patients the dysregulation of this stress hormone system emerges in response to chronic stress and is characterized by changes in neuropeptide-secreting systems. In addition to the abovementioned findings of elevated stress hormone secretion, the impaired function of the HPA axis has also been ascertained by studies using neuroendocrine function tests.

The DST for example examines the suppressive effect of synthetic glucocorticoid dexamethasone on the production of cortisol. Carroll *et al.* [220] attempted to validate the DST for the diagnosis of melancholia, but the phenomenon of nonsuppression has also been shown in other psychiatric diseases [221]. Using the DST as a state biomarker for depression, most studies have

reported a substantial number of patients showing nonsuppression of plasma cortisol levels after dexamethasone administration [222–225]. Holsboer assumes that cortisol nonsuppression occurs as a result of an impaired function of corticosteroid receptors that results in decreased inhibition of the central neuropeptides vasopressin and CRH that drive the HPA axis activity at the pituitary level [159]. Cortisol nonsuppression is also often found to be persistent when there is no remission of symptoms. These observations pointed to the fact that there is a possible predictive value of the DST. Indeed, some studies could demonstrate that persistent cortisol nonsuppression after DST is associated with early relapse or poor clinical outcome in depression [226,227].

A further neuroendocrine test with presumably predictive value is the CRH stimulation test. After intravenous administration of CRH in the evening, depressed patients show a blunted secretion of ACTH but a normal secretion of cortisol [228,229]. This well-documented finding has been taken as evidence for the existence of desensitized pituitary CRH receptors that occur as a result of CRH hypersecretion [229–231].

Although both tests, the DST and the CRH stimulation test, have been widely applied, the sensitivity to detect HPA alterations in depressed patients has been criticized by some authors, for example [221]. To solve the problem of sensitivity, Holsboer *et al.* [232,233] suggested a combination of these two tests, the dexamethasone suppression/CRH stimulation test. For this test, patients receive 1.5 mg dexamethasone at 23 p.m. for oral intake. On the next day, 100 μg cortisol is administered intravenously at 15 p.m. One hour before and three hours after the injection, ACTH and cortisol concentrations were measured via blood samples that were drawn every 15 min. It has repeatedly been shown that the sensitivity of this combined test is superior to that of the single DST [234–236]. An almost overall finding in depressed patients is an elevated plasma cortisol response to the Dex/CRH test [232,233,237], which is indicative for alterations in the HPA system. In addition to the superior sensitivity as a state marker during an acute depressive disorder, a further major advantage of the Dex/CRH test is its use as a biomarker of drug efficacy and treatment response. A series of studies could demonstrate that normalization of the test results is a prerequisite for clinical response to antidepressant treatment [170,238–240]. Regarding the predictive value in antidepressant treatment response, Holsboer-Trachsler *et al.* [241] found that elevated plasma ACTH responses to the Dex/CRH test were associated with negative treatment outcome after six weeks in trimipramine-treated patients. However, the majority of studies reported no associations of Dex/CRH test results and the response to antidepressant treatment [240,242,243]. Considering that a single test cannot detect a treatment-induced improvement of the HPA system, Ising *et al.* [192] decided to conduct two consecutive Dex/CRH tests. In fact, they could demonstrate that reduced cortisol responses to the second Dex/CRH test after two to three weeks were associated with better treatment outcomes after five weeks and with higher remission rates at the end of the hospitalization period. In contrast to that, patients who still showed elevated cortisol responses to the second Dex/CRH test were not likely to respond to the current treatment. Further support for a consecutive Dex/CRH test during the antidepressant treatment comes from Schüle *et al.* [244]. They assume that an early attenuation of the HPA axis activity within one or two weeks has the best predictive values for antidepressant treatment outcome, although this is not a prerequisite for a positive response. Over all, the Dex/CRH test has a high relevance as a potential biomarker because it can predict the response to antidepressant treatment, but further evidence with larger sample sizes is needed to approve the Dex/CRH test as a reliable biomarker in clinical practice.

Electrophysiology

Several different electrophysiological biomarkers such as event-related potentials (ERPs), changes in electroencephalography (EEG) frequency bands, subjective and objective sleep show promise for predicting antidepressant treatment outcome.

Event-related potentials

The loudness dependence of auditory evoked potentials (LDAEP) is modulated by the serotonergic system [245]. A high intensity dependence of auditory evoked N1/P2-component is believed to reflect low central serotonergic neurotransmission. Because serotonergic dysfunction has a key role in the pathogenesis of depression, but only a subset of patients respond to SSRI agents, this differential paradigm could be helpful in deciding whether patients suffering from depression will benefit from an SSRI treatment. Several studies have demonstrated that patients with a strong pretreatment LDAEP had a significantly greater decrease of depressive symptoms under treatment with SSRIs [246–248], whereas patients with a flat LDAEP were more likely to respond to the nonserotonergic antidepressant reboxetine [248,249].

The P300 is an auditory ERP that is commonly elicited in oddball paradigms when a target stimulus occurs in a sequence of standard stimuli and when the subject is actively engaged in the detection task [250]. Kalayam and Alexopoulos [251] showed that depressed patients who achieved remission after antidepressant drug treatment had a longer pretreatment P300 latency. To date, it seems premature to judge whether ERPs will reach clinical significance in treatment prediction. More replication studies with larger sample sizes are necessary to strengthen the prediction value.

Alpha band power and alpha hemispheric asymmetry

Studies investigating the association of antidepressant treatment outcome and alpha band power in MD repeatedly showed that a greater pretreatment alpha power served as a predictor for better outcome. Ulrich *et al.* [252] were the first to show an association between the average alpha band activity before treatment and the severity of psychopathology after a four-week treatment with amitriptyline or pirlindol. Responders had a 1.5-fold higher pretreatment alpha frequency that, unlike among nonresponders, further increased during treatment with amitriptyline or pirlindol, with a tendency toward a left lateralization of the occipital alpha power. Bruder *et al.* [253] replicated the finding of a predictive value of alpha band power in a 12-week antidepressant treatment. In their study, fluoxetine responders had greater alpha power with the largest differences at occipital sites compared with nonresponders and healthy control subjects. Unlike the findings of Ulrich *et al.*, responders showed greater alpha (and therefore hypoactivity) over the right compared with the left hemisphere, whereas nonresponders showed the opposite asymmetry. Results from an

earlier study by Bruder *et al.* pointed to the same direction with respect to alpha asymmetry [254].

Theta band power: QEEG measures

Three quantitative electroencephalographic (QEEG) measures have repeatedly been shown to predict antidepressant treatment outcome in the course of early treatment: cordance, the Antidepressant Treatment Response Index (ATR) and low-resolution brain electromagnetic tomography (LORETA). Cordance is calculated from a full scalp electrode array and integrates information from absolute and relative power measures of EEG spectra in a single measurement. Cordance is sensitive to cortical deafferentation and has been proven to show moderate associations with underlying cerebral perfusion [255,256]. A considerable body of research supports the assertion that an early reduction in prefrontal EEG cordance can serve as a predictor of the response to antidepressant medication and this is particularly the case for theta frequency ranges [257–263]. A recent study additionally suggested that frontal theta cordance also served as a predictor of treatment by deep brain stimulation [264]. Moreover, Pawlowski *et al.* [265] measured antidepressant-response-related differences in cordance derived from sleep EEG in the first treatment week and also reported an association of week 1 theta cordance with HAM-D score at week 5. However, brain functional changes indicated by prefrontal cordance during treatment with antidepressant medication or placebo can only be interpreted within the context of prior antidepressant treatment: in a single-blind placebo-controlled study depressed patients treated with antidepressants or placebo did not differ regarding their prefrontal cordance changes [266]. In summation, theta cordance has the potential of becoming an important indicator for therapy outcome. However, it is only applicable to the early treatment course and can therefore not serve as a pretreatment predictor. Even though this measure can be helpful in adjusting an ineffective treatment after one week only, other biomarkers are needed to facilitate the initial treatment selection.

The ATR index incorporates alpha and theta EEG features and is calculated from data collected from only five electrodes in frontal brain regions making it more suitable for clinical implementation. It is measured at baseline and one week after treatment initiation and is scaled to range from 0 (low probability) to 100 (high probability of antidepressant treatment response) [267]. In a large multicenter trial the ATR index proved useful to predict differential response to either escitalopram or bupropion monotherapy [268].

Like cordance, LORETA [269] is also collected from whole-head electrode montages and enables the characterization of deeper brain structures [270]. It proposes an inverse solution by assuming that (i) neighboring neurons are likely to be similarly active and (ii) the signal measured at the scalp originates from cortical gray matter [271,272]. LORETA computes current density at each voxel. To reduce errors due to interindividual anatomical differences or electrode placement, the signal is spatially smoothed. In an attempt to improve localization accuracy further, standardized LORETA (sLORETA) uses standardization of the current density estimates [273]. Pizzagalli *et al.* [274] studied depressed patients before and after treatment with the TCA nortriptyline and, using the LORETA algorithm, found that responders showed higher pretreatment theta activity in the rostral anterior cingulate cortex (rACC). Further, in a more recent study, Hunter *et al.* [275] measured rACC theta current density five weeks and immediately before treatment initiation with sertraline. The authors showed that activity measured immediately before treatment initiation had a better predictive value, indicating that rACC activity can serve as a state rather than a trait marker for antidepressant response.

Polysomnographic measures

Impaired sleep is one of the hallmark symptoms of patients suffering from MD. One characteristic sleep abnormality consists of rapid eye movement (REM) sleep disinhibition (e.g. shortened REM onset latency, prolonged REM periods and elevated REM density) [276]. To date, numerous studies have explored the effects of antidepressants upon sleep but less research has focused on the use of sleep-EEG parameters as biomarkers for the therapeutic effects of antidepressant medication. In a prospective case–control study with a relatively large sample size, Thase *et al.* [277] found that abnormal sleep-EEG profiles were associated with poor cognitive behavioral therapy response. Moreover, Dew *et al.* [278] found that poor subjective and objective sleep quality predicted poor response profiles in geriatric depression after 18 weeks of treatment with nortriptyline and interpersonal psychotherapy. Two commonly reported biomarkers for therapeutic response are (i) a pretreatment elevated REM disinhibition and (ii) an initial tonic REM suppression measured at the beginning of treatment. Considering purely pharmacological studies, pretreatment reduced REM latency has been proposed as a (non-differential) predictor for response to pharmacotherapy [279,280]. However, another study employing REM latency as a predictor for fluoxetine treatment response failed to do so. In this study, REM latency could only serve as a predictor of placebo nonresponse [281]. Regarding polysomnographic measures at the beginning of treatment, Kupfer *et al.* [282–284] were the first to show that treatment response to amitriptyline could be predicted from the amount of REM sleep suppression and REM onset latency during the first treatment nights. The association of REM sleep suppression in early treatment course and clinical outcome was also demonstrated by Gillin *et al.* [285] and Höchli *et al.* [286]. Furthermore, Murck *et al.* [287] recorded sleep EEGs at day 7 and at day 42 of treatment with paroxetine and tianeptine and found that REM density served as a predictor of paroxetine treatment response: changes in REM density showed an inverse correlation with changes in HAM-D scores. In summary, most studies point toward REM disinhibition before treatment and REM suppression at treatment initiation as predictors for better antidepressant treatment outcome. A special situation was recently reported by Kimura *et al.* [288] who showed that only transgenic mice overexpressing CRH in the prefrontal cortex (PFC) had REM sleep disinhibition which normalized when a CRHR1 antagonist was administered. These results point to a link between REM sleep and CRH overexpression, a phenomenon thought to be present in many patients with MD. This is of particular interest because an early Phase II study administering CRH on one antagonist showed that depressed patients with increased REM density responded much better to the investigational drug than those where REM sleep disinhibition was absent

[289]. REM disinhibition could therefore be of important differential prediction value.

Brain imaging

Several studies have addressed the question as to whether brain functional or structural measures provide information regarding antidepressant treatment outcome. The evidence supporting brain functional then structural biomarkers is considered separately below.

Functional imaging

On the basis of brain electrical tomography, Pizzagalli [290] advocated increased rACC activity as a robust biomarker of antidepressant treatment response and two more recent studies were in line with this notion [291,292]. The predictive value of rACC activation was further replicated using functional imaging measures in attentional, facial perception and picture processing tasks [293–296]. One of the best documented measures of brain function is the abovementioned QEEG power measure cordance [270] that can also reflect activity of areas such as the ACC.

Using fluorodeoxyglucose positron emission tomography (PET), Mayberg *et al.* [297] were the first to show that an increased resting glucose metabolism in the rACC before the onset of pharmacological treatment predicted better treatment response in MD, whereas blunted rACC activity predicted poor response. Accordingly, Milak *et al.* [298] showed that after three months of monoaminergic medication remitted and nonremitted patients with MD differed in pretreatment regional brain glucose uptake in the midbrain. These findings are consistent with a previous PET study by Wu *et al.* [299], which found lower glucose uptake in the midbrain using sleep deprivation as treatment.

As an alternative to assessing isolated regional differences, a growing body of research suggests that an altered connectivity between brain regions could serve as a general biomarker for depression [300–302]. Anand *et al.* [303] were the first to show that cortico–limbic connectivity increased with remission of MD. Additionally, in a recent study using resting functional connectivity MRI (fcMRI), Kozel *et al.* [304] found that connectivity between the subcallosal cortex and the left ACC had important associations with antidepressant treatment response.

Structural imaging

Many studies agreed that changes in volumes of brain areas are associated with depression. Foremost, hippocampal volume reductions in these patients are a robust finding that is also confirmed in meta-analyses [305–307]. Also, volume difference of PFC areas such as the orbitofrontal cortex (OFC) [308,309] and the subgenual subdivision of the ACC [308,310] were reported. Only a few studies have examined whether structural MRI can provide information about antidepressant treatment outcome. In fact, there is a paucity of longitudinal studies on the temporal development of volumetric changes and their potential to inform the clinician in charge.

Some reports supported that smaller hippocampal volumes are associated with poor treatment outcome [311], whereas larger hippocampal volumes predicted beneficial response to treatment [312,313]. Although morphological and biochemical underpinnings of these changes remain unclear, hippocampal volumetry has high potential as a prognostic tool. Volumetry that focuses upon the subgenual PFC also suggested that higher volumes were prognostically beneficial [314].

Gray matter volume in ACC could also provide clinically relevant information. Chen *et al.* found that enhanced onset of clinical improvement following fluoxetine treatment was associated with greater gray matter volumes in ACC and other PFC subdivisions, including insula and right temporal cortex [293]. Also, Frodl *et al.* showed that larger ACC volumes had a better response to antidepressants than those with smaller ACC volumes [311]. Interestingly, there were no differences in ACC sizes between patients and healthy controls, pointing to the marginal degree of such changes. Analyses of other subdivisions (e.g. posterior cingulate cortex and frontal striatum) also indicated that smaller volumes predict unfavorable treatment outcome.

Diffusion tensor imaging is another technique that enables measuring of the structural integrity between different brain areas by mapping the diffusion of water in brain tissue. Using this imaging technique, microstructural white matter abnormalities have been linked to treatment response. Depressed patients who remained symptomatic after treatment with escitalopram had lower fractional anisotropy in several cortico-striato-limbic white matter areas relative to depressed elderly patients who achieved remission [315,316].

Taken together, all these imaging studies have potential, but immediate transferral to clinical practice seems premature. One pertinent issue is the effect of previous treatment episodes, where humoral disturbances on many levels as well as treatment could impact upon brain areas that are particularly sensitive to homeostatic changes, such as the hippocampus. In this sense, the reduced volumes found to be prognostically unfavorable could simply reflect the fact that the affected brain areas have adapted to the homeostatic turmoil as a sequel of increased number of previous episodes. Longitudinal studies have confirmed that an increased number of previous episodes are predictive of more difficult to treat and longer lasting current episodes. This disputes a causal relationship between sizes of specific brain areas and predictive value of structural imaging. In fact, only one published study has taken this into account [314]. A more recent effort by Sämann *et al.* [317] tried to overcome this problem and studied a large sample ($n = 167$) of diagnostically heterogeneous depressed patients treated with antidepressants. Aiming to explore the potential of structural MRI under naturalistic clinical conditions this study introduced a novel composite marker and suggested that variability of the cortex volume of specific brain areas and measures of hippocampal size indeed predicted treatment outcome independently of number of previous episodes.

Concluding remarks

This overview demonstrates that many genetic and systemic laboratory abnormalities exist among people suffering from MD. The pertinent question to be raised is: how can these data be used by industry for making better drugs and by clinicians to optimize treatment?

For industry the situation became sobering because – owing to an increasing public acceptance of depression and its treatment – markets grow while revenues decrease. The latter results from more and more second-generation antidepressants that lost patent

protection and are now much cheaper than successor drugs that have, if any, only incremental clinical advantage. In fact, only few pharmaceutical industries and biotech companies are still pursuing the goal of discovery and development of better antidepressants but even these mostly adhere to the 'one-size-fits-all' blockbuster model prevalent throughout the past decades. Genetests and biomarkers are not yet fully implemented into the drug development process, but it is foreseeable that this situation will soon be remedied and oncology could serve as a template here. All currently used antidepressants target monoaminergic neurotransmission and new drug candidates are only modifications of drugs that have marketed for over 50 years. These drugs help too few people and it takes too long until they work. A recent meta-analysis proved that when based on statistical symptom outcome antidepressants are as good as most other drugs used in medicine in general [318]. However, full remission and prevention of relapse still await breakthroughs that can only be achieved if results from basic depression research are translated into drug discovery. Most evidence coming from basic research relies on statistically significant differences between responders and nonresponders. Although such differences can imply scientific meaningfulness, they do not necessarily provide information about clinical meaningfulness. To ensure reliance on biomarkers for treatment prediction in clinical settings, a consistent scientific process and framework for biomarker evaluation such as proposed by the Intitute of Medicine (IOM) might prove helpful.

As demonstrated in this review, several DNA-sequence variations are associated with antidepressant response but identification of a particular genetic mutation that is causal has not been found. That is unsurprising because MD results from gene–environment interactions where genetic disposition has an important but not the only role. Studies that emphasize the importance of variations in the *ABCB1* gene encoding the P-gp molecule that determines penetration of drugs into the brain tissue are promising in this context. Similar to CYP isoenzymes, the *ABCB1*-encoded extrusion pump determines bioavailability of a drug but gives no hint whether the patient might respond to that specific compound. Therefore, physiological or systems biological data are needed to identify specific targets. The stress hormone system is a particular case in point. Neuroendocrine research has built a robust fundament that shows involvement of the central stress hormone system in development and course of depression but no drug that intervenes at this system (e.g. corticosteroid receptor antagonists or antagonists at central neuropeptide receptors involved in stress regulation) has made it to clinical routine application so far.

The lesson learned from many clinical trials testing a novel specific drug against a much less specific antidepressant and placebo in an unspecified population is that the unspecific antidepressant is always superior. In the case of CRHR1 antagonism, for example, we need biomarkers that help us to identify those depressed patients where a central CRH hypersecretion is causally involved in the clinical phenotype. Sleep-EEG analysis, proteomic data and genetests could ultimately provide a set of laboratory tests that identify individuals that benefit from CRHR1 antagonists. Thus, encouraging industry to pursue personalized medicine (but in a way where the administration of a specific drug is based upon results of an appropriate companion test) is a high demand. Up to now, only few biomarkers in psychiatry have reached clinical application. An example of a successful clinical implementation of genetic testing could be that of carbamazepine therapy which is often prescribed to patients with bipolar disorder. A more serious side effect of carbamazepine is hypersensitivity reactions such as Steven–Johnson syndrome and toxic epidermal necrolysis; both can prove fatal. However, predisposition to these hypersensitivity reactions has been linked to the human leukocyte antigen (HLA) genotype, particularly in Asian patients. Because of the important practical implications of these findings, some hospitals are now requiring HLA genotyping for at-risk individuals before starting a carbamazepine therapy.

Along that line, a set of genetests and biomarkers that inform the clinician which drug to choose for the individual patient will improve the patient's trust and adherence. Up to now there are cycles of public skepticism against medications where doctors are suspected to follow marketing efforts of companies, opinion leaders and average results from large controlled trials. The 'average' patient, however, does not exist and the high variability in main and adverse effects of drugs demonstrates that. Humans regard themselves as individual persons, and patients that interact with the healthcare system maintain this perception which is also biologically well founded.

As demonstrated in this review, genetic research and clinical systems biology have built a strong fundament that already now allows stratification of patient samples that differ according causal mechanisms of the disease and would require specific treatments. Although it is predictable that a set of biomarkers that includes genetests, hormone tests, neuroimaging and sleep-EEG recordings, among others, can create a cluster of patients that would benefit from a drug targeting a specific mechanism, we must realize that the pharmaceutical industry does not yet provide such tools. In fact, transformation from 'blockbuster medicine' to 'personalized medicine' is a difficult process for the pharmaceutical industry which is usually not engaged in the diagnostic biomarker business. Other aspects of a biomarker-driven rebuilding phase of healthcare are very practical: we are currently confronted with prevalence figures for depression that are extremely high. Cases of severe depression, a potentially hazardous disease requiring full attention by medical professionals, are diluted by cases of minor depression, subthreshold disorders, dysthymia or the 'burn-out' syndrome (a current hype in German speaking countries). What the field needs is to fix a pragmatic threshold in the continuum from ordinary sadness to severe depression; if, based only on verbally communicated information and not on biomarkers that are integrated into diagnostic algorithms, the skepticism to a psychiatric diagnosis is to continue.

Finally, genetests and biomarkers will help us to make a judgment for our personal risk to suffer one day from MD. We will not address the issue of ethical concerns of predicting medicine but simply bring up that biomarkers in prevention of common diseases are not a new concept. Measurements of cholesterol, uric acid, glucose or prostate-specific antigen (PSA) are blood-borne biomarkers that indicate the risk for cardiovascular disease, gout, diabetes or prostate cancer. Of course, these diseases are complex and such biomarkers cannot make precise risk predictions and have limitations for general population screens. Nevertheless, a person having a high familiar load for depression might feel more comfortable when checking sleep-EEG or stress hormone related

biomarkers that might inform him or her and the doctor about the individual disease risk. This view is justified because we know from vulnerability studies at the Max Planck Institute of Psychiatry that sleep-EEG, stress hormone changes and genetests can inform the clinician about the inherent risk of depression and even the onset of a first episode.

Characterizing patients with genetests and biomarkers and healthy individuals at risk is timely and appropriate. These laboratory measures help industry to develop a new business model where academic institutions and pharmaceutical and diagnostic companies join forces to promote personalized medicine, offering the right antidepressant to the right patient. Implementation of genetests and biomarkers into clinical psychiatry offers objective measures and will improve the relationship between patients and the therapeutic team. That makes the field less burdened with ambiguity, and offers therapeutic approaches that are pragmatic and humane.

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