

Human Biomarkers of Rapid Antidepressant Effects

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Mood disorders such as major depressive disorder and bipolar disorder—and their consequent effects on the individual and society—are among the most disabling and costly of all medical illnesses. Although a number of antidepressant treatments are available in clinical practice, many patients still undergo multiple and lengthy medication trials before experiencing relief of symptoms. Therefore a tremendous need exists to improve current treatment options and to facilitate more rapid, successful treatment in patients suffering from the deleterious neurobiological effects of ongoing depression. Toward that end, ongoing research is exploring the identification of biomarkers that might be involved in prevention, diagnosis, treatment response, severity, or prognosis of depression. Biomarkers evaluating treatment response will be the focus of this review, given the importance of providing relief to patients in a more expedient and systematic manner. A novel approach to developing such biomarkers of response would incorporate interventions with a rapid onset of action—such as sleep deprivation or intravenous drugs (e.g., ketamine or scopolamine). This alternative translational model for new treatments in psychiatry would facilitate shorter studies, improve feasibility, and increase higher compound throughput testing for these devastating disorders.

Key Words: Antidepressant, biomarker, cholinergic, depression, glutamate, ketamine, muscarinic, *N*-methyl-D-aspartate, scopolamine, sleep deprivation

Mood disorders such as major depressive disorder (MDD) and bipolar disorder (BD)—and their consequent impairments on the individual, family, work force, and society—are among the most disabling and costly of all medical illnesses (1). The serendipitous discovery of the mood-enhancing effects of antituberculosis drugs in the 1950s introduced biological targets (i.e., serotonin and norepinephrine neurotransmitters) that were initially pursued to decipher the etiology and pathogenesis of MDD. Our increasing knowledge of these neurotransmitter systems led to the creation of a number of antidepressant drugs (e.g., tricyclic antidepressants, monoamine oxidase inhibitors, selective serotonin reuptake inhibitors) currently being used in standard clinical practice. Nevertheless, many patients continue to undergo multiple and lengthy medication trials before experiencing relief of symptoms, and many do not respond to the current array of antidepressant agents. Furthermore, until full antidepressant effects manifest, patients experience considerable disruption to their lives and remain at risk for suicidal behavior. More importantly, individuals continue to be exposed to the deleterious neurobiological effects associated with ongoing depression. Thus, a tremendous need exists to facilitate more rapid and effective treatments for patients with mood disorders.

In developing any new therapeutic, the ability to assess both efficacy and safety is paramount. Testing these endpoints in clinical trials often requires significant time and has contributed to the escalating cost of validating investigational new drugs. In psychiatric and central nervous system (CNS) trials, developing biomarkers could provide surrogate indices of clinically relevant

endpoints. Similarly, biomarkers could contribute to insights with regard to neurobiological correlates of treatment response (2). For this review, a biomarker is defined as “a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacological responses to a therapeutic intervention” (3). Mood disorders research has focused on identifying biomarkers that might be involved in prevention, diagnosis, treatment response, severity, or prognosis—although their value in terms of personalizing treatment remains unclear (4). Table S1 in Supplement 1 broadly summarizes common biomarker tools used in treatment trials for mood disorders. Biomarkers evaluating rapid treatment response will be the focus of this review, given the significance of providing relief to patients in a more expedient and systematic manner.

One prominent limitation for developing biomarkers of response for existing traditional antidepressants is that many of these treatments require 6 weeks or more to exert an adequate treatment response. Other similar limitations are highlighted in Table S2 in Supplement 1. A novel approach that would resolve some of these limitations is the incorporation of interventions with a rapid onset of action (e.g., intravenous ketamine or scopolamine). This alternative translational approach could ultimately facilitate shorter studies, improve feasibility, and promote testing of putative biomarkers with overall higher compound throughput. Moreover, once such biomarkers are identified, they can be used a priori to guide additional research by classifying patients on the basis of expected clinical response to treatment.

Sleep Deprivation

Case observations of sleep deprivation (SD) in the early 1970s provided the first evidence that this treatment modality is a rapid-acting, nonpharmacological antidepressant therapy (5). Since then, several studies have demonstrated relatively rapid reversal (24–48 hours) of depressive symptoms in approximately 40%–60% of depressed patients (6). The SD interventions include total sleep deprivation (TSD) (studies vary from 26–36 to 36–40 hours) (5), partial sleep deprivation (approximately 20 hours, often with less-pronounced antidepressant effects) (7), and selective rapid eye movement (REM) SD.

Multiple biological factors have been implicated in the neurobiological mechanisms underlying the rapid antidepressant effects associated with SD, and a detailed review of these studies is beyond the scope of this article. However, Table 1 highlights much of the past work evaluating potential human biomarkers to

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Received Sep 17, 2012; revised Nov 13, 2012; accepted Nov 30, 2012.

Table 1. Biomarkers Used to Predict Treatment Response to SD

Biomarkers in SD	Design	Results	Reference
Neurophysiological EEG	<i>n</i> = 16 MDD, TSD	Responders to treatment were rated as significantly more depressed and revealed a more “depressed” EEG sleep pattern before sleep deprivation than NRs.	Duncan <i>et al.</i> (20)
	<i>n</i> = 16 MDD, TSD/SPA	SD responders showed a steady decrease of SWA across successive NREM episodes; a high DSR positively predicted SD response.	Nissen <i>et al.</i> (21)
	<i>n</i> = 33 MDD, PSD/TSD	With cutoffs of 30%, 35%, 40%, and 50% to dichotomize responders and NRs, PSG variables were evaluated for between-group differences; continuity differed between responders and NRs on baseline and recovery nights; no response cutoff tested was clearly “best” in terms of detecting the most PSG differences between groups.	Clark <i>et al.</i> (75)
	<i>n</i> = 17 MDD, BSL/SWD/RCV	Reduction in depressive symptoms correlated with the overnight dissipation of fronto-central SWA on baseline sleep, the rebound in right frontal all-night SWA on recovery sleep, and the amount of REM sleep on the SWD night.	Landsness <i>et al.</i> (22)
Auditory-evoked potentials	<i>n</i> = 17 depressed inpatients, TSD	The most prominent changes (responders and NRs) were found for the amplitude of the P300 component. Responders showed smaller N1 amplitudes before TSD but a higher increase after TSD than NRs.	Danos <i>et al.</i> (76)
Neuroimaging SPECT/HMPAO	<i>n</i> = 10 MDD - melancholic, TSD	All depressed patients (<i>n</i> = 5) showed relative hypoperfusion in the left anterolateral PFC before and after TSD; responders showed hyperperfusion in limbic system at baseline with reduction in limbic region after TSD.	Ebert <i>et al.</i> (77)
	<i>n</i> = 20 (15 MDD, 2 BD, 3 dysthymic), TSD	Responders (<i>n</i> = 11) showed increased CBF to left temporal and mainly right parietal regions; CBF values and the severity of depression correlated inversely.	Volk <i>et al.</i> (78)
	<i>n</i> = 20 MDD, melancholic, TSD	Before TSD, responders (<i>n</i> = 11) showed hyperperfusion in the right ACC and in the right and left fronto-orbital cortex and basal cingulate gyrus.	Ebert <i>et al.</i> (79)
	<i>n</i> = 10 MDD, TSD	Responders (<i>n</i> = 5) showed decrease of basal ganglia D2 receptor occupancy after TSD compared with NRs; data suggests enhanced dopamine release in responders.	Ebert <i>et al.</i> (80)
	<i>n</i> = 15 (13 MDD, 2 BD), PSD	Responders (<i>n</i> = 9) to PSD had higher perfusion in the right OFC than NRs before PSD; multiple regression analysis showed right orbitofrontal/basal cingulate perfusion before PSD, and left inferior temporal perfusion after PSD, as fairly accurate predictors of change in depression scores.	Volk <i>et al.</i> (81)
	<i>n</i> = 14 (12 MDD, 2 BD), TSD	Before TSD, responders (<i>n</i> = 8) had higher anterior cingulate perfusion than the NRs that normalized after TSD; baseline left hypoperfusion in left PFC in all patients, which responders normalized on remission.	Holthoff <i>et al.</i> (82)
	PET/FDG	<i>n</i> = 15 MDD, TSD	Depressed responders (<i>n</i> = 4) had higher cingulate cortex metabolic rate than depressed NRs before TSD; this normalized after TSD.
<i>n</i> = 6 MDD, elderly, TSD		Greatest reductions in normalized, relative glucose metabolism after TSD were observed in the ACC (Brodmann area 24); results persisted after recovery sleep and antidepressant treatment (paroxetine).	Smith <i>et al.</i> (84)
<i>n</i> = 36 MDD, TSD		Responders (<i>n</i> = 12) had higher metabolic rates in the medial PFC, ventral ACC (Brodmann area 24), and posterior subcallosal gyrus at baseline than depressed NRs and control subjects; responders had decreases in the medial PFC and frontal pole after TSD.	Wu <i>et al.</i> (85)
<i>n</i> = 12 MDD, elderly, TSD		Early metabolic alterations in the right cingulate gyrus and the persistence of these adaptive changes were associated with improvement in depressive symptoms.	Smith <i>et al.</i> (86)
<i>n</i> = 6 BD/MDD, TSD		Positive correlations (decreased depression with reduced relative cerebral glucose metabolism) were found in the inferior frontal gyrus and inferior frontal/orbital frontal cortex; negative correlations were found in the dorsolateral prefrontal cortex.	Wu <i>et al.</i> (16)

Table 1. Continued

Biomarkers in SD	Design	Results	Reference
fMRI	<i>n</i> = 17 MDD, PSD	Baseline bilateral amygdalar perfusion was greater in responders (<i>n</i> = 5) than NRs; differential amygdalar perfusion changes were noted with PSD between responders and NRs.	Clark <i>et al.</i> (87)
	<i>n</i> = 20 BD, repeat TSD with LT	<i>SERTPR</i> genotype predicted response to treatment and influenced baseline neural responses in the ACC and the DLPFC.	Benedetti <i>et al.</i> (88)
MRS	<i>n</i> = 13 MDD, TSD	In the DLPFC, TSD did not change Glx or its elements, whereas the total creatine and choline signal increased marginally. No change noted in the POC.	Murck <i>et al.</i> (89)
	<i>n</i> = 19 BD, repeat TSD and LT	Decrease in the Glx/creatine ratio significantly correlated with the improvement of both objective and subjective measures of depression.	Benedetti <i>et al.</i> (90)
Genetics			
<i>5-HTTLPR</i>	<i>n</i> = 68 BD, TSD	Patients homozygotic for the long variant of <i>5-HTTLPR</i> showed significantly better mood after TSD than heterozygotic and homozygotic patients with short variant.	Benedetti <i>et al.</i> (91)
	<i>n</i> = 56 MDD, PSD	<i>5-HTTLPR</i> gene variants showed no difference with reduction in depression scores.	Baghai <i>et al.</i> (92)
	<i>n</i> = 22 BD, TSD, LT	Light therapy sustained the effect of TSD. The effect was more marked in homozygotes for the long variant of <i>5-HTTLPR</i> than in heterozygotes and homozygotes for the short variant.	Benedetti <i>et al.</i> (93)
	<i>n</i> = 122 BD, TSD	Triple interaction of <i>5-HTTLPR</i> , rs334558 (promoter variant for GSK3β), and treatment on severity of depression noted. Among rs334558 T/T homozygotes the best antidepressant response was associated with <i>5-HTTLPR</i> I/I homozygosity, and among the rs334558 C carriers the <i>5-HTTLPR</i> s/s showed the best response to treatment.	Benedetti <i>et al.</i> (94)
COMT	COMT gene (rs4680) and response to TSD combined with light treatment, <i>n</i> = 87, BD inpatients	Patients homozygotic for the Val/Val variant showed less efficient antidepressant effect after the night awake than those who were heterozygotic and homozygotic for the Met variant.	Benedetti <i>et al.</i> (95)
<i>5-HT_{2A}</i> SNP	<i>n</i> = 80 BD, repeat TSD	All genotype groups showed comparable acute effects of the first TSD, but patients homozygous for the T variant had better perceived and observed benefits from treatment than carriers of the C allele.	Benedetti <i>et al.</i> (11)
Peripheral Markers			
BDNF	<i>n</i> = 51, repeat TSD, ± sertraline	Serum BDNF levels were significantly lower at baseline in both treatment groups compared with control subjects; decreased levels of BDNF were also negatively correlated with depression scores.	Gorgulu <i>et al.</i> (27)
	Serum VEGF/BDNF, <i>n</i> = 11 MDD, TSD	As depression scores decreased after TSD, VEGF plasma levels increased; no association found with BDNF levels.	Ibrahim <i>et al.</i> (28)
IL-6	<i>n</i> = 10 BD, TSD/SPA	A significant inverse correlation was observed between IL-6 levels and VAS scores after TSD (Day 2) and after SPA (Day 3); no correlation on measures after Day 1.	Benedetti <i>et al.</i> (96)
Neuroactive steroids	<i>n</i> = 29 MDD, PSD	PSD did not affect the concentrations of neuroactive steroids in either responders (<i>n</i> = 20) or NRs.	Schule <i>et al.</i> (97)
RAAS	<i>n</i> = 7 MDD, PSG, TSD	TSD in patients with depression led to an increase in renin secretion and a concomitant trend for a decrease in HPA axis activity in the recovery night.	Murck <i>et al.</i> (98)

5HT_{2A}, serotonin-2A; 5HTTLPR, 5-HTT linked polymorphic region; ACC, anterior cingulate cortex; BD, bipolar disorder; BDNF, brain-derived neurotrophic factor; BSL, baseline; CBF, cerebral blood flow; COMT, catechol-O-methyltransferase; DLPFC, dorsolateral prefrontal cortex; DSR, δ sleep ratio; EEG, electroencephalogram; FDG, fluorodeoxyglucose; fMRI, functional magnetic resonance imaging; Glx, sum-peak of glutamate, glutamine, and γ aminobutyric acid (GABA); GSK3β, glycogen synthase kinase 3-β; HMPAO, Technetium -99- hexamethyl propyleneamine oxime; HPA, hypothalamic pituitary adrenal; IL-6, interleukin-6; LT, light therapy; MDD, major depressive disorder; MRS, magnetic resonance spectroscopy; NREM, non-rapid eye movement; NRs, nonresponders; OFC, orbitofrontal cortex; PET, positron emission tomography; PFC, prefrontal cortex; POC, parieto-occipital cortex; PSD, partial sleep deprivation; PSG, polysomnography; RAAS, renin-angiotensin-aldosterone system; RCV, recovery sleep nights; SD, sleep deprivation; SERTPR, promoter region of the serotonin transporter; SNP, single nucleotide polymorphism; SPA, sleep phase advance; SPECT, single photon emission computerized tomography; SWA, slow wave activity; SWD, slow wave deprivation intervention; TSD, total sleep deprivation; VAS, visual analogue scale; VEGF, vascular endothelial growth factor.

predict treatment response to SD. In the following, we briefly focus on some of the more notable and recent translational studies.

Sleep Deprivation: Genetics

The serotonin-2A (5-HT_{2A}) receptor, which is associated with depression and suicide (8), influences slow wave sleep regulation (9) and contributes to improved sleep response after mirtazapine, a 5-HT_{2A} blocker (10). The effects of rs6313, a single nucleotide polymorphism (SNP) of the 5-HT_{2A} receptor gene, and repeated TSD were evaluated in patients with BD ($n = 80$) (11). Although no difference among groups occurred after the first TSD, homozygotes for the T variant (rs6313 T/T) experienced a 36% larger response to treatment after the first recovery night than carriers of the C allele (rs6313 T/C, C/C) (11).

The noradrenergic and dopaminergic systems are well-established targets for antidepressants (12), and variants of the catechol-*O*-methyltransferase (*COMT*) gene (a major degrading enzyme for dopamine and norepinephrine) influence response to traditional antidepressants (13,14). The *COMT* Val (108/158) Met polymorphism (rs4680) was evaluated relative to response after SD combined with light therapy in patients with BD. Patients homozygous for the Val/Val variant showed less of an antidepressant response than those who were heterozygous and homozygous for the Met variant. Interestingly, the effects of rs4680 were similar to those observed with paroxetine (13) and fluoxetine (14) in that the magnitude of the effect was promoted by the negative presence of the Val/Val genotype but opposite to that of ketamine (discussed in detail below). Such findings highlight not only how treatment responses can vary with the same genotype but also how personalizing treatment on the basis of underlying neurobiology could be applied. Other genetic findings are summarized in Table 1.

Sleep Deprivation: Functional Neuroimaging

Earlier work using positron emission tomography with 18-fluorodeoxyglucose or single photon emission computerized tomography with Technetium-99-hexamethyl propyleneamine oxime showed that patients who subsequently responded to SD had increased metabolism at baseline compared with non-responders in the orbital prefrontal cortex (PFC) and ventral anterior cingulate cortex (ACC), and normalization of these areas paralleled treatment response to SD (15). Higher-resolution positron emission tomography scans with 18-fluorodeoxyglucose were used with patients taking sertraline and lithium before and after SD. Correlations between treatment response and glucose metabolism were found in the inferior frontal gyrus, inferior frontal/orbital frontal cortex, and dorsolateral PFC (16). The interested reader is referred to Benedetti and Smeraldi (15) for a more detailed review.

Sleep Deprivation: Sleep Architecture

Sleep disturbances play a prominent role in diagnostic criteria for MDD, and abnormalities can include shortening of REM latency, increased REM density, overall disturbance of sleep continuity (17,18), and reduced slow wave sleep (slow δ electroencephalogram [EEG] activity) (19). Patients who responded to SD exhibited a greater rebound of slow wave sleep and total sleep time after recovery sleep compared with baseline (20). Moreover, a high δ sleep ratio (DSR) (ratio of slow wave activity [SWA] in the first to the second REM sleep cycle) on the night before SD predicted antidepressant response (21). More recently, a selective slow wave deprivation (SWD) technique was assessed

in MDD patients to evaluate the role of slow wave homeostasis in antidepressant response to SD with high-density EEG. Participants experienced a small decrease in depressive symptoms that correlated with the overnight dissipation of fronto-central SWA on baseline sleep, rebound in right frontal all-night SWA on recovery sleep, and amount of REM sleep on the SWD night (22).

Sleep Deprivation: Neurotrophic Factors

One of the most studied neurotrophic factors in mood disorders is brain-derived neurotrophic factor (BDNF) (23). The BDNF is extensively expressed in the CNS and mediates neurogenesis and synaptic plasticity in depressed patients (24). One recent review ($n = 1504$ subjects) noted that BDNF levels increased after antidepressant treatment in a manner that correlated with treatment response (25). BDNF levels are also implicated in sleep-wake physiology (26), and researchers showed that a single TSD in MDD patients rapidly increased serum BDNF levels in a manner that correlated with treatment response (27). Although others have failed to replicate these findings (28), overall these data lend support to the neurotrophic hypothesis of depression (27).

Sleep Deprivation: Glutamatergic System

Abnormalities in glutamatergic and γ aminobutyric acid (GABA)ergic neurotransmission in MDD (29) have been of particular recent interest, in light of findings that the *N*-methyl-D-aspartate antagonist ketamine rapidly improves depressive symptoms (30,31). Magnetic resonance spectroscopy (MRS) allows researchers to assess glutamate-related metabolites *in vivo*. A recent review of MRS studies in mood disorders found relatively consistent and widespread patterns of Glx-level (reflecting the sum of glutamate, glutamine, and GABA concentrations) reductions in MDD and elevations in BD (32). Research also shows that reduced levels of Glx normalized after electroconvulsive therapy (33). These findings suggest that the glutamatergic system is a viable target for further evaluation of potential biomarkers of antidepressant treatment response.

Novel Rapid-Acting Antidepressants: Ketamine and Scopolamine

Ketamine

Recent reviews have detailed the significant antidepressant effects of ketamine in patients with treatment-resistant mood disorders (34,35). Several neurobiological correlates of the antidepressant effects of ketamine are being investigated via a multimodal approach to both inform the likelihood of response and provide insights into the mechanisms of action of ketamine (Figure 1, Table 2). Toward this end, identifying these or similar biomarkers would promote the development of new rapid-acting antidepressants and help identify patients who will favorably respond. This work is still preliminary, and thus larger replication studies will be required to validate this approach. This section briefly highlights some of the more prominent biomarker studies involving ketamine.

Ketamine: Genetics. The Val66Met SNP has been linked to psychiatric disorders and impaired trafficking/regulation of BDNF (36). Animal studies found that Val/Val mice exhibited increased antidepressant response to ketamine (and PFC synaptogenesis) (37). Building on this work, one recent study ($n = 62$) evaluated whether rs6265 (Val66Met SNP) was associated with ketamine response in patients with MDD. Results showed that patients with

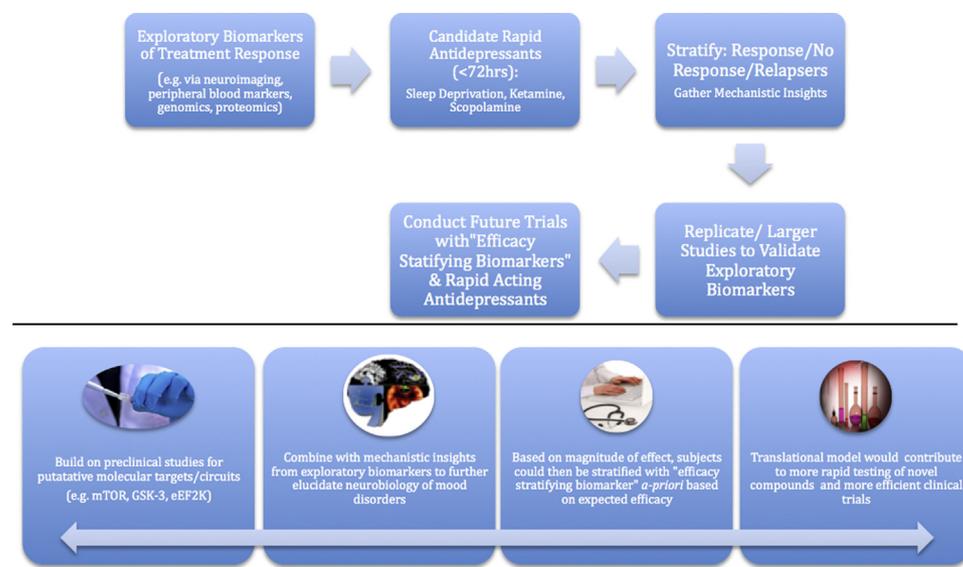


Figure 1. Conceptual framework of translating biomarkers of treatment response to develop rapid acting antidepressants. This model characterizes our approach to the study of biomarkers and is designed to enhance our ability to rapidly identify and test surrogate clinical and biological endpoints that predict treatment outcomes (e.g., $\geq 50\%$ antidepressant response) in mood disorders. The method uses novel agents or other interventions that produce rapid antidepressant clinical effects (i.e., ≤ 72 hours). Results lead to both prompt evaluation of efficacy and potential insights into relevant neural and molecular correlates of outcome (e.g., mammalian target of rapamycin [mTOR] activation, eukaryotic elongation factor 2 kinase [eEF2K] inhibition). The benefits of developing biomarkers within this model are contrasted with the model used to evaluate conventional antidepressant treatments (Table S2 in Supplement 1). The long-term goal of this model is to validate successful biomarkers of response, where patients can then be stratified a priori on the basis of expected efficacy. Overall, this will contribute to more efficient prospective trials and lead to the identification of enriched biological subgroups. In this figure, ketamine can be used as a prototype: approximately 50% of subjects achieve response within 4 hours, thus permitting the assessment of multiple biomarkers (e.g., functional magnetic resonance imaging, magnetoencephalography, polysomnography, single nucleotide polymorphism) and resulting neural and molecular correlates of outcome (Table 2). The antidepressant effects of ketamine in most patients with treatment-resistant depression seem to fade in 1 to 2 weeks. Thus, this time point also permits the opportunity to assess the molecular and neural correlates of relapse in mood disorders. GSK-3, glycogen synthase kinase 3.

the Val/Val BDNF allele were more likely to have an increased antidepressant response to ketamine than Met carriers (38).

Ketamine: Functional Neuroimaging. Salvatore *et al.* (39) used magnetoencephalography (MEG) to measure response to fearful faces in the rostral ACC in drug-free patients with MDD. As noted earlier, higher pretreatment ACC metabolism predicted antidepressant response to both SD and some antidepressant treatments (40). This MEG study demonstrated that higher pretreatment levels of rostral ACC activity correlated positively with the magnitude of subsequent antidepressant response to ketamine (4 hours later), with healthy individuals displaying lower activity in this region (39).

Similarly, a working memory task (n-back task) was administered to drug-free patients with MDD during MEG recordings. One to three days after scanning, subjects received an infusion of ketamine. Participants with the least engagement of the pregenual anterior cingulate cortex (pgACC) as working memory load increased (pretreatment) showed the greatest symptomatic improvement within 4 hours of ketamine administration. In addition, pretreatment levels of functional connectivity between the pgACC and left amygdala correlated negatively with antidepressant response to ketamine. Taken together, these studies suggest that high pgACC response to emotionally salient stimuli but low pgACC response to increased cognitive demands predicts antidepressant response to ketamine (41). Given that these studies are congruent with the extant literature supporting the role of ACC activity as a promising predictor of antidepressant response, it seems that pretreatment ACC activity might be a putative biomarker of treatment response to antidepressant interventions with different mechanisms of action (42).

Lastly, a proton MRS study was conducted to predict treatment outcome after ketamine administration, given that GABA and Glx levels are reduced in the medial and dorsal anterolateral PFCs of patients with MDD (43). Correlation analyses were conducted to determine whether pretreatment levels of GABA, glutamate, and Glx/glutamate ratio would predict changes in depressive or anxiety symptoms 230 min postketamine administration in the ventromedial PFC and the dorsomedial/dorsal anterolateral PFC. Pretreatment Glx/glutamate ratio in the dorsomedial/dorsal anterolateral PFC was found to negatively correlate with improvement. Because the Glx/glutamate ratio is altered by changes in glutamine, the authors suggested that MDD patients who show the greatest clinical improvement with ketamine might be characterized by larger reductions in glial concentrations (44). This hypothesis is supported by postmortem studies that found prominent reductions in glial pathology in MDD patients (45). Thus, glial cellular deficits might serve as unique targets for novel strategies in the treatment of MDD.

Ketamine: Sleep Architecture. As noted earlier, decreased slow wave sleep is a prominent feature of depression. A recent study of patients with treatment-resistant MDD investigated the acute effects of ketamine on depressive symptoms relative to EEG SWA, individual slow wave parameters, and plasma BDNF (230 min postinfusion). Prior research had shown that SWA and individual slow wave parameters are sensitive markers of cortical synaptic strength, thus serving as surrogate markers of central synaptic plasticity (46,47). In this study, early sleep SWA (during the first non-REM episode) and BDNF levels increased compared with baseline. Those patients who responded to ketamine had changes in BDNF proportional to changes in EEG

Table 2. Controlled Trials of Scopolamine and Ketamine with Biomarkers to Predict Treatment Response

Study	Biomarker Used	Sample/Design	Administration Route	Rating Scale	Clinical Outcome	Biomarker Finding
Scopolamine						
Furey et al. (69)	fMRI BOLD + face-identify and face-emotion WM tasks	MDD ($n = 15$; 11 male, 4 female, mean age 32.9 yrs); outpatients; drug-free for 3 weeks before study drug. Double blind, placebo-controlled design. Inclusion: MADRS ≥ 20 (mean MADRS baseline 30). Comorbidity permitted except for current nicotine use, lifetime history of substance dependence, or substance abuse within 1 yr	IV 4 μ g/kg	MADRS	Antidepressant response at first post drug assessment (3–5 days after infusion) ($p < .001$; mean decrease in MADRS from baseline to study end $63 \pm 29\%$)	Baseline BOLD response in bilateral middle occipital cortex, selectively during the stimulus processing components of the emotion WM task (no significant correlation during the identity task), correlated with treatment response magnitude. Change in BOLD after scopolamine in the same middle occipital areas while performing the same task conditions also correlated with clinical response.
Furey et al. (73)	Self-rating mood scales	MDD ($n = 37$) and BD ($n = 14$); outpatients; drug-free for 3 weeks before study drug. Double blind, placebo-controlled design. Inclusion: MADRS ≥ 20 (mean MADRS baseline 30). Comorbidity permitted except for current nicotine use, lifetime history of substance dependence, or substance abuse within 1 yr	IV 4 μ g/kg	MADRS	Antidepressant response at first post drug assessment (3–5 days after infusion) ($p < .001$; mean decrease in MADRS from baseline to study end $63 \pm 29\%$)	Baseline self-rating mood scales (POMS and VAS) separated responders from NRs in a discriminant function; the discriminant function also classified over 85% of patients as responders/NRs.
Ketamine						
Cornwell et al. (99)	MEG recordings + passive tactile stimulation (baseline and 6–7 hours after ketamine)	MDD ($n = 22$; 15 male, 5 female, mean age 46 yrs); TRD inpatients; drug-free for 2 weeks before study drug. Inclusion: MADRS ≥ 22 (mean MADRS baseline 33). Comorbidity permitted except for drug or alcohol dependence or abuse in the last 3 months	Ketamine .5 mg/kg IV infusion over 40 min	MADRS	MADRS significantly improved at all time points before and at 230 min postinfusion ($p < .001$); responders: ($\geq 50\%$ in MADRS scores at 230 min postinfusion ($n = 9$); NRs ($< 50\%$ improvement) ($n = 11$))	Patients with robust improvements in depressive symptoms 230 min after infusion (responders) exhibited increased cortical excitability. Stimulus-evoked somatosensory cortical responses increased after infusion relative to pretreatment responses in responders, but not in treatment NRs.
Duncan et al. (48)	EEG sleep recordings SWA, EEG activity (between 1 and 4 Hz) day before, day of, and day after ketamine infusion; BDNF plasma (before infusion and	MDD ($n = 30$; 20 male, 10 female, mean age 48 yrs); TRD inpatients; drug-free for 2 weeks before study drug. Inclusion: MADRS ≥ 22 (mean MADRS baseline 32.5). Comorbidity permitted except for drug or alcohol dependence or abuse in the last 3 months	Ketamine .5 mg/kg IV infusion over 40 min	MADRS	Percent change in MADRS improvement at 230 min postinfusion ($-41.46 \pm 6.62\%$; $p < .00001$), at 1 day postinfusion ($-40.38 \pm 6.61\%$; $p < .00001$) and at 2 days postinfusion ($-39.75 \pm 6.54\%$; $p < .00001$). Responders: ($\geq 50\%$ in MADRS scores at 230	Compared with baseline, BDNF levels and early sleep SWA (during the first non-REM episode) increased after ketamine. Changes in BDNF levels were proportional to changes in SWA parameters. This link was present only in patients who responded to

Table 2. Continued

Study	Biomarker Used	Sample/Design	Administration Route	Rating Scale	Clinical Outcome	Biomarker Finding
	at 230 min postinfusion)				min postinfusion ($n = 13$); NRs (<50% improvement) ($n = 17$)	ketamine treatment, suggesting that enhanced synaptic plasticity—as reflected by increased SWA, individual slow wave parameters, and plasma BDNF—is part of the physiological mechanism underlying ketamine's antidepressant effects.
Duncan <i>et al.</i> (49)	EEG sleep recordings (DSR); DSR was calculated as the quotient of normalized SWA in the first to the second NREM episode	MDD ($n = 30$; 20 male, 10 female, mean age 47 yrs); TRD inpatients; drug-free for 2 weeks before study drug. Inclusion: MADRS ≥ 22 (mean MADRS baseline 33). Comorbidity permitted except for drug or alcohol dependence or abuse in the last 3 months	Ketamine .5 mg/kg IV infusion over 40 min	MADRS	Responders: ($\geq 50\%$ in MADRS scores at 230 min postinfusion ($n = 12$); NRs (<50% improvement) ($n = 18$))	A significant positive correlation was observed between baseline DSR and reduced MADRS scores from baseline to Day 1 ($p = .02$). After dividing the patient group on the basis of a threshold $DSR \leq 1$ ($SWA_{NREM1} = SWA_{NREM2}$), MADRS ratings over 7 days showed a significant interaction between patients with low and high DSR scores ($p = .015$). Individuals with low DSR scores showed a greater and more sustained clinical improvement than individuals with higher DSR scores.
Zarate <i>et al.</i> (100)	1) Plasma concentrations of ketamine and its metabolites: NK, DHNK, HNK, and HK; 2) Cytochrome P450 enzymes: CYP2A6, CYP2B6, CYP2C9, CYP2C19, CYP3A4, and CYP3A5	$n = 67$, MDD 45 (male 28), BD 22 (male 6), mean age 46 yrs); TRD inpatients; MDD drug-free for 2 weeks before study drug; BD only on lithium or valproate; MADRS ≥ 22 (mean MADRS baseline MDD = 33, BD = 32). Comorbidity permitted except for drug or alcohol dependence or abuse in the last 3 months	Ketamine .5 mg/kg IV infusion over 40 min	MADRS, BPRS, CADSS	Percent change in MADRS at 230 min postinfusion MDD (-37.3 ± 32.1), BD (-46.5 ± 33.6)	Ketamine, NK, DHNK, four of six HNKs, and HK were present during the first 230 min postinfusion. Patients with BD had higher plasma concentrations of DHNK, (2S,6S;2R,6R)-HNK, (2S,6R;2R,6S)-HNK, and (2S,5S;2R,5R)-HNK than patients with MDD, who in turn had higher concentrations of (2S,6S;2R,6R)-HK. Higher (2S,5S;2R,5R)-HNK concentrations were associated with nonresponse to ketamine in BD patients. DHNK, HNK4c, and HNK4f levels were significantly negatively correlated with psychotic and dissociative symptoms at 40 min. P450 genes were not associated with response.

Table 2. Continued

Study	Biomarker Used	Sample/Design	Administration Route	Rating Scale	Clinical Outcome	Biomarker Finding
Salvadore et al. (44)	1H-MRS (GABA, glutamate, Glx/ glutamate ratio) 1–3 days pretreatment with ketamine; regions: DM/DA-PFC; VM-PFC	MDD ($n = 14$; 9 male, 5 female, mean age 50 yrs); TRD inpatients; drug-free for 2 weeks before study drug. Inclusion: MADRS ≥ 22 (mean MADRS baseline 33.4). Comorbidity permitted except for drug or alcohol dependence or abuse in the last 3 months	Ketamine .5 mg/kg IV infusion over 40 min	MADRS, HAM-A	Pretreatment MADRS score was 33.4 ± 5.9 , and the mean MADRS score 230 min after ketamine was 25.1 ± 11 ; $p = .006$; HAM-A pretreatment score: 20.9 ± 4.1 ; mean HAM-A score 230 min after ketamine: 13.64 ± 4.5 ; $p \leq .001$)	Pretreatment GABA and glutamate concentrations did not correlate with improvement of depressive symptoms in either region of interest. Pretreatment Glx/ glutamate ratio in the DM/DA-PFC was negatively correlated with clinical improvement to ketamine ($p = .04$). Ketamine was associated with a significant improvement in HAM-A scores ($p \leq .001$; pretreatment mean HAM-A: 20.9 ± 4.1 ; mean HAM-A score 230 min after ketamine: 13.64 ± 4.5). Glutamate levels in the ventromedial voxel revealed a significant association with reduction in anxiety symptoms 230 min after ketamine administration ($p = .042$). Twenty-four hours postinfusion, no significant correlation with change in MADRS score was observed.
Salvadore et al. (41)	MEG recordings + WM task 1–3 days pretreatment with ketamine; regions: pgACC, amygdala, and long-range connectivity between these regions	MDD ($n = 14$; 9 male, 5 female, mean age 50 yrs); TRD inpatients; drug-free for 2 weeks before study drug. Inclusion: MADRS ≥ 22 (mean MADRS baseline 33). Comorbidity permitted except for drug or alcohol dependence or abuse in the last 3 months	Ketamine .5 mg/kg IV infusion over 40 min	MADRS, HAM-A	Pretreatment MADRS score was 33.5 ± 4.9 , and the mean MADRS score 230 min after ketamine was 21.0 ± 11.6 ($p = .006$); HAM-A pretreatment score: 23.8 ± 5.7 ; mean HAM-A score 230 min after ketamine: 13.64 ± 5.4 ($p \leq .001$)	Patients who showed the least engagement of the pgACC in response to increased WM load showed the greatest symptomatic improvement within 4 hours of ketamine administration ($r = .82$, $p = .0002$). Pretreatment functional connectivity between the pgACC and the left amygdala was negatively correlated with antidepressant ($r = -.73$, $p = .0021$) and anti-anxiety symptom change.
Machado-Vieira et al. (101)	BDNF plasma levels at baseline, 40, 80, 110, and 230 min postinfusion	MDD ($n = 23$; 14 male, 9 female, mean age 43.9 yrs); TRD inpatients; drug-free for 2 weeks before study drug. Inclusion: MADRS ≥ 22 (mean MADRS baseline 33.5). Comorbidity permitted except for drug or alcohol dependence or abuse in the last 3 months	Ketamine .5 mg/kg IV infusion over 40 min	MADRS	Significant decrease in MADRS scores from baseline to 230 min postinfusion ($p < .001$); Responders: $\geq 50\%$ in MADRS scores at 230 min postinfusion ($n = 11$); NRs: $<50\%$ improvement ($n = 12$)	No significant changes in BDNF levels were observed in subjects after they received ketamine compared with baseline. No association was found between antidepressant response and BDNF levels.

Table 2. Continued

Study	Biomarker Used	Sample/Design	Administration Route	Rating Scale	Clinical Outcome	Biomarker Finding
Phelps <i>et al.</i> (56)	Family history of alcoholism	MDD ($n = 26$; 14 male, 12 female, mean age 43.5 yrs); TRD inpatients; drug-free for 2 weeks before study drug. Inclusion: MADRS ≥ 22 (mean MADRS baseline 32.8). Comorbidity permitted except for drug or alcohol dependence or abuse in the last 3 months; family history collected by FIGS; FHP defined as the presence of at least one affected first-degree relative or at least two second-degree relatives. Individual histories of alcohol abuse or dependence determined by SCID	Ketamine .5 mg/kg IV infusion over 40 min	MADRS, HAM-D, BPRS, CADSS, BDI	Response (MADRS: 50% decrease) 43%; 12 were FHP, 14 were FHN	Subjects with FHP showed significantly greater improvement in MADRS scores compared with subjects without FHP. The FHP group had a significantly higher response rate (67%) than the FHN group (18%; $p = .02$). The FHP group had significantly lower MADRS scores at 120 min ketamine postinfusion. HAM-D and BDI confirmed these results, showing significant differences between the FHP and FHN groups from 80 to 230 min. Significant interactions between group and time were present for both measures (HDRS: $p = .047$; BDI: $p = .03$).
Salvadore <i>et al.</i> (39)	MEG recordings + fearful faces task 1–3 days pretreatment with ketamine; regions: pgACC	MDD ($n = 11$; 7 male, 4 female, mean age 44 yrs); TRD inpatients; drug-free for 2 weeks before study drug. Inclusion: MADRS ≥ 22 (mean MADRS baseline 32). Comorbidity permitted except for drug or alcohol dependence or abuse in the last 3 months; 11 healthy control subjects	Ketamine .5 mg/kg IV infusion over 40 min	MADRS, HAM-A	Pretreatment MADRS score was 31.9 ± 3.3 , and the mean MADRS score 230 min after ketamine was 20.4 ± 1.2 ($p = .005$); HAM-A pretreatment score: 23.4 ± 6.5 ; mean HAM-A score 230 min after ketamine: 14.3 ± 7.8 ($p \leq .01$)	Patients with MDD compared with healthy control subjects showed robust increases in pretreatment ACC activity; this increase was positively correlated with subsequent antidepressant response to ketamine ($p < .05$). Exploratory analyses showed that pretreatment right amygdala activity was negatively correlated with change in depressive symptoms ($p < .05$).

BDI, Beck Depression Inventory; BOLD, blood oxygen level–dependent; BPRS, Brief Psychiatric Rating Scale; CADSS, Clinician Administered Dissociative States Scale; CES-D, Center for Epidemiological Studies Depression Scale; DHNK, dehydronorketamine; DM/DA-PFC, dorsomedial/dorsal anterolateral prefrontal cortex; FHN, no family history of alcohol dependence; FHP, positive family history of alcohol dependence; FIGS, Family Interview for Genetic Studies; HAM-A, Hamilton Anxiety Rating Scale; HDRS/HAM-D, Hamilton Depression Rating Scale; HK, hydroxyketamine; HNK, hydroxynorketamine; MADRS, Montgomery-Åsberg Depression Rating Scale; MEG, magnetoencephalography; NK, norketamine; pgACC, pregenual anterior cingulate cortex; POMS, Profiles of Mood State; SCID, Structured Clinical Interview for DSM-IV; TRD, treatment-resistant depression; VM-PFC, ventromedial prefrontal cortex; WM, working memory; 1H-MRS, proton magnetic resonance spectroscopy; other abbreviations as in Table 1.

parameters (48), although the study was limited by the lack of a placebo control.

Baseline DSRs have also been examined as putative predictors of rapid antidepressant response to ketamine. DSR is defined by the ratio of SWA between the first two non-REM sleep episodes and is lower in depressed patients than healthy control subjects. A significant positive correlation was found between baseline DSR and reduced Montgomery-Åsberg Depression Rating Scale scores from baseline to Day 1, postketamine infusion (49). Low baseline DSR scores also predicted an improved response the following week, suggesting that Day 1 ratings preceded a more sustained treatment response. Interestingly, these effects are similar to those seen after antidepressant treatment in general, which normalizes slow wave sleep and DSR (50,51), suggesting that DSR might reflect a biomarker of response to ketamine (49).

Ketamine: Clinical Predictors. Although clinical predictors of antidepressant response might not represent biological markers directly, they facilitate the identification of patient subgroups that differentially respond to treatment, which can subsequently guide additional research aimed at identifying viable biological markers.

Data from the STAR*D (Sequenced Treatment Alternatives to Relieve Depression) study showed that 46% of participants had a positive family history of substance abuse (52). Recent research has implicated the glutamatergic system in the pathogenesis of alcohol dependence (53). Ethanol inhibits the functioning of *N*-methyl-D-aspartate subunit receptors (54), and healthy individuals with a positive family history of alcohol dependence (FHP) show a diminished response to the psychotomimetic effects of ketamine compared with those without a positive family history (FHN) (55).

Phelps *et al.* (56) showed that MDD patients with FHP had a higher response rate (67%) to ketamine (230 minutes postinfusion) than FHN patients (18%). Moreover, the FHP group had fewer dysphoric symptoms than the FHN group. A recent post hoc analysis of BD-I or -II subjects pooled from two randomized and placebo-controlled studies (57,58) showed that, compared with those with FHN, subjects with FHP had attenuated psychotomimetic and dissociative scores (but not dysphoria) in response to ketamine and had greater improvement on Montgomery-Åsberg Depression Rating Scale scores up to 3 days postinfusion.

Overall, familial and epigenetic mechanisms might explain the relationship between FHP and ketamine response. Likewise, a genetic variation in the NR2A subunit might be involved in susceptibility to alcohol dependence (59), suggesting a neurobiological subtype that could modulate ketamine response. Future prospective studies will explore these exciting associations.

Scopolamine

The muscarinic receptors of the cholinergic neurotransmitter system were implicated in mood disorders as early as the 1970s (60) when researchers demonstrated that muscarinic receptors were hypersensitive in MDD and BD but were only recently shown to be a viable antidepressant target (61). Randomized, controlled clinical trials found that the antimuscarinic agent scopolamine had rapid antidepressant effects in MDD and BD patients (61,62). The rapid clinical improvement observed offers the opportunity to efficiently evaluate potential biomarkers of response, as with ketamine. Moreover, the identification of biomarkers that predict response to scopolamine (Table 2) might provide important insights with regard to underlying mechanisms of antidepressant action and contributes to the overall development of more rapid and effective therapeutic options.

Scopolamine: Genetics. Several genes associated with the cholinergic system have been implicated in mood disorders. The cholinergic muscarinic-2 receptor gene (*CHRM2*) has been linked to risk of developing depression (63), and the distribution volume of this receptor is reduced in BD (64). Recently, Cannon *et al.* (65) evaluated the influence of six SNPs for *CHRM2* on M2-receptor binding and found an allelic effect on distribution volume of the M2 receptor in the pregenual and subgenual areas of the ACC in patients with BD versus healthy control subjects. Moreover, genotype was related to severity of illness (65). These studies identified genetic cholinergic markers in mood disorders that are ideal candidates to evaluate as potential predictors of treatment response to scopolamine.

Scopolamine: Functional Neuroimaging. The cholinergic system is also centrally implicated in cognition (66), and the existing pharmacology literature on cholinergic function during cognitive tasks highlights the potential for cognitive studies in patients with cholinergic dysfunction to be informative. Cholinergic activity has been hypothesized to act via stimulus processing mechanisms [reviewed in Furey (67)], and thus cholinergic function/dysfunction likely influences cognition by modifying neural representations of stimuli (67). The best-characterized cognitive feature in mood disorders is described as a negative stimulus processing bias, where negative emotional stimuli are processed preferentially over positive emotional stimuli (67,68). The excessive cholinergic activity in mood disorders might underlie this negative processing bias (67), and thus assessment of the negative processing bias might provide a potential biological marker of treatment response to scopolamine.

A working memory task was used to determine whether neural activity in response to emotional information during visual stimulus processing could predict subsequent clinical response to scopolamine (69). Participants viewed emotional faces, attending to either facial identity or facial emotion during working memory as neural response was assessed on the basis of magnetic resonance imaging blood oxygen level-dependent (BOLD) signal. Pretreatment levels of neural response in the visual processing area of middle occipital cortex (MOC) when patients attended to facial emotion correlated with subsequent treatment response. Critically, no correlation emerged when patients were processing the same stimuli while attending to facial identity, emphasizing the selectivity of this effect to emotion processing (69).

A selective attention task with emotional faces (happy and sad) was also used to determine whether pretreatment BOLD response could predict treatment outcome to scopolamine in patients with MDD. Here, patients were presented with two pictures comprising superimposed images of faces (happy or sad) and houses and were instructed to selectively attend to either the face or house stimulus component and perform a matching task. The magnitude of treatment response after scopolamine was correlated with difference in BOLD response magnitude to emotional faces (happy vs. sad) when attending to faces (explicit emotional processing) and when attending to houses (implicit emotional processing). Significant correlations were observed during implicit processing in the MOC and ACC (70). No correlation was observed with the explicit emotional processing condition, again highlighting the selectivity of this effect. Taken together, these functional magnetic resonance imaging findings might indicate that the level of underlying cholinergic dysfunction in MDD is expressed in baseline levels of neural response to emotional information and that this underlying level of

cholinergic dysfunction represents a biomarker for subsequent response to scopolamine.

Scopolamine: Sleep Architecture. As described above, patterns of sleep dysfunction in mood disorders include increased REM density and reduced REM latency, both of which could be explained by increased muscarinic sensitivity (71). Although these features of sleep architecture have yet to be evaluated as potential biomarkers for response to scopolamine, the implication of cholinergic dysfunction in these basic sleep features of mood disorders renders them targets of high interest.

Scopolamine: Clinical Predictors. Identifying clinical subtypes that respond differentially to antidepressant treatments has been a focus in psychiatric research. Diagnostic subtypes of primary mood disorders (MDD vs. BD) show similar magnitudes of treatment response to scopolamine, as do patients with and without a comorbid anxiety disorder (61). A differential response on the basis of gender is reported (72), with women showing greater improvement after scopolamine than men.

In an effort to identify subgroups that might preferentially respond to scopolamine, baseline self-rating scales (Profile of Mood States and Visual Analogue Scale) were submitted to discriminant function analysis. This analysis separated treatment responders from nonresponders for both MDD and BD subgroups, and the discriminant function accurately classified over 85% of participants. These findings indicate that the relative pattern of scores on these specific mood scales might reflect features of patient subgroups that preferentially respond to scopolamine and suggest that self-rating mood scales have the potential to predict treatment response to scopolamine in individual patients (73).

Conclusions

This article provides an overview of biomarkers associated with treatments that produce rapid antidepressant effects. These findings offer tremendous hope that eventually we will be able to successfully apply these techniques to clinical populations.

The fields of psychiatry and neuroscience have made sufficient progress that we now can begin to ask questions with regard to what has been learned and how this knowledge can guide further research. One important question is what biomarkers of treatment response can teach us about specific therapeutic agents. Relatedly, will their predictive ability generalize across antidepressant options? For instance, ACC function was identified as a biomarker for each of the antidepressant methods discussed in this review and has been identified in association with other treatments as well (42). Although the answer to this question remains empirical, the growing body of literature would argue for ongoing consideration of this particular brain region as a generalized biomarker of antidepressant response. In contrast, we do not have sufficient data to address some important questions, such as the differential benefit of biomarkers on the basis of diagnostic features; we anticipate that this will be possible in the future.

Treatment-specific biomarkers might also be expected. Because patient response to treatment is quite variable, and because this variability might reflect differences in underlying pathophysiology, some biomarkers might reflect the likelihood of response to specific agents. For example, carriers of the COMT Val/Val genotype showed a reduced antidepressant response to SD relative to other genotypes, whereas the BDNF Val/Val genotype was associated with larger responses to ketamine. In addition, the MOC might prove to be specific to antimuscarinic treatments, because this finding might be related specifically to cholinergic dysfunction in the processing

of emotional stimuli. However, this would need to be tested empirically with other agents (eg, ketamine) in order to determine whether the biomarker effect associated with MOC is specific to scopolamine, or also occurs with other rapid-acting antidepressant agents. Such biomarkers might prove to be extremely useful in clinical decisions related to the application of specific agents.

Finally, these findings might promote various targets as viable markers of treatment response. The biomarkers identified to date encompass aspects of known underlying dysfunction in mood disorders. The ACC and the amygdala show functional and structural abnormalities in mood disorders. Genes associated with illness vulnerability and features of SD that characterize mood disorders have been identified as biomarkers of treatment response. Thus, focusing on targets that encompass known aspects of underlying neurobiological dysfunction has proven to be highly successful, and this knowledge can continue to guide research.

As research efforts to improve treatments for patients with mood disorders move forward, we should consider broader directions for the future. For example, the field might benefit from the testing of biomarkers within the context of multiple treatments to determine whether individual markers will be generalizable or treatment-specific. As Figure 1 and Table S2 in Supplement 1 highlight, the biomarkers with the largest effect sizes could then be incorporated into larger prospective studies. This would lead to more efficient trial designs, where patients could be randomized by “efficacy stratifying biomarkers.” Furthermore, promising biomarkers might lead to new therapeutics in a fashion similar to the field of cardiovascular drug delivery, where lipid biomarkers play a role in both phenotyping disease processes and developing parallel therapeutic strategies (74). Moving in such directions would ultimately facilitate the development of personalized treatment, increasing the probability of success. Although significant challenges to applying this paradigm in clinical settings and altering current practices lie ahead, this is a goal worth pursuing to promote better patient care.

Funding for this work was supported by the Intramural Research Program at the National Institute of Mental Health, National Institutes of Health, and Department of Health and Human Services; a (Brain and Behavior Research Foundation) NARSAD Independent Investigator award to CAZ; and a Brain and Behavior Mood Disorders Research award to CAZ.

A patent application for the use of ketamine in depression has been submitted, listing CAZ among the inventors; he has assigned his rights on the patent to the United States government but will share a percentage of any royalties that might be received by the government. A patent application for the use of scopolamine in depression has been submitted, listing MLF among the inventors; she has assigned her rights on the patent to the US government but will share a percentage of any royalties that might be received by the government. DCM reports no biomedical financial interests or potential conflicts of interest.

We gratefully acknowledge the support of the Intramural Research Program at the National Institute of Mental Health, National Institutes of Health, and Department of Health and Human Services. Ioline Henter provided excellent editorial assistance.

Supplementary material cited in this article is available online.

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