The Comparison of Effectiveness of Various Potential Predictors of Response to Treatment With SSRIs in Patients With Depressive Disorder

Martin Bares, MD, PhD, Tomas Novak, MD, PhD, Martin Brunovsky, MD, PhD, Miloslav Kopecek, MD, PhD, and Cyril Höschl, MD, DrSc

Abstract: The substantial non-response rate in depressive patients indicates a continuing need to identify predictors of treatment outcome. The aim of this 6-week, open-label study was (1) to compare the efficacy of a priori defined predictors: ≥20% reduction in MADRS score at week 1, ≥20% reduction in MADRS score at week 2 (RM ≥ 20% W2), decrease of cordance (RC), and increase of serum and plasma level of brain-derived neurotrophic factor at week 1; and (2) to assess whether their combination yields higher efficacy in the prediction of response to selective serotonin re-uptake inhibitors (SSRIs) than when used singly. Twenty-one patients (55%) achieved a response to SSRIs. The RM ≥20% W2 (areas under curve—AUC = 0.83) showed better predictive efficacy compared to all other predictors with the exception of RC. The identified combined model (RM ≥ 20% W2 + RC), which predicted response with an 84% accuracy (AUC = 0.92), may be a useful tool in the prediction of response to SSRIs.

Key Words: Depressive disorder, treatment outcome, predictors, predictive model, selective serotonin reuptake inhibitors

(*J Nerv Ment Dis* 2017;205: 618–626)

Major depressive disorder (MDD) is a common condition that often takes a chronic course and fails to respond to treatment. Remission is achieved in only about one-third of depressed patients in response to a first antidepressant treatment (Trivedi et al., 2006). Furthermore, many residual symptoms persist at the time of response and in remission (Madhoo and Levine, 2015).

Many clinical, neurophysiological, neuroimaging, and other factors have been correlated with the outcome of antidepressant treatment, but very few have reached the level of usefulness as clinical predictors (Breitenstein et al., 2014; Labermaier et al., 2013).

Currently, the most convincing clinical predictor of response to antidepressant treatment is an early change of depressive symptoms, usually defined as a ≥20% score reduction on the Hamilton Depression Rating Scale (HAM-D) (Hamilton, 1960) or Montgomery and Åsberg Depression Rating Scale (MADRS) (Montgomery and Åsberg, 1979) at week 2 of treatment, a finding that has been repeatedly evaluated for various types of antidepressants (Kudlow et al., 2014). Furthermore, some studies have also demonstrated predictive efficacy for the change of depressive symptoms after the first week of treatment (Bares et al., 2012b; Calker et al., 2009).

Several QEEG indicators (*e.g.*, alpha power, alpha asymmetry, frontal theta activity, prefrontal theta cordance, Antidepressant Treatment Response Index, etc.) have been identified as potentially useful markers in the prediction of response to antidepressants in MDD (Bares et al., 2015b; Iosifescu, 2011; Olbrich and Arns, 2013; Olbrich et al., 2015).

Cordance is a QEEG method combining information from the absolute and relative power of EEG spectra (Leuchter et al., 1994a) and has a stronger correlation with cerebral perfusion than standard EEG spectral analysis (Cook et al., 1998; Leuchter et al., 1994b).

It has been hypothesized that the findings obtained with prefrontal theta cordance could be interpreted in terms of an abnormal pattern of metabolism or perfusion in the prefrontal cortex and anterior cingulate areas that are involved in the pathogenesis of MDD (Palazidou, 2012). Decrease of prefrontal theta cordance, calculated at the frontal electrodes after 1 week of treatment, consistently predicts clinical response to various antidepressants, as was demonstrated in several studies of patients with depression performed by two independent groups (Bares et al., 2008, 2010; Cook et al., 2002, 2005). Furthermore, the predictive ability of prefrontal cordance decrease has also been demonstrated for the response to low-frequency repetitive transcranial magnetic stimulation and for treatment outcome in bipolar depression (Bares et al., 2012a, 2015a).

Brain-derived neurotrophic factor (BDNF) is a neurotrophin related to neuronal survival, synaptic signaling, and synaptic consolidation. The neurotrophin hypothesis of depression postulates that depression results from stress-induced decreases in BDNF expression and that antidepressants are efficacious because they increase BDNF expression (Duman and Monteggia, 2006; Molendijk et al., 2011).

Some, but not all, studies have shown that the increase of serum/plasma level of BDNF (s/pBDNF) after 1 or 2 weeks of antidepressant intervention may predict the response to treatment especially in conjunction with early assessment of change of depressive symptoms (Brunoni et al., 2008; Dreimuller et al., 2012; Mikoteit et al., 2014; Tadic et al., 2011).

Despite the many encouraging outcomes in the efforts to obtain individual predictors of treatment outcome, it is likely that multiple factors combined in predictive scores or algorithms will be necessary to achieve a clinically meaningful prediction (Baskaran et al., 2012; Leuchter et al., 2010).

Taking account of these findings, the present study aimed (1) to compare the efficacy of early change in depressive symptoms (changes in MADRS at week 1 and week 2) and changes of prefrontal theta cordance and s/pBDNF at week 1 in the prediction of response to treatment with selective serotonin re-uptake inhibitors (SSRIs); (2) to compare the efficacy of a priori defined predictors: ≥20% reduction in MADRS score at week 1 (RM ≥ 20% W1), ≥20% reduction in MADRS score at week 2 (RM ≥ 20% W2), decrease of cordance value (RC), and increase of s/pBDNF at week 1 (IsBDNF, IpBDNF); and (3) to assess whether the possible combinations of these markers yield

National Institute of Mental Health Czech Republic, Klecany; and Department of Psychiatry and Medical Psychology of Third Medical Faculty, Charles University, Prague, Czech Republic.

This study was supported by the grants of the Ministry of Health of Czech Republic No. NT 14287, AZV CR 15-29900A, MH CZ-DRO (NIMH-CZ, 00023752) and by the project "National Institute of Mental Health (NIMH-CZ)," number ED2.1.00/03.0078, and the European Regional Development Fund.

Send reprint requests to Martin Bares, MD, PhD, National Institute of Mental Health Czech Republic, Topolova 748, Klecany 250 63, Czech Republic. E-mail: martin.bares@nudz.cz.

ISSN: 0022-3018/17/20508–0618
DOI: 10.1097/NMD.0000000000000574

more robust predictive power than a single predictor alone, *i.e.*, to postulate a combined predictive model based on clinical, neurophysiological, and neurotrophic variables.

METHODS

The Prague Psychiatric Center/National Institute of Mental Health Czech Republic (PPC/NUDZ) Institutional Review Board reviewed and approved the 6-week open-label study. Written informed consent to participate in the research was obtained from all subjects. The study was carried out in accordance with the latest version of the Declaration of Helsinki (Tokyo, 2004) and was registered at Current Controlled Trials, Ltd.—ISRCTN25983493 (www.controlled-trials.com).

Subjects

The participants in the study were hospitalized in the Open Department of PPC/NUDZ with major depressive disorder (recurrent or single episode) without psychotic symptoms according to *DSM IV* criteria (American Psychiatric Association, 1994), confirmed using The Mini-International Neuropsychiatric Interview—M.I.N.I., Czech version 5.0.0 (Sheehan et al., 1998). Patients fulfilled at least Stage I criteria for resistant depression (≥1 adequate antidepressant treatment in current episode) according to Thase and Rush (1997). The last treatment of patients before enrollment is displayed in Table 1. Only subjects (18–65 years old) who reached MADRS score ≥25 points and Clinical Global Impression (CGI) (Guy, 1976) score ≥4 points were included. We excluded patients with comorbidity on axis I and II according to *DSM IV* in the 6 months before enrollment to the study, severe and unstable somatic disorders (cardiovascular disease, neoplasms, endocrinology disorders, etc.), and neurological disorders (epilepsy, head trauma with loss of consciousness). Additional exclusion criteria associated with treatment comprised contraindications of treatment with SSRIs, unsuccessful treatment trial with more than one SSRI during the index episode, and electroconvulsive treatment within 3 months before enrollment to the study. The patient's selection was based on a psychiatric examination by one of the investigators (M.B., T.N., M.K.).

We assessed 50 patients for eligibility. Ten subjects did not fulfill inclusion criteria or consent to participation in the study. Forty patients started study treatment. Eleven patients dropped out. One patient was excluded due to alcohol intoxication in the first week of the study. Three patients refused to continue in the study. Seven patients did not finish the study due to worsening of clinical status (one dropped out in the first week). Altogether, 29 patients finished the study and 38 patients were suitable for the planned intent-to-treat analysis (ITT).

Study Treatment

After the signing of informed consent, patients were treated with SSRIs (fluoxetine, fluvoxamine, sertraline, citalopram, escitalopram, paroxetine) according to the clinical judgment of the attending psychiatrists, taking into account the history of previous treatments and clinical status. The antidepressants that had been ineffective in the treatment of the current episode were excluded, but new treatment with another SSRI was allowed because efficacy of a within-class change of SSRIs has been demonstrated (Papakostas et al., 2008). A short wash-out

TABLE 1. Baseline, Clinical, and Treatment Characteristics of Responders and Non-Responders in the Study

	Non-Responders (n = 17)	Responders (n = 21)	Statistical Significance Level
Age	48.0 (39.8–53.3)	48.4 (37.3–52.8)	0.60[c]
Sex (F/M)	14:3	15:6	0.48[d]
No. previous depressive episodes	2 (1–3)	3 (1–5)	0.49[c]
No. previous adequate treatments of current episode	1 (1–2)	1 (1–1.8)	0.24[c]
Last treatment before the enrollment	AD + SGA-4, CAD-7, MASSA-2, NaSSA-1, SARI-1, SNRI-2	AD + SGA-1, AD + TS-2, CAD-8, MASSA-1, NDRI-1, SARI-1, SNRI-2, SSRI-4, TCA-1	NA
Treatment in the study	CIT-1, ESC-3, FLX-2, FLU-2, PAR-2, SER-7	ESC-9, FLX-2, PAR-2, SER-8	NA
FLX equivalent dose[a] W1, W2, final (mg/d)	40.6 (23.5–40.6) 40.6 (40.0–44.4) 56.0 (44.4–60.9)	40.6 (22.0–44.0) 44.4 (40.6–44.4) 44.4 (44.4–60.9)	0.60[c] 0.31[c] 0.29[c]
Subjects taking bzd B[b]	7	3	0.08[d]
Subjects taking hypnotics W1, W2	5 6	8 8	0.73[d] 1.00[d]
Subjects taking hydroxyzine W1, W2	6 6	7 7	1.00[d] 1.00[d]
Smokers	6	13	0.19[d]

Data are presented as median (interquartile range) or number of cases.

[a]According to Hayasaka et al. (2015).

[b]Unchanged dose during the study.

[c]Mann–Whitney *U* test.

[d]Fisher's exact test.

B indicates baseline; bzd, benzodiazepines; CAD, combination of antidepressants; CIT, citalopram; ESC, escitalopram; F, females; FLU, fluvoxamine; FLX, fluoxetine; M, males; MASSA, melatonin agonist and selective serotonin antagonists; NA, not applicable; NaSSA, noradrenergic and specific serotoninergic antidepressants; NDRI, norepinephrine and dopamine reuptake inhibitors; PAR, paroxetine; SARI, serotonin antagonist and reuptake inhibitors; SER, sertraline; SGA, second-generation antipsychotics; SNRI, serotonin and norepinephrine reuptake inhibitors; SSRI, selective serotonin reuptake inhibitors; TCA, tricyclics; TS, thymostabilizers; W1, week 1; W2, week 2.

period (1–4 days) was applied before starting a new antidepressant treatment that was applied in flexible doses within the range cited in the Summary of Product Characteristics (www.sukl.cz-Czech State Institute for Drug Control). The duration of treatment was 6 weeks. The use of other psychotropic drugs (mood stabilizers, second-generation antipsychotics, etc.) and formal psychotherapy was not allowed. Patients who were taking stable doses of anxiolytic and hypnotic drugs were permitted to continue them during the study. The use of anxiolytics (hydroxyzine) and hypnotics (zolpidem) by subjects was allowed in cases of severe anxiety or insomnia.

Clinical Assessment

The primary efficacy measure was MADRS score. The patients were assessed with MADRS, Quick Inventory of Depressive Symptoms–Self-Report (QIDS-SR) (Rush et al., 2003) and CGI at baseline, weeks 1, 2, and 4, and at the end of study. QIDS-SR is a self-rated scale that includes *DSM-IV* criterion items required to diagnose a major depressive episode. Ratings were performed by highly experienced clinical psychiatrists (M.B., T.N., M.K.), who were trained to the criterion of intraclass correlation of at least 0.80 for each clinician, before conducting the ratings (Kobak et al., 1996). The raters were blind to EEG and BDNF results. Response to treatment was defined as a reduction of the MADRS score ≥50%.

Prefrontal Theta Cordance Calculations and EEG Techniques

The EEG was recorded for 10 minutes at baseline and after 1 week of treatment. Data were captured during eyes-closed resting state using a Brainscope differential amplifier (unimedis Ltd., Czech Republic) with 21 electrodes placed according to the international 10/20 system and referenced to the electrode situated between electrodes Fz and Cz in the midline (FCz). The data sampling rate was 250 Hz and the acquired signals were filtered with a band-pass filter of 0.15 to 70 Hz. The EEG reviewer was blind to patient's and treatment outcome. Artifacts were eliminated using the artifact detection and removal function of the NeuroGuide Deluxe software v. 2.3.7 (© 2002–2007 Applied Neuroscience, Inc.). In addition, EEG epochs were visually inspected to eliminate residual artifacts or a decrease in alertness. Split-half reliability tests and test-retest reliability tests were conducted on the edited EEG segments, and only epochs with >90% reliability were then subjected to processing after digital filtering of 0.5 to 30 Hz. In each EEG, 30 to 60 seconds of artifact-free data were selected to be processed.

Fast Fourier transformation was used to calculate absolute and relative power in each of four frequency bands (Nuwer et al., 1999): delta (1–4 Hz), theta (4–8 Hz), alpha (8–12 Hz), and beta (12–20 Hz). QEEG cordance was calculated by our EEG software (WaveFinder v.1.70; unimedis, Prague) using the algorithm which has been previously described elsewhere in greater detail (Leuchter et al., 1994a). In brief, this algorithm normalizes power across both electrode sites and frequency bands in three consecutive steps: First, absolute power values are reattributed to each individual electrode by averaging power from all bipolar electrode pairs sharing that electrode. In the second step, the maximum absolute and relative power values (AMAXf, RMAXf) in each frequency band (f) are determined to obtain normalized absolute (ANORM (s,f)) and normalized relative (RNORM (s,f)) power values (absolute and relative power values at each electrode site (s) and for each frequency band (f) are divided by AMAXf and RMAXf, respectively). In the third step, the cordance values at each electrode site (s) for each frequency band (f) are calculated by summing the ANORM and RNORM values, after half-maximal values (0.5 on the normalized scale) are subtracted: CORDANCE (s,f) = (ANORM (s,f) − 0.5) + (RNORM (s,f) − 0.5). Average cordance values from three frontal electrodes (Fp1, Fp2, and Fz) in theta frequency band (4–8 Hz) were subjected to statistical analysis.

Measurement of s/pBDNF-Laboratory Analysis

Blood (fasting condition) was collected from the antecubital vein (between 07.30 and 8.00 AM), at baseline and day 7, into separator tubes (BD Vacutainer Lithium heparin for plasma and BD Vacutainer SST II Advance for serum samples; BD Diagnostics, Franklin Lakes, NJ). After 30 minutes of clotting time, whole blood was centrifuged at 1,000×*g* for 15 minutes. Plasma samples were re-centrifuged at 10,000×*g* for 15 min at 4 °C. Samples were stored in polypropylene Eppendorf tubes at −80 °C before assaying BDNF concentration with an enzyme-linked immunosorbent assay kit (catalog no. BD00; R&D Systems, Wiesbaden, Germany) according to the manufacturer's recommendations.

All samples were thawed only once. Assays were performed in duplicate; 50 µl of sample (4× diluted plasma or 50× diluted serum in RD6P diluent, or BDNF standard) was used for each well together with 100 µl of Assay Diluent RD1S. After 2 hours of incubation at room temperature, 100 µl of BDNF conjugate was added to each well and incubation continued for 1 hour at RT. Wells were then washed 3× with 0.3 ml of wash buffer and 200 µl of substrate solution was pipetted to each well at controlled intervals (15 seconds). Color reaction proceeded while protected from light until it reached desired intensity (20–30 minutes), after which it was stopped by addition of 50 µl of stop solution to each well. Optical density of each well was measured with a microplate reader (Thermo Multiscan EX) set to 450 nm, with wavelength correction set to 620 nm. BDNF concentrations were calculated from a calibration curve (at concentration range 60–4000 pg/ml) by fitting with a four-parameter logistic regression. The serum probes of each patient were analyzed on one ELISA plate and plasma probes on another. Intra-assay coefficients of variation in our sample for serum and plasma levels were 3.0% and 4.1%. Patients with sBDNF and pBDNF changes from baseline to day 7 ≤ +3.0% or +4.1% were classified as having no sBDNF or pBDNF increase, respectively. Relevant to this part of the study protocol, we observed smoking habits and risk of binge drinking as potential factors influencing BDNF level (Bus et al., 2011).

Statistical Methods and Data Analyses

The primary outcome variable was the response to treatment, defined as a reduction of the MADRS score ≥50%. The primary efficacy analyses were based on the intent-to-treat (ITT) data set, which was defined as the subset of patients who completed baseline and at least two post-baseline visits (week 2) with last observation carried forward (LOCF) method.

Demographic, clinical, and treatment characteristics including fluoxetine equivalent doses (Hayasaka et al., 2015) at weeks 1 and 2 and the end of study were analyzed using unpaired Mann–Whitney *U* test (M-W-U) and Fisher's exact test. The predictive efficacy of changes of MADRS score at weeks 1 and 2 and s/pBDNF and prefrontal cordance value at week 1 were compared by areas under curve (AUC) values with exact binomial 95% confidence interval (CI) of the receiver operating characteristics (ROC). ROC analysis was also applied to find an optimal threshold for response prediction. The pairwise comparison of AUC values was carried out by using z-statistic.

The primary analysis for each a priori defined predictor (RM ≥ 20% W1, RM ≥ 20% W2, RC, IsBDNF, and IpBDNF) was conducted to detect a difference between the number of responders and nonresponders with the presence of predictor (Fisher's exact test).

The positive and negative predictive values (PPV, NPV), number needed to diagnose (NND), accuracy, and AUC values of ROC analyses of potential predictive factors or combination models were calculated.

TABLE 2. Results of the Clinical Rating Scales in the Study

	Non-Responders (n = 17)	Responders (n = 21)	Statistical Significance[a]
MADRS B	28 (26–30)	28 (25–29)	0.54
MADRS W1	26 (23–27.3)	24 (21.3–25)	0.14
MADRS score reduction W1 (%)	10 (6–13.5)	14 (7.5–24)	0.04
MADRS W2	23 (21–26)	19 (15.8–20.3)	<0.001
MADRS score reduction W2 (%)	14 (4–22)	34 (26–39.3)	<0.001
MADRS W4	23 (18–26.3)	15 (8–18)	<0.001
MADRS final	24 (19–26.3)	12 (7.8–12.3)	<0.001
QIDS-SR B	19 (15.5–21.3)	17 (14–20.3)	0.31
QIDS-SR W1	18 (14.8–19)	13 (9.3–17.3)	0.04
QIDS-SR W2	16 (13.8–19.5)	10 (7.8–13.3)	<0.001
CGI B	4 (4–5)	4 (4–5)	0.71
CGI W1	4 (4–5)	4 (4–4)	0.18
CGI W2	4 (4–4.3)	4 (3–4)	<0.01

Data are presented as median (interquartile range).

[a]Mann–Whitney U test.

B indicates baseline; CGI, Clinical Global Impression; MADRS, Montgomery and Åsberg Depression Rating Scale; QIDS-SR, Quick Inventory of Depressive Symptoms–Self-Report; W1, week 1; W2, week 2.

All a priori predictors were considered as components of a logistic regression model that examined the relative contribution of each variable to the accuracy of prediction. The identified model was adjusted for baseline confounders (sex, age, duration of index episode, number of previous episodes, MADRS score, and use of benzodiazepines) (Furukawa et al., 2015). Finally, we compared the predictive ability of the combined model, identified by logistic regression, to the individual predictors.

All tests were two-sided and an exact significance level of 0.05 was adopted. The analyses were performed using Statistica, version 9.1 (StatSoft, Inc. (2010)) and MedCalc, version 14.10.2 (MedCalc Software, Ostend, Belgium).

We planned to enroll 40 patients. A power analysis indicated that this sample size would be sufficient to detect an effect size (w) of 0.5 (Fischer exact test) with 81% power at a 5% level of statistical significance with compensation for patients who failed to qualify for ITT analysis. A comparable effect size was detected post hoc in the previous studies evaluating the efficacy of analyzed factors (predictors) (Bares et al., 2010; Dreimuller et al., 2012; Szegedi et al., 2009; Tadic et al., 2011).

RESULTS

Baseline Characteristics, Clinical Measures, Prefrontal Theta Cordance, s/pBDNF Levels, and Treatment

The sample comprised 38 inpatients (28 females, 10 males, mean age of whole sample 45. 5 ± 10.8 years). The overall response rate was 55% (n = 21).

Responders and non-responders did not differ in baseline demographic characteristics, including the use of concomitant treatment. For treatment and numerical details, see Table 1. Significant differences in scores of rating scales were found from week 2 through to endpoint, with the exception of QIDS-SR where the difference was detected already at week 1 (p = 0.04). Differences in the percentage reduction of MADRS score at weeks 1 and 2 were found at both time periods. For

TABLE 3. Prefrontal Theta Cordance, sBDNF, and pBDNF Values in the Study

	Non-Responders (n = 17)	Responders (n = 21)	Statistical Significance[a]
Prefrontal cordance value B	−0.03 (−0.52 to 0.29)	0.22 (−0.36 to 0.38)	0.32
Prefrontal cordance value W1	0.05 (−0.25 to 0.35)	0.15 (−0.42 to 0.27)	0.77
Change of prefrontal cordance values W1	0.16 (−0.02 to 0.27)	−0.15 (−0.42 to −0.003)	0.02
sBDNF B	22.40 (19.72 to 25.48)	19.39 (15.29 to 24.10)	0.47
sBDNF W1	18.46 (16.32 to 23.55)	19.14 (16.86 to 22.50)	0.82
Change of sBDNF W1	−1.85 (−6.08 to 0.86)	−1.00 (−6.14 to 1.92)	0.50
pBDNF B	2.48 (1.44 to 3.17)	2.45 (1.63 to 3.26)	0.79
pBDNF W1	2.28 (1.71 to 3.25)	2.42 (1.92 to 3.47)	0.64
Change of pBDNF W1	−0.08 (−0.62 to 1.06)	0.31 (−0.78 to 1.11)	0.91

Data are presented as median (interquartile range).

[a]Mann–Whitney U test.

B indicates baseline; pBDNF, plasma brain-derived neurotrophic factor level (ng/ml); sBDNF, serum brain-derived neurotrophic factor level (ng/ml); W1, week 1.

TABLE 4. Area Under Curve (AUC) Values of MADRS Score Change at Week 1 and 2, and Changes of Cordance and s/pBDNF at Week 1 for Prediction of Response

Parameter	AUC (95% CI)	Optimal Cut-off for Prediction	PPV (95% CI)	NPV (95% CI)
Change of MADRS (%) W1	0.70 (0.52–0.83)	>13%	0.78 (0.52–0.94)	0.65 (0.41–0.85)
Change of MADRS (%) W2	0.90 (0.76–0.97)	>19%	0.80 (0.59–0.93)	0.92 (0.62–1.00)
Change of cordance W1	0.73 (0.56–0.86)	≤−0.01	0.80 (0.56–0.94)	0.72 (0.47–0.90)
Change of sBDNF W1	0.56 (0.39–0.72)	>1.5	0.78 (0.40–0.97)	0.52 (0.33–0.71)
Change of pBDNF W1	0.51 (0.35–0.68)	>−0.04	0.65 (0.41–0.85)	0.57 (0.31–0.79)

AUC indicates area under a curve of receiver operating characteristics; CI, confidence interval; MADRS, Montgomery and Åsberg Depression Rating Scale; NPV, negative predictive value; PPV, positive predictive value; pBDNF, plasma brain-derived neurotrophic factor level; sBDNF, serum brain-derived neurotrophic factor level; W1, week 1; W2, week 2.

numerical details, see Table 2 (QIDS-SR and CGI values are displayed only for baseline, weeks 1 and 2 visits).

We have also identified differences between responders and non-responders in the change of prefrontal cordance at week 1. Prefrontal cordance and s/pBDNF values at baseline and week 1 did not differ nor did the change of s/pBDNF at week 1—for numerical details, see Table 3.

To explore the potential influences of smoking and drinking habits on BDNF level and the effect of benzodiazepines on cordance values, we compared the number of responders and non-responders suffering from excessive drinking (≥14 U/week; only one excessive drinker in the whole sample), current smokers, and users of benzodiazepines in the study (see Table 1).

Patients with and without benzodiazepines did not differ in the baseline (M-W-U; $p = 0.32$) and week 1 ($p = 0.52$) cordance values. The baseline s/pBDNF (serum—M-W-U, $p = 0.44$; plasma—$p = 0.67$) were not different in smokers and non-smokers, nor was s/pBDNF at week 1 (serum—$p = 0.77$; plasma—$p = 0.62$).

Predictive Values of Prefrontal Cordance Change at Week 1, Change of Depressive Symptoms at Week 1 and 2, and Changes of s/pBDNF at Week 1

The AUCs of ROC analyses of prefrontal cordance and s/p BDNF changes at week 1 and changes of depressive symptoms at weeks 1 and 2 with detected optimal cut-off points for prediction of response and corresponding predictive values are displayed in Table 4. The pairwise comparisons of AUCs of the abovementioned parameters (z-statistic) showed that the change of MADRS score at week 2 achieved a significantly higher value of AUC (predictive ability) than other analyzed predictors, with the exception of cordance change at week 1 (only a statistically nonsignificant trend for superiority of MADRS change was observed; $p = 0.09$). Other parameters did not differ in the comparisons.

Predictive Values of A Priori Defined Parameters and Prediction Models

Significant differences were found between the number of responders and non-responders with presence of the RM ≥20% W1 (Fisher's exact test, $p = 0.03$), RM ≥20% W2 ($p < 0.0001$), and RC ($p < 0.01$) but not in the occurrence of IsBDNF ($p = 0.72$) and IpBDNF ($p = 0.49$).

Predictive parameters and AUCs for response prediction of all a priori defined predictors are displayed in Table 5. Pairwise comparison (z-statistic) revealed significant differences only in the predictive ability (AUC values) between RM ≥20% W2 and RM ≥20% W1 ($p = 0.03$), and RM ≥20% W2 and IsBDNF ($p < 0.01$) and RM ≥20% W2 and IpBDNF ($p = 0.02$).

Among all predictors that entered the logistic regression model, only RM ≥20% W2 and RC emerged as predictors for response (pseudo $R^2 = 0.69$, $\chi^2 = 27.52$, $df = 2$, $p < 0.0001$; odds ratio: RM ≥ 20% W2 ≥ 20%—66.9, 95% CI 4.2–1051.4; RC—15.4, 95% CI 1.5–156.4). Predictive parameters of the non-adjusted model are displayed in Table 5. After the adjustment for the baseline confounders (sex, age, duration of index episode, number of previous episodes, MADRS score, use of benzodiazepines), the model results remained almost unchanged (adjusted $R^2 = 0.70$, $\chi^2 = 26.52$, $df = 2$, $p < 0.0001$; adjusted odds ratio: RM ≥ 20% W2—59.8, 95% CI 3.7–965.0; RC—17.6, 95% CI 1.7–185.9).

This two-parameter model achieved significantly higher value of AUC than RM ≥20% W1 ($p = 0.01$), IsBDNF ($p = 0.0001$), and IpBDNF ($p < 0.001$) and numerically higher value than RC ($p = 0.07$) and RM ≥ 20% W2 ($p = 0.24$).

TABLE 5. Characteristics of Predictors and Predictive Model for Treatment Response

Predictors or Predictive Model	PPV (95% CI)	NPV (95% CI)	NND	AUC (95% CI)	Accuracy
RM ≥ 20% W1	0.89 (0.52–1.00)	0.55 (0.37–0.74)	3.1	0.66 (0.49–0.81)	0.63
RM ≥ 20% W2	0.80 (0.59–0.93)	0.92 (0.64–1.00)	1.6	0.83 (0.67–0.97)	0.84
RC	0.80 (0.56–0.94)	0.72 (0.46–0.90)	1.9	0.76 (0.60–0.89)	0.76
IsBDNF	0.67 (0.35–0.90)	0.50 (0.30–0.70)	6.9	0.57 (0.40–0.73)	0.55
IpBDNF	0.65 (0.41–0.85)	0.56 (0.31–0.78)	4.8	0.60 (0.43–0.76)	0.61
RM ≥ 20% W2 + RC	0.95 (0.76–1.00)	0.71 (0.44–0.90)	1.4	0.92 (0.78–0.98)	0.84

AUC indicates area under a curve of receiver operating characteristics; BDNF, brain-derived neurotrophic factor; CI, confidence interval; IsBDNF, increase of serum BDNF level at week 1; IpBDNF, increase of plasma BDNF level at week 1; MADRS, Montgomery and Åsberg Depression Rating Scale; NND, number needed to diagnose; NPV, negative predictive value; PPV, positive predictive value; RM ≥ 20% W1, ≥20% reduction in MADRS score at week 1; RM ≥ 20% W2, ≥20% reduction in MADRS score at week 2; RC, reduction of cordance value at week 1.

TABLE 6. Characteristics of Models Combining Increase of BDNF and Early Change of Depressive Symptoms

Predictive Models	PPV (95% CI)	NPV (95% CI)	NND	AUC (95% CI)	Accuracy
RM ≥ 20% W1 + IpBDNF W1	1.00 (0.47–1.00)	0.52 (0.34–0.59)	4.2	0.62 (0.45–0.77)	0.58
RM ≥ 20% W2 + IpBDNF W1	0.87 (0.60–0.98)	0.65 (0.43–0.84)	2.0	0.75 (0.58–0.88)	0.74
RM ≥ 20% W1 + IsBDNF W1	1.00 (0.29–1.00)	0.49 (0.32–0.66)	7.0	0.57 (0.40–0.73)	0.53
RM ≥ 20% W2 + IsBDNF W1	0.80 (0.44–0.97)	0.54 (0.34–0.72)	3.8	0.63 (0.46–0.78)	0.61

AUC, area under a curve of receiver operating characteristics; CI, confidence interval; IsBDNF W1, increase of serum BDNF level at week 1; IpBDNF W1, increase of plasma BDNF level at week 1; MADRS, Montgomery and Åsberg Depression Rating Scale; NND, number needed to diagnose; NPV, negative predictive value; PPV, positive predictive value; RM ≥ 20% W1, ≥20% reduction in MADRS score at week 1; RM ≥ 20% W2, ≥20% reduction in MADRS score at week 2.

In addition, despite the fact that logistic regression did not identify IsBDNF and IpBDNF as predictors, we have calculated predictive values of models combining RM ≥20% W1 or W2 with increases of s/pBDNF levels at week 1 (for results, see Table 6) to compare our results with the findings of German pilot studies (Dreimuller et al., 2012; Tadic et al., 2011). The best model identified in these analyses (RM ≥ 20% W2 + IpBDNF) achieved comparable AUC value to RM ≥20% W2 alone ($p = 0.39$) and significantly lower than RM ≥20% W2 + RC ($p = 0.04$).

DISCUSSION

The predictive efficacy of the change of depressive symptoms (MADRS) at week 2 in terms of AUC value was significantly better compared to other predictors, with the exception of prefrontal cordance change at week 1, where only a trend for superiority was detected.

A similar pattern of results was found when analyzing efficacy of a priori defined predictors: significantly higher value of AUC of RM ≥20% W2 compared to the other predictors, with the exception of RC W1.

The predictive efficacy (AUC) of the model (RM ≥ 20% W2 + RC) for the response was significantly better than both BDNF-based predictors and RM ≥20% W1, but only a numerical difference was found compared to RC and RM ≥20% W2. Nevertheless, the derived AUC value of 0.92 indicates excellent ability of the model to differentiate between responders and non-responders.

The predictive values of RM ≥20% W1, RC were comparable to those obtained in previous studies or slightly higher for RM ≥20% W2 (Bares et al., 2015b; Iosifescu, 2011; Kudlow et al., 2014; Szegedi et al., 2009).

Increase of s/pBDNF at week 1 demonstrated only limited predictive value and was inferior to the clinical predictor (RM ≥ 20% W2).

Several meta-analyses have demonstrated increased BDNF level after antidepressant treatment or electroconvulsive therapy and the correlation between changes of BDNF level and depression scores (Brunoni et al., 2008, 2014a), but there are also studies that did not show normalization or increase of BDNF after antidepressant intervention (Deuschle et al., 2013; Matrisciano et al., 2009) or noninvasive brain stimulation (repetitive transcranial magnetic stimulation, transcranial direct current stimulation—tDCS) (Brunoni et al., 2015).

A few recent studies have demonstrated poor ability of change of s/pBDNF to predict outcome of treatment with antidepressants (SSRIs, duloxetine) or tDCS (Brunoni et al., 2014b; Deuschle et al., 2013; Yoshimura et al., 2014). Tadic et al. and Dreimüller et al. characterized the predictive efficacy of the changes of BDNF (week 1 or 2) as limited unless combining them with change of depressive symptoms (Dreimuller et al., 2012; Tadic et al., 2011). Furthermore, the dynamics of BDNF changes are probably complex, not completely clear (Mikoteit et al., 2014), and could be dependent on the type of antidepressant used (Balu et al., 2008; Molendijk et al., 2011). A small study has indicated a possible difference among various SSRIs in their ability to induce change of BDNF (Matrisciano et al., 2009).

Generally, SSRIs are considered as antidepressants that are associated with an increase in sBDNF in depressed patients (Molendijk et al., 2011). In addition, contrary to Mikoteit et al. (2014), we did not find any difference in the baseline value of s/pBDNF between subjects with positive and negative treatment outcome.

Stepwise logistic regression identified only RM ≥20% W2 and RC as significant predictors.

Unlike our previous naturalistic study (Bares et al., 2015b), RM ≥20% W1 did not enter in the model. The AUC of the current model is identical to the previous one (RM ≥ 20% W2 + RM ≥ 20% W1 + RC). The predictive efficacy of RM ≥20% W1 is probably less reliable due to the potential influence of side effects of antidepressants (sedation, increased appetite, etc.) or placebo effect (hospitalization, patient's regular daily schedule, regular evaluation of patient's status, etc.) (Quitkin et al., 1996).

Despite the fact that the predictive values of Is/pBDNF for response were limited, we found, similarly to Tadic et al. and Dreimüller et al. (Dreimuller et al., 2012; Tadic et al., 2011), high PPV for combinations of Is/pBDNF and RM ≥20% W1 for the prediction of positive treatment outcome (*i.e.*, high PPV of non-increase of s/pBDNF in combination with non-reduction of MADRS score for non-response). Nevertheless, accuracy of the prediction for both models was low. In terms of AUC for response prediction, the best model combining BDNF and clinical parameters (IpBNDF + RM ≥ 20% W2) did not show better results compared to RM ≥20% W2 alone and was worse than RM ≥20% W2 + RC.

It is questionable if the identified combined model (RM ≥ 20% W2 + RC) is more clinically useful than the individual clinical predictor (RM ≥ 20% W2). There are disadvantages associated with logistic problems or costs (two EEGs in 1 week, need for trained EEG specialist, and immediate availability of EEG findings) for a small difference in predictive values compared to clinical predictor. However, the combination of clinical factor and objective neurophysiologic parameter would be more reliable. It is necessary to keep in mind that the efficacy of prediction of treatment outcome using early reduction of depressive symptoms alone would vary according to rating scales used or duration of treatment (Gorwood et al., 2013). Furthermore, in the available studies, PPVs of early improvement (≥20% reduction of scores of used rating scales) at 2 weeks ranged 26 to 84% and NPVs were 35% to 92%, *i.e.*, in a very wide range (Kudlow et al., 2014). The predictive efficacy of RC was repeatedly evaluated and confirmed in other studies (Bares et al., 2010, 2015b; Cook et al., 2002, 2005). PPVs and NPVs of RC in the available predictive studies ranged 60% to 90% and 69% to 100%, respectively.

Various limitations of the present study require mention. First, our sample size was limited. The relatively small number of participating subjects would increase type II errors, reducing the chance of finding significant results. However, the study was designed to detect large,

clinically relevant differences between responders and non-responders. In addition, with a small sample size, we cannot exclude overfitting a regression model. To address this issue, we applied the same model to the independent dataset from our previous study ($n = 87$, various antidepressants) (Bares et al., 2015b) with very similar results (adjusted $R^2 = 0.74$) (data not shown).

Secondly, because of the 6-week duration of the study, we cannot exclude the possibility of a further clinical response emerging during longer treatment (Trivedi et al., 2006). Because the relatively short treatment period is probably not sufficient to achieve full remission, our results have been evaluated only in terms of response to treatment (Rush et al., 2006).

Third, we did not analyze functionally relevant BDNF-gene polymorphisms such as the val66met polymorphism that could influence the probability of response to treatment (Zou et al., 2010).

Fourth, it was an open-label, uncontrolled study. The lack of a placebo group did not allow us to compare the association of the changes of evaluated parameters with treatment. However, there is evidence of a different pattern of cordance change in placebo responders (increase of cordance value) (Leuchter et al., 2002). Szegedi described early improvement of depressive symptoms in the prediction of response to placebo (Szegedi et al., 2009). According to our literature review, there are no studies describing a change of s/pBDNF associated with the placebo treatment of depression with the exception of the recent study of Brunoni's team that did not describe any change of pBDNF in patients treated with placebo or sertraline and tDCS (Brunoni et al., 2014b). Furthermore, the Institutional Review Board of Prague Psychiatric Centre/National Institute of Mental Health, Czech Republic would not have approved a 6-week, placebo-controlled study in the treatment of resistant patients.

Finally, we used various SSRIs in our patient population, and so we have not been able to carry out analysis for specific antidepressants. Using one compound would provide more specific results but these could not then have been generalized for the whole class of antidepressants.

Despite these limitations, the present study demonstrated and replicated the potential clinical usefulness of the combination of prefrontal theta cordance and early improvement of depressive symptoms that was shown in our previous study (Bares et al., 2015b) for the specific antidepressant class, SSRIs. Larger prospective studies are needed to confirm our results.

Our findings have added to the growing body of evidence about the usefulness of combined prediction models (Mikoteit et al., 2014; Mulert et al., 2007; Riedel et al., 2011; Spronk et al., 2011). This paradigm is currently under investigation in several large studies that are now recruiting patients or beginning to present results: iSPOT-D (Palmer, 2015), EMBARC (Thase, 2014), and CAN-BIND (https://clinicaltrials.gov/ct2/show/NCT01655706?term=CAN-bind&rank=1). However, the identification of an early change of s/pBDNF as a clinically useful predictor in view of our results and other predictive studies seems to be premature and needs further evaluation.

CONCLUSION

Our findings indicate that an early reduction of depressive symptoms alone and in the combination with the reduction of prefrontal theta cordance may be useful in the prediction of response to SSRIs.

ACKNOWLEDGMENTS

The authors thank Mr. Robin Fears for valuable help in the manuscript preparation.

DISCLOSURE

C.H.—Clinical trials: coordinator of a multicentric study for Servier. Consultant: Advisory board member, Lilly and BMS. Grant: Lilly. Paid lectures for Lilly, Janssen Cilag, BMS, Angelini, Nycomed, Krka, and Lupin. Other: faculty member, Lundbeck International Neuroscience Foundation. M.K.—paid lectures for Lundbeck. M. Bares—paid lecture for Lundbeck.

All other authors declare no conflict of interest.

REFERENCES

American Psychiatric Association (1994) *Diagnostic and statistical manual of mental disorders* (4th ed). Washington DC: American Psychiatric Press.

Balu DT, Hoshaw BA, Malberg JE, Rosenzweig-Lipson S, Schechter LE, Lucki I (2008) Differential regulation of central BDNF protein levels by antidepressant and non-antidepressant drug treatments. *Brain Res*. 1211:37–43.

Bares M, Brunovsky M, Kopecek M, Novak T, Stopkova P, Kozeny J, Sos P, Krajca V, Höschl C (2008) Early reduction in prefrontal theta QEEG cordance value predicts response to venlafaxine treatment in patients with resistant depressive disorder. *Eur Psychiatry*. 23:350–355.

Bares M, Brunovsky M, Novak T, Kopecek M, Stopkova P, Sos P, Höschl C (2015a) QEEG theta cordance in the prediction of treatment outcome to prefrontal repetitive transcranial magnetic stimulation or venlafaxine ER in patients with major depressive disorder. *Clin EEG Neurosci*. 46:73–80.

Bares M, Brunovsky M, Novak T, Kopecek M, Stopkova P, Sos P, Krajca V, Höschl C (2010) The change of prefrontal QEEG theta cordance as a predictor of response to bupropion treatment in patients who had failed to respond to previous antidepressant treatments. *Eur Neuropsychopharmacol*. 20:459–466.

Bares M, Novak T, Brunovsky M, Kopecek M, Stopkova P, Krajca V, Höschl C (2012a) The change of QEEG prefrontal cordance as a response predictor to antidepressive intervention in bipolar depression. A pilot study. *J Psychiatr Res*. 46:219–225.

Bares M, Novak T, Kopecek M, Brunovsky M, Stopkova P, Höschl C (2015b) The effectiveness of prefrontal theta cordance and early reduction of depressive symptoms in the prediction of antidepressant treatment outcome in patients with resistant depression: Analysis of naturalistic data. *Eur Arch Psychiatry Clin Neurosci*. 265:73–82.

Bares M, Novak T, Kopecek M, Stopkova P, Kozeny J, Höschl C (2012b) The early improvement of depressive symptoms as a potential predictor of response to antidepressants in depressive patients who failed to respond to previous antidepressant treatments. Analysis of naturalistic data. *Eur Psychiatry*. 27:522–527.

Baskaran A, Milev R, McIntyre RS (2012) The neurobiology of the EEG biomarker as a predictor of treatment response in depression. *Neuropharmacology*. 63:507–513.

Breitenstein B, Scheuer S, Holsboer F (2014) Are there meaningful biomarkers of treatment response for depression? *Drug Discov Today*. 19:539–561.

Brunoni AR, Baeken C, Machado-Vieira R, Gattaz WF, Vanderhasselt MA (2014a) BDNF blood levels after electroconvulsive therapy in patients with mood disorders: A systematic review and meta-analysis. *World J Biol Psychiatry*. 15: 411–418.

Brunoni AR, Baeken C, Machado-Vieira R, Gattaz WF, Vanderhasselt MA (2015) BDNF blood levels after non-invasive brain stimulation interventions in major depressive disorder: A systematic review and meta-analysis. *World J Biol Psychiatry*. 16:114–122.

Brunoni AR, Lopes M, Fregni F (2008) A systematic review and meta-analysis of clinical studies on major depression and BDNF levels: Implications for the role of neuroplasticity in depression. *Int J Neuropsychopharmacol*. 11:1169–1180.

Brunoni AR, Machado-Vieira R, Zarate CA Jr, Vieira EL, Vanderhasselt MA, Nitsche MA, Valiengo L, Bensenor IM, Lotufo PA, Gattaz WF, Teixeira AL (2014b) BDNF plasma levels after antidepressant treatment with sertraline and transcranial direct current stimulation: Results from a factorial, randomized, sham-controlled trial. *Eur Neuropsychopharmacol*. 24:1144–1151.

Bus BA, Molendijk ML, Penninx BJ, Buitelaar JK, Kenis G, Prickaerts J, Elzinga BM, Voshaar RC (2011) Determinants of serum brain-derived neurotrophic factor. *Psychoneuroendocrinology*. 36:228–239.

Calker D, Zobel I, Dykierek P, Deimel CM, Kech S, Lieb K, Berger M, Schramm E (2009) Time course of response to antidepressants: Predictive value of early improvement and effect of additional psychotherapy. *J Affect Disord*. 114:243–253.

Cook IA, Leuchter AF, Morgan M, Witte E, Stubbeman WF, Abrams M, Rosenberg S, Uijtdehaage SH (2002) Early changes in prefrontal activity characterize clinical responders to antidepressants. *Neuropsychopharmacology.* 27:120–131.

Cook IA, Leuchter AF, Morgan ML, Stubbeman W, Siegman B, Abrams M (2005) Changes in prefrontal activity characterize clinical response in SSRI nonresponders: A pilot study. *J Psychiatr Res*. 39:461–466.

Cook IA, O'Hara R, Uijtdehaage SH, Mandelkern M, Leuchter AF (1998) Assessing the accuracy of topographic EEG mapping for determining local brain function. *Electroencephalogr Clin Neurophysiol*. 107:408–414.

Deuschle M, Gilles M, Scharnholz B, Lederbogen F, Lang UE, Hellweg R (2013) Changes of serum concentrations of brain-derived neurotrophic factor (BDNF) during treatment with venlafaxine and mirtazapine: Role of medication and response to treatment. *Pharmacopsychiatry.* 46:54–58.

Dreimuller N, Schlicht KF, Wagner S, Peetz D, Borysenko L, Hiemke C, Lieb K, Tadic A (2012) Early reactions of brain-derived neurotrophic factor in plasma (pBDNF) and outcome to acute antidepressant treatment in patients with major depression. *Neuropharmacology.* 62:264–269.

Duman RS, Monteggia LM (2006) A neurotrophic model for stress-related mood disorders. *Biol Psychiatry.* 59:1116–1127.

Furukawa TA, Levine SZ, Tanaka S, Goldberg Y, Samara M, Davis JM, Cipriani A, Leucht S (2015) Initial severity of schizophrenia and efficacy of antipsychotics: Participant-level meta-analysis of 6 placebo-controlled studies. *JAMA Psychiatry.* 72:14–21.

Gorwood P, Bayle F, Vaiva G, Courtet P, Corruble E, Llorca PM (2013) Is it worth assessing progress as early as week 2 to adapt antidepressive treatment strategy? Results from a study on agomelatine and a global meta-analysis. *Eur Psychiatry.* 28:362–371.

Guy W (1976) *ECDEU Assessment Manual for Psychopharmacology: Revised*. *National Institute of Mental Health, Publication (ADM) 76-338*. Rockville, MD: US Dept. Health, Education and Welfare.

Hamilton M (1960) A rating scale for depression. *J Neurol Neurosurg Psychiatry.* 23: 56–62.

Hayasaka Y, Purgato M, Magni LR, Ogawa Y, Takeshima N, Cipriani A, Barbui C, Leucht S, Furukawa TA (2015) Dose equivalents of antidepressants: Evidence-based recommendations from randomized controlled trials. *J Affect Disord*. 180: 179–184.

Iosifescu DV (2011) Electroencephalography-derived biomarkers of antidepressant response. *Harv Rev Psychiatry.* 19:144–154.

Kobak KA, Greist JH, Jefferson JW, Katzelnick DJ (1996) Computer-administered clinical rating scales. A review. *Psychopharmacology (Berl)*. 127:291–301.

Kudlow PA, McIntyre RS, Lam RW (2014) Early switching strategies in antidepressant non-responders: Current evidence and future research directions. *CNS Drugs*. 28:601–609.

Labermaier C, Masana M, Muller MB (2013) Biomarkers predicting antidepressant treatment response: How can we advance the field? *Dis Markers*. 35:23–31.

Leuchter AF, Cook IA, Hamilton SP, Narr KL, Toga A, Hunter AM, Faull K, Whitelegge J, Andrews AM, Loo J, Way B, Nelson SF, Horvath S, Lebowitz BD (2010) Biomarkers to predict antidepressant response. *Curr Psychiatry Rep*. 12:553–562.

Leuchter AF, Cook IA, Lufkin RB, Dunkin J, Newton TF, Cummings JL, Mackey JK, Walter DO (1994a) Cordance: A new method for assessment of cerebral perfusion and metabolism using quantitative electroencephalography. *Neuroimage*. 1: 208–219.

Leuchter AF, Cook IA, Mena I, Dunkin JJ, Cummings JL, Newton TF, Migneco O, Lufkin RB, Walter DO, Lachenbruch PA (1994b) Assessment of cerebral perfusion using quantitative EEG cordance. *Psychiatry Res*. 55:141–152.

Leuchter AF, Cook IA, Witte EA, Morgan M, Abrams M (2002) Changes in brain function of depressed subjects during treatment with placebo. *Am J Psychiatry.* 159:122–129.

Madhoo M, Levine SZ (2015) Initial severity effects on residual symptoms in response and remission: A STAR*D study during and after failed citalopram treatment. *J Clin Psychopharmacol*. 35:450–453.

Matrisciano F, Bonaccorso S, Ricciardi A, Scaccianoce S, Panaccione I, Wang L, Ruberto A, Tatarelli R, Nicoletti F, Girardi P, Shelton RC (2009) Changes in BDNF serum levels in patients with major depression disorder (MDD) after 6 months treatment with sertraline, escitalopram, or venlafaxine. *J Psychiatr Res*. 43:247–254.

Mikoteit T, Beck J, Eckert A, Hemmeter U, Brand S, Bischof R, Holsboer-Trachsler E, Delini-Stula A (2014) High baseline BDNF serum levels and early psychopathological improvement are predictive of treatment outcome in major depression. *Psychopharmacology (Berl)*. 231:2955–2965.

Molendijk ML, Bus BA, Spinhoven P, Penninx BW, Kenis G, Prickaerts J, Voshaar RC, Elzinga BM (2011) Serum levels of brain-derived neurotrophic factor in major depressive disorder: State-trait issues, clinical features and pharmacological treatment. *Mol Psychiatry.* 16:1088–1095.

Montgomery SA, Åsberg M (1979) A new depression scale designed to be sensitive to change. *Br J Psychiatry.* 134:382–389.

Mulert C, Juckel G, Brunnmeier M, Karch S, Leicht G, Mergl R, Moller HJ, Hegerl U, Pogarell O (2007) Prediction of treatment response in major depression: Integration of concepts. *J Affect Disord*. 98:215–225.

Nuwer MR, Lehmann D, da Silva FL, Matsuoka S, Sutherling W, Vibert JF (1999) IFCN guidelines for topographic and frequency analysis of EEGs and EPs. The International Federation of Clinical Neurophysiology. *Electroencephalogr Clin Neurophysiol Suppl*. 52:15–20.

Olbrich S, Arns M (2013) EEG biomarkers in major depressive disorder: Discriminative power and prediction of treatment response. *Int Rev Psychiatry.* 25: 604–618.

Olbrich S, van Dinteren R, Arns M (2015) Personalized medicine: Review and perspectives of promising baseline EEG biomarkers in major depressive disorder and attention deficit hyperactivity disorder. *Neuropsychobiology.* 72:229–240.

Palazidou E (2012) The neurobiology of depression. *Br Med Bull*. 101:127–145.

Palmer DM (2015) Biomarkers for antidepressant selection: iSPOT-D study. *Curr Behav Neurosci Rep*. 2:137–145.

Papakostas GI, Fava M, Thase ME (2008) Treatment of SSRI-resistant depression: A meta-analysis comparing within- versus across-class switches. *Biol Psychiatry.* 63: 699–704.

Quitkin FM, McGrath PJ, Stewart JW, Taylor BP, Klein DF (1996) Can the effects of antidepressants be observed in the first two weeks of treatment? *Neuropsychopharmacology.* 15:390–394.

Riedel M, Möller HJ, Obermeier M, Adli M, Bauer M, Kronmuller K, Brieger P, Laux G, Bender W, Heuser I, Zeiler J, Gaebel W, Schennach-Wolff R, Henkel V, Seemuller F (2011) Clinical predictors of response and remission in inpatients with depressive syndromes. *J Affect Disord*. 133:137–149.

Rush AJ, Trivedi MH, Ibrahim HM, Carmody TJ, Arnow B, Klein DN, Markowitz JC, Ninan PT, Kornstein S, Manber R, Thase ME, Kocsis JH, Keller MB (2003) The 16-Item Quick Inventory of Depressive Symptomatology (QIDS), clinician rating (QIDS-C), and self-report (QIDS-SR): A psychometric evaluation in patients with chronic major depression. *Biol Psychiatry.* 54:573–583.

Rush AJ, Trivedi MH, Wisniewski SR, Nierenberg AA, Stewart JW, Warden D, Niederehe G, Thase ME, Lavori PW, Lebowitz BD, McGrath PJ, Rosenbaum JF, Sackeim HA, Kupfer DJ, Luther J, Fava M (2006) Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: A STAR*D report. *Am J Psychiatry.* 163:1905–1917.

Sheehan DV, Lecrubier Y, Sheehan KH, Amorim P, Janavs J, Weiller E, Hergueta T, Baker R, Dunbar GC (1998) The Mini-International Neuropsychiatric Interview (M.I.N.I.): The development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *J Clin Psychiatry.* 59(suppl 20):22–33.

Spronk D, Arns M, Barnett KJ, Cooper NJ, Gordon E (2011) An investigation of EEG, genetic and cognitive markers of treatment response to antidepressant medication in patients with major depressive disorder: A pilot study. *J Affect Disord*. 128: 41–48.

Szegedi A, Jansen WT, van Willigenburg AP, van der Meulen E, Stassen HH, Thase ME (2009) Early improvement in the first 2 weeks as a predictor of treatment

outcome in patients with major depressive disorder: A meta-analysis including 6562 patients. *J Clin Psychiatry.* 70:344–353.

Tadic A, Wagner S, Schlicht KF, Peetz D, Borysenko L, Dreimuller N, Hiemke C, Lieb K (2011) The early non-increase of serum BDNF predicts failure of antidepressant treatment in patients with major depression: A pilot study. *Prog Neuropsychopharmacol Biol Psychiatry.* 35:415–420.

Thase ME (2014) Using biomarkers to predict treatment response in major depressive disorder: Evidence from past and present studies. *Dialogues Clin Neurosci.* 16: 539–544.

Thase ME, Rush AJ (1997) When at first you don't succeed: Sequential strategies for antidepressant nonresponders. *J Clin Psychiatry.* 58(suppl 13):23–29.

Trivedi MH, Rush AJ, Wisniewski SR, Nierenberg AA, Warden D, Ritz L, Norquist G, Howland RH, Lebowitz B, McGrath PJ, Shores-Wilson K, Biggs MM, Balasubramani GK, Fava M (2006) Evaluation of outcomes with citalopram for depression using measurement-based care in STAR*D: Implications for clinical practice. *Am J Psychiatry.* 163:28–40.

Yoshimura R, Kishi T, Hori H, Katsuki A, Sugita-Ikenouchi A, Umene-Nakano W, Atake K, Iwata N, Nakamura J (2014) Serum levels of brain-derived neurotrophic factor at 4 weeks and response to treatment with SSRIs. *Psychiatry Investig.* 11: 84–88.

Zou YF, Ye DQ, Feng XL, Su H, Pan FM, Liao FF (2010) Meta-analysis of BDNF Val66Met polymorphism association with treatment response in patients with major depressive disorder. *Eur Neuropsychopharmacol.* 20:535–544.