Running title: Predictors of response to SSRIs

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Complete Title: The comparison of effectiveness of various potential predictors of response to treatment with SSRIs in patients with depressive disorder.

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The comparison of effectiveness of various potential predictors of response to treatment with SSRIs in patients with depressive disorder.

Abstract:

The substantial non-response rate in depressive patients indicates a continuing need to identify predictors of treatment outcome. The aim of 6-week, open-label study was 1) to compare 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

Introduction

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 first antidepressant treatment (Trivedi et al., 2006). The incorporation of biological, clinical or other markers in the treatment of MDD could help understand and improve the efficiency of treatment trials and, ultimately, speed remission.

Many clinical, neurophysiological, neuroimaging and others 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 rating scale 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 D. et al., 2009).

Extensive research has additionally focused on the identification of cost-effective and widely available electroencephalogram (EEG)-based biomarkers (quantitative EEG-QEEG-measures, connectivity measures, EEG vigilance-based measures, sleep-EEG-related measures etc.) that not only allow distinguishing between patients and healthy controls but also have predictive value for treatment outcome for a variety of antidepressive interventions (Olbrich and Arns, 2013). Several QEEG methods e.g. alpha band activity, frontal theta activity, prefrontal theta cordance, Antidepressant Treatment Response Index etc. were identified as potentially useful in the prediction of response to antidepressants in MDD (Iosifescu, 2011).

Cordance is a QEEG method combining information from 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 findings using prefrontal theta cordance could be interpreted as demonstrating 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). In multiple studies of subjects suffering from resistant or non-resistant depression treated with various antidepressants, decrease in prefrontal theta cordance calculated at three frontal electrodes (Fp1, Fp2, Fz) after one week of treatment has consistently predicted clinical response and this finding was confirmed by two independent groups (Bares et al., 2008; Bares et al., 2010; Cook et al., 2002; Cook et al., 2005). Furthermore the predictive ability of prefrontal cordance decrease has also been demonstrated for the response to low frequency repetitive transcranial magnetic stimulation and in the prediction of treatment outcome of bipolar depression (Bares et al., 2012a; Bares et al., 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). Consistent with this hypothesis are the findings that depression is associated with decreased central and peripheral levels of BDNF (serum level of BDNF-sBDNF; plasma level of BDNF-pBDNF) and that antidepressants or electroconvulsive therapy elicit an increase in BDNF levels in depressed patients humans (Brunoni et al., 2008; Brunoni et al., 2014a; Sen et al., 2008). Some, but not all, studies have shown that an increase of s/pBDNF after one or two weeks of antidepressant intervention may predict 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 observations that many potential individual predictors of treatment outcome seem to be promising, it is likely that multiple factors combined in predictive scores or algorithms will be needed to achieve a clinically meaningful prediction (Baskaran et al., 2012; Leuchter et al., 2010). For example, the studies evaluating predictive potential s/p BDNF showed that the combination of lack of sBDNF increase and early improvement after 2 weeks of treatment increases PPV for nonresponse to AD and vice versa (Dreimuller et al., 2012; Tadic et al., 2011). Our group have demonstrated the potential clinical usefulness of a model combining early improvement of depressive symptoms (≥20% reduction in Montgomery and Åsberg Depression Rating Scale - MADRS) (Montgomery and Asberg, 1979) total score at week 1 and 2, and the decrease of prefrontal theta cordance at week 1. This combination of assessments yielded high accuracy of prediction of response (0.83) and was significantly better than individual predictors alone. (Bares et al., 2015b).

Taking account of these findings, our present study with depressive patients aimed: 1) to compare the efficacy of 1 and 2 week change (MADRS) in depressive symptoms, 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 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 to assess whether the possible combinations of these factors yields more robust predictive power than a single predictor alone, i.e. to postulate a combined predictive model (clinical, neurophysiological and neurotrophic factors).

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 (Thase and Rush, 1997). The last treatment of patients before enrollment is displayed in Table 1. Only subjects (18 to 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 SSRIs during index episode and electroconvulsive treatment in the 3 months before enrollment to the study. The patients´ 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 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 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 within-class change of SSRIs has been demonstrated (Papakostas et al., 2008). A short wash-out 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.) as well as 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) 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, week 1, 2, 4 and at the end of study. 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, prior to conducting the ratings (Kobak et al., 1996). 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 on 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 – 70 Hz. The EEG reviewer was blind to patient´s treatment and the outcome of treatment. 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 0.5–30 Hz. In each EEG, 30-60 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 a 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 3 frontal electrodes (Fp1, Fp2 and Fz) in theta frequency band (4-8 Hz) were subjected to statistical analysis.

Measurement of s/p BDNF-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, New Jersey, U.S.A.). After 30 min of clotting time, whole blood was centrifuged at 1000 ×g for 15 min. 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 (cat.no BD00, R&D Systems, Wiesbaden, Germany) according to manufacturer recommendations.

All samples were thawed only once. Assay was performed in duplicate; 50 µl of sample (4x diluted plasma or 50x diluted serum in RD6P diluent, or BDNF standard) was used for each well together with 100 µl of Assay Diluent RD1S. After 2h 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 3x with 0.3 ml of Wash Buffer and 200 µl of Substrate Solution was pipetted to each well at controlled intervals (15 sec). Color reaction proceeded while protected from light until it reached desired intensity (20-30 min), 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 calibration curve (at concentration range 60-4 000 pg/ml) by fitting with four parameters 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 the last observation analysis (LOAN) method. Demographic, clinical and treatment characteristics including fluoxetine equivalent doses (Hayasaka et al., 2015) at week 1, 2 and the end of study were analyzed using unpaired Mann-Whitney U-test (M-W-U) and Fisher Exact test. The predictive efficacy of changes of MADRS score at week 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 pair-wise 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 difference between the number of responders and non-responders with the presence of predictor (Fisher 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. All a priori predictors were considered as components of a logistic regression model that examined the relative contribution of each variable to accuracy of prediction. Finally, we compared the predictive ability of the combined model identified by logistic regression to the individual predictors.

All tests were 2–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/p BDNF 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 with the exception of QIDS-SR where the difference was detected already from week 1 (p=0.04). Differences in the percentage reduction of MADRS score at week 1 and 2 were found at both time periods. For numerical details see Table 2 (QIDS-SR and CGI values are displayed only for baseline, week 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 potential influences of smoking and drinking habits on BDNF level as well as 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). Furthermore, 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 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/pBDNF changes at week 1 as well as changes of depressive symptoms at week 1 and 2 with detected optimal cut-off points for prediction of response and corresponding predictive values are displayed in Table 4. The pair-wise comparisons of AUCs of abovementioned parameters (z-statistic) showed that the change of MADRS score at week 2 achieved significantly higher value of AUC (predictive ability) than other analyzed predictors with the exception of cordance change at week 1 (only a statistically

non-significant 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 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. Pair-wise comparison (z-statistic) revealed significant differences only in the predictive ability (AUC values) between RM≥20% W2 and RM≥20% W1 (p=0.03) as well as RM≥20% W2 and IsBDNF (p<0.01) and RM≥20% W2 and IpBDNF (p=0.02).

Among all predictors which entered the logistic regression model, only RM≥20% W2 and RC emerged as a predictors for response (pseudo R^2=0.69, X^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 model are displayed in Table 5.

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).

In addition, despite the fact that IsBDNF and IpBDNF were not identified as predictors using logistic regression we also calculated predictive values of models combining RM≥20% W1 or W2 with increases of s/p BDNF levels at week 1 (for results see Table 6) in order to compare our results with the findings of German pilot studies (Dreimuller et al., 2012; Tadic et al., 2011). The best identified model 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 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 within the range described 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 it was inferior to the clinical predictor (RM≥20% W2).

Some meta-analyses have demonstrated increased BDNF level after antidepressant treatment or electroconvulsive therapy and correlation between changes of BDNF level and depression scores (Brunoni et al., 2008; Brunoni et al., 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 non-invasive brain stimulation (repetitive transcranial magnetic stimulation, transcranial direct current stimulation-tDCS) (Brunoni et al., 2015).

Three current studies demonstrated poor ability of change of s/pBDNF to predict outcome of treatment with antidepressants (SSRIs, duloxetine) or tDCS (Brunoni et al., 2014c; Deuschle et al., 2013; Yoshimura et al., 2014). Tadic et al. and Dreimüller et al. characterized the

predictive efficacy of the change of BDNF (week 1 or 2) as limited unless combination 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 possible difference among various SSRIs in the ability to induce change of BDNF (Matrisciano et al., 2009). In addition, contrary to Mikoteit et al. (Mikoteit et al., 2014), we did not find any difference between subjects with positive and negative treatment outcome in the baseline value of s/pBDNF.

Stepwise logistic regression identified only RM≥20% W 2 and RC W1 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% W 1 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 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 term 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 individual clinical predictor (RM≥20% W2). There are disadvantages associated

with logistic problems or costs (two EEGs in one week, need of trained EEG specialist and immediate availability of EEG findings) for a relatively small difference in predictive values comparing 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 26–84 % and NPVs were 35–92 % , 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; Bares et al., 2015b; Cook et al., 2002; Cook et al., 2005). PPVs and NPVs of RC in available predictive studies ranged 60-90% and 69-100%, 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.

Secondly, due to the six 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 term of response to treatment (Rush et al., 2006).

Third, we did not analyze functionally relevant BDNF-gene-polymorphisms like the val66met polymorphism that could influence 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).

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 showed 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), CAN-BIND (https://clinicaltrials.gov/ct2/show/NCT01655706?term=CAN-bind&rank=1). However, the identification of early change s/pBDNF as a clinically useful predictor in view of results of our and other predictive studies seems to be premature and needs further evaluation.

Conclusion

Our findings indicate that early reduction of depressive symptoms alone as well as in the combination with the reduction of cordance may be useful in the prediction of response to SSRIs.

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Conflicts of Interest

Author Höschl - 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, Lupin. Other: faculty member, Lundbeck International Neuroscience Foundation. Author Kopecek - Paid lectures for: Lundbeck.

All other authors declare that they have no conflicts of interest.

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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 [a]
sex (F:M)	14:3	15:6	0.48 [b]
number of previous depressive episodes	2 (1-3)	3 (1-5)	0.49 [a]
number of previous adequate treatments of current episode	1 (1-2)	1 (1-1.8)	0.24 [a]
last treatment before the enrolment	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[1] 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 [a] 0.31 [a] 0.29 [a]
subjects taking bzd B[2]	7	3	0.08 [b]
subjects taking hypnotics W1, W2	5 6	8 8	0.73 [b] 1.00 [b]

subjects taking hydroxyzine W1, W2	6 6	7 7	1.00 [b] 1.00 [b]
smokers	6	13	0.19

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

[1]- according to Hayasaka et al., 2015, [2]unchanged dose during the study, [a] –Mann-Whitney U test, [b] -Fisher's Exact test, B-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, NS-nonsignificant, 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-week2

Table

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

Table

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 (-0.52-0.29)	0.22 (-0.36-0.38)	0.32
prefrontal cordance value W1	0.05 (-0.25-0.35)	0.15 (-0.42-0.27)	0.77
change of prefrontal cordance values W1	0.16 (-0.02 – 0.27)	-0.15 (-0.42 - -0.003)	0.02
sBDNF B	22.40 (19.72-25.48)	19.39 (15.29-24.10)	0.47
sBDNF W1	18.46 (16.32-23.55)	19.14 (16.86-22.50)	0.82
change of sBDNF W1	-1.85 (-6.08-0.86)	-1.00 (-6.14-1.92)	0.50
pBDNF B	2.48 (1.44-3.17)	2.45 (1.63-3.26)	0.79
pBDNF W1	2.28 (1.71-3.25)	2.42 (1.92-3.47)	0.64
change of pBDNF W1	-0.08 (-0.62-1.06)	0.31 (-0.78-1.11)	0.91

Data are presented as median (interquartile range)

[a]-Mann-Whitney U test, B-baseline, pBDNF-plasma brain-derived neurotrophic factor level (ng/ml), sBDNF- serum brain-derived neurotrophic factor level (ng/ml), NS-nonsignificant, W1-week 1

Table

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-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

Table

Table 5 The 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 - 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

Table 6 The 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