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ORIGINAL ARTICLE

Predictors of response in the treatment of moderate depression

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Objective: To identify neurocognitive and sociodemographic variables that could be associated with clinical response to three modalities of treatment for depression, as well as variables that predicted superior response to one treatment over the others.
Method: The present study derives from a research project in which depressed patients (n=272) received one of three treatments – long-term psychodynamic psychotherapy (n=90), fluoxetine therapy (n=91), or a combination thereof (n=91) – over a 24-month period.
Results: Sociodemographic variables were not found to be predictive. Six predictive neurocognitive variables were identified: three prognostic variables related to working memory and abstract reasoning; one prescriptive variable related to working memory; and two variables found to be moderators.
Conclusions: The results of this study indicate subgroups of patients who might benefit from specific therapeutic strategies and subgroups that seem to respond well to long-term psychodynamic psychotherapy and combined therapy. The moderators found suggest that abstract reasoning and processing speed may influence the magnitude and/or direction of clinical improvement.

Keywords: Depression; psychotherapy; fluoxetine; moderators; predictors; neurocognition

Introduction

Psychodynamic psychotherapy, pharmacotherapy with fluoxetine, and a combination of psychotherapy and pharmacotherapy are all effective treatment methods for depression.[1,2] Despite the efficacy of these methods in reducing depressive symptoms, the processes that mediate improvement in a treatment outcome are not clear.

Predictive variables are treatment outcome mediators. A predictive variable is a pretreatment variable that can influence treatment outcome or the natural history of a disease, and may therefore become a prognostic, prescriptive, and/or moderator variable.[3] A prognostic variable predicts outcome independently of the treatment being used, while a prescriptive variable anticipates different patterns of outcome between two or more types of treatment.[4] A moderator variable, by definition, has the ability to influence the magnitude and/or direction of the relationship between the dependent and independent variables being studied.[3]

When two or more treatment modalities do not have significantly different impacts on the healing process and treatment outcome, an investigation may be necessary to identify the predictive variables that are capable of mediating the healing process, by identifying patients who improve more substantially than others do. These predictive variables can be prescriptive and/or prognostic. The identification of predictive variables promotes clinical gain for patients and mental health professionals alike, because it enables individual patients to receive the most efficacious treatment for their condition. In addition, predictive variables are likely to speed treatment decisions and improve cost-benefit aspects. Prognostic variables also help identify patients who are usually treatment-resistant, regardless of the treatment modality; this helps determine which patients need alternative therapeutic interventions.

One example of a predictive variable is therapeutic alliance (i.e., the relationship between a healthcare professional and a patient), as described in one study on psychodynamic psychotherapy[5] which found that changes in therapeutic alliance in early therapy predicted symptom change at the end of treatment. Similarly, other studies have shown that therapeutic alliance predicts improvements in symptoms.[6]

Most studies focused on identifying response predictors have not compared different types of treatments for depression. An extensive literature review on response predictors is beyond the scope of this study, but we found a few studies that have produced notable results on predictors within one type of treatment for depression.[7-9]

These studies reported that patient age did not interfere with clinical outcome in adults with depression treated with antidepressants. They also found that depression severity in inpatients was negatively associated with patient discharge, while physical health status and level of education were positively associated with discharge.

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An important limitation in single-treatment studies seeking prediction variables is that they have little prescriptive potential. In assessing only one type of treatment, these studies offer information on the prognosis for the treatment studied but fail to discuss appropriate treatments for patients with different needs and characteristics.[10]

Predictive analysis studies comparing two or more types of treatments of depression have identified important predictive variables. One study compared pharmacotherapy, cognitive psychotherapy, and placebo, and found that patients with more severe depression tended to have better responses to medication.[11] Thus, the prescriptive variable was severity of depression at the onset of treatment.

In another study that used the Beck Depression Inventory (BDI), authors found predictive variables among patient statements in the measure.[12] A close look at the findings revealed that BDI items pessimism and lack of energy helped identify patients who needed additional or alternative therapeutic methods.

Some studies have tried to associate patient sociodemographic variables with mood/anxiety disorders by comparing short-term therapy (STT) and long-term psychodynamic psychotherapy (LTPP).[13] Results suggested that married patients with high levels of education responded better to STT, while patients coming from single-parent homes and divorced patients responded better to LTPP or did not respond to either treatment.

In a prospective trial of 180 patients randomized to receive cognitive psychotherapy, antidepressant medication, or placebo, the authors identified prognostic variables (chronic depression, older age, and lower intelligence) and prescriptive variables (marriage, unemployment, and having experienced a greater number of recent life events). These findings showed that alternative treatments were beneficial to some patients, while cognitive psychotherapy was beneficial to others.[10]

Until recently, only minor attention had been given to neurocognitive performance as a moderator of treatment outcome in studies on depression,[14] despite studies on the association between cognitive variables and depressive symptoms.[15,16] Some authors have described the relevance of neurocognitive variables for predicting symptomatic improvement.[17] For instance, neurocognitive function at baseline was not predictive of symptom improvement in depression.[18]

Although some speculate that cognition may mediate change in psychotherapy,[3] a definite statement that neurocognitive processes serve as mediators of therapeutic change would be premature, because researchers are only beginning to study the relationship between neurocognition and treatment outcome. For this reason, using neurocognitive variables as possible predictors is relevant for intervention research.

At present, the literature offers little evidence on which variables might serve as prescriptive, prognostic, and/or moderator variables in different treatments for depression. Furthermore, intrinsic problems in statistical analysis tend to complicate results and cast doubt on some existing conclusions. A contributing factor to these complications is that the statistical power associated with interaction effects between a predictive variable and a certain treatment group tends to be low. These complications have been noted in the standard statistical approaches for identifying predictive variables,[3,10] such as covariance analyses, multiple regressions, and logistic regression models.[19]

In the present study, multilevel techniques were used to identify pretreatment variables that might be associated with the clinical response of outpatients with moderate depression. Use of multilevel model techniques (or mixed models) for analysis enables statisticians to make fewer statistical assumptions, producing more precise estimates and parameters, along with the ability to use all of the data collected at a given moment in time.[20] Potential predictor variables are viewed as belonging to two different potential predictor domains: sociodemographic and neurocognitive. Because of the high number of possible predictor variables in these domains, using multilevel model techniques for statistical analysis maximizes the odds of identifying response markers (i.e., prognostic, prescriptive, and/or moderator variables) without increasing the possibility that results would be due to chance.

After identifying predictive variables in this study, we reexamined each one to verify that all variables remained statistically significant as predictive of treatment outcome, given that all predictors had been tested simultaneously in the same final statistical model. This model followed recommendations presented in previous studies.[10]

Method

Design

The present study derives from a randomized clinical trial comparing LTPP, fluoxetine treatment (FLU), and a combination of the two (COM) in adult patients with moderate depression. Patients were assessed five times: at baseline and at 6, 12, 18, and 24 months of treatment. Independent researchers blinded to treatment allocation carried out the assessments. The full design and results of this project are described elsewhere.[21,22]

Participants

Participants were adult outpatients treated in a psychiatric clinic (women, 62%; mean age, 30 years). The inclusion criteria were presence of major depressive disorder, according to the DSM-IV-TR criteria; moderate level of depressive symptoms (as measured by BDI); and provision of written informed consent. The exclusion criteria were DSM-IV-TR Axis I and II comorbidities (as assessed by the structured clinical interview for DSM disorders, SCID-I and II), suicide risk, use of other medications that influence mental functioning, severe somatic diseases, and contraindications for fluoxetine use. Patients who agreed to participate (n=272) were randomized into three treatment groups (LTPP, n=90; FLU, n=91; COM, n=91). There were no significant differences between groups regarding clinical and sociodemographic features at baseline.

Treatments

The model of LTPP used in this study was similar to one previously described and widely used.[23] LTPP was received once a week for 24 months. FLU was administered 20 mg/day for the first 2 weeks. Intake was evaluated and adjusted at bimonthly psychiatric appointments until an appropriate dosage was reached (up to 60 mg/day). Subsequently, patients went to monthly appointments, where they received the medication and treatment compliance was verified. Combined therapy included both LTPP and FLU received concomitantly by a given patient. No statistically significant differences were found for variables related to psychotherapists (women, n=16; men, n=8; mean duration of clinical experience, 11 years; mean age, 35 years) and psychiatrists (women, n=3; men, n=3; clinical experience, n=6 years; mean age, 31 years) in tests of variables between conditions.

Instruments and outcome measures

The outcome measure for depression was the BDI,[24] which has been validated for use in Brazil.[25] The BDI measures severity of depression and classifies results as minimal (score, 0-11), mild (score, 12-19), moderate (score, 20-35), or severe (score, 36-63).

The Wechsler Intelligence Scale for Adults, Third Edition (WAIS-III) was the main instrument used to assess neurocognitive function and intelligence.[26] This scale, which has been adapted and validated for Brazilian populations,[27] is used throughout Brazil and Latin America, but its successor (WAIS-IV) has not been validated in Brazil. The WAIS-III consists of 14 subtests that assess specific neurocognitive functions: Vocabulary, Similarities (SIM), Arithmetic, Digit span, Information, Comprehension, Letter-number sequencing (LNS), Picture completion, Digit-symbol coding (DSC), Block design, Matrix reasoning (MR), Picture arrangement, Symbol search, and Object assembly. We conducted a psychometric reliability study of the WAIS-III to ensure that results would be reliable in depressed patients. The results showed that all subtests of the WAIS-III had good levels of reliability.[28] The association between cognitive problems and depression has been reported in previous studies,[29] and confirmed by neuroimaging studies.[30] Some researchers believe that, in addition to monitoring neurocognitive functioning, the WAIS-III may be extremely useful in predicting clinical response to treatment.[15]

Potential predictors

Potential predictors of response to treatment were measured prior to randomization. Available variables were assigned to two different domains.

The first domain included sociodemographic data. The available variables measured were sex, age, marital status, and level of education.

The second domain included neurocognitive variables, assessed by the WAIS-III. Previous researchers have viewed cognitive variables as potential predictors, as evidence suggests that cognitive changes occur prior to clinical improvement in depressed patients.[31] The possibility exists that neurocognitive deficits precede the onset of depression symptoms,[15] and the pretreatment status of cognitive processes (e.g., abstract reasoning) is considered a possible mediator of therapeutic change in psychotherapy.[3] Therefore, each WAIS-III subtest was considered a variable. These are listed in Table 1.

Statistical analysis

Mixed model analyses, commonly used for longitudinal data, are appropriate in evaluating the relationship between the dependent variable and time. Regression curves are adjusted for each subject, and regression coefficients are allowed to vary randomly among subjects. Because this variation occurs on intercepts and on slopes, we adjusted the random coefficient model (which arithmetically describes the relationship between observations and time). The growth curves of the groups consider the parameters of individual growth curves, as well as the average growth curve.[32]

A diagonal covariance structure was used to shape the correlation between intercepts and slopes. All available data were analyzed under the intention-to-treat assumption. Maximum likelihood procedures were used for all models.

The first statistical analyses aimed to investigate the association between possible improvement predictive variables (prognostics, predictive, and/or moderators) over the 24-month study period. BDI results were analyzed using growth curve models (i.e., with the time measure used as a covariate), and subjects were set as random effects. Therefore, the BDI results and growth curve of each subject at the end of treatment were derived from a collection of that subject's specific parameters.

To identify relevant predictors, we considered three approaches proposed in earlier studies.[3,4,10] Interactions among treatment conditions (groups), time, and interest predictors were examined.

Prognostic variables were those in which the lower-order term was statistically significant (i.e., representing only the main variable). In this study, treatment outcome depended on the score of this predictor, regardless of the treatment received by the subject.

Prescriptive variables were those in which the lower-order term and the term representing the variable $\times$ treatment interaction were significantly related to outcome. In this study, these variables indicated that different treatment effects were occurring (depending on the value of the variable in question).

Finally, moderator variables were those in which the lower-order term and the term representing the variable $\times$ time interaction were statistically significant. This means that there were interactions with the linear time effect (i.e., over time, the BDI score depends on the variable value, as it indicates that some characteristic of this variable influences the magnitude and/or direction of the relationship between intervention and outcome).

A stepwise model was used within each domain. The first step was to verify whether the model that included all the variables of each domain was statistically significant.

Table 1 Neuropsychological meaning of WAIS-III subtests and their test-retest reliability coefficients

Subtest	Meaning*	Reliability coefficients (r)†
Vocabulary	The degree to which the person learned and was able to comprehend and verbally express vocabulary.	0.98
Similarities	Abstract verbal reasoning.	0.97
Arithmetic	Concentration on the task of manipulating mental mathematical problems.	0.96
Digit span	Attention and concentration, working memory.	0.72
Information	Level of general cultural knowledge acquired.	0.99
Comprehension	Capacity to deal with abstract social conventions, rules, and social values.	0.97
Letter-number sequencing	Working memory, attention, concentration, capacity to change reference mental scheme.	0.73
Picture completion	Attention to visual details.	0.92
Digit-symbol coding	Processing speed, working memory, coordination.	0.88
Block design	Spatial perception and problem solving.	0.96
Matrix reasoning	Abstract non-verbal problem solving, inductive reasoning, spatial reasoning, abstract reasoning.	0.78
Picture arrangement	Logical reasoning, capacity to understand social conventions.	0.97
Symbol search	Processing speed, attention, and concentration.	0.95
Object assembly	Capacity of analysis, synthesis, and holistic potential.	0.98

* Neuropsychological and clinical meaning of the cognitive variables, according to the interpretation criteria proposed.[26,27]
† Test-retest reliability coefficients from a subsample of the study participants.[28]

Table 2 Final model

Predictor	M	SD	*b*-value	*t* (df)	p-value	Attribute*
Similarities	13.27	2.78	0.31	2.71 (580)	0.007	Prognostic
Letter-number sequencing	9.68	2.30	-1.17	-6.28 (635)	0.000	Prognostic
Matrix reasoning	10.95	2.00	-0.47	-3.14 (944)	0.002	Prognostic
Digit-symbol coding	10.10	2.42	0.01	0.09 (682)	0.924	None
Similarities × Time			-0.01	-3.24 (564)	0.001	Moderator
LNS × Treatment			1.16	4.24 (419)	0.000	Prescriptive
DSC × Treatment			-0.94	-3.64 (727)	0.000	Moderator

df = degrees of freedom; M = mean; SD = standard deviation.
b values represent unstandardized beta coefficients of Beck Depression Inventory (BDI) scores. For lower single terms, values represent effects averaged across the treatment groups. Negative values indicate outcomes that are more desirable (lower BDI scores along treatments). For interaction terms with treatment, values indicate the difference between treatments in the magnitude of the effect in each point of measurement. For interaction terms with time, values indicate that the variable has a characteristic that influences the direction or strength of the relation between an intervention and the outcome. In this case, a significant predictor × time interaction term suggests an interaction with the linear time effect, i.e., the speed of linear BDI change over time depends on the predictor value.
* Prescriptive and prognostic predictors were qualified according to previous recommendations.[10] Moderators were qualified according to previous recommendations.[3]

The second step was to keep only those predictors significant at $p < 0.20$. The third step retained predictors with $p < 0.10$, while the fourth retained only those with $p < 0.05$. Once all predictive variables had been identified, they were entered into a final model containing all remaining significant predictors. Thus, the effects of each variable were tested again while simultaneously controlling for the others.

Results

Because the results of our stepwise analysis of the sociodemographic domain (first domain) did not reach statistical significance, this domain was removed from the predictor model.

The second domain included the neurocognitive variables defined on the basis of the subtests of the WAIS-III (see Table 1) and their interaction with time and treatment. Six significant predictors were identified: SIM, LNS, and MR as lower-order terms (i.e., prognostics); SIM × Time and DSC × Treatment as terms that moderate outcome; and LNS × Treatment as a treatment-prescriptive term (Table 2).

For lower-order effects (variables without interactions), *b* estimates can be interpreted as representing changes in mean BDI scores for each unit of change in the predictor variable, controlling for all other predictors in the model. An isolated predictive term indicates only a main effect of the variable (i.e., the variable pretreatment value is associated with BDI mean scores in all periods). As the variable does not depend on group or time, it is considered prognostic.

On the other hand, when the term in question is statistically significant as a main term and the term variable × time is also statistically significant, this means that there is an interaction of the term in question with the effect of time. In this case, the magnitude or direction of change in the BDI mean score over time depends on

the value of the interaction variable. The variable is then considered a moderator. Similarly, when the term interacts with treatment (variable × treatment) but the main term is not statistically significant, the variable can also be considered a moderator, as this indicates that the term in question has a characteristic that causes a difference in the magnitude or direction of the relationship between outcome (dependent variable) and treatment (independent variable). Finally, when the term in question is statistically significant as the main term and interacts with treatment (variable × treatment), it becomes a prescriptive variable.

With regard to prognostic variables, higher baseline scores in SIM predicted higher BDI scores in all periods, whereas higher baseline scores in LNS and MR predicted lower BDI scores. More specifically, adding a single unit to the SIM baseline score each time yielded a 0.31 raise in BDI mean score each time it was measured. On the other hand, a one-unit increase in LNS and MR baseline scores was associated with a reduction of 1.17 and 0.47 in the BDI mean score, respectively, each time it was measured.

The LNS variable was considered treatment-prescriptive. Improvement differences in BDI scores when LTPP and COM were compared were not statistically significant. However, both treatments stood out significantly when compared to FLU. Patients with the same LNS baseline score responded better to LTPP and COM than to FLU.

Nevertheless, the SIM × Time interaction showed that lower SIM baseline scores predicted smaller decreases in mean BDI scores over time, which did not depend on treatment but depended on time. The DSC × Treatment interaction indicated that the direction of the relationship between the independent variable (treatment) and the dependent variable (BDI score) depended on the DSC variable. Higher baseline scores on the DSC were negatively associated with BDI scores in the FLU treatment. However, higher baseline DSC scores were positively associated with BDI scores in LTPP and COM. In other words, higher baseline DSC scores predicted lower BDI scores in patients who received FLU. In addition, higher baseline DSC scores predicted higher BDI scores in patients who had LTPP and COM. Therefore, the DSC variable moderated the direction of the relationship between treatment and outcome.

Final model with all significant predictors

Once identified, the prescriptive, prognostic, and/or moderator markers were simultaneously entered into a final model, so that the effect of each marker could be maintained while controlling for the effects of the other markers. As Table 2 shows, each effect remained statistically significant when all effects were covaried.

Table 3 shows the final BDI mean scores for the variables SIM, LNS, and MR (lower-order terms) in five different baseline scores (i.e., sample mean, one and two SDs above the mean, and one and two SDs below the mean). This division in baseline score (above and below the mean) was carried out deliberately to demonstrate specific subgroup differences.

Table 3 BDI results for the three prognostic variables at five different levels of baseline value

Prognostic variable	Value	Final BDI mean*
Similarities†	- 2 SD (7.71)	7.84
	- 1 SD (10.49)	7.97
	Mean (13.27)	8.10
	+ 1 SD (16.05)	8.24
	+ 2 SD (18.83)	8.37
Letter-number sequencing	- 2 SD (5.07)	13.57‡
	- 1 SD (7.38)	12.27‡
	Mean (9.68)	10.98
	+ 1 SD (11.98)	9.68
	+ 2 SD (14.29)	8.38
Matrix reasoning	- 2 SD (6.95)	8.27
	- 1 SD (8.95)	8.19
	Mean (10.95)	8.11
	+ 1 SD (12.95)	8.03
	+ 2 SD (14.95)	7.95

BDI = Beck Depression Inventory; SD = standard deviation.
*Values represent the BDI scores at the end of treatment for different values of the predictor variables, independent of treatment type.
†The variable Similarities is also a moderator, as it interacts with time.
‡Did not reach clinical significance: BDI cutoff point < 11.[25]

The variables LNS and DSC had a statistically significant interaction with treatment. Table 4 shows these variables in each treatment at different baseline scores, to illustrate the differences in within- and between-treatment subgroups.

A positive association was noted between SIM baseline scores and BDI scores. Each SIM unit above the baseline sample mean represented more BDI-measured symptoms at each time point of measurement. On the other hand, a negative association was noted between BDI scores and the variables LNS and MR at the end of treatment. Each LNS and MR point above the baseline sample mean was associated with less BDI points for each time it was measured.

Subjects with baseline LNS scores one SD below the mean did not reach the clinical cutoff point for treatment outcome, regardless of treatment modality. Therefore, low pretreatment LNS scores may be prognostic of poor treatment outcome. For instance, patients receiving FLU treatment would need to have very high LNS scores to achieve the BDI clinical cutoff point. This suggests that low LNS scores may contraindicate FLU alone for patients with moderate depression.

There were no statistically significant differences between LTPP and COM, but both were significantly different from FLU. Figure 1 shows differences between treatments in terms of final BDI mean scores associated with the LNS prescriptive variable, $t_{419} = 4.23$, $p < 0.001$, Cohen's $d = 1.43 \pm 0.59$ (95% confidence interval). As LNS baseline scores increased, participants in the LTPP and COM groups had significantly fewer BDI points at the end of treatment when compared to the participants in the FLU group.

Table 4 BDI results for the prescriptive variable and the moderator variable in each of the treatments at five different levels of baseline value*

Variable	Value	Final BDI		
		LTPP	FLU†	COM
LNS (prescriptive)	- 2 SD (5.07)	6.00	15.39	4.21
	- 1 SD (7.38)	5.80	15.20	4.00
	Mean (9.68)	5.61	15.02	3.80
	+ 1 SD (11.98)	5.41	14.83	3.59
	+ 2 SD (14.29)	5.21	14.64	3.38
DSC (moderator)	- 2 SD (5.27)	5.34	15.02	3.36
	- 1 SD (7.68)	5.48	15.01	3.59
	Mean (10.10)	5.62	15.00	3.83
	+ 1 SD (12.51)	5.76	14.99	4.06
	+ 2 SD (14.92)	5.90	14.98	4.29

BDI = Beck Depression Inventory; COM = combined therapy; FLU = fluoxetine treatment; LTPP = long-term psychodynamic psychotherapy; SD = standard deviation.
* Values represent BDI scores at the end of the different treatments for different values of the predictor variable and the moderator variable.
† Did not reach clinical significance: BDI cutoff point < 11.[25]

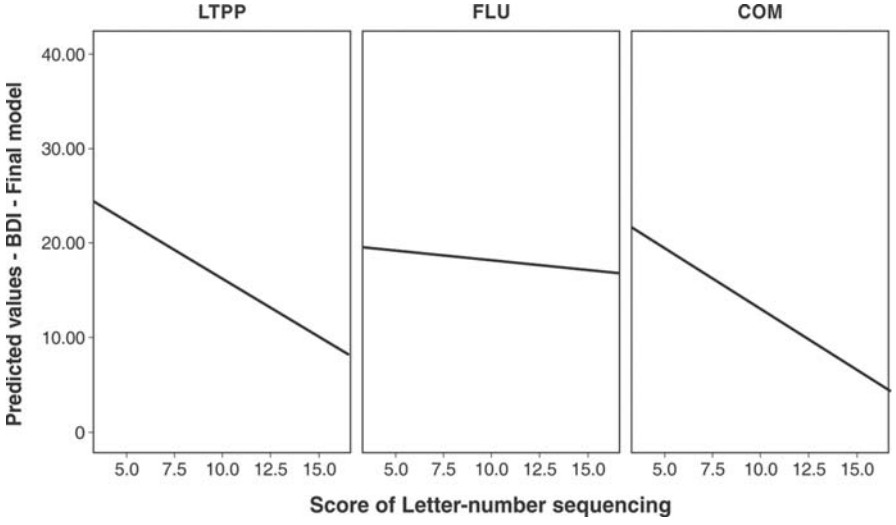

Figure 1 Linear slope estimates for the LNS × Treatment interaction. The slope of a line is the ratio of the change in *y* over the change in *x*. This is also known as "rise over run," i.e., the slope or gradient of a line describes its steepness, incline, or grade. A higher slope value indicates a steeper incline. Slope is normally described by the ratio of the "rise" divided by the "run" between two points on a line. BDI = Beck Depression Inventory; COM = combined therapy; FLU = fluoxetine treatment; LTPP = long-term psychodynamic psychotherapy.

The final model, with three prognostic variables, one prescriptive variable, and two moderator variables, accounted for approximately 46% of the between-subject variance among treatments. This variance occurred in the final BDI mean scores and in the linear slope estimates.

Discussion

This study aimed to investigate outcome predictors for three different treatments for depression. The objective was to identify prognostic, prescriptive, and/or moderator variables that could help guide clinical protocols.

Although a number of studies on the association between cognitive variables and depressive symptoms have been published,[15,16] we found no studies using neurocognitive markers (obtained from WAIS-III) as predictive variables when comparing different treatments. Three studies that used the WAIS-III in a long-term psychoanalytic psychotherapy context reported only test-retest changes in patients and did not attempt to find predictive outcome variables.[16,21,33]

In the present study, the sociodemographic domain did not result in statistically significant predictive variables (i.e., age, sex, marital status, and level of education). Some studies, however, identified age as a predictor of slower response to treatment,[7,26] while others found no association between age and treatment outcome.[7,8] Level of education may be positively associated with treatment outcome.[9] Other examples of potential demographic predictors of treatment outcome include gender, marital

status, family history of treatment response, and socioeconomic level.[34]

It is worth noting that the sample of patients for this study was very homogeneous in terms of sociodemographic and clinical profiles, which constitutes a definite limitation of this study, and that this homogeneity may have contributed to the lack of statistical significance in the sociodemographic domain. Participants were mostly young women with good socioeconomic level and educational attainment, who tended to adapt to psychotherapy more easily.[35] The possibility exists that other patients (i.e., older women or men and women with a lower social and education levels) might have difficulty adapting to psychotherapy or other long-term treatments. This discrepancy in adaptation to long-term treatment would reduce the external validity of our results. Homogeneous samples generally are not representative of the huge variety of outpatients. The antithesis between external and internal validity of data has been widely discussed.[36]

In this study, most participants had a moderate level of depression (as measured by the BDI). Two studies have shown a correlation between severity of depression and treatment outcome.[9,11] This finding appears to be more likely when a wider range of patients with depression is evaluated. Predictors for treatment outcome include symptoms, patient treatment preference, early life stress, personality characteristics, and previous treatment.

With regard to neurocognitive variables with prognostic features, higher LNS baseline scores (which are associated with working memory and attention) predicted lower BDI results at outcome. Two studies have associated working memory function with depression treatment outcome.[14,17] Similarly, it has been reported that lower attention predicts poorer response to depression treatment.[37] These findings suggest that patients who are less impaired in functions such as working memory and attention have a better prognosis, regardless of the type of treatment they are receiving.

Another prognostic variable is abstract reasoning (MR), which some researchers believe may be important in clinical improvement.[3] The MR subtest, however, demands special consideration. Some studies have associated the results of this test at least partially with performance in tests that assess executive functioning,[38] such as the Wisconsin Card Sorting Test. Poor executive functioning tends to lead to a poor prognosis in patients with depression. In sum, better baseline performance in executive functions suggest better treatment outcomes.

These findings are consistent with those of the present study, and appear to support the idea that executive functioning and working memory are related to treatment outcome in patients with moderate depression. Likewise, according to evidence showing an association between neuropsychological abnormalities and alterations on functional neuroimaging,[39] data from the present study suggest an association between the frontotemporal circuitry of the brain and treatment outcomes in depression.

Neuroimaging studies corroborate this association, identifying other brain regions that are potentially involved in clinical improvement mechanisms. Changes in the prefrontal limbic region in patients with depression 15 months after LTPP,[40] as well as changes in some cortical regions (prefrontal, anterior cingulate, and insula), may be considered biological markers for treatment response and predictors of treatment outcome in patients with depression.[41]

A higher baseline score in verbal abstract reasoning (SIM) was considered a prognostic predictor of slightly higher BDI scores with time. SIM is also considered an excellent test for general mental ability.[26] A possible interpretation is that a subject's level of verbal abstract reasoning may act upon his or her interpretations of BDI statements and, consequently, upon the choice of statement to be checked in the scale. Hypothetically, depressed subjects with higher levels of verbal abstract reasoning tend to be more pessimistic when choosing BDI statements, tending to score slightly higher, regardless of the treatment they are receiving. This hypothesis is supported by consistent findings showing that clinical depression is followed by negative alterations in perceptive content, which could cause negative thoughts, considerations, and judgments.[42] Findings such as this may indicate a very limited prognostic effect of the SIM variable and must be interpreted with caution. At one time, SIM was also considered an outcome moderator due to its interaction with the time variable, suggesting that some characteristic of this variable actually may interfere with outcome. Further studies must be carried out with the cognitive construct verbal abstract reasoning in patients with depression in order to clarify the time variable's possible interference with outcome, as it could be an anomalous finding in the context of so many predictors.

DSC is another moderator variable that is usually associated with processing speed and working memory. This variable apparently has characteristics that alter the direction of the relationship between the independent (treatments) and dependent (BDI score) variables, indicating a trend of different patterns of response in the three treatments compared. In the LTPP and COM groups, the DSC variable apparently moderated a positive relationship, whereas in the FLU group, that relationship was negative. These data suggest that differences within treatment processes may be involved.

Regarding the prescriptive variable LNS, linear slopes indicated that LTTP and COM were more clinically efficient than FLU in patients with a higher capacity of working memory and attention. Other studies have pointed out that combined treatments tend to be more effective than FLU alone in patients with mild to moderate depression.[43] We found no data on working memory capacity and its interaction with LTPP. This gap caused some LTPP findings in this study to appear relatively obscure. Secondary analyses dividing the FLU group into treatment responders and non- responders should help clarify this.

Many factors that can influence patients' cognition have been emphasized in the literature: everyday experiences, physiology, psychological alterations, and cultural factors. Understanding the underlying mechanisms of therapeutic change can provide inputs for enhancement of clinical treatment results.[44] The lack of answers regarding fundamental questions on how treatments trigger clinical

changes in patients precludes many patients from receiving the benefits of more adequate treatments for their individual profiles.[3]

In addition, an individual's neurocognitive profile may be a marker of prognostic and prescriptive criteria for the treatment of depression. The results of the present study should be considered cautiously because of the possible presence of multiple predictor variables. Furthermore, identification of predictive (prognostic, prescriptive, and/or moderator) effects may provide more information for creating better tools for clinical decision-making. Understanding treatment moderators is key to choosing appropriate treatments and guiding clinical practice. Further studies are strongly suggested.

Finally, some of the limitations to this study have been reported elsewhere.[21,22] Because of the sample homogeneity, our findings are applicable to only a particular profile of outpatients – i.e., those diagnosed with moderate depression and treated for 24 months with the therapies used in this study. Other patients or treatments could result in different predictive variables. Another limitation is that the selection of possible variables used here was made among variables that were readily available. Inclusion of other variables could also alter results of the analyses employed.

Disclosure

The authors report no conflicts of interest.

References

1 Kaplan B, Sadock V. Kaplan & Sadock's concise textbook of psychiatry. Philadelphia: Lippincott, Willians & Wilkins; 2008.
2 Leichsenring F, Rabung S. Effectiveness of long-term psychodynamic psychotherapy: a meta-analysis. JAMA. 2008;300:1551-65.
3 Kazdin AE. Mediators and mechanisms of change in psychotherapy research. Annu Rev Clin Psychol. 2007;3:01-27.
4 Kraemer HC, Wilson GT, Fairburn CG, Agras WS. Mediators and moderators of treatment effects in randomized clinical trials. Arch Gen Psychiatry. 2002;59:877-83.
5 Barber JP, Connoly MB, Crits-Christoph P, Gladis L, Siqueland L. Alliance predicts patient's outcome beyond in-treatment change in symptom. J Consul Clin Psychol. 2000;68:1027-32.
6 Tang TZ, DeRubeis RJ. Sudden gains and critical sessions in cognitive-behavioral therapy for depression. J Consult Clin Psychol. 1999;67:894-904.
7 Szadoczky E, Rozsa S, Zambori J, Furedi J. Predictors for 2-year outcome of major depressive episode. J Affect Disord. 2004;83:49-57.
8 Petersen T, Papakostas GI, Bottonari K, Iacoviello B, Alpert J, Fava M, et al. NEO-FFI factor scores as predictors of clinical response to fluoxetine in depressed outpatients. Psychiatry Res. 2002;109:09-16.
9 Harbeck S, Kliem S, Wollburg E, Braukhaus C, Kröger C. [Remission, response, and its prediction in depressive inpatients]. Psychother Psychosom Med Psychol. 2013;63:272-9.
10 Fournier JC, DeRubeis RJ, Shelton RC, Hollon SD, Amsterdam JD, Gallop R. Prediction of response to medication and cognitive therapy in the treatment of moderate to severe depression. J Consult Clin Psychol. 2009;77:775-87.
11 Elkin I, Gibbons RD, Shea MT, Sotsky SM, Watkins JT, Pilkonis PA, et al. Initial severity and differential treatment outcome in the National Institute of Mental Health Treatment of Depression Collaborative Research Program. J Consult Clin Psychol. 1995;63:841-7.
12 van Noorden MS, van Fenema EM, van der Wee NJ, Zitman FG, Giltay EJ. Predicting outcome of depression using the depressive symptom profile: the Leiden Routine Outcome Monitoring Study. Depress Anxiety. 2012;29:523-30.
13 Joutsenniemi K, Laaksonen MA, Knekt P, Haaramo P, Lindfors O. Prediction of the outcome of short- and long-term psychotherapy based on socio-demographic factors. J Affect Disord. 2012;141:331-42.
14 Kaneda Y. Working memory in patients with major depressive disorder. Psychology. 2012;3:758-61.
15 Basso M, Miller A, Estevis E, Combs D. Neuropsychological deficits in major depressive disorder: correlates and conundrums. In: Arnett P. Secondary influences on neuropsychological test performance. New York: Oxford University; 2013.
16 Bastos AG, Trentini CM. Psicoterapia psicodinâmica e tratamento biológico com fluoxetina: Comparação de resposta cognitiva em paciente deprimidos. Psic Teor Pesq. 2013;29:437-46.
17 Marcos T, Portella MJ, Navarro V, Gasto C, Rami L, Lazaro L, et al. Neuropsychological prediction of recovery in late-onset major depression. Int J Geriatr Psychiatry. 2005;20:790-5.
18 Biringer E, Mykletun A, Sundet K, Kroken R, Stordal KI, Lund A. A longitudinal analysis of neurocognitive function in unipolar depression. J Clin Exp Neuropsychol. 2007;29:879-91.
19 Aguinis H, Stone-Romero EF. Methodological artifacts in moderated multiple regression and their effects on statistical power. J Appl Psychol. 1997;82:192-206.
20 Singer J, Willett J. Applied longitudinal data analysis: modeling change and event occurrence. New York: Oxford University; 2003.
21 Bastos AG, Guimarães LS, Trentini CM. Neurocognitive changes in depressed patients in psychodynamic psychotherapy, therapy with fluoxetine and combination therapy. J Affect Disord. 2013;151: 1066-75.
22 Bastos AG, Guimarães LS, Trentini CM. The efficacy of long-term psychodynamic psychotherapy, fluoxetine and their combination in the outpatient treatment of depression. Psychother Res. 2015;25: 612-24.
23 Gabbard G. Long-term psychodynamic psychotherapy: a basic text. 2nd ed. Arlington: American Psychiatric; 2010.
24 Beck A, Steer R. Beck depression inventory. San Antonio: Psychological Corporation; 1993.
25 Cunha J. Manual da versão em português das Escalas Beck. São Paulo: Casa do Psicólogo; 2001.
26 Lezak M, Howieson D, Loring D. Neuropsychological assessment. 4th ed. Oxford: University Press; 2004.
27 Nascimento E. Manual da Escala de Inteligência Wechsler para adultos. São Paulo: Casa do Psicólogo; 2004.
28 Bastos AG, Gomes BM, Bandeira DR, Trentini CM. Reliability of the Brazilian WAIS-III in depression. Interam J Psychol. 2011;45:419-28.
29 Marvel CL, Paradiso S. Cognitive and neurological impairments in mood disorders. Psychiatr Clin North Am. 2004;27:19-36.
30 Thomas EJ, Elliott R. Brain imaging correlates of cognitive impairment in depression. Front Hum Neurosci. 2009;03:30.
31 Dunkin JJ, Leuchter AF, Cook IA, Kasl-Godley JE, Abrams M, Rosenberg-Thompson S. Executive dysfunction predicts nonresponse to fluoxetine in major depression. J Affect Disord. 2000;60: 13-23.
32 Brown H, Prescott R. Applied mixed models in medicine. Chichester: John Wiley & Sons; 2006.
33 Yazigi L, Semer NL, Amaro TC, Fiore MLM, Silva JFR, Botelho NLP. Rorschach and the WAIS-III after one and two years of psychotherapy. Psicol Reflex Crit. 2011;24:10-8.
34 Trivedi MH, Rush AJ, Wisniewski SR, Nierenberg AA, Warden D, Ritz L, et al. Evaluation of outcomes with citalopram for depression using measurement-based care in STAR*D: implications for clinical practice. Am J Psychiatry. 2006;168:28-40.
35 Houle J, Villaggi B, Beaulieu MD, Lespérance F, Rondeau G, Lambert J. Treatment preferences in patients with first episode depression. J Affect Disord. 2013;147:94-100.
36 Roth A, Fonagy P. What works for whom? A critical review of psychotherapy research. New York: Guilford; 2005.
37 Weiland-Fiedler P, Erickson K, Waldeck T, Luckenbaugh DA, Pike D, Bonne O, et al. Evidence for continuing neuropsychological impairments in depression. J Affect Disord. 2004;82:253-8.
38 Perkins L. An investigation of the relationship of student performance on the Wisconsin card sorting test with other clinical measures. Philadelphia: Philadelphia College of Osteopathic Medicine; 2009.
39 Navarro V, Gastó C, Lomeña F, Torres X, Mateos JJ, Portella MJ, et al. Prognostic value of frontal functional neuroimaging in late-onset severe major depression. Br J Psychiatry. 2004;184:306-11.

40 Buchheim A, Viviani R, Kessler H, Kächele H, Cierpka M, Roth G, et al. Changes in prefrontal-limbic function in major depression after 15 months of long-term psychotherapy. PLoS One. 2012;7: e33745.
41 Wang Y, Xu C, Cao X, Gao Q, Li J, Liu Z, et al. Effects of an antidepressant on neural correlates of emotional processing in patients with major depression. Neurosci Lett. 2012; 527:55-9.
42 Chepenik LG, Cornew LA, Farah MJ. The influence of sad mood on cognition. Emotion. 2007;7:802-11.
43 Curry J, Rohde P, Simons A, Silva S, Vitiello B, Kratochvil C, et al. Predictors and moderators of acute outcome in the Treatment for Adolescents with Depression Study (TADS). J Am Acad Child Adolesc Psychiatry. 2006;45:1427-39.
44 Bastos AG. Diagnóstico psiquiátrico e clínica psicanalítica. Interacao Psicol. 2014;18:109-17.