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Lorenzo Lorenzo-Luaces

University of Pennsylvania, lorenzl@sas.upenn.edu

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Heterogeneity In Major Depression: Influence On Treatment Outcomes And Processes-Outcome Relations

Abstract

Some have proposed that all psychotherapies for depression, as well as for other common mental disorders, are equally efficacious and that they all work through common processes, especially a relationship with a therapist. One reason it may be difficult to discern differential efficacy among treatments, as well as how they exert their effects, is that depression and other disorders are heterogeneous in both presentation and prognosis. The studies presented in the dissertation aimed to explore how heterogeneity in depression may moderate treatment effects and process-outcome relations. In study 1, a prognostic index (PI) was developed and treatment differences along the PI were explored in a sample of patients (N = 622) randomized to treatment as usual (TAU) or stepped care starting with brief therapy (BT) or with cognitive-behavioral therapy (CBT). The PI comprised five variables: unemployment status, depression severity, hostility, sleep problems, and lower positive emotionality, all of which predicted a lower likelihood of recovery. For patients whose PI indicated a high likelihood of recovery (73% of the sample), recovery rates were similarly high across the treatments. Among patients whose PI indicated a lower likelihood of recovery, patients in the CBT condition experienced a substantially higher recovery rate (65%) than patients in TAU (40%) or BT (44%). In study 2, variability in the predictive relationship between the therapeutic alliance and depressive symptom change was explored in a sample of patients receiving cognitive therapy (CT) for depression (N = 60). The alliance predicted outcome in the subgroup of clients with 0–2 prior episodes ($r = .52$), but not in those with 3 or more prior episodes ($r = -.02$). In study 3, these findings were replicated in an independent sample of patients receiving CBT for depression, but they did not extend to patients in a psychodynamic therapy condition. Taken together, these findings suggest that there may be identifiable subgroups of patients for whom factors common to all treatments will promote symptom change. By contrast, complementary subgroups, such as those with poorer prognoses or more recurrent histories of depression, may reveal differences in the efficacies of treatments and their active mechanisms.

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**HETEROGENEITY IN MAJOR DEPRESSION: INFLUENCE ON TREATMENT
OUTCOMES AND PROCESSES-OUTCOME RELATIONS**

Lorenzo Lorenzo-Luaces

A DISSERTATION

in

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2017

Supervisor of Dissertation

Graduate Group Chairperson

Dr. Robert J. DeRubeis

Dr. Sara Jaffee

Samuel H. Preston Term Professor in
the Social Sciences

Professor of Psychology

Dissertation Committee

Dr. Ayelet Meron Ruscio (Chair), Associate Professor of Psychology

Dr. Dianne Chambless, Professor of Psychology

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ABSTRACT

HETEROGENEITY IN MAJOR DEPRESSION: INFLUENCE ON TREATMENT OUTCOMES AND PROCESSES-OUTCOME RELATIONS

Lorenzo Lorenzo-Luaces

Robert J. DeRubeis

Some have proposed that all psychotherapies for depression, as well as for other common mental disorders, are equally efficacious and that they all work through common processes, especially a relationship with a therapist. One reason it may be difficult to discern differential efficacy among treatments, as well as how they exert their effects, is that depression and other disorders are heterogeneous in both presentation and prognosis. The studies presented in the dissertation aimed to explore how heterogeneity in depression may moderate treatment effects and process-outcome relations. In study 1, a prognostic index (PI) was developed and treatment differences along the PI were explored in a sample of patients (N = 622) randomized to treatment as usual (TAU) or stepped care starting with brief therapy (BT) or with cognitive-behavioral therapy (CBT). The PI comprised five variables: unemployment status, depression severity, hostility, sleep problems, and lower positive emotionality, all of which predicted a lower likelihood of recovery. For patients whose PI indicated a high likelihood of recovery (73% of the sample), recovery rates were similarly high across the treatments. Among patients whose PI indicated a lower likelihood of recovery, patients in the CBT condition experienced a substantially higher recovery rate (65%) than patients in TAU (40%) or BT (44%). In study 2, variability in the predictive relationship between the therapeutic alliance and depressive symptom change was explored in a sample of patients receiving cognitive therapy (CT) for depression (N = 60). The alliance predicted outcome in the subgroup of clients with 0–2 prior episodes ($r = .52$), but not in those with 3 or more prior episodes ($r = -.02$). In study 3, these findings were replicated in an independent sample of patients receiving CBT for depression, but they did not extend to patients in a psychodynamic therapy condition. Taken together, these findings suggest that there may be identifiable subgroups of patients for whom factors common to all treatments will promote symptom change. By contrast, complementary subgroups, such as those with poorer prognoses or more recurrent histories of depression, may reveal differences in the efficacies of treatments and their active mechanisms.

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**CHAPTER 1: A PROGNOSTIC INDEX AS A MODERATOR OF OUTCOMES IN THE
TREATMENT OF MOOD DISORDERS: COMBINING MULTIPLE VARIABLES TO
INFORM STEPPED CARE ASSIGNMENT**

Lorenzo Lorenzo-Luaces¹ (M.A.), Annemieke van Straten (Ph.D.),
Robert J. DeRubeis¹ (Ph. D.)

1 Department of Psychology, University of Pennsylvania, ² Department of
Clinical Psychology, VU University Amsterdam

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ABSTRACT

Prognostic indices (PIs) that combine more than one variable to predict subsequent depression risk may help guide the selection of treatments that differ in intensity. We demonstrate the development of a PI and show its promise in guiding treatment decisions between treatment as usual (TAU), stepped care starting with a low intensity treatment (brief therapy (BT)), or stepped care starting with a high intensity treatment (cognitive-behavioral therapy (CBT)). We utilized data from depressed patients (N = 622) who participated in a randomized comparison of TAU, BT, and CBT in which no statistically significant differences in the primary measure of outcome emerged between the three treatments. We developed a PI by predicting depression risk at follow-up across the entire sample using a LASSO-style bootstrap ranking variable selection procedure. We then examined between-treatment differences in outcome as a function of the PI. Unemployment status, depression severity, hostility, sleep problems, and lower positive emotionality at baseline predicted a lower likelihood of recovery across treatments. The resulting PI incorporating these variables produced a good classification accuracy ($c = 0.73$). The PIs of 73% of the patients indicated a high likelihood of recovery from MDD within the 2-year study period. Of these, 81% recovered irrespective of condition. Among the 27% of the sample with the lowest PIs, patients in the CBT condition experienced a higher recovery rate (65%) than patients in TAU (40%) or BT (44%). Replicable PIs may aid treatment selection and help streamline stepped models of care. For most individuals who are depressed, the differences between existing treatments for depression appears to be negligible. Thus, all else equal, lower intensity treatments should be prioritized over more intensive ones. For individuals with a more severe

course, greater functional impairment, and a higher vulnerability to depression, more intensive interventions should be considered.

INTRODUCTION

There is a wide variety of treatments for depression, and these treatments differ in how intense they are in terms of the investment and resources required from patients and mental health providers. Despite the availability of these different types of interventions, current models for the delivery of mental health care for depression are known to be inadequate. At one end of the spectrum, some patients receive higher intensity interventions than they require to experience symptom relief, for example undergoing antidepressant treatment or long-term psychotherapy when they could experience comparable benefit from briefer therapies or lifestyle changes (Lorenzo-Luaces, DeRubeis, & Bennett, 2015; Lovell & Richards, 2000). Conversely, many patients do not receive the intensity of care that they might require to experience symptom relief, for example receiving supportive listening when they might benefit more from the combination of antidepressant medications and an evidence-based psychotherapy (Kocsis et al., 2008; Lecrubier, 2007). It is difficult to match patients to the appropriate level of care they need because there are few variables that are known to affect treatment response (van Straten, Hill, Richards, & Cuijpers, 2015), and mood disorders are extremely heterogeneous in their presentation and prognosis (Lorenzo-Luaces, 2015; Parker, 2005). We describe an approach to combining variables into a prognostic index (PI) that can be used when selecting between treatments that differ in intensity.

It is well appreciated that even when two treatments are equally efficacious there may be important subgroups of patients who would respond preferentially to one of the treatments over the other (DeRubeis et al., 2014; Kang, Janes, & Huang, 2014; Kraemer, 2013; Wallace, Frank, & Kraemer, 2013). Even when one treatment approach is known to be superior, on average, to another treatment or a control, it is

still possible that the efficacy of the stronger treatment is confined to a subset of the population and that patients can be matched to the intensity of care most appropriate to them (Delgadillo, Moreea, & Lutz, 2016). For example, although on average antidepressants are reported to be more efficacious than placebos, their superiority over placebos seems to be limited to patients with more severe depression (Barbui, Cipriani, Patel, Ayuso-Mateos, & van Ommeren, 2011; Fournier et al., 2010; Khan, Leventhal, Khan, & Brown, 2002; Kirsch et al., 2008). Similar findings have been reported for psychotherapy (Driessen, Cuijpers, Hollon, & Dekker, 2010). Although few would argue that these findings should be interpreted to mean that antidepressants and psychotherapy are no more than placebo controls, it appears that patients with non-severe depression stand to benefit as much from interventions that are less intensive or less expensive than treatments that are more intensive.

Stepped models of care for depression and other health conditions rely on the logic that many patients can benefit from less intensive interventions before requiring high intensity ones, and there is some empirical support for this assumption. In a recent study comparing face to face cognitive-behavioral therapy (CBT) to stepped care, there were no differences between the two treatments conditions and most patients who recovered in stepped care did so in the less intensive phases of treatments (Nordgreen et al., 2016). Although stepped models of care represent an improvement over other traditional models of care, they could be substantially streamlined if one knew, *a priori*, who is likely to respond to a low intensity treatment and who is likely to require a stronger or more intensive treatment. Given the findings suggesting that the efficacy of antidepressants and psychotherapy is limited to patients with more severe depression, a logical

recommendation for improving treatment delivery would be to start patients with severe depression on a high intensity treatment like CBT or an antidepressant and, for patients with mild to moderate depression, to start with a lower intensity intervention. Indeed, the NICE Guidelines utilize severity as one of the main variables guiding treatment selection (National Institute for Clinical Excellence, 2004). While this is an evidence-based approach to the care of individuals with depression, it has as a notable limitation in that it relies on a single variable.

Findings from studies comparing psychotherapy, medications, and their combination highlights the importance of considering the influence of multiple variables when deciding between treatments of different intensities. For example, in an individual patient data meta-analysis (IPD), comparing monotherapy with CBT or interpersonal psychotherapy (IPT) to the combination of either psychotherapy and an antidepressant, Thase et al. (1997) reported that combined therapy was not superior to CBT or IPT monotherapy in mild depressions. However, combined treatment yielded superior recovery rates (60%) than psychotherapy alone (19%) for patients with severe *and* recurrent depression. Similarly, Hollon et al. (2014) reported that the superiority of combined treatment with CBT and medications relative to medications alone (72.6% vs. 62.5% overall) was limited to the subset of patients with severe *and* non-chronic recurrent major depression, where the difference was 81.3% vs. 51.7%.

It would be hard to argue that combining two active treatments like psychotherapy and antidepressants is not likely to yield stronger overall effects than just using one of these treatments (Forand, Amsterdam, & DeRubeis, 2015). Indeed, the findings of Hollon et al. (2014) and Thase et al. (1997) suggested that, overall, there was a small advantage for the presumably stronger treatment approach (i.e.,

combination therapy) vs. the relatively weaker one (i.e., monotherapy with medications or psychotherapy). However, it appears that this small average difference was the product of a large difference in one group of patients and a small or negligible difference in another group(s). A striking feature of these reports is that the proportion of the sample that was expected to show a large advantage of the stronger treatment approaches was rather low (32.7% for Thase et al.; 32.3% for Hollon et al.). Despite this, the differences that were found between the combined treatments versus the monotherapies in the respective studies were larger than what is commonly reported in the treatment literature. An even more striking example of the importance of considering more than one variable in examining the efficacy of a strong vs. a weak (or no) treatment was provided by Nelson et al. (2013). These authors explored moderator of response to placebo vs. antidepressants in a very large sample of patients (N = 2283) with late-life depression. Overall, a minimal difference between antidepressants and placebos was observed. For patients with non-chronic depression, there were actually no differences between the two treatments. However, a large differences ($d = 0.70$) was obtained for patients who had chronic *and* severe depression.

Despite the fact that these studies are promising in that they suggest that severity and an additional variable could be used to guide treatment decisions, there is a series of issues associated with combining multiple moderator by treatment interactions, as done by Thase et al. (1997), Hollon et al. (2014), and Nelson et al. (2013). Individual variables may be weak moderators by themselves but, in conjunction with other variables, may be part of an overall stronger moderator variable. Illustrating this point, Cloitre, Petkova, Su, and Weiss (2016) explored moderators of the efficacy of skills training + exposure vs. exposure + supportive

listening vs. skills training+ supportive listening for post-traumatic stress disorder (PTSD). In that trial, the skills training + exposure condition was superior to the other two conditions overall, especially in regard to assessments that took into account the follow-up. Although none of the six moderator variables that were tested in interaction with treatment predicted outcomes, a composite variable was a strong moderator of outcomes in the comparison of exposure only versus social skills training only. A similar approach was recommended by Kraemer (2015) who asserted that "if there are multiple [moderators] related to the same underlying construct, these ... should be combined in order both to increase the reliability of the measurement of that construct and to avoid problems associated with multicollinearity in combining them." DeRubeis, Gelfand, German, Fournier and Forand (2014) argued for the existence of one such construct when they discussed patient response profiles. According to these authors, patients differ in the extent to which they can benefit from active psychotherapy processes and strong treatment approaches. Subsets of patients who are likely to improve much irrespective of interventions, as is characteristic of samples of patients with depression, are unlikely to reveal specific intervention effects.

Another way of framing the question of whether the active benefit of treatments is circumscribed or especially pronounced in one patient group is in terms of a prognostic index (PI). PIs can be thought of as predictive of patients' symptomatology in a future time frame. This information can be considered absent the consideration of what treatment will be provided. For example, patients with less severe depression are more likely to recover from their depressive episode than patients with more severe depression, irrespective of the treatment they receive. However, information from a PI can also be used to determine the intensity level of

care a patient should receive. Indices that reflect prognosis are also used in health research to determine the intensity or an intervention or whether one is needed at all. Summarizing findings from a prevention study in which the benefits were most pronounced in a specific subgroup of patients, Garber et al. (2016) stated that information “based on purely prognostic indices, allows for more efficient use of resources and suggests possible prevention targets so as to increase the power of the intervention.” (p. 2) A similar recommendation was made by Delgadillo et al. (2016) who used a PI to predict the likelihood of experiencing clinically significant improvement in a sample of patients with anxiety and depression from the Improving Access to Psychological Therapies (IAPT) programme, which included low-intensity and high-intensity psychotherapy conditions (see also Saunders, Cape, Fearon, & Pilling, 2016). When these authors stratified patients according to predicted likelihood of improvement, they found differences in likelihood of improvement across both treatments conditions and within each treatment condition. Patients with the highest likelihood of improvement were likely to improve in anxiety irrespective of high- (59%) vs. low-(56%) intensity treatment. By contrast, an advantage of the high intensive interventions vs. low-intensity interventions was observed (31% vs. 20%) for patients who had a lower likelihood of improvement.

In the context of a clinical trial in which there were no differences in outcome overall between treatment as usual (TAU), stepped care starting with brief therapy (BT) or stepped care starting with CBT (CBT), we hypothesized that prognostic status would moderate this effect. Among patients who, based on pre-treatment characteristics, are predicted to do well, few if any differences in outcome were expected between these treatments. However, we predicted that for patients with a poorer prognosis the more intensive CBT should outperform TAU and BT.

METHODS

The aim of the trial from which these data were drawn was to compare TAU to each of two stepped care regimens. One of the regimens began with a low intensity treatment (i.e., BT) and the other began with a high intensity treatment (i.e., CBT; Van Straten, Tiemens, Hakkaart, Nolen, & Donker, 2006). The trial was designed so as to mimic conditions found in routine care settings. Patients were sampled from a representative subsample of 7 of the 47 regional mental health care centers (MHCs) that provide mental health care in the Netherlands.

Outpatients between the ages of 18 and 65 years (N = 5,219) were screened for participation in the trial. Exclusion criteria were: the presence of psychotic or manic symptoms, a thought disorder, dependence on hard drugs (patients with alcohol abuse or dependence were not excluded), high suicide risk, or poor command of the Dutch language. Patients who were not excluded on the basis of these criteria were screened for the presence of mood and/or anxiety disorders with the INSTEL screen, which is a Dutch modified version of the Goldberg-screen (Goldberg, Bridges, Duncan-Jones, & Grayson, 1988; Tiemens, 1999). All remaining patients (i.e., those who screened positive for a mood or anxiety diagnosis and did not meet exclusion criteria, n = 1,608) were followed up for an at-home interview (baseline assessment) by a trained research assistant to determine the presence of mood- and/or anxiety disorders, using the composite international diagnostic interview (CIDI; Wittchen, Robins, Semler, Cottler, & Organization, 1993). Of these patients, 214 could not be reached. Patients in the original trial were eligible if they met the criteria for any of the following DSM IV (American Psychiatric Association, 2000) disorders: MDD, dysthymia, panic disorder, social anxiety, or generalized anxiety disorder. Of the 1,394 patients who were reached for interview, 214 did not have a DSM-IV mood or

anxiety disorder present, 17 had poor command of the Dutch language, and 396 refused to participate in the study. Thus, in total, 702 patients consented and participated in the parent study. In the present paper we focus on the 622 patients who met criteria for MDD.

Brief therapy. In the 1980s, brief therapy (BT) was introduced in the Netherlands as a remedy for lengthy waiting lists. In this study, BT was provided for a total of 5 sessions with a maximum of 2 booster sessions in the six-month period following treatment completion. During the first session, a scheme was used to assess presenting problems (e.g., main symptom complaints, interpersonal functioning, and life areas to be worked on). The aim of BT in this study was to create hope by clarifying problems and emphasizing and strengthening the patient's own competence and coping skills.

Cognitive-behavioral therapy. In this study, CBT consisted of five modules spanning 11-15 sessions: a) introduction (one session), b) providing information about the aim and the procedure of the treatment and assessing patients' cognitions (three sessions); iii) changing cognitions by challenging them (three sessions); iv) changing behavior by performing behavior experiments while challenging cognitions (three sessions); v) integrating new behavior in patients' lives by additional behavior experiments (one to five sessions).

The TAU condition consisted of matched care as it was conducted in the Netherlands at the time: an interdisciplinary mental health care team reviewed each case and patients were assigned to the treatment that they were expected to benefit the most from. Treatments varied by type (e.g., dynamic, supportive), format (e.g., group, online), and intensity (i.e., duration). TAU, BT, and CBT were considered as first steps in a stepped-care model. Therefore, all patients were allowed to switch

treatments, during or after treatment completion, if either the patient or the therapist was convinced that the clinical effects were insufficient. In other words: although the BT and CBT conditions had a set protocol and number of session patients were allowed to 'step up' from these treatments or from TAU. Patients who met the criteria for severe depression in any of the three treatment conditions were allowed to receive antidepressant medication in addition to the psychological treatment. Following the baseline assessment, initiation of treatment occurred after a naturalistic waiting period (in days: TAU: $M = 89$, $SD = 69$; BT: $M = 50$, $SD = 43$; CBT: $M = 83$, $SD = 58$).

Outcomes and missing data

Patients were interviewed at baseline and then every 3 months, irrespective of the timing of treatment initiation and termination. The baseline and one-year assessments, as well as the final follow-up, were conducted via face-to-face interviews. The primary outcome for the current analyses was recovery at the final follow-up, defined by the absence of MDD status. The final follow-up interview occurred at least 18 months after enrollment in the study. The first 59 patients who entered the study were followed for 24 months; subsequent enrollees were followed for 21 months ($n = 105$) or 18 months ($n = 256$). In these analyses we controlled for follow-up duration, although there was no indication that the follow-up time by itself, or in any of the treatment conditions, was related to recovery status. We also examined recovery at the one-year assessment.

Rates of missing data on baseline co-variables were low (all $<10\%$, see table 1.1). At the end of the study 68% of the participants ($n = 420$) were available to be interviewed. There were no statistically significant differences in lost-to-follow-up (LTFU) between the three treatments ($ps > .66$). When comparing the 201

participants who were LTFU with those who were reached for the final interview, depressed patients who were LTFU were more likely to have had a recurrent course (62.2% vs. 53.3%, $\chi^2(1) = 4.66, p = .031$). To address missing data and LTFU issues, we used a non-parametric missing value imputation procedure using random forests with the R package *missForest* (Stekhoven & Bühlmann, 2012). Imputation via random forests has the appealing feature of producing a single dataset for analysis and has been shown to yield a lower imputation error than the more commonly-known approach of multiple imputation via chained equations (MICE; see Stekhoven & Bühlmann, 2012; Waljee et al., 2013). To check for the potential that missing data imputation influenced our results, we re-ran the analyses described below with the listwise-deleted version of the dataset ($n = 417$). The results were, by and large, quite similar so we report the results obtained with the imputed data.

Analytic approach

A total of 23 variables were available for analysis. These variables included demographics, clinical variables, personality traits as assessed by the NEO Five Factor Inventory (Costa & MacCrae, 1992), and the clinical subscales of the Dutch translation of the Symptom Checklist 90 (Derogatis, 1996; Table 1.1). In choosing which of these variables we would explore as predictors of treatment outcomes, we cross-referenced a recent review by Kessler et al. (2016) on predictors of depression treatment outcomes that have been replicated at least once. We also took into account multicollinearity, redundancy, and observed variability. Thirteen of the 23 variables were thus retained (Table 1.1). To determine which of the 13 variables would be included in our PI, as well as their weights in the algorithm that would be used to predict recovery, we utilized a bootstrap ranking procedure with a 10-fold

cross-validated LASSO (least absolute shrinkage and selection operator) penalty in 1,000 bootstrapped samples (see SparseLearner package; Guo et al., 2015).

LASSO approaches belong to the family of penalized regression models (Tibshirani, 1996, 2011) and have been recommended and used in other efforts to predict MDD status (Kessler et al., 2016). They are meant to address the shrinkage that is expected to occur when using a model in a sample or population in which it was not developed. Variables are standardized, all coefficients are shrunk, and those that are close to zero are set to zero. This is done by specifying a shrinkage tuning parameter that sets an upper limit on the sum of the regression coefficients in the final LASSO equation. The entirety of the LASSO solutions for all possible values of Lambda can be given by a modification of the least angle regression algorithm. In this procedure, a first variable is entered into the regression equation based on how highly it correlates with the residual from the intercept. The coefficient for that variable is increased, starting from zero, in the direction of the correlation until another variable is more highly correlated with the residuals and the process continues until all variables are in the model. The LARS algorithm can give all possible LASSO solutions by setting some variables' non-zero coefficient to zero. To this effect, the LASSO can be used for variable selection (i.e., zero coefficients were not selected). In the analyses we conducted with each of the 1,000 bootstrap samples, we used 10-fold cross-validation to select, among a range of Lambda values, the value that yielded the smallest estimate of the prediction error. This procedure converges on a final LASSO solution in which the variables are given the set of weights that minimizes prediction error. We refer to this estimate as the patient's value on the PI. Because the PI is derived for a prediction of a binary

variable, it is in the form of log odds. To facilitate interpretation, we convert it to an estimate of the probability of recovery (PI%).

We used the traditional interpretation of the c-statistic/area under the curve to evaluate the performance of the PI in predicting depression recovery (Austin & Steyerberg, 2012). To determine whether outcomes varied between the three treatment conditions, we ran binary logistic regressions predicting outcomes at follow-up with dummy variables for each of the two active treatment conditions (i.e., CBT vs. TAU and BT vs. TAU), the PI, and the respective interactions between the PI and treatment condition. We conducted a parallel logistic regression comparing CBT vs. BT. In these analyses we controlled for the duration of the follow-up phase (18, 21, or 24 months) and the number of treatment sessions the patient attended, although the inclusion of these covariates did not affect the pattern of results. To probe significant interactions, when they occurred, between the PI and treatment condition, we used the Johnson-Neyman technique (Hayes & Matthes, 2009). The Johnson-Neyman technique is an alternative to the commonly-used method of probing interactions between a moderator and a predictor by calculating slopes at ± 1 standard deviation of the mean of the moderator variable. It gives a value of the moderator at which the significance of the predictor on outcome changes. In our analyses, the Johnson-Neyman would help us establish a point in the prognostic index at which treatment effects begin to be evident.

RESULTS

Descriptive statistics are presented in table 1. As would be expected given the null results obtained in the full sample in the parent trial, there were no statistically significant differences in the rate of MDD recovery between TAU (68.4%) and either of the stepped care conditions (BT = 74.9%, OR = 1.30, B = 0.34, SE = 0.23, $\chi^2 =$

1.33, $p = 0.25$; CBT = 75.0%, OR = 1.41, B = 0.34, SE = 0.22, $\chi^2 = 2.53$, $p = 0.11$). Five of the 13 potential predictor variables submitted to the LASSO procedure were retained. Being unemployed, having more severe symptoms of depression, higher levels of hostility, and having more sleep problems predicted a lower likelihood of recovery. Higher levels of extraversion/positive emotionality were associated with a higher likelihood of recovery. Table 2.1 shows the standardized beta weights assigned to these variables by the LASSO model, along with the results obtained when the five variables were entered into a single logistic regression predicting likelihood of recovery. The effects of the bootstrapped LASSO procedure on the model coefficients can be observed by comparing the LASSO coefficients to the respective betas in the logistic regression. For example, the model coefficient for unemployment, which was the highest in each of the modeling approaches, shrank from -0.62 in the standard regression to -0.48 in the LASSO. By contrast, little shrinkage was evident in the coefficient for severity (from -0.18 to -0.16), which was the lowest in each of the approaches. The resulting PI, generated from the LASSO, evidenced fair predictive accuracy ($c = 0.73$, 95% CI = 0.68 – 0.77, $p < 0.001$).

The PI was developed by predicting treatment outcomes ignoring the main effect of treatment condition on outcomes, which, albeit small and not statistically significant, was in the expected direction. Before examining whether the PI was related to outcomes across the treatments, we carried out a series of analyses to rule out the possibility that there was a systematic influence of treatment condition on the PI. First, we evaluated the treatment comparisons in a regression that contained the five variables selected previously: unemployment status, depression severity, hostility, sleep problems and extraversion. The inclusion of these effects in a model containing all the prognostic variables did not affect their statistical

significance or the strength of their predictive relation *vis a vis* outcome. We then examined whether the PIs themselves differed between the treatment conditions and found no differences ($F(2, 618) = 0.95, p = 0.39$). Taken together, these results suggest that treatment assignment did not influence the PI.

In the primary analyses predicting recovery at follow-up, the test of the interaction of the PI and the CBT vs. TAU contrast was significant. The direction of the effect indicated that, consistent with our hypothesis, the poorer the overall prognosis, the greater the advantage of CBT relative to TAU (OR = 1.91, 95% CI: 1.18 – 3.10, $B = 0.65, SE = 0.25, \chi^2 = 7.00, p = 0.008$). The BT/TAU contrast, however, did not interact with the PI in the prediction of outcome (OR = 0.94, 95% CI: -0.601 – 0.49, $B = 0.06, SE = 0.28, \chi^2 = 0.05, p = 0.83$). This pattern was not evident in the data from the 1-year assessment (all $ps > .35$).

The Johnson-Neyman technique was employed to follow up the significant interaction of the PI with the CBT/TAU contrast at follow-up. The result of this procedure suggested a cutoff on the PI that reflected a 63% likelihood of recovery, and which divided the sample into the 23% with the worst prognoses (i.e., with $PI\% < 60\%$) and the 77% with better prognoses (i.e., with $PI\% \geq 60\%$). Of the patients with better prognoses, 81% recovered and, per Johnson-Neyman, there was no difference between the conditions in recovery rates (see Figure 1). By contrast, among the patients with poorer prognoses, a significantly higher percentage recovered in CBT (65.2%) relative to TAU (39.7%; OR = 2.82, 95% CI: 1.24 – 6.20, $B = 1.04, SE = 0.40, \chi^2 = 4.01, p = 0.045$). In the BT condition, the recovery rate among patients with poor prognoses, 43.5%, was similar to what was observed in the TAU condition.

To assess whether any single variable unduly influenced the PI, we recalculated it five times, each time removing one of the five variables. The results remained the same: there was an interaction between the PI and the CBT vs. TAU contrast (ORs > 1.69, $ps < 0.013$). This interaction was not present in the context of the BT vs. TAU contrast ($ps < 0.60$). We also tested the interactions between treatment condition and each of the five patient variables separately. None of the interaction effects was significant (all $ps > 0.09$).

DISCUSSION

We described a procedure that yields a multi-variable prognostic index that can be used in determining which patients are most likely to benefit more from a high intensity intervention, relative to a lower intensity one. We tested this procedure in the context of a randomized trial of TAU versus BT versus CBT, focusing on the patients in the study with a diagnosis of MDD. Despite the trial being adequately powered to detect moderate differences and despite the fact that the three treatments differed in intensity, across all patients there were only small, nonsignificant between-treatment differences in outcomes. Using our prognostic index, we identified a subgroup of patients – those with the worst prognoses – for whom the effects of CBT were substantially greater than those of TAU or BT. The TAU and BT treatment arms in this study were conducted in a naturalistic context in which the aim was to treat patients to improvement, even if this required augmenting the patient's original treatment. Thus, it is noteworthy that large differences between the interventions were observed in the subset of patients with poorer prognoses, according to our index. To put this in context, the difference between CBT and TAU that we found (OR = 2.87) is outside the 95% CI of estimates of comparisons of CBT vs. TAU reported in the latest meta-analysis exploring long-

term outcomes between psychotherapies (Karyotaki et al., 2016). This suggests the effect we found is not negligible.

There has been great interest in the use of patient characteristics to match patients to the treatments that might be most suitable to them, often in the context of treatment options of similar high intensity that are known to be approximately equally effective (e.g., CBT, IPT, and antidepressant medications; (DeRubeis et al., 2014; Huibers et al., 2015; Kang et al., 2014; Kraemer, 2013; Wallace et al., 2013)). Somewhat less attention has been paid to the use of information about patient characteristics to assist in the matching of patients to the level of intensity of care that is appropriate to them (Delgadillo, Moreea, & Lutz, 2016). The method we have described provides a demonstration of how a statistical method could be used to achieve this aim. The first step that is needed is the development of a prognostic algorithm estimating the likelihood of being free of MDD at a later point in time. We accomplished this by modeling MDD status at follow-up, ignoring treatment assignment. This appeared to be reasonable approach in a trial such as this one in that there were no statistically significant differences in outcomes between the treatments. An analogous example is provided by Huang et al. (2006) in the use of breast conservation therapy (BCT). They examined the risk of cancer recurrence as a function of patients' score on a previously-developed prognostic index (Chen et al., 2005) in BCT, relative to mastectomy plus radiation. Although BCT had previously been found to yield a slightly higher risk of recurrence relative to the higher intensity mastectomy plus radiation, for patients with good prognoses (a majority of those in the sample), there were no differences in recurrence rates between the two condition. For patients who were highest on the risk index, rates of relapse were substantially higher with BCT group (61%) relative to mastectomy plus radiation

(19%). The similarity of this finding with our finding as well as those of Hollon et al. (2014), Nelson et al. (2013), and Thase et al. (1997) suggest that across areas of health care, prognostic status may serve to moderate the efficacy of higher versus lower intensity interventions (see DeRubeis et al., 2014b). For most patients, there might be little if any advantage of engaging in the higher intensity treatments. Even so, a small and potentially identifiable subgroup of patients could experience considerable benefit from higher intensity treatments.

An alternative approach to developing PIs, as suggested by Kessler et al. (2016), is to develop risk models based on variables that are known, from naturalistic studies, to predict treatment response. This risk estimate could then be tested as a moderator of outcomes in a comparative clinical trial. Kessler et al. argue that this approach is more valid than one based, as is the approach we used, on the relations derived from a clinical trial. Even if they are correct, one limitation is that there might not, in a given context, be convergence on the variables collected in epidemiological studies and clinical trials. Moreover, it may be difficult to generalize from epidemiological data to populations of patients who meet MDD criteria in clinical trial samples, as the latter tend to be more severely impaired, on average (Wiltsey-Stirman, DeRubeis, Crits-Christoph, & Brody, 2003; Zimmerman et al., 2016).

Variables that predict differential response to two treatments (i.e., prescriptive or moderator variables) are difficult to identify, especially in studies underpowered for this purpose, including most published clinical trials. By contrast, prognostic variables are easier to identify in that they require less statistical power, may be easier to replicate, and may be derived from more naturalistic contexts. The variables that were included in our prognostic index, depressive symptom severity, unemployment status, sleep complaints, hostility, and extraversion, have been found

to predict outcomes in other investigations. Symptom severity (Driessen et al., 2010; Fournier et al., 2010; Khan et al., 2002; Kirsch et al., 2008), employment status (Delgadillo et al., 2016; Jarrett et al., 2013; Rush, Wisniewski, Warden, & et al., 2008; Trivedi et al., 2006), and sleep complaints (Andreescu et al., 2008; Dew et al., 1997; Troxel et al., 2011) have been directly implicated as predictors of outcome in depression. The various constructs captured by the measures of hostility and extraversion – negative affect, low positive emotionality, difficulty in interpersonal relationships, and overall maladaptive personality traits— have also been reported to predict outcomes across various investigations (see Kessler et al., 2016). These variables have in common the fact that they capture vulnerability to depression, severity, and impairment associated with MDD. Less intensive treatments like BT and TAU may not be sufficient to address the vulnerability and level of illness severity that patients with a poorer prognosis have.

It is widely accepted that all evidence-based psychotherapies for depression are equally efficacious (Barth et al., 2013; Cuijpers et al., 2014; Cuijpers, van Straten, Andersson, & van Oppen, 2008). However, insofar as comparisons of psychotherapies for depression have been conducted with populations that include a high proportion of patients who are expected to improve irrespective of treatment type, relative differences in the potencies of psychotherapies may have been obscured. Providing support for this conjecture, the efficacy of psychotherapy relative to controls differs as a function of symptom severity (Driessen et al., 2010). Moreover, in several RCTs in which between-treatment differences were not found in the full sample, differences were identified in subsamples that comprised the more severely depressed patients (Dimidjian et al., 2006; Driessen et al., 2014; Elkin et al., 1995; Luty et al., 2007).

Although we found differences between CBT and both BT and TAU, it is worth noting that differences emerged in the follow-up phase of the study and were limited to a relatively small proportion of the sample. Regarding the first point, it is possible that differential effects of psychotherapy are most evident in the long-term (Bell, Marcus, & Goodlad, 2013; Bockting, Hollon, Jarrett, Kuyken, & Dobson, 2015; Cloitre et al., 2016) in that shorter term outcomes may index remoralization or nonspecific effects. Longer term outcomes may reflect whether patients' underlying vulnerability to psychopathology was addressed or whether they acquired tools from therapy to deal with their problems (Bell, Marcus, & Goodlad, 2013). Regarding the second point, in other instances in which significant differences have been reported in subgroups but not in full samples, the subgroups have tended to constitute a minority of the sample (Hollon et al., 2014; Nelson et al., 2013). Though it has been recognized that most individuals who meet the criteria for MDD show high rates of response in any evidence-based treatment, this observation has not been incorporated into most guidelines for the treatment of depression. For example, Middleton, Shaw, Hull, and Feder (2005) argue that while the UK's NICE guidelines are clear on how to best treat severe depression, there is little guidance available on how to treat mild to moderate depression most efficiently. Thus, stepped care models that begin with a low-intensity intervention, perhaps an intervention of even a lower intensity than the BT implemented in the present study, should be investigated further. Exercise, unguided self-help, and internet-based psychotherapies all are promising interventions in this regard. Although there is little evidence that these interventions are superior to high intensity interventions for patients with mild to moderate MDD, they might be preferable in that they achieve similar outcomes with lower costs.

Table 1.1 Baseline demographic, personality, and clinical characteristics of subjects randomized to treatment as usual (TAU), brief therapy (BT), or cognitive-behavioral therapy (CBT)

	TAU		BT		CBT		χ^2	<i>p</i>	% <i>miss.</i>
	%	(n)	%	(n)	%	(n)			
Female ^a	66%	(154)	62%	(110)	59%	(123)	2.17	0.34	
Dutch immigrant ^{a,b}	6%	(13)	10%	(16)	14%	(27)	7.51	0.02	10%
Problematic drinking ^b	11%	(24)	13%	(21)	10%	(19)	0.69	0.71	9%
Unemployed	36%	(77)	30%	(48)	31%	(57)	2.04	0.36	9%
Educational attainment							6.47	0.37	10%
None	12.6%	(26)	9.90%	(16)	11.7%	(22)			
Lower	39.1%	(84)	43.80%	(71)	46.3%	(87)			
Middle	38.1%	(82)	30.20%	(49)	30.9%	(58)			
High	10.7%	(23)	16.00%	(26)	11.2%	(21)			
Somatic illnesses (#)							4.12	0.85	8%
1.00	30.10%	(65)	32.70%	(53)	30.30%	(57)			
2.00	16.70%	(36)	20.40%	(33)	18.60%	(35)			
3.00	9.70%	(21)	8.60%	(14)	9.60%	(18)			
4+	12.50%	(27)	7.40%	(12)	8.50%	(16)			
Anxiety co-morbidity	44.90%	(105)	45.80%	(82)	48.60%	(101)	0.63	0.73	
Severe MDD (CIDI)	39.50%	(90)	38.20%	(66)	41.80%	(84)	1.97	0.74	3%
Recurrent MDD (CIDI)	57.70%	(135)	49.20%	(88)	60.60%	(126)	5.43	0.07	
	M	SD	M	SD	M	SD	F	<i>p</i>	
Age	35.98	(10.29)	36.53	(10.27)	36.63	(9.9)	0.26	0.77	
Symptom Checklist 90									
Sleep	9.22	(3.85)	9.26	(3.85)	9.29	(3.66)	0.02	0.98	9%
Agoraphobia ^{a,c}	13.29	(6.31)	13.96	(7.03)	14.27	(6.77)	1.13	0.32	9%

Anxiety ^c	26.06	(8.85)	26.18	(8.97)	27.41	(8.77)	1.35	0.26	9%
Depression ^c	48.58	(12.35)	47.99	(14.24)	49.15	(12.68)	0.34	0.71	9%
Hostility	12.95	(5.37)	12.49	(5.28)	12.44	(5.36)	0.57	0.57	9%
Insufficiency ^{a,c}	24.93	(7.51)	24.11	(7.95)	25.33	(7.57)	1.14	0.32	9%
Interpersonal sensitivity ^c	42.48	(15.56)	40.87	(15.06)	43.87	(14.96)	1.69	0.19	9%
Somatic ^c	29.51	(9.55)	28.24	(9.52)	28.34	(9.14)	1.12	0.33	9%
Other ^{a,c}	19.32	(5.87)	18.79	(5.92)	19.47	(6.16)	0.61	0.54	9%
NEO									
Conscientiousness ^a	3.25	(1.95)	2.79	(1.7)	3.11	(1.84)	2.22	0.11	9%
Agreeableness	4.43	(2.06)	4.27	(2.)	4.21	(2.)	0.49	0.62	9%
Extraversion	2.23	(1.83)	3.22	(1.94)	3.12	(1.84)	0.18	0.84	9%
Neuroticism	7.77	(1.13)	1.89	(1.07)	7.88	(1.11)	0.55	0.58	9%
Openness	4.99	(1.87)	4.80	(2.07)	5.39	(1.9)	3.22	0.04	9%

Note. % miss – percentage missing data at baseline. MDD – major depressive disorder. CIDI - Composite International Diagnostic Interview. NEO- NEO Five Factor Inventory. || variable explored as a predictor of outcomes. A – variable not explored as a predictor of outcomes because no prior research suggests it is predictive of outcomes in depression treatment, b - variable not explored as a predictor of outcomes because there was low variability, c - variable not explored as a predictor of outcomes because it was co-linear with some variables and represented by other variables

Table 1.2 LASSO solution for predictor variables used in prognostic index (PI) predicting recovery at follow-up and model estimates from logistic regression using these variables

	LASSO	B	SE	OR	
Unemployment status	-0.48	-0.62	0.20	0.54	**
Depression severity	-0.16	-0.18	0.11	0.84	
Hostility (SCL)	-0.38	-0.45	0.10	0.64	***
Sleep complaints (SCL)	-0.27	-0.31	0.11	0.73	**
Extraversion (NEO)	0.29	0.39	0.11	1.47	***

Note: Vertical lines separates results of LASSO solution from results of logistic regression. *** $p < 0.001$, ** $p < 0.01$, * $p < 0.05$. SCL: Symptom Checklist 90-R subscale. NEO: NEO Five Factor Inventory subscale.

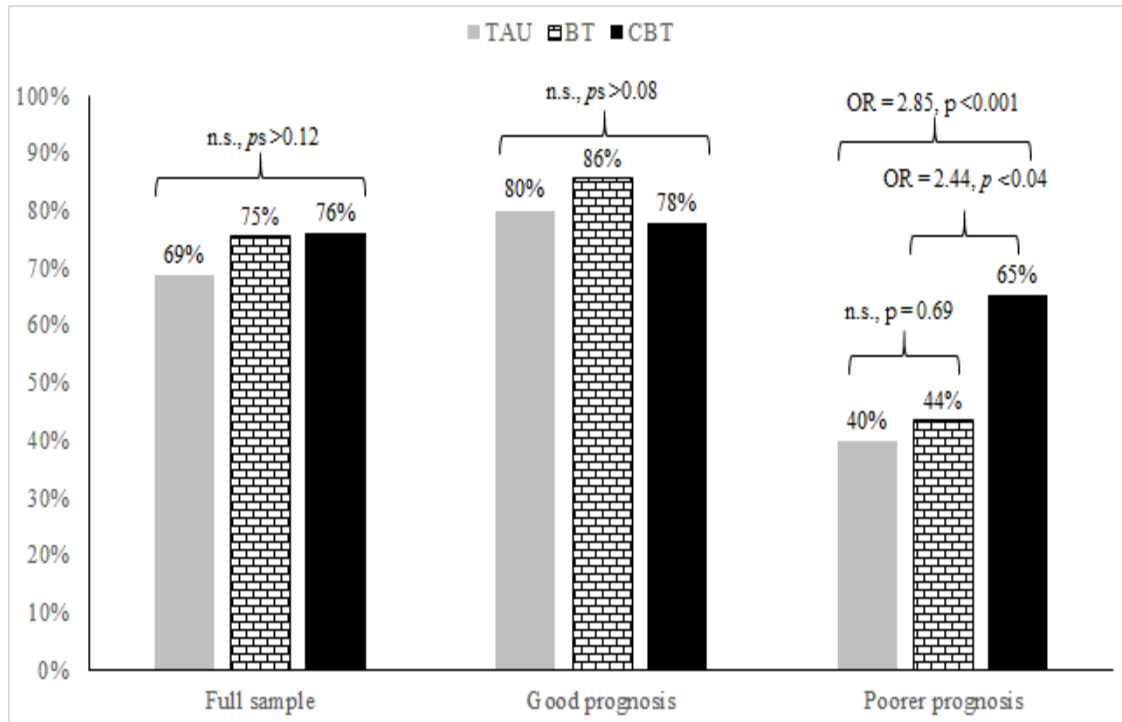


Figure 1.1 Recovery rates at follow-up between treatment as usual (TAU), and stepped care starting with brief therapy (BT) or cognitive-behavioral therapy (CBT)

**CHAPTER 2: CLIENT CHARACTERISTICS AS MODERATORS OF THE RELATION
BETWEEN THE THERAPEUTIC ALLIANCE AND OUTCOME IN COGNITIVE
THERAPY FOR DEPRESSION**

Lorenzo Lorenzo-Luaces¹ (M.A.), Robert J. DeRubeis¹ (Ph. D.), Christian C. Webb²
(Ph.D.)

¹ Department of Psychology, University of Pennsylvania; ² Department of Psychiatry,
Harvard Medical School

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ABSTRACT

Little is known about the variability of the alliance–outcome correlation across identifiable client subsets. This question was explored in a sample of 60 clients receiving cognitive therapy for depression, from which an overall correlation of .23 was observed between alliance ratings and subsequent symptom change. We examined interactions between the observer-rated version of the Working Alliance Inventory–Short Observer-Rated version (WAI–O; Tracey & Kokotovic, 1989) and client demographics, features of depression, personality, and other clinical features in predicting subsequent symptom change. After corrections for multiple comparisons, interactions between the WAI–O and the number of prior depressive episodes, as well as the severity of baseline anxiety symptoms, were significant predictors of symptom change. When both interactions were controlled for, number of prior depressive episodes emerged as a statistically significant moderator. The alliance predicted outcome in the subgroup of clients with 0–2 prior episodes ($r = .52$), but not in those with 3 or more prior episodes ($r = .02$). These findings were obtained despite similar univariate distributions on the alliance and symptom change in the 2 subgroups. Differences that were observed in the predictive relation of alliance to outcome as a function of number of prior episodes suggest that different therapy processes may account for change in these subgroups. If the pattern observed in the present study is replicated, it would suggest that the alliance–outcome association has been both under- and overestimated.

INTRODUCTION

Estimates from meta-analytic reviews indicate a small- to medium-sized association between the therapeutic alliance and treatment outcomes (Horvath, Del Re, Flückiger, & Symonds, 2011). Although methodological issues in research on the alliance have prompted questions about the direction of the causal influence in the relation between symptom change and the alliance (e.g., DeRubeis, Brotman, & Gibbons, 2005), the alliance remains an important construct in psychotherapy research and practice. A relatively unexplored question is to what extent alliance–outcome associations are moderated by identifiable client characteristics.

Research on client characteristics and the alliance has, for the most part, focused on predictors of the alliance (Castonguay, Constantino, & Holtforth, 2006) or on the alliance as a mediator of the relationship between client characteristics and outcome (e.g., Shahar, Blatt, Zuroff, & Pilkonis, 2003). Less severe clinical pictures, fewer difficulties in interpersonal relationships, and improvement during therapy tend to be associated with higher alliance scores. A separate question, which is the focus of this report, is whether client characteristics moderate the alliance–outcome relationship. Using simulations, DeRubeis, Gelfand, German, Fournier, and Forand (2013) have shown that the magnitude of the association between process variables and outcome can be heavily influenced by characteristics of the client sample in which the correlation is studied. In a meta-analysis that illustrates this point, Sharf, Primavera, and Diener (2010) found that the association between the alliance and study dropout tends to be smaller in studies that contain higher proportions of clients who completed high school.

Although moderation of the alliance–outcome relationship has been explored in other meta-analyses (e.g., Del Re, Flückiger, Horvath, Symonds, & Wampold,

2012), a meta-analysis allows one to make inferences about samples, not individuals. To our knowledge, only Falkenström, Granström, and Holmqvist (2013) have used individual patient data to test client variables as moderators of the alliance–outcome relationship. The objective of the present study is to identify client characteristics that moderate the alliance–outcome correlation in cognitive therapy (CT) for depression. We explored demographic variables, personality traits, and other clinical features that have been hypothesized to affect the alliance or its relation to outcome.

Insofar as demographic features, such as gender, age, and marital status, influence clients' perceptions of interpersonal relationships, these may interact with the alliance in promoting change (see Flückiger et al., 2013). Personality traits have also been explored in relation to the alliance and improvement in psychotherapy. Del Re et al. (2012) found that the percentage of clients with personality disorders in studies of the alliance was unrelated to the strength of the alliance–outcome relationship. However, in a large, heterogeneous sample of mental health clinic outpatients, Falkenström et al. (2013) found that the alliance–outcome relationship was stronger in clients with personality problems. It has also been suggested that in depression, the alliance might be of particular importance with clients with more severe, chronic, and recurrent forms (see Arnow et al., 2013). Finally, features that reflect the complexity of a client's clinical picture, including, for example, comorbid anxiety (Horvath et al., 2011) or substance use (Flückiger et al., 2013), have been considered potential moderators of the alliance–outcome associations.

METHOD

Data were drawn from the CT arm (N = 60) of a randomized controlled trial comparing CT versus antidepressants in the treatment of moderate to severe major

depressive disorder (DeRubeis et al., 2005). The study was approved by the local institutional review boards.

Measures

Beck Depression Inventory—Second Edition (BDI-II; Beck, Steer, & Brown, 1996). Depressive symptoms were assessed with the BDI-II, a 21-item self-report measure that was completed by all clients before the start of each therapy session as well as at the end of the 16-week treatment period. When a client did not provide an end-of-treatment BDI-II, which happened for nine dropouts, we used the last available BDI-II score to represent outcome on this instrument.

Working Alliance Inventory—Short Observer-Rated version (WAI-O; Tracey & Kokotovic, 1989). On the WAI-O, observers rate 12 items assessing agreement in the goals and tasks of therapy and the affective bond on a 7-point scale (from 0 = never to 6 = always; range: 0–72). Ratings used in the present brief report constitute a subset of the ratings used by Webb et al. (2011). For each of the 59 clients who completed at least three sessions of CT, two raters (from a pool of five) rated an early session of therapy (Session 3 if available; otherwise Session 2 or 4). Raters were assigned sessions according to a balanced incomplete block design. Pooled ratings for each session yielded estimates of the quality of the alliance. Raters received training on the WAI-O and were unaware of the treatment outcomes. They achieved adequate reliability (ICC = .73; see Webb et al., 2011, for a more thorough description of the procedure).

Potential moderators

Demographics. We included age (in years), sex, years of education, marital status (married or cohabiting with a partner vs. single), and estimated IQ (derived from the Shipley-Harford Living Scale; Shipley, 1940).

Personality. We included the five factors of the NEO Five-Factor Inventory. Openness, Conscientiousness, Extraversion, Agreeableness, and Neuroticism (Costa & McCrae, 1992) and the number of Cluster B and C symptoms individuals endorsed in the Structured Clinical Interview for DSM–IV Axis II disorders (Gibbon, Spitzer, & First 1997).

History and features of depression. This set consisted of depression severity (Hamilton Rating Scale for Depression; Hamilton, 1960), atypical depression, duration of current episode, age at first episode, number of prior episodes, and number of prior depression treatments (all assessed by the Structured Clinical Interview for DSM–IV–TR Axis I Disorders; First, Spitzer, Gibbon, & Williams, 2001).

Other clinical features. We also included number of life events (Psychiatric Epidemiology Research Interview Life Events Scale; Dohrenwend, Askenasy, Krasnoff, & Dohrenwend, 1978), history of substance abuse (from the Structured Clinical Interview for DSM–IV–TR Axis I Disorders interview), severity of anxiety symptoms (Hamilton Anxiety Rating Scale; Hamilton, 1959), hopelessness (Beck Hopelessness Scale; Beck, Weissman, Lester, & Trexler, 1974) and total score on the Attributional Style Questionnaire (ASQ; Peterson et al., 1982).

Analytic plan

Continuous variables were centered at their mean. Binary ones were coded ± 0.5 . Outliers at three or more standard deviations were winsorized, and nonnormal variables were transformed to meet linearity assumptions. The outcome variable was residualized subsequent change in depressive symptoms, calculated as the difference between the BDI–II score from before the start of the rated session and the end-of-treatment BDI–II score, controlling for the session BDI–II score. For each of the 23

potential moderators, we ran regression models predicting residualized change from (a) the WAI-O, (b) the main effect of the potential moderator, and (c) the interaction of the potential moderator and the WAI-O. We corrected for multiple comparisons with the Benjamini-Hochberg method (Benjamini & Hochberg, 1995), using a false discovery rate of $p < .05$. After this correction, potential moderators and their respective interactions with the WAI-O were included together in a regression model predicting subsequent change. We used Pothoff's modification to the Johnson-Neyman technique to assess the effect of interactions (Hayes & Matthes, 2009). This yields an estimate of the point along the values of the moderator at which the predictor-criterion association transitions between statistically significant and nonsignificant.

RESULTS

Table 2.1 presents descriptive statistics as well as the correlations of all 23 pretreatment variables with the WAI-O and subsequent change. By itself, the WAI-O was related to subsequent symptom change, $\beta = 0.23$, $\chi^2(1) = 11.31$, $p < .001$. The main effect of none of the 23 variables was significant in the prediction of symptom change. However, 4 of the 23 tests of moderation (interaction with the alliance) were significant at the $p < .05$ level (uncorrected). The alliance-outcome relationship became stronger with increasing severity of baseline anxiety symptoms, $\beta = 0.23$, $\chi^2(1) = 14.89$, $p < .001$; increasing levels of self-reported conscientiousness, $\beta = 0.22$, $\chi^2(1) = 4.60$, $p = .03$; lower scores on measured IQ, $\beta = -0.19$, $\chi^2(1) = 4.68$, $p = .03$; and fewer prior episodes, $\beta = -0.30$, $\chi^2(1) = 18.45$, $p < .001$. After we corrected for multiple comparisons, only the interactions with anxiety severity and number of prior depressive episodes remained significant. When a model predicting subsequent change contained the WAI-O, these two

moderators, and their interactions, only the interaction between the WAI-O and prior episodes remained significant, $\beta = -0.25$, $\chi^2(1) = 4.20$, $p = .04$. The interaction between the WAI-O and anxiety was reduced to a trend, $\beta = 0.40$, $\chi^2(1) = 3.07$, $p = .08$.

The region of significance for predicting outcome with the WAI-O was estimated by the Johnson-Neyman technique as all values of prior episodes below 1.89. Figure 2.1 provides a graphical representation of this association. As depicted in Figure 2.2, among clients with zero to two prior episodes of depression, the WAI-O predicted symptom change, $r = .52$, 95% confidence interval (CI) [.22, .73], $p = .001$, and its prediction of symptom change was higher than in the group with three or more prior episodes, $r = -.02$, 95% CI [-.41, .38], $p = .89$. The difference between these correlation coefficients was statistically significant ($Z = -2.19$, $p = .03$). These relationships held for the WAI-O total and were not specific to either of its subscales. The means of WAO-I scores were similar for those with zero to two versus three or more prior episodes (51.2 vs. 53.6), $t(57) = 1.65$, $p = .10$, as were the variances (5.23 vs. 5.67), $F = 0.95$, $p = .34$. Residualized change in BDI-II score was also similar between the groups (11.42 vs. 13.20), $t(57) = -0.80$, $p = .43$; variances: 8.64 versus 8.40, $F = 0.18$, $p = .67$.

DISCUSSION

In this sample, the overall alliance-outcome correlation of .23 was well within the range of values produced by the latest meta-analysis (Horvath et al., 2011). However, the size of this relation varied substantially as a function of the number of prior episodes of depression reported at baseline. For clients with fewer than three prior depressive episodes, the alliance-outcome correlation was substantially higher than what is commonly observed in the literature. In contrast, in the sample of 24

patients who had experienced three or more episodes, the alliance was not predictive of symptom change. If replicated, this would suggest that by ignoring interactions with patient variables, the alliance–outcome correlation can be both over- and underestimated.

Tests of interaction effects require larger sample sizes than tests of main effects do. The present study could thus be considered underpowered. In an adequately powered study, we may have identified more moderators. The small sample also precluded tests of therapist effects or the interaction of therapist and client characteristics. Because of the paucity of research on interactions of client characteristics and the alliance, we conducted exploratory analyses of multiple potential moderators.

Despite these limitations, the study makes a novel contribution in finding a significant interaction between the alliance and an important client variable in predicting outcome. That this finding was obtained after correcting for multiple comparisons and that it remained significant after controlling for several potential confounds suggest it may be robust. The data were well-suited for our research question, as they allowed for the control of temporal confounds such as prior symptom change, and that the alliance ratings were obtained from observers who were unaware of the treatment outcomes as well as most client characteristics. Additionally, using observer ratings avoids the potential for the shared variance confound that exists when clients' ratings are used both for the alliance and for the outcome variable. It is important to note that the interaction between prior episodes and the alliance in the prediction of outcome could not be accounted for by differences in the means or variances of the measures of alliance or outcome. Thus, it does not appear to be a statistical artifact.

Ma and Teasdale (2004) found evidence that patients with three or more prior episodes of depression report more childhood adversity, an earlier age of first onset of depression, and depressive relapses that more often came out of the blue when compared with patients with less recurrent forms of depression. Additionally, it is this group with three or more prior episodes of depression that evidences the benefit of an intervention to prevent relapse. These findings may be taken to suggest that patients who have had zero to two versus three or more prior depressive episodes represent essentially different subgroups. Consistent with this research, less recurrent forms of depression may be more reactive to negative as well as positive life events, whereas more recurrent forms may indicate the presence of ruminative and autonomous depressogenic processes. Similarly, Wakefield and Schmitz (2013) argued that the recurrence of depressive episodes can be understood as an indicator of underlying pathology in the individual, as opposed to reactions to life stressor and contextual variables. It is possible that patients with less recurrent depressions tend to be more reactive to positive and negative interpersonal interactions, including those that are captured in assessments of the therapeutic alliance. For those with recurrent depressions, however, the relationship with their therapist, as is true of their interpersonal experiences generally, might have little impact on the course of their depressive episode, relative to therapy processes that address the intrapsychic processes that are known to be especially problematic in this group.

Although it is widely held that clients are helped differentially by different aspects of therapy, few findings in the literature speak to this. The existence of an interaction between prior depressive episodes and the alliance in the prediction of subsequent symptom change, as well as other interactions between process variables and client characteristics (e.g., Strunk, Brotman, DeRubeis, & Hollon,

2010), adds empirical support to this clinical intuition. However, these findings also present a challenge for psychotherapy research and theories of the mechanisms of therapeutic change. Indeed, the existence of substantial moderators of process–outcome correlations might be responsible for the difficulty in identifying mechanisms of change in therapy (DeRubeis et al., 2013). Therapist variables are also likely to interact with client characteristics and the alliance to influence outcome. Thus, in the interest of achieving a better and more nuanced understanding of mechanisms of change in treatment, there is a great need to explore client and therapist variables that moderate this and other process–outcome relationships. Consistent with recent calls to personalize treatments according to patient characteristics (DeRubeis et al., 2014), this type of research would facilitate the tailoring of psychological interventions to specific individuals.

Table 2.1 Characteristics of the sample and bivariate associations between client baseline characteristics, WAI-O ratings and subsequent change

	M or %	(SD) or n	WAI-O <i>r</i>	Symptom change <i>r</i>
WAI-O	52.5	(5.41)	--	0.23***
Subsequent Change in BDI	12.2	(8.51)	0.23***	--
Demographics				
Years of education	14.6	(2.50)	-0.10	0.08
Female %	58%	35	0.02	0.02
Age	40.3	(11.51)	0.03	0.06
Married or cohabiting %	30%	18	-0.05	0.17
IQ	109.7	(10.21)	-0.12	0.17
Personality				
NEO - FFI				
Agreeableness (0 – 48)	28.4	(6.38)	0.27	0.12
Conscientiousness (0 – 48)	26.6	(8.63)	0.17	0.07
Extraversion (0 – 48)	20.7	(6.53)	0.08	0.01
Neuroticism (0 – 48)	32.4	(7.56)	0.00	0.05
Openness (0 – 48)	28.4	(6.72)	-0.06	0.15

Number of Cluster B Criteria	2.4	(2.49)	-0.08	-0.24
Number of Cluster C Criteria	4.3	(3.50)	-0.11	-0.01
History of depression				
Met atypical depression criteria %	28%	17	0.01	0.00
Depression severity – HRSD (0–53)	23.9	(3.08)	-0.20	-0.14
Duration of current episodes (mo.)	31.4	(35.23)	-0.19	-0.04
Number of prior episodes	2.3	(2.00)	-0.19	0.01
Prior antidepressant treatments	1.7	(1.81)	-0.26	-0.04
Age of onset of first episode	24.2	(12.95)	0.17	0.09
Other clinical features				
Number of life events – PERI (0 – 102)	6.8	(4.37)	0.14	0.15
Past history of substance abuse %	28%	17	-0.07	0.14
Attributional Style - ASQ	0.36	(3.05)	-0.23	-0.14
Anxiety severity – HAM-A (0 – 48)	16.6	(5.93)	-0.17	0.09
Hopelessness – BHS (0 – 20)	11.2	(5.16)	0.18	0.08

Note. WAI – O – Working Alliance Inventory, Observer ratings, Symptom change – residualized change in the BDI, IQ – Intelligent Quotient, HRSD – Hamilton Rating Scale for Depression, NEO – FFI – NEO – Five Factor Inventory, PERI – Psychiatric Epidemiology Research Interview Life Events Scale, ASQ – Attributional Styles Questionnaire (positive – negative), HAM-A – Hamilton Anxiety Rating Scale, BHS – Beck Hopelessness Scale. *** $p < .001$. For dichotomous variables, point-biserial correlations with the WAI-O and subsequent change are provided. For continuous variables, Pearson product-moment correlations with the WAI-O and subsequent change are provided.

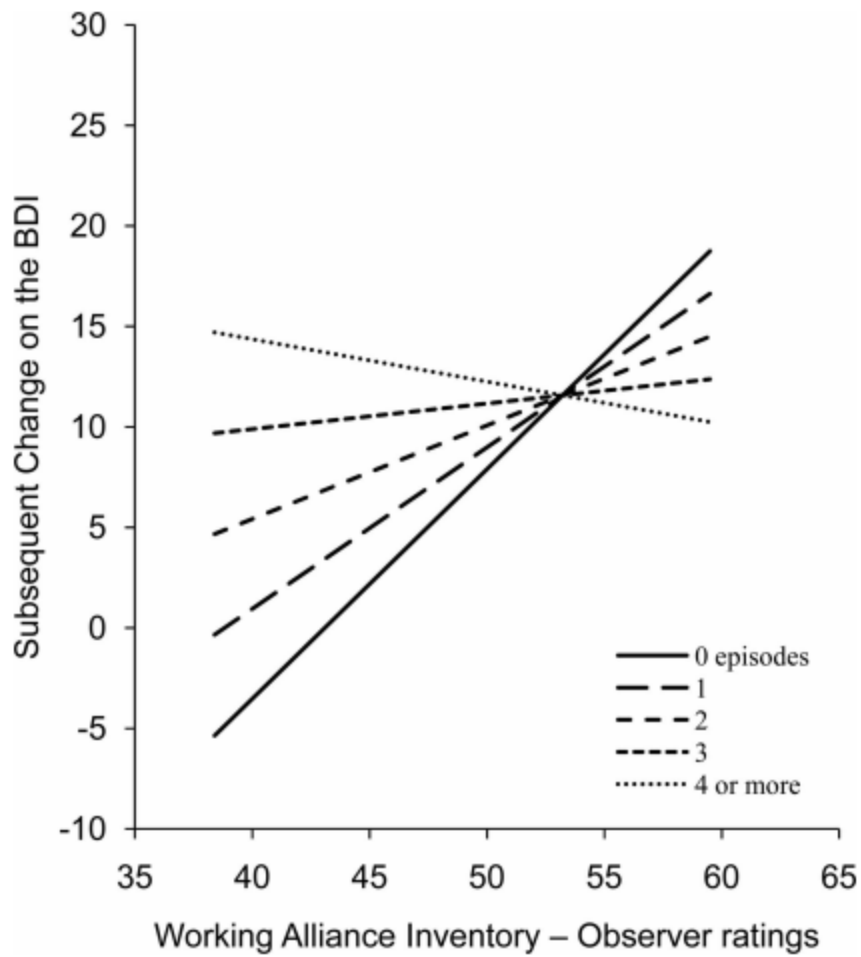


Figure 2.1 Predicted association between therapeutic alliance and subsequent symptom change across prior depressive episodes. BDI = Beck Depression Inventory—Second Edition.

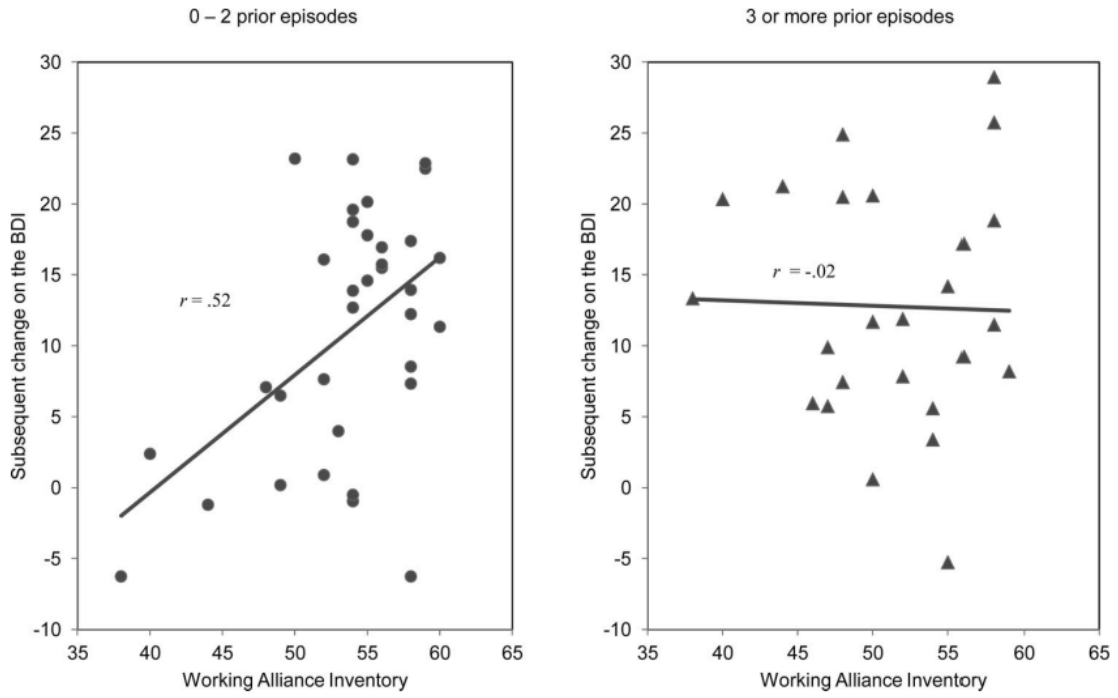


Figure 2.2 Observed relationship between early ratings of the therapeutic alliance and subsequent change, by prior number of episodes. BDI =Beck Depression Inventory—Second Edition.

**CHAPTER 3: MODERATION OF THE ALLIANCE-OUTCOME ASSOCIATION BY
PRIOR EPISODES: A DIFFERENTIAL EFFECT IN COGNITIVE-BEHAVIORAL VS.
PSYCHODYNAMIC THERAPY FOR DEPRESSION**

Lorenzo Lorenzo-Luaces¹ (M.A.), Ellen Driessen ² (Ph.D.), Robert J. DeRubeis¹
(Ph.D.), Henricus L. Van³ (M.D., Ph.D.), John R. Keefe¹ (M.A.), Mariëlle Hendriksen³
(Ph.D.), Jack Dekker^{2,3} (Ph.D.)

¹Department of Psychology, University of Pennsylvania, Philadelphia, PA, USA;

²Department of Clinical Psychology, VU University Amsterdam, Amsterdam, The
Netherlands; ³Arkin Mental Health Care, Amsterdam, The Netherlands

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psychodynamic therapy

ABSTRACT

A prior study suggested that, in cognitive-behavioral therapy (CBT), the association between the working alliance and depression improvement varies as a function of prior history of depression. We sought to replicate these findings in CBT and extend them to short-term psychodynamic supportive psychotherapy (SPSP) in a sample of patients who were randomized to one of these treatments and were administered the Helping Alliance Questionnaire (N = 282). Overall, the alliance was a predictor of symptom change ($d = 0.37, p < .001$). In SPSP, the alliance predicted symptom change for patients with 0-1 episodes ($d = 0.33, p = .003$) as well for patients with 2 or more prior episodes ($d = 0.39, p = .008$). By contrast, in CBT, the alliance was related to symptom change for patients with 0-1 prior episodes ($d = 0.79, p < .001$) but not for those with 2 or more prior episodes ($d = 0.06, p = .72$). These findings suggest a complex interaction between patient features and common vs. specific therapy processes. In CBT, the alliance relates to change for patients with less recurrent depression whereas other CBT-specific processes may account for change for patients with more recurrent depression.

INTRODUCTION

The therapeutic alliance, broadly understood to capture the bond between a patient and a therapist as well as the agreement in the goals and tasks of therapy, is widely believed to be a robust predictor of outcomes in psychotherapy. For example, reviewing the literature on the alliance, Del Re, Horvath, Flückiger, Symonds, and Wampold (2012) asserted that:

“the alliance and outcome have shown a remarkably robust association ... across different moderating variables such as measures of the alliance, measures of outcomes (primary symptom measure and non-targeted measures), rating perspectives, type of treatment (e.g., evidence-based, manualized, focused on specific ingredients), and context in which treatment was delivered.” (p. 643)

Indeed, the alliance-outcome correlation has been reported across various patient populations and treatments (Horvath, Del Re, Flückiger, & Symonds, 2011). However, there have been few primary analyses of the moderation of this association, and even fewer analyses that have focused on patient characteristics as potential moderators (De Bolle, Johnson, & De Fruyt, 2010; Falkenström, Granström, & Holmqvist, 2013; Lorenzo-Luaces, DeRubeis, & Webb, 2014). Thus, whether the alliance is an equally important predictor of outcomes for all patients and whether it is an equally important predictor of outcomes across psychotherapies are still key questions in alliance research (Barber, 2009). Moreover, the answers to these questions may not be independent. In other words, it is possible that the effect of the alliance on outcome is contingent on the interaction between the type of patient undergoing treatment and the type of treatment that is being delivered. In one of the few studies examining patient-level moderators of the alliance-outcome correlation, Lorenzo-Luaces et al. (2014) reported that the alliance-outcome correlation in cognitive therapy (CT) for depression was moderated by the number of

prior episodes patients reported at baseline. The aim of this report is to replicate these findings and extend them to psychodynamic psychotherapy.

Depressive recurrence

Lorenzo-Luaces et al. (2014) reported that for patients with fewer than three prior episodes of depression, the alliance-outcome correlation was larger in magnitude ($r = 0.52$) than what is commonly reported in the literature ($r = 0.28$; see Horvath et al., 2011). By contrast, for patients with three or more prior depressive episodes, the working alliance did not predict outcome ($r = -0.02$). Drawing on prior work on recurrent depression these authors hypothesized that, for patients with a highly recurrent course, depression had become more autonomous, likely triggered by internal processes such as rumination or cognitive reactivity (Ma & Teasdale, 2004; Monroe & Harkness, 2005; Wakefield & Schmitz, 2013). Individuals with more recurrent courses are more likely to report depressive episodes that come “out of the blue” (Ma & Teasdale, 2004). By contrast, patients with less recurrent courses experience depressive episodes that are more closely linked to life stressors (Monroe & Harkness, 2005). For these patients, agreement on the goals and tasks of CT, which are often focused on concrete changes in behavior and thinking, may be sufficient to engender changes in life circumstances and depressed mood. Adding support to this hypothesis, Sasso et al. (2014) found that, in the same sample investigated by Lorenzo-Luaces et al., therapists’ use of behavioral homework was predictive of symptom change for less recurrent depression. It may be that concrete behavioral changes, agreed on with the therapist, are sufficient to produce substantial symptom change in less recurrent depression. An alternative account of symptom change in less recurrent depression is that these patients may be better able to benefit from nonspecific influences such as a positive bond with a caring therapist.

Patients with a more recurrent course depression may have, or may develop during their clinical course, a greater vulnerability to depression that needs to be addressed in order for treatment to be efficacious. For these patients, agreement on the goals and tasks of CT, which are focused on concrete changes in behavior and modification of negative automatic thoughts, may not be sufficient to engender symptom change. Adding support to this hypothesis, Sasso et al. (2014) found that, in the same sample investigated by Lorenzo-Luaces et al. (2014), therapists' greater use of cognitive methods (vs. behavioral homework) was predictive of symptom change for clients with more recurrent courses of depression. Keefe et al. (2016) found evidence that the specific use of interventions targeted at identifying, assessing, and challenging patients' core beliefs was specifically efficacious for patients with more recurrent depression. Taken together, these findings are consistent with the notion that CBT for patients with a more recurrent course of depression needs to address underlying vulnerability factors, perhaps pertaining to underlying core beliefs or schemas, in order to produce symptom change. This is consistent with Ma and Teasdale's (2004) proposition of "escalating cycles of ruminative cognitive-affective processing" (p. 31) in more recurrent depressions. Mindfulness-based CT (MBCT) was developed with the intent of interrupting these processes and MBCT appears to be particularly superior to treatment as usual only among patients with more recurrent forms of depression (Piet & Hougaard, 2011). Taken together, findings from these studies suggest that the number of prior episodes is a moderator of treatment outcomes as well as of process-outcome relationships in cognitive-behavioral therapies (CBTs). Thus, the number of prior episodes is an important variable to consider in the context of research on treatments for depression.

The alliance across psychotherapies

Meta-analytic reviews suggest that the magnitude of the alliance-outcome correlation does not differ substantially between different therapeutic modalities (Horvath et al., 2011). These findings could be taken to support the notion that the therapeutic alliance is a common factor contributing to treatment outcomes in different psychotherapies. However, these findings are not consistent with the fact that schools of therapy emphasize the alliance to different degrees. For example, in CBTs a positive therapeutic alliance is generally regarded as a necessary condition for the implementation of cognitive-behavioral interventions, which are in turn assumed to drive therapeutic change (Beck, 2011). In psychodynamic psychotherapies, however, the alliance is more than a prerequisite in that interventions often rely on the therapeutic relationship as a model. For example, the therapist might focus on the relationship as a new and secure environment in which the patient is invited to experience and talk about emotions that had previously been avoided. Alternatively, the transference aspects of the relationship may be used to improve insight into maladaptive expectations with regards to interpersonal relationships (de Jonghe et al., 2013). Therapies might also be expected to differ in regard to the role of the alliance because a component of the alliance is agreement on task and goals, and therapies differ on their stated goals, as well as on the tasks that are used.

Consistent with the differential roles of the therapeutic alliance, several research groups have reported that treatments moderates the strength of the association between the alliance and outcome. In a study of patients with chronic depression, Arnou et al. (2013) found that the alliance was a significantly stronger predictor of outcomes in cognitive behavioral analysis systems of psychotherapy (CBASP) than it was in a supportive therapy. The authors hypothesized that the difference was accounted for by CBASP's greater emphasis on tasks and goals, a

component of the alliance that may be more strongly related to outcomes than the affective bond (see Rector, Zuroff, & Segal, 1999; Webb et al., 2011). Similarly, Bedics, Atkins, Harned, and Linenhan (2015) reported that, in dialectical behavioral therapy (DBT), the therapeutic alliance was associated with decreases in self-injurious behavior, whereas this relation was not observed in non-behavioral community treatment. Recently, Snippe et al. (2015) reported that the alliance predicted symptom change in CBT for depression, but not in MBCT. Taken together, these tests of moderation suggest a different role for the alliance across therapy modalities (see also Strunk et al., 2010; Zilcha-Mano, Roose, Barber, & Rutherford, 2015), possibly varying according to how directive or task-oriented therapy is.

Objectives

In a new sample of patients with a major depressive episode (Driessen et al., 2013), we aimed to replicate the finding of an interaction between number of prior episodes and the alliance in CBT (Lorenzo-Luaces et al., 2014a). Moreover, we attempt to extended the test of this interaction to psychodynamic therapy. Replication attempts are extremely rare in psychology (Makel, Plucker, & Hegarty, 2012), and the rate of unsuccessful replications has spurred a crisis of confidence in the findings derived from psychological studies (Open Science Collaboration, 2015). Thus, our findings should make a substantial contribution to the field. The exploration of patient characteristics and treatment as moderators of the alliance-outcome correlation is of special importance for treatment research. If the alliance is only a predictor of outcomes in some patients but not in others, this could help explain why in some studies the alliance predicts outcomes when accounting for prior symptom change (Falkenström, Granström, & Holmqvist, 2014) but in others it does not (Hendriksen, Peen, Van, Barber, & Dekker, 2014). Moreover, exploring the intersection of patient characteristics, common factors, and specific therapeutic factors can inform the personalized delivery of psychotherapeutic interventions

(Beutler, Forrester, Gallagher-Thompson, Thompson, & Tomlins, 2012; Beutler & Martin, 2001).

METHODS

Design. This paper draws upon data from a randomized clinical trial (RCT) comparing CBT and short-term psychodynamic supportive psychotherapy (SPSP) for patients with depression (N = 341; 164 in CBT and 177 in SPSP). This intervention study was registered as ISRCTN31263312 with Current Controlled Trials (<http://www.controlled-trials.com>). The study design and the study protocol were approved by the Dutch Union of Medical-Ethic Trial Committees for mental health organizations (Driessen et al., 2007).

Participants. Participants were referred by their general practitioner to one of three psychiatric outpatient clinics in Amsterdam, The Netherlands. Inclusion criteria were: 1) presence of a major depressive episode according to the *MINI-International Neuropsychiatric Interview – Plus DSM-IV* criteria (Sheehan et al., 1998); 2) *Hamilton Rating Scale for Depression* (HRSD; Hamilton, 1960) scores ≥ 14 ; 3) age between 18 and 65 years; 4) written informed consent after description of the study. Exclusion criteria and other design features have been described elsewhere (Driessen et al., 2007; Driessen et al., 2013). Briefly, participants were excluded if they were experiencing psychotic or manic symptoms, severe suicidality, problematic substance use in the preceding 6 months, or if they were pregnant or unable to attend the study assessments, or if they were using medications that might influence mental functions. In this trial, the therapeutic alliance was assessed at week 5. By this point, 59 patients had dropped out of the trial, 36 in CBT and 23 in SPSP ($p = 0.15$, Fisher's exact test). This report is focused on the remaining 282 patients (82.6% of the sample; 141 in CBT, 141 in SPSP).

Interventions. Both therapies consisted of 16 individual sessions in the course of 22 weeks and were conducted according to published treatment manuals

(de Jonghe, 2005; Molenaar, Don, van den Bout, Sterk, & Dekker, 2009). CBT was based on the principles described by Beck (1976) and included behavioral activation and cognitive restructuring according to a session-by-session protocol with homework assignments. SPSP involved an open patient-therapist dialogue in which supportive and insight-facilitating techniques are used (de Jonghe et al., 2013). Its core technique is adequate psychoanalytic support. The therapist aims to address the emotional background of depression by discussing current relationships, internalized past relationships, and interpersonal patterns (de Jonghe et al., 2013).

Psychotherapists in both conditions were trained psychiatrists or psychologists. Therapy sessions were not rated for adherence; manual fidelity was checked by means of bi-weekly supervision sessions, chaired by a study supervisor, in which audio-taped material was discussed.

Severely depressed (HRDS>24) patients at baseline, as well as moderately depressed patients at baseline who developed severe symptoms during treatment (HRDS>24), were offered adjunctive antidepressant medication. Medications were administered by a psychiatrist (not the patient's therapist) according to a protocol starting with extended-release venlafaxine 75 mg/day that could be raised to a maximum of 225 mg/day. In cases of intolerance or complete nonresponse, patients were switched to either citalopram or nortriptyline. Pharmacotherapy consults addressed symptom evaluation, side-effects and adherence. The number of patients starting pharmacotherapy at baseline or during psychotherapy did not differ significantly between the treatment conditions (see Driessen et al., 2013).

Measures

Depression severity. We used continuous scores on the HRSD, a 17-item observer-rated measure of depressive symptoms, as the primary outcome measure. The HRSD was assessed at baseline, weeks 5, and 10, and at the end of treatment (i.e., week 22). HRSD assessors were trained master-level clinical psychology

students, not blind to treatment condition, who assessed the HRSD according to the Dutch scoring manual (de Jonghe, 1994). The average intraclass correlation coefficient over 46 audiotaped assessments scored by multiple assessors was .97. Of the 282 patients who remained in the trial through week 5, 247 (88%) provided an HRSD score at week 5.

Therapeutic alliance. The alliance was assessed with the Helping Alliance Questionnaire (HAQ-I; Luborsky, Crits-Christoph, Alexander, Margolis, & Cohen, 1983), an 11-item self-report questionnaire measuring the perceived helpfulness of the therapy as well as the quality of the cooperative or working alliance. Items are rated on a 7-point Likert scale, with higher scores indicating a stronger therapeutic alliance. Because the items measuring the perceived helpfulness of therapy are contaminated by prior symptom change, only items 6 – 10, which tap the collaborative aspect of the relationship, were analyzed (hereafter we refer to this as the HAQ-Ic; de Weert-Van Oene, de Jong, Jörg, & Schrijvers, 1999; Hendriksen et al., 2010). Of the patients who remained in the trial by week 5, 197 (70%) completed the HAQ-Ic. The internal consistency of the subscale was 0.88.

Depressive recurrences. History of prior depression was ascertained from patient's self-report as part of an unstructured clinical interview with a master's level clinician. Patients indicated whether they had 0, 1, or 2 or more prior depressive episodes.

Analytic Plan

Missing HAQ-Ic and HRSD data were handled using non-parametric imputation via random forests with the missForest package in R (Stekhoven & Bühlmann, 2012). Covariates used for the imputations were the HAQ-Ic and HRSD scores, treatment condition, prior episodes, and the other baseline variables displayed in Table 3.1. All descriptive and inferential analyses were conducted in IBM SPSS v.22. Data were centered according to Kraemer and Blasey's (2004)

recommendations. We used hierarchical linear models (HLMs) to predict change over time on the HRSD, the primary study outcome. In all analyses, we controlled for early symptom change (baseline to week 5), whether the patients were on medications, and the medication by treatment interaction.

To control for the nesting of data within therapists, a variable representing therapists was specified as a random effect. We controlled for early symptom change, as opposed to including baseline and week 5 HRSD scores, because adding early change to the statistical models increased fit more than did adding baseline and week 5 scores. Additionally, controlling for baseline HRSD scores would prohibit controlling for medication status because these variables are non-independent (i.e., baseline HRSD determined whether patients received medication or not). Controlling for baseline severity and week 5 severity instead of early change does not change the pattern of results.

We first estimated the overall effect of the alliance on outcomes by modeling change on the HRSD as a function of the alliance and the alliance by time interaction. Then, to probe whether the alliance interacted with the number of prior episodes, we explored the interaction of time, the alliance, and prior episodes, with all lower-order interactions and the statistical controls (i.e., early symptom change, medications, medications X treatment, and their interactions with time). We also present the tests of the alliance X episode X time interaction according to treatment condition. To probe whether the relation of prior episodes and alliance in predicting outcomes varied as a function of treatment condition, we analyzed the interaction of alliance X prior episodes X treatment X time, with the lower-order interactions and statistical controls. We present effect size estimates in accordance with the framework of Feingold (2013).

RESULTS

An HAq-Ic was available for a higher proportion of clients with 2+ prior episodes (76%), compared to those with 0-1 prior episodes (64%; $p = 0.038$, Fisher's exact test [FET]). A higher proportion of HAq-Ics were available for clients in the SPSP condition (74%) than for clients in the CBT condition (65%), but this difference was not significant ($p = 0.12$, FET). There was a tendency for clients in the medication condition (63%) to be less likely to provide an HAq-Ic, relative to those not on medication (74%; $p = 0.06$, FET). There were no differences between participants who provided a HAq-I and those who did not on any of the other variables listed in Table 3.1 (all $ps > 0.16$).

On average, clients rated their alliance with their therapist as high ($M = 5.24$, $SD = 1.01$, where the possible range was 1-7; see Table 3.1). Alliance scores were non-significantly higher in CBT condition ($M = 5.32$, $SD = 0.90$) relative to the SPSP condition ($M = 5.15$, $SD = 1.11$; $t(280) = 1.37$, $p = 0.17$). Alliance scores were not correlated with the number of prior episodes reported ($r = 0.004$, $p = 0.95$) and the test of the interaction of treatment condition with the number of prior episodes in predicting the HAq-Ic scores was not significant ($B = 0.06$, $SE = 0.14$, $\chi^2 = 0.23$, $p = 0.63$). These results indicate that, as expected, the levels of alliance did not vary as a function of the number of prior episodes, treatment condition, or their interaction.

The model predicting change on the HRSD yielded a significant relation of the alliance to outcome ($B = -1.99$, $SE = 0.38$, $t(715.8) = -5.18$, $p < 0.001$; $d = 0.37$). The interaction between prior episodes and the alliance was not significant in the SPSP condition ($B = 0.20$, $SE = 0.58$, $t(367.38) = 0.36$, $p = 0.72$). However, in the CBT condition, there was a statistically significant interaction between prior episodes and the alliance in predicting outcomes ($B = 1.88$, $SE = 0.66$, $t(349.50) = 2.83$, $p = 0.005$). Although the interaction between time, the alliance, prior episodes and treatment did not reach statistical significance ($p = 0.059$), examination of the effect

sizes associated with changes in the alliance (see Figure 3.1) shows that the alliance was a predictor of outcomes in SPSP for participants with 0 – 1 prior episodes ($B = -2.09$, $SE = 0.69$, $t(172.69) = -3.00$, $p = 0.003$, $d = 0.33$) as well as for those with 2+ episodes ($B = -1.79$, $SE = 0.66$, $t(191.66) = -2.70$, $p = 0.008$, $d = 0.39$). By contrast, in CBT the alliance was a strong predictor of outcomes for those with 0 – 1 prior episodes ($B = -4.24$, $SE = 0.93$, $t(179.96) = -4.56$, $p < 0.001$, $d = 0.79$) but not for those with 2+ episodes ($B = -0.30$, $SE = 0.86$, $t(166.33) = -0.36$, $p = 0.72$, $d = 0.06$).

DISCUSSION

We aimed to replicate and extend the findings of Lorenzo-Luaces et al. (2014) that, in CBT, the association between the therapeutic alliance and subsequent change in depression varied as a function of the number of prior depressive episodes clients reported at baseline. The present findings suggest that whereas in psychodynamic psychotherapy the therapeutic alliance is a robust predictor of outcomes, in CBT the effect of the alliance on outcomes is contingent on a client characteristic indexed by the number of previous depressive episodes. This finding contributes to the small number of studies on the moderation of process-outcome relations by suggesting that process-outcome correlations can vary as a function of the interaction of common and specific therapeutic processes and identifiable client features (Beutler & Harwood, 2002; Beutler & Martin, 2001; DeRubeis, Gelfand, German, Fournier, & Forand, 2013).

Limitations and strengths

A number of limitations, some of which are the consequences of analyzing data collected in a naturalistic context, must be considered when interpreting the findings from the present analyses (see Driessen et al., 2007; 2013) for discussions of the limitations of the parent RCT). Some of the most notable limitations of the trial from which these data were analyzed were the fact that HRSD raters were not

blinded to treatment conditions as well as the fact that treatment adherence was not formally addressed. We examined moderation of the alliance-outcome relation only in the subset of clients who remained in treatment for at least five weeks. Although we imputed missing data for clients who were in treatment at week 5 but did not complete an alliance assessment, we chose not to impute data for those who dropped out early, as this is a systematic reason for missingness. In this way, the generalizability of our results is limited. We note, however, that even considering only the clients with complete data, the sample size in this study is larger than more than 90% of the studies included in the most recent alliance-outcome meta-analysis (Horvath et al., 2011).

Only week 5 assessments of the alliance were available in this trial. Earlier assessments are preferable because they are less likely to be contaminated by symptom change. We controlled for prior change statistically, but we cannot rule it out as a source of contamination. Moreover, the number of prior episodes in this trial was assessed as either zero vs. one vs. two or more. This did not allow us to estimate the alliance-outcome correlation for the subset of clients who would have reported an even higher number of prior episodes.

Although the four-way interaction between time, the alliance, prior episodes, and the treatment condition did not cross the traditional threshold for statistical significance, the interaction between time, the alliance, and prior episodes was significant in the CBT condition, in the direction and magnitude reported previously (Lorenzo-Luaces et al., 2014). The current report thus is noteworthy, especially given the so-called replication crisis in psychology (Open Science Collaboration, 2015) and the fact that interactions are especially difficult to replicate (Benassi & Belli, 1989). It is also important to observe that this replication effort occurred in a different cultural context, with different measures of both the alliance and of depressive symptoms. This suggests that the original findings were unlikely to have

resulted from artifacts of the measures used in that study, but that instead they reflect true relations between these constructs.

The alliance in different therapies

The therapeutic alliance is not a mechanism within the client that mediates symptom change, nor is it a set of therapist behaviors. Thus, an account of symptom change that invokes the alliance must also consider the behavior of therapists as well as the psychological targets that such behavior is presumed to influence. Change in overly negative thinking appears to be a general mechanism of change in psychotherapies for depression (Lorenzo-Luaces, German, & DeRubeis, 2015). These negative thinking patterns are more rigidly held and more easily activated in recurrent depression. It is possible that they need to be addressed directly for symptom change to occur (Ma & Teasdale, 2004; Monroe & Harkness, 2005).

Although the goal of changing negative thinking patterns is common to psychodynamic and cognitive therapies, the ways in which such changes are targeted differs markedly between the therapies. In CBTs, agreement on the goals and tasks of therapy, which involve cognitive and behavioral work aimed at fostering cognitive change, has been shown to predict subsequent symptom improvement (Rector et al., 1999; Webb et al., 2011). In short-term psychodynamic therapy, the development of a secure therapeutic relationship is seen as a vital process thought to facilitate the development of insights that reveal maladaptive patterns of expectations in the context of interpersonal relationships. Moreover, the client is encouraged to experience affect that has been avoided. Given that a core technique in SPSP is the provision of support, alliance building *is* technique and vice versa. Thus, the therapeutic alliance ratings may represent somewhat different constructs across psychotherapies in that they relate to the different roles that the alliance is assigned, and the different ways in which change is promoted. Findings from studies in which the alliance is measured either in placebo or pharmacotherapy conditions

also supports the view that ratings of the therapeutic alliance may represent different constructs across treatments (Barber et al., 2014; Strunk et al., 2010; Zilcha-Mano et al., 2015).

Less recurrent depression. Patients with less recurrent depression may have less of a latent vulnerability to depressive episodes (Monroe & Harkness, 2005). In these patients, the alliance in CBT and SPSP appears to lead to symptom change. Life stressors often trigger depression in these individuals. One possibility is that they benefit sufficiently from the provision of non-specific support on part of the therapist as a way of remoralizing the patient or helping him or her to overcome specific problems. Areán et al. (2015) conjectured that the provision of specific psychotherapeutic techniques meant to address psychopathology may not be necessary for all patients and that many individuals could experience improvement in functioning with the provision of assistance dealing with current life stresses. In other words, for some patients it may not so much matter whether therapists attempt to foster symptom change by engaging in specific techniques like encouraging behavioral change, cognitive change, providing support, or exploring interpersonal patterns. Rather, engaging in any of these behaviors as a way of helping to resolve interpersonal stressors and countering patients' depressed mood may drive symptom change. For these patients, perhaps it is the agreement between them and their therapist in a course of action, irrespective of what is being agreed about, that promotes symptom change. It is worth observing that the effects of the alliance for those with less recurrent courses of depression appeared stronger in CBT than in SPSP. One possibility is that it may more conducive to symptom change for patients and therapists to focus on concrete (Keefe et al., 2016), especially behavioral (Sasso et al., 2014), changes, possibly because they are easier for both the patient and the therapist to carry out. This hypothesis should be explored in future work. There already are treatment approaches that rely on behavioral

strategies as first steps in the treatment of depression only to be succeeded by other therapeutic strategies if the behavioral methods do not produce symptom change (Alexopoulos & Areán, 2014).

More recurrent depression. Individuals with more recurrent courses of depression often experience depressive episodes as if they came “out of the blue” (Ma & Teasdale, 2004). Evidence suggests that individuals with more recurrent depression, as those who are considered at high risk for depression, may actually be experiencing depression in response to stressors that are very minor, including even so-called “daily hassles” (Monroe & Harkness, 2005; Sher, 2004). These minor stressors, in vulnerable individuals, may be enough to trigger the cognitive-affective networks associated with self-perpetuating depressed mood. Individuals with a recurrent history of depression have long histories of experiencing these shifts in mood and may therefore may not experience them as being connected to cognitive or meta-cognitive patterns. For these individuals, agreement with their therapists in the goals and tasks of CBT did not appear to lead to symptom change. It is important to observe that individuals with more recurrent depression did not experience worse outcomes in CBT than in SPSP, but rather the outcomes were not linked to the level of agreement in the goals of CBT. It is possible that agreement in the concrete goals and tasks of therapy, at least as they have been discussed early in treatment, (i.e., to promote behavioral change and change on negative automatic thoughts) does not promote symptom change. Cognitive work at the deeper level of schemas (Keefe et al., 2016) that is meant to address the underlying vulnerability to depression may be required to promote symptom change. In other words, it may not be the work on automatic thoughts per se, a concrete goal of CBT, that leads to symptom change, but rather it is the identification of patterns of maladaptive thoughts and their underlying schemas that promote symptom change. Alternatively, other processes that were not explicit goals of CBT may also account for symptom

change in CBT for recurrent depression. For example, a standard course of CBT may increase mindfulness (Manicavasagar, Perich, & Parker, 2011), or it may promote affective shifts (Hayes et al., 2007), both of which have been hypothesized to reduce vulnerability to depression.

The finding of this study as well of Lorenzo-Luaces et al. (2014), that measures of the therapeutic alliance did not predict outcomes for clients with more recurrent depression in CBT, should not be taken to mean that the quality of the alliance is unimportant for these clients. High scores on measures of the therapeutic alliance are typical in most studies of the alliance (Barber, 2009). It is possible that if the lower range of alliance scores were sampled, a relationship of the alliance and outcomes would be evident for clients with more recurrent depression in CBT. That is, even if other therapeutic elements of CBT are promoting symptom change in clients with more recurrent depression, it is possible that these require the presence of an at least “good enough” therapeutic alliance.

The finding of an interaction between prior episodes and the alliance in CBT raises the question of why such an interaction would not be found in psychodynamic therapy. In psychodynamic therapies, the alliance is hypothesized to be key to structural change for all clients. Inasmuch as therapist interventions are performed using the therapeutic alliance, the alliance may represent a process of psychodynamic therapies that is active across all clients. Our findings can be taken to lend credence to this view that the alliance is instrumental in psychodynamic therapy. It may be that the SPSP goal to analyze maladaptive depressogenic patterns that occur throughout the life course (de Jonghe et al., 2013), which is done using the therapeutic alliance, produces symptom change because it reveals the cognitive-affective schemas that are activated in the context of depression. Alternatively, the exploration of affect, which is a stated goal of SPSP but not of CBT, may also promote symptom change (Hayes et al., 2007).

Conclusions

The current findings suggest that psychodynamic and cognitive-behavioral therapists achieve symptom change via different means with different clients, rather than through the common pathway suggested by proponents of the common factors of psychotherapy. Beutler and colleagues have argued for a move away from theories of common vs. specific factors of therapy and towards personalizing treatments by applying therapeutic procedures that match clients' presenting style (Beutler et al., 2012; Beutler & Harwood, 2002; Beutler & Martin, 2001). Our results suggest that the number of prior depressive episodes clients report before initiating treatment is an important variable to consider when tailoring treatments to individuals. Within psychodynamic therapies, the alliance, in conjunction with other processes engaged in treatment, leads to positive outcomes irrespective of the number of prior episodes. By contrast, in CBT, it would appear that the processes captured by measures of the therapeutic alliances are only predictive of outcomes for clients with less recurrent forms of depression. Other CBT processes, for example, a greater focus on cognitive change, may better account for symptom change in clients with more recurrent depression.

Table 3.1 Baseline characteristics of 282 clients assigned to cognitive-behavioral therapy (CBT) or short-term psychodynamic supportive psychotherapy (SPSP) for depression

	M	SD	% miss.
HAq-Ic	5.24	1.18	30
Baseline HRSD	23.38	5.38	0
Early HRSD change	3.59	5.85	12
HRSD week 5	19.79	7.39	12
HRSD week 10	18.30	8.12	16
HRSD week 22	15.09	8.74	19
	%	N	% miss.
Female	68	193	0
Married	25	70	0
Treatment allocation			0
CBT	50	141	
SPSP	50	141	
Medication	37	105	0
Prior episodes			0
0 - 1 episodes	50	141	
2+ episodes	50	141	
Duration of depression			4
< 6 months	26	74	
6-12 months	23	66	
12 - 24 months	14	38	
> 24 months	35	93	
Age			1
19-29	26	70	
30-39	23	80	
40-49	14	86	
50-64	33	46	
Female	68	193	0
Married	25	70	0
Employment status			0
Employed	39	111	
Student	4	10	
Unemployed or other	57	161	
Educational attainment			1
Low	21	59	
Intermediate	46	130	
High	32	90	

Note. HAq-Ic- Helping Alliance Questionnaire, Cooperation subscale, Alliance subscale. % miss = percentage missing data at baseline. HRSD – Hamilton Rating Scale for Depression. Early HRSD change – change from week 1 to week 5.

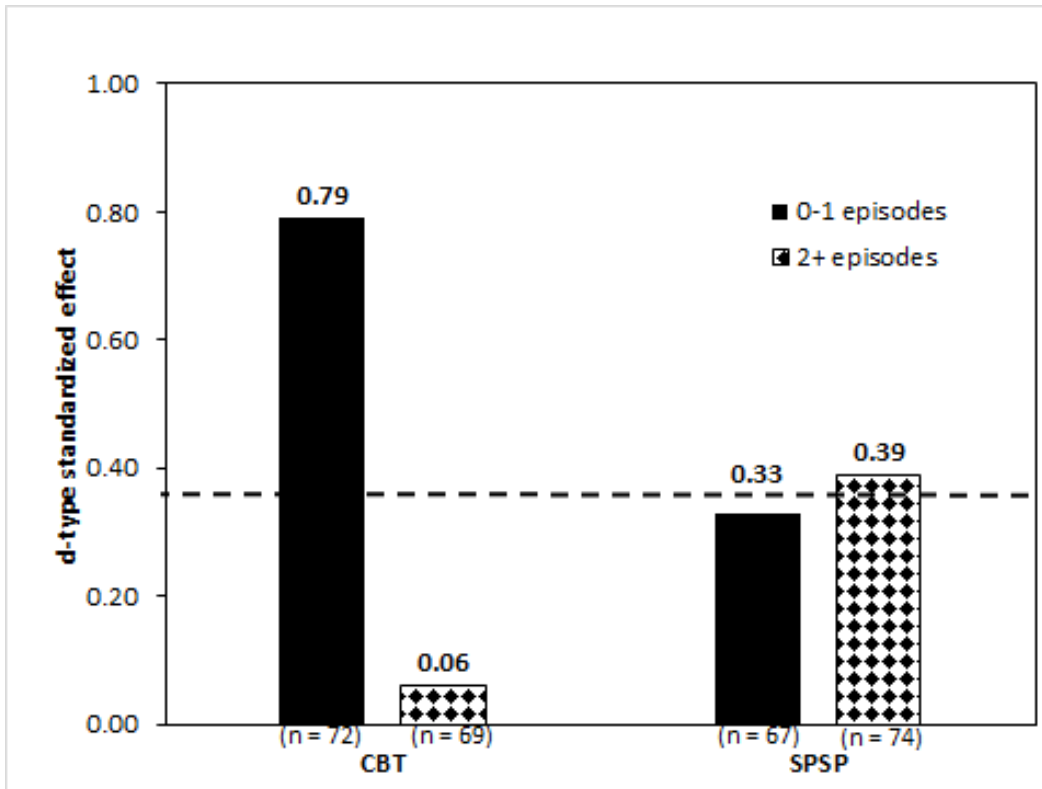


Figure 3.1 Association between the alliance and symptom change by treatments and prior episodes

Note: Prediction of change on the Hamilton Rating Scale for Depression from the mean score on items 6-10 on the Helping Alliance Questionnaire HAQ-Ic, controlling for therapist effects, medication status, and early symptom change. The dashed line represents the effect of HAQ-Ic on symptom change for the whole sample, controlling for early change, treatment condition, medication status, and the interaction of treatment condition and medication status. CBT = cognitive behavioral therapy, SPSP = short-term psychodynamic supportive psychotherapy

CHAPTER 4: GENERAL DISCUSSION

The studies presented as a part of the dissertation explored ways in which the heterogeneous nature of depression moderates treatment effects and the effects of treatment processes on outcomes. Taken together, the findings suggest that the efficacy of evidence-based psychotherapies and the effects of specific psychotherapy processes are limited to specific, potentially identifiable, subsets of clients. Although it might seem obvious that heterogeneity should be considered when interpreting treatment effects and psychotherapy process research findings, there is very little work that specifically addresses this issue.

The first study explored differential treatment outcomes in the context of a trial that reported negligible differences between a high-intensity treatment regime starting with CBT, a lower-intensity stepped care condition starting with BT, and treatment as usual (TAU). A closer examination of the data revealed that the treatments were equally efficacious for most of the sample, but that CBT was superior to BT and TAU in the subset of clients who were expected to have a poorer prognosis. The second study explored the variability of the effects of the working alliance, a psychotherapy construct traditionally associated with nonspecific or common psychotherapy effects that has been reported to have a moderate and consistent relation to outcomes. In a sample of clients receiving CT for depression, for clients with less recurrent depression the alliance was a stronger predictor of outcomes than is generally reported in the research literature. By contrast, for clients with more recurrent depression, the alliance did not predict outcomes. In the third study, these findings were replicated in the CBT condition of a randomized controlled trial (RCT). However, the findings did not generalize to the short-term psychoanalytic supportive psychotherapy (SPSP) condition in the RCT, suggesting that this pattern may be specific to CBT.

In the study of psychotherapy effectiveness, equivalent outcomes between different forms of therapy have often been reported, leading to an assumption of equipotency of psychotherapies dubbed the “Dodo bird verdict” (Luborsky, Singer, & Luborsky, 1975; Messer & Wampold, 2002; Rosenzweig, 1936). Some have gone so far as to argue that TAU psychotherapy and manualized evidence-based treatments produce equivalent outcomes (Flückiger, Del Re, Munder, Heer, & Wampold, 2014; Spielmans et al., 2013). One account that has been given for why all treatments should or would be equally efficacious is the common factors theory of symptom change (Laska et al., 2014). The proponents of common factors theory assert that all psychotherapeutic interventions delivered with the intent of being efficacious (e.g., TAU, CBT) are equally effective because they all include:

“factors that are necessary and sufficient for change: (a) an emotionally charged bond between the therapist and patient, (b) a confiding healing setting in which therapy takes place, (c) a therapist who provides a psychologically derived and culturally embedded explanation for emotional distress, (d) an explanation that is adaptive ... and is accepted by the patient, and (e) a set of procedures or rituals engaged by the patient and therapist that leads the patient to enact something that is positive, helpful, or adaptive.” (Laska et al., 2014; p. 469)

An alternative account to the Dodo and the common factors theory is that, although many treatments might be equally effective for many clinical conditions, some are better suited for dealing with specific problems (DeRubeis, Brotman, & Gibbons, 2005). Evidence has recently accumulated to support this position (Bell, Marcus, & Goodlad, 2013; Forman et al., 2012; Marcus, O'Connell, Norris, & Sawaqdeh, 2014; Poulsen et al., 2014; Tolin, 2010, 2014). For example, Marcus et

al. found CBT to be superior to other treatments for anxiety and eating disorders, but not for depression. These authors stated that their findings:

“are consistent with Chambless’ (2002) suggestion that there may be higher levels of treatment equivalence for some disorders such as depression and greater treatment differences for disorders like panic disorder. In other words, there may be Dodo disorders and non-Dodo disorders. Similarly, Westen, Novotny, and Thompson-Brenner (2004) noted that short-term targeted treatments may be most effective for treating disorders characterized by specific discrete symptoms (e.g., panic disorder), but may be less effective for treating “generalized affect states” (p. 655) or more characterological conditions such as depression or GAD.” (p. 527)

The findings from study 1 suggest that –even within “Dodo disorders”– there is variability in the extent to which treatment differences will be evident. For clients with a favorable prognosis, treatment differences may be small or non-existent. In this context, it is not too surprising that treatment researchers are frequently disappointed by the size of the effect of interventions. Although meta-analytic reviews, even those conducted by researchers who are not proponents of evidence-based practices (EBPs), have yielded estimates suggesting that EBPs are superior to TAU (Flückiger et al., 2014; Spielmans et al., 2013; Stewart & Chambless, 2009; Wampold et al., 2011; Weisz, Jensen-Doss, & Hawley, 2006), these findings have often been dismissed on the grounds that the differences do not appear to be large. To the extent that these studies have been conducted in client samples with a favorable prognosis, it is to be expected that differences between active treatments and controls, as well as between treatments that might differ in their potency, will be small. In depression, most comparisons between treatments have been conducted in samples of clients with mild to moderate depression (Barth et al., 2013), precisely

the types of clients we would expect to benefit from any intervention (Barbui, Cipriani, Patel, Ayuso-Mateos, & van Ommeren, 2011; Bower et al., 2013; Driessen, Cuijpers, Hollon, & Dekker, 2010; Fournier et al., 2010; Khan, Leventhal, Khan, & Brown, 2002; Kirsch et al., 2008). Subgroup analyses by severity have shown some differences between psychotherapies but these findings have been inconsistent (Dimidjian et al., 2006; Driessen et al., 2014; Elkin et al., 1995; Luty et al., 2007). Moreover, severity is only one variable that indexes prognosis. In one study that looked at the interaction of variables, Driessen et al. (2014) reported that CBT was slightly more effective than SPSP for clients with severe depression ($d = 0.36$) especially if it was not chronic ($d = 0.86$) whereas a small advantage for SPSP was detected in severe and chronic MDD ($d = 0.31$). These findings suggest that the relationship between expected prognosis and treatment outcomes may be curvilinear or otherwise more complex than we have presented.

The fact that for many clients any treatment will lead to symptom change should not be dismissed as a statistical artifact or as a reason to focus only on those clients who provide evidence of differences between treatments. An understanding of the lack of differences between active treatments and controls or TAU, or between treatments, has important implications for the delivery of mental health care. Given that for clients with a good prognosis there seem to be few appreciable differences between treatments, average treatment outcomes cannot be the consideration taken when giving treatment to these clients. Other variables, such as cost or ease of dissemination, must be considered. For example, it has been argued that behavioral activation (BA) should be considered a first-line treatment for depression given that it may engender as much change, on average, as CBT, and it is expected by many to be easier to disseminate than CBT. Although there are few published data that speak to former assertion, and no data that address the latter conjecture, these questions

are currently being explored in the United Kingdom (Rhodes et al., 2014). Analogously, Alexopoulos and Arean (2014) have developed and tested a stepped therapeutic approach that begins with behavioral activation and only adds other components of CBT (e.g., cognitive restructuring, emotion regulation skills) if it is deemed that they are needed. Although both of these studies represent notable advances in research on psychotherapy, the underlying assumption in these approaches is that individual therapist contact is required for therapeutic improvement. However, as the findings of chapter 1 and the findings from meta-analytic reviews (Barbui et al., 2011; Bower et al., 2013; Driessen et al., 2010; Fournier et al., 2010; Khan et al., 2002; Kirsch et al., 2008) suggest, clients with a more favorable prognosis may not need high-intensity treatments requiring therapist contact. As has been noted by others (Kazdin & Blase, 2011), self-help, media-based, and technology-assisted interventions may all contribute to reducing the burden of disease in clients with a better prognosis.

In addition to helping guide treatment selection, parsing out heterogeneity in depression and other disorders might be required in order to uncover mechanisms of treatment and of pathology. As shown in Chapters 2 and 3, processes that are assumed to be part of causal chains in psychotherapy may operate differently across client types, and even across the type of psychotherapy that is delivered. For individuals with less recurrent depression, a positive working alliance irrespective of therapy modality (Chapters 2 and 3), the use of behavioral homework (Sasso et al., 2015), and clients' self-reported behavioral changes (Lorenzo-Luaces, German, & DeRubeis, 2014) appear to be associated with symptom change. In individuals with more recurrent depression, cognitive change (Lorenzo-Luaces, German, & DeRubeis, 2014) and a positive working alliance in psychodynamic therapy (Chapter 3) are associated with symptom change. These findings may be interpreted in light of

theories of stress sensitization in depression which posit that prior depressive episodes change individuals in ways that leave them at a higher risk of developing subsequent depressive episodes (Monroe & Harkness, 2005).

One way in which depression may render individuals at higher risk for subsequent depression is by strengthening cognitive-affective networks associated with depressive states (Segal, Williams, Teasdale, & Gemar, 1996). Depression then, in individuals with more recurrent trajectories, may result from the activation of internal vulnerabilities with little or only minor stress, or even autonomously (Ma & Teasdale, 2004; Monroe & Harkness, 2005). If this is so, recovery from depression for individuals with more recurrent courses may require addressing the internal factors (e.g., cognitive reactivity) that underlie the individual's vulnerability to depression. As suggested by the results of post-hoc analyses of the trial from which the data in Chapter 2 were derived, addressing cognitive vulnerabilities may be one way of fostering symptom change (Lorenzo-Luaces, German, & DeRubeis, 2015; Sasso et al., 2015). In the analyses presented in Chapter 3, psychodynamic therapy and CBT achieved similar levels of symptom change among clients with more recurrent depression, and in dynamic therapy the alliance was related to symptom change.

In a case description of a course of SPSP, de Jonghe et al. (2013) provided information that is suggestive of processes that may account for symptom change in recurrent depression with SPSP. In the first few sessions, the therapist provides psycho-education and discusses day to day coping with symptoms but refrains from giving further advice. Next, explanations for depression are explored and the therapist emphasizes the relation of depression to circumstances ("there was a lot to do ... "But somehow I was not 'there' at work; it was as if I was constantly somewhere else in my thoughts. I was criticized for that and it upset me a great

deal." [p. 618]). At first glance, emphasizing the relation between events and moods might not seem highly applicable to clients with a more recurrent course. However, the therapist complements this approach by saying: "Everybody's life ... is highly determined by what happens and *even more by the way events are perceived*" (p. 618, emphasis added). As the therapy progresses, patterns from troubling and depressogenic situations are extracted in a supportive-expressive manner ("The therapist values her growing awareness of an interfering pattern or theme in her life ["being overlooked"])" (p. 619) This is followed by a shift in focus to internal life and it is revealed that "[the client] seldom speaks her mind from fear she might "give the wrong answer. 'I am always afraid they'll think I am a stupid, fat girl'." (p. 619). The client and the therapist have jointly discovered that "the problem is not out there but inside her" (p. 619). The subsequent stages of the treatment involve trying to uncover the roots of depressive thinking and recognizing that they might be related to early life experiences and hence are not facts that should be acted upon.

It is thus possible to conceptualize the SPSP treatment of recurrent depression as providing a meaningful narrative for depression rather than accepting that it has simply arisen out of the blue or with little provocation. It might be that it does not so much matter whether the narrative is "accurate" but rather whether the client is able to recognize depressive thinking when it is activated and counter it with adaptive, opposite, beliefs and behaviors. It is of note that the therapist and the client worked slowly and collaboratively through this explanation and it required the use of supportive interventions that were not meant to challenge thoughts, especially early on. Thus, a positive working relationship in which the client and the therapist are able to construct a narrative for depression that involves depressogenic thinking might explain symptom change in recurrent depression with SPSP. SPSP also entails exploration of affect in the working relationship with the therapist and in that sense

may produce cognitive change in a manner similar to what likely occurs in exposure-based CT treatments (Hayes et al., 2007).

A CBT approach towards promoting symptom change in recurrent depression might have been in some sense more straightforward than the SPSP approach described above. It may have begun by focusing on thoughts, somewhat reducing the importance of a highly positive working alliance. Providing support for this view, a recent dismantling trial suggested that the cognitive psychoeducational part of mindfulness-based CT may, on average, account for its efficacy in recurrent depression relative to the full MBCT package and to TAU (Williams et al., 2014). Note that this is not meant to imply that a positive working alliance is not needed for clients with recurrent depression undergoing CBT. That is an empirical question that existing trials are ill-equipped to answer because most ratings of the therapeutic alliance, whether by clients, therapists, or observers, suggest that good working relationships characterize the great majority of client-therapist dyads. The most that can be said is that, given the “good enough” levels of the working relationship that appear to have been present in nearly all the dyads studies in Chapters 2 and 3, in CBT the presence of an even better working relationship with a recurrently depressed individual did not appear to be necessary for promoting substantial symptom change.

Individuals with less recurrent depression typically experience depressive episodes that are triggered by life stress. It is possible that for many of these individuals the process of change in psychotherapy may be better conceptualized as one of remoralization and reengagement with positive and rewarding experiences (Connor & Walton, 2011). In a similar vein, in a study that failed to find a significant difference between problem-solving therapy (PST) and clinical management (CM) + PST in a low-income, medically ill population, Areán et al. (2015) conjectured that the resolution of health and psychosocial stressors from CM was enough to drive

change in depression and increase self-efficacy and problem-solving skills. It may have been the case that many of these clients did not have deficits in problem-solving skills, the pathology PST targets, but were struggling to adjust to their environments. It should be an aim of future research to identify subgroups of clients that may better be helped by therapeutic techniques that focus more on helping clients solve external problems than on helping to alleviate pathology.

One of the guiding assumptions of the research on common factors of psychotherapy, like the therapeutic alliance, is that these factors account for symptom change for all clients. At the statistical level, an assumption like this can be evaluated by conducting a test of whether process-outcome correlations are moderated by client features. Meta-analytic reviews have presented tests of whether the strength of the magnitude of process-outcome correlations varies as a function of the client samples in which studies are conducted. The results of these studies suggest that the alliance-outcome correlation diminishes insofar as the study samples contain individuals who are more educated (Sharf, Primavera, & Diener, 2010), have substance use disorders (Flückiger et al., 2013), or belong to racial and ethnic minority groups (Flückiger et al., 2013). Because meta-analyses refer to studies, and not to individual clients, more primary tests of moderation like the ones conducted in Study 2 and 3 are needed.

Our findings suggest that the alliance is not a common factor either across types of clients or across therapeutic modalities. These findings can be understood if we consider that agreement on the goals and tasks of the therapy cannot be a common factor because the goals and tasks of therapies differ. However, providing explanations for processes of change that incorporate the alliance and therapy-specific variables can prove very challenging at a conceptual level and will probably be difficult to detect statistically. Data-mining enterprises such as the ones

conducted in Chapter 1 and 2 may reveal interesting relationships that have not been theorized. The important issue will be to attempt to replicate and extend these findings as in Chapter 3.

The findings of heterogeneity as affecting treatment effects and process-outcome correlations also have important implications for the classification of depression. Insofar as there are cases of MDD that may be better understood as demoralization, it may be that those individuals lack the pathologies traditionally associated with MDD (e.g., maladaptive negative cognitive biases). As such, these individuals may not be helped more by treatments that are meant to target the pathologies in MDD (e.g., cognitive therapy) more than they would be helped by TAU, brief, or low-intensity interventions. It should be the aim of future work to differentiate between individuals who are more in need of active and specific treatments vs. lower-intensity interventions and to uncover mechanisms of pathology that can be linked to treatment effects.

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