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Therapeutic Alliance in Antidepressant Treatment: Cause or Effect of Symptomatic Levels?

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Key Words

Depression · Alliance · Antidepressant treatment · Psychopharmacology · Placebo effect · Therapy process

Abstract

Background: Previous studies have shown that in psychotherapy alliance is a predictor of symptomatic change, even while accounting for the temporal precedence between alliance and symptoms. However, the extent to which alliance predicts outcomes in psychopharmacology is yet to be fully investigated considering the fact that alliance can be the result, rather than the cause, of symptomatic change. The current prospective study examined whether the alliance predicts outcomes in psychopharmacology, while controlling for previous symptomatic change throughout the course of treatment. ***Methods:*** Data from a psychopharmacological randomized controlled trial for the treatment of adult major depression (n = 42), including the patients' rating of the alliance with the physicians, were analyzed. Multilevel models controlling for autoregressive lag of the dependent variable were used in all analyses to examine the effect of alliance on outcome. ***Results:*** The effect of alliance on outcome, while controlling for prior symptomatic levels, was significant and restricted to the middle phase of treatment (week 4, p = 0.005), when most of the reductions in symptoms were observed. Exploratory analyses of the differences between placebo and medication conditions suggest that the differences between the patients in their average alliance levels predicted a greater reduction in symptoms in the placebo compared to the medication conditions (p = 0.008). The main limitation is the small cohort size. ***Conclusions:*** The findings suggest an effect of alliance on outcome in psychopharmacology, which is not merely the result of previous symptomatic levels. This effect may be more robust in conditions that do not include active treatment (placebo), possibly serving as a compensatory effect.

Introduction

Therapeutic alliance is commonly defined as the emotional bond established in the therapeutic dyad and the agreement between patient and therapist as to the goals and tasks of treatment [1, 2]. The association between the alliance and the treatment outcome is well documented, with a recent meta-analysis of more than 14,000 treatments showing a small-to-moderate (r = –0.27) correlation between the alliance and outcome with no significant differences among treatment orientations [3]. Based on the association between alliance and symptoms, it has

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been suggested that a strong positive alliance leads to a better outcome.

However, the assumption that a better alliance leads to better outcomes has been questioned [4]. Some researchers have proposed that a good alliance may be the result of symptomatic change, rather than the other way around [5, 6]. While several studies evaluating the correlation between the alliance and the outcome demonstrated that early symptomatic change predicted alliance and that the alliance by itself could not predict subsequent changes in symptoms [7], other studies found that the alliance makes a unique contribution to the prediction of outcome, even after controlling for early symptomatic change [8]. Lately, while using specific statistical methods to explore the temporal relationship between alliance and symptoms, it has been shown that a stronger alliance predicts lower levels of depressive symptoms, even while accounting for temporal precedence between alliance and symptoms throughout the course of treatment [9].

While there have been many studies that have attempted to elucidate the alliance-outcome association, they have mostly focused on psychotherapy, rather than the working alliances in the clinical management of mental health, and its potential to improve responses to pharmacotherapy [10]. Although several authors acknowledged the importance of nonpharmacological factors, such as the physician-patient alliance, in pharmacotherapy [11, 12], few studies have been conducted on the alliance in pharmacotherapy. These studies demonstrated that a better alliance was related to a larger reduction in symptoms [13]. Based on this association, it has been suggested that the alliance between patients and their therapists in case management is an important therapeutic component contributing to the success of psychopharmacology treatment [14]. Specifically, it has been suggested that a good alliance may have a positive effect on the patient's compliance, retention and engagement in treatment [15, 16] and on medication adherence [17], thus further exposing patients to the active ingredients of treatment. However, 2 main questions with regard to the alliance-outcome association in pharmacotherapy – one relating to causality and the other to alliance effect in placebo versus medication – require further exploration.

The first question refers to causation: previous studies, which found that alliance predicts outcome in pharmacotherapy, may have been impeded by a methodological issue of reverse causation between the alliance and the symptoms. Specifically, a patient feeling that the medical treatment (e.g. a selective serotonin reuptake inhibitor) is effective may be more satisfied by his or her treatment and may also view the alliance with the therapist as more positive. In such a case, the alliance could be the result, rather than the cause, of symptomatic change. Therefore, it is an open question whether alliance in pharmacotherapy is the cause or effect of symptoms.

The second question is whether the alliance effect on symptoms is similar in both placebo and medication treatments [18]. If similar mechanisms of change (other than the active ingredient of the medication) underlie both placebo and medication effects, the effect of alliance on outcomes should be identical in both conditions. However, if there are different mechanisms, such as potential compensatory mechanisms in the placebo condition (where no active medication is given), then the alliance may play a more active role in placebo treatment. Consistent with this compensatory mechanism hypothesis are the findings that when treated with placebo, additional meetings with the therapist appeared to explain a large proportion of the symptomatic change, with 2 additional visits associated with twice the reduction in the level of depressive symptoms compared to 1 [19]. Additional meetings with the therapist had a less notable effect in the medication condition.

Using data from a recent randomized controlled trial [20, 21], the current study aimed to investigate the ability of the alliance to predict outcomes in a pharmacotherapy setting, while examining the 2 open questions mentioned above, reverse causation and medication (escitalopram or citalopram) versus placebo comparison. Furthermore, consistent with the methodological literature on longitudinal analyses, the nature of the alliance effect on outcome – whether improvements in alliance throughout the treatment or a general tendency to form a good alliance predict symptomatic change – was evaluated as well.

Methods

Design

The present study is a secondary analysis of a previously published randomized controlled trial [20, 21]. The main outcome results from this study demonstrated that the expectancy of therapeutic improvement was affected by a manipulation on the probability of receiving active antidepressant medication and that higher baseline expectancy of improvement, in turn, showed a trend toward a significant correlation with better outcome. Further details regarding the study procedures are available in Rutherford et al. [20, 21].

Participants

Prior to the initiation of the study, all procedures were approved by the New York State Psychiatric Institute (NYSPI) Insti-

tutional Review Board. Adult outpatients were recruited through physician referral and radio and newspaper advertisements to the Adult and Late Life Depression Clinic of the NYSPI. Inclusion criteria were: (1) men or women aged 18–65 years, (2) DSM-IV [22] unipolar major depressive disorder, (3) a 24-item Hamilton Rating Scale for Depression (HRSD) [23] score ≥16 and (4) capable of providing informed consent. Exclusion criteria were: (1) pregnant or lactating women, (2) current psychosis or history of a psychotic disorder, (3) substance dependence other than nicotine, (4) score >2 on the HRSD suicide item, (5) acute severe or unstable medical illness, (6) nonresponse to treatment with escitalopram 10 mg/day or citalopram 20 mg/ day given for at least 4 weeks during the current episode and (7) a Clinical Global Impressions-Severity (CGI-S) [24] score of 7 at baseline.

Alliance and Outcome Measures

Therapeutic alliance

The quality of the therapeutic alliance was assessed with the 24-item patient-rated version of the California Psychotherapy Alliance Scale (CALPAS) [25]. Items were rated on a 5-point Likert scale ranging from 0 (not at all) to 4 (very much). Higher scores indicated a better alliance. In the current study, the internal reliability range for the 3 time points was 0.78–0.84.

Depressive Symptoms

The severity of depressive symptoms was assessed with the 24-item clinician-administered semistructured interview version of the HRSD [23], with higher scores indicating a greater severity of depression. The HRSD was scored by a trained rater who was blind to the patients' assignment.

Procedure

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

After describing the study to the patients, written informed consent was obtained. At baseline, a psychiatrist conducted a medical and psychiatric evaluation, and a research rater completed the Structured Clinical Interview for the DSM-IV axis I disorders (SCID) [26] and the 24-item HRSD interview. One week after the baseline evaluation, the patients were randomized to either the placebo-controlled (receiving escitalopram or placebo) or the comparator group (receiving escitalopram or citalopram) and began treatment (week 0). The HRSD was completed immediately after the initial visit (week 0) and weekly thereafter until week 8. Patients also completed the alliance questionnaire, the CALPAS, immediately after the initial visit and at the week 4 and week 8 visits. For the current analyses, 4 scheduled time points were used for HRSD evaluations (baseline, weeks 0, 4 and 8), and 3 were used for the CALPAS ratings (weeks 0, 4 and 8).

Supportive care in all conditions was administered weekly by the senior author, who was blind to the patients' assignment, and lasted 20 min on average for each session of interpersonal clinical interaction. The sessions were conducted according to the Manual for Pharmacological Clinical Management of Depression [27]. The sessions included assessment of risk, side effects and symptoms as well as acknowledgment of gains and the providence of support and encouragement but refrained from engaging in formal psychotherapeutic techniques such as problem solving.

Statistical Analyses

Examining the Ability of Alliance to Predict Outcome while Controlling for Prior Symptomatic Levels

Due to the hierarchical structure of the data (measures nested within individuals), analyses were conducted using Proc Mixed in SAS for linear mixed models [28]. In order to examine the association between the therapeutic alliance (as measured by the CALPAS scores) and symptoms (as measured by the HRSD scores) over time while controlling for prior symptomatic levels, we employed autoregressive lagged modeling (ARCL) [29, 30]. Controlling for the autoregressive lag of the dependent variable (HRSD) allowed us to examine whether the current level of CALPAS ($CALPAS_T$) predicted the concurrent HRSD level ($HRSD_T$) throughout treatment, while controlling for the previous level of HRSD ($HRSD_{T-1}$). In this analysis, week was introduced as a categorical variable in order to examine whether the association between alliance and symptoms was strongest during midtreatment, when most of the symptomatic change in this sample occurred [21].

Since the data included repeated measures over time, we had to statistically disentangle the between-patients and within-patient components of stability and change [31]. In order to disentangle the alliance within-patient effect (i.e. improvements in the alliance throughout the treatment as a predictor of greater symptomatic change) and between-patients effect (i.e. general tendencies of the patients to form a good alliance as a predictor of the patients' lower mean symptomatic level [31]), we followed the recommendations by Raudenbush and Bryk [32]: the CALPAS was centered within context (grouped-mean centered at the lower level of the analysis) with the reintroduction of the subtracted means at the group level (the patient level, which is the upper level of the analysis). Such a procedure results in independent coefficients for within- and between-patients effects [31]. We examined the 2-way interactions of each CALPAS component (within- and between-patient effects) with time to predict $HRSD_T$, while controlling for $HRSD_{T-1}$.

Examining Differences between Placebo and Medication Conditions in the Ability of Alliance to Predict Outcome

Following the initial analysis, we explored the differences between the placebo and the medication conditions. The 3-way interaction of the between-patient differences in $CALPAS_T$, time and treatment condition (a 2-level categorical variable: placebo vs. medication) as well as the 3-way interaction of within-patient changes in $CALPAS_T$, time and treatment condition were added to the model predicting $HRSD_T$ with all the lower-order effects, while controlling for $HRSD_{(T-1)}$. In order to avoid the potential confounding of patient expectancy on treatment condition [21], we controlled for patient expectancy at week 0 (after randomization).

Results

The Ability of the Alliance to Predict Outcome while Controlling for Prior Symptomatic Levels

Of the 42 patients randomized in the original study, 37 had at least 2 measurement points of alliance and depression and were therefore included in the analyses. We tested whether the alliance predicted the outcome, while controlling for prior symptomatic levels throughout the

Table 1. Estimates of alliance effect on outcome while controlling for previous symptomatic levels

Label	Estimate	Standard error	d.f.	t	p
Model 1 (alliance effect on outcome at week 4)					
Previous symptomatic levels ($\beta_{1.4}$)	0.67	0.09	97	6.74	<0.0001
Alliance between-patients ($\beta_{2.4}$)	–0.16	0.10	97	–1.57	0.11
Alliance within-patients ($\beta_{3.4}$)	–0.69	0.24	97	–2.85	0.005
Model 2 (changes across time in between-alliance effect on outcome in placebo vs. medication)					
Placebo ($\beta_{4.1}$)	–0.19	0.06	78.1	–3.01	0.003
Medication ($\beta_{4.2}$)	–0.01	0.02	30	–0.58	0.56
$\delta = \beta_{4.2} - \beta_{4.1}$	0.18	0.06	84.9	2.73	0.008

Model 1: Y_{ij} (outcome for individual *i* on week *j*) = $\beta_{0,j} + \beta_{1,j} \times Y_{i(j-1)} + \beta_{2,j}$ (alliance between-patients at $week_j$) + $\beta_{3,j}$ (alliance within-patients at $week_j$) + β_7 (expectancy) + $u_i + e_{ij}$. Consistent with our hypothesis regarding model 1, the estimates are reported for week 4. Model 2: Y_{ij} (outcome for individual *i* in group *j*) = $\beta_{0,j} + \beta_1 \times Y_{i(j-1)} + \beta_{2,j} \times$ week + $\beta_{3,j}$ (alliance between-patients) + $\beta_{4,j}$ (alliance between-patients × week) + $\beta_{5,j}$ (alliance within-patients) + $\beta_{6,j}$ (alliance within-patients × week) + β_7 (expectancy) + $u_i + e_{ij}$.

course of the treatment. The 2-way interaction between time and within-patients differences (deviation from the patient's mean) was significant, $F(2, 97) = 3.60$, $p = 0.03$. The estimated slope of the alliance at week 4 significantly predicted symptomatic levels, indicating that an increase in a patient's alliance level at the midpoint of treatment (when most of the reductions in symptoms occurred) predicted better treatment outcomes, while controlling for prior symptomatic levels (table 1). The other 2-way interaction, between time and between-patients differences in CALPAS in predicting outcome was not significant, $F(2, 97) = 0.52$, $p = 0.59$.

Differences between Placebo and Medication in the Ability of the Alliance to Predict Outcome

Exploratory analyses examined the differences between the placebo and medication conditions. The first 3-way interaction of between-patient differences in CALPAS, time and treatment condition (a 2-level categorical variable: placebo vs. medication), while controlling for previous symptomatic levels and patient expectancy, was significant, $F(1, 73.2) = 7.25$, $p = 0.008$. The estimated effect of the alliance on outcome in the placebo condition was significantly larger compared to the estimated effect of the alliance on outcome in the medication condition (table 1). Thus, higher average alliance levels predicted a lower mean symptomatic level in the placebo compared to the medication condition. The other 3-way interaction of within-patient differences in CALPAS, time and treatment condition, while controlling for previous symptomatic levels and expectations, was not significant, $F(1, 87) = 0.46$, $p = 0.49$.

Discussion

The current study examined whether the alliance between the patient and therapist in psychopharmacology might affect the response to both active medication and placebo when treating major depression or whether the alliance is merely a by-product of the response to an effective treatment. We found that the alliance can predict symptomatic change in psychopharmacology, specifically in the midphase of treatment, when most of the reduction in symptoms in this randomized controlled trial occurred. The effect of alliance on symptoms is a within-patient effect, meaning that an increase in the alliance throughout the treatment predicts a greater reduction in symptoms throughout the treatment. Moreover, this effect cannot be explained by previous symptomatic levels, therefore reducing the risk for reverse causation. These findings suggest that improvement in the alliance may be an important ingredient in bringing about therapeutic change, even in pharmacological treatment.

Several potential mechanisms can be suggested to explain the effect of the alliance on treatment outcome. First, the alliance may provide the conditions in which pharmacotherapy can be effectively implemented. Specifically, the therapeutic alliance may help create a supportive and collaborative environment in which the compliance to treatment is enhanced. Such an environment would aid the therapist in addressing and resolving the patient concerns, such as fears of dependence on medication, resistance and demoralization regarding the delayed or variable effects of medication or placebo and the difficulty tolerating the discomforts of side effects [13, 33].

A second potential mechanism is the formation of a benevolent, helpful alliance which may be therapeutic in and of itself. In support of this view, we found that the effect of alliance on outcomes was a within-patient effect. Another potential explanation is that alliance and symptomatic change cannot be entirely disentangled (e.g. in the present study, most of the effect of alliance on outcome occurred when the antidepressants started to show their effects), although the greatest effect still occurred when no active medication was given (placebo condition). While each of the above-mentioned potential mechanisms should be examined in future research, the current findings suggest that the effect of the therapeutic alliance on outcomes extends beyond psychotherapy to case management, with implications for the way in which pharmacotherapy is conceptualized and practiced.

Interestingly, the exploratory analysis suggested that the alliance has a greater active effect in placebo treatment compared to medication. This finding should be interpreted with caution because of the small sample size. If validated in future studies, this finding suggests that in the placebo condition, nonspecific elements (alliance) may be more essential to symptom reduction throughout the treatment, as no active treatment has been administered. These nonspecific elements refer to elements of treatment that are shared across virtually all therapeutic interventions [34]; however, their impact may be stronger in some treatments as opposed to others [11]. Specifically, these elements may compensate for the lack of other active ingredients in placebo conditions. If supported by future studies, this finding may shed new light on the efforts to discover ways to minimize placebo response in clinical trials and maximize placebo response in clinical practice [35].

The possible compensatory effect of alliance in placebo treatments would destabilize the traditional paradigm, which evaluates the effect of medication as the medication-placebo difference, and is based on the axiom that any mechanism of change that contributes to the placebo effect must also contribute in the very same manner to the medication effect (in other words, that the medication effects are additive to the placebo response). Other findings in the literature may also support the role of differential mechanisms [36]. For example, Papakostas and Fava [37] reported that when the likelihood of receiving placebo increased by 10%, the probability of responding to an antidepressant decreased by 1.8%, and the probability of responding to placebo decreased even more, by 2.6%. The current findings, which suggest a compensatory effect of the alliance in placebo, are also consistent with the findings that patients who received active medication benefit approximately 50% less from increased therapeutic contact than patients who received placebo [19]. The findings are consistent with the call for a greater focus on examining nonspecific elements, such as the patient-physician relationship, in order to better understand and influence the effectiveness of treatment for everyday patient management [38].

The main limitations of the current study are its small sample size and the exploratory nature of the analyses aimed at evaluating the differences between the placebo and medication conditions. Future studies should examine the same questions in a larger sample that is equal in size for medication and placebo. Studies with a larger sample size will also have the statistical power required to examine the association between the alliance and patients' expectancy of therapeutic improvement in predicting outcome. Another limitation of the current study is the use of 4 time points for symptomatic levels and 3 for alliance. Although the use of 3 or 4 time points is common in the fields of psychotherapy and pharmacology and is also statistically adequate [39], the use of additional time points would have been preferable and should be implemented in future studies. Additionally, it is important to stress that while the analyses conducted in this study were aimed at ruling out the possibility of reversed causality, our results do not necessarily imply a causal role, since additional unmeasured variables may still influence both alliance and symptoms. Future studies measuring potential theoretically relevant variables to explain the mechanisms behind this association, measured at exactly the same time points as alliance and symptoms are examined, will assist in the systematic process of inferring causality between alliance and symptoms. Finally, in the current study no systematic adherence evaluation has been conducted. Additionally, the same therapist treated all patients, which is a strength of the study in terms of internal validity but is a weakness in terms of the external validity and the ability to generalize the findings, especially since physician attitudes may affect treatment outcomes [40].

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Disclosure Statement

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References

1 Hatcher RL, Barends AW: How a return to theory could help alliance research. Psychotherapy 2006;43:292–299.
2 Bordin E: The generalizability of the psychoanalytic concept of the working alliance. Psychotherapy 1979;16:252–260.
3 Horvath AO, Del Re AC, Fluckiger C, Symonds D: Alliance in individual psychotherapy. Psychotherapy 2011;48:9–16.
4 DeRubeis RJ, Feeley M: Determinants of change in cognitive therapy for depression. Cognit Ther Res 1990;14:469–482.
5 Barber JP: Toward a working through of some core conflicts in psychotherapy research. Psychother Res 2009;19:1–12.
6 DeRubeis RJ, Brotman MA, Gibbons CJ: A conceptual and methodological analysis of the nonspecifics argument. J Clin Psychol 2005;12:174–183.
7 Barber JP, Luborsky L, Crits-Christoph P, Thase ME, Weiss R, Frank A, Onken LS, Gallop R: Therapeutic alliance as a predictor of outcome in treatment of cocaine dependence. Psychother Res 1999;9:54–73.
8 Barber JP, Connolly MB, Crits-Christoph P, Gladis L, Siqueland L: Alliance predicts patients' outcome beyond in-treatment change in symptoms. J Consult Clin Psychol 2000;68:1027–1032.
9 Zilcha-Mano S, Dinger U, McCarthy K, Barber J: Does alliance predict symptomatic change, or is it the other way around? J Consult Clin Psychol 2014;82:931–935.
10 Crits-Christoph P, Gibbons MBC, Mukherjee D: Psychotherapy process-outcome research; in Lambert MJ (ed.): Bergin and Garfield's Handbook of Psychotherapy and Behavior Vhange, ed 6. Hoboken, Wiley, 2013, pp 298–340.
11 Uhlenhuth EH, Rickels K, Fisher S, Park LC, Lipman RS, Mock J: Drug, doctor's verbal attitude and clinic setting in the symptomatic response to pharmacotherapy. Psychopharmacologia 1966;9:392–418.
12 Bech P: Karl Rickels: a tribute on his 90th birthday. Psychother Psychosom 2014;83:131–135.
13 Krupnick JL, Sotsky SM, Simmens S, Moyer J, Elkin I, Watkins J, Pilkonis PA: The role of the therapeutic alliance in psychotherapy and pharmacotherapy outcome: findings in the National Institute of Mental Health Treatment of Depression Collaborative Research Program. J Consult Clin Psychol 1996;64:532–539.
14 Wolfaardt UB, Reddon JR, Joyce AS: Assessing the efficacy of antidepressants: the transactional paradigm. Med. Hypotheses 2005;64:1229–1236.
15 Ekeland T: The healing context and efficacy in psychotherapy: psychotherapy and placebo phenomenon. Int J Psychother 1997;2:77–87.
16 Marshall M, Gray A, Lockwood A, Green R: Case management for people with severe mental disorders. Cochrane Database Syst Rev 2000;2:CD0000050.
17 Dilallo JJ, Weiss G: Motivational interviewing and adolescent psychopharmacology. J Am Acad Child Adolesc Psychiatry 2009;48:108–113.
18 Strunk DR, Stewart MO, Hollon SD, DeRubeis RJ, Fawcett J, Amsterdam JD, Shelton RC: Can pharmacotherapists be too supportive? A process study of active medication and placebo in the treatment of depression. Psychol Med 2010;40:1379–1387.
19 Posternak MA, Zimmerman M: Therapeutic effect of follow-up assessments on antidepressant and placebo response rates in antidepressant efficacy trials: meta-analysis. J Ment Sci 2007;190:287–292.
20 Rutherford B, Sneed J, Devanand D, Eisenstadt R, Roose S: Antidepressant study design affects patient expectancy: a pilot study. Psychol Med 2010;40:781–788.
21 Rutherford BR, Marcus SM, Wang P, Sneed JR, Pelton G, Devanand D, Duan N, Roose SP: A randomized, prospective pilot study of patient expectancy and antidepressant outcome. Psychol Med 2013;43:975–982.
22 American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders: DSM-IV_TR, ed 4. Washington, American Psychiatric Association, 2000.
23 Hamilton M: A rating scale for depression. J Neurol Neurosurg Psychiatry 1960;23:56–62.
24 Guy W: Clinical Global Impressions. New Clinical Drug Evaluation Unit (ECDEU) Assessment Manual for Psychopharmacology. Rockville, National Institute of Mental Health, 1976, pp 218–222.
25 Gaston L, Marmar CR: The California Psychotherapy Alliance Scales; in Horvath AO, Greenberg LS (ed): The Working Alliance: Theory, Research, and Practice. Oxford, Wiley, 1994, pp 85–108.
26 First MB, Spitzer RL, Gibbon M, Williams JBW: Structured Clinical Interview for DSM-IV Axis I Disorders, Clinician Version (SCID-CV). Washington, American Psychiatric Press, 1996.
27 Fawcett J, Epstein P, Fiester SJ, Elkin I, Autry JH: Clinical management – imipramine/placebo administration manual: NIMH Treatment of Depression Collaborative Research Program. Psychopharmacol Bull 1987;23:309–324.
28 Littell RC, Milliken GA, Stroup WW, Wolfinger RD, Schabenberger O: SAS for Mixed Models, ed 2. Cary, SAS Institute, 2006.
29 Collins LM, Sayer AG: New Methods for the Analysis of Change. Washington, American Psychological Association, 2001.
30 Zilcha-Mano S, Dinger U, McCarthy KS, Barrett MS, Barber JP: Changes in well-being and quality of life in a randomized trial comparing dynamic psychotherapy and pharmacotherapy for major depressive disorder. J Affect Disord 2014;152:538–542.
31 Curran PJ, Bauer DJ: The disaggregation of within-person and between-person effects in longitudinal models of change. Annu Rev Psychol 2011;62:583–619.
32 Raudenbush SW, Bryk AS: Hierarchical Linear Models, ed 2. Thousand Oaks, Sage, 2002.
33 Harrington A: The Placebo Effect. Cambridge, Harvard University Press, 1999.
34 Frank JD: Persuasion and Healing. Baltimore, Johns Hopkins University Press, 1961.
35 Rutherford BR, Roose SP: A model of placebo response in antidepressant clinical trials. Am J Psychiatry 2013;170:723–733.
36 Zilcha-Mano S, Barber J: Instability of depression severity at intake as a moderator of outcome in treatment for major depressive disorder. Psychother Psychosom 2014;83:382–383.
37 Papakostas GI, Fava M: Does the probability of receiving placebo influence clinical trial outcome? A meta-regression of double-blind, randomized clinical trials in MDD. Eur Neuropsychopharmacol 2009;19:34–40.
38 Fava GA, Guidi J, Rafanelli C, Sonino N: The clinical inadequacy of evidence-based medicine and the need for a conceptual framework based on clinical judgment. Psychother Psychosom 2015;84:1–3.
39 Kenny D, Harackiewicz J: Cross-lagged panel correlation: practice and promise. J Appl Psychol 1979;64:372–379.
40 Di Blasi Z, Kleijnen J: Context effects: powerful therapies or methodological bias? Eval Health Prof 2003;26:166–179.