The Role of the Alliance in the Pharmacologic Treatment of Depression

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Background: The purpose of this study was to determine the influence of the therapeutic alliance on the efficacy of pharmacotherapy for depression.

Method: The sample consisted of 31 depressed outpatients treated with antidepressants. The alliance was measured by the patient and therapist versions of the California Pharmacotherapy Alliance Scale. Treatment outcome was measured by the Hamilton Rating Scale for Depression and the Beck Depression Inventory, and the Symptom, Sign, Side-Effect Checklist was also completed.

Results: The alliance measures accounted for between 21% and 56% of the variance in the three outcome measures. By averaging across outcome measures, therapist perceptions of the alliance predicted 41% of the variance in improvement in depressive symptoms, where patient perceptions predicted 25%. Scores on both alliance measures were lower than those reported in studies of psychotherapy. Patient attitude toward medication was correlated with somatic complaints, but not with depression scores. Therapist perception of patient hostility correlated with patient depression. Patients differed in the way their alliance and outcome interacted, so that the association might be positive or negative.

Conclusion: Alliance is correlated with outcome in pharmacotherapy management of depression, although there may be interindividual variability across patients. In the pharmacotherapy of depression, therapist perception of alliance is a better predictor of symptom outcome than patient perception, while the reverse is usually found in psychotherapy.

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Previous research has demonstrated that the alliance between therapist and client in psychotherapy is the most robust predictor of outcome.[1] It seems somewhat less obvious that the alliance would be a predictor of outcome in the course of pharmacologic therapies in which the therapeutic agent is understood to be an alteration in neurotransmission, over and above the relationship between doctor and patient.

In a previous study[2] of the role of therapeutic alliance in the treatment of schizophrenia with both psychotherapy and medication, the alliance accounted for 11% of the variance of outcome at 2 years, after controlling for the association between outcome and alliance at 6 months. Even with disorders such as schizophrenia, which are understood to be organically based, and where the first-line treatment is medication, the doctor/patient relationship appears to play a significant role in determining the patient's response.

There are many reasons to consider that the relationship between alliance and outcome might be even more powerful for depression than for schizophrenia. Depression is viewed as a profoundly interpersonal illness.[3] The hopelessness, poor self-esteem, and self-blame that are characteristic of depression are sensitive to therapist interventions, even when these are framed as education around the disorder within a pharmacotherapy context. In fact, some of the treatment assumptions of pharmacotherapy can be seen as powerful psychotherapeutic interventions in their own right. For example, informing the patient that he or she has a biological abnormality can be a powerful method of addressing the intense self-blame of the depressed person. The initiation of medication is a powerful and dramatic act that often restores a lost sense of hope. The somatic effects of medication, such as the immediate effect on restoration of sleep, may allow the patient to reframe his intense psychic pain as "a chemical imbalance," rather than "the unbearable burden" posed by his life circumstance. We therefore hypothesized that even pharmacologic management with medication is a type of "therapy" and that it might be expected to have many of the same process mechanisms as other psychotherapies.

There is empirical evidence to support this hypothesis. The National Institute of Mental Health (NIMH) Treatment of Depression Collaborative Research Program

(TDCRP) found that although pharmacotherapy was superior in treating severe depression, diverse psychotherapies were equally efficacious in managing milder depression.[4] Further data from this project found that the alliance was predictive of outcome in pharmacologic management of depression, explaining 21% of outcome variance, as in the psychotherapy modalities.[5]

We hypothesized that therapist and patient perceptions of the alliance would correlate with outcome in pharmacologic treatment of depression. On the basis of previous work[1] examining correlations of alliance and outcome in psychotherapy research, we hypothesized that the patient's perception of the alliance, rated by using the California Pharmacotherapy Alliance Scale (CALPAS)-Patient Version (P), would be a better predictor of outcome than the therapist's perception of the alliance, rated with the CALPAS-Therapist Version (T). We hypothesized that the patient's attitude toward medication would be one variable contributing to the correlation between alliance and outcome and that the therapist's perceptions of the patient's hostility on the CALPAS-T would correlate with the patient's depressive symptomatology. Finally, we hypothesized that there would be individual differences across patients in the association to be found between alliance and outcome.

METHOD

Subjects

Recruitment and selection. Patients were referred by general practitioners or psychiatrists in the community to an affective disorders clinic. All patients referred to the clinic during 2 years of this study were asked to participate if they fulfilled the inclusion and exclusion criteria cited below. There were no refusals.

Patients accepted in the study were adults (18–65 years) meeting the DSM-III-R criteria for major depressive disorder and presenting a score of 14 or greater on the Hamilton Rating Scale for Depression (HAM-D).[6] Exclusion criteria included severe suicidal intent requiring hospitalization, organic mental disorder, substance abuse, psychosis, mania, and severe eating disorders. Comorbid anxiety and personality disorders were not excluded.

Characteristics. A total of 31 patients participated in the study. Their mean ± SD age was 41.9 ± 12.4. There were 11 men (36%) and 20 women (64%). All but 1 patient was white. About half (57%; N = 16) had attended college, and their mean yearly income was $52,260. Occupational status included 23% householders or unskilled workers (N = 7), 10% unemployed (N = 3), 33% skilled workers (N = 10), 7% students (N = 2), and 27% professionals (N = 8). The majority lived with their own family (64%; N = 20), while 16% (N = 5) lived alone and 20% (N = 6) lived with their parents. A quarter of the sample was single, 16% (N = 5) were divorced or separated, and 59% (N = 18) were married. At intake, 10 patients (32%) were rated as mildly to moderately depressed on the HAM-D (scores between 14 to 20), and 21 (68%) as severely depressed (scores greater than 20).

Our sample was a rather typical primary care group of depressed patients that included acute depression, double depression, recurrent depression, and chronic depression. No treatment-resistant patients with a history of multiple medication failures were included. The past psychiatric history obtained in the screening indicated that a majority of the patients did have some past history of periods of depression, even dating back to childhood. It was sometimes unclear if these periods would or would not have met formal diagnostic criteria.

Definitive data on past psychiatric history were available for 24 of the 31 patients in the study. Eight of these patients had no history of prior depression, and 16 had a history of prior depression. Of the 16 patients with a past history of depression, 7 had one previous episode, 3 had two or more episodes, 1 had three episodes, 1 had four episodes, and 1 had more than five episodes. For 3 patients the number of prior episodes was unclear. Of the 16 patients with prior depressions, 6 had had prior treatment of some type, and 10 had not. Only 1 patient had a history of prior hospitalization for depression.

Chronicity data were available on 21 patients, and once again reflect the mixed nature of the sample. Nine patients were clearly acute, with depressions that had lasted from 6 weeks up to 3 months, prior to presenting for treatment. Six patients presented with depression of more than 1 year's duration, the longest being 3 years. Six presented with acute episodes on top of chronic depression. For example, 1 patient had been depressed for 4 years and had worsened in the last 4 months, and another patient had had symptoms of chronic mild depression for 7 to 8 years, with a more severe episode of 2 months' duration.

Of the patients who started treatment, 8 (26%) terminated treatment before the therapist recommended it. These patients were included in the analyses since they represented an important source of variance in the alliance. One of these patients left during the initiation of medication, after the placebo trial and after the first several weeks of titration of medication. Patients were followed through continuation and maintenance phases for up to the 2 years of the study. The mean ± SD number of sessions was 11.45 ± 7.28. The data therefore reflect all phases of treatment.

Treatment and procedure. A psychosocial and psychiatric history performed by one of four treating psychiatrists was used as the screening instrument. Each patient had a physical examination and routine laboratory tests. Patients who met study criteria were started on placebo at the end of the screening session, and those who responded with a drop of at least 25% in their HAM-D scores during the first week were maintained on placebo unless they

later deteriorated. Patients who returned to Session 1 (the first session after the screening) and did not show a 25% improvement in depressive symptoms were started on imipramine. The purpose of the 1-week placebo trial was to assess the correlation of initial alliance and placebo response (Gaston L, Weiss M, Wisebord S. 1995. Unpublished data). Patients were seen weekly during initiation of medication, then every 2 weeks until stable, and monthly during maintenance. Medication was titrated up slowly, starting at 75 mg and increasing by 25 mg every 3 days as tolerated. Medication was gradually discontinued when patients had been in remission for at least 4 months. Patients were seen weekly during discontinuation and then followed for two more monthly visits. This schedule was flexible.

Patients who did not respond to imipramine, or who could not tolerate the side effects, were changed to another antidepressant. All patients were kept in the study whatever their treatment outcome, including placebo responders, drug nonresponders, patients who later required hospitalization, and patients who obtained additional alternative treatment. Several patients sought treatment outside the study from counselors, chiropractors, or their religious leader, but the impact of this type of auxiliary treatment on the alliance was not assessed. During the course of the study, 1 patient required brief hospitalization.

The treating psychiatrists followed the guidelines described in the NIMH *Manual for Pharmacological Clinical Management of Depression*.[7] No systematic psychotherapy, cognitive therapy, or family therapy was carried out, but flexible use of support and family education consistent with usual pharmacologic management could be undertaken where necessary. Compliance with medication was measured by counting unused pills and random assessment of drug levels, and noncompliance was found to be negligible.

To ensure that our research setting reflected the optimization of the alliance that would occur in usual clinical practice, and to minimize the effects of the research protocol itself on the alliance, the clinicians felt that they required the option of some flexibility in the protocol. This included allowing clinicians to choose their most preferred medication where imipramine failed, referring patients to other therapies as needed after treatment was completed, and adjusting the frequency or timing of sessions. Deviations from the protocol turned out to be rare. It was our impression that some patients tested the therapist's allegiance to "them" versus "the protocol," but when they learned that the therapist would put their needs first, few actual deviations from protocol were required.

Measures

Outcome of depression. Depression was measured objectively by the clinician with the 17-item Hamilton Rating Scale for Depression (HAM-D)[6] and subjectively by the patient through the Beck Depression Inventory (BDI).[8]

Symptom, Sign, Side-Effect Checklist. The Symptom, Sign, Side-Effect Checklist (SSSEC)[9] was used as a measure of the somatic disturbance experienced by the patient during the course of treatment. This is a 47-item scale that is designed to measure treatment-emergent signs and symptoms. A wide range of somatic complaints is included. Patients were asked to subjectively rate each of these possible somatic complaints as not present, mild, moderate, or severe. We did not attempt to analyze whether the somatic complaints were secondary to depression, medication, or somatization on the patient's part. Patients cannot reliably disentangle these various etiologies, and the objective of measuring somatic distress was to determine whether patients' subjective experience of their somatic status was correlated with their treatment alliance. Our clinical experience with the scale used in this way suggested that subjective perception and evaluation of somatic distress by the patient is a reliable concept which is distinct from clinician evaluation of side effects. Some patients with few if any apparent side effects described profound somatic distress, while other patients described classic side effects that they rated as mild and/or eventually as not present.

Alliance. The alliance was measured by the California Pharmacotherapy Alliance Scale (CALPAS) (Gaston L, Marmar CR. 1991. Unpublished scale). The CALPAS aims at assessing the purposeful and active collaboration between doctor and patient. It contains 24 items that cover alliance dimensions such as the patient's capacity to work in therapy, the patient's commitment to the treatment until completion, the doctor-patient agreement on goals and strategies of treatment, and the therapist's understanding and involvement. The patient and therapist pharmacotherapy alliance scales are reproduced in Appendices 1 and 2, respectively. Each item is rated on a 5-point scale, ranging from 0 (not at all) to 4 (very much). Patients were assured that their responses would remain confidential from the therapist. The CALPAS has the distinct advantage that it allows us to measure the patient's and therapist's independent and subjective perceptions of the alliance, respectively on the CALPAS-P and CALPAS-T. A previous study (Gaston L, Beauclair L. 1990. Unpublished data) has determined that the CALPAS-P and CALPAS-T have adequate internal consistency (Cronbach's α of .83 and .73, respectively). Adequate test-retest reliability coefficients of .52 and .59, respectively, were obtained when scores were gathered at the second and eighth sessions of pharmacotherapy. This indicated some variation as well as some stability in alliance scores, as could be expected. The association between the CALPAS-P and CALPAS-T was found to equal .23 and .31 at the second and eighth sessions. Low correlations between patient and therapist versions of alliance

measures are also found in psychotherapy research, and they support the use of both versions in the present study. The associations between the CALPAS-P scores at the second session and HAM-D and BDI scores at intake were found to equal .32 and –.06, respectively, while they equalled .14 and .11 for the CALPAS-T scores at the second session. These better findings support the discriminant construct validity of those two versions of the CALPAS.

Patient attitude toward medication. To measure patient attitude toward medication, we analyzed one item of the CALPAS-P independently. Item 16 reads, "Did you feel skeptical about the value of taking medication?" This item reflecting the patient's attitude to medication was not found to be significantly correlated with the total score of the CALPAS-P, either at screening or over the course of treatment ($r = .03$, $df = 29$, $p > .05$ and $r = –.03$, $df = 29$, $p > .05$, respectively).

Hostility index. The CALPAS-T includes a separate factor designed to reflect the therapist's perception of the patient's hostility. The hostility index was found to have a Cronbach's α of .91 (mean ± SD = 2.63 ± 0.89).

Design

This research project was designed to focus on the process of pharmacotherapy rather than solely on its outcome. To maximally capture process, it was necessary to measure the alliance over time, that is, after every session. In this study, a multiple time-series design was employed to investigate the alliance-outcome association over time, within patients, as well as across patients. This method allows one to investigate individual differences, an aspect of change which is lost in group analyses. A multiple time-series design also allows us to investigate the time frame of the association between alliance and outcome, to see whether it is concurrent or lagged.

Data Analyses

Across patients. To examine the association between alliance and symptomatology across patients, hierarchical regression analyses were conducted with each dependent variable (BDI, HAM-D, SSSEC). To control for initial severity of illness, symptom scores at screening were always entered as first step, followed by the mean CALPAS-P or CALPAS-T scores. The mean CALPAS scores represent the average of the scores obtained over the course of treatment. Separate analyses were also conducted controlling for patient skepticism, after entering initial symptomatology and before entering CALPAS data.

Within patients. To test whether the alliance predicted outcome sequentially within patients, a time-series multiple regression analysis or generalized least-squares (GLS) method was used. As an extension of the ordinary least-squares (OLS) model, the GLS consists of a multiple regression approach that takes into account the autocorrelation present in the dependent variable gathered over time by extracting it. Variable X at time 0 can influence variable X at time 1, time 2, and so on.[10] The GLS analysis extracts this influence within the dependent variable across time points. In the present study, the GLS analyses were conducted using the software package SHAZAM.[11] The GLS analyses were performed with the HAM-D or BDI scores as dependent variable. With each variable, an analysis specified CALPAS-P scores at lag 0 (same visit) and CALPAS-P at lag 1 (previous visit) as predictors, and another analysis specified CALPAS-T scores at lag 0 and CALPAS-T at lag 1 as predictors. This equation assessed the contribution of both concurrent alliance scores (lag 0) and preceding alliance scores (lag 1) to outcome levels.

Given that the association between alliance and outcome can vary across individuals, the four GLS analyses mentioned above were conducted within individual patients. Only if no differential associations were to be observed, which would potentially be due to a lack of power, would GLS analyses be conducted, collapsing the data of all subjects together. To ensure a minimum reliability to the findings, the GLS analyses were conducted on subjects' data for which there were at least 10 data points, assuring 5 observations per predictor. A total of 15 patients provided 10 data points or more.

RESULTS

Treatment Response

Of the 31 patients who underwent treatment, 70% (N = 22) were responders based on a 50% drop in their HAM-D scores. Nine patients left treatment against medical advice, but only 1 of these patients left during the titration of medication. Only 1 patient responded to placebo and remained on placebo for the duration of treatment.

At screening, BDI scores correlated with HAM-D scores at .43 ($p < .01$), whereas after treatment this correlation increased to .75 ($p < .001$).

Parameters of the Alliance

The mean CALPAS-P was 3.27 ± .36. This is significantly lower than the mean CALPAS-P that has been obtained in studies of the alliance in psychotherapy ($t = 20.34$, $df = 176$, $p < .01$).[12] Comparison between psychotherapy and pharmacotherapy scores may be limited by differences between the two instruments which were incorporated to ensure their relevance to the two different treatment settings. The mean CALPAS-T score was 2.70 ± 0.50.

The scores on the CALPAS-P and CALPAS-T at screening and after treatment were compared. At screening, there was no significant correlation between the therapist's perception of the alliance and the patient's perception of the alliance. After treatment, the correlation between the CALPAS-P and the CALPAS-T was .67

($p < .001$). The correlation of the mean scores of the therapist and patient alliance scales (averaged over treatment) was .50 ($p < .004$).

The correlation between the CALPAS-P in the first session after the initial screening and the mean CALPAS-P score over the course of therapy was not significant. The correlation between the CALPAS-T in the first session after the screening and the average CALPAS-T score over the course of therapy was .58 ($p < .001$).

Patient Hostility and Symptom Severity

At the screening session, the therapist's measure of whether or not the patient was hostile toward the therapist correlated strongly with the HAM-D; that is, it correlated with the therapist's perception of whether the patient was depressed ($r = .59$, $df = 29$, $p < .001$). The hostility index did not correlate with SSSEC or BDI.

We also wanted to know if the therapists continued to see patients as hostile after remission. The change in the hostility index between screening and termination was found to be highly correlated with the change in HAM-D ($r = .48$, $df = 29$, $p < .004$). This correlation was evident even when patients assessed their own symptomatology. Changes in the hostility index correlated with changes in the patients' self report as measured by change in BDI scores ($r = .33$, $df = 29$, $p < .05$).

Patient Attitude Toward Medication

There was no significant correlation between the patient's skepticism rating and the CALPAS-P total score at screening or the CALPAS-P score averaged over the course of treatment.

The regression analyses were repeated with initial severity as first predictor, patient's skepticism toward medication as second predictor, CALPAS-P as third predictor, and CALPAS-T as fourth predictor. The patient's attitude toward medication did not account for outcome in terms of depressive symptoms (HAM-D, BDI), nor did it mediate the impact of either alliance variable to account for improvement in depression. However, how the patient perceived medication explained 22% of the variance in somatic complaints, as measured by the SSSEC ($p < .01$).

Alliance and Outcome Association

Across patients. When the alliance scores were averaged over all treatment sessions, both patient and therapist perceptions of the alliance were strongly correlated with the three outcome measures, as shown in Table 1, accounting for between 21% ($p < .05$) and 56% ($p < .001$) of the outcome variance. At Session 2, therapist perception of the alliance accounted for 33% ($p < .01$) of the outcome variance of the SSSEC.

Within patients. GLS analyses were conducted for 15 patients having at least 10 data points over time. The maximum and minimum partial correlations observed within patients between alliance and outcome scores are presented in Table 2, along with the median partial correlation and the number of significant positive or negative partial correlations obtained across patients. All partial correlations reported as significant were found to be significant at $p < .05$.

Table 1. Percentage of Outcome Variance Accounted for by Alliance Ratings in 31 Depressed Outpatients*

	CALPAS-Patient		CALPAS-Therapist	
Outcome Measure	Session 2	Averaged	Session 2	Averaged
BDI	6	26[a]	18[b]	28[a]
HAM-D	3	29[a]	11	40[a]
SSSEC	0	21[b]	33[a]	56[c]

*After controlling for initial severity of symptoms. The CALPAS scores were averaged over therapy sessions. Abbreviations:
BDI = Beck Depression Inventory; CALPAS = California Pharmacotherapy Alliance Scale; HAM-D = Hamilton Rating Scale for Depression; SSSEC = Symptom, Sign, Side-Effect Checklist.
[a] $p < .01$.
[b] $p < .05$.
[c] $p < .001$.

Results revealed that there was a correlation between alliance and outcome for some patients, but the correlation varied considerably across patients, from high negative to high positive coefficients. Thus, as expected, some patients experienced a greater alliance with their therapist as they got better (negative correlation). But the converse is also true: some patients experienced a greater alliance with their therapist even though they were feeling worse (positive correlation). To add to the complexity, the alliance was sometimes predicting outcome in the same week (lag 0), and sometimes it was the alliance from the previous week (lag 1) that predicted outcome.

These results were consistent whether it was the therapist or the patient measuring alliance or outcome. Looking at whether the alliance predicted improvement during the same week (lag 0), 20% of patients showed a significant negative correlation between CALPAS-P and HAM-D scores, and 33% with CALPAS-T and HAM-D scores. Forty percent of patients showed a significant negative correlation between CALPAS-P and BDI scores, and 27% with CALPAS-T and BDI scores. In terms of the difference between lags 0 and 1, more patients showed a significant negative correlation between alliance and outcome in the same week or lag 0 (20% to 40%) than from the previous week or lag 1 (7% to 20%). However, significant positive correlations with outcome were obtained in 0% to 7% of patients using the alliance at the same week as a predictor (lag 0), and 7% to 14% of patients with the alliance assessed at the previous week (lag 1). This represents 1 to 2 patients in the total sample of 15 patients.

DISCUSSION

We elaborated a research design to investigate the descriptive parameters of the alliance in as naturalistic a

Table 2. Partial Correlations of CALPAS-P or CALPAS-T Scores at Lag 0 and Lag 1 With HAM-D or BDI Scores Within Patients*

Predictor	Minimum Partial Correlation	Maximum Partial Correlation	Median Correlation	No. of Significant Negative Partial Correlations	No. of Significant Positive Partial Correlations
HAM-D as outcome					
CALPAS-P					
Lag 0	–.87	.43	–.13	3 (20%)	0 (0%)
Lag 1	–.76	.56	–.19	3 (20%)	1 (7%)
CALPAS-T					
Lag 0	–.77	.78	–.17	5 (33%)	1 (7%)
Lag 1	–.66	.61	–.01	1 (7%)	1 (7%)
BDI as outcome					
CALPAS-P					
Lag 0	–.69	.07	–.54	6 (40%)	0 (0%)
Lag 1	–.81	.71	–.06	2 (14%)	2 (14%)
CALPAS-T					
Lag 0	–.67	.61	–.28	4 (27%)	1 (7%)
Lag 1	–.47	.38	–.07	1 (7%)	1 (7%)

*All partial correlations significant at $p < .05$ were reported. Analyses were conducted for 15 patients who had a minimum of 10 data points over time.

setting as possible, and with attention to the evolution of the process of pharmacotherapy over time, from both the patient's and therapist's perspectives.

The alliance in pharmacotherapy was found to be highly correlated with outcome. Overall, 41% of outcome variance was explained by therapists' ratings of alliance, and 25% by patients' ratings, when alliance scores were averaged across treatment sessions. However, the predictive power of the alliance was less when measured from the beginning of therapy: 21% of outcome variance was explained by initial therapist ratings of alliance, and 3% by initial patient ratings of alliance. These initial alliance ratings are uncontaminated by symptomatic improvement, and therefore more representative of the alliance predictive value. It would be interesting in future research to determine at what point in time during therapy the predictive power of the alliance starts to become significant.

There is a marked contrast between these findings and the data on alliance and outcome obtained in psychotherapy research. In our data, it was the therapist's perception of the alliance that best predicted outcome, whereas in psychotherapy it is the patient's perception of the alliance which best predicts outcome.[1] In this study, therapists were also better than patients at predicting how the alliance would develop later in treatment. The correlation between CALPAS-T in the first session and the mean CALPAS-T was highly significant, whereas there was no correlation between how the patient saw the alliance at the beginning of therapy and how they perceived the alliance later on. In addition, therapists perceived the alliance less positively than did patients.

Overall, the alliance ratings were lower in the pharmacotherapy situation than has been found in psychotherapy.[12] These findings suggest that the alliance formed in psychotherapy and pharmacotherapy reflect two different situations. Several hypotheses may be generated to explain the lower alliance scores in pharmacotherapy. The lack of a significant correlation between the patients' attitude toward medication, as measured by the skepticism rating, and the CALPAS total score suggests that patients can feel one way about medication, while they feel differently about the therapist or treatment in general. This implies that it may not be attitude toward medication itself that determines the lower alliance scores in pharmacotherapy.

There are, however, other factors that are unique to pharmacotherapy of depression that could explain the observed lower alliance. First, medical treatment for depression is an unusual and somewhat alien experience for many patients. Second, pharmacotherapy tends to be clinician directed, whereas psychotherapy tends to be patient directed, and the alliance may be correlated with the degree of control over treatment that the patient experiences. Third, patients coming for psychiatric treatment of depression have typically been brought to treatment by family and then referred for pharmacotherapy by their family physician, whereas patients coming for psychotherapy have typically sought out treatment themselves and are self-referred.

We hypothesized that the patient's attitude toward medication would influence outcome. We found that the patient's attitude toward medication is distinct from the alliance as a whole and must be analyzed as a separate variable. When this was done, we found that patients who were skeptical about medication had more somatic complaints, although their depressive symptoms remitted to the same extent as those who were less skeptical. The skepticism factor accounted for 22% of the variance in somatic complaints, but did not account for outcome on depression measures. This remained true even over the course of treatment. Furthermore, introducing the patient skepticism variable into the hierarchical regression did not influence the association between alliance and outcome. Part of the task of the pharmacotherapist could thus

be conceptualized as engaging the skeptical patient in treatment despite ongoing somatic complaints, in order to achieve a good outcome. The language by which patients communicate to their pharmacotherapist their dislike of the treatment they are receiving, as well as the language by which therapists hear their patients' dissatisfaction, appears to be somatic. The therapist's perception of the alliance predicted 56% of the variance in the somatic complaints measured at the end of treatment, suggesting that therapists intuitively derived from these somatic communications a sense of the strength of the alliance. Another interpretation may be that therapists misinterpreted somatic complaints as a negative alliance, whether or not this really reflects the patient alliance.

We have shown that there was a strong correlation between therapists' ratings of patient hostility and therapists' ratings of depression. Moreover, the therapists' perception of patient hostility dissipated as treatment progressed and the depression improved, whether the improvement was measured by therapist or patient. This offers empirical evidence to support the clinical wisdom that therapists should be very cautious in making a personality diagnosis in the context of active depressive symptomatology. For the pharmacotherapist to manage the patient through the process of medication, he must not only work with the patient's fragile alliance, but also contain his reaction to the patient's hostility.

The time-series regression analyses, performed within patients, allowed us to look at the correlations between alliance and outcome more closely. We were able to determine individual differences in terms of how the alliance was sequentially associated with getting better. Significant high correlations between alliance and outcome were seen in up to 40% of patients looking at the association in the same week, and in up to 20% of patients looking at the previous week. This suggests that the alliance may be driving symptomatic improvement for some patients. The fact that these effects vary between patients suggests that only in some cases can the influence of the alliance on outcome be considered a direct effect. Between 7% and 14% of patients (between 1 and 2 patients in a sample of 15 patients), for example, show an inverse correlation between alliance and improvement. These patients may be treatment resistant, they may be expressing relief that the therapist did not give up on them, or they may be expressing regressive personality disorders. Therefore, the descriptors we obtained for the alliance in pharmacotherapy may fit the majority of patients, while it remains true that the art of pharmacotherapy may include identifying and adapting to individual differences in this process.

In designing future research looking at the alliance in pharmacotherapy, since such wide variability exists among individuals (from a positive to a negative correlation between alliance measures and outcome), it is important to be cautious in making clinical generalizations for all patients based on statistical correlations averaged across patients. To our knowledge, the extensive research data on alliance and psychotherapy have never been analyzed using a within-patient time-series regression design. Future research will also need to address the disparity between patient and therapist ratings of the alliance, rather than assuming that these necessarily reflect a similar process. Future research on the relationship between alliance and any form of therapy should also account for patient depression, which we have shown to correlate with the therapist's perceptions of patient hostility.

This study is limited by the small number of patients and the small number of therapists. Our findings may also be unique to the setting of a tertiary referral center, using skilled therapists who have specialized in this area. These findings on the therapeutic alliance reflect a mixed population of acute, chronic, recurrent, and double depressed patients. Further study of the alliance in the pharmacotherapy of depression using more carefully defined samples of depressed patients is required, since the correlation of alliance and outcome may vary with chronicity of illness and past treatment. As in all correlations, it is impossible to determine cause and effect. Although the time-series data tend to suggest that, for most patients, the association between alliance and outcome reflects more than just a halo effect, this cannot be confirmed.

The strengths of this study are its naturalistic design and analyses by patient as well as by group. This is the first study we are aware of to investigate the parameters of the alliance in the pharmacotherapy of depression using a prospective design dedicated to this purpose.

These findings on the nature of the alliance in the pharmacotherapy of depression may be used clinically to improve the effectiveness of treatment. Clinical use of the CALPAS may allow the pharmacotherapist to systematically assess the alliance and the patient's attitude toward medication. This might facilitate the capacity of pharmacotherapists to discuss their patient's reservations about pharmacotherapy directly, rather than somatically. The awareness that a skeptical attitude toward medication is an important determinant of somatic complaints, but not the alliance or outcome, suggests that psychiatrists need not be discouraged by some patients' negative attitude toward medications. Patients undertaking medication for the first time might well benefit from the knowledge that many other patients have shared their reservations, but have come to achieve a good outcome and a positive view of the potential therapeutic value of pharmacotherapy over the course of treatment.

We often pay lip service to the importance of a good alliance in pharmacotherapy. This study has empirically determined some of the parameters of this relationship. Further investigation of these parameters may make it possible to train pharmacotherapists to better handle the

fragile alliance they juggle so effectively and intuitively in their daily routine.

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Appendix 1. California Pharmacotherapy Alliance Scale: Patient Version (CALPAS-P)*

Name: _____ Date: _____

Directions: The questions listed below describe attitudes people might have about their treatment and doctor. Think about the session you just completed and, for each item, decide which category best describes your attitude. Using the scale provided below, circle the number corresponding to that category. Please answer all items.

Reminder: Your responses are confidential and will not be seen by your doctor. You are, of course, free to discuss with your doctor any of these questions.

	Not at All	A Little Bit	Moderately	Quite a Bit	Very Much
1. Did your doctor show a sincere desire to understand you and your problems?	0	1	2	3	4
2. Did you feel free to express things that were worrying you?	0	1	2	3	4
3. Do you feel confident that efforts will lead to change?	0	1	2	3	4
4. Did you find it difficult to ask questions concerning your medication/illness?	0	1	2	3	4
5. Did your doctor understand what you wished to accomplish in your treatment?	0	1	2	3	4
6. When your doctor commented about one aspect of your medication, did you think of other related issues?	0	1	2	3	4
7. Did you feel pressured by your doctor to make changes before you were ready?	0	1	2	3	4
8. Did your doctor's comments lead you to believe that his or her goals for treatment differ from yours?	0	1	2	3	4
9. Did your doctor seem irritated, annoyed, or disappointed with you?	0	1	2	3	4
10. When you asked for additional information, did you get satisfactory answers?	0	1	2	3	4
11. Do you feel that even if you might have moments of doubt, confusion, or mistrust, that overall treatment was worthwhile?	0	1	2	3	4
12. Did your doctor follow his or her own plans, ignoring your view of how treatment should proceed?	0	1	2	3	4
13. Are you willing to take the medication despite the fact that negative side effects have occurred or may occur?	0	1	2	3	4
14. When your doctor commented about one aspect of your medication/illness, did it bring to mind other related aspects?	0	1	2	3	4
15. Did you feel that it was important for you to come to this appointment?	0	1	2	3	4
16. Did you feel skeptical about the value of taking medication?	0	1	2	3	4
17. Did you feel that your doctor understood what you hoped to get out of this treatment?	0	1	2	3	4
18. Did you find it hard to follow your treatment as prescribed, that is, the amount and timing of your medication?	0	1	2	3	4
19. Did your doctor's comments help you to see your difficulties in a new light?	0	1	2	3	4
20. Do you feel so dissatisfied with your treatment that you consider stopping it before the time it would ordinarily come to an end?	0	1	2	3	4
21. Did your doctor fail to provide you with instructions that you could easily understand?	0	1	2	3	4
22. Did the treatment you received match with your idea about what helps people in overcoming their difficulties?	0	1	2	3	4
23. Did your doctor show a lack of confidence in helping you with your problems?	0	1	2	3	4
24. During this session, have you been able to involve yourself in the decisions that were taken?	0	1	2	3	4

Appendix 2. California Pharmacotherapy Alliance Scale: Therapist Version (CALPAS-T)*

Name: _____ Date: _____

Directions: The items listed below describe experiences doctors and patients may have in a session of pharmacotherapy. Think about the session you just completed and, for each item, decide which category best describes your experience using the scale provided below. Circle the number corresponding to that category. Please answer all items.

	Not at All	A Little Bit	Moderately	Quite a Bit	Very Much
1. It was easy for me to show a sincere desire to understand the patient and his/her problems.	0	1	2	3	4
2. The patient expressed the things that were worrying him/her.	0	1	2	3	4
3. The patient is confident that efforts will lead to change.	0	1	2	3	4
4. The patient had difficulties in asking questions concerning the medication.	0	1	2	3	4
5. I understood what the patient wished to accomplish in the treatment.	0	1	2	3	4
6. When I commented about one aspect of the medication, the patient brought up other related issues concerning the medication.	0	1	2	3	4
7. I put pressure on the patient to make the necessary changes.	0	1	2	3	4
8. The patient's comments led me to believe that his/her goals for treatment differ from my own.	0	1	2	3	4
9. At times, I felt irritated, annoyed, or disappointed with the patient.	0	1	2	3	4
10. I made sure that my answers were satisfactory for the patient.	0	1	2	3	4
11. The patient participated in the treatment despite moments of doubt, confusion, or mistrust.	0	1	2	3	4
12. I followed my view of how treatment should proceed, even if it was counter to the patient's plans.	0	1	2	3	4
13. The patient was willing to take the medication despite the fact that negative side effects have occurred or may occur.	0	1	2	3	4
14. When I commented about one aspect of patient illness, the patient brought up other related aspects of his/her illness.	0	1	2	3	4
15. It was important for the patient to come to this appointment.	0	1	2	3	4
16. The patient was skeptical about the value of taking medication.	0	1	2	3	4
17. I understood what the patient hoped to get out of this treatment.	0	1	2	3	4
18. The patient finds it hard to follow the treatment as prescribed, that is, the amount and timing of medication.	0	1	2	3	4
19. Making use of my comments, the patient was able to see his/her difficulties in a new light.	0	1	2	3	4
20. The patient is committed to go through treatment to completion.	0	1	2	3	4
21. I may have failed to provide the patient with instructions that he/she could easily understand.	0	1	2	3	4
22. The treatment matches the patient's ideas about what helps people in overcoming difficulties.	0	1	2	3	4
23. I feel confident in helping the patient with his/her problems.	0	1	2	3	4
24. The patient involved himself/herself in the decisions that were taken during this appointment.	0	1	2	3	4
25. The patient conveys an expectation of easy cure without work on his/her part.	0	1	2	3	4
26. The patient acted in a hostile, attacking, critical manner.	0	1	2	3	4
27. The patient seemed mistrustful and suspicious.	0	1	2	3	4
28. The patient engages in a power struggle, attempting to control the treatment.	0	1	2	3	4
29. The patient defies my efforts to promote change.	0	1	2	3	4
30. The patient holds me at arm's length with a flood of words.	0	1	2	3	4

Alliance Scales: Patient Commitment: items 3, 11, 13, 15, 20, and 24; Patient Working Capacity: items 2, 4, 6, 14, 18, and 19; Therapist Understanding and Involvement: items 1, 7, 9, 10, 21, and 23; Goal and Working Strategy Consensus: items 5, 8, 12, 16, 17, and 22.
Resistance Scale: Patient Hostile Resistance: items 25 to 30.