Patient Preference as a Moderator of Outcome for Chronic Forms of Major Depressive Disorder Treated With Nefazodone, Cognitive Behavioral Analysis System of Psychotherapy, or Their Combination

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Background: Little is known about moderators of response to psychotherapy, medication, and combined treatment for chronic forms of major depressive disorder (MDD). We hypothesized that patient preference at baseline would interact with treatment group to differentially affect treatment outcome.

Method: We report outcomes for 429 patients who participated in a randomized multicenter trial of nefazodone, Cognitive Behavioral Analysis System of Psychotherapy (CBASP), or combination therapy for chronic forms of MDD (DSM-IV criteria) and who indicated their preference for type of treatment at study entry. The primary outcome measures were total scores on the 24-item Hamilton Rating Scale for Depression (HAM-D-24) and categorical definitions of remission or partial response. The patients were recruited between June 1996 and December 1997.

Results: There was an interactive effect of preference and treatment group on outcome. The treatment effect varied as a function of preference, and was particularly apparent for patients who initially expressed preference for one of the monotherapies. Patients who preferred medication had a higher remission rate (45.5%) and lower mean HAM-D-24 score (11.6) at study exit if they received medication than if they received psychotherapy (remission rate, 22.2%; mean HAM-D-24 score, 21.0). Patients who preferred psychotherapy had a higher remission rate (50.0%) and lower mean HAM-D-24 score (12.1) if they received psychotherapy than if they received medication (remission rate 7.7%, mean HAM-D-24 score 18.3). Nevertheless, treatment preference was not associated with risk of dropout from the study.

Conclusions: These results suggest that patient preference is a potent moderator of treatment response for patients with chronic forms of MDD; however, relatively low proportions of the patient sample preferred one of the monotherapies, participants were not blinded to treatment assignment, and there was no placebo group.

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About one third of all episodes of major depressive disorder (MDD) are chronic, i.e., have lasted longer than 2 years with no period of remission. Three percent to 5% of the U.S. population experience chronic depression during their lifetime.[1–3] Chronic forms of depression are associated with severe impairments in social and work functioning[4–6] and relatively higher rates of suicide, hospitalization, and health care utilization than acute major depression.[7,8] The clinical and public health significance of chronic depression highlight the importance of understanding how to best match patients to available treatments. Clinical experience suggests that many patients (and therapists) have strong feelings about receiving or providing psychotherapy or medication as treatments.[9] Patient-therapist agreement on treatment choice enhances the therapeutic alliance,[10,11] patient motivation, placebo effect, and treatment outcome.[12] Patient preference has been shown to affect treatment response for MDD,[13–16] although not invariably.[17–19] Thus patient preference may be a crucial variable to consider in randomized controlled trials contrasting medication and psychotherapy. Randomization procedures are performed in order to maximize the internal validity of treatment outcome studies. However, randomization may undermine the external validity or generalizability of these studies if treatment preferences are ignored. For example, van Schaik et al.,[20] in a Dutch study of the treatment of depressive disorder in a primary care setting, reported that

patients with strong preferences, mostly for psychotherapy, were likely not to enter antidepressant treatment or randomized clinical trials if their preferences were not supported. Patient preference may also impact attrition based on whether or not patients receive their preferred treatment.

This report presents results of an investigation of the effect of patient preference on outcome and attrition in a study that compared the Cognitive Behavioral Analysis System of Psychotherapy (CBASP),[21] the antidepressant medication nefazodone, and their combination in treating chronic forms of MDD. During the initial 12 weeks of acute-phase treatment, patients treated with combination therapy (73%) responded to treatment at significantly higher rates than those treated with nefazodone alone (48%) and CBASP alone (48%).[22] We hypothesized that patient preference at baseline would interact with the type of treatment given to differentially affect treatment outcome across the 3 treatment groups.

METHOD

The study's rationale and methods, including methods of recruitment, structured assessments, evaluation of prior treatments, therapist training, treatment delivery, interrater reliability, and rater blinding, are reported elsewhere.[22] The methods are briefly summarized here.

Subjects

We recruited 681 outpatients into the acute phase of the study from 12 academic centers between June 1996 and December 1997. Men and women 18 to 75 years of age were eligible for study entry if they met DSM-IV criteria, confirmed by Structured Clinical Interview for DSM-IV, for a current episode of MDD of at least 2 years' duration, current MDD superimposed on antecedent dysthymic disorder ("double depression"), or recurrent MDD with incomplete interepisode recovery with a total continuous illness duration of at least 2 years. Study entry required a 24-item Hamilton Rating Scale for Depression (HAM-D-24)[23] total score ≥ 20 both at screening and at baseline following a 2-week drug-free period.

Patients with a history of seizures, abnormal electroencephalogram, stroke, severe head trauma, psychotic symptoms or schizophrenia, bipolar disorder, eating disorders without remission in the last year, obsessive-compulsive disorder, or dementia were excluded. Further exclusion criteria included high suicide risk, certain personality disorders (antisocial, schizotypal, or severe borderline), and a principal diagnosis within the last 6 months of panic disorder, generalized anxiety disorder, posttraumatic stress disorder, social phobia, or substance abuse or dependence. Patients were excluded if they had failed to respond to 3 previous adequate antidepressant trials (of at least 2 different classes), 2 trials of empirically supported psychotherapy, or electroconvulsive therapy during the past 3 years. Patients with a comorbid serious, unstable medical condition and women of childbearing age with inadequate contraception were excluded. Patients could not receive concurrent psychotherapy, anxiolytics, sedatives, hypnotics, or any other pharmacologic or behavioral sleep aids during the study.

Following a 2-week evaluation period, patients were randomly assigned to 12 weeks of nefazodone treatment, CBASP, or their combination. Remission during the acute phase was defined a priori as a HAM-D-24 score ≤ 8 at both weeks 10 and 12. Partial response was defined as ≥ 50% reduction from baseline in the HAM-D-24 score plus a total score ≤ 15 and > 8 at weeks 10 and 12. Participants who did not meet criteria for remission or partial response were classified as nonresponders.

By study design, patients who were nonresponders to monotherapy were crossed over and subsequently treated with the other monotherapy. Patients knew they would be crossed over if they did not respond. Thus patient preference for either medication or psychotherapy would eventually be honored for nonresponders in the trial.

Institutional review boards at each participating site approved the study. All patients provided written informed consent.

Study Drug and Psychotherapy Administration

During the acute phase, nefazodone was titrated from 200 mg/day to a maximum of 600 mg/day in weekly increments of 100 mg/day to maximize response and tolerability, with a required minimum dose of at least 300 mg/day of nefazodone by the third week of treatment. Medication management sessions (15 to 20 minutes in duration), guided by a manual,[24] focused on a review of symptoms, side effects, intercurrent illnesses, and concomitant medications. Medication visits were scheduled weekly for the first 4 weeks and fortnightly for the final 8 weeks of the acute phase. Pharmacotherapists were directed not to provide any psychotherapeutic interventions.

Cognitive Behavioral Analysis System of Psychotherapy is an innovative form of psychotherapy developed by McCullough[21] specifically for chronically depressed patients. It is a cognitive-behavioral approach that emphasizes the development of interpersonal problem-solving skills. Patients randomly assigned to CBASP received twice-weekly sessions through the first 4 weeks of treatment and weekly sessions for the remainder of the acute phase. Twice-weekly sessions could be continued until week 8 if patients were slower in acquiring problem-solving skills.

Assessments

Patient preference was assessed at baseline by a single written question asking if the patient preferred medication, psychotherapy, combination treatment, or had no

Table 1. Selected Demographic and Clinical Variables of Patients With MDD

Variable	Total	Preference			
		None	Medication	Psychotherapy	Combination
N	429	88	33	53	255
% Female	65	65	61	74	63
% White	92	89	100	93	91
% Married	46	50	42	38	47
% With a prior antidepressant trial	58	52	58	51	62
Mean age, y	45	45	45	44	44
Mean MDD duration, y	7.6	7.1	7.8	8.5	7.5
Mean HAM-D-24 score	27.1	26.8	26.6	27.7	27.2

Abbreviations: HAM-D-24 = 24-item Hamilton Rating Scale for Depression, MDD = major depressive disorder.

preference. The patient preference question was an optional "add-on" to the parent study. Ten of the 12 sites participated in this aspect of the study.

Trained, reliable independent evaluators, unaware of treatment assignment or patients' treatment preferences, completed the HAM-D-24 at each assessment visit. Assessments occurred weekly for 4 weeks and biweekly thereafter during the 12-week acute-phase trial (i.e., baseline and study weeks 1, 2, 3, 4, 6, 8, 10, and 12).

Data Analyses

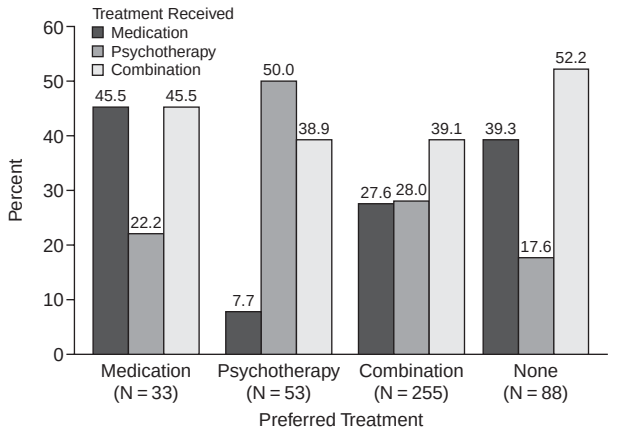
The analyses of the moderating effect of patient preference were perforce limited to subjects who completed the patient preference form. Mixed-effects analyses examined the main effects and interaction of treatment and preference. Each model included site and baseline HAM-D-24 as covariates, as well as a random intercept and a random slope. Interactions were tested using likelihood ratio tests and are expressed as χ^2 values. The models included subjects with incomplete data, using the available observations from each subject. No imputation was used for these analyses. Mixed-effects linear regression models[25] examined the HAM-D-24, repeatedly measured at baseline and weeks 1, 2, 3, 4, 6, 8, 10, and 12. Mixed-effects ordinal logistic regression models[26] examined ordinal levels of response for each of the 9 assessment weeks. In these analyses, each subject had a maximum of 9 weekly observations of response status. The clinical status of each subject (i.e., remission, response, nonremission) was classified for each of the 9 weekly assessments as noted above.

RESULTS

Subject Characteristics

Among the 681 patients in the overall project, 429 enrolled at the 10 sites that participated in this substudy. Of these, 88 (20.5%) indicated no preference, 33 (7.7%) preferred medication, 53 (12.4%) preferred psychotherapy, and 255 (59.4%) preferred combined treatments. Selected clinical and demographic characteristics of the analyzable sample are shown in Table 1. These did not differ significantly across the preference groups and were similar to the characteristics of the sample of the parent study.

Figure 1. Intent-to-Treat Remission Rates by Treatment Preference and Treatment



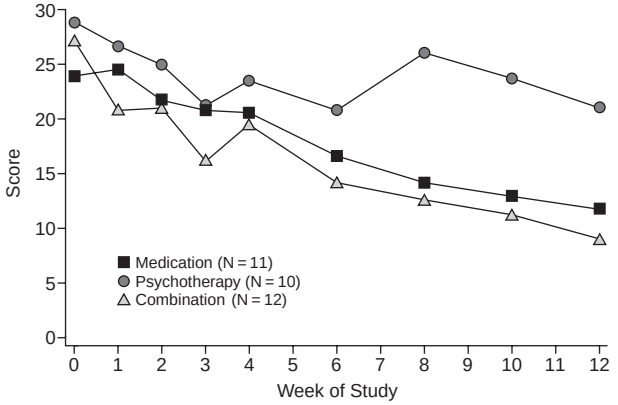
Treatment Response

Of 681 patients enrolled in the 12-week acute phase study, patients treated with the combination of nefazodone and CBASP (73%) responded to treatment at significantly higher rates than nefazodone alone (48%) and CBASP alone (48%).[22] Of the 429 patients who completed the patient preference questionnaire, a significantly greater proportion receiving combination treatment (69%) responded (i.e., had either partial response or remission) compared to nefazodone alone (48%) and CBASP alone (49%) ($\chi^2 = 15.36$, df = 2, p = .0005). Remission rates were 42%, 29%, and 29%, respectively, in the 3 treatment groups. Consistent with the results of the parent study, remission and response rates were significantly higher for the combination group than for either monotherapy group ($\chi^2 = 6.49$, df = 2, p = .039).

Effects of Patient Preference on Treatment Response

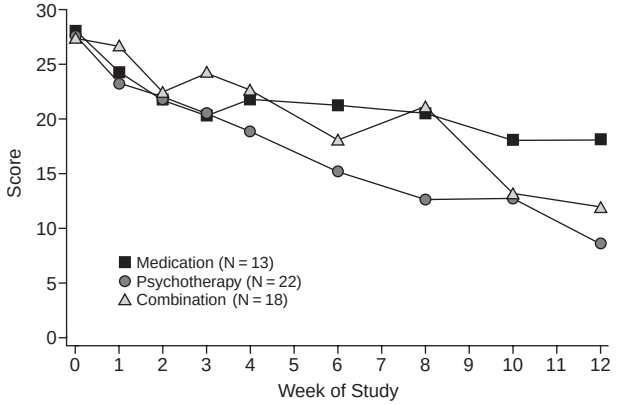
The mixed-effects ordinal logistic regression analyses found a statistically significant interaction between

Figure 2. Weekly Mean HAM-D-24 Scores for Subjects Who Prefer Medication



Abbreviation: HAM-D-24 = 24-item Hamilton Rating Scale for Depression.

Figure 3. Weekly Mean HAM-D-24 Scores for Subjects Who Prefer Psychotherapy

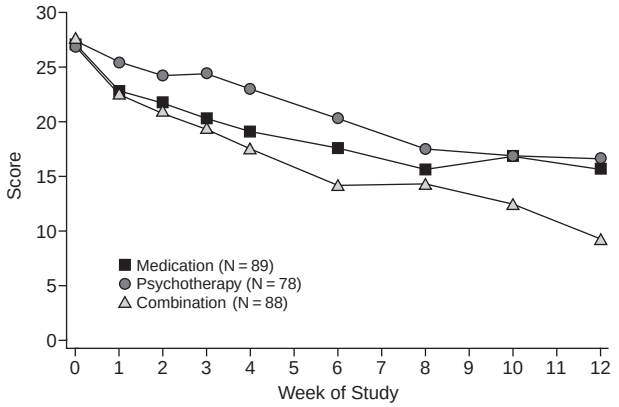


Abbreviation: HAM-D-24 = 24-item Hamilton Rating Scale for Depression.

preference and treatment on outcome ($\chi^2 = 13.29$, df = 6, p = .039). Subjects who received a treatment concordant with their preference were significantly more likely to achieve either remission or partial response over the course of the trial. This effect was particularly apparent for patients who initially expressed a preference for either of the monotherapies. In an attempt to depict a simplified version of this interaction involving repeated assessments over time, Figure 1 presents the ordinal categorical last-observation-carried-forward (LOCF) remission rates for the 3 treatment groups, stratified by expressed treatment preference. Patients who expressed preference for medication had a remission rate of 45.5% if they received medication and 22.2% if they received psychotherapy. Patients who expressed preference for psychotherapy had a remission rate of 50.0% if they received psychotherapy and 7.7% if they received medication.

Among those who received medication only, LOCF outcome was poorest for those who preferred psychotherapy. In addition, receiving medication alone produced a greater remission rate in those who preferred medication alone than in those who received combination therapy (45.5% vs. 27.6%). These results suggest that relatively few patients who stated a preference for medication (alone or in combination with psychotherapy) benefited much from psychotherapy. A parallel finding was observed among the patients who received psychotherapy alone. Specifically, for patients who preferred psychotherapy, psychotherapy alone was more likely to lead to remission than the combination treatment (50.0% vs. 38.9%). These results suggest that few patients who stated a preference for psychotherapy benefited much from the addition of medication. Among patients receiving combination treatment, the remission rate was 39.1% if combination was preferred, but 42.2% if they preferred either of the monotherapies. This is an interesting reversal of the pattern seen in the monotherapy cells. We had expected to find less difference in outcome in this group because everyone got what they wanted, and two thirds got more. Finally, patients who reported no preference did worst in CBASP.

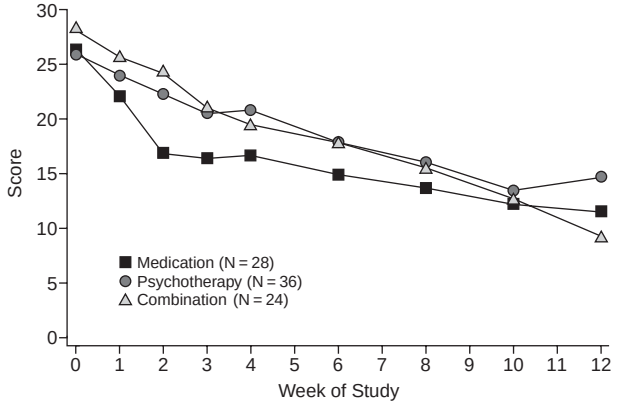
Figure 4. Weekly Mean HAM-D-24 Scores for Subjects Who Prefer Combined Treatments



Abbreviation: HAM-D-24 = 24-item Hamilton Rating Scale for Depression.

Figures 2–5 show weekly HAM-D-24 mean scores separated according to expressed treatment preference at baseline. The figures indicate that subjects whose treatment matched their preference had less severe depressive symptoms during the 12-week randomized controlled trial. Patients who preferred medication had a lower mean HAM-D-24 score (11.6) at study exit if they received medication than if they received psychotherapy (mean HAM-D-24 score, 21.4). Patients who preferred psychotherapy had a lower mean HAM-D-24 score (12.2) if they received psychotherapy than if they received medication (mean HAM-D-24 score, 18.3). Again consistent with the results of the parent study, scores were significantly lower for the combination group than for either monotherapy group for the total sample (likelihood ratio $\chi^2 =$ 19.65, df = 2, $p < .001$. The mixed-effects linear regres-

Figure 5. Weekly Mean HAM-D-24 Scores for Subjects With No Preference for Treatment



Abbreviation: HAM-D-24 = 24-item Hamilton Rating Scale for Depression.

Table 2. Mixed-Effects Linear Regression Model With HAM-D-24 as the Dependent Variable[a]

Variable	Estimate	SE	Z	p Value
Intercept	21.924	1.006	21.796	< .001
Time (weeks)	–0.894	0.071	–12.611	< .001
Randomized treatment[b]				
Psychotherapy	2.979	1.349	2.209	.027
Combination	4.571	1.481	3.087	.002
Treatment preference[c]				
Medication	1.738	1.861	0.934	.350
Psychotherapy	3.835	1.773	2.163	.031
Combination	2.382	1.139	2.092	.036
Treatment-by-time interaction				
Week by psychotherapy	–0.099	0.099	–0.992	.321
Week by combination	–0.421	0.098	–4.283	< .001
Treatment-by-preference interaction				
Psychotherapy by medication	1.191	2.674	0.445	.656
Psychotherapy by psychotherapy	–4.265	2.278	–1.873	.061
Psychotherapy by combination	–0.503	1.562	–0.322	.748
Combination by medication	–4.716	2.639	–1.787	.074
Combination by psychotherapy	–2.415	2.415	–1.000	.317
Combination by combination	–4.489	1.662	–2.701	.007

[a]The number of subjects included in the model is 429. The number of observations is 3287.
[b]The reference condition for randomized treatment is medication.
[c]The reference condition for treatment preference is no preference.
Abbreviation: HAM-D-24 = 24-item Hamilton Rating Scale for Depression.

sion analyses detected a statistically significant interaction between preference and treatment on outcome ($\chi^2 = 40.93$, df = 6, $p < .001$). The parameter estimates of the model are presented in Table 2. There was a pattern of greater within-group change (Table 3) when the preferred monotherapy treatment was delivered.

Effects of Patient Preference on Attrition

Failure to attend the randomized treatment, which can be seen as a proxy for refusal of randomization, occurred in 3% of those assigned to nefazodone, 5% of those assigned to CBASP, and less than 1% of those assigned to combination therapy. Table 4 shows attrition rates across treatments categorized by preference. Patients who preferred psychotherapy actually had a somewhat higher dropout rate if they received psychotherapy than if assigned to medication or combination treatment. Patients who preferred medication also had a somewhat higher dropout rate if they received medication than if they received psychotherapy or combination treatment. Neither of these differences was statistically significant. Thus the effects of preference on treatment outcome cannot be attributed to differential attrition.

Table 3. HAM-D-24 at week 0 Versus HAM-D-24 at Endpoint (LOCF) by Treatment Group and Preference

Treatment Group/Preference	Paired Differences Mean	SD	N	95% CI Upper	95% CI Lower	Within-Group Effect Size (d = mean÷SD)[a]
Medication						
None	13.429	10.210	28	9.469	17.388	1.315
Medication	12.273	7.913	11	6.957	17.589	1.551
Psychotherapy	9.846	6.962	13	5.639	14.053	1.414
Combination	9.876	10.607	89	7.642	12.111	0.931
Psychotherapy						
None	8.444	9.458	36	5.244	11.645	0.893
Medication	7.400	13.591	10	–2.322	17.122	0.544
Psychotherapy	15.273	11.490	22	10.178	20.367	1.329
Combination	9.500	9.856	78	7.278	11.722	0.964
Combination						
None	16.000	9.241	24	12.098	19.902	1.731
Medication	15.583	11.008	12	8.589	22.577	1.416
Psychotherapy	14.056	7.825	18	10.164	17.947	1.796
Combination	15.886	8.867	88	14.008	17.765	1.792

[a]Refers to Cohen's d.
Abbreviations: HAM-D-24 = 24-item Hamilton Rating Scale for Depression, LOCF = last observation carried forward.

Table 4. Attrition Rates by Treatment and Preference Group

Preference/ Treatment Group	Completer, N (%) No	Yes	Total, N (%)
No preference			
Medication	5 (17.9)	23 (82.1)	28 (100.0)
Psychotherapy	11 (30.6)	25 (69.4)	36 (100.0)
Combination	5 (20.8)	19 (79.2)	24 (100.0)
Preferred medication			
Medication	3 (27.3)	8 (72.7)	11 (100.0)
Psychotherapy	2 (20.0)	8 (80.0)	10 (100.0)
Combination	3 (25.0)	9 (75.0)	12 (100.0)
Preferred psychotherapy			
Medication	3 (23.1)	10 (76.9)	13 (100.0)
Psychotherapy	9 (40.9)	13 (59.1)	22 (100.0)
Combination	6 (33.3)	12 (66.7)	18 (100.0)
Preferred combination			
Medication	30 (33.7)	59 (66.3)	89 (100.0)
Psychotherapy	22 (28.2)	56 (71.8)	78 (100.0)
Combination	19 (21.6)	69 (78.4)	88 (100.0)
Total	118 (27.5)	311 (72.5)	429 (100.0)

DISCUSSION

The results of these analyses supported the hypothesis that patient preference powerfully moderated treatment

response for patients with chronic forms of MDD. This effect was particularly relevant when patients expressed preference for a single treatment modality. Outcomes for the overall sample revealed a significant advantage for combination treatment and lower but similar remission rates for nefazodone and CBASP. However, among those who preferred either monotherapy, we observed a different outcome pattern, with remission rates significantly higher for the preferred monotherapy compared to the alternate. Furthermore, among patients who preferred medication, the remission rate for those who received their preference was similar to those who received combination treatment. Among patients who preferred psychotherapy, the remission rate was even higher for those receiving psychotherapy than for those who received combination treatment.

Few studies have examined relationships between patient preference and treatment outcome in randomized clinical trials of MDD patients. Some studies[18,27] have employed comprehensive cohort designs in which participants expressing a strong treatment preference were given the treatment of their choice whereas those without a preference were randomized.[28] Such investigations are suitable for examining, among those receiving the same treatment, whether the presence or absence of preference is associated with differential outcome. They are not appropriate for comparing, among patients expressing a preference, outcomes of those who do and do not receive the favored treatment.

However, our findings differ markedly from those reported recently by Leykin et al.,[19] who found no differences in outcome among patients who did, and did not, receive their preferred treatment in a randomized clinical trial comparing cognitive therapy[29] and antidepressant medication for moderately to severely depressed outpatients.[30] Several factors could explain the differences. First, since neither we nor Leykin et al.[19] assessed strength of patient preference, we cannot rule out the possibility that differences in preference strength in the 2 samples accounted for the discrepant findings. A second, related point is that our study included a combined treatment arm; the study by Leykin et al.[19] did not. Differences in study design are likely to attract patients with different treatment preferences.[31] The preference for monotherapy in a trial that includes combined treatment may have a different meaning than the same preference expressed in a trial offering only the 2 monotherapies. For example, preference for medication alone in the current study could reflect a stronger aversion to psychotherapy than preferences expressed in the Leykin et al. study,[19] in which no possibility of receiving combined treatment existed and participants were choosing between 2 mutually exclusive options, medication or psychotherapy. Third, in our study, monotherapy patients who failed to respond to their initial assigned treatment were assured of eventually being offered the alternate monotherapy, which was not the case for Leykin et al.[19]

Combined treatment studies often report differential attrition in monotherapy cells. Researchers have attributed this phenomenon to patient preference, using the rationale that patients who receive combined treatment get their desired treatment even if they also get an unwanted one, whereas patients randomized against their treatment preference are unhappy and drop out.[32] Yet many of these trials have not actually examined patient treatment preference as we have done here. In this trial, most patients did not strongly prefer a monotherapy, and no differential attrition was found.

Randomization procedures are performed to maximize the internal validity of treatment outcome studies. Yet randomization may undermine the external validity or generalizability of these studies by ignoring or contradicting treatment preferences. Such preferences may influence whether people participate in randomized trials, whether they refuse randomization, or whether they complete the assigned treatment. In a comprehensive review of these issues in medical clinical trials, King et al.[28] found that treatment preferences led a substantial proportion of people to refuse randomization, but found less evidence of bias in the characteristics of individuals agreeing to be randomized. Differences in outcome across trials between randomized and preference groups were generally small, particularly in large trials and after accounting for baseline differences in measures of outcome. Thus, there was little evidence that preferences substantially interfered with the internal or external validity of randomized trials. Van Schaik and colleagues[20] systematically reviewed the literature on patient preferences regarding psychotherapy and medication as antidepressant treatment in primary care and their impact on treatment outcome. They found that a substantial percentage of well-informed patients (ranging from 51%–69% across 5 studies reviewed) preferred psychotherapy. Patients with strong preferences, mostly favoring psychotherapy, were likely not to enter antidepressant treatment or randomized clinical trials if their preferences were not supported. Two trials in this review used a partially randomized patient-preference design: patients who did not accept randomization were given the treatment of their preference. Neither of the studies found significant differences in outcome between participants who were randomized to psychotherapy and those who chose it.

Our study had low rates of randomization refusal, supporting the external validity of the trial. Furthermore, the effects of preference on treatment outcome did not seem attributable to differential attrition.

Iacoviello and colleagues[11] investigated the influence of treatment preferences on the development of the therapeutic alliance in a randomized controlled trial comparing supportive-expressive psychotherapy, sertraline, and pill

placebo treatment of MDD. The authors opined that because alliance is a robust predictor of outcome, treatment preferences might need careful consideration in randomized controlled trial settings. They reported that patients preferring and receiving psychotherapy reported an increasing alliance over time, whereas those preferring psychotherapy and receiving medication or placebo experienced decreases. Patients preferring pharmacotherapy reported no differences in alliance development whether they received psychotherapy, active medication, or placebo. Thus, the congruence of patients' treatment preference and the treatment that they ultimately received influenced the development of the therapeutic alliance. That report did not correlate preference or alliance with treatment outcome, however.

A strength of the current study was its size, which provided adequate power to address preference hypotheses. A limitation of the study was the single-item query about preference. A more subtle probing of attitudes toward treatment might have further honed the already impressive findings by exploring beliefs about the etiology of depression,[33] treatment stigma,[34] or fears, e.g., that medication is addicting[35] or a crutch or that talking therapy is hogwash.[36] We recommend such probes for future studies.

It is noteworthy that most patients did not express a strong initial preference for a monotherapy, and the vast majority of participants preferred combination treatment. This may reflect a relatively sophisticated approach to treatment acceptability or, alternatively, a lack of familiarity with both CBASP and nefazodone, as neither were well-known treatments at the time of the trial.

Future research contrasting pharmacotherapy and psychotherapy, or even radically different psychotherapeutic approaches (e.g., exposure versus nonexposure treatments),[37] should assess patient preference as a moderator. Exploration of what factors determine patient preferences, including prior treatment experience, cultural expectations, and etiologic beliefs surrounding the nature of psychiatric illness, may also be worthwhile.

Drug name: sertraline (Zoloft and others).

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