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Association between physician beliefs regarding assigned treatment and clinical response: Re-analysis of data from the *Hypericum* Depression Trial Study Group

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Abstract

Background—We have previously shown an association between patient belief and treatment response in the *Hypericum* Depression Trial Study Group's 2002 study. We re-examined these data to determine whether clinical improvement was associated with physician belief about assigned therapy.

Methods—340 adults with major depression and baseline scores ≥ 20 on the 17-item Hamilton Depression Scale (HDRS-17) were randomized to *Hypericum* 900-1500 mg/d, sertraline 50-100 mg/d, or placebo for 8 weeks. At week 8, physicians guessed their patients' treatment. We analyzed 277 subjects with at least one post-baseline visit and physician guess data. We examined association between guess and improvement in HDRS-17 and whether treatment assignment moderated the effect of belief on remission (final HDRS-17 score < 8).

Results—Patient and doctor guesses agreed at 53% for sertraline, 68% for *Hypericum*, and 52% for placebo ($\kappa = 0.37$). Doctors guessed placebo correctly (38%) more than sertraline (18%) or *Hypericum* (19%) ($p = 0.001$). Adverse event scores were significantly greater among subjects for which the clinicians guessed *Hypericum* ($p < 0.001$) or sertraline ($p = 0.005$) compared to placebo. Significant improvements in HDRS-17 score were found when comparing the *Hypericum*-guess ($p < 0.001$) or the sertraline-guess group ($p < 0.001$) against the placebo-guess group. Remission rates were significantly greater for subjects whose clinicians guessed sertraline ($p < 0.001$) or *Hypericum* ($p < 0.001$) versus placebo.

Conclusion—Doctors tended to guess placebo more easily than *Hypericum* or sertraline, and their guesses tended to favor active therapies when improvement was more robust. Results show association but not causation, and merit more careful investigation.

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Keywords

Major Depressive Disorder; *Hypericum*; St. John's Wort; sertraline; placebo; physician; treatment guess

Introduction

Patients' expectations have been shown to exert a powerful influence in many physiological processes and disease states¹⁻⁶. Increasing evidence suggests that patient expectations should need to be taken into consideration when designing clinical trials, since a higher expectation of receiving an active treatment can influence clinical outcome. For example, a recent meta-analysis of randomized controlled trials comparing antidepressants to a placebo or active comparator in geriatric outpatients with major depressive disorder (MDD) found that response and remission rates were higher in comparator trials than placebo controlled trials⁷.

Health care providers, such as physicians, nurses, and pharmacists, can also impact the generation and alteration of patients' expectations⁸⁻¹¹. One study of 200 patients who presented to a general practice with symptoms but no definite diagnosis found that those receiving a "positive consultation" did better than those receiving a "negative consultation," regardless of whether they received treatment. Specifically, recovery was increased by words suggesting that the patient "would be better in a few days" rather than pessimism for recovery¹². Similarly, a more recent study found that placebo response increased from 44% to 62% when the doctor treated patients with "warmth, attention, and confidence"¹³. Using a within-subjects study design, Slavenka Kam-Hansen and colleagues recently demonstrated how manipulation of expectancy can influence outcome in patients with migraines receiving both active medications and placebo¹⁴.

Several mechanisms have been hypothesized to explain the effect of clinician expectations on clinical outcome. One study suggested that "clinicians' beliefs about their own adequacy significantly predicted actual efforts to enhance adherence"¹⁵. It has also been stated that physicians may subtly transmit their expectations to the patients and that these expectations may have a larger effect on outcomes than the patient's own expectancies¹⁶. For example, significant correlations have been observed between clinician expectations of pain relief and the amount of relief reported by patients¹⁷. Similarly, Rabkin et al¹⁸ have argued that "the doctor's enthusiasm, generated by his belief that the patient is taking active drug, may be communicated to the patient, whose clinical status thus may be influenced."

These data support the notion that the doctor-patient relationship is responsible for at least part of the improvement that patients experience. Indeed, physicians frequently make use of the power of alliance; a systematic review of 22 surveys of placebo use in general practice in 12 countries found that 17% to 80% of practitioners had used pure placebos at least once in their career¹⁹. Less is known, however, about whether patient beliefs may impact on clinician beliefs about treatment.

In a recent reanalysis of data from a large randomized controlled trial investigating the comparative efficacy of St. John's wort (*Hypericum perforatum*) for treatment of MDD²⁰,

our group showed that the magnitude of patients' clinical improvement was strongly associated with subjects' guesses of which treatment they had received, and this effect appeared to be modulated by the combination of treatment guessed and treatment received. Subjects who guessed an active treatment improved significantly more than those who guessed placebo, and those who guessed *Hypericum* had a modest advantage over those guessing sertraline²¹. Considering that the original study had failed to demonstrate superiority for any of the three treatment arms in terms of the two primary outcome measure, these findings were particularly striking.

The original study also queried the blinded study physicians who saw the patients at their regular study visits, regarding their beliefs about the treatments patients received. Given the positive association between patient guesses and clinical improvement described above, we decided to reanalyze the data with a focus on whether physician guesses about patients' treatment were associated with clinical outcome, regardless of which treatment patients had actually received. We hypothesized that physicians' beliefs that a particular subject was receiving an active therapy would be associated with greater clinical improvement, regardless of treatment assignment. Likewise, we hypothesized that physician beliefs would be strongly associated with patient beliefs about treatment received.

Methods

Detailed methods for the parent trial have been described elsewhere¹⁹. In brief, the study was conducted at 12 academic or community psychiatry research clinics in the United States. Three hundred and forty outpatients, 18 years old, who met criteria for a current major depressive episode according to the Structured Clinical Interview for DSM-IV (SCID)²², were recruited. Inclusion criteria included screening and baseline 17-item Hamilton Depression Rating Scale²³ (HDRS-17) score > 20 and Global Assessment of Functioning²⁴ (GAF) ≥ 60.

Subjects were randomized equally to receive double blind treatment with *Hypericum*, sertraline, or placebo. After a 1-week placebo run-in, patients entered an 8-week acute phase. At baseline, patients received *Hypericum* (900 mg/day), sertraline (50 mg/day), or placebo. Daily doses could be increased to 1200 mg of *Hypericum*, 75 mg of sertraline, or placebo equivalent after weeks 3 or 4, and to 1500 mg *Hypericum*, 100 mg sertraline, or placebo equivalent at week 6 if the Clinical Global Improvement scale²⁵ (CGI-S) score was ≥ 4 at week 3 or ≥ 3 at weeks 4 or 6. At the end of the acute phase (Week 8) responders (≥ 50% decrease in HDRS-17 score, HDRS-17 ≤ 12, CGI-I ≥ 2) could enter an 18-week double-blind continuation phase. The HDRS-and other outcome measures, including the Beck Depression Inventory (BDI)²⁶ were assessed at all visits. At the week 8 visit (or at study exit in cases of early discontinuation), patients and study clinicians were asked to guess which of the 3 treatment assignments each patient had received.

This reanalysis focused on the acute treatment phase only (baseline-week 8). For the main Intent-to-Treat (ITT) sample we initially selected all subjects with at least one post-baseline visit and for which physicians made a guess about treatment assignment. To examine *agreement* between patients and clinicians, we selected patients for which both patient and

clinician guess data were available. In a previous examination of this database by Vitiello et al²⁷, 1 in 6 placebo patients had measurable hyperforin, and 1 in 6 *Hypericum* patients had no measurable hyperforin, whereas all sertraline subjects had measurable sertraline or desmethylsertraline. Since the main focus of our investigation was physician guess, we did not exclude patients whose blood tests suggested nonadherence, since physicians would not likely know about it. If guess data were missing for clinicians or for patients, these cases were excluded from the analysis.

Descriptive statistics were carried out to determine how many clinicians and patients guessed each treatment, as well as which actual treatments were received, so as to obtain correct guess rates among clinicians. Significance for comparisons of correct guess rates between the different clinician guess groups were assessed by chi-squared analysis. Agreement between clinician and subject guesses was similarly examined, and a Kappa coefficient was calculated to determine strength of agreement.

Adverse Event (AE) data were obtained by systematic assessment at every visit. AE scores were calculated based on the number of AEs reported by each patient that were, in the clinician's judgment, attributed to treatment, as designated in the study database. AE scores were compared between clinician guess groups by independent samples t-test. To determine whether AEs might influence clinician guess, logistic regression was carried out with clinician treatment guess, AE score, treatment assignment, baseline HDRS-17 score, and patient guess as the covariates.

Improvement in HDRS-17 score over 8 weeks was initially determined for each clinician guess group and assessed for significance by the paired t-test. Comparisons between the 3 treatment groups within each guess group were made by one-way between-groups ANOVA. Univariate ANOVA was then carried out controlling for the impact of potential confounders, including patient guess, assigned treatment, baseline depressive severity, and adverse events. Effect sizes were calculated using partial eta-squared (η_p^2).

To examine the interaction between clinician treatment guess and treatment assignment with regard to remission, chi-square analyses were carried out comparing remission rates between the 3 treatment groups within each guess group. Effect sizes were calculated by odds ratio (OR). Logistic regression was carried out to control for patient guess, assigned treatment, baseline depressive severity, and adverse events.

For all analyses, two-tailed statistical significance was set at $p < 0.05$. Where appropriate, correction for multiple comparisons was made by the Bonferroni correction. All calculations were performed with SPSS version 17.0 (Chicago, Illinois).

Results

Sample Demographics

The intent-to-treat (ITT) sample consisted of 277 patients (mean age 44 ± 13 years, 66% female) with available clinician treatment guess information at the conclusion of the acute treatment phase. The sample was composed of Caucasians (77%; $n = 213$), Blacks (11%; n

= 29), Hispanics (7%; n = 18), Asians (4%; n = 12), Native Americans (0.4%; n = 1), and unknown ethnicity (1%; n = 4).

Measurement of Correct Guess Rates among Clinicians

We initially examined correct treatment guess rates by clinicians (Table 1). Among clinicians guessing sertraline, 18% guessed correctly; 19% of *Hypericum* guesses were correct; and 38% of placebo guesses were correct. Correct guess rates for placebo were significantly greater than for sertraline ($\chi^2 = 7.50$, $p = 0.006$), *Hypericum* ($\chi^2 = 8.23$, $p = 0.004$), or either active treatment ($\chi^2 = 11.30$, $p = 0.001$). Correct guess rates for *Hypericum* versus sertraline did not differ significantly ($\chi^2 = 0.03$, $p = 0.862$).

Agreement between Clinician and Patient Guesses

We identified 242 patients for whom data for both clinician and patient guesses were available, and examined agreement between clinician and patient guess (Table 2). Agreement was more than 50% for each guess dyad (sertraline-sertraline, *Hypericum-Hypericum*, and placebo-placebo), with the strongest agreement for *Hypericum-Hypericum* (68%; $\chi^2 = 79.52$, $p < 0.001$). Agreement between clinicians and subjects produced a kappa coefficient of 0.37, indicating fair agreement.

Association between Clinician Guess and Adverse Events

Adverse Events (AE) data were available for 262 of the 277 subjects in our ITT sample. AE scores for each subject were based on the total number of reported AEs attributed to treatment²⁰, and ranged from 0-34, with mean score = 5.0 ± 5.5 ; median = 3.0, mode = 0. Subjects whose clinicians guessed they were receiving sertraline had a mean AE score of 5.4 ± 6.4 ; those whose clinicians guessed *Hypericum* had a score of 6.4 ± 5.7 ; and those whose clinicians guessed placebo had a score of 3.0 ± 3.6 . Comparisons of AE scores between pairs of clinician guess groups by independent samples t test reached significance only for sertraline versus placebo ($t = 2.873$, $df = 113$, $p = 0.005$) and for *Hypericum* versus placebo ($t = 4.967$, $df = 172$, $p < 0.001$).

To determine whether the presence of adverse events predicted clinician guess, we performed logistic regressions (with clinician guess as the dependent variable and the AE score, treatment assignment, baseline HDRS-17 score, and patient guess as covariates) for each guess pair (sertraline-placebo, sertraline-*Hypericum*, and *Hypericum*-placebo). The comparison between sertraline and *Hypericum* was not significant (Wald = 1.21, $df = 1$, $p = 0.271$, Exp (B) = 1.030, 95% CI = 0.977-1.085). The comparisons between sertraline and placebo (Wald = 7.63, $df = 1$, $p = 0.006$, Exp (B) = 0.905, 95% CI = 0.843-0.971) and between *Hypericum* and placebo (Wald = 17.91, $df = 1$, $p < 0.001$, Exp (B) = 0.839, 95% CI = 0.773-0.910) were significant, and remained significant after adjusting for treatment assignment, baseline HDRS-17 score, and patient guess.

Association between Clinician Guess and Continuous Measures of Improvement (Change in HDRS-17 score)

As an initial analysis of the association between clinician guess and clinical improvement, we examined the change in HDRS-17 score in each guess group (Table 3). All 3 clinician

guess groups improved significantly with regard to HDRS-17 score by paired t-test ($p < 0.001$ for all), with the sertraline-guess and *Hypericum*-guess groups having the strongest improvement. Significant differences in clinical improvement were found by one-way between-groups ANOVA when comparing the *Hypericum*-guess ($t = -9.497$, $df = 199$, $p < 0.001$, $\eta_p^2 = 0.312$) or the sertraline-guess group ($t = -9.195$, $df = 167$, $p < 0.001$, $\eta_p^2 = 0.336$) against the placebo-guess group. No significant differences were found in improvement between the *Hypericum*-guess versus the sertraline-guess groups ($t = -0.450$, $df = 182$, $p = 0.653$, $\eta_p^2 = 0.001$). Results of ANOVA including all 3 guess groups was significant ($F = 58.25$, $df = 2$, $p < 0.001$; $\eta_p^2 = 0.298$).

Next, we carried out a univariate ANOVA controlling for the impact of patient guess (fixed factor), assigned treatment (fixed factor), baseline depressive severity (covariate), and adverse effect scores (covariate) on the relationship between physician guess (independent variable) and change in HDRS-17 score (dependent variable). Assigned treatment was not significantly associated with clinical improvement ($F = 0.443$, $df = 2$, $p = 0.643$; $\eta_p^2 = 0.004$); however, clinician guess was significantly associated with clinical improvement ($F = 24.41$, $df = 2$, $p < 0.001$; $\eta_p^2 = 0.196$). There was a significant interaction between patient guess and treatment received ($F = 2.66$, $df = 4$, $p = 0.034$, $\eta_p^2 = 0.050$), suggesting that the combination of the two were related to clinical improvement. All other interactions, including clinician guess $\times$ treatment, clinician guess $\times$ patient guess, and clinician guess $\times$ patient guess $\times$ treatment, were nonsignificant.

Association between Clinician Guess and Categorical Measures of Improvement (Remission Rates)

Remission rates were 43% ($n = 33/76$) for subjects whose clinicians guessed sertraline, 33% ($n = 36/108$) for those whose clinicians guessed *Hypericum*, and 7% ($n = 6/93$) for those whose clinicians guessed placebo (Table 3). Remission rate comparisons between clinician guess groups yielded significant differences for sertraline versus placebo ($\chi^2 = 32.20$, $p < 0.001$, OR = 6.73, 95% CI = 2.99-15.21), and for *Hypericum* versus placebo ($\chi^2 = 21.85$, $p < 0.001$, OR = 5.17, 95% CI = 2.28-11.71), but not for sertraline versus *Hypericum* ($\chi^2 = 1.94$, $p = 0.164$, OR = 1.30, 95% CI = 0.90-1.89). Within each clinician guess group, no significant differences in remission rates were observed between the different treatment groups ($p > 0.05$ for all).

Next, we performed logistic regression, controlling for the impact of covariates including patient guess, assigned treatment, baseline depressive severity, and adverse event scores on the relationship between physician guess and remission rates (dependent variable). Clinician guess produced a significant effect, when comparing sertraline-guess vs placebo-guess (Wald = 30.88, $df = 1$, $p < 0.001$, Exp (B) = 0.233, 95% CI = 0.140-0.390) and for *Hypericum*-guess vs placebo-guess (Wald = 37.37, $df = 1$, $p < 0.001$, Exp (B) = 0.044, 95% CI = 0.016-0.120). Comparison between sertraline-guess and *Hypericum*-guess was not significant (Wald = 0.51, $df = 1$, $p = 0.477$, Exp (B) = 1.319, 95% CI = 0.615-2.831). Confounding variables of patient guess, assigned treatment, baseline depressive severity, and adverse event scores produced non-significant effects.

Discussion

In a randomized controlled trial investigating the comparative efficacy of St. John's Wort for treatment of MDD, clinicians' guesses regarding subjects' treatment assignments were significantly associated with improvement in HDRS-17 scores and remission rates, regardless of treatment received. Clinicians tended to guess that patients had received placebo when the improvement was modest, and tended to guess an active treatment (sertraline or *Hypericum*) when improvement was large (Table 3).

Doctors were most likely to guess placebo correctly (38%) and were less successful at correctly guessing sertraline (18%) or *Hypericum* (19%) (Table 1). This may be due to the difficulty of choosing between two “active” treatments that may produce side effects. Another consideration is that the doses of sertraline used in this study (50-100 mg) may be considered sub-optimal, whereas the doses of *Hypericum* (900-1500 mg) may be considered higher than usual, and this may have influenced rates of adverse events and hence guess accuracy. Correct guess rates were generally low across all arms, and 25% overall, which is lower than the 33% that chance would predict. This is consistent with our findings for study patients²¹ and suggests that the blind integrity of the study was well maintained, thus facilitating assessment of whether beliefs might influence outcomes or vice versa^{28,29}.

Despite the relatively low success rates of guessing, agreement between doctors' and subjects' guesses occurred in about 59% of cases (Table 2). These findings are consistent with previous research suggesting that physicians may transmit their expectations to their patients¹⁶, though it would be worth exploring the reverse hypothesis as well, whether patients somehow communicate their expectations regarding a hoped-for treatment to their physicians.

The fact that the most robust agreement between doctors and subjects occurred for *Hypericum* (68%) is particularly striking. As discussed in our previous report²¹, the study was conceived and advertised as a clinical trial of St. John's wort for MDD, and subjects who chose to enroll may have been especially enthusiastic about alternative therapies. This conclusion is supported by the relatively higher numbers of subjects who expressed a belief that they were receiving *Hypericum* (n=107) as opposed to sertraline (n=83) or placebo (n=52). Indeed, doctors' guesses also favored *Hypericum* (n=97) over sertraline (n=72) or placebo (n=73). While study participants may have been herb enthusiasts, there is no reason to assume that the investigators would be, given that most of their research involves conventional treatments. The higher than expected guess rate for *Hypericum* may therefore suggest a doctor-patient engagement in subtle alterations of expectancy during the trial. Of note, physicians' personal beliefs about the credibility of *Hypericum* as an antidepressant were not assessed and could potentially influence guessing rates and outcomes. For instance, a physician who views *Hypericum* as an effective treatment may exude optimism to the patient by instilling faith in the effectiveness of the treatment.

As in our previous report²¹, there appeared to be some interaction between treatment guessed and treatment received. When *Hypericum* was both the treatment guessed by physicians and received by subjects, the magnitude of improvement was greatest (with a

mean $\pm$ SD change in HDRS-17 of 15.57 ± 3.94 ; Table 3). Meanwhile, when placebo was both the treatment guessed by physicians and received by subjects, the magnitude of improvement was smallest (mean $\pm$ SD change in HDRS-17 of 2.97 ± 5.96 ; Table 3). The sertraline-treated group showed less of an HDRS-17 spread across its guess groups. This pattern within the treatment guess groups again suggests a possible interaction between treatment guess and assignment in the case of *Hypericum* and placebo.

The results of this reanalysis are consistent with our previous study examining the association between patients' beliefs regarding assigned treatment and clinical response²¹. The mechanism by which clinician beliefs interact with outcomes is unknown but may be multifactorial and/or bidirectional: clinician beliefs may be transmitted to patients, thereby altering expectation and outcome, and patient beliefs may likewise be transmitted to clinicians, influencing their guess. Clinicians would also be expected to more accurately assess adverse events attributed to treatment, and degree of clinical improvement experienced by patients, conferring an advantage in terms of guessing correctly, though as noted above, the lower than chance success rates suggest non-violation of the blind integrity. Furthermore, all patients demonstrated significant improvements in HDRS-17 regardless of treatment guessed or received; therefore it would be difficult to argue that clinicians' accurate assessment of degree of improvement could have accounted for all of the association between guess and clinical outcome.

This reanalysis has several limitations. Treatment guesses were elicited only after subjects had completed the acute treatment phase, and clinicians may have therefore been influenced by symptomatic improvement or reported adverse events. If patients were improving at 8 weeks, clinicians might be more likely to guess an active treatment, suggesting that outcome predicts treatment guess; this may not necessarily be the case with patient beliefs, which may be more likely influenced by preconceived ideas about the treatment. Prior studies with designs and outcomes similar to ours have also been limited by the difficulty of proving causality, especially in a retrospective analysis²⁸. Also, the study clinicians were not asked to give reasons for why they guessed the way they did. Future investigations would benefit from asking subjects and clinicians about the reasoning behind their treatment guess, and by eliciting treatment guess at various stages of the study, since belief is likely to evolve and be influenced by various factors, such as adverse events and rapidity of response, and is therefore likely to change over the course of treatment. Clinicians and patients were expected to choose one of the three treatment arms when guessing, and could not declare themselves as “undecided.” It is, however, unlikely that a clinician or patient would decline to answer based on not being sure of the assignment.

As mentioned in the Methods section, this reanalysis included patients who may have been nonadherent, based on blood tests for hyperforin, sertraline, and desmethylsertraline. Because we could not be sure how nonadherence might influence patient guesses, we also analyzed the data without the patients whose blood tests were suspicious, and the results were essentially unchanged (data not shown), probably due to the relatively low number of nonadherent patients. Furthermore, the database had no information about actual levels of metabolites in the blood, only whether they were measurable, which prevents exclusion of patients with “low” levels of metabolites who may be adherent but rapid metabolizers. And

of course, it is impossible to control for everything that a patient may take without telling the clinician.

Finally, we calculated adverse event (AE) score based on the number of AEs reported by each patient that were attributed to treatment, but AE severity (e.g., one particularly significant AE) could have also had an impact on the association between clinician guess and outcome. This possibility could not be analyzed because AE severity data were not available.

Conclusion

These results are consistent with our previous observations about patient belief and treatment response. Clinician beliefs regarding their patients' assigned treatment may also have a stronger association with clinical outcome compared to the actual medication received. These findings need to be replicated in other studies, including those that do not use *Hypericum* or other natural remedies, as our sample may not be representative of individuals with depression in general. Likewise, future physician expectation studies on conditions with lower placebo response rate such as schizophrenia, social anxiety disorder, and ADHD may further clarify the importance of diagnosis on the association between clinician beliefs and outcome. Such studies may have implications for how physicians' conveyance of beliefs about treatment may influence patient outcomes, and for utilizing the potentially therapeutic effects of clinicians' beliefs in clinical practice.

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Table 1
Physician Treatment Guess and Actual Treatment Assignments in the Intent to Treat Sample (N=277 patients with clinician guess data)

Treatment Guessed	Total Guesses (N = 277) % (n) of guesses	Treatment Received		
		Sertraline (n = 90) % (n) of guesses	Hypericum (n = 88) % (n) of guesses	Placebo (n = 99) % (n) of guesses
Sertraline	27.4% (76)	18.4% (14)	34.2% (26)	47.4 % (36)
Hypericum	39.0% (108)	54.6% (59)	19.4% (21)	25.9% (28)
Placebo	33.6% (93)	18.3% (17)	44.1% (41)	37.6% (35)*

* Correct guess rates were significantly greater for clinicians guessing placebo than for clinicians guessing sertraline ($\chi^2 = 7.50$, $p = 0.006$), *Hypericum* ($\chi^2 = 8.23$, $p = 0.004$) or an active treatment ($\chi^2 = 11.30$, $p = 0.001$). Correct guess rates for *Hypericum* versus sertraline did not differ significantly ($\chi^2 = 0.03$, $p = 0.862$).

All significant comparisons held significance after Bonferroni correction for 3 comparisons: $\alpha = 0.05/3 = 0.0167$

Table 2
Agreement between Clinician and Patient guess (N=242 with available clinician and patient guess data)

Clinician Guess	Patient Guess			
	Total Guesses (N = 242) % (n) of guesses	Sertraline (n = 83) % (n) of guesses	<i>Hypericum</i> (n = 107) % (n) of guesses	Placebo (n = 52) % (n) of guesses
Sertraline	29.8% (72)	52.8% (38)	37.5% (27)	9.7% (7)
<i>Hypericum</i>	40.1% (97)	24.7% (24)	68% (66)	7.2% (7)
Placebo	30.2% (73)	28.8% (21)	19.2% (14)	52.1% (38)

Chi-squared for clinician versus patient guess : $\chi^2=79.52$, df=4, **p<0.001**; overall Kappa = 0.37.

Table 3
HDRS-17 Score Improvement and Remission Rates by Clinician Guess and Treatment Assignment in the Intent-to-Treat (ITT) Sample (N=277)

Treatment Guessed	Treatment Received			
	ALL (n=277)	Sertraline (n=90)	Hypericum (n=88)	Placebo (n=99)
Sertraline (n=76)				
Mean (SD)	13.04 (6.04)	11.93 (2.95)	12.65 (6.20)	13.75 (6.81)
Remission rate, % (n)	43.4% (33)	28.6% (4)	38.5% (10)	52.8% (19)
Hypericum (n=108)				
Mean (SD)	12.63 (6.11)	12.19 (5.90)	15.57 (3.94)	11.36 (7.27)
Remission rate, % (n)	33.3% (36)	32.3% (19)	38.1% (8)	32.1% (9)
Placebo (n=93)				
Mean (SD)	4.51 (5.97)	7.00 (5.06)	4.78 (6.06)	2.97 (5.96)
Remission rate, % (n)	6.5% (6)	5.9% (1)	9.8% (4)	2.9% (1)

Significance of HDRS-17 score improvement for each guess group by paired t-test:

Sertraline guess: $t = -18.83$, $df = 75$, $p < 0.001$

Hypericum guess: $t = -21.48$, $df = 107$, $p < 0.001$

Placebo guess: $t = -7.25$, $df = 92$, $p < 0.001$

One-way between groups ANOVA for all 3 guess groups (HDRS-17 score improvement): $F = 58.25$, $df = 2$, $p < 0.001$; $\eta_p^2 = 0.298$

For guess = Sertraline vs Hypericum: $t = -0.450$, $df = 182$, $p = 0.653$, $\eta_p^2 = 0.001$

For guess = Sertraline vs placebo: $t = -9.195$, $df = 167$, $p < 0.001$, $\eta_p^2 = 0.336$

For guess = Hypericum vs placebo: $t = -9.497$, $df = 199$, $p < 0.001$, $\eta_p^2 = 0.312$

All significant comparisons held significance after Bonferroni correction for 3 comparisons: $\alpha = 0.05/3 = 0.0167$