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Do early changes in the HAM-D-17 anxiety/somatization factor items affect treatment outcome among depressed outpatients? Comparison of two controlled trials of St John's Wort (*Hypericum Perforatum*) versus an SSRI

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Abstract

Objective—To assess whether early changes in HAM-D-17 anxiety/somatization items predict remission in two controlled studies of hypericum perforatum (St. John's wort) versus an SSRI for major depressive disorder (MDD).

Methods—The Hypericum Depression Trial Study Group (NIMH) study randomized 340 subjects to hypericum, sertraline, or placebo for 8 weeks. The MGH study randomized 135 subjects to hypericum, fluoxetine, or placebo for 12 weeks. We examined whether remission was associated with early changes in anxiety/somatization symptoms.

Results—In the NIMH study, significant associations were observed between remission and early improvement in the anxiety-psycho item (sertraline arm), somatic-gastrointestinal item (hypericum arm), and somatic symptoms-general (placebo arm). None of the three treatment arms of the MGH study showed significant associations between anxiety/somatization symptoms and remission. When both study samples were pooled, we found associations for anxiety-psycho (SSRI arm), somatic-gastrointestinal and hypochondriasis (hypericum arm), and anxiety-psycho and somatic symptoms-general (placebo arm). In the entire sample, remission was associated with improvement in the anxiety-psycho, somatic-gastrointestinal, and somatic symptoms-general items.

Conclusions—The number and type of anxiety/somatization items associated with remission varied depending on the intervention. Early scrutiny of the HAM-D-17 anxiety/somatization items may help predict remission of MDD.

Keywords

Depression; Antidepressants; St. John's wort; Anxiety; Predictors; Remission

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Introduction

With growing scrutiny of antidepressant efficacy (Khan et al., 2003; Kirsch et al., 2008), it has become important for clinicians to assess treatment efficacy more efficiently and rapidly. Several studies have found encouraging evidence that response and/or remission may be predicted as early as 1–4 weeks into treatment, based on initial response, with a variety of standard antidepressant agents and herbal remedies such as St John's wort, as well as cognitive behavioral therapy (Coryell et al., 1982; Quitkin et al., 1984; Downing et al., 1985; Stassen et al., 1993; Nierenberg et al., 1995, 2000; Bech, 2001; Kieser et al., 2005; Szegedi et al., 2003, 2009; Henkel et al., 2009; Wade et al., 2009; Nakajima et al., 2010; Tadic et al., 2010).

Along these lines, investigators have also examined clinical parameters that may predict eventual response or remission. Studies with various antidepressants have found evidence that early improvement in individual items from the Hamilton Depression Rating Scale (HAM-D) (Hamilton, 1960) may predict eventual response or remission; examples include the HAM-D scale depressed mood item (Bech, 2001; Katz et al., 2004, 2010), motor retardation (Katz et al., 2004, 2010), anxiety (Katz et al., 2004, 2010; Farabaugh et al., 2005, 2010), cognition and psychomotor changes (Tollefson and Holman, 1994; Kilts et al., 2009), hopelessness (Kilts et al., 2009), and somatic complaints (Small et al., 1995). In some cases, predictive changes may occur as early as 1–2 weeks after initiating treatment. By identifying predictors of response early in the course of treatment, clinicians may determine whether it is worthwhile to continue a full course of an antidepressant, augment or combine with another agent, or switch to another therapy. An expeditious modification in therapy could potentially accelerate a good outcome, and save the patient weeks or even months of suffering.

Given the overlap between depression and anxiety (Fava et al., 2000a), various groups have examined whether anxiety symptoms predict treatment response in depressed patients (Fava et al., 2000b; Dunner et al., 2003; Katz et al., 2004; Farabaugh et al., 2005, 2010; Rynn et al., 2006). For example, in patients with anxious depression, fluoxetine and sertraline resulted in greater improvement in anxiety/somatization items of the HAM-D scale by week 1 compared to paroxetine (Fava et al., 2000b); and Hamilton-A scores at week 1 and 2 predicted response by week 3 for both antidepressants and placebo (Rynn et al., 2006).

The anxiety/somatization factor of the HAM-D-17, frequently used to define anxious depression, includes six items: anxiety-psychic, anxiety-somatic, somatic symptoms-gastrointestinal, somatic symptoms-general, hypochondriasis, and insight. Observed early changes in these symptoms may accelerate identification of treatment responders and help guide management. In a previous study, we examined whether early changes (between baseline and the first week of treatment) in the anxiety/somatization factor of the HAM-D-17 predicted response to treatment with fluoxetine, hypericum, or placebo (Farabaugh et al., 2005). We found that a greater reduction in the somatic symptoms-general item (often interpreted as a measure of fatigue) during the first week of therapy predicted greater remission rates with antidepressants. While the post-hoc, exploratory nature of this analysis prevented us from concluding whether this was a true or chance finding, our results were later shown to be consistent with the STAR*D findings of lower chances of remission in anxious depression (Fava et al., 2008).

More recently, we assessed the relationship between early changes (from baseline to week 1 of treatment) in HAM-D-17 anxiety/somatization factor items and treatment outcome among Major Depressive Disorder (MDD) patients participating in a 12-week study of fluoxetine monotherapy (Farabaugh et al., 2010). In an attempt to replicate the STAR*D findings (Fava

et al., 2008), we assessed whether the presence of anxious depression (defined as having an anxiety/somatization factor score of 7 or greater at baseline) predicted poorer chances of remission in a previously published 12-week, open-label, fixed-flexible dose trial of fluoxetine for MDD (McGrath et al., 2006). After adjusting for baseline HAM-D-17 scores, patients with greater early improvement in somatic symptoms-gastrointestinal were significantly more likely to attain remission ($\text{HAM-D-17} < 8$) at endpoint than those without early improvement (Farabaugh et al., 2010). Early changes in the remaining items did not predict remission, nor did anxious depression at baseline.

Given that these convergent findings suggest a role for anxiety symptoms as potential predictors of remission with antidepressants, we sought to expand on the results from Farabaugh et al. (2005) by examining the database from the Hypericum Depression Trial Study Group's recent placebo-controlled study comparing St John's Wort (SJW) to sertraline (Hypericum Depression Trial Study Group, 2002). Since the studies from the Hypericum Depression Trial Study Group and our group had similar designs and used similar agents, it was possible to compare the findings from each study as well as to combine the two study databases together to attempt to expand on our original findings in a larger pooled sample. We thus examined the relationship between early changes in HAM-D-17 anxiety/somatization items and treatment outcome. We hypothesized that early improvement in anxiety/somatization items in patients receiving SSRIs or hypericum would be associated with patterns of remission similar to those from Farabaugh et al. (2005).

Methods

The investigation was approved by the MGH Institutional Review Board (IRB). Methods for the two parent studies, which compared the efficacy of hypericum perforatum (St. John's wort) versus an SSRI are detailed elsewhere (Hypericum Depression Trial Study Group, 2002; Fava et al., 2005). The Hypericum Depression Trial Study Group's study, conducted at multiple sites and funded by the NIMH, used sertraline as the standard comparator; the single-site MGH study, which was industry-funded, used fluoxetine.

The NIMH study recruited 340 adult outpatients (66% women; mean age = 42.8 ± 13.2 ; baseline HAM-D-17 = 22.8 ± 2.7) with MDD and a baseline HAM-D-17 score of ≥ 20 . Subjects were randomized to receive St. John's wort, sertraline, or placebo for 8 weeks. The dose of St. John's wort was flexible, depending on clinical response, from 900–1500 mg/day and that of sertraline was 50–100 mg/day. The single-site MGH study was a 12-week trial with 135 subjects (57% women; mean age = 37.3 ± 11.0 ; baseline HAM-D-17 = 19.7 ± 3.2) with MDD and a baseline HAM-D-17 score of 16 or greater, randomized to receive fixed doses of hypericum 900 mg/day, fluoxetine 20 mg/day, or placebo.

We examined whether early changes in anxiety/somatization symptoms (from baseline to week 1 of treatment) predicted remission at study endpoint. This reanalysis defined remission as a final HAM-D-17 score of less than 8 and analyzed the intent-to-treat (ITT) samples of the studies (comprised of patients having at least one post-baseline visit). The data in both studies were analyzed with logistic regressions, t-tests, and ANOVAs to investigate whether changes in HAM-D-17 anxiety/somatization factor items between baseline and week 1 were associated with treatment outcome for participants receiving SSRI or SJW or placebo. Baseline HAM-D-17 scores were considered covariates. Alpha values were set at $p < 0.05$ and, where indicated, the Bonferroni correction ($p \leq 0.008$) was used for multiple comparisons. We examined the three treatment arms in both studies separately and pooled together, and also collapsed both samples together to analyze all the data as one entity. We analyzed the data in this manner in order to rigorously investigate any trends and

their power, independent of study and treatment group. Data analyses were conducted using SPSS version 17.0.

Results

NIMH Study results

Preliminary analysis of the NIMH ITT study sample (N=320) showed no significant association between remission (HAM-D-17<8) at study endpoint and baseline HAM-D-17 scores for the sertraline group (n=104; remitters, mean = 21.92±2.02; nonremitters, mean = 22.65±2.53; p=0.198), for the hypericum group (n=104; remitters, mean = 22.09±1.88; nonremitters, mean = 23.42±3.00; p=0.051), and for the placebo group (n=112; remitters, mean = 22.50±2.68; nonremitters, mean = 22.90±2.83; p=0.497).

In the sertraline group, after controlling for initial severity of depression, logistic regression showed a significant association for anxiety-psychic (p=0.003, $r^2=0.164$), and somatic symptoms-gastrointestinal (p=0.044, $r^2=0.090$), the latter of which lost significance after Bonferroni correction (Table 1). In the hypericum group, we found a significant association for anxiety-psychic (p=0.012, $r^2=0.160$), anxiety-somatic (p=0.039, $r^2=0.130$), somatic symptoms-gastrointestinal (p=0.002, $r^2=0.200$), and hypochondriasis (p=0.010, $r^2=0.167$), but only somatic symptoms-gastrointestinal retained significance after Bonferroni correction (Table 1). In the placebo group, remission was significantly associated with an early change in the HAM-D-17 item of anxiety-psychic (p=0.018, $r^2=0.083$), somatic symptoms-gastrointestinal (p=0.047, $r^2=0.059$) and somatic symptoms-general (p<0.001, $r^2=0.209$), only the last of which maintained significance after Bonferroni correction (Table 1).

MGH Study Results

Preliminary analysis of the MGH ITT study sample (N=125) showed that remission (HAM-D-17 < 8) at study endpoint was significantly associated with baseline HAM-D-17 scores for fluoxetine (n=41; remitters, mean = 17.80±1.48; nonremitters, mean = 19.87±2.96; p=0.041) and for hypericum (n=43; remitters, mean = 17.80±1.70; nonremitters, mean = 20.64±3.83; p=0.023), but not for the placebo group (n=41; remitters, mean = 18.11±1.05; nonremitters, mean = 20.38±3.11; p=0.058).

After controlling for severity of depression, logistic regression showed a significant association between remission and early change in the anxiety-psychic factor (p=0.026, $r^2=0.396$) in the fluoxetine group, and somatic symptoms-gastrointestinal (p=0.042; $r^2=0.384$) in the hypericum group, but significance of these was lost after Bonferroni correction. No significant associations were observed in the placebo group (Table 2).

Results for Pooled Samples

With participants from both studies grouped together in a preliminary analysis (N=445), remission at endpoint was significantly associated with a lower baseline HAM-D-17 score in the SSRI group (n=145; remitters, mean = 20.71±2.66; nonremitters, mean = 21.87±2.93; p=0.042) and in the hypericum group (n=147; remitters, mean = 20.39±2.78; nonremitters, mean = 22.71±3.44; p=0.001). In the placebo group there was no significant association (n=153; remitters, mean = 21.49±3.03; nonremitters, mean = 22.19±3.11; p=0.220). The full model predicted statistically significantly, χ^2 (1, N = 292) = 17.93, p < 0.001, indicating that the model was able to distinguish between participants who were remitters and those who were not at week 8. The model as a whole explained between 60% (Cox and Snell r^2) and 89% (Nagellerke r^2) of the variance in remission status, and correctly classified 75.3% of the participants' status at week 8, final endpoint of study.

In the SSRI group (sertraline and fluoxetine), after controlling for initial severity of depression in the logistic regression, remission was significantly associated with an early change in the HAM-D-17 item of anxiety-psychic ($p<0.001$, $r^2=0.184$). In the hypericum group, remission was significantly associated with an early change in the HAM-D-17 item of anxiety-psychic ($p=0.025$, $r^2=0.184$), somatic symptoms-gastrointestinal ($p<0.001$, $r^2=0.262$), somatic symptoms-general ($p=0.04$, $r^2=0.175$), and hypochondriasis ($p=0.004$, $r^2=0.218$), but after Bonferroni correction, the significance held only for somatic symptoms-gastrointestinal and hypochondriasis. In the placebo group, remission was significantly related to an early change in the HAM-D-17 items of anxiety-psychic ($p=0.003$, $r^2=0.110$) and somatic symptoms-general ($p=0.001$, $r^2=0.118$), both of which remained significant after Bonferroni correction (Table 3).

NIMH and MGH study results collapsed

When the two study samples were collapsed, i.e. taken together so that all four groups (active treatment and placebo in each sample) were examined as one entity ($N=445$), results showed a statistically significant association between the rate of remission and a lower baseline HAM-D-17 score (remitters, mean = 20.87 ± 2.85 ; nonremitters, mean = 22.25 ± 3.17 ; $p<0.001$). After controlling for initial severity of depression in the logistic regression, remission was significantly associated with an early change in the HAM-D-17 items of anxiety-psychic ($p<0.001$, $r^2=0.143$), anxiety-somatic ($p=0.029$; $r^2=0.073$), somatic symptoms-gastrointestinal ($p<0.001$, $r^2=0.106$), and somatic symptoms-general ($p<0.001$, $r^2=0.104$), but significance after the Bonferroni correction was lost for anxiety-somatic (Table 5).

Table 5 summarizes the overall findings in both study samples individually, pooled and collapsed.

Discussion

In the NIMH study, each treatment arm, including placebo, showed a significant association between remission and one specific HAM-D anxiety/somatization factor item. No significant associations were found in the MGH study when we analyzed each treatment arm individually as opposed to when we pooled hypericum and fluoxetine together in the Farabaugh et al. study (2005). The greater number of statistically significant changes in anxiety/somatization factor items in the NIMH study compared to the MGH study is intriguing because the MGH study supported the efficacy of St. John's wort more readily than the NIMH study, showing a trend to significance for hypericum compared to placebo (Fava et al., 2005). The observed benefit, however, may have been related to HAM-D-17 items not associated with anxiety/somatization.

In the pooled sample, the significant associations between remission and anxiety/somatization factor items were essentially consistent with those from the NIMH sample, with the addition of hypochondriasis, which attained significance in the pooled hypericum arms, and anxiety-psychic, which attained significance in the pooled placebo arms (Table 5). When we collapsed both studies and treatment groups, we found three strong overall predictors of remission: anxiety-psychic, somatic symptoms-gastrointestinal, and somatic symptoms-general (Table 5). These again were likely driven by the NIMH study sample, and appear to be strong enough predictors to "override" the non-significant findings of the MGH study.

The combination and contrast of the two studies is somewhat difficult to interpret. The larger NIMH study revealed a stronger placebo and active treatment effect with regard to anxiety/somatization symptoms, despite a generally weaker overall clinical improvement for

the active treatments than in our study. This suggests that, a) anxiety/somatization items are tractable to placebo, not just to active medications; and b) early improvement in anxiety/somatization factors may not be universally relevant to overall clinical improvement over time.

A number of limitations must be noted. The consensus definition of remission as dichotomous rather than quantitative, on the basis of an absolute HAM-D-17 cutoff value, may lead to a correlation with baseline severity, and this methodological issue cannot necessarily be solved by just controlling for baseline depressive severity. However, given that both studies required HAM-D scores in the range of at least moderate depression (MGH) and moderate-to-severe depression (NIMH) suggests that patients who achieve remission should have obtained a robust improvement of at least 50% or more.

Another potential limitation of this investigation is that both studies used a natural product as one of the active treatments, and some have suggested that placebo effects in MDD studies may be especially relevant when CAM therapies are used, given expectation factors on the part of study participants (Astin et al, 1998). The literature has certainly been varied in its support for hypericum as a treatment for MDD (Linde et al., 1996; Linde et al., 2008). However, the growing analysis of databases of FDA-approved antidepressants suggests a narrower than previously thought efficacy differential between CAM and standard therapies, and even a lower placebo response rate for CAM trials as opposed to standard antidepressant trials (Freeman et al, 2010). In contrasting the findings for SSRIs and hypericum, it appeared that SSRIs tended to interact with the anxiety-psychic item, and hypericum with the somatic symptoms-gastrointestinal and hypochondriasis items, while placebo interacted with the anxiety-psychic and somatic symptoms-general items. These data suggest that CAM-based as opposed to synthetic antidepressants or placebo may have different mechanisms by which they manifest their clinical effects, and further investigation in this regard would be of value.

Our findings, along with previous reports, support the prediction of remission based on early improvement in specific HAM-D items. However, the varied and inconsistent body of data thus far makes it difficult to methodically select target symptoms for response prediction, and so the clinical significance of these predictors--particularly whether early non-improvement warrants clinical action--remains controversial. Also, some have suggested that placebo response may have a trajectory similar to antidepressant response (Stassen et al., 1993) and may also be predictable on the basis of early improvement. In our study, HAM-D anxiety/somatization factors were associated with response to both active drugs and placebo. This makes it difficult to offer generalizable conclusions about predictors of response to antidepressants per se. If clinical improvement can be obtained and predicted with either an active treatment or a placebo, this suggests that the true nature of "treatment response" requires further investigation.

To conclude, while the above studies did not show a clear benefit of active antidepressant treatment over placebo, the findings do support scrutiny of the HAM-D-17 anxiety/somatization items as early predictors of remission. Practitioners may want to measure the HAM-D-17 anxiety/somatization items early in the course of treatment, as a potential guide to whether or not to continue monotherapy with a given antidepressant, but this recommendation should be followed with caution. Further characterization of predictors of remission and their association with specific antidepressant agents and placebo is warranted.

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Table 1

Early changes in HAM-D-17 Anxiety/Somatization factor items in relationship to remission in the Intent-to-Treat NIMH study sample

Item	Treatment	Remitters mean change from baseline to week 1	Nonremitters mean change from baseline to week 1	z	X ²	P value	Odds Ratio	95% CI
Anxiety (psychic)	Sertraline	1.00 ± 0.93	0.29 ± 0.92	1.10	1.20	0.003 *	2.26	1.32–3.88
	Hypericum	0.70 ± 0.88	0.12 ± 0.87	2.50	6.25	0.012	2.08	1.17–3.69
	Placebo	0.47 ± 0.97	0.02 ± 0.88	2.36	5.57	0.018	1.84	1.11–3.04
Anxiety (somatic)	Sertraline	0.33 ± 0.70	0.03 ± 0.93	1.66	2.76	0.096	1.60	0.92–2.77
	Hypericum	0.52 ± 0.85	0.12 ± 0.71	2.07	4.28	0.039	1.92	1.04–3.55
	Placebo	0.27 ± 0.79	0.29 ± 0.78	0.13	0.02	0.896	0.96	0.56–1.66
Somatic (GI)	Sertraline	0.21 ± 0.72	−0.09 ± 0.68	2.02	4.07	0.044	2.20	1.02–4.74
	Hypericum	0.52 ± 0.59	0.06 ± 0.62	3.04	9.27	0.002 *	3.67	1.59–8.46
	Placebo	0.43 ± 0.68	0.15 ± 0.63	1.99	3.96	0.047	1.99	1.01–3.91
Somatic (General)	Sertraline	0.17 ± 0.48	0.11 ± 0.39	0.68	0.46	0.498	1.46	0.49–4.39
	Hypericum	0.30 ± 0.64	0.12 ± 0.43	1.37	1.89	0.169	1.83	0.77–4.35
	Placebo	0.63 ± 0.77	0.10 ± 0.46	3.75	14.1	<0.001 *	4.48	2.05–9.80
Hypochondriasis	Sertraline	0.08 ± 0.72	0.28 ± 0.86	0.85	0.73	0.392	0.78	0.43–1.39
	Hypericum	0.57 ± 0.99	0.14 ± 0.67	2.58	6.64	0.010	2.45	1.24–4.85
	Placebo	0.53 ± 0.73	0.32 ± 0.83	1.40	1.95	0.163	1.46	0.86–2.48
Insight	Sertraline	0.00 ± 0.30	0.08 ± 0.38	1.00	1.01	0.314	0.49	0.12–1.98
	Hypericum	0.13 ± 0.34	0.06 ± 0.33	0.48	0.23	0.633	1.41	0.34–5.83
	Placebo	0.10 ± 0.31	0.01 ± 0.29	1.35	1.83	0.177	2.68	0.64–11.18

Bonferroni correction: 0.05/6 = 0.008

* Significant p ≤ 0.008 after Bonferroni

z=SQR (X²) = SQR (Wald)

X²= Wald

Odds Ratio = Exp (B)

Early changes in HAM-D-17 Anxiety/Somatization factor items in relationship to remission in the Intent-to-Treat MGH study sample

Table 2

Item	Treatment	Remitters mean change from baseline to week 1	Nonremitters mean change from baseline to week 1	z	X ²	P value	Odds Ratio	95% CI
Anxiety (psychic)	Fluoxetine	0.90 ± 0.99	0.29 ± 0.90	2.23	4.97	0.026	3.28	1.15–9.33
	Hypericum	0.53 ± 1.13	0.39 ± 0.96	0.48	0.23	0.632	1.17	0.61–2.24
	Placebo	0.78 ± 1.09	–0.03 ± 0.95	1.83	3.34	0.068	2.91	0.93–9.17
Anxiety (somatic)	Fluoxetine	0.00 ± 0.47	–0.10 ± 0.79	0.14	0.02	0.880	0.92	0.31–2.75
	Hypericum	0.33 ± 0.82	0.36 ± 1.03	0.20	0.04	0.851	0.93	0.46–1.91
	Placebo	0.22 ± 0.67	0.00 ± 0.97	0.55	0.30	0.581	1.32	0.50–3.50
Somatic (GI)	Fluoxetine	–0.20 ± 0.63	0.13 ± 0.50	1.37	1.88	0.170	0.27	0.04–1.77
	Hypericum	0.33 ± 0.62	0.11 ± 0.42	2.03	4.14	0.042	5.82	1.07–31.81
	Placebo	0.00 ± 0.50	0.03 ± 0.61	0.20	0.04	0.839	1.17	0.26–5.33
Somatic (General)	Fluoxetine	0.40 ± 0.84	0.23 ± 0.56	0.91	0.82	0.366	1.87	0.48–7.25
	Hypericum	0.60 ± 0.99	0.14 ± 0.76	1.65	2.72	0.099	2.04	0.87–4.77
	Placebo	0.22 ± 0.67	0.32 ± 0.61	0.10	0.01	0.908	0.93	0.28–3.12
Hypochondria	Fluoxetine	0.20 ± 0.42	0.23 ± 0.12	0.17	0.03	0.858	0.92	0.36–2.36
	Hypericum	0.53 ± 0.83	0.07 ± 0.94	1.27	1.62	0.203	1.65	0.76–3.56
	Placebo	–0.11 ± 0.60	0.32 ± 0.91	0.59	0.35	0.554	0.67	0.18–2.55
Insight	Fluoxetine	0.20 ± 0.63	–0.03 ± 0.18	1.32	1.73	0.189	4.97	0.46–54.35
	Hypericum	0.00 ± 0.00	–0.04 ± 0.19	0.00	0.00	1.00	8.6E8	NA
	Placebo	–0.11 ± 0.78	0.00 ± 0.26	0.75	0.56	0.456	0.51	0.09–2.95

Bonferroni correction: 0.05/6 = 0.008

* Significant p ≤ 0.008 after Bonferroni

z=SQR (X²) = SQR (Wald)

X²= Wald

Odds Ratio = Exp (B)

Early changes in HAM-D-17 Anxiety/Somatization factor items in relationship to remission in the Intent-to-Treat Pooled (NIMH plus MGH) study samples

Table 3

Item	Treatment	Remitters mean change from baseline to week 1	Nonremitters mean change from baseline to week 1	z	X ²	P value	Odds Ratio	95% CI
Anxiety (psychic)	SSRI	0.97 ± 0.94	0.29 ± 0.91	3.54	12.55	<0.001 *	2.31	1.45–3.67
	Hypericum	0.63 ± 0.97	0.19 ± 0.90	2.24	5.02	0.025	1.63	1.06–2.49
	Placebo	0.54 ± 1.00	0.01 ± 0.89	2.99	8.93	0.003 *	1.94	1.26–3.01
Anxiety (somatic)	SSRI	0.24 ± 0.65	–0.01 ± 0.89	1.65	2.72	0.099	1.50	0.93–2.44
	Hypericum	0.45 ± 0.83	0.18 ± 0.81	1.52	2.32	0.127	1.43	0.90–2.27
	Placebo	0.26 ± 0.75	0.21 ± 0.84	0.36	0.13	0.715	1.09	0.69–1.70
Somatic (GI)	SSRI	0.04 ± 0.71	–0.03 ± 0.64	1.10	1.22	0.269	1.42	0.76–2.66
	Hypericum	0.45 ± 0.60	0.07 ± 0.57	3.60	12.99	<0.001 *	4.04	1.89–8.63
	Placebo	0.33 ± 0.66	0.12 ± 0.62	1.91	3.66	0.056	1.77	0.99–3.19
Somatic (General)	SSRI	0.24 ± 0.61	0.14 ± 0.44	0.83	0.69	0.407	1.39	0.64–3.02
	Hypericum	0.42 ± 0.79	0.13 ± 0.53	2.05	4.20	0.040	1.84	1.03–3.29
	Placebo	0.54 ± 0.76	0.16 ± 0.53	3.21	10.33	0.001 *	2.73	1.48–5.03
Hypochondriasis	SSRI	0.12 ± 0.64	0.26 ± 0.93	0.75	0.57	0.452	0.84	0.53–1.34
	Hypericum	0.55 ± 0.92	0.12 ± 0.74	2.86	8.20	0.004 *	2.13	1.27–3.56
	Placebo	0.38 ± 0.75	0.32 ± 0.85	0.83	0.69	0.406	1.22	0.76–1.95
Insight	SSRI	0.06 ± 0.42	0.05 ± 0.34	0.1	0.01	0.916	1.06	0.36–3.14
	Hypericum	0.08 ± 0.27	0.04 ± 0.30	0.72	0.52	0.473	1.62	0.44–5.97
	Placebo	0.05 ± 0.46	0.01 ± 0.28	0.71	0.50	0.478	1.52	0.48–4.77

Bonferroni correction: 0.05/6 = 0.008

* Significant $p \leq 0.008$ after Bonferroni

$z = \text{SQR}(X^2) = \text{SQR}(\text{Wald})$

$X^2 = \text{Wald}$

Odds Ratio = Exp (B)

Early changes in HAM-D-17 Anxiety/Somatization factor items in relationship to remission in all collapsed data (all treatment arms of NIMH and MGH study samples)

Table 4

Item	Remitters mean change from baseline to week 1	Nonremitters mean change from baseline to week 1	z	X ²	P value	Odds Ratio	95% CI
Anxiety (psychic)	0.70 ± 0.98	0.16 ± 0.90	4.99	24.91	<0.001*	1.89	1.47–2.42
Anxiety (somatic)	0.32 ± 0.75	0.13 ± 0.85	2.18	4.76	0.029	1.34	1.03–1.74
Somatic (GI)	0.30 ± 0.67	0.05 ± 0.61	3.83	14.67	<0.001*	2.06	1.42–2.98
Somatic (General)	0.41 ± 0.73	0.14 ± 0.50	3.82	14.63	<0.001*	2.04	1.41–2.93
Hypochondria	0.36 ± 0.80	0.23 ± 0.85	1.91	3.68	0.055	1.30	0.99–1.69
Insight	0.06 ± 0.39	0.03 ± 0.31	0.86	0.740	0.390	1.34	0.69–2.62

Bonferroni correction: 0.05/6 = 0.008

* Significant $p \leq 0.008$ after Bonferroni

$z = \text{SQR} (X^2) = \text{SQR} (\text{Wald})$

$X^2 = \text{Wald}$

Odds Ratio = Exp (B)

Table 5

Summary of Findings in Both Studies: Significant Predictors of Remission

	MGH Study (Fava et al, 2005)	NIMH Study (Hypericum Depression Trial Study Group, 2002)	Pooled NIMH and MGH Studies	Collapsed sample (all treatment arms from both studies combined)
SSRI*	None	Anxiety-psyhic	Anxiety-psyhic	
Hypericum	None	Somatic symptoms-GI	Somatic symptoms-GI Hypochondriasis	Anxiety-psyhic Somatic symptoms-GI
Placebo	None	Somatic symptoms-general	Anxiety-psyhic Somatic symptoms-general	Somatic symptoms-general

* Sertraline in the NIMH study; fluoxetine in the MGH study.