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The Treatment of Minor Depression with St. John's Wort or Citalopram: Failure to Show Benefit over Placebo

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Abstract

This paper presents new data addressing two important controversies in psychiatry: the construct of Minor Depression (MinD) and the efficacy of St. John's Wort for milder forms of depressive disorders. Data are from a three-arm, 12 week, randomized clinical trial of investigating the efficacy of St. John's Wort (810 mg/day), citalopram (20 mg/day), or placebo for acute treatment of MinD. Due to a high placebo response on all outcome measures, neither St. John's Wort nor citalopram separated from placebo on change in depressive symptom severity, quality of life, or well-being. However, systematic assessment of potential adverse effects (AEs) led to three important observations: (1) prior to the administration of study compound, 60% of subjects endorsed items that would be characterized as AEs once study compound was administered, (2) St. John's Wort and citalopram were each associated with a significant number of new or worsening AEs during treatment, and (3) using a structured interview for identifying AEs at baseline and during treatment is informative. MinD was not responsive to either a conventional antidepressant or a nutraceutical, and both compounds were associated with a notable side effects burden. Other treatment approaches for MinD should be investigated.

BACKGROUND

Although there have been a number of different definitions for minor depression employed in literature, it is clear that the field is coming to a consensus that "less than Major Depressive Disorder," with clinically significant distress and/or impairment, is a problem for patients that merits study (Rapaport et al., 2002; Howland et al., 2008; Nierenberg et al.,

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CONTRIBUTORS

Drs. Rapaport, Nierenberg, Howland, and Mischoulon designed the study, obtained funding for it, oversaw the conduct of the study, and contributed to writing and editing the manuscript. Dr. Rapaport wrote the first draft of sections of the manuscript on the background and conclusions. Dr. Dording was the primary clinician for the study at MGH. Dr. Schettler contributed to development of the study database, performed the statistical analyses, and wrote the first draft of the sections on methods and results. All of the authors contributed to and have approved the final manuscript.

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2010). Data from epidemiological studies suggest that both younger and older adults suffer from minor depression and for many individuals this is not an evanescent condition (Romanoski et al., 1992; Sherbourne et al., 1994; Kessler et al., 1997). Although defined in various ways, Minor Depressive Disorder in adults, particularly in older individuals, has also been associated with significant impairment in quality of life and function (Wells et al., 1989; Broadhead et al., 1990; Johnson et al., 1992; Alexopoulos et al., 2001; Rapaport et al., 2002; Howland et al., 2008; Nierenberg et al., 2010).

Few treatment studies have focused specifically on Minor Depressive Disorder. Although there have been case reports, case series, and active control studies with antidepressants, the vast preponderance of work has investigated the efficacy of selective serotonin reuptake inhibitors (SSRIs). The largest acute placebo controlled study to-date was performed by Judd and colleagues (2004). In this 3-site, 12-week study, fluoxetine 10–20 mg/daily (N=78) was clinically and statistically more effective than placebo (N=79) in decreasing symptoms of depression on several standardized measures. Williams et al. (2000) demonstrated that, for elderly patients with minor depression, paroxetine treatment improved mental health scores on the 36-item short form of the Medical Outcomes Study more than placebo within the group who were most impaired at baseline.

Currently there is significant public concern about the use of antidepressants to treat depression that is “less than Major Depressive Disorder.” In Europe, natural products like St. John’s Wort (SJW) have been widely accepted as a treatment for less severe forms of Major Depressive Disorder and depressive spectrum disorders. However, recent placebo-controlled studies investigating the efficacy of SJW in Major Depressive Disorder, have been negative or uninformative (Linde et al., 2008). In the Shelton et al. (2001) study comparing and contrasting placebo with SJW, neither treatment group demonstrated significant clinical effect, and SJW was no more effective than placebo. Moreover, when subjects with less severe symptoms (i.e., those with a median Hamilton score of less than 22) were analyzed separately, there was no significant difference in outcome between SJW and placebo. In the Hypericum Depression Trial Study Group’s report (2002), which compared and contrasted St. John’s Wort with sertraline and placebo, neither active treatment separated from placebo. A secondary analysis found that patients with a lower Hamilton scores at baseline had a greater rate of full response, but this finding held for all 3 treatment arms. In contrast, Lecrubier and colleagues (2002) found that SJW was more effective than placebo. However, in a secondary analysis of individuals with mild depression and minor depression baseline Hamilton scores of less than 22), there was no significant difference in outcome between SJW and placebo. In a review of placebo-controlled studies of SJW, Volz and Laux (2000) dichotomized outcome according to initial Hamilton severity scores (<20 or ≥20). SJW was more effective than placebo in this analysis and there was no consistent difference in outcome based on initial depression severity. In an analysis of original data from two double-blind placebo-controlled clinical trials and the acute phase of a long-term study, Kasper et al. (2008) found that SJW was significantly more effective than placebo among subjects with a baseline Hamilton score less than 21. These findings are inconsistent with unpublished analysis of the work of Judd and colleagues (personal communication), which found that the greater reduction in depressive severity scores reported for fluoxetine compared to placebo (Judd et al., 2004) occurred almost exclusively among the more severely ill individuals with Minor Depressive Disorder (those with baseline clinician-rated 30-item Inventory of Depressive Symptomatology scores >24).

The lack of any established treatment for less severe depression prompted us to perform a balanced 3-arm study comparing and contrasting St. John’s Wort, citalopram, and placebo as treatment for subjects with Minor Depressive Disorder. We believed that such a study would accomplish two major goals: (1) make a significant contribution to the limited placebo-

controlled body of data evaluating the efficacy of an SSRI as a treatment for Minor Depressive Disorder; and (2) determine SJW's efficacy in an acute trial as compared with both an established antidepressant approved for the treatment of Major Depressive Disorder (citalopram) and placebo in a carefully diagnosed and characterized study population with a milder form of Depressive Spectrum Disorder. We hypothesized that treatment with either citalopram or St. John's Wort would be more effective than placebo in reducing depressive symptom severity, for subjects with Minor Depressive Disorder. Our secondary postulates were that both active treatments would cause greater improvement in secondary global symptom measures and measures of quality of life and well-being compared to the placebo-treated group.

MATERIALS AND METHODS

Subjects and Assessments

The study was reviewed and approved by the Institutional Review Boards at the Massachusetts General Hospital (Boston, MA), the Cedars-Sinai Medical Center (Los Angeles, CA), and the University of Pittsburgh Medical Center (Pittsburgh, PA). All subjects signed written informed consent. Subjects participated in a 12-week double-blind randomized study comparing St. John's Wort, citalopram, and placebo. Subjects were recruited through clinical referrals and community advertising. Data were obtained at the baseline visit (just prior to randomization) and at post-randomization visits conducted at 2-week intervals for the next 12 weeks, for a modified intent-to-treat sample consisting of all 73 subjects with at least 1 post-randomization visit (evaluable sample).

Minor depression was defined as the presence of two to four symptoms of major depression according to DSM-IV criteria (American Psychiatric Association, 1994), with at least one symptom being depressed mood or anhedonia for at least six months, but not longer than two years. Subjects must not have met criteria for major depression or dysthymia in the last year, but could have had a prior history of major depression [in contrast to the DSM-IV-TR definition (American Psychiatric Association, 2000)] or dysthymia. Subjects with organic mental disorders, substance use disorders (current or within one year of psychotic symptoms or disorders, bipolar disorder, or antisocial personality disorder were excluded). Anxiety disorders were allowed as comorbidity if they were considered secondary to depression or were in remission. Inclusion and exclusion diagnoses were established using the Structured Clinical Interview for DSM-IV (SCID) (First et al., 1996).

Subjects must have met specific entry criteria on the 17-item Hamilton Rating Scale for Depression (HAM-D) (Hamilton, 1960), the Global Assessment of Functioning (GAF) scale (American Psychiatric Association, 1994), and the Medical Outcomes Study 36-item Short-Form scale (MOS) (Ware et al., 1993). These criteria were a HAM-D score between 10 and 17, a GAF score of less than 70, and either an MOS Social Functioning score of 75% or less or an MOS Emotional Role Functioning score of 67% or less. The GAF and MOS screening criteria were identical to a previous study of minor depression (Rapaport et al., 2002; Judd et al., 2004), but the previous study did not employ the HAM-D score criteria.

Depressive symptoms and illness severity were assessed using the HAM-D, the 30-item Inventory of Depressive Symptomatology-Self Report (IDS-SR) and Clinician Rated (IDS-C) scales (Rush et al., 1996; Rush et al., 2000; Trivedi et al., 2004), the Clinical Global Impressions Severity Scale (CGI) (Guy, 1976), and the Global Assessment of Functioning (GAF) scale (American Psychological Association, 1994).

Psychosocial and health functioning were assessed using the MOS (Ware et al., 1993). Psychological Well-Being (PWB) was assessed by the 84-item version of the PWB scale

(containing 14 items for each of 6 scales) (Ryff, 1989; Ryff & Singer, 1996; Singer, 2006). For this analysis, PWB scores were created based on the 9-item version of each scale, so that raw scores could be standardized around gender-specific norms obtained from the Wisconsin Longitudinal Study (Sewell et al., 2002; see details in footnote to Table 3).

Quality of life was assessed using the short form of the Quality of Life, Enjoyment and Satisfaction Questionnaire (Q-LES-Q) that has been used to measure quality of life in psychiatric and non-psychiatric populations (Endicott et al., 1993; Schechter et al., 2007). Each item is self-rated on a 5-point scale (from 1= 'very poor' to 5= 'very good') indicating how satisfied the individual has been over the past week with 14 specific aspects of his or her life. A separate item assesses medication satisfaction, and an overall summary item measures overall life satisfaction.

Subjects were evaluated at every study visit with the HAM-D, IDS-C, IDS-SR, GAF, CGI Severity, and Q-LES-Q. The MOS and WBS were administered only at baseline and the final visit within the 12-week study. An adaptation of the SCID Mood Module was administered at all post-randomization visits, to evaluate possible progression to MDD status and to continue monitoring subjects' level of suicidal risk. The Patient-Rated Inventory of Side Effects (PRISE; see form in Appendix) (Rush et al., 2004) was administered at baseline and all subsequent visits. This is a well validated structured interview for obtaining information not only about the presence or absence of 32 specific adverse events (and the opportunity to write in "others"), but whether those were present at a tolerable or distressing level or constituted a serious adverse event. Vital signs and medication compliance were also assessed at each visit during treatment.

Randomization and Treatment

Prior to the start of the study, randomization lists were generated by the Pittsburgh site's Data Coordinating Center and given to each site's pharmacy. In order to equalize past depression history across the 3 treatment groups, randomization was performed within strata defined by presence or absence of a history of MDD and/or dysthymia. Within each stratum, patients were randomly assigned to one of the 3 treatment arms within blocks of 6 subjects (2 per treatment). Pharmacy staff at each site assigned qualifying patients sequentially to the next open slot on the appropriate randomization list. Standard and consistent procedures for allocation concealment were followed at the three participating sites, to ensure that all project staff and patients remained blind to patients' actual treatment assignment throughout the trial.

Based on their randomized treatment assignment, subjects received either 810 mg/day of St. John's Wort, 20 mg/day of citalopram, or double-dummy (look-alike) placebo. The St. John's Wort was supplied by Cederroth International and contained the aerial portions of the plant that was extracted, dried, and compounded according to the Swedish authority's guidelines. All batches were evaluated for quality control, composition, purity, and rate of decomposition over time. Batches of St. John's Wort were replaced every 12 months. The dosage of St. John's Wort was 270 mg/tablet. Three tablets or 810 mg/day was selected as a reasonable therapeutic target dose based on review of the literature and the existing Cederroth clinical data base. The choice of 20 mg/day of citalopram was based on the results of the Judd, et al. (2004) study with low dose fluoxetine.

Statistical Analysis

Descriptive statistics were run for key demographic and clinical characteristics of the overall sample of 73 evaluable subjects. Differences in baseline characteristics between study completers and early terminators were evaluated by means of t-tests, Chi-Square, or Fisher's

Exact Test. The significance of baseline differences across treatment groups was determined by means of analysis of variance or Chi-Square. All statistical analysis was carried out using SAS 8.2 software (SAS Institute, 2001). An alpha level of 0.05 was used to determine statistical significance.

Mixed model repeated measures (MMRM) analysis was carried out to evaluate treatment group differences in the overall rate of change (improvement) since baseline for all outcome measures (IDS-C, IDS-SR, HAM-D, CGI-S, and Q-LES-Q total scores, 8 MOS scales, and 6 WBS scales). In a preliminary step, it was determined that an auto-regressive within-subject covariance structure provided the best fit to the data for all measures. In further preliminary analysis, it was found that group means for the 3 treatment groups improved in an approximately linear fashion over the first 5 post-randomization visits for outcome measures assessed at every visit (IDS-C, IDS-SR, HAM-D, CGI-S, and Q-LES-Q), while mean scores on these measures leveled off or worsened slightly at the 6th and final acute visit. This is not uncommon, as subjects anticipate the conclusion of a treatment trial. (In this case, subjects knew that the acute phase of the study would be followed up with randomized cross-over treatment for acute phase non-responders.) In such cases, it is appropriate to perform the MMRM analysis on outcome measures during the period of linear improvement -- i.e., from baseline to the next-to-final visit. In the present study, MMRM analysis was carried out based on change in 5 outcome measures from baseline (change = zero) to the 5th post-randomization visit (treatment week 10). Although this was not the original analysis plan submitted in the application, we made this adjustment in order to minimize any complications that discontinuation effects might have on our findings. Since the MOS and WBS were only administered at baseline and subjects' final visit, the MMRM analyses for subscales of those instruments were performed on change over the entire 12-week trial, unless a subject terminated early in which case change was analyzed to an earlier final visit. For all outcome measures, a full-model MMRM was performed testing the significance of fixed effects of treatment, visit, and the treatment-by-visit interaction, as well as the covariates of site, baseline score, and the interaction of baseline score with visit (which was significant for all except 2 WBS subscales). An overall F-test for the significance of differences across treatment groups is presented in this report (Table 3), in addition to the least-square mean (and se) of change from baseline to treatment week 10 or 12 for each treatment group. The standardized effect size (Cohen *d*) (Cohen, 1988) for each pair of treatment groups was computed by dividing the difference between the week 10 or 12 least-square mean change for the 2 treatment groups by their pooled sd, computed from se's of the least-square means.

RESULTS

Figure 1 illustrates the fate of subjects who signed consent to participate in the study. Of 169 subjects screened, 100 met the rigorous inclusion criteria for the study. Nineteen subjects discontinued prior to randomization; the most common reason for electing to discontinue at this point was a concern that the time commitment required by the study was too great. Initially 29 subjects were randomized to St. Johns' Wort, 27 subjects to citalopram and 25 subjects were randomized to placebo. Reasons for discontinuation after randomization are given in Figure 1 and show no evidence of differential rates of attrition. It should be noted that four subjects in the citalopram-treated group discontinued due to side effects versus two in the placebo-treated cohort and one in the St. John's Wort cohort. Study completers (N=59) were similar to early terminators (N=14) in terms of background characteristics and baseline severity (Table 1 in the Appendix). Table 1 presents the demographic data, psychiatric history, and the baseline depression rating scores for the overall sample of 73 evaluable subjects. Aside from the group randomized to St. John's Wort being younger, the three treatment groups were virtually identical in terms of demographic and clinical

characteristics (Table 2 in the Appendix), as well as measures of symptom severity, quality of life or psychological well-being (Table 2). The group randomized to St. John's Wort had slightly lower CGI-Severity scores and slightly lower Q-LES-Q scores than the other two groups of subjects. Subjects in the placebo group had lower SF-36 Vitality scores at baseline. (When one considers the number of variables evaluated in this study such findings are not surprising and should not be over-interpreted.)

MMRM results summarized in Table 3 indicate that the 3 treatment conditions in this study were equally effective in decreasing the symptoms of minor depression, improving quality of life and improving psychological well-being. Mixed model repeated measures analysis of the primary outcome measure for this study, reduction in clinician-rated IDS-C₃₀ scores, showed only slightly greater mean improvement by week 10 for citalopram than placebo, and slightly less mean improvement for St. John's Wort than placebo (treatment-by-time interaction $P=0.771$). By the conventional measure of treatment response, $\geq 50\%$ reduction in the primary efficacy measure, the placebo group had a higher rate of response on IDS-C₃₀ (52.2%) than either citalopram (41.7%) or St. John's Wort (38.5%).

The lack of differentiation between the putative active treatments and placebo appears to be due to the *consistently large placebo response across all outcome measures*, rather than to the study being under-powered.

At baseline, prior to any type of treatment compound being dispensed, almost 60% of all subjects endorsed one or more symptoms on the PRISE that would be characterized as an adverse event once study compounds were ingested by a subject. The mean number of symptoms endorsed at baseline was 5.7 for subjects randomized to St. John's Wort, 4.7 for subjects randomized to placebo, and 4.0 for subjects randomized to citalopram. Table 4 summarizes information about PRISE symptoms present at baseline or emerging as adverse events during the course of the treatment trial, separated into physical symptoms and items commonly associated with depression. At baseline, prior to any compound being dispensed, 49% of all subjects endorsed one or more physical symptoms on the PRISE. The mean number of physical symptoms endorsed at baseline was 2.3 for subjects randomized to St. John's Wort, 1.5 for subjects randomized to placebo, and 1.8 for subjects randomized to citalopram. The most commonly endorsed physical symptom categories at baseline (see Table 3 of the Appendix) were skin (28%), gastrointestinal (26%), nervous system (24%), genital/urinary (22%), and heart-related symptoms (19%), followed by symptoms of the eyes or ears (11%). Not surprisingly in subjects seeking treatment for depression, 58% of subjects endorsed one or more of the depression-related items on the PRISE at baseline (see Table 3 of the Appendix): fatigue (43%), sleep disturbance (42%), poor concentration (41%), decreased energy (40%), anxiety (36%), general malaise (30%), and problems in sexual functioning (30%).

During the course of this study 84.6% of the St Johns Wort-treated group, 100% of the citalopram-treated group and 91.3% of the placebo-treatment group reported the development of a new adverse event or exacerbation of one present at baseline. The percentage of subjects reporting emergence/worsening of side effects to a subjectively distressing level was 34.6% and 39.1% for the St. John's Wort and placebo groups, respectively, but 60.0% for the citalopram-treated group. The percentage of subjects reporting any emerging or worsening depression-related symptoms was notably higher for subjects taking citalopram (92%) than for those taking St. John's Wort (69%) or placebo (65%) ($P=0.062$), although the mean *number* of depressive symptom adverse events per subject was about the same for citalopram as for placebo (6.1 vs. 6.0) (see Table 4). Although the adverse event profile was generally benign, it is important to note that the percentage of gastrointestinal and sleep problems was substantially higher among subjects

taking either St. John's Wort or citalopram than among the placebo-treated group (Table 5). Rates of these and other categories of problems were similar for subjects treated with citalopram and St. John's Wort, except for the higher rates of adverse events reported for typical SSRI-related items: sexual function (48% vs. 27%), increased perspiration (16% vs. 4%), and fatigue (40% vs. 11%).

DISCUSSION

Data from our study do not support our hypotheses that citalopram and St. John's Wort would statistically differentiate from placebo-treatment on primary or secondary outcome measures for subjects with Minor Depressive Disorder (Table 3). In this study all three treatment groups responded exceedingly well to the structure of being in a clinical trial, as evidenced by clinically meaningful improvements in measures of symptom severity, quality of life, and psychological well-being. Thus, neither of our pharmacological treatment interventions provided additional benefit over placebo treatment. The sample size, although relatively small (N=79), would have had sufficient power to detect a clinically relevant advantage of either active treatment over placebo, such as was found for fluoxetine vs. placebo in the study of minor depression by Judd et al. (2004). In the present study, however, the placebo group consistently demonstrated clinically meaningful improvement on all primary and secondary outcome measures. The degree of benefit in the placebo cohort suggests that subjects with minor depression may be responsive to brief non-pharmacologic treatment approaches.

We employed a validated structured assessment of adverse events beginning at the randomization visit. Surprisingly, approximately 60% of the study sample endorsed symptoms that would have been construed as treatment-emergent adverse effects prior to the ingestion of any study compound. In fact, they reported an overall mean of 4.8 PRISE symptoms per subject at baseline. This suggests that it is important to identify systematically, at baseline, the presence and severity of symptoms that otherwise might be misconstrued as treatment-emergent adverse events during the course of a study. Thus, employing a systematic approach to the assessment of adverse events with a validated instrument like the PRISE, yields much more complete and informative data about both baseline levels of events and the emergence or worsening of events during the course of treatment. A second important finding is that all three groups of subjects reported a high rate of adverse events during the study. However, fewer than 40% of the St. John's Wort and placebo-treated groups reported that any of these adverse effects were distressing as compared to 60% of subjects in the citalopram-treated group. This higher overall rate of adverse events during treatment with citalopram compared to St. John's Wort, along with higher rates for emerging/worsening problems with increased perspiration, sexual dysfunction, and fatigue, would be likely to be statistically significant in larger study samples. Although the absolute number of adverse events during treatment was not significantly different for the St. John's Wort and placebo-treated groups, the St. John's Wort group, like the citalopram group, did endorse significantly more gastrointestinal adverse events than the group receiving placebo, and substantially (although not significantly) more sleep problems. This serves as an important reminder that "natural" products should not be assumed to be benign.

There may be several explanations for the fact that neither active treatment separated from placebo on efficacy outcomes in this study. One possible factor was that we used very stringent inclusion and exclusion criteria for subjects with Minor Depressive Disorder. Individuals could not meet a primary diagnosis for any other psychiatric condition, and although they could have a past history of Major Depressive Disorder, they needed to have a sustained period of remission prior to developing Minor Depressive Disorder. In addition,

based on guidance from the Initial Review Group, we limited the range of depressive severity for subjects on the 17-item Hamilton Depression Rating Scale to those with scores from 10 to 17 (inclusive) over the past week. The stringent criteria for this study may have yielded a sample of subjects whose depression was too mild to show added benefit for either active treatment, beyond the general therapeutic effects of study participation evident in the placebo-treated group, let alone differentiation between the two putative active treatments. As previously mentioned, the secondary analysis performed in the Lecrubier et al. study (2002), and an unpublished analysis of the study by Judd, et al. (personal communication), suggested that the active treatments had greater separation from placebo only in the most severely ill groups of individuals with MinD. In a secondary analysis of our sample, we did not find that subjects with greater severity ratings were more responsive to active treatment or less responsive to placebo). Another feature that may have confounded our findings is our overall study design: This design biases recruitment to attract subjects willing to commit to a longer-term treatment trial, and by virtue of the crossover, may create an expectancy favoring treatment response. Thus, one cannot know whether the study design, which included 12 weeks of acute treatment plus 12 weeks of continuation or cross-over treatment, could have contributed to the high placebo effect.

Another challenge faced by this study was the common use of St. John's Wort and SSRI's for the treatment of mild Major Depressive Disorder and depressive spectrum disorders in the community. Potential subjects may have been less motivated to enter an active comparator, placebo-controlled study of St. John's Wort. An additional factor that may have influenced recruitment was the evolution of subject compensation policies that emerged over the course of this study. When this study was conceptualized, subjects were not commonly remunerated for participation, and so this was not budgeted for in our application. By the time this study was initiated, sites in our communities were advertising and paying subjects several thousand dollars to participate in such longer-term trials. We believe this affected our recruitment of subjects into the study and may have subtly influenced the characteristics and treatment expectations in this trial. (The original plan was to recruit 300 patients -- 100 to each treatment arm.) A fourth issue that might account for the lack of separation of St. John's Wort and citalopram from placebo was a higher than previously observed placebo-response. Although this placebo response rate is not different from that reported in recent trials of Major Depressive Disorder, it is higher than the range of placebo response rates identified in the studies reviewed by Volz and Laux (2000) for subthreshold and mild depression. Original power analyses for this study were based on findings from the Judd et al. study (2004) of nearly twice as large a mean change in IDS-C₃₀ scores for MinD subjects treated with fluoxetine vs. placebo over 12 weeks [mean=7.6 (9.6) vs. 3.9 (9.0); N=77 in each group], with a standardized treatment effect size of 0.4 (P=0.012). As was noted earlier, the benefit of fluoxetine was almost exclusively in the most severely ill group, who were omitted from the present study. The 1-point difference in mean change in IDS-C₃₀ scores found between citalopram and placebo in the present study is consistent with many more recent publications that suggest there is a more modest separation between active antidepressant treatments and placebo for subjects with MDD than previously documented (Khan et al., 2002; Zimmerman et al., 2002; Kirsch et al., 2008; Turner et al., 2008; Moreno et al., 2009; Fournier et al., 2010). These articles proposed that study-related and patient-related factors, similar to those identified above, may affect treatment response. Our findings are also consistent with a recent review and meta-analysis of the few available placebo controlled trials for Minor Depressive Disorder (Barbui et al., 2011), which concluded that antidepressant treatment fails to show a clinically meaningful advantage over placebo treatment for this disorder. It is also worth noting that a secondary investigation on the Hypericum Depression Trial Study (Vitiello et al. 2005), which compared hypericum versus sertraline for MDD, found that 17% of hypericum patients had no measurable hyperforin, and 17% of placebo patients had measurable serum hyperforin, suggesting that many

patients were noncompliant and others were obtaining hypericum over the counter. We did not include metabolite measurements in our study, and so we cannot rule out the possibility that subject adherence problems may have contributed to the response patterns we observed.

The current NICE Guideline on the Treatment and Management of Depression in Adults (National Institute for Health and Clinical Excellence, 2010) recommends that antidepressant therapy is not a first-line treatment for mild depression or subthreshold depressive symptoms, specifically because of concerns about risk-to-benefit ratio. For people with mild to moderate depression or persistent subthreshold depressive symptoms, the NICE guidelines recommend low-intensity psychosocial interventions. Antidepressant treatment should be reserved for people with persistent symptoms (particularly if unresponsive to other interventions), suicidal risk, or a past history of moderate or severe depression. This recommendation is consistent with the Canadian Network for Mood and Anxiety Treatments guidelines as well (Parikh et al., 2009). As summarized in the recent meta-analysis by Barbui et al. (2011), no specific pharmacologic treatment has been demonstrated to be effective for MinD to-date. However, the best non-pharmacologic treatment for Minor Depressive Disorder is also an area that requires extensive investigation. Minor Depressive Disorder may represent a variant of a depressive spectrum subtype that might be particularly responsive to a brief, focused psychotherapeutic intervention based either on a cognitive behavioral or an interpersonal therapy model (Szigethy et al., 2007; Allart-van Dam et al., 2007; Cuijpers et al., 2005; Maina et al., 2005). We believe that this would be an important area of further research.

In conclusion, this study suggests that neither St. John's Wort nor citalopram treatment has a clinically or statistically significant benefit for acute treatment of Minor Depressive Disorder when compared to placebo treatment. These findings were clearly due to a consistently high placebo response rate on all outcome measures. Our results suggest that more extensive investigation of Depressive Spectrum Disorders, their natural course, and most effective treatment modalities, is warranted.

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APPENDIX

Appendix, Table 1

Characteristics of Study Completers vs. Early Terminators 12-Week Study of St. John's Wort vs. Citalopram vs. Placebo for Treatment of Minor Depression

Characteristic			Study Completers (N = 59)	Early Terminators (N = 14) ^a	Significance ^b
DEMOGRAPHICS					
Study Site	N (%)	Massachusetts General Hosp.	22 (37.3)	5 (35.7)	$\chi^2=0.736$; df=2; P=0.692
	N (%)	Pittsburgh	11 (18.6)	4 (28.6)	
	N (%)	Cedars Sinai Medical Center	26 (44.1)	5 (35.7)	
Age ^c	Mean (sd)		47.8 (14.6)	49.5 (17.0)	t=0.37; df=71; P=0.712
Gender	N (%)	Female	30 (50.8)	7 (50.0)	FET P=1.000
Race	N (%)	Caucasian	51 (86.4)	12 (85.7)	FET P=1.000
Ethnicity ^d	N (%)	Hispanic/Latino	2 (3.4)	1 (7.1)	FET P=0.483
Education	N (%)	At Least Some College	59 (100.0)	14 (100.0)	--
Marital Status	N (%)	Married/Living Together	21 (36.2)	5 (38.5)	$\chi^2=0.037$; df=2; P=0.982

Characteristic			Study Completers (N = 59)	Early Terminators (N = 14) ^a	Significance ^b
Employment	N (%)	Separated/Divorced/Widowed	10 (17.2)	2 (15.4)	FET P=1.000
	N (%)	Never Married	27 (46.6)	6 (46.1)	
	N (%)	Employed	39 (66.1)	9 (64.3)	
SCID DIAGNOSES					
Depression History	N (%)	MDD	10 (17.0)	4 (28.6)	χ^2 (Yates)=0.489; df=3; P=0.921
	N (%)	MinD/Dysthymia	14 (23.7)	2 (14.3)	
	N (%)	Both MDD & MinD/ Dysthymia	5 (8.5)	2 (14.3)	
Current Co-Morbid Disorders (Non-Primary)	N(%)	Neither (1 st Depressive Episode)	30 (50.8)	6 (42.9)	FET P=0.124
	N (%)	Any Anxiety Disorder	4 (6.8)	3 (21.4)	
	N (%)	Any Eating Disorder	1 (1.7)	0 (0.0)	
Lifetime Co-Morbid Disorders	N (%)	Any Co-morbid Disorder	5 (8.5)	3 (21.4)	FET P=0.175
	N (%)	Any Anxiety Disorder	6 (10.2)	4 (28.6)	FET P=0.091
	N (%)	Any Eating Disorder	1 (1.7)	0 (0.0)	FET P=1.000
	N (%)	Any Substance Use Disorder	12 (20.3)	1 (7.1)	FET P=0.527
	N (%)	Any Co-morbid Disorder	16 (27.1)	5 (35.7)	FET P=0.440
BASELINE DEPRESSION					
IDS-C ₃₀	Mean (sd)		21.7 (5.7)	21.7 (3.9)	t=0.04; df=71; P=0.972
HAM-D ₁₇	Mean (sd)		13.0 (2.4)	13.6 (2.1)	t=0.92; df=71; P=0.359

^aIncludes N=13 subjects who received study medication and had at least one post-randomization visit, but terminated during the 12-week acute treatment phase.

^bSignificance is by t-test, χ^2 , or Fisher's Exact Test (FET) 2-sided.

^cInformation is missing for 1 completer and 1 early terminator.

^dInformation is missing for 1 completer.

Appendix, Table 2

Characteristics of N=73 Evaluable Cases by Randomized Treatment Group 12-Week Study of St. John's Wort vs. Citalopram vs. Placebo for Treatment of Minor Depression

Characteristic	St. John's Wort (N = 26)			Citalopram (N = 24)	Placebo (N = 23)	Significance ^d
DEMOGRAPHICS						
Study Site	N (%)	Massachusetts General Hosp.	9 (34.6)	9 (37.5)	9 (39.1)	χ^2 (Yates)=0.106; df=4; P=0.999
	N (%)	Pittsburgh	6 (23.1)	5 (20.8)	4 (17.4)	
	N (%)	Cedars Sinai Medical Center	11 (42.3)	10 (41.7)	10 (43.5)	
Age ^b	Mean (sd)		42.2 (14.1)	51.3 (12.5)	51.4 (16.6)	F=3.24; df=2; P=0.045
Gender	N (%)	Female	13 (50.0)	13 (54.2)	11 (47.8)	χ^2 =0.196; df=2; P=0.906
Race	N (%)	Caucasian	22 (84.6)	19 (79.2)	22 (95.6)	χ^2 (Yates)=1.521; df=2; P=0.467
Ethnicity ^c	N (%)	Hispanic/Latino	0 (0.0)	2 (8.3)	1 (4.6)	--
Education	N (%)	At Least Some College	26 (100.0)	24 (100.0)	23 (100.0)	--
Marital Status	N (%)	Married/Living Together	8 (32.0)	7 (30.4)	11 (47.8)	
	N (%)	Separated/Divorced/Widowed	4 (16.0)	6 (26.1)	2 (8.7)	χ^2 (Yates)=1.916; df=4; P=0.751
	N (%)	Never Married	13 (52.0)	10 (43.5)	10 (43.5)	
Employment Status	N (%)	Employed	15 (57.7)	17 (70.8)	16 (69.6)	χ^2 =1.17; df=2; P=0.556
SCID DIAGNOSES						
Depression History	N (%)	MDD	8 (30.8)	3 (12.5)	3 (13.0)	
	N (%)	MinD/Dysthymia	7 (26.9)	6 (25.0)	3 (13.0)	
	N (%)	Both MDD & MinD/Dysthymia	2 (7.7)	1 (4.2)	4 (17.4)	χ^2 (Yates)=4.566; df=6; P=0.601
	N (%)	Neither (1 st Depressive Episode)	9 (34.6)	14 (58.3)	13 (56.5)	
Current Co-Morbid Disorders (Non-Primary)	N (%)	Any Anxiety Disorder	2 (7.7)	4 (16.7)	1 (4.4)	--
	N (%)	Any Eating Disorder	0 (0.0)	0 (0.0)	1 (4.4)	--
	N (%)	Any Co-morbid Disorder	2 (7.7)	4 (16.7)	2 (8.7)	--
Lifetime Co-Morbid Disorders	N (%)	Any Anxiety Disorder	3 (11.5)	4 (16.7)	3 (13.0)	--
	N (%)	Any Eating Disorder	0 (0.0)	0 (0.0)	1 (4.4)	--
	N (%)	Any Substance Use Disorder	7 (26.9)	2 (8.3)	4 (17.4)	χ^2 (Yates)=1.863; df=2; P=0.394
	N (%)	Any Co-morbid Disorder	9 (34.6)	6 (25.0)	6 (26.1)	χ^2 (Yates)=0.232; df=2; P=0.890
STUDY COMPLETION	N (%)	Completed 12-Week Study	22 (84.6)	18 (75.0)	19 (82.6)	χ^2 (Yates)=0.277; df=2; P=0.871

Characteristic	N (%)	Terminated before 12 Weeks	St. John's Wort (N = 26)	Citalopram (N = 24)	Placebo (N = 23)	Significance ^a
			4 (15.4)	6 (25.0)	4 (17.4)	

^aSignificance is not computed for categorical variables with 50% or more of expected frequencies less than 5.

^bInformation is missing for 1 subject randomized to St. John's Wort and 1 randomized to Citalopram.

^cInformation is missing for 1 subject randomized to placebo.

Appendix, Table 3

Subjects Endorsing PRISE Items at Baseline Visit for 12-Week Study of St. John's Wort vs. Citalopram vs. Placebo for Treatment of Minor Depression N = 74 Evaluable Subjects (All Treatment Groups Combined)

Type of Adverse Event	Subjects Endorsing Item at Tolerable or Distressing Level at Baseline N (%)	Subjects Endorsing Item at Distressing Level at Baseline N (%)
PHYSICAL SYMPTOMS (ANY)	36 (48.6)	5 (6.8)
Gastrointestinal (Any)	19 (25.7)	0
Diarrhea	9 (12.2)	0
Constipation	2 (2.7)	0
Dry Mouth	15 (20.3)	0
Nausea/Vomiting	2 (2.7)	0
Heart (Any)	14 (18.9)	1 (1.4)
Palpitations	9 (12.2)	1 (1.4)
Dizziness on Standing	8 (10.8)	0
Chest Pain	3 (4.0)	1 (1.4)
Skin (Any)	21 (28.4)	0
Rash	3 (4.0)	0
Increased Perspiration	7 (9.5)	0
Itching	8 (10.8)	0
Dry Skin	13 (17.6)	0
Nervous System (Any)	18 (24.3)	2 (2.7)
Headache	15 (20.3)	1 (1.4)
Tremors	3 (4.0)	0
Poor Coordination	2 (2.7)	0
Dizziness	8 (10.8)	1 (1.4)
Eyes/Ears (Either)	8 (10.8)	2 (2.7)
Blurred Vision	1 (1.4)	0
Ringing in Ears	7 (9.5)	2 (2.7)
Genital/Urinary (Any)	16 (21.6)	0
Difficulty Urinating	1 (1.4)	0
Painful Urination	1 (1.4)	0
Frequent Urination	14 (18.9)	0
Menstrual Irregularity (Females)	5/37 (13.5)	0
Other Physical Symptoms	4 (5.4)	0
DEPRESSIVE SYMPTOMS (ANY)^a	43 (58.1)	11 (14.9)
Sleep (Either)	31 (41.9)	2 (2.7)
Difficulty Sleeping	25 (33.8)	2 (2.7)

Type of Adverse Event	Subjects Endorsing Item at Tolerable or Distressing Level at Baseline N (%)	Subjects Endorsing Item at Distressing Level at Baseline N (%)
Sleeping Too Much	10 (13.5)	0
Sexual Functioning (Any)	22 (29.7)	6 (8.1)
Loss of Sexual Desire	20 (27.0)	6 (8.1)
Trouble Achieving Orgasm	4 (5.4)	1 (1.4)
Trouble with Erections (Males)	3/37 (8.1)	0
Other Depressive Symptoms		
Anxiety	27 (36.5)	6 (8.1)
Poor Concentration	30 (40.6)	4 (5.4)
General Malaise	22 (29.7)	3 (4.0)
Restlessness	15 (20.3)	0
Fatigue	32 (43.2)	2 (2.7)
Decreased Energy	30 (40.5)	1 (1.4)

^aThese common symptoms of depression are included in the PRISE form, but are not a comprehensive set.

Subject ID - - Visit Indicator

Subject Initials Visit Date

M M D D Y Y Y Y

PRISE Adverse Event Visit Checklist
 Ask the patients if they have experienced any problem related to each GENERAL SYMPTOM CATEGORY since their last visit. If so, indicate the specific symptoms present by rating them as tolerable or distressing. Indicate if was an SAE.

Please use a blue or black pen. correct: ● incorrect: ○

Any Adverse Event since last visit? ☐ No (0) Form completed. Please initial at bottom.
☐ Yes (1) Answer next question and fill out chart below.

Were any Adverse Events serious? ☐ No (0) Fill out chart below.
☐ Yes (1) Fill out chart below, plus Serious Adverse Event Form (SAE).

	Not Present (0)	Tolerable (1)	Distressing (2)	Fill in Below If Serious
GASTROINTESTINAL				
Diarrhea	☐	☐	☐	☐
Constipation	☐	☐	☐	☐
Dry Mouth	☐	☐	☐	☐
Nausea/vomiting	☐	☐	☐	☐
HEART				
Palpitations (skipping a beat)	☐	☐	☐	☐
Dizziness on standing	☐	☐	☐	☐
Chest pain	☐	☐	☐	☐
SKIN				
Rash	☐	☐	☐	☐
Increased perspiration	☐	☐	☐	☐
Itching	☐	☐	☐	☐
Dry Skin	☐	☐	☐	☐
NERVOUS SYSTEM				
Headache	☐	☐	☐	☐
Tremors	☐	☐	☐	☐
Poor coordination	☐	☐	☐	☐
Dizziness	☐	☐	☐	☐
EYES / EARS				
Blurred vision	☐	☐	☐	☐
Ringing in ears	☐	☐	☐	☐
GENITAL / URINARY				
Difficulty urinating	☐	☐	☐	☐
Painful urination	☐	☐	☐	☐
Frequent urination	☐	☐	☐	☐
Menstrual irregularity	☐	☐	☐	☐
SLEEP				
Difficulty sleeping	☐	☐	☐	☐
Sleeping too much	☐	☐	☐	☐
SEXUAL FUNCTIONING				
Loss of sexual desire	☐	☐	☐	☐
Trouble achieving orgasm	☐	☐	☐	☐
Trouble with erections	☐	☐	☐	☐
OTHER				
Anxiety	☐	☐	☐	☐
Poor concentration	☐	☐	☐	☐
General malaise	☐	☐	☐	☐
Restlessness	☐	☐	☐	☐
Fatigue	☐	☐	☐	☐
Decreased energy	☐	☐	☐	☐
Other, specify:	☐	☐	☐	☐

Staff Initials

AUTHORS' CONFLICT OF INTEREST STATEMENTS

Mark Hyman Rapaport, MD

Dr. Rapaport has provided consulting services to Affectis Pharmaceuticals, Methylation Sciences, PAX Pharmaceuticals, and Johnson & Johnson Pharmaceuticals. He has served on the Scientific Advisory Boards of NIMH, Brain Cells, Inc., Astellas Pharma, and Pfizer. He served on a DSMB for Quintiles (for an Astra Zeneca protocol). His wife, Jacqueline Calavan, worked for Forest Laboratories until June of 2003. Forest supplied Citalopram for this study at no charge.

Andrew A. Nierenberg, MD

Dr. Nierenberg has served as a consultant to the American Psychiatric Association (only travel expenses were paid) and to Appliance Computing, Inc. Through the MGH Clinical Trials Network and Institute, he has consulted for Brain Cells, Inc.; Dianippon Sumitomo/Sepracor, Novartis, PGx Health, Shire, Schering-Plough, Targacept, and Takeda/Lundbeck Pharmaceuticals. He has received grant/research support through MGH from NIMH, PamLabs, Pfizer Pharmaceuticals, and Shire. He has received honoraria from Belvior Publishing, University of Texas Southwestern Dallas, Hillside Hospital, American Drug Utilization Review, American Society for Clinical Psychopharmacology, Baystate Medical Center, Columbia University, IMEDEx, MJ Consulting, New York State, MBL Publishing, Physicians Postgraduate Press, SUNY Buffalo, University of Wisconsin, and the University of Pisa. Dr. Nierenberg is a presenter for the Massachusetts General Hospital Psychiatry Academy (MGHPA). The education programs conducted by the MGHPA were supported through Independent Medical Education (IME) grants from the following pharmaceutical companies in 2008: Astra Zeneca, Eli Lilly, and Jarssen Pharmaceuticals; in 2009 by Astra Zeneca, Eli Lilly, and Bristol Meyers Squibb. He is on the advisory boards of Appliance Computing, Inc.; Brain Cells, Inc.; Eli Lilly and Company, Takeda/Lundbeck, and Targacept. Dr. Nierenberg owns stock options in Appliance Computing, Inc., and Brain Cells, Inc. Through MGH, he has a patent extension application for the combination of buspirone, bupropion, and melatonin for the treatment of depression.

Robert Howland, MD

Dr. Howland has no conflict of interest.

Christina Dording, MD

Dr. Dording has received Research Support from Abbott Laboratories, Alkermes, Aspect Medical Systems, Astra-Zeneca, Bristol-Myers Squibb Company, Cephalon, Eli Lilly & Company, Forest Pharmaceuticals Inc., GlaxoSmithkline, J & J Pharmaceuticals, Lichtwer Pharma GmbH, Lorex Pharmaceuticals, Novartis, Organon Inc., PamLab, LLC, Pfizer Inc, Pharmavite, Roche, Sanofi-Aventis, Solvay Pharmaceuticals, Inc., Synthelabo, Wyeth-Ayerst Laboratories. Dr Dording has served as an advisor/consultant for Takeda. Dr. Dording has been a speaker for Wyeth-Ayerst Laboratories.

Pamela Schettler, PhD

Dr. Schettler has provided statistical consulting services to the National Institute of Mental Health (NIMH), the Department of Psychiatry at the University of California San Diego (UCSD) School of Medicine, the Department of Psychiatry at the Cedars-Sinai Medical Center, the Depression and Clinical Research Program at the Massachusetts General Hospital, the Department of Psychiatry and Behavioral Science at the University of Texas Medical Branch at Galveston, the Department of Neurology at the Johns Hopkins University School of Medicine, Eli Lilly & Co., BrainCells, Inc., Methylation Sciences, and Novartis BioVentures, Ltd.

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Figure 1.

Patient Flow Chart 12-Week Study of St. John's Wort vs. Citalopram vs. Placebo for Treatment of Minor Depression

a. Reasons for termination after randomization but before returning for any post-randomization visit are as follows: St. John's Wort: 2 due to protocol violations (not taking meds as prescribed) and 1 lost to follow-up; Citalopram: 1 due to adverse events (9 of them, continuing since screening) and 1 withdrew consent; Placebo: 2 lost to follow-up.

b. 1 subject in the citalopram group had information on adverse events but no post-randomization visit data.

c. Reasons for termination during acute treatment phase are as follows:

St. John's Wort: 1 adverse event (became MDD), 1 felt well and decided to stop, 1 had time constraints, 1 lost to follow-up; Citalopram: 4 due to adverse events (1 gastrointestinal, 1 severe agitation, 1 ringing in ears, and 1 fatigue & headaches), 1 due to time constraints associated with new job, and 1 lost to follow-up; Placebo: 2 due to adverse events (1 sexual side effects, and 1 "wiped out" and "fuzzy headed"), 1 due to insufficient clinical response, and 1 "PCP advised against continuing in study."

Table 1

Characteristics of N=73 Evaluable Cases in 12-Week Study of St. John's Wort vs. Citalopram vs. Placebo for Treatment of Minor Depression

DEMOGRAPHICS			
Study Site	N (%)	Massachusetts General Hosp.	27 (37.0)
	N (%)	Pittsburgh	15 (20.5)
	N (%)	Cedars Sinai Medical Center	31 (42.5)
Age	Mean (sd) [Range]		48.1 (15.0) [21–82]
Gender	N (%)	Female	37 (50.7)
Race	N (%)	Caucasian	63 (86.3)
	N (%)	African American	1 (1.4)
	N (%)	American Indian/Alaskan Native	0 (0.0)
	N (%)	Asian	2 (2.7)
	N (%)	Native Hawaiian/Pacific Islander	0 (0.0)
	N (%)	Did Not Provide Information	7 (9.6)
Ethnicity	N (%)	Hispanic/Latino	3 (4.2)
Education	N (%)	At Least Some College	73 (100.0)
Marital Status	N (%)	Married/Living Together	26 (36.6)
	N (%)	Separated/Divorced/Widowed	12 (16.9)
	N (%)	Never Married	33 (46.5)
Employment Status	N (%)	Employed	48 (65.8)
SCID DIAGNOSES			
Depression History	N (%)	MDD	14 (19.2)
	N (%)	MinD/Dysthymia	16 (21.9)
	N (%)	Both MDD & MinD/Dysthymia	7 (9.6)
	N (%)	Neither (1 st Depressive Episode)	36 (49.3)
Current Co-Morbid Disorders (Non-Primary)	N (%)	Any Anxiety Disorder	7 (9.6)
	N (%)	Any Eating Disorder	1 (1.4)
	N (%)	Any Co-morbid Disorder	8 (11.0)
Lifetime Co-Morbid Disorders	N (%)	Any Anxiety Disorder	10 (13.7)
	N (%)	Any Eating Disorder	1 (1.4)
	N (%)	Any Substance Use Disorder	13 (17.8)
	N (%)	Any Co-morbid Disorder	21 (28.8)
DEPRESSION SEVERITY AT BASELINE			
IDS-C ₃₀	Mean (sd) [Range]		21.7 (5.4) [9–36]
HAM-D ₁₇	Mean (sd) [Range]		13.1 (2.3) [8–18]

^aInformation is missing for 2 subjects.

^bInformation is missing for 1 subject.

Baseline Values by Treatment Group for N=73 Evaluable Subjects In 12-Week Study of St. John's Wort vs. Citalopram vs. Placebo for Treatment of Minor Depression

Table 2

Scale	St. John's Wort (N = 26)		Citalopram (N = 24)		Placebo (N = 23)		Significance	
	Mean (sd)		Mean (sd)		Mean (sd)		F	df
Inventory for Depressive Symptomatology Clinician Rated (30-Item Version) (IDS-C ₃₀)	22.2 (6.2)		20.0 (4.8)		22.9 (4.9)		1.84	2, 70
Inventory for Depressive Symptomatology – Self-Rated (30-Item Version) (IDS-SR ₃₀)	24.9 (9.5)		22.0 (7.2)		22.8 (7.8)		0.81	2, 70
Hamilton Depression Rating Scale - 17-Item Version (HAM-D ₁₇)	13.6 (2.4)		12.5 (2.1)		13.3 (2.4)		1.61	2, 70
Clinical Global Impression – Severity of Depression (CGI-S)	2.9 (0.4)		3.1 (0.6)		3.2 (0.4)		2.39	2, 70
Global Assessment of Functioning Scale (GAF)	63.2 (4.6)		62.9 (3.9)		62.3 (4.0)		0.30	2, 70
Quality of Life Enjoyment & Satisfaction (Q-LES-Q) % of Max. Possible, Items 1–14	51.8 (13.0)		56.8 (8.3)		59.8 (13.0)		2.99	2, 70
Medical Outcomes Study - 36-Item Short-Form Health Survey Scale (MOS-SF-36):								
Social Function	58.5 (21.6) ^{N=25}		59.2 (16.9) ^{N=23}		54.9 (21.6)		0.31	2, 68
Emotional Role Function	29.5 (36.9)		26.4 (24.0)		23.2 (29.2)		0.26	2, 70
Physical Role Function	67.3 (35.9)		60.9 (41.2) ^{N=23}		56.8 (40.2) ^{N=22}		0.44	2, 68
Physical Function	79.0 (21.7)		85.4 (17.1)		82.8 (24.5)		0.57	2, 70
Bodily Pain	69.6 (22.6) ^{N=24}		67.1 (19.5)		71.9 (22.6)		0.29	2, 68
Mental Health	53.8 (15.3) ^{N=25}		59.7 (11.1) ^{N=23}		54.4 (14.9)		1.26	2, 68
Vitality	42.7 (18.8) ^{N=24}		42.7 (23.3)		27.6 (15.7)		4.62	2, 68
General Health	60.8 (22.6) ^{N=25}		66.6 (19.0)		64.2 (17.7)		0.52	2, 69
Psychological Well-Being Scale (WBS) Scores (Standardized by Gender):								
Environmental Mastery	-2.41 (1.29)		-1.87 (0.90)		-2.05 (1.07)		1.56	2, 70
Self-Acceptance	-2.13 (1.19)		-1.74 (1.08)		-1.77 (1.27)		0.84	2, 70
Purpose in Life	-1.41 (0.96)		-1.12 (0.98)		-1.17 (1.05)		0.62	2, 70
Positive Relations with Others	-0.94 (1.20)		-1.21 (1.45)		-1.14 (1.60)		0.26	2, 70
Personal Growth	-0.47 (0.67)		-0.53 (0.87)		-0.66 (0.92)		0.32	2, 70
Autonomy	-0.56 (1.57)		-0.32 (1.02)		-0.54 (1.26)		0.26	2, 70

Table 3

Change from Baseline to Week 10 or Week 12^a for N = 73 Evaluable Subjects Based on Mixed Model Repeated Measures Analysis^b

Scale	Least-Square Means (se) of Change			Significance of Treatment-by-Time Interaction			Standardized Effect Size ^d		
	St. John's Wort (N = 26)	Citalopram (N = 24)	Placebo (N = 23)	F	df ^c	P	SJW vs. Placebo	Citalopram vs. Placebo	SJW vs. Citalopram
	LS-Mean (se)	LS-Mean (se)	Mean (se)						
Inventory for Depressive Symptomatology Clinician Rated (30-Item Version) (IDS-C ₃₀)	-9.35 (1.23)	-11.47 (1.36)	-10.49 (1.37)	0.26	2, 264	0.771	+0.178	-0.148	+0.328
Inventory for Depressive Symptomatology - Self-Rated (30-Item Version) (IDS-SR ₃₀)	-9.38 (1.23)	-9.67 (1.35)	-8.87 (1.38)	0.05	2, 278	0.950	-0.079	-0.121	+0.045
Hamilton Depression Rating Scale - 17-Item Version (HAM-D ₁₇)	-5.58 (0.71)	-7.36 (0.79)	-7.09 (0.79)	0.76	2, 259	0.468	+0.408	-0.070	+0.476
Clinical Global Impression - Severity of Depression (CGI-S) ^e	-0.47 (0.15)	-1.10 (0.16)	-0.99 (0.17)	1.58	2, 267	0.209	+0.659	-0.138	+0.814
Global Assessment of Functioning Scale (GAF)	+8.80 (1.38)	+10.47 (1.47)	+10.60 (1.51)	0.18	2, 286	0.834	-0.252	-0.018	-0.235
Quality of Life Enjoyment & Satisfaction (Q-LES-Q) % of Max. Possible, Items 1-14	+7.18 (1.52)	+8.88 (1.68)	+9.02 (1.68)	0.26	2, 269	0.768	-0.233	-0.017	-0.213
Medical Outcomes Study - 36-Item Short-Form Health Survey Scale (MOS-SF-36):									
Social Function	+10.98 (3.35) ^{N=25}	+12.45 (3.47) ^{N=23}	+10.64 (3.42)	0.06	2, 79.5	0.940	+0.020	+0.110	-0.088
Emotional Role Function	+35.00 (6.32)	+27.89 (6.51)	+38.90 (6.55)	0.65	2, 124	0.522	-0.122	-0.348	+0.222
Physical Role Function	+16.08 (4.89)	+20.83 (4.93) ^{N=23}	+2.07 (5.17) ^{N=22}	0.12	2, 83.5	0.884	-0.188	+0.005	-0.195
Physical Function	+5.66 (1.48)	+4.08 (1.55)	+1.89 (1.55)	1.03	2, 86.3	0.361	+0.503	+0.291	+0.209
Bodily Pain	+4.14 (2.82) ^{N=24}	+9.18 (2.83)	+6.45 (2.84)	0.42	2, 86.2	0.658	-0.170	+0.197	-0.364
Mental Health	+5.65 (2.16) ^{N=25}	+9.14 (2.26) ^{N=23}	+8.50 (2.24)	0.51	2, 82.2	0.605	-0.265	+0.059	-0.323
Vitality	+12.23 (3.25) ^{N=24}	+12.72 (3.18)	+10.60 (3.33)	0.05	2, 80	0.949	+0.102	+0.134	-0.031
General Health	+9.68 (2.27) ^{N=25}	+4.42 (2.32)	+10.01 (2.32)	1.16	2, 826	0.318	-0.029	-0.497	+0.463
Psychological Well-Being Scale (WBS) Scores (Standardized by Gender):									

Scale	Least-Square Means (se) of Change				Significance of Treatment-by-Time Interaction			Standardized Effect Size ^d	
	St. John's Wort (N = 26)	Citalopram (N = 24)	Placebo (N = 23)		F	df ^e	P	SJW vs. Placebo	Citalopram vs. Placebo
	LS-Mean (se)	LS-Mean (se)	Mean (se)						SJW vs. Citalopram
Environmental Mastery	+0.58 (0.14)	+0.66 (0.15)	+0.93 (0.15)		0.99	2, 123	0.376	-0.489	-0.371
Self-Acceptance	+0.29 (0.15)	+0.33 (0.16)	+0.71 (0.16)		1.25	2, 123	0.290	-0.548	-0.490
Purpose in Life	+0.27 (0.14)	+0.41 (0.14)	+0.62 (0.15)		0.81	2, 122	0.448	-0.489	-0.299
Positive Relations with Others ^f	+0.40 (0.11)	+0.65 (0.12)	+0.31 (0.12)		1.11	2, 123	0.332	+0.159	+0.584
Personal Growth	+0.41 (0.14)	+0.53 (0.14)	+0.60 (0.14)		0.26	2, 122	0.715	-0.274	-0.103
Autonomy	+0.29 (0.11)	+0.37 (0.12)	+0.28 (0.12)		0.07	2, 123	0.933	+0.018	+0.155

^aIDS-C30, IDS-SR30, HAM-D17, CGI-S, GAF, and Q-LES-Q were administered at Baseline and all 6 visits (at 2-week intervals) during the 12-week study. For these measures, scores tended to improve for all treatment groups in a linear fashion from Baseline to Week 10, then level off or worsen from Week 10 to Week 12 (prior to possible assignment to a different treatment for the second phase of the study). MMRM analyses were performed on change from Baseline to Week 10 for these measures. Since MOS and WBS scales were only assessed at Baseline and Week 12, MMRM analyses were performed on change during this interval.

^b A full-model MMRM was performed testing the significance of effects of treatment, visit, and treatment-by-visit interaction, as well as the covariates of site, baseline score and baseline score-by-visit interaction. (The latter term was significant for all except two WBS subscales.)

^c Degrees of freedom are determined using the Satterthwaite approximation method

^d By Cohen's *d* effect size = (difference between LS-Mean change/pooled sd for each pair of treatments (sd per group computed from se of LS-Mean from MMRM)).

^e St. John's Wort < Citalopram (P=0.005) and < Placebo (P=0.029).

^f Citalopram > Placebo (P=0.046).

Table 4

Summary of PRISE Items^a Endorsed at Baseline and Adverse Events (AEs) Emerging or Worsening during 12-Week Study of St. John's Wort vs. Citalopram vs. Placebo for Treatment of Minor Depression for N=74 Subjects in Safety Sample, by Treatment Group

PRISE Item or Subject Count	St. John's Wort (N=26)	Citalopram (N=25)	Placebo (N=23)	χ^2 and Significance (df=2) ^b
ITEMS ENDORSED AT BASELINE				
Number of Items Endorsed				
Physical Symptoms	Mean (sd) [Range]	1.5 (2.6) [0–12]	1.8 (2.5) [0–9]	Kruskal-Wallis $\chi^2 = 0.678$; P=0.712
Depressive Symptoms	Mean (sd) [Range]	2.3 (3.0) [0–9]	2.9 (2.8) [0–7]	Kruskal-Wallis $\chi^2 = 1.061$; P=0.588
Subjects with Any Item(s) Endorsed				
Physical Symptoms	N (%)	11 (44.0)	12 (52.2)	$\chi^2 = 0.350$; P=0.839
Depressive Symptoms	N (%)	15 (57.7)	13 (56.5)	$\chi^2 = 0.062$; P=0.969
Number of Items at Distressing Level				
Physical Symptoms	Mean (sd) [Range]	0.2 (0.5) [0–2]	0.0 (0.0) [0]	Kruskal-Wallis $\chi^2 = 2.876$; P=0.237
Depressive Symptoms	Mean (sd) [Range]	0.4 (1.1) [0–4]	0.2 (0.9) [0–4]	Kruskal-Wallis $\chi^2 = 1.242$; P=0.538
Subjects with Any Distressing Item(s)				
Physical Symptoms	N (%)	3 (11.5)	0 (0.0)	χ^2 (Yates) = 1.237; P=0.539 ^e
Depressive Symptoms	N (%)	5 (19.2)	2 (8.0)	χ^2 (Yates) = 0.592; P=0.744
AEs EMERGING OR WORSENING DURING TREATMENT				
Number of AEs Emerging or Worsening ^c				
Physical Symptoms	Mean (sd) [Range]	5.0 (4.5) [0–14]	4.7 (4.4) [0–17]	Kruskal-Wallis $\chi^2 = 0.773$; P=0.679
Depressive Symptoms	Mean (sd) [Range]	3.5 (4.0) [0–15]	6.1 (7.1) [0–24]	Kruskal-Wallis $\chi^2 = 1.930$; P=0.381
Subjects with Any AE Emerging/Worsening				
Physical Symptoms	N (%)	22 (84.6)	23 (92.0)	χ^2 (Yates)=0.910; P=0.634
Depressive Symptoms	N (%)	18 (69.2)	23 (92.0)	$\chi^2 = 5.573$; P=0.062
Number of AEs Emerging/Worsening to a Distressing Level ^d				
Physical Symptoms	Mean (sd) [Range]	0.3 (0.6) [0–2]	0.6 (1.1) [0–5]	Kruskal-Wallis $\chi^2 = 2.769$; P=0.250
Depressive Symptoms	Mean (sd) [Range]	0.5 (0.9) [0–4]	1.4 (1.9) [0–7]	Kruskal-Wallis $\chi^2 = 3.537$; P=0.171
Subjects with Any AE Emerging/Worsening to a Distressing Level				
Physical Symptoms	N (%)	5 (19.2)	10 (40.0)	$\chi^2 = 3.261$; P=0.196

PRISE Item or Subject Count	St. John's Wort (N=26)	Citalopram (N=25)	Placebo (N=23)	χ^2 and Significance (df=2) ^b
Depressive Symptoms	N (%) 8 (30.8)	11 (44.0)	5 (21.7)	$\chi^2 = 2.759$; P=0.252

^aPRISE physical symptoms (items 1–21) include gastrointestinal, heart, skin, nervous symptoms, eyes/ears, and genital/urinary, plus “other” (item 33) which were all physical symptoms in this sample. Depressive symptoms (items 22–32) include sleep difficulty, sexual dysfunction, anxiety, poor concentration, general malaise, restlessness, fatigue, and decreased energy.

^bThe distribution of values for number of items/symptoms is highly non-normal, so comparison of treatment groups was by Kruskal-Wallis χ^2 on Wilcoxon Rank Sums (after assigning tied values their mean rank). For number of subjects with a baseline or emerging/worsening category of symptoms, χ^2 was calculated with Yates’ correction if any expected frequency was less than 5.

^c+1 was added to the count for *each* post-baseline visit in which an adverse event rating exceeded its value at baseline (on a scale where 0 = absent; 1 = tolerable; 3 = distressing).

^d+1 was added to the count for *each* post-baseline visit in which an adverse event reached the distressing level, but was either absent or tolerable at baseline.

^e χ^2_{test} may not be valid due to 50% of cells having expected frequency less than 5.

Table 5

Subjects with Emerging or Worsening PRISE Adverse Events during 12-Week Study of St. John's Wort vs. Citalopram vs. Placebo for Treatment of Minor Depression N=74 Subjects in Safety Sample, by Treatment Group

Type of Adverse Event	Emerging or Worsening				Emerging or Worsening to a Distressing Level ^a			
	St. John's Wort (N=26)	Citalopram (N=25)	Placebo (N=23)	Significance (df=2)	St. John's Wort (N=26)	Citalopram (N=25)	Placebo (N=23)	
	N (%)	N (%)	N (%)	χ^2	P	N (%)	N (%)	N (%)
PHYSICAL SYMPTOMS								
Gastrointestinal (Any)	16 (61.5)	15 (60.0)	7 (30.4)	5.86	0.054	2 (7.7)	2 (8.0)	2 (8.7)
Diarrhea	8 (30.8)	8 (32.0)	1 (4.4)	6.55	0.038	1 (3.8)	1 (4.0)	1 (4.4)
Constipation	8 (30.8)	6 (24.0)	3 (13.0)	2.19	0.335	0 (0.0)	0 (0.0)	0 (0.0)
Dry Mouth	6 (23.1)	6 (24.0)	0 (0.0)	6.47	0.039 ^a	0 (0.0)	0 (0.0)	0 (0.0)
Nausea/Vomiting	7 (26.9)	6 (24.0)	4 (17.4)	0.65	0.723	1 (3.8)	1 (4.0)	1 (4.4)
Heart (Any)	8 (30.8)	5 (20.0)	8 (34.8)	1.40	0.496	0 (0.0)	1 (4.0)	2 (8.7)
Palpitations	3 (11.5)	3 (12.0)	4 (17.4)	0.43	0.806 ^a	0 (0.0)	1 (4.0)	0 (0.0)
Dizziness on Standing	4 (15.4)	5 (20.0)	3 (13.0)	0.45	0.800 ^a	0 (0.0)	0 (0.0)	1 (4.4)
Chest Pain	1 (3.8)	1 (4.0)	4 (17.4)	3.86	0.145 ^a	0 (0.0)	0 (0.0)	1 (4.4)
Skin (Any)	5 (19.2)	8 (32.0)	4 (17.4)	1.76	0.414	0 (0.0)	1 (4.0)	0 (0.0)
Rash	2 (7.7)	2 (8.0)	1 (4.4)	0.31	0.857 ^a	0 (0.0)	0 (0.0)	0 (0.0)
Increased Perspiration	1 (3.8)	4 (16.0)	1 (4.4)	3.16	0.206 ^a	0 (0.0)	1 (4.0)	0 (0.0)
Itching	2 (7.7)	1 (4.0)	2 (8.7)	0.47	0.789 ^a	0 (0.0)	0 (0.0)	0 (0.0)
Dry Skin	3 (11.5)	2 (8.0)	1 (4.4)	0.85	0.655 ^a	0 (0.0)	0 (0.0)	0 (0.0)
Nervous System (Any)	11 (42.3)	10 (40.0)	12 (52.2)	0.80	0.669	1 (3.8)	3 (12.0)	1 (4.4)
Headache	6 (23.1)	10 (40.0)	11 (47.8)	3.43	0.180	1 (3.8)	3 (12.0)	0 (0.0)
Tremors	4 (15.4)	4 (16.0)	0 (0.0)	4.05	0.132 ^a	0 (0.0)	1 (4.0)	0 (0.0)
Poor Coordination	3 (11.5)	1 (4.0)	1 (4.4)	1.46	0.483 ^a	0 (0.0)	1 (4.0)	0 (0.0)
Dizziness	4 (15.4)	3 (12.0)	5 (21.7)	0.86	0.652 ^a	0 (0.0)	1 (4.0)	1 (4.4)
Eyes/Ears (Either)	6 (23.1)	7 (28.0)	4 (17.4)	0.76	0.683	1 (3.8)	1 (4.0)	0 (0.0)

Type of Adverse Event	Emerging or Worsening				Emerging or Worsening to a Distressing Level ^a			
	St. John's Wort (N=26)	Citalopram (N=25)	Placebo (N=23)	Significance (df=2)	St. John's Wort (N=26)	Citalopram (N=25)	Placebo (N=23)	
	N (%)	N (%)	N (%)	χ^2	N (%)	N (%)	N (%)	N (%)
Blurred Vision	6 (23.1)	5 (20.0)	4 (17.4)	0.25	0.884	0 (0.0)	0 (0.0)	0 (0.0)
Ringing in Ears	1 (3.8)	3 (12.0)	0 (0.0)	3.56	0.168 ^a	1 (3.8)	1 (4.0)	0 (0.0)
Genital/Urinary (Any)	4 (15.4)	4 (16.0)	4 (17.4)	0.04	0.981	1 (3.8)	1 (4.0)	2 (8.7)
Difficulty Urinating	0 (0.0)	0 (0.0)	0 (0.0)	--	--	0 (0.0)	0 (0.0)	0 (0.0)
Painful Urination	1 (3.8)	0 (0.0)	1 (4.4)	1.06	0.588 ^a	1 (3.8)	0 (0.0)	1 (4.4)
Frequent Urination	3 (11.5)	2 (8.0)	1 (4.4)	0.85	0.655 ^a	0 (0.0)	0 (0.0)	1 (4.4)
Menstrual Irregularity (Females)	0/13 (0.0)	2/13 (15.4)	3/11 (27.3)	3.85	0.146 ^a	0/13 (0.0)	1/13 (7.7)	1/11 (9.1)
Other Physical Symptoms	10 (38.5)	10 (40.0)	6 (26.1)	1.21	0.546	1 (3.8)	3 (12.0)	1 (4.4)
DEPRESSIVE SYMPTOMS								
Sleep (Either)	16 (61.5)	14 (56.0)	8 (34.8)	3.82	0.148	5 (19.2)	6 (24.0)	3 (13.0)
Difficulty Sleeping	13 (50.0)	10 (40.0)	7 (30.4)	1.94	0.379	5 (19.2)	6 (24.0)	2 (8.7)
Sleeping Too Much	5 (19.2)	7 (28.0)	1 (4.4)	4.70	0.095 ^a	0 (0.0)	0 (0.0)	1 (4.4)
Sexual Functioning (Any)	7 (26.9)	12 (48.0)	8 (34.8)	2.48	0.289	1 (3.8)	3 (12.0)	4 (17.4)
Loss of Sexual Desire	4 (15.4)	7 (28.0)	5 (21.7)	1.20	0.550	1 (3.8)	1 (4.0)	3 (13.0)
Trouble Achieving Orgasm	5 (19.2)	8 (32.0)	5 (21.7)	1.25	0.535	1 (3.8)	3 (12.0)	0 (0.0)
Trouble with Erections (Males)	1/13 (7.7)	5/12 (41.7)	2/12 (16.7)	4.51	0.105 ^a	0/13 (0.0)	3/12 (25.0)	1/12 (8.3)
Other Depressive Symptoms								
Anxiety	5 (19.2)	5 (20.0)	9 (39.1)	3.17	0.205	3 (11.5)	2 (8.0)	1 (4.4)
Poor Concentration	7 (26.9)	6 (24.0)	7 (30.4)	0.25	0.882	1 (3.8)	3 (12.0)	2 (8.7)
General Malaise	2 (7.7)	7 (28.0)	5 (21.7)	3.60	0.165 ^a	0 (0.0)	3 (12.0)	2 (8.7)
Restlessness	8 (30.8)	3 (12.0)	6 (26.1)	2.72	0.257	0 (0.0)	0 (0.0)	0 (0.0)
Fatigue	3 (11.5)	10 (40.0)	5 (21.7)	5.73	0.057	1 (3.8)	5 (20.0)	1 (4.4)
Decreased Energy	5 (19.2)	9 (36.0)	5 (21.7)	2.15	0.342	0 (0.0)	4 (16.0)	2 (8.7)

^a χ^2 test not valid due to 50% of cells having expected counts less than 5.