# How Effective Is St. John's Wort? The Evidence Revisited

Ursula Werneke, M.R.C.Psych.; Oded Horn, B.Soc.Sci.(Hons); and David M. Taylor, Ph.D.

***Background:*** St. John's wort (*Hypericum perforatum*) has been identified as an effective treatment for depression in controlled studies and subsequent meta-analyses. However, 3 recently published large studies failed to demonstrate robust efficacy. Updated meta-analysis and assessment of publication bias may help determine the true effect of St. John's wort.

***Method:*** Meta-analysis to reevaluate the effectiveness of St. John's wort as an antidepressant, funnel plot analysis, and meta-regression to assess the impact of publication bias, small-study effects, and variation in trial characteristics were performed. We conducted 2 analyses: a reproduction of a recent meta-analysis including 15 studies (Meta-15) and a meta-analysis extended by the 3 studies published since then (Meta-18). The studies in Meta-15 were identified through MEDLINE and EMBASE searches conducted in June 2000. The search terms used were *St. John's wort, hypericum, hypericin, depression,* and *antidepressant,* and no language restrictions were applied. For both meta-analyses, we compared funnel plots, Begg's rank correlation, Egger's regression, trim and fill method, and meta-regression.

***Results:*** In both analyses, effect sizes in recent studies were smaller than those reported in earlier studies; the addition of more recent studies into the analyses resulted in reduced effect size. In Meta-15, St. John's wort was significantly more effective than placebo with a risk ratio (RR) of 1.97 (CI = 1.54 to 2.53). In Meta-18, the RR was reduced to 1.73 (CI = 1.40 to 2.14). On funnel plot analysis, the Meta-18 plot proved to be much more skewed than the Meta-15 plot. Meta-regression showed that increase in effect size was associated with smaller sample size only. The impact of baseline severity of depression could not be evaluated as the studies used different versions of the Hamilton Rating Scale for Depression.

***Conclusion:*** St. John's wort may be less effective in the treatment of depression than previously assumed and may finally be shown to be ineffective if future trials confirm this trend.

*(J Clin Psychiatry 2004;65:611–617)*

*Received June 8, 2003; accepted Oct. 6, 2003. From the Centre for the Economics in Mental Health, Institute of Psychiatry (Dr. Werneke); the Academic Department of Psychological Medicine, King's College School of Medicine and Dentistry and Institute of Psychiatry (Mr. Horn); and the Pharmacy Department, Maudsley Hospital (Dr. Taylor), London, United Kingdom.*

*Dr. Werneke has received grant/research support from Pfizer and has received honoraria from and participated in speakers/advisory boards for Lilly. Dr. Taylor has received grant/research support from Lilly and Pfizer; has received honoraria from Lilly, Wyeth, and Pfizer; and has participated in speakers/advisory boards for GlaxoSmithKline and Lundbeck. Mr. Horn reports no financial affiliation or other relationship relevant to the subject matter of this article.*

*Corresponding author and reprints: Ursula Werneke, M.R.C.Psych., Homerton Hospital, East Wing, Department of Psychiatry, Homerton Row, London E9 6SR, UK (e-mail: Ursula.Werneke@elcmht.nhs.uk).*

The efficacy of St. John's wort (*Hypericum perforatum*) for the treatment of depression has been widely studied in randomized controlled trials (RCTs). These RCTs have been subject to meta-analyses that conclusively found St. John's wort to be effective. The first meta-analysis was published in 1996 and reported an odds ratio of 2.67 with a 95% confidence interval (CI) from 1.78 to 4.01.[1] Subsequent meta-analyses reported smaller treatment effects with risk ratios (RRs) of 1.9 (CI = 1.2 to 2.8)[2] and 1.98 (CI = 1.49 to 2.62).[3] Since the publication of the latest meta-analysis,[3] 2 more recent and larger studies have been published that failed to demonstrate robust efficacy in depression: the Hypericum Depression Trial Study Group[4] reported an RR of 0.88 (CI = 0.64 to 1.21), and Lecrubier and coworkers[5] achieved an RR of 1.24 (CI = 1.00 to 1.54).

Emerging evidence thus suggests that the effectiveness of St. John's wort may have been overestimated in the past; this may have been due to publication bias. For instance, concerns have been expressed about the number of double publications.[1] In addition, identification of publication bias through visual inspection of funnel plots has been difficult.[3] Therefore, we evaluated currently available evidence with the following goals: (1) to reevaluate the effectiveness of St. John's wort as an antidepressant, (2) to assess the impact of publication bias, and (3) to explore any other factors such as heterogeneity, small-study effects (i.e., the tendency of smaller studies in a meta-analysis to show larger treatment effects) as complementary explanations to publication bias,[6] and the effect of variability in the clinical characteristics of the included trials.

## METHOD

### Selection of Studies

We conducted and compared 2 meta-analyses: (1) a reproduction of the meta-analysis by Whiskey et al.[3] including 15 studies (Meta-15) and (2) the same analysis extended by 3 studies[4,5,7] published since then (Meta-18) (see Table 2). MEDLINE and EMBASE searches for the studies in Meta-15 were conducted in June 2000; the additional studies in Meta-18 were identified in September 2003 using the same search strategy. No language restriction was applied. Trials published from 1979 to 2003 involving use of St. John's wort in the treatment of depression were identified. Search terms used were *St. John's wort, hypericum, hypericin, depression,* and *antidepressant*. All reference sections from retrieved articles were scrutinized for further relevant publications. U.W. and O.H. abstracted the identified papers using a standardized template. The quality of the trials was assessed by checking random allocation, blinding, description of dropouts and withdrawals, and availability of data for intention-to-treat analysis. We then included trials that used the Hamilton Rating Scale for Depression (HAM-D), 17- or 21-item version, for the diagnosis of depression and that used a uniform criterion of treatment success, i.e., 50% reduction of baseline HAM-D score. Trials in which St. John's wort was used in combination with other herbal preparations and those that targeted other psychiatric conditions were excluded. We also excluded trials that did not meet the outlined criteria (Table 1).

**Table 1. Trials Excluded From the Meta-Analyses of St. John's Wort Studies**

| Study | Reason for Exclusion |
|---|---|
| Fava et al, 2002[8] | Reduction of HAM-D score to 8 or less was used as the outcome criterion. This exceeds a 50% reduction in score on either HAM-D version, and thus the trial cannot be compared with the others |
| Volz et al, 2000[9] | The trial excluded placebo responders after a single-blind run-in phase and thus was likely to overestimate treatment effects systematically, as exclusion of placebo responders would have favored the St John's wort group |
| Montgomery et al, 2000[10] | Two centers with very high placebo results were removed from the analysis after termination of the study, thereby violating the intention-to-treat criteria |
| Kaufeler et al, 2001[11] | This report summarizes a trial[12] included in the meta-analyses |

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

### Statistical Analysis

Both analyses were based on relative risks, and fixed and random effect size models were calculated after testing homogeneity using a p value of ≤ .05. We then conducted a funnel plot analysis for both trial sets and compared the statistics on the hypothesis that publication bias, i.e., the omission of negative studies, and small-study effects, i.e., the preference for studies reporting large effect sizes due to limited power, should be less in the second meta-analysis including more studies. The following statistical procedures were used:

- Funnel plot; plotting the relative risk on the horizontal axis against the sample size on the vertical axis. If there were no biases, the plot would be symmetrical, assuming the shape of an inverted funnel. However, if such effects played a role, the plot could be expected to be asymmetrical.[6]
- Begg's rank-correlation method using Kendall's tau correlating the standardized treatment effect against the variance that is a measure of the sample size.[13]
- Egger's regression method, a linear regression of the standard normal deviate (effect size divided by precision) and precision.[14] This approach assumes that when there is no publication bias or small-study effects, the y intercept will have an expected value of 0, and the slope will be an estimate of the true treatment effect. However, if there were biases, the regression line would not pass through 0, and the size of the intercept could be taken as a measure of the size of the bias.[14]
- Trim and fill, a method starting with a visual inspection of the funnel plot. The number of asymmetric studies that are on the right (effective) side of the funnel plot and have no left (ineffective) counterpart is estimated. These trials are then removed, or "trimmed," from the funnel, leaving a symmetric remainder from which the true center of the funnel is estimated by standard meta-analysis procedures. The trimmed trials are then replaced and their missing counterparts are imputed or "filled," and the "true" treatment effect is recalculated.[15]
- Meta-regression, a regression model assessing the impact of trial characteristics on the treatment effect. This method is particularly useful for examining alternative explanations to publication bias for heterogeneous effect sizes.[16]

All statistics were calculated using STATA Version 7 (STATA Statistical Software, College Station, Tex.).

## RESULTS

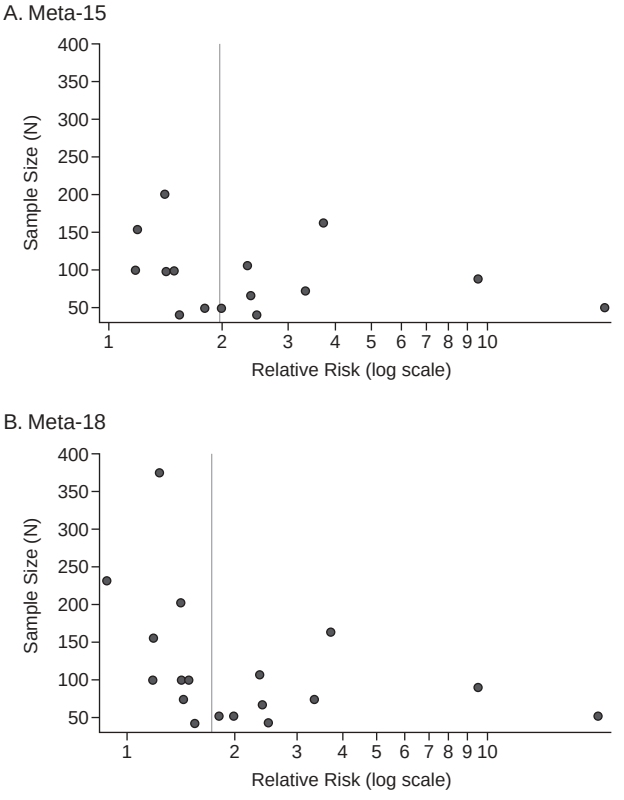
In Meta-15, 7 studies produced nonsignificant results. This number increased to 10 studies in Meta-18 (Table 2).

**Table 2. Studies of St. John's Wort Versus Placebo**

| Study | RR | 95% CI |
|---|---|---|
| Schmidt et al, 1989[17] | 2.50 | 0.94 to 6.66 |
| Halama, 1991[18] | 21.00 | 1.30 to 340.02 |
| Reh et al, 1992[19] | 1.82 | 1.12 to 2.95 |
| Lehrl et al, 1993[20] | 2.00 | 0.40 to 9.95 |
| Quandt et al, 1993[21] | 9.67 | 3.18 to 29.41 |
| Schmidt and Sommer, 1993[22] | 2.41 | 1.31 to 4.43 |
| Hänsgen et al, 1994[23] | 3.35 | 1.85 to 6.08 |
| Hübner et al, 1994[24] | 1.56 | 0.89 to 2.73 |
| Sommer and Harrer, 1994[25] | 2.37 | 1.39 to 4.04 |
| Witte et al, 1995[26] | 1.43 | 1.03 to 1.98 |
| Laakmann et al, 1998[27] | 1.50 | 0.92 to 2.46 |
| Laakmann et al, 1998[27a] | 1.19 | 0.70 to 2.03 |
| Schrader et al, 1998[12] | 3.75 | 2.15 to 6.55 |
| Philipp et al, 1999[28] | 1.20 | 0.94 to 1.52 |
| Shelton et al, 2001[29] | 1.42 | 0.84 to 2.40 |
| Kalb et al, 2001[7] | 1.45 | 0.92 to 2.29 |
| Hypericum Depression Trial Study Group, 2002[4] | 0.88 | 0.64 to 1.21 |
| Lecrubier et al, 2002[5] | 1.24 | 1.00 to 1.54 |

[a]Lower hyperforin content.
Abbreviation: RR = risk ratio.

**Figure 1. Funnel Plots for 2 Meta-Analyses of St. John's Wort Studies**




Both meta-analyses were shown to be heterogeneous, so only random effect size estimates are presented. In Meta-15, St. John's wort proved significantly more effective than placebo with an RR of 1.97 (CI = 1.54 to 2.53). The effect size was reduced in Meta-18 to an RR of 1.73 (CI = 1.40 to 2.14).

On visual inspection of funnel plots, the Meta-18 plot proved to be much more skewed than the Meta-15 plot (Figures 1A and 1B), and this was statistically confirmed using Begg's rank correlation, Egger's regression, and the trim and fill method (Table 3).

However, as the statistics cannot distinguish between publication bias, other small-study effects, and trial characteristics, we conducted a meta-regression. In a first step, we listed all possible variables for inclusion in the regression models. HAM-D baseline score was not included because the HAM-D versions used varied between studies, if information on the version was available at all. Placebo response was also rejected, as it was a covariate to the outcome. Sample size measured as SE of log RR, dose ($\geq 900$ or $< 900$ mg), and language of publication were included (Table 4).

In the resulting models (Table 5), ratios of RRs below 1 reflect a smaller treatment effect of St. John's wort. Both models, Meta-15 and Meta-18, showed similar results. On univariate analysis, decrease in sample size (expressed as unit increase in SE of log RR) was associated with increase in effect size in both meta-analyses. Additionally, in Meta-18, publication in English was associated with decreased effect size. On multivariate regression, language of publication became insignificant. The impact of effect size weakened, although it remained highly significant.

As more recent studies produced a reduction in effect size (Table 1), we conducted a stepwise meta-analysis

**Table 3. Funnel Plot Statistics for 2 Meta-Analyses of St. John's Wort Studies**

| Statistical Test | Meta-15 | Meta-18 |
|---|---|---|
| Begg's rank correlation, Kendall's score (SD) | 49 (20.2)* | 85 (26.4)** |
| Egger's regression, bias (SD) | 2.59 (0.70)** | 2.68 (0.65)** |
| Trim and fill | | |
| No. of studies added | 1 | 8 |
| New risk ratio (CI) | 1.94 (1.51 to 2.50) | 1.30 (1.03 to 1.64) |

*p < .05.
**p < .005.

adding one study at a time, ordered by year of publication. We estimated the pooled random effects at each step. The cumulative, i.e., successive stepwise estimated, RRs showed that the effectiveness of St. John's wort decreased over time with the number of studies entered into the meta-analysis (Table 6). This effect was demonstrable at each step.

## DISCUSSION

Our meta-analyses show that St. John's wort may be less effective in the treatment of depression than previously assumed. In our cumulative analysis, we also identi-

**Table 4. Characteristics of St. John's Wort Studies**

| Study | Mean Total HAM-D Score | HAM-D Version | Dose (mg) | SE (log RR) | Language | Placebo Reponse (%) |
|---|---|---|---|---|---|---|
| Schmidt et al, 1989[17] | ≥ 20 | ? | < 900 | 0.50 | German | 20.0 |
| Halama, 1991[18] | < 20 | ? | ≥ 900 | 1.42 | German | 0.0 |
| Reh et al, 1992[19] | < 20 | ? | < 900 | 0.25 | German | 44.0 |
| Lehrl et al, 1993[20] | ≥ 20 | ? | ≥ 900 | 0.82 | German | 8.0 |
| Quandt et al, 1993[21] | < 20 | 21 | < 900 | 0.57 | German | 7.1 |
| Schmidt and Sommer, 1993[22] | < 20 | ? | ≥ 900 | 0.31 | German | 27.3 |
| Hänsgen et al, 1994[23] | ≥ 20 | ? | ≥ 900 | 0.30 | German | 23.7 |
| Hübner et al, 1994[24] | < 20 | ? | ≥ 900 | 0.29 | German | 45.0 |
| Sommer and Harrer, 1994[25] | < 20 | ? | ≥ 900 | 0.27 | English | 23.6 |
| Witte et al, 1995[26] | ≥ 20 | ? | < 900[a] | 0.17 | German | 51.0 |
| Laakmann et al, 1998[27] | ≥ 20 | 17 | ≥ 900 | 0.25 | English | 32.7 |
| Laakmann et al, 1998[27] | ≥ 20 | 17 | < 900[a] | 0.27 | English | 32.7 |
| Schrader et al, 1998[12] | < 20 | 21 | < 900 | 0.28 | English | 14.8 |
| Philipp et al, 1999[28] | ≥ 20 | 17 | ≥ 900 | 0.12 | English | 63.8 |
| Shelton et al, 2001[29] | ≥ 20 | 17 | ≥ 900 | 0.27 | English | 18.6 |
| Kalb et al, 2001[7] | < 20 | 17 | < 900 | 0.23 | English | 42.9 |
| Hypericum Depression Trial Study Group, 2002[4] | ≥ 20 | 17 | ≥ 900 | 0.16 | English | 50.0 |
| Lecrubier et al, 2002[5] | ≥ 20 | 17 | ≥ 900 | 0.11 | English | 42.0 |

[a]Contains only 0.5% hyperforin.
Abbreviations: HAM-D = Hamilton Rating Scale for Depression, RR = risk ratio. Symbol: ? = not reported.

**Table 5. Meta-Regression of St. John's Wort Studies**

| | Univariate Analysis | | Controlling for All Variables | |
|---|---|---|---|---|
| Study Characteristic | Ratio of RRs (95% CI) | p | Ratio of RRs (95% CI) | p |
| Sample size, unit increase in SE of log RR | | | | |
| Meta-15 | 11.89 (3.43 to 41.13) | < .001 | 8.77 (2.11 to 36.43) | < .01 |
| Meta-18 | 13.98 (4.27 to 45.71) | < .001 | 8.98 (2.36 to 34.11) | < .005 |
| Dose, < 900 vs ≥ 900 mg | | | | |
| Meta-15 | 0.86 (0.51 to 1.44) | NS | 0.93 (0.64 to 1.34) | NS |
| Meta-18 | 0.79 (0.50 to 1.26) | NS | 0.92 (0.67 to 1.26) | < .05 |
| Language, German vs English | | | | |
| Meta-15 | 0.69 (0.43 to 1.11) | NS | 0.85 (0.58 to 1.25) | NS |
| Meta-18 | 0.61 (0.41 to 1.90) | < .01 | 0.80 (0.57 to 1.13) | NS |

Abbreviations: NS = not significant, RR = risk ratio.

fied a trend toward a decrease in effect size as the number of studies available over time increased. In addition, we were able to highlight the importance of exploring individual study characteristics beyond standard statistical testing to gain insight into the full scope of factors that affect heterogeneity of effect sizes.

Our findings were more suggestive of variability in the clinical trial characteristics and small-study effects rather than publication bias, although the latter two are related. We initially assumed that such effects would become less important as the number of studies included in the meta-analysis increased. However, we found that these effects were not identifiable in Meta-15 and only became obvious when 3 further studies were added in Meta-18; this suggests that meta-analyses relying on small studies not only may overestimate effect size but also are not sufficiently powerful to detect publication bias, small-study effects, and effects of trial characteristics.

In our meta-regression, both univariate and multivariate analyses showed that sample size was the only statistically significant factor; dose and language of publication were not relevant. Language of publication was significant in Meta-18, but this was lost when we controlled for the other 2 variables. Ideally, we would have included severity of depression as a factor in our regression models because baseline severity is likely to have an impact on treatment impact. However, this was not possible as the studies did not offer a consistent definition of mild, moderate, and severe depression, and several studies did not indicate which version of the HAM-D was used. Future trials should apply much stricter baseline criteria minimizing overlap between categories of depression. Also, the RCTs did not mention how standardized use of the HAM-D was ensured.

We also looked at the discrepancy between the response to St. John's wort and placebo, since both could be expected to follow the same trend. We found that in 6 trials, the placebo response was below 20%.[11,17,19,20,26,27] Only in the Lehrl et al.[20] and Shelton et al.[29] trials were the placebo responses consistent with relatively low

**Table 6. Cumulative Pooled RR Estimates for St. John's Wort Studies**

| No. of Studies in Meta-Analysis | Study Added in This Step | Cumulative RR | 95% CI |
|---|---|---|---|
| 1 | Schmidt et al, 1989[17] | 2.50 | 0.94 to 6.66 |
| 2 | Halama 1991[18] | 4.78 | 0.70 to 32.6 |
| 3 | Reh et al, 1992[19] | 2.33 | 1.15 to 4.72 |
| 4 | Lehrl et al, 1993[20] | 2.06 | 1.34 to 3.19 |
| 5 | Quandt et al, 1993[21] | 3.34 | 1.54 to 7.27 |
| 6 | Schmidt and Sommer, 1993[22] | 2.89 | 1.69 to 4.95 |
| 7 | Hänsgen et al, 1994[23] | 2.91 | 1.90 to 4.46 |
| 8 | Hübner et al, 1994[24] | 2.60 | 1.76 to 3.83 |
| 9 | Sommer and Harrer, 1994[25] | 2.51 | 1.82 to 3.46 |
| 10 | Witte et al, 1995[26] | 2.30 | 1.68 to 3.14 |
| 11 | Laakmann et al, 1998[27] | 2.16 | 1.63 to 2.86 |
| 12 | Laakmann et al, 1998[27a] | 2.03 | 1.55 to 2.65 |
| 13 | Schrader et al, 1998[12] | 2.17 | 1.65 to 2.85 |
| 14 | Philipp et al, 1999[28] | 2.04 | 1.56 to 2.67 |
| 15 | Shelton et al, 2001[29] | 1.97 | 1.54 to 2.53 |
| 16 | Kalb et al, 2001[7] | 1.91 | 1.52 to 2.40 |
| 17 | Hypericum Depression Trial Study Group, 2002[4] | 1.81 | 1.43 to 2.29 |
| 18 | Lecrubier et al, 2002[5] | 1.73 | 1.41 to 2.14 |

[a]Lower hyperforin content.
Abbreviation: RR = risk ratio.

hypericum responses. Therefore, the possibility arises that a systematic bias was introduced into the other studies, e.g., during recruitment, randomization, or conduct of the study. The difference in response between St. John's wort and placebo was not included as a variable in the meta-regression as cutoff points for the response differences would be arbitrary and a covariate to the outcome variable. Nevertheless, exploring the effects of variability in the clinical trial characteristics through techniques such as meta-regression may reveal the limited utility of funnel plot analysis and statistical tests in accounting for heterogeneity of effect sizes in meta-analyses. Systematic evaluation of trial characteristics for potential inclusion into meta-regression is useful to identify major methodological problems that may not be highlighted otherwise. Thus, funnel plot and statistical tests identify bias, but not its cause, and meta-regression may be required to identify the factors that drive the outcome of a meta-analysis. This approach is preferable to the exclusion of smaller studies of presumably lower quality, which would introduce a further bias as the studies had met the inclusion criteria set forth prior to analysis.

Given that there was a trend toward reduction of effect size, can St. John's wort still be recommended for the treatment of depression? If the trend continued, then St. John's wort might finally be proven to be ineffective. This prediction is supported by the trim and fill statistic for Meta-18, which showed that after imputation of 8 additional studies to achieve funnel plot symmetry, the effect size was reduced to 1.30, which was just marginally significant with a confidence interval of 1.03 to 1.64. On the other hand, effect sizes for conventional antidepressants are also surprisingly low. For instance, a meta-analysis by Bech et al.[30] found that 37.8% of patients responded to fluoxetine and 24.2% responded to placebo.

Inclusion of unpublished studies could have reduced the effect size of St. John's wort further. However, the goal of our study was to demonstrate the statistical assessment of publication bias, thereby making a published meta-analysis robust in the light of emerging data. It would be impossible to identify all unpublished data available, and inclusion of some unpublished studies but not others would be arbitrary.

The question of whether St. John's wort is effective in patients with mild depression remains unresolved. Approximately 7 groups of pharmacologically active compounds have been identified from preparations of *Hypericum perforatum*.[31] Suggested modes of antidepressive action include monoamine oxidase inhibition and GABAergic activity,[32] monoamine reuptake,[33,34] up-regulation of 5-$HT_{1A}$ and 5-$HT_{2A}$ receptors,[35] and modulation of cytokine production thought to be involved in the development of depression in susceptible individuals.[36]

Although the active ingredient is currently considered to be the extract in toto,[37] attempts have been made to identify the pharmacologically active substance. Hypericin, a red photosensitive pigment, was originally thought to be responsible for the antidepressant effect.[38,39] However, recent in vitro receptor binding studies demonstrated that pure hypericin had affinity only for *N*-methyl-D-aspartate receptors.[32] Studies now seem to indicate that hyperforin inhibits the reuptake of monoamines and thus may be the pharmacologically active component.[40,41] Future trials should test extracts in which the hyperforin content is maximized.

The side effects of St. John's wort resemble those of conventional antidepressants, albeit at lower frequen-

cies than are seen with other antidepressants. The meta-analysis by Whiskey et al.[3] reported pooled side effects that included dry mouth (3.7%), headaches (1.8%), nausea and vomiting (1.6%), fatigue/sedation (1.2%), abdominal pain (1.3%), vertigo and dizziness (1.0%), and restlessness (1.0%). Because of its serotonergic properties, St. John's wort is likely to interact with other serotonergic antidepressants and increase the risk of serotonin syndrome, which has already been reported for several selective serotonin reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors.[42,43] In addition, St. John's wort induces cytochrome P450 3A4, 1A2, and 2C9 and interacts with a variety of drugs including human immunodeficiency virus (HIV) protease inhibitors, HIV non-nucleoside reverse transcriptase inhibitors, warfarin, cyclosporin, oral contraceptives, anticonvulsants, digoxin, and theophylline.[44–48] These adverse factors are important since St. John's wort is often recommended as a "safe" and "natural" treatment for depression and, because of this, the possibility of relatively less robust efficacy compared with synthetic antidepressants is often willingly accepted by patients and prescribers. Increased awareness of the possible adverse consequences of St. John's wort coupled with increased doubt over its efficacy may well alter significantly patient and prescriber perceptions.

Our study has highlighted the need to systematically evaluate publication bias and small-study effects when conducting meta-analyses. In doing this, we have cast considerable doubt on the efficacy of St. John's wort. Although our meta-analyses indicated that St. John's wort was effective in the treatment of depression, we established a trend toward reduction of cumulative effect size over time. St. John's wort may finally be shown to be ineffective if future trials continue this trend. Clinicians need to bear this in mind when discussing the use of St. John's wort with their patients.

*Drug names:* cyclosporin (Gengraf, Neoral, and others), digoxin (Lanoxin and others), fluoxetine (Prozac and others), theophylline (Aerolate, Theo-24, and others), warfarin (Coumadin and others).

## REFERENCES


1. Linde K, Ramirez G, Mulrow CD, et al. St John's wort for depression: an overview and meta-analysis of the randomised clinical trials. BMJ 1996;313:253–258
2. Williams JW, Mulrow CD, Chiquette E. A systematic review of newer pharmacotherapies for depression in adults. Ann Intern Med 2000; 132:743–756
3. Whiskey E, Werneke U, Taylor D. A systematic review of *Hypericum perforatum* in depression. Int Clin Psychopharmacol 2001;16:239–252
4. Hypericum Depression Trial Study Group. Effect of *Hypericum perforatum* (St John's wort) in major depressive disorder: a randomized control trial. JAMA 2002;287:1807–1814
5. Lecrubier Y, Clerc G, Didi R, et al. Efficacy of St John's wort extract WS 5570 in major depression: a double-blind, placebo-controlled trial. Am J Psychiatry 2002;159:1361–1366
6. Sterne JAC, Gavaghan D, Egger M. Publication and related bias in meta-analysis: power of statistical tests and prevalence in the literature. J Clin Epidemiol 2000;53:1119–1129
7. Kalb R, Trautmann-Sponsel RD, Kieser M. Efficacy and tolerability of hypericum extract WS 5572 versus placebo in mildly to moderately depressed patients: a randomized double-blind multicentre trial. Pharmacopsychiatry 2001;34:96–103
8. Fava M, Alpert J, Nierenberg A, et al. A double-blind placebo randomised trial of St John's wort, fluoxetine and placebo in major depressive disorder. In: New Research Program and Abstracts of the 155th Annual Meeting of the American Psychiatric Association; May 21, 2002; Philadelphia, Pa. Abstract NR 252:69
9. Volz HP, Eberhardt R, Grill G. Wirksamkeit und Verträglichkeit des Johanniskrautextraktes D-0496 bei leichten bis mittelschweren Depression. Nervenheilkunde 2000;19:401–405
10. Montgomery SA, Hübner WD, Grigoleit HG. Efficacy and tolerability of St John's wort extract compared with placebo compared with mild to moderate depressive disorder [abstract]. Phytomedicine 2000;7 (suppl 2):107
11. Kaufeler R, Meier B, Brattstrom A. Efficacy and tolerability of Ze 117 St. John's wort extract in comparison with placebo, imipramine and fluoxetine for the treatment of mild to moderate depression according to ICD-10: an overview. Pharmacopsychiatry 2001;34(suppl 1): S49–S50
12. Schrader E, Meier B, Brattström A. Hypericum treatment of mild-moderate depression in a placebo-controlled study: a prospective, double-blind, randomised, placebo-controlled, multicentre study. Hum Psychopharmacol 1998;13:163–169
13. Begg CB, Mazdumar M. Operating characteristics of a rank correlation test for publication bias. Biometrics 1994;50:1088–1099
14. Egger M, Davey Smith G, Schneider M, et al. Bias in meta-analysis detected by a simple graphical test. BMJ 1997;315:629–634
15. Duval S, Tweedie R. Trim and fill: a simple funnel-plot–based method of testing and adjusting for publication bias in meta-analysis. Biometrics 2000;56:455–463
16. Sterne JAC, Davey Smith G, Egger M. Investigating and dealing with publication and other biases. In: Egger M, Davey Smith G, Altman DG, eds. Systematic Reviews in Healthcare: Meta-Analysis in Context. 2nd ed. London, England: BMJ Books; 2001
17. Schmidt U, Schenk N, Schwarz I. Hypericin-Applikation. Zur therapie depressiver Verstimmungen. Psycho 1989;15:665–671
18. Halama P. Wirksamkeit des Johanniskrautextraktes LI 160 bei depressiver Verstimmung. Nervenheilkunde 1991;10:250–253
19. Reh C, Laux P, Schenk N. Hypericum-Extrakt bei Depressionen–eine wirksame Alternative. Therapiewoche 1992;42:1576–1581
20. Lehrl S, Willemsen A, Papp R, et al. Ergebnisse von Messungen der kognitiven Leistungsfähigkeit bei Patienten unter der Therapie mit Johanniskraut-Extrakt. Nervenheilkunde 1993;12:281–284
21. Quandt J, Schmidt U, Schenk N. Ambulante Behandlung leichter und mittelschwerer Verstimmungen. Der Allgemeinarzt 1993;2:97–102
22. Schmidt, U, Sommer H. Johanniskraut-Extrakt zur ambulanten Therapie der Depression. Fortschr Med 1993;111:339–342
23. Hänsgen KD, Vesper J, Ploch M. Multicentre double-blind study examining the antidepressant effectiveness of the hypericum extract LI 160. J Geriatr Psychiatry Neurol 1994;7(suppl 1):15–18
24. Hübner WD, Lande S, Podzuweit H. Hypericum treatment of mild depressions with somatic symptoms. J Geriatr Psychiatry Neurol 1994;7(suppl 1):12–14
25. Sommer H, Harrer G. Placebo-controlled double blind study examining the effectiveness of an hypericum preparation in 105 mildly depressed patients. J Geriatr Psychiatry Neurol 1994;7(suppl 1):9–11
26. Witte B, Harrer G, Kaplan T, et al. Behandlung depressiver verstimmungen mit einem hochkonzentrierten Hypericumpräparat. Fortschr Med 1995;113:404–408
27. Laakmann G, Schule C, Baghai T, et al. St John's wort in mild to moderate depression: the relevance of hyperforin for the clinical efficacy. Pharmacopsychiatry 1998;31(suppl 1):54–59
28. Philipp M, Kohnen R, Hiller KO. Hypericum extract versus imipramine or placebo in patients with moderate depression: randomised multicentre study of treatment for eight weeks. BMJ 1999;319:1534–1538
29. Shelton RC, Keller MB, Gelenberg A, et al. Effectiveness of St John's wort in major depression: a randomized controlled trial. JAMA 2001;285:1978–1986
30. Bech P, Ciadella P, Haugh MC, et al. Meta-analysis of randomised controlled trials of fluoxetine v. placebo and tricyclic antidepressants

in short term treatment of major depression. Br J Psychiatry 2000;176: 421–428
31. Nahrstedt A, Butterweck V. Biologically active and other chemical constituents of the herb of *Hypericum perforatum* L. Pharmacopsychiatry 1997;30:129–134
32. Cott JM. In vitro receptor binding and enzyme inhibition by *Hypericum perforatum* extract. Pharmacopsychiatry 1997;30(suppl 2):108–112
33. Perovic S, Müller WE. Pharmacological profile of hypericin extract: effect on serotonin uptake by postsynaptic receptors. Arzneimittelforschung 1995;45:1145–1148
34. Neary JT, Bu Y. Hyperforin inhibits uptake of serotonin and norepinephrine in astrocytes. Brain Res 1999;816:358–363
35. Teufel-Mayer R, Gleitz J. Effect of long term administration of hypericum extracts on the affinity and density of the central serotonergic $5HT_{1A}$ and $5HT_{2A}$ receptors. Pharmacopsychiatry 1997;30(suppl 2):113–116
36. Thiele B, Brink I, Ploch M. Modulation of cytokine expression by hypericin extract. J Geriatr Psychiatry Neurol 1994;7(suppl 1):S60–S62
37. Bombardelli E, Morazzoni P. *Hypericum perforatum*. Fitoterapia 1995; 66:43–67
38. Suzuki O, Katsumata Y, Oya M, et al. Inhibition of monoamine oxidase by hypericin. Planta Med 1984;50:272–274
39. Bladt S, Wagner H. Inhibition of MAO by factions and constituents of hypericum extract. J Geriatr Psychiatry Neurol 1994;7(suppl 1):S57–S59
40. Müller WE, Singer A, Wonnemann M, et al. Hyperforin represents the neurotransmitter reuptake inhibiting constituent of hypericum extract. Pharmacopsychiatry 1998;31(suppl 1):16–21
41. Chatterjee SS, Nolder M, Koch E, et al. Antidepressant activity of *Hypericum perforatum* and hyperforin: the neglected possibility. Pharmacopsychiatry 1998;31(suppl 1):7–15
42. Lantz MS, Buchalter E, Giambanco V. St John's wort and antidepressant drug interactions in the elderly. J Geriatr Psychiatry Neurol 1999;12:7–10
43. Prost N, Tichadou L, Rodor F, et al. St John's wort–venlafaxine interaction [letter]. Presse Med 2000;29:1285–1286
44. Committee on Safety of Medicines and Medicines Control Agency. Reminder: St John's wort (*Hypericum perforatum*) interactions. Curr Prob Pharmacovigil 2000;26:6–7
45. Ernst E. Second thoughts about safety of St John's wort. Lancet 1999; 354:2014–2016
46. Johne A, Brockmöller J, Bauer S, et al. Pharmacokinetic interaction of digoxin with an herbal extract from St John's wort (*Hypericum perfor*atum). Clin Pharmacol Ther 1999;66:338–345
47. Piscitelli SC, Burstein HB, Chaitt D, et al. Indinavir concentrations and St John's wort. Lancet 2000;355:547–549
48. Ruschitzka F, Meier PJ, Turina M. Acute heart transplant rejection due to St John's wort. Lancet 2000;355:584–589