St John’s Wort and Major Depression

To the Editor: Dr Shelton and colleagues1 found that St John’s wort (Hypericum perforatum) was ineffective to treat chronic major depression. St John’s wort, however, is generally recommended for use in mild-to-moderate depressive disorders. From the study design, it is unclear whether any medication would have been effective in this sample since no patient received conventional antidepressant medications and an unusually low placebo response rate occurred (18.6%, as compared with the usual 30% to 50% placebo response in other trials on depression). We find no evidence in this study that precludes potential benefits for patients who were less severely and chronically depressed. In fact, according to one definition of remission, a significantly greater percentage of patients responded to St John’s wort (14.3%) than to placebo (4.9%), even in this study.

Finally, these data were reported at the American Psychiatric Association meeting in May 2000.2 However, the number of dropouts was reported to be 43 (23.4%) at the meeting but only 28 in their article. The authors must account for this discrepancy.

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To the Editor: Dr Shelton and colleagues1 conducted an 8-week intervention trial comparing St John’s wort extract with placebo for the treatment of major depression. Ironically, their study was limited by the same criticisms they leveled against previous studies of St John’s wort—a flawed protocol and inappropriately generalized findings. Shelton et al concluded that the herbal extract was not effective for treatment of major depression, but their trial did not include a prescription antidepressant arm to indicate whether the study was sensitive enough to detect effectiveness.

In addition to their flawed study design, the investigators also overstated their findings. While warning against generalizing results based on a homogeneous patient sample, the authors did exactly that in concluding “there is no credible evidence to support the efficacy of St John’s wort for people with depression.” Depression is a complex and heterogeneous disorder, with symptoms ranging from mild to severe and debilitating. Nonetheless, the investigators rejected the positive results from 31 previous peer-reviewed clinical trials for mild-to-moderate depression and extended their dubious findings to all people with depression. Furthermore, by exposing 200 patients with severe depression to placebo or an herbal extract they believed was not shown to be effective for even mild depression, the authors may have acted unethically.3

Shelton et al also failed to acknowledge the 1999 government report—generated by an evidence-based review—entitled “Treatment of Depression and Newer Pharmacotherapies,”4 published by the Agency for Healthcare Research and Quality. While recognizing possible publication bias, the report concluded: “Hypericum (St John’s wort) appears to be more effective than placebo for short-term treatment of mild to moderately severe depressive disorders.” At least Shelton et al correctly reported that St John’s wort is safe and well tolerated.

No responsible party—herbalist, pharmacognosist, physician, or industry expert—advocates the use of St John’s wort for self-medication of major depression. All agree that patients with major depression should be under an expert physician’s care. Shelton et al, however, dismissed a substantial body of evidence supporting the value of St John’s wort for mild-to-moderate depression. Consumers are as likely to be confused by this conclusion as they would be by outlandish and unfounded claims of benefit.

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To the Editor: In stating that “in this study, St John’s wort was not effective for treatment of major depression,” Dr Shelton and...
colleagues have made the same error they criticized in earlier studies of St John’s wort vs standard antidepressants. Failure to find statistically significant differences between 2 treatments, they correctly note, does not alone support a conclusion of equal efficacy. Nonetheless, the authors inappropriately interpreted failure to detect statistically significant differences with placebo as evidence of equal lack of efficacy.

The authors reported that their study had 80% power to detect a response rate of 36.1%, which is 1.9 times the 18.6% rate they observed for placebo. That standard may be overly stringent. A systematic review in 1998 of 28 randomized controlled trials showed, in comparisons of selective serotonin reuptake inhibitor (SSRI) with placebo in primary care, a mean relative response rate of 1.6 (95% confidence interval [CI], 1.2-2.1).

If this observed 60% benefit of SSRI is accepted as clinically meaningful and if St John’s wort were in fact to confer such a benefit, then the study of Shelton et al only had a power of 46% to find a statistically significant difference.

In addition to 1 measure in which the authors did find a statistically significant improvement over placebo, they report differences in response and remission rates as statistically not significant with \( P = .07 \). These results have 95% CIs that suggest they could not rule out that St John’s wort may have had a response rate as high as 44.1% and a remission rate as high as 30.7%. If these were the true rates and not just the upper limits of the CIs, they would be clinically meaningful.

This does not mean that there is sufficient evidence of a difference or positive efficacy of St John’s wort compared with placebo. Rather, these data do not support either a difference or a lack of difference. As often happens, an overly broad conclusion of “not effective” in the report became the take-home message of press accounts of the study. It will do no good to exceed or blur the limits of statistical inference when we are urging the public to submit popular remedies to rigorous scientific examination.

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To the Editor: Dr Shelton and colleagues concluded that “St John’s wort was not effective for treatment of major depression.” These authors may have been overly skeptical in interpreting their data. In the intent-to-treat analysis, according to the study’s response criterion, 26.5% of subjects receiving St John’s wort vs 18.6% of patients in the placebo group responded to treatment \( (P = .15) \), and according to the study’s remission criterion, 14.3% vs 4.9% showed remission \( (P = .02) \).

If one evaluates this trial in the context of other similar studies, it is noteworthy that the comparisons of St John’s wort vs placebo in this study is in the same direction as studies with a positive outcome, although it does not reach statistical significance. What is surprising about these data is the low response rate to placebo. A placebo response of 20% to 30% is routine in studies of depression. Thus, an equally reasonable conclusion is that St John’s wort was perhaps better than placebo in the treatment of major depression. A third arm with an established antidepressant might have resolved these difficulties.

The authors criticize our double-blind study, in which St John’s wort was shown to be as efficacious as an established antidepressant (sertraline hydrochloride), by claiming that the severity of depression was low in our sample. But that was the purpose of our study: we set out to evaluate St John’s wort in patients with mild-to-moderate depression and made no other claims about severe depression. Shelton et al conducted a reanalysis of patients with Hamilton depression (HAM-D) scores of 22 or lower (ie, 20-22) to determine whether results would differ in patients with less severe depression (they did not), but it should be noted that in our study patients with even lower HAM-D scores (17 or more) were selected.

We suggest that a proper conclusion for the study of Shelton et al is that, in patients with major depression, no consistent superiority of St John’s wort over placebo could be demonstrated. The efficacy of St John’s wort in patients with mild-to-moderate depression was not evaluated.

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To the Editor: Dr Shelton and colleagues do not provide the actual data on which their conclusions are based. The Hamilton depression (HAM-D) scores are presented only as unadjusted group means. As HAM-D scores 20 and higher were required for trial entry, the subgroup analysis of “less severely depressed” subjects (HAM-D score < 22) could only include subjects with a HAM-D score of 20 or 21. It is arbitrary to des-
Ignite an individual with a score of 21 as less severely depressed than a score of 22. Similarly, the authors state that the mean (SD) duration of current major depressive disorder was 2.3 (6.3) years in the treated group and 2.7 (5.6) years in the placebo group. The SDs show that the distribution is dramatically skewed, perhaps to an extent as to possibly affect the statistical analyses.

The authors describe 7 categories of limitations of previous trials. "Diagnostic practices/heterogeneity" and "lack of standardized symptom ratings" are fair criticisms of study limitations. Other "design limitations," however, are unsubstantiated. The category "less experienced investigators" is vague and subjective; "low depression severity" (inclusion of subjects with HAM-D scores < 18) seems arbitrary; deliberate inclusion of subjects with mild depression is hardly a design flaw; "small sample size/inadequate power" is irrelevant in placebo-controlled trials (if differences were detected between groups, then power is not an issue). "Low comparator dose/no plasma levels" is an odd pairing. Lower doses in some early trials were standard therapeutic doses at the time and in the country where the studies were performed; besides, most trials used adequate comparators. Lack of plasma levels of antidepressant medications is not a methodological flaw; such levels are not routinely obtained in depression studies. "Low St John's wort dose" (defined as "<600 mg/d") is not based on data. Doses of 350 to 500 mg/d of extract (containing 0.5-0.75 mg/d of hypericin) have achieved positive results compared with placebo in at least 4 placebo-controlled trials. The authors also criticize inadequate study duration, despite the fact that their 8-week study is not markedly longer than previous studies, as 20 of 31 were 6 or more weeks.

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In Reply: Although several writers take issue with the lack of a drug treatment arm in our study, the simple placebo controlled trial is a widely accepted design. A power analysis indicated that a 2-cell study of this size would yield a power greater than 0.85 to detect a 2-point difference at end point on the HAM-D. A 3-group study would have required a prohibitively large sample size.

Dr Cott and colleagues are concerned about the low placebo response rate in our study. In trials of therapy for depression, use of sensitive measures of outcome lead to higher placebo response rates. Our design was intended to minimize placebo response to detect any therapeutic advantage with St John's wort. We did note the possibility of a sampling bias in our article. A total of 33 participants dropped out of our study (after final data accounting) not the 43 originally reported. Cott et al and Drs Fomous and Cardellina take issue with out concerns regarding previous research with St John's wort. Other authors, however, have arrived at the same conclusion that we did. The conclusions of the Agency for Healthcare Research and Quality were based on the best evidence available at the time, but not necessarily on strong scientific grounds.

Several writers are concerned that we only studied patients with major depression. We point out that major depression is a diagnostic category in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, that can include depression that is mild, moderate, or severe. Many previous studies with St John's wort have included persons with depression of moderate severity or greater. Cott et al state "We find no evidence...that precludes potential benefit for less severely depressed patients." In our article, we clearly said the same.

The ethical issues raised by Fomous and Cardellina were discussed in our article. Taking their reasoning to the logical conclusion, no research could ever be conducted with new treatments since the benefit of the new approach would be unknown.

By focusing on the response and remission rates, Drs Cohen and Marantz, as well as Dr Brenner and colleagues, have overlooked the fact that the longitudinal random coefficient analyses were the primary statistical approach. The longitudinal analysis is much more powerful than comparison of response rates and would have detected even small differences between treatment groups.

Applying a ratio of response rates of 1.6 from outpatient primary care studies obscures the fact that the mean placebo response rate in these studies is higher than in ours. Cohen and Marantz also argue that we should have accepted a P = .07 as meaningful. While there is nothing magical about the P = .05 level of significance, it is the general scientific standard. Further research is needed to see if the response rates we obtained are typical for this population with moderate depression.

In response to Dr Fugh-Berman, we reported the adjusted HAM-D means and SDs in our article. The duration of the depressive episode was not significantly different, nor was there a problem with skewness. Our description of the results of the groups with more or less severe depression was included on the request of a reviewer.

Fugh-Berman takes issue with several of our criticisms of prior trials. A study by Nikolson et al showed that only about one third of supposedly expert sites were able to produce consistent results in depression studies. Our concern about "inexperienced investigators" relates to the many studies that used nonexpert raters, primarily clinicians in fields other than psychiatry, whose ratings are of questionable validity. The possibility of an inadvertent breaking of the blind has been noted by others. Furthermore, a low placebo response in patients with mild depression, significant differences achieved in very small placebo-controlled studies, and the use of very low doses of St John's wort raise concerns about internal validity. Finally, the dosage and plasma levels of tricyclic antidepressants have been
established for more than 2 decades. Low doses invalidate the studies even if community standards were followed.

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Prenatal Cocaine Exposure as a Risk Factor for Later Developmental Outcomes

To the Editor: The meta-analysis by Dr Frank and colleagues concluded that cocaine exposure in utero does not affect physical or behavioral development in offspring. As pointed out by the authors, many inconsistent observations have been reported in the clinical literature, and confounding factors, such as polydrug use, further complicate the interpretation of these studies.

It was disappointing, however, that the authors did not highlight the results of recent studies in which children have been prospectively followed up. These studies have shown subtle but consistent deficits in cognitive and attentional processes in 6- and 7-year-old children, effects that may become more prominent as their cognitive and social development continues. Cocaine has potent effects on neurotransmitters with known effects on the development of limbic cortical circuitry. Thus, it is not surprising that in utero exposure to cocaine might lead to cognitive and emotional difficulties in older children and even into adulthood—impairments that simply cannot be assessed in younger children nor with crude global measures. Thus, the conclusions drawn by the authors may be premature.

Furthermore, the types of neurobehavioral deficits observed in children prenatally exposed to cocaine are reminiscent of deficits documented in studies of animal models, which do not have the same methodological limitations as clinical reports. Models in rodents, nonhuman primates, and rabbits all suggest that administration of cocaine during pregnancy induces permanent cellular, biochemical, and behavioral changes. In fact, low-dose cocaine exposure during a short but key period of gestation in animals, comparable with the second trimester in humans, is sufficient to produce measurable deficits in dopamine-rich cortical regions and even permanent loss of signaling via a key dopamine receptor system.

In summary, although the authors should be commended for their analysis of initial studies in neonates and infants and their appropriate repudiation of the “crack baby” stereotype, their analysis de-emphasizes the important contributions of a subset of the reports. To date, the evidence from animal and clinical studies on the effects of in utero cocaine exposure strongly argues for the existence of permanent changes in the structure and function of selective brain circuits in the offspring. Continued longitudinal studies on children who were exposed to cocaine in utero and mechanistic studies using animal models are warranted to better characterize the nature of the deficits and generate useful therapeutics for these children.

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To the Editor: In their analysis of a large and contradictory literature on the developmental effects of prenatal cocaine exposure, Dr Frank and colleagues concluded that, “After controlling for confounders, there was no consistent negative association between prenatal cocaine exposure and a number of developmental outcomes. Although the authors carefully qualified that they were assessing unique effects of cocaine in comparison with those of multiple other risk factors, one concern is that this review will be interpreted as indicating that there are no negative effects of prenatal cocaine exposure.

Two considerations are important. First, the authors have taken a conservative, behavioral teratological approach that attempts to isolate cocaine exposure from all other associated risk factors. However, evidence exists that prenatal cocaine exposure is not randomly associated with other child developmental risk factors, including, as the authors note, poor caregiving, child maltreatment, domestic violence, and prenatal exposure to other substances. Although the effect of these risk factors can be controlled statistically, they cannot be isolated in an individual child. From the perspective of public health

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policy, there is reason for concern about prenatal cocaine exposure because of the clustering of numerous risk factors with maternal crack/cocaine use.

Second, the articles reviewed represent less than 50% of the 74 articles found in the authors’ search. Many of the studies included had small sample sizes and may not have had the statistical power to detect a cocaine effect, particularly with the need to control for numerous covaried risk factors, while other studies had follow-up rates as low as 39%. Three studies from our laboratory on 2 separate cohorts were cited as not meeting inclusion criteria for the review because lack of prospective recruitment or of lack of masked examiners. These studies, which included cohorts of 199 subjects (98 who were exposed to cocaine and 101 who were not exposed) and 216 subjects (160 who were exposed to cocaine and 56 who were not exposed), found independent effects of cocaine exposure in utero on mental and motor development of the children.

We agree with Frank et al that it is important to refrain from premature causal conclusions and punitive public policies. However, accumulating evidence indicating that cocaine exposure in utero is related to negative developmental outcomes should not be disregarded simply because such outcomes are also related to other negative factors in the child’s environment. Rather, until complex neuroteratogenic models of development can be refined and tested, we should not minimize the potential additional harm prenatal exposure to cocaine may have on a child’s development.

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To the Editor: As in 1992 when Mayes et al1 urged against a rush to judgment of the effects of prenatal cocaine exposure, the review by Dr Frank and colleagues2 provided a rational voice in an irrational environment. While we agree with many of the conclusions, the lay community has consistently underestimated the risk of prenatal exposure to cocaine. In our own community, this review has been interpreted to mean that there are no long-term effects of prenatal cocaine exposure. Clearly, the effects on the fetuses, newborns, and infants, including dose-response relations, are evident. Although disregarding these risks was not the intent of this review, it may well be a consequence.

Frank et al misinterpreted our studies3,4 by indicating that we reported results from only 1 cohort. Two cohorts from non-successive birth years were actually assessed. Mothers were prospectively evaluated for prenatal exposure to cocaine by the Fetal Alcohol Research Center. Results from both cohorts identified behavioral problems at school age. In the latter (≥500 children and 200 exposed to cocaine prenatally), behavioral problems and language delays5 persisted after control for other exposures and social and home environmental characteristics.

We also are concerned about the limited data currently available. Frank et al note that some infancy studies suggest that higher exposure to cocaine has resulted in more consequences. Until there is better knowledge of the childhood and adolescent outcomes from studies quantifying prenatal exposure, potential risks should not be minimized. We are completing manuscripts describing dose-response relationships between prenatal cocaine exposure and school behavior and achievement. Such a relationship is in keeping with results from both the infancy studies and the literature on prenatal alcohol exposure. Had we, as a scientific community, been willing to judge prenatal alcohol exposure on the basis of a dichotomous (yes/no) exposure variable, we might still be unaware of the alcohol-related neurobehavioral disorder. Quantifying prenatal cocaine exposure is even more challenging. Only with more and better research for all types of prenatal exposures will these critical questions be answered.

Finally, we agree with Frank et al that women who use cocaine during pregnancy and their children, like all patients, must be treated rationally and ethically.

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For the School-Based (SCHOO-BE) Research Team


In Reply: These correspondents share 2 concerns. The first is disagreement with our selection criteria for articles1—that the criteria were excessively stringent in restriction to human samples, peer review, masked assessment, and prospective recruitment, and simultaneously inadequately selective with respect to attrition and sample size. Animal studies are, as the thalidomide tragedy showed, unreliable indicators of a terato-
genicity of a substance or its safety in humans. Methodologic issues also influence interpretation of animal data—whether cocaine effects are found varies by species, sex, timing of exposure, mode of administration, age at assessment, and whether control animals were pair fed with exposed animals. Except for the article by Leech et al., which was presented in detail in our review, the other articles with human subjects cited by Drs Stanwood and Levitt were in a non-peer-reviewed publication. Without the exception of the methods demanded by a peer-reviewed journal, these works-in-progress cannot be interpreted with confidence. We make no apologies for excluding, in spite of large sample sizes, articles that lack prospective recruitment or masked assessment; these criteria were justified in detail in our review.

We concur with Drs Singer and Arendt that the selection criteria could have been even more stringent. However, had we excluded studies with small sample sizes or high attrition it would have only strengthened our conclusions, since we would have predominantly omitted studies suggesting a cocaine effect.

The second concern is that the findings and conclusions from our systematic review (not as the popular press and Stanwood and Levitt misstated, a meta-analysis) will be misused to foreclose ongoing research in this still evolving area or to minimize the public health importance of parental substance abuse. The point of our review is not that prenatal cocaine exposure, particularly at high levels, has no impact on children who were exposed, but that scientists must evaluate cocaine exposure as one risk indicator among many. Prenatal cocaine exposure neither dooms exposed children nor justifies punitive and discriminatory public policies toward their mothers. However, we agree that it is premature to conclude that there are no persistent independent negative effects of high-dose prenatal cocaine exposure. We quote from our original article, “the increasing cognitive demands and social expectations of school or puberty may unmask sequelae of exposure not previously identified.” Deflating the grotesque myth of the “crack baby” does not undermine the critical public health agenda of identifying and treating families and children affected by substance abuse. As we wrote, care of such families should be comprehensive and not irrationally shaped by social prejudices that demonize some drugs and drug users and not others.

We would like to thank Dr Delaney-Black and colleagues for correcting our misreading of their data. We apologize for this error, which does not in any way change our conclusions.

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Informed Consent for Public Automated External Defibrillation

To the Editor: “He died a natural death when he was 90. Just keeled over,” a young man once said to me, describing the death of his grandfather. When I talk with patients about end-of-life issues, I sometimes ask them what manner of death they would prefer, if they could choose. Many say that they hope for a quick death and fear a prolonged death.

It was therefore intriguing to read the article by Dr Marenco and colleagues. They found that automated external defibrillators (AEDs), a technology intended to avert sudden death, are rapidly infiltrating public spaces. As one who talks with people daily about choices, I like to imagine some supernatural being, perhaps a guardian angel, entering the scene as a woman who has collapsed in an airport is about to have an AED applied to her chest. The angel wants to learn the patient’s preferences for end-of-life care and fortunately he can stop time briefly, thus not exposing the patient to further risks, while the angel conducts his discussion. Important topics would include the person’s current state of health (other illnesses and their expected course); the likelihood that this is the only chance the patient will get to die suddenly as opposed to slowly; the diseases from which she might die the next time—those most likely, and those most unpleasant. She might, for instance, want to ponder the possibility of death from Alzheimer disease, breast or colon cancer, stroke, or amyotrophic lateral sclerosis. For the fact remains that she will eventually die of something. The angel might also feel obliged to mention the possibility that the patient will outlive some of her children or that she might spend years in a nursing home.

Of course, such a discussion cannot happen at the time of a person’s collapse, and the results of past discussions of advance directives will not be available. While most of us would prefer to die later rather than sooner, we will all have to die, and we should have explicit discussions about the trade-offs involved in our attempts to avoid a particular death at a particular time. I am not sure that everyone thinks the kind of death the AEDs are meant to prevent is such a bad one. How are those people to make their wishes known?

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This letter was shown to Dr Estes, who declined to reply.—Ed

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