Hypericum perforatum (St John's Wort) for Attention-Deficit/Hyperactivity Disorder in Children and Adolescents

A Randomized Controlled Trial

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Context Stimulant medication can effectively treat 60% to 70% of youth with attention-deficit/hyperactivity disorder (ADHD). Yet many parents seek alternative therapies, and *Hypericum perforatum* (St John's wort) is 1 of the top 3 botanicals used.

Objective To determine the efficacy and safety of *H perforatum* for the treatment of ADHD in children.

Design, Setting, and Participants Randomized, double-blind, placebo-controlled trial conducted between March 2005 and August 2006 at Bastyr University, Kenmore, Washington, among a volunteer sample of 54 children aged 6 to 17 years who met *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition) criteria for ADHD by structured interview.

Intervention After a placebo run-in phase of 1 week, participants were randomly assigned to receive 300 mg of *H perforatum* standardized to 0.3% hypericin (n=27) or a matched placebo (n=27) 3 times daily for 8 weeks. Other medications for ADHD were not allowed during the trial.

Main Outcome Measures Performance on the ADHD Rating Scale–IV (range, 0-54) and Clinical Global Impression Improvement Scale (range, 0-7), and adverse events.

Results One patient in the placebo group withdrew because of an adverse event. No significant difference was found in the change in ADHD Rating Scale–IV scores from baseline to week 8 between the treatment and placebo groups: inattentiveness improved 2.6 points (95% confidence interval [CI], –4.6 to –0.6 points) with *H perforatum* vs 3.2 points (95% CI, –5.7 to –0.8 points) with placebo ($P=.68$) and hyperactivity improved 1.8 points (95% CI, –3.7 to 0.1 points) with *H perforatum* vs 2.0 points (95% CI, –4.1 to 0.1 points) with placebo ($P=.89$). There was also no significant difference between the 2 groups in the percentage of participants who met criteria for improvement (score ≤2) on the Clinical Global Impression Improvement Scale (*H perforatum*, 44.4%; 95% CI, 25.5%-64.7% vs placebo, 51.9%; 95% CI, 31.9%-71.3%; $P=.59$). No difference between groups was found in the number of participants who experienced adverse effects during the study period (*H perforatum*, 40.7%; 95% CI, 22.4%-61.2% vs placebo, 44.4%; 95% CI, 25.5%-64.7%; $P=.78$).

Conclusion In this study, use of *H perforatum* for treatment of ADHD over the course of 8 weeks did not improve symptoms.

Trial Registration clinicaltrials.gov Identifier: NCT00100295

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ATTENTION-DEFICIT/HYPERACTIVITY disorder (ADHD) affects 3% to 12% of children in the United States.[1,2] Up to 30% of these children do not respond to pharmaceutical medications or have adverse effects such as nausea, insomnia, or weight loss from the medications.[3] For these reasons, many parents seek complementary or alternative medicine for their children with ADHD.[4] Complementary or alternative medicine treatments used for pediatric ADHD include massage, dietary changes, dietary supplements, and herbal treatments.[5-9] In the United States, the most common herbal treatments used by children with ADHD are St John's wort, *Echinacea* species, and *Ginkgo biloba*.[5]

Extracts from St John's wort, also known by its Latin botanical name, *Hypericum perforatum,* have been studied extensively for the treatment of depression in adults, with mixed results, and in 2 open-label studies in children and adolescents with depression.[10-16] *Hypericum perforatum* has been found to

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inhibit reuptake of serotonin, norepinephrine, and dopamine.[17] The only medication with similar actions is bupropion hydrochloride, which is sometimes used by pediatricians or child psychiatrists to treat children and adolescents with ADHD.[17,18] However, bupropion is not believed to strongly inhibit serotonin reuptake and it is not approved by the US Food and Drug Administration (FDA) for this indication. In the last decade, a new nonstimulant selective norepinephrine reuptake inhibitor, atomoxetine, was approved by the FDA for the treatment of ADHD in children and adolescents.[19-21] Because *H perforatum* is believed to act as a norepinephrine reuptake inhibitor, we hypothesized that *H perforatum* may be beneficial in the treatment of ADHD.

We conducted a small placebo-controlled trial of *H perforatum* in children and adolescents with ADHD. The primary goal of the study was to determine if *H perforatum* was effective in lessening the severity of ADHD symptoms, as measured by the ADHD Rating Scale–IV (ADHD RS-IV) and the Clinical Global Impression (CGI) Improvement Scale.[22,23]

METHODS

An 8-week randomized, placebo-controlled, double-blind trial of *H perforatum* for the treatment of ADHD in children and adolescents was conducted at Bastyr University, Kenmore, Washington. All screening appointments and study visits occurred in the university's clinical research facility. The study was approved by the Office of Scientific and Ethical Review and Institutional Review Board of Bastyr University and the Human Subjects Division of the University of Washington.

Participants

Healthy children and adolescents aged 6 to 17 years who met *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition) (*DSM-IV*) criteria for ADHD based on a structured diagnostic interview using the Kiddie Schedule for Affective Disorders and Schizophrenia–Epidemiologic Version (K-SADS) were enrolled in the trial between March 2005 and August 2006.[24,25] To be eligible, participants scored more than 1.5 SDs above age and sex norms on the ADHD RS-IV[22]; parents and participants could read the consent and assent forms in written English; parents and participants were able to attend all study visits; and participants were capable of swallowing pills. Children with severe depression or an active suicide plan, a history or current diagnosis of bipolar disorder or severe conduct disorder, or psychotic symptoms were excluded from the trial. All structured interviews were conducted by the principal investigator (W.W.), who had been trained in the pediatric psychopharmacology research laboratory of J.B. at Massachusetts General Hospital to a high degree of interrater reliability with experienced child and adult board-certified psychiatrists. Diagnostic uncertainties were resolved by consensus among J.B., J.M., and W.W. Participants at risk of becoming pregnant during the study period or who used medications or over-the-counter products that were metabolized by the CYP 3A4 isoenzyme of the cytochrome P450 system were also excluded. *H perforatum* is known to interact with the metabolism of up to 50% of medications, decreasing the circulating levels of these medications by inducing P450 isoenzymes in the liver, including CYP 3A4.[26] No other ADHD treatments were allowed during the study period, including prescription pharmaceutical medications. A washout period was required for all participants who discontinued pharmaceutical medications prior to starting the trial (1 week for stimulant medications and 2 weeks for all other medications). Children who had previously used *H perforatum* for more than 2 weeks were not allowed to participate. Multivitamins, essential fatty acid supplements, and counseling were allowed as long as the child had been consistently using the treatment for at least 3 months and was expected to continue at the same dose or frequency.

Study participants were referred from multiple sites, including the Bastyr Center for Natural Health and naturopathic physician offices in the Seattle area. Recruitment advertisements were published in a Seattle-area parenting magazine, a Seattle-area co-op grocery store newsletter, the Bastyr Center for Natural Health newsletter, the Bastyr University student and staff bulletin, and on the Bastyr University Web site. Interested parents called the study line for details and were asked screening questions over the telephone. Eligible participants were scheduled for 2 screening visits with the principal investigator. At the first screening visit, the study was explained and written informed consent and assent were obtained. At the screening visits, parents provided information on the child's medical and family history; participants were given a physical examination by the principal investigator; a parent completed a structured interview (K-SADS); and the ADHD RS-IV was completed by interview of the parent. Participants who were aged 12 years or older were also interviewed directly by the principal investigator using a structured interview (K-SADS). Participants and parents were remunerated and could receive up to $75 each for attending all study visits and completing the trial.

Intervention

A placebo run-in phase of 1 week was built in from the time of the screening visit to the baseline visit. Participants who were less than 80% adherent as assessed by pill count or who had a dramatic placebo response (>25% decrease in ADHD RS-IV or score of 1 on the CGI Improvement Scale) during the run-in phase were excluded from the trial prior to randomization.[22,23] Participants who remained eligible after the placebo run-in were randomized to receive *H perforatum* or placebo for 8 weeks of treatment. The *H perforatum* product was standardized to 0.3% hypericin and was free of heavy metals, pesticides, and adulterants. The placebo pills contained a mixture of rice protein powder and a small amount of

activated charcoal (for coloring purposes). *Hypericum perforatum* and placebo were encapsulated in identical opaque capsules and provided by Vital Nutrients Inc (Middletown, Connecticut). An Investigational New Drug application for this clinical trial was filed with the FDA (IND 65162 protocol 2). Participants were instructed to take 1 capsule (300 mg) 3 times every day for the duration of the study, ideally before school, after school, and before bed.

Outcomes

Once randomized, participants were evaluated by the principal investigator during study visits at baseline and weeks 1, 2, 4, 6, and 8. The primary outcomes for the study were changes in ADHD symptoms from baseline to week 8 as measured by the ADHD RS-IV, changes on the CGI Improvement Scale from baseline to week 8, and safety as assessed by monitoring children for adverse effects.[22,23] The ADHD RS-IV is an 18-item standardized, valid, reliable instrument for the diagnosis and weekly assessment of treatment response among children and adolescents with ADHD.[22] Each item on the instrument describes 1 of the symptoms of ADHD rated on a 0- to 3-point Likert scale (never or rarely, sometimes, often, or very often).[22] The principal investigator, blinded to treatment assignment, administered the ADHD RS-IV to the parent at each study visit. Nationally representative norms are available for the scale and were used to determine eligibility.[22] Participants in the study were at least 1.5 SDs above the norm for the child's age and sex on at least 1 of the scales (total, inattentiveness, or hyperactivity/impulsivity). The CGI Improvement Scale was used at weeks 4 and 8 to rate the worsening, maintenance, or improvement in global impairment of participants enrolled in the study compared with baseline.[23] The CGI Improvement Scale includes 8 options for scoring: 0=not assessed; 1=very much improved; 2=much improved; 3=minimally improved; 4=no change; 5=minimally worse; 6=much worse; and 7=very much worse.[23] Clinical response at week 8 was defined as a rating of much or very much improved (1 or 2), which is considered to be a clinically meaningful response.

Safety was the third primary outcome for the study and was assessed by administering the Monitoring of Side Effects System to ascertain whether participants had experienced any adverse events since the last visit.[27] This scale lists 76 possible adverse effects, which are rated on a 6-point Likert scale: 0=not present; 1=minimal, no care required; 2=mild, over-the-counter treatment needed; 3=moderate, needed to see a health care professional; 4=severe, prevented function for more than 2 hours; and 5=an FDA "serious" adverse effect. Expected potential adverse events included rash, nausea/vomiting, headache, and sunburn. Height and weight were also measured at each study visit.

Sample Size

Sample size calculations were performed to determine the number of participants needed to detect effect sizes similar to those that have been reported in recent ADHD medication trials.[19,28] A 5-point reduction in the ADHD RS-IV total score was expected in the placebo group and a 13-point change, which had been used to define a clinically meaningful effect in a previous study,[28] was expected in the *H perforatum* group. Therefore, this study was powered to detect an 8-point difference between the groups.[28] A sample size of 26 per group was required to achieve 80% power with a 2-tailed significance level of .05, assuming an equivalent SD of 10.1 in both groups. Estimating a 10% dropout during the study, a minimum of 58 total participants was needed to reach the target of 26 participants per group.

Randomization and Blinding

The study medication allocation sequence was applied in random blocks of 4 and 6 to ensure that approximately equal numbers of participants received *H perforatum* and placebo. An independent pharmacy technician placed the study medication in consecutively numbered bottles that were identical in appearance. An independent data manager created the randomization sequence, allowing the principal investigator and recruitment staff to remain blinded to the randomization code until the database was locked. Two independent data safety officers were provided with a summary of adverse events (with groups coded as A or B) twice during the study to evaluate if the study needed to be terminated because of the occurrence of disproportionately more adverse events in one of the groups. To assess the success of the blinding procedure at the end of the study, the participant, parent and investigator were asked whether they believed the child was taking *H perforatum* or placebo. To determine adherence, pills were counted both prior to being dispensed to participants and on return of study medication at the next study visit.

Statistical Analysis

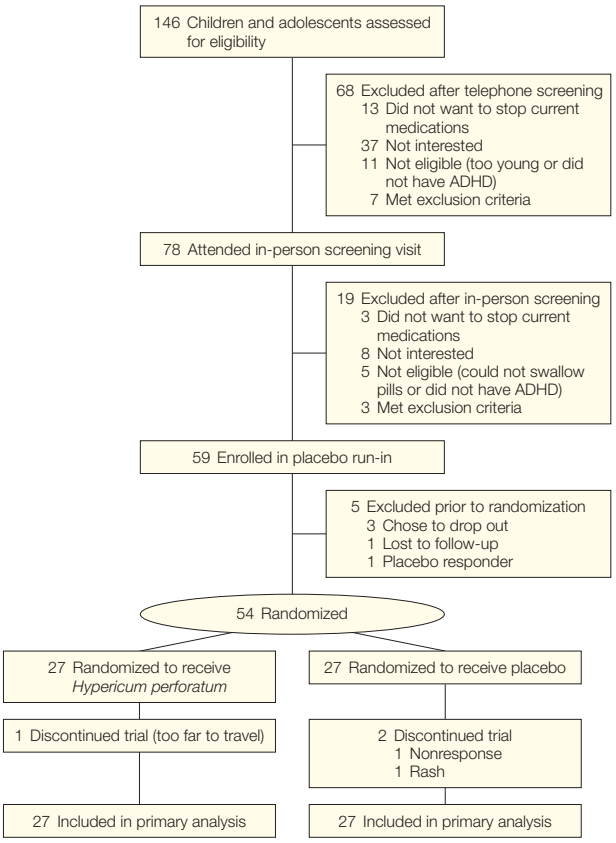
Descriptive statistics were performed to characterize the study participants. Baseline characteristics included age, sex, race/ethnicity, median household income, comorbid mental health conditions, and ADHD RS-IV scores. To help readers determine if the study results generalize to their patient populations, race/ethnicity categories were created by the principal investigator based on the National Institutes of Health clinical trial reporting requirements. Parents were asked to identify the race/ethnicity category that most closely described their child's race/ethnicity or were allowed to select more than 1 category of race/ethnicity. Median household income was obtained by searching the US Census Bureau 2000 census data for median household income based on participant address.[29] Baseline characteristics were examined as potential confounders in adjusted analyses if binary variables yielded at least a 15% difference in absolute risk between the groups. Age and household income were also examined as potential confounders because they are commonly controlled for in studies of childhood psychopathology.

All primary analyses are intention to treat with the significance level set at $P < .05$ (2-sided). Two-sample *t* tests were performed to evaluate the difference between the change in score in the *H perforatum* group vs the placebo group for each of the ADHD RS-IV scales: inattentiveness, hyperactivity/impulsivity, and total. For participants who dropped out of the study prior to week 8, the last available ADHD RS-IV score was carried forward. Two sample *t* tests were also performed to compare the difference from baseline to week 8 in age- and sex-normalized percentile score change between the 2 groups for each of the scales. The χ^2 test was performed to compare the number of individuals with a CGI Improvement Scale score of 2 or less vs those with higher scores in the *H perforatum* and placebo groups. χ^2 Tests were performed to compare the difference in numbers of total potential adverse events and each of the specific potential adverse events (rash, nausea/vomiting, headache, and sunburn). κ Coefficients were calculated to measure the chance-corrected agreement between study medication allocation and predicted medication status as reported by the parent, participant, and principal investigator.

Secondary analyses examined the effect of *H perforatum* vs placebo in participants who completed the trial according to the protocol. Participants were excluded from this analysis if they dropped out of the study early (n=3), were inadvertently randomized to receive study medication or placebo despite an early placebo response during the run-in period (see "Results" section for explanation) (n=6), or if they took less than 75% of their study medication during the entire trial (n=4). All analyses were conducted using Stata/SE, version 10.0.[30]

Additional analyses explored the effect of *H perforatum* on the child's behavior as measured by the parent-reported Child Behavior Checklist for all children and the Youth Self Report Form for children aged 11 years or older.[31] These measures have been used extensively in pediatric research because of their high reliability and validity.[31] The effect of the treatment on behavior as measured by the Conners Parent Rating Scale was also evaluated.[32] Finally, the effect of *H perforatum* on quality of life was examined, using both parent- and child-reported versions of the Pediatric Quality of Life Inventory Version 4.0 Generic Core Scales (PedsQL), a standardized measure used in the pediatric population.[33] For all of these additional measures, differences in scores between baseline and end of study were computed for each participant and mean differences were compared with 2-sample *t* tests.

Figure 1. Participant Flow



ADHD indicates attention-deficit/hyperactivity disorder.

RESULTS

Of the 146 screened potential participants, 104 met eligibility criteria, and of those, 59 agreed to participate in the study. A total of 59 participants were enrolled in the trial, and 54 (27 per group) were randomized (FIGURE 1). Six participants had a large response during the placebo-run-in period and should have been dropped from the study prior to randomization; however, they were erroneously randomized, 2 to study medication and 4 to placebo. Because they had been randomized, these participants were allowed to remain in the trial and are included in the intention-to-treat analysis. Fifty percent of participants were referred from advertisements in parenting or co-op newsletters, 20% from Bastyr University publications or Web sites, and 30% from other sources.

The demographic characteristics of the participants are displayed in TABLE 1. Forty-one percent of participants randomized to receive *H perforatum* and 44% of participants random-

ized to receive placebo had previously used medications to treat their ADHD symptoms. There were small differences between most demographic characteristics of the 2 groups. The *H perforatum* group did, however, have a higher percentage of boys (20/27 in the *H perforatum* group vs 14/27 in the placebo group) and a lower percentage with co-occurring oppositional defiant disorder (9/27 in the *H perforatum* group vs 15/27 in the placebo group). Randomized study participants took a mean of 82.0% of study medication (95% confidence interval [CI], 77.5%-86.4%) during the study, and there was no significant difference in medication adherence between the *H perforatum* and placebo groups.

In the primary intention-to-treat analysis, no significant difference was seen between the 2 groups in the change in ADHD RS-IV scores from baseline to week 8. The improvement in ADHD RS-IV total score was 5.2 points (95% CI, –9.4 to –1.1 points) in the placebo group, whereas the improvement in ADHD RS-IV total score in the *H perforatum* group was 4.4 points (95% CI, –7.9 to –0.9 points) (FIGURE 2). When the inattentiveness and hyperactivity scales were examined for differences, again, there was no significant difference in the change in scores between the groups (TABLE 2). Analysis of age- and sex-normalized percentile scores revealed no differences between the groups. There was no difference in the proportion of participants who were rated as much or very much improved on the CGI Improvement Scale (12/27 [44.4%] in the *H perforatum* group [95% CI, 25.5%-64.7%] and 14/27 [51.9%] in the placebo group [95% CI, 31.9%-71.3%]; $P=.59$).

No statistically significant difference was found between the 2 groups in the proportion of participants who experienced 1 or more rash, nausea/vomiting, headache, or sunburn adverse events during the trial (TABLE 3). Participants in the *H perforatum* group gained 3.3 lb (1.5 kg) (95% CI, 2.2-4.5 lb [1.0-2.0 kg]), and those in the placebo group gained 2.3 lb (1.0 kg) (95% CI, 1.3-3.4 lb [0.6-1.5 kg]) over the 8-week trial ($P=.22$). No significant difference was seen in change in height between the groups during the 8-week trial.

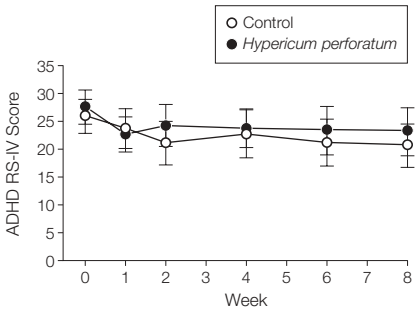
Additional analyses were conducted to determine if use of *H perforatum* was associated with improved ADHD RS-IV scores in the participants who completed the study according to protocol. As shown in Figure 1, 3 participants, 1 from the *H perforatum* group and 2 from the placebo group, dropped out of the study and were excluded from the per-protocol analysis. In addition, 4 participants were excluded from the *H perforatum* group (2 for poor adherence and 2 because of a large placebo response during the

Table 1. Baseline Characteristics of Study Participants[a]

Characteristics	Placebo (n = 27)	*Hypericum perforatum* (n = 27)
Age, mean (95% CI), y	9.7 (8.5-10.7)	9.9 (8.7-11.0)
Male sex	14 (51.9)	20 (74.1)
Race/ethnicity		
Hispanic	4 (14.8)	4 (14.8)
White	21 (77.8)	25 (92.6)
Native American	0	1 (3.7)
>1 Race reported	6 (22.2)	1 (3.7)
Home environment		
Biological parents married	18 (69.2)	17 (63.0)
Biological parents divorced	4 (15.4)	1 (3.7)
Biological parents never married	3 (11.5)	4 (15.8)
Adoptive parents	1 (3.9)	2 (7.4)
Other	0	3 (11.1)
Household income, mean (95% CI), $	61 452 (54 462-68 262)	58 264 (52 743-63 785)
Duration of ADHD, mean (95% CI), y	6.2 (5.0-7.4)	7.0 (5.7-8.2)
Parent rating of ADHD severity at baseline		
Mild	2 (7.4)	1 (3.7)
Moderate	17 (63.0)	14 (51.9)
Severe	8 (29.6)	12 (44.4)
Previous treatment for ADHD		
Counseling only	2 (7.4)	3 (11.1)
Medication only	2 (7.4)	2 (7.4)
Medications and other treatment	10 (37.0)	9 (33.3)
Natural treatment only	3 (11.1)	3 (11.1)
No previous treatment	10 (37.0)	10 (37.0)
Co-occurring conditions		
Current depression	2 (7.4)	1 (3.7)
Past depression	4 (14.8)	3 (11.1)
Any current anxiety	12 (44.4)	11 (40.7)
Current oppositional defiant disorder	15 (55.6)	9 (33.3)
Current sleep disturbance	6 (22.2)	3 (11.1)

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; CI, confidence interval.
[a]Data are reported as No. (%) of participants unless otherwise indicated.

Figure 2. Mean ADHD RS-IV Total Scores at Each Study Visit



ADHD RS-IV indicates Attention-Deficit/Hyperactivity Disorder Rating Scale–IV. Error bars indicate 95% confidence intervals around the mean score for each study visit. N=27 for each group at each time point, with the last observation carried forward for missing data.

run-in phase) and 6 participants from the placebo group (2 for poor adherence and 4 with a large placebo run-in response). In the per-protocol analyses, no statistically significant differences were seen between the groups in ADHD RS-IV scores (from baseline to week 8 on the ADHD RS-IV total score, the *H perforatum* group improved 4.8 points [95% CI, –8.7 to –0.9 points] and the placebo group improved 6.1 points [95% CI, –11.7 to –0.4 points]; *P*=.69) or in the percentage of participants who were responders on the CGI Improvement Scale (*H perforatum*, 40.9%; 95% CI, 20.7%-63.6% vs placebo, 42.1%; 95% CI, 20.3%-66.5%; *P*=.94).

Medication status was not associated with a statistically significant improvement in ADHD RS-IV total score in the regression analysis that controlled for age, sex, household income, parental rating of ADHD severity, and co-occurring oppositional defiant disorder at baseline (β coefficient for effect of medication status, –0.68; 95% CI, –5.54 to 4.18; *P*=.78).

In the blinding analysis, parents correctly identified the medication status 52.9% (95% CI, 38.5%-67.1%) of the time (κ, 0.07; *P*=.31). Children correctly identified their medication status 43.1% (95% CI, 29.3%-57.8%) of the time (κ, 0.17; *P*=.84) and the principal investigator correctly identified the medication status 56.9% (95% CI, 42.2%-70.7%) of the time (κ, 0.14; *P*=.16).

In analyses conducted to determine if use of *H perforatum* had an effect on other behavioral problems, as measured by the Child Behavior Checklist and Youth Self Report Form, there were no significant differences between the *H perforatum* and placebo groups for the a priori selected scales: internalizing problems, externalizing problems, total problems, *DSM-IV* affective, *DSM-IV* anxiety, *DSM-IV* oppositional, and *DSM-IV* conduct (TABLE 4). No differences between the *H perforatum* and placebo groups were found in the subscales of the Conners' Parent Rating Scale: for the Conners ADHD Index, from baseline to week 8, the *H perforatum* group improved 4.6 points (95% CI, –8.5 to –0.8 points) and the placebo group improved 7.8 points (95% CI, –12.3 to –3.2 points; *P*=.29) and for the Conners *DSM-IV* Total ADHD Scale, the *H perforatum* group improved 3.7 points (95% CI, –7.9 to 0.5 points) and the placebo group improved 6.9 points (95% CI, –11.5 to –2.2 points; *P*=.30). Finally, there were no differences in the quality of life of participants in the *H perforatum* and placebo groups as measured by the PedsQL. From baseline to week 8 on the parent-rated PedsQL total score, the *H perforatum* group improved 1.1 points (95% CI, –2.5 to 4.8 points) and the placebo group improved 5.1 points (95% CI, 1.1-9.2 points; *P*=.13); on the child-rated PedsQL total score, the *H perforatum* group improved 5.0 points (95% CI, 1.4-8.6 points) and the placebo group improved 6.1 points (95% CI, 1.5-10.8 points; *P*=.69). Analysis of the subgroup of children who had never previously taken pharmaceutical medication for their ADHD symptoms revealed no significant improvement of ADHD symptoms with the use of *H perforatum* vs placebo (from baseline to week 8 on the ADHD RS-IV total score, the *H perforatum* group improved 6.4 points [95% CI, –10.7 to –2.1 points] and the placebo group improved 7.6 points [95% CI, –13.0 to –2.1 points]; *P*=.71).

Table 2. ADHD RS-IV Scores

ADHD RS-IV Scales[a]	Scores, Mean (95% CI)		*P* Value
	Placebo (n = 27)	*Hypericum perforatum* (n = 27)	
Hyperactivity			
Baseline	10.3 (8.0 to 12.6)	11.8 (9.4 to 14.2)	.34
Week 4	8.8 (6.3 to 11.2)	10.4 (7.7 to 13.0)	.37
Week 8	8.3 (5.9 to 10.6)	10.0 (7.1 to 12.9)	.34
Difference, baseline to week 8	–2.0 (–4.1 to 0.1)	–1.8 (–3.7 to 0.1)	.89
Inattentiveness			
Baseline	15.6 (14.0 to 17.3)	15.8 (14.1 to 17.5)	.87
Week 4	14.0 (11.6 to 16.4)	13.4 (11.6 to 15.1)	.66
Week 8	12.4 (10.2 to 14.7)	13.2 (11.1 to 15.4)	.59
Difference, baseline to week 8	–3.2 (–5.7 to –0.8)	–2.6 (–4.6 to –0.6)	.68
Total			
Baseline	25.9 (22.9 to 28.8)	27.6 (24.6 to 30.7)	.32
Week 4	22.8 (18.5 to 27.0)	23.7 (20.3 to 27.2)	.72
Week 8	20.7 (16.7 to 24.6)	23.22 (18.9 to 27.6)	.37
Difference, baseline to week 8	–5.2 (–9.4 to –1.1)	–4.4 (–7.9 to –0.9)	.76

Abbreviations: ADHD RS-IV, Attention-Deficit/Hyperactivity Disorder Rating Scale–IV; CI, confidence interval.
[a]The ADHD RS-IV is an 18-item instrument for the assessment of ADHD symptoms. Each item is rated on a 0- to 3-point Likert scale (never or rarely, sometimes, often, or very often). A maximum score of 54 is possible and a 13-point reduction in the total score has been cited as a clinically meaningful change.

Table 3. Adverse Events

Adverse Events	Participants, % (95% Confidence Interval)		*P* Value
	Placebo (n = 27)	*Hypericum perforatum* (n = 27)	
Rash	15 (4-34)	0 (0-13)	.04
Nausea/vomiting	11 (2-29)	26 (11-46)	.16
Headache	22 (9-42)	15 (4-34)	.48
Sunburn	4 (0.1-19)	4 (0.1-19)	>.99
Any of the above	44 (25-65)	41 (22-61)	.78

COMMENT

To our knowledge, this is the first placebo-controlled trial of *H perforatum* in children and adolescents. The results of this study suggest that administration of *H perforatum* has no additional benefit beyond that of placebo for treating symptoms of child and adolescent ADHD. In our study, those in the

H perforatum group experienced neither more nor fewer adverse events than the placebo group.

Participants were recruited from the general population with advertisements in Seattle-area parenting magazines, as well as from Bastyr University's publications and Web site. To facilitate comparisons with pharmaceutical ADHD medication trials, this trial used similar enrollment criteria and the same rating scales as previous trials to monitor improvement in symptoms over the course of the study. The placebo response seen on the ADHD RS-IV is nearly identical to the placebo response seen in 1 of the atomoxetine trials.[19] The participants in this clinical trial were similar in age, sex, and comorbidity status to those treated in other ADHD clinical trials.[19,21,34,35] This study enrolled a lower percentage of participants who had previously been treated with stimulant medications than children with ADHD in national surveys (41%-44% vs 55%-74%).[36-38] As with other trials, this trial excluded participants with a history of bipolar disorder, severe depression, active suicide plan, severe conduct disorder, or psychosis.[19,20,28,34,35,39] Thus, the results of this study cannot necessarily be generalized to children with these co-occurring conditions.

This trial was designed as a single-agent clinical trial, so the results pertain only to the use of *H perforatum* in isolation for the treatment of ADHD. It is possible that *H perforatum* may work synergistically with other botanicals, vitamins, minerals, or supplements. In addition, independent testing at the beginning of the trial confirmed that the product was standardized to 0.3% hypericin. Initially in the study of *H perforatum*, focus was on the constituent hypericin, a napthodianthrone, which was believed to work as a monoamine oxidase inhibitor, but it was not found to reach levels in the blood that would be physiologically active. More recently, the attention has turned to hyperforin, a phloroglucinol derivative, which is believed to be responsible for the reuptake inhibition of serotonin, dopamine, and norepinephrine.[17] The product used for this study was not one of the newly marketed "high-hyperforin" products that range from 3% to 5% hyperforin. The product used in this trial was tested for hypericin and hyperforin content at the end of the trial and contained only 0.13% hypericin and 0.14% hyperforin. Hyperforin is a very unstable constituent that quickly oxidizes and then becomes inactive, which is likely what happened to the product used in this clinical trial.[40] The majority of *H perforatum* products on the market are at risk of oxidation due to their delivery as 2-part capsules. It is possible that a product standardized to at least 3% hyperforin could benefit children with ADHD symptoms if it were delivered in a method that limits oxidation.

Another limitation of the trial is that despite randomization, there were some baseline differences between groups. Even though these differences did not reach statistical significance, they were adjusted for in the analysis.

Table 4. Measures of Behavior as Reported by Parents and Children Aged 11 Years or Older

	Baseline		Difference, Baseline to Follow-up		
	Placebo	*Hypericum perforatum*	Placebo	*Hypericum perforatum*	*P* Value
Child Behavior Checklist measures, mean (95% CI)[a]	n = 27	n = 26	n = 25	n = 25	
Internalizing	59.0 (49.7 to 68.4)	63.8 (52.8 to 74.8)	–13.6 (–24.1 to –3.1)	–3.8 (–12.0 to 4.4)	.14
Externalizing	73.1 (63.5 to 82.7)	67.7 (56.9 to 78.4)	–12.5 (–21.2 to –3.9)	–3.9 (–10.3 to 2.4)	.10
Total	80.1 (74.3 to 85.9)	81.0 (74.4 to 87.6)	–15.2 (–23.8 to –6.6)	–4.8 (–10.3 to 0.7)	.04
DSM-IV scales					
Affective	69.4 (63.1 to 75.7)	75.9 (68.9 to 83.0)	–4.8 (–11.3 to 1.7)	–1.9 (–7.3 to 3.4)	.48
Anxiety	67.0 (60.0 to 74.1)	69.3 (62.1 to 76.4)	–5.3 (–10.4 to –0.3)	–2.9 (–7.5 to 1.7)	.47
Oppositional	77.7 (71.5 to 84.0)	75.8 (68.3 to 83.4)	–4.0 (–9.9 to 1.8)	–4.0 (–9.7 to 1.6)	.99
Conduct	74.7 (66.9 to 82.4)	72.8 (65.0 to 80.6)	–3.6 (–9.4 to 2.2)	–0.7 (–6.8 to 5.4)	.48
Youth Self Report Form measures, mean (95% CI)[a]	n = 12	n = 10	n = 12	n = 10	
Internalizing	37.6 (17.7 to 57.5)	48.2 (21.3 to 75.1)	–2.5 (–12.9 to 8.0)	–13.2 (–30.2 to 3.8)	.23
Externalizing	52.4 (37.7 to 67.2)	47.5 (26.1 to 68.9)	–5.4 (–13.9 to 3.2)	–4.1 (–21.1 to 12.9)	.88
Total	51.7 (34.3 to 69.1)	54.5 (31.2 to 77.8)	–5.0 (–13.4 to 3.4)	–12.7 (–26.7 to 1.3)	.29
DSM-IV scales					
Affective	66.6 (54.1 to 79.0)	67.9 (52.5 to 83.3)	–8.9 (–16.6 to –1.2)	–7.6 (–19.1 to 3.9)	.83
Anxiety	56.3 (52.1 to 60.4)	62.0 (50.4 to 73.6)	1.7 (–9.9 to 13.4)	–5.1 (–16.7 to 6.5)	.36
Oppositional	65.1 (57.8 to 72.3)	68.6 (57.3 to 79.9)	–3.9 (–10.7 to 3.0)	–1.4 (–14.4 to 11.6)	.70
Conduct	62.3 (52.8 to 71.9)	62.5 (52.0 to 73.0)	3.2 (–2.4 to 8.8)	–1.1 (–12.5 to 10.3)	.44

Abbreviations: CI, confidence interval; *DSM-IV*, *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition).

[a] The parent-reported Child Behavior Checklist was completed for all children and the Youth Self Report Form was completed by children 11 years of age or older. Each instrument asks the parent/youth to rate more than 100 symptoms of behavior and emotional problems on a 3-point Likert scale (not true, somewhat or sometimes true, or very true). Scores reported here are T scores, with a T score of 50 representing average functioning (SD of 10). A score of at least 64 represents symptoms in the clinical range for the 2 broadband dimensions (internalizing and externalizing problems) and a score of at least 69 represents symptoms in a clinical range for the *DSM-IV*–oriented scales (affective, anxiety, oppositional, and conduct).

Finally, the relatively short duration (8 weeks) and small sample size of this trial are limitations. The placebo group did somewhat but not significantly better than the *H perforatum* group in this study, with a mean 5.2-point reduction in total symptoms on the ADHD RS-IV total score (95% CI, 1.1- to 9.4-point reduction) vs a 4.4-point reduction (95% CI, 0.9- to 7.9-point reduction) in the *H perforatum* group. The number of participants who took part in this study was too small to completely reject the possibility of a modest benefit in terms of symptom reduction compared with placebo. The study is also too small to provide evidence that there are no adverse effects associated with the use of *H perforatum* in children. With a sample size of 27 participants per group, our study was powered to detect a 40% difference in the occurrence of adverse events between the 2 groups. Larger trials of *H perforatum* in children would be needed to assess less common events. The results of this study do not support further research on the use of *H perforatum* as formulated in this study for the treatment of ADHD in children. Nonetheless, if an *H perforatum* product with stable and high hyperforin content became available for investigation, it would be worthwhile to conduct a study to determine whether a clinically meaningful benefit could be achieved.

Author Contributions: Dr Weber had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Weber, Vander Stoep, Weiss, Biederman, McClellan.
Acquisition of data: Weber, McCarty.
Analysis and interpretation of data: Weber, Vander Stoep, Weiss, Biederman, McClellan.
Drafting of the manuscript: Weber.
Critical revision of the manuscript for important intellectual content: Weber, McCarty, Vander Stoep, Weiss, Biederman, McClellan.
Statistical analysis: Weber, Vander Stoep.
Obtaining funding: Weber, Biederman, McClellan.
Administrative, technical, or material support: Weber, McCarty, Biederman, McClellan.
Study supervision: Weber, Biederman, McClellan.
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Art . . . should simplify. That, indeed, is very nearly the whole of the higher artistic process; finding what conventions of form and what detail one can do without and yet preserve the spirit of the whole.
—Willa Cather (1873-1947)