

A Compound Herbal Preparation (CHP) in the Treatment of Children With ADHD: A Randomized Controlled Trial

M. Katz, A. Adar Levine, H. Kol-Degani and L. Kav-Venaki

Journal of Attention Disorders 2010 14: 281 originally published online 12 March 2010

DOI: 10.1177/1087054709356388

The online version of this article can be found at:

<http://jad.sagepub.com/content/14/3/281>

Published by:



<http://www.sagepublications.com>

Additional services and information for *Journal of Attention Disorders* can be found at:

Email Alerts: <http://jad.sagepub.com/cgi/alerts>

Subscriptions: <http://jad.sagepub.com/subscriptions>

Reprints: <http://www.sagepub.com/journalsReprints.nav>

Permissions: <http://www.sagepub.com/journalsPermissions.nav>


Citations: <http://jad.sagepub.com/content/14/3/281.refs.html>

>> [Version of Record](#) - Oct 26, 2010

[OnlineFirst Version of Record](#) - Mar 12, 2010

[What is This?](#)

A Compound Herbal Preparation (CHP) in the Treatment of Children With ADHD: A Randomized Controlled Trial

Journal of Attention Disorders
14(3) 281–291
© 2010 SAGE Publications
Reprints and permission:
sagepub.com/journalsPermissions.nav
DOI: 10.1177/1087054709356388
http://jad.sagepub.com


M. Katz,¹ A. Adar Levine,² H. Kol-Degani,² and L. Kav-Venaki²

Abstract

Objective: Evaluation of the efficacy of a patented, compound herbal preparation (CHP) in improving attention, cognition, and impulse control in children with ADHD. **Method:** Design: A randomized, double-blind, placebo-controlled trial. Setting: University-affiliated tertiary medical center. Participants: 120 children newly diagnosed with ADHD, meeting *DSM-IV* criteria. Intervention: Random assignment to the herbal treatment group ($n = 80$) or control group (placebo; $n = 40$); 73 patients in the treatment group (91%) and 19 in the control group (48%) completed the 4-month trial. Outcome measure: Test of Variables of Attention (TOVA) administered before and after the treatment period; overall score and 4 subscales. **Results:** The treatment group showed substantial, statistically significant improvement in the 4 subscales and overall TOVA scores, compared with no improvement in the control group, which persisted in an intention-to-treat analysis. **Conclusions:** The well-tolerated CHP demonstrated improved attention, cognition, and impulse control in the intervention group, indicating promise for ADHD treatment in children.

Keywords

ADHD, Attention Deficit Hyperactive disorder, ADHD treatment

Background

An estimated 4.4 million school-age children (ages: 3–17) in the United States are reported to have a history of ADHD diagnosis (Bloom & Cohen, 2006; National Center for Health Statistics, 2007); of these, more than 2.5 million (over 56%) are reported to be taking medication for the disorder (Centers for Disease Control and Prevention, 2003; Froehlich et al., 2007).

Recent neurobiological studies have indicated that alterations in catecholaminergic transmitter functions (mainly dopaminergic and noradrenergic), dysfunction of the reticular activating system, and diminished perfusion and cortical activity are related to ADHD symptoms (Hunt, Mandl, Lau, & Hughes, 1991; Kaplan & Sadock, 1995; Volkow et al., 1998; Zametkin & Liotta, 1998).

Additionally, the ADHD brain may be lacking in neural density. The right hemisphere of the ADHD brain appears on functional magnetic resonance imaging to be, on average, 5% smaller than that of control groups, including a smaller right anterior frontal cortex and less white matter in the right frontal lobe, which can impair sustained or focused attention. Children with ADHD exhibit global cortical thinning, predominantly in prefrontal regions, associated with attentional mechanisms (Bunge, Dudukovic, Thomason, Vaidya, & Gabrieli, 2002; Castellanos et al., 2002; Shaw et al., 2006; Swanson & Castellanos, 2002; Vaidya et al., 2005).

Psychostimulants have been proven effective in short-term controlled studies for reducing ADHD symptoms and are prescribed frequently (American Psychiatric Association, 2000; Chatfield, 2002). However, for individuals with counterindications to current drug therapies, there are few alternatives available that have demonstrated comparable effectiveness.

Additionally, controversy over long-term safety concerns surrounding drug therapies may contribute to noncompliance, or even failure, to seek treatment altogether (Charach, Figueroa, Chen, Ickowicz, & Schachar, 2006; Charach, Ickowicz, & Schachar, 2004; Jensen et al., 2007; Poulton, 2005; Scarnati, 1986; Spencer et al., 2006; Vitiello, 2008; Zachor, Roberts, Hodgens, Isaacs, & Merrick, 2006). Alternate, safe, and well-tolerated ADHD interventions, which demonstrate efficacy in improving functional parameters of ADHD and can potentially broaden therapeutic options available to patients and clinicians, warrant study and consideration.

¹ADHD and Adaptation Clinic, Sheba Medical Center, Tel Hashomer, Israel

²Tree of Healing-LD Clinic, Herzliya, Israel

Corresponding Author:

H. Kol-Degani, 5 Yodfat Street, Tree of Healing-LD Clinic, Herzliya, Israel
Email: HadassaKolDegani@gmail.com

For this purpose, we designed a randomized, double-blind, placebo-controlled clinical trial of a compound herbal preparation (referred to henceforth as “CHP”) for the treatment of ADHD. The CHP formula, a patented blend of nutritive, food-grade herbs called Nurture & Clarity, was designed by a team of Israeli herbalists (authors Levine, Kol-Degani, & Kav-Venaki), based on extensive clinical experience in treating children with ADHD, utilizing traditional Chinese medicine (TCM) protocols.

The herbs in the CHP, some considered legendary for centuries for their cognition-enhancing properties in various herbal medicine traditions, seem to demonstrate enhancement of several brain, neurological, and performance parameters as shown by a growing body of research concerning ADHD (Bensky & Gamble, 1993; Blumenthal, 1998; Brinkhaus, Lindner, Schuppan, & Hahn, 2000; Carlini, 2003; Ciferri & Tiboni, 1985; Hostettmann, Marston, Maillard, & Hamburger, 1995; Keys, 1976; Otles & Pire, 2001; Tohda et al., 2005).

Therapeutic mechanisms of the CHP herbal ingredients that enhance cognition, attention, and impulse control appear to involve enhancement of catecholaminergic transmitter functions (Wake et al., 2000), acetylcholinesterase (AChE) inhibitory activity (Kuboyama et al., 2002; Vinutha et al., 2007), noradrenaline-releasing action (Liu et al., 2002), stimulation of growth of axons and dendrites in human neuroblastoma cells (Kuboyama et al., 2002; Tohda, Kuboyama, & Komatsu, 2000; Zhao et al., 2002), enhancement of cerebral oxygenation (Liu, Lin, Xian, & Zhu, 2006), GABA mimetic activity (Mehta, Binkley, Gandhi, & Ticku, 1991), and nutritive and antioxidant effects (Bhattacharya, Satyan, & Ghosal, 1997; Paladini et al., 1999) (see appendix).

Pediatric psychopharmacology involves a developing neurobiology. Pediatric brain maturation is characterized by complex, ongoing molecular, anatomic, and organizational changes. Proliferative trophic nerve growth factors in the developing nervous system, neurons, cell processes, and neurotransmitters are critical to rapid neural network formation, growth, and development.

Increasing research indicates that this prolific growth in the developing nervous system requires adequate external intake of crucial essential nutrients, through diet or supplementation, to avoid possible compromise to optimal brain growth and development (Baynes & Dominiczak, 1999; Harding, Judah, & Gant, 2003; Makrides, Neumann, Simmer, Pater, & Gibson, 1995; Schnoll, Burshteyn, & Cea-Aravena, 2003; Stevenson, 2006).

Increasing evidence suggests that these nutritional deficiencies are common in ADHD and may even exacerbate any already existing pathology, regardless of original specific etiology (Harding et al., 2003; Kidd, 1999, 2000; Schnoll et al., 2003; Sinn, 2007; Stevenson, 2006; Wurtman, 1988; Zimmer et al., 2002).

Table 1. Baseline Characteristics of the Treatment and Placebo Groups Who Completed the Trial

| Characteristics | Treatment Group ^a | Placebo Group ^b | p-Value |
|------------------------------|------------------------------|----------------------------|-------------------|
| Age (<i>M</i> ± <i>SD</i>) | 9.82 ± 1.56 | 9.36 ± 1.97 | 0.29 ^c |
| Sex (% male) | 75 | 79 | 1.00 ^d |
| Omission score | 79.1 ± 25.9 | 87.6 ± 24.5 | 0.94 ^c |
| Commission score | 99.5 ± 14.9 | 100.1 ± 11.2 | 0.87 ^c |
| Response time (msec) | 81.9 ± 15.7 | 90.1 ± 16.3 | 0.05 ^c |
| Variability | 81.8 ± 15.9 | 86.3 ± 13.7 | 0.26 ^c |
| Overall score | 85.6 ± 12.2 | 88.8 ± 12.3 | 0.31 ^c |

a. *N* = 73.

b. *N* = 19.

c. Age and TOVA comparisons by *t*-test.

d. Fisher's exact test.

The CHP herbal ingredients supply these essential nutrients, including essential fatty acids, phospholipids, essential amino acids, B-vitamins, minerals, and other micronutrients needed for normal brain growth and development (Brinkhaus et al., 2000; Ciferri & Tiboni, 1985; Otles & Pire, 2001). Preliminary evidence supports the idea that supplementation with these nutrients may help to ameliorate ADHD symptoms, regardless of etiology (Benton & Roberts, 1998; Bornstein et al., 1990; Coleman et al., 1979; Dean, Morgenthaler, & Fowkes, 1993; Hodge et al., 2007; Koziellec & Starobrat-Hermelin, 1997; Lozoff, 1989; Sinn & Bryan, 2007; Toren, Eldar, & Sela, 1996).

The CHP formula under study was hypothesized to improve cognition, attention, and impulse control in the treatment group, as compared with the control group. The study was approved by the Sheba Medical Center Ethical Review Board, in compliance with the Helsinki declaration, and by the Israeli Ministry of Health. The Israeli Ministry of Health approved the CHP herbal ingredients as safe, food-grade botanicals.

Trial registration: Current Controlled Trials ISRCTN-10628149.

Method

Participants

A total 120 children, aged 6-12 years, participated in this study (see Table 1). All participants were recruited at the Sheba Medical Center (one of the largest university-affiliated tertiary care centers in Israel) Pediatric ADHD and Adaptation Clinic. None had a history of prior treatment for ADHD. Patients were diagnosed with ADHD (all types) by a specialized pediatric psychiatrist (author Katz), based on *Diagnostic and Statistical Manual of Mental Disorders* (4th ed.; *DSM-IV*) criteria and assessment interviews with participants and their parents. The clinical trial was

performed using a 2:1 assignment ratio for the treatment group ($n = 80$) and a control group ($n = 40$). Participants were given the CHP formula or placebo. In light of the authors' prior positive clinical experience with this CHP, the 2:1 assignment ratio was designed to minimize the number of untreated controls, yet still provide adequate statistical power (77%) to detect an improvement in test of variables of attention (TOVA) scores in the intervention versus the control group, in the order of one half of a standard deviation of the baseline scores.

During the course of the clinical trial, the participants were treated only with the CHP or placebo. Parents were given full explanations and signed informed consent forms. Verbal agreement to participate in the study was obtained from the children.

The Compound Herbal Preparation (CHP)

The CHP being evaluated consisted of a patented blend of nutritive, food-grade herbs, prepared as a highly stable, dilute ethanol extract called Nurture & Clarity. The primary active herbal ingredients of the CHP include *Paeoniae Alba*, *Withania Somnifera*, *Centella Asiatica*, *Spirulina Platensis*, *Bacopa Monieri*, and *Mellissa Officinalis* (see appendix).

The raw herbs, purchased from MayWay Co. Ltd. (Auckland, California), and a local supplier, were examined and certified as free of bacteria, fungus, and heavy metals and were approved by the Israeli Ministry of Health as safe, food-grade herbs. Standardization was ensured utilizing TLC (thin layer chromatography). The herbal formulation was prepared by the pharmacy laboratory of the Tree of Healing-LD Clinic, Herzliya, Israel.

The placebo preparation was prepared by a pharmaceutical contractor and was designed to taste, smell, and look similar to the herbal formula. The CHP and placebo formulations were supplied in identical glass containers. When evaluated by 20 medical students, they were unable to distinguish it from the CHP. A dose of 3 ml of the CHP or placebo was taken by the participants 3 times daily, before meals, diluted in 50 to 60 ml of water.

Pretreatment Screening and Baseline Assessment

None of the participants had received any form of treatment for ADHD prior to the clinical trial. Children, 6-12 years of age, who met *DSM-IV* criteria for ADHD (all types; American Psychiatric Association, 2000), as assessed utilizing a structured diagnostic interview by a specialized pediatric psychiatrist (author Katz), were eligible to participate.

All patients were required to meet a symptom severity threshold: a score of at least 1.5 standard deviations above age and gender norms, as assessed by the pediatric psychiatrist-administered and -scored parent version of the ADHD Rating

Scale-IV, and a CGI Severity ADHD Rating greater than or equal to 4 (DuPaul, Power, Anastopoulos, & Reid, 1998; Faries, Yalcin, Harder, & Heiligenstein, 2001). Other assessments included the Conners' Parent Rating Scale-Revised: Short Form (Conners, Sitarenios, Parker, & Epstein, 1998a), and the Conners' Teacher Rating Scale-Revised: Short Form (Conners et al., 1998b). Confirmation that the child's ADHD symptoms interfered with classroom performance was obtained from a review of the ADHD Rating Scale completed by the teacher, as well as through telephone contact with the teacher.

Comorbid psychiatric conditions were assessed clinically by the specialized pediatric psychiatrist (author Katz), who conducted joint parent and child clinical interviews to screen for anxiety, depression, bipolar disorder, psychosis, or other comorbid conditions, and confirmed by the Schedule for Affective Disorders and Schizophrenia for School-Age Children—Present and Lifetime Version (K-SADS-PL; Kaufman, Birmaher, Brent, Rao, & Ryan, 1996).

The screening included a medical history and a physical examination. Routine clinical laboratory tests and electrocardiogram were performed at the screening visit and at the trial end point. Exclusion criteria included all identified medical conditions or illnesses (such as anemia, hypoglycemia, thyroid disorders, etc.), psychiatric comorbid conditions, or ongoing use of any medications.

Following a clinical evaluation of each participant, children meeting the *DSM-IV* criteria for inclusion in the study were evaluated with the TOVA (Leark, Dupuy, Greenberg, Corman, & Kindschi, 1996), establishing an objective baseline for performance of tasks. Study inclusion required a standard score of below 85 on at least one of the TOVA subscales: omission, commission, response rate, or variability. The TOVA requires tracking of visual stimuli with differential response/nonresponse to target and nontarget stimuli, measuring deviations of inattention, impulsivity, response rate, and consistency (Leark et al., 1996). The trial evaluated each parameter separately as well as an overall score.

Trial Procedure

A randomized, double-blind, placebo-controlled trial was conducted over a 4-month period. Participants were randomly assigned, using a table of random numbers, to one of two groups: the treatment group ($n = 80$), or the control group ($n = 40$). Randomization was performed by a research assistant, who was distant from the intervention; had no contact with participants; was the only member of the team responsible for dispensing the appropriate formula for each participant—in identical glass bottles, labeled by name; and had no further involvement in the trial. Distribution to participants was then carried out by a blinded team member, according to the name on the label. Participants

were to receive either the CHP or a placebo, according to their random allocation.

The CHP or placebo was home administered by parents throughout the study. The identical glass bottles, labeled by patients' names, were dispensed to the parents at the regular individual meetings, at 3- to 4-week intervals. Compliance record forms, which were to be checked off and signed after each dose administration, were collected at each meeting. Parents were instructed how to prepare (dilute in water) the daily dosage for the entire day. The morning, afternoon, and evening doses were administered at home before breakfast, lunch, and dinner. Alternatively, the noon/afternoon dose was taken at school, administered by an assigned teacher, who then checked off and signed the compliance record form.

Additionally, a detailed parent-rated, daily questionnaire diary was developed for this study, which included possible adverse events, such as insomnia, abdominal pains, nightmares, anxiety, rashes, dizziness, appetite loss, and so on. Clinical assessment interviews to detect side effects were conducted 3 times during the trial period by the pediatric psychiatrist (author Katz), who was blinded as to the treatment allocation.

Figure 1 displays the flow diagram of study participants from randomization to trial completion. During the course of the trial (following randomization and coded bottle distribution), 4 participants withdrew from the intervention group and 18 from the control group. A further 6 participants, who completed the trial but had not submitted their baseline TOVA tests—3 in each group, were excluded from the main analysis, leaving 73 of those allocated to treatment (91%) and 19 of those allocated to placebo (48%), with full data. The inequality in withdrawals is unlikely to be due to chance ($p < .0001$). The reasons parents cited for dropout were (a) parental unwillingness to continue treatment in the absence of immediate improvement (2 = placebo, 0 = treatment); (b) parent perceived school pressure to begin drug treatment in cases of disruptive behavior and in the absence of immediate improvement (4 = placebo, 1 = treatment); (c) failure or inability of parents or children to comply with daily dosage administration (6 = placebo, 2 = treatment); (d) contraction of routine minor illness by participant, including throat infection, which required antibiotic treatment (1 = placebo, 0 = treatment); (e) common cold or other minor condition in which the participant discontinued daily dosage administration for more than 1 week (1 = placebo, 1 = treatment); (f) objection to CHP taste, as not sufficiently pleasant (1 = placebo, 0 = treatment); (g) family moved from area (1 = placebo, 0 = treatment); and (h) unknown (2 = placebo, 0 = treatment). Double masking of treatment status was strictly maintained by the study team. Parents, children, and the investigators remained blinded to treatment status until completion of the trial.

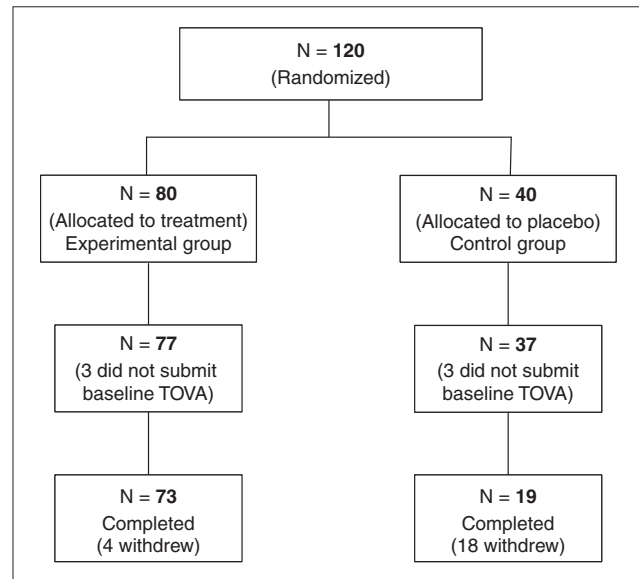


Figure 1. Flow diagram of study participants

Posttreatment Assessment

Upon completion of the 4-month trial period, each patient was reevaluated using the TOVA, which was administered by a psychology student blinded as to treatment status.

Safety Analyses

The trial was monitored for safety and tolerability by way of individual meetings at 3- to 4-week intervals, in which adverse events were systematically assessed by the primary clinician (authors Kol-Degani or Kav-Venaki) via open-ended discussion with each participant and their parents, as well as by regular monitoring of weight and vital signs, including heart rate and blood pressure. Additionally, the pediatric psychiatrist (author Katz) conducted clinical assessment interviews with each participant and his or her parents 3 times during the trial period.

No serious adverse events were reported, and the rate of even mild adverse events among CHP-treated patients was actually less than that of placebo. All complaints were mild, transient, and did not persist past the first 2 weeks of treatment. Complaints included the following:

- Gastrointestinal discomfort: Placebo group ($n = 3$) and treatment group ($n = 2$),
- Nausea: Placebo group ($n = 2$) and treatment group ($n = 2$),
- Headache: Placebo group ($n = 1$) and treatment group ($n = 2$),
- Decreased appetite: Placebo group ($n = 2$) and treatment group ($n = 1$),
- Sleep disturbance: Placebo group ($n = 4$) and treatment group ($n = 1$),

- Vomiting: Placebo group ($n = 2$) and treatment group ($n = 0$),
 Sedation: Placebo group ($n = 1$) and treatment group ($n = 1$),
 Emotional lability: Placebo group ($n = 4$) and treatment group ($n = 2$), and
 Accidental injury: Placebo group ($n = 2$) and treatment group ($n = 1$).

None of the adverse events were more frequent in the CHP group than in the placebo group. There were no significant alterations in clinical laboratory test results. There were no significant changes in weight from baseline to endpoint in either group that differed from normal growth chart rates, with no significant differences between groups.

Statistical Method

The data were analyzed using SPSS software, version 14 (SPSS Inc. Chicago, IL, USA). Fisher's exact test was used to assess the differences in categorical variables between comparison groups; t tests were applied to appraise differences in interval or continuous variables, such as the 4 TOVA subscales. Paired t tests were used to test within-subject change from baseline to completion of the trial. There was no material difference in response among the different ADHD types (ADHD-PI, ADHD-HI, and ADHD-C); consequently, they were pooled in the analysis. As the TOVA scores were not normally distributed (although reasonably so), we also undertook a nonparametric analysis using the Mann-Whitney U test, to assess the difference between the experimental groups for the change in TOVA scores, from baseline to the end of the trial.

The findings were entirely consistent with the one-way ANOVA. We next adjusted for the baseline scores of each of the 4 subscales, and the overall TOVA score by GLM ANOVA, and then added age and sex as covariates in multivariable models, to appraise the treatment effect independently of between-group differences in baseline TOVA scores, age, and sex. In addition, we undertook a conservative intention-to-treat analysis. For the 21 children in the placebo group who did not complete the trial, we allocated overall TOVA scores that reflected the mean improvement in TOVA of the 73 children in the treatment group who completed the trial and for the 7 children in the treatment group who did not complete the trial, we allocated TOVA scores that reflected no improvement during the trial.

Results

Characteristics of those allocated to treatment or placebo were similar with respect to gender (78% and 83% boys, respectively; $p = .64$). The intervention group was slightly older (9.72 ± 1.58 vs. 9.20 ± 1.82 , $p = .11$) but resembled

the control group in regard to the baseline TOVA scores (85.8 ± 12.1 vs. 87.8 ± 12.6 , $p = .53$, for the composite TOVA score). The treatment and placebo groups that completed the trial ($n = 73$ and $n = 19$, respectively) were similar in regards to age, gender, and the baseline TOVA subscales, and overall score (Table 1). There were no significant differences in sex, age, or baseline TOVA scores between control group participants who withdrew and those who persisted, 86.7 ± 13.2 ($n = 18$) vs. 88.7 ± 12.3 ($n = 19$), $p = .63$, for the baseline overall TOVA score.

In the treatment group, there was a highly significant improvement ($p < .0001$) in all 4 dimensions of the TOVA, as well as for the overall score, in contrast with the control group in which there was no significant difference in all the measures during the 4-month trial period (Table 2). A comparison of the before and after differences between the treatment and placebo groups showed that these were largest for the response time and variability subscales, substantially exceeding a full standard deviation of the baseline values in magnitude but statistically significant for the other two dimensions, as well as for the overall score, for which the difference was considerable. We controlled for the baseline values of each of the subscales by ANOVA; the findings persisted largely undiminished: treatment effect (i.e., before vs. after difference between intervention and control group scores) for omission: 15.5 (95% CI 6.5-24.5), commission: 8.0 (95% CI 1.9-14.1), response time: 15.4 (95% CI 7.4-23.5), variability: 20.2 (95% CI 10.4-29.9), and overall TOVA: 14.9 (95% CI 8.9-20.8). In a nonparametric analysis (Mann-Whitney U test; Table 3), we compared the median change in TOVA scores from the baseline values to completion of the trial between the treatment and placebo groups. The findings were entirely consistent with the previous analysis, being statistically significant for all dimensions of the TOVA, but strongest for variability, response time, and the overall score. Next, using multivariable GLM ANOVA, we assessed treatment differences for each of the 4 subscales and for the overall TOVA score adjusting for age, sex, and baseline TOVA score, to control for (nonsignificant) between-group inequalities in baseline characteristics (Table 4). The adjusted mean treatment effect for the overall TOVA score (14.8, $SE = 3.0$, $p < .0001$) was only slightly attenuated from the unadjusted difference (16.8, $SE = 3.5$). Findings for each of the 4 subscales persisted strongly. The proportion of the variance in the before versus after differences attributable to treatment group was 13.5% for omission, 7% for commission, 13.6% for response time, 16.1% for variability, and 21.9% for the full TOVA score. Finally, in a conservative intention-to-treat analysis, we included all 120 participants: 80 in the treatment group and 40 in the controls (see Methods). The treatment effect remained statistically significant ($p = .004$ when controlled for the baseline TOVA, and $p = .004$ for the multivariable model).

Table 2. Mean TOVA Score Comparisons Before and After Trial Completion Between Trial Groups Mean TOVA Scores (and Standard Deviations) in the Treatment and Placebo Groups at Baseline and After Completion of the Trial, Within Group Differences and Comparisons Between Trial Groups.

| | Treatment Group ^a | | | | Placebo Group ^b | | | | Treatment-Placebo Comparison (Difference Between the Differences) | | |
|---------------|------------------------------|--------------|-------------|----------------------|----------------------------|-------------|-------------|----------------------|--|--|----------------------|
| | Baseline | Post-trial | Difference | p-Value ^c | Baseline | Post-trial | Difference | p-Value ^c | Mean Difference ± Std. Error Difference | 95% Confidence Interval of the Difference | p-Value ^d |
| | | | | | | | | | | | |
| Omission | 79.1 ± 25.9 | 93.3 ± 18.7 | 14.3 ± 22.9 | <.0001 | 78.6 ± 24.5 | 77.7 ± 23.5 | -0.9 ± 27.6 | .89 | 15.2 ± 6.2 | 0.98-29.3 | .016 |
| Commission | 99.5 ± 14.9 | 106.6 ± 12.5 | 7.1 ± 13.8 | <.0001 | 100.1 ± 11.1 | 98.8 ± 16.5 | -1.3 ± 16.3 | .74 | 8.4 ± 3.7 | 1.0-15.7 | .026 |
| Response time | 81.9 ± 15.7 | 95.5 ± 14.5 | 13.5 ± 17.5 | <.0001 | 90.1 ± 16.3 | 83.7 ± 23.9 | -6.4 ± 17.8 | .14 | 19.9 ± 4.5 | 10.9-28.9 | <.0001 |
| Variability | 81.8 ± 15.8 | 96.3 ± 18.1 | 15.5 ± 22.6 | <.0001 | 86.3 ± 13.7 | 76.9 ± 22.5 | -9.4 ± 23.8 | .10 | 23.9 ± 5.9 | 12.2-35.6 | <.0001 |
| Overall score | 85.6 ± 12.2 | 97.9 ± 11.3 | 12.4 ± 12.9 | <.0001 | 88.8 ± 12.3 | 84.3 ± 15.7 | -4.5 ± 16.7 | .26 | 16.8 ± 3.5 | 9.8-23.8 | <.0001 |

a. N = 73.

b. N = 19.

c. Paired T-test.

d. t-test.

Table 3. Non-Parametric Comparison Between Intervention and Control Groups of Median Change in TOVA Subscales and Overall TOVA Score Over the Course of the Trial

| | Treatment Group | Placebo Group | p-Value ^a |
|---------------------------|-----------------|---------------|----------------------|
| Standard Omission score | 6 | 0 | .034 |
| Standard Commission score | 6 | 0 | .029 |
| Response time (m sec) | 13 | -2 | .0002 |
| Variability | 13 | -6 | .0004 |
| Overall score | 11 | -4.75 | <.0001 |

a. Mann-Whitney *U* test; the scores shown represent the median change over the period of the trial.

Table 4. Prediction of Post-Trial TOVA Scores by Treatment Status (treatment vs. Placebo group), Adjusted for Baseline TOVA Scores, Age and Sex Using Multivariable GLM ANOVA

| | B | SE | p | 95% CI ^a |
|--------------------------------|------|------|--------|---------------------|
| Intercept | 50.9 | 10.4 | <.0001 | 30.2-71.6 |
| Treatment versus Placebo group | 14.8 | 3.0 | <.0001 | 8.8-20.7 |
| Baseline TOVA scores | 0.31 | 0.11 | .005 | 0.09-0.52 |
| Sex (male vs. female) | 5.4 | 2.9 | .07 | -0.5-11.3 |
| Age (years) | 0.2 | 0.7 | .80 | -1.3-1.6 |

a. The adjusted treatment effects for the four subscale scores were 15.8 (95% CI 7.3-24.3) for Omission, 8.0 (95% CI 1.8-14.2) for Commission, 15.2 (95% CI 7.1-23.4) for Response time, and 20.3 (95% CI 10.4-30.2) for Variability.

Discussion

Individuals with ADHD can experience long-term chronic difficulties, often resulting in significant academic, behavioral, psychological, and social problems. A safe, well-tolerated ADHD intervention, with demonstrated efficacy in improving functional parameters of ADHD, which can offer an alternative to current drug therapy, warrants consideration and further investigation.

This study demonstrates that treatment with the CHP over a 4-month period led to improvement in all dimensions of the TOVA, which was strongest for variability, response time, and for the overall score, an improvement that was absent in the control group. This treatment effect persisted on adjustment for age, sex, and baseline TOVA values.

At termination of the trial, all children who participated in the trial were eligible for treatment with the CHP for 6

months, and those who chose this continued to be subject to regular monthly assessment monitoring, as before, with similar tolerability.

Limitations

A limitation of our trial is the differential loss to follow-up in the treatment and placebo groups, leaving 73 of the initial 80 in the treatment group and only 19 of the initial 40 in the control group for analysis. Although masking of treatment status was scrupulously maintained by the study team, the highly significant difference in the rates of completion in both trial groups ($p < .0001$) suggests that patients (or their surroundings) may have perceived their lack of improvement (largely in the control group) and may have guessed their treatment status. The high withdrawal rate revealed in the control group on completion of the trial, additionally, exacerbated the initial designed inequality between both trial groups. The investigators structured the study with a 2:1 assignment ratio (80 in the treatment group and 40 in the control group), in order to limit the number of untreated controls (under the assumption of a positive treatment effect), yet still provide adequate power.

Such unequal withdrawal can potentially lead to selection bias. The fact that the treatment and control groups that completed the trial were similar in their baseline characteristics partly alleviates this concern. Furthermore, we assume that parents of children in the control group who showed improvement would be unlikely to withdraw them from the trial. It would seem more likely that these withdrawn children would have similar or worse TOVA change scores than the control children who persisted in the trial. The supposition is supported by an analysis of the main reasons given for withdrawal—6 children of the placebo versus 1 of the treatment group withdrew because they noted no immediate improvement or due to school pressure to commence therapy (and opted for conventional drugs, which suggests no improvement), and 6 children in the placebo group versus 2 in the treatment group withdrew because they were unable to comply with the treatment regime (plus another child who did not like the taste of the placebo), which suggests a lack of motivation to continue (also indicative of no rewarding improvement).

Furthermore, significant differences between the trial groups persisted in an intention-to-treat analysis, which assumed that the children withdrawn from the placebo group experienced an improvement in their TOVA scores equal to the average improvement of the intervention group and that children withdrawn from the treatment group had no improvement. Therefore, we conclude that although unequal withdrawal remains a concern in interpreting the results of our trial, we consider that it was unlikely to produce the treatment effect noted.

Conclusion

This initial, double-blind, randomized, placebo-controlled trial suggests that the CHP is a safe, well-tolerated, effective treatment for ADHD. The treatment group demonstrated improved TOVA scores in all 4 dimensions of the TOVA that were largest for Response time and Variability. The improved TOVA scores were similar among ADHD-PI, ADHD-HI, and ADHD-C patients, compared to the placebo. No improvement in the control group was evident. Unequal withdrawal from the two trial groups might potentially have led to selection bias; however, based on the available evidence, it is unlikely that it could have influenced the trial finding in anyway.

A safe, well-tolerated therapy that effectively improves functional parameters of ADHD and may supply essential brain nutrients to children throughout critical years of brain growth and development would show promise as a potentially valuable ADHD intervention, broadening the therapeutic options available to patients and clinicians.

The need for safe and effective, well-tolerated therapeutic options for ADHD in children motivated this trial. Based on the results from this pilot study, given the safety, tolerability, and efficacy of this treatment, the CHP (Nurture & Clarity) may hold promise as an alternate treatment modality for ADHD and warrants further confirmatory investigation.

Appendix

CHP: The Ingredients

The primary active herbal ingredients of the CHP include Paeoniae Alba, Withania Somnifera, Centella Asiatica, Spirulina Platensis, Bacopa Monieri, and Melissa Officinalis.

CHP: Bio-active Therapeutic Mechanisms

Paeoniae Alba: Paeoniflorin (PF), a monoterpene glucoside isolated from Paeoniae Alba (Ohta, Ni, Matsumoto, Watanabe, & Shimizu, 1993) has demonstrated improved information transfer function of the cholinergic neuron synapses (Wake et al., 2000), seems to increase noradrenaline-releasing action (Liu et al., 2002), and enhancement of cerebral oxygenation (Liu et al., 2006; Watanabe, 1997).

Withania Somnifera: Withania Somnifera has been found to stimulate growth of axons and dendrites in human neuroblastoma cells (Kuboyama et al., 2002; Tohda et al., 2000; Zhao et al., 2002), in addition to increasing acetylcholine receptor capacity (Bhattacharya et al., 1997) and AChE inhibitory activity (Vinutha et al., 2007).

Centella Asiatica: Centella Asiatica demonstrated increased neurite elongation, dendritic growth (Moser, 1999; Soumyanath et al., 2005), and improved learning and

memory (Engert & Bonhoeffer, 1999; Nalini, Aroor, Karanth, & Rao, 1992). Centella Asiatica is especially high in B-vitamins (Brinkhaus et al., 2000): cofactors in the synthesis and functioning of serotonin, norepinephrine, dopamine, acetylcholine, as well as GABA (Baynes & Dominiczak 1999; Coleman et al., 1979).

Spirulina Platensis: Spirulina Platensis supplies essential fatty acids, B vitamins, folic acid, vitamin C, vitamin D, and vitamin E, as well as potassium, calcium, chromium, copper, iron, magnesium, manganese, phosphorus, selenium, and zinc, and all essential amino acids (Ciferri & Tiboni, 1985; Otles & Pire, 2001). Preliminary evidence supports the idea that supplementation with these nutrients may help to ameliorate ADHD symptoms (Benton & Roberts, 1998; Bornstein et al., 1990; Coleman et al., 1979; Dean et al., 1993; Hodge et al., 2007; Koziolec & Starobrat-Hermelin, 1997; Lozoff, 1989; Sinn & Bryan, 2007; Toren et al., 1996).

CHP Formula Variation (CHP- H)

The identical CHP formula was administered to all ADHD types, except that the ADHD Hyperactive-Impulsive variation (CHP-H) contained an additional calming constituent: Chrysin (5,7-dihydroxyflavone), a monoflavonoid, central benzodiazepine (BDZ) receptor ligand, naturally occurring in *Matricaria Recutita* (Chamomile), and *Passiflora Incarnata* flowers, which has demonstrated a mild calming effect (Paladini et al., 1999), with no known cognitive-enhancing effect (Blumenthal, 1998; Hostettmann et al., 1995). No sedative effect was reported among any CHP-H treated patients. As the primary CHP formula ingredients were identical and there was no material difference in the response to the slight formula variation, they were combined in the analysis and are jointly referred to as the CHP.

Disclosures

This study was funded by the Tree of Healing-LD Clinic, Herzliya, Israel. Authors Hadassah Kol-Degani and Liora Kav-Venaki are cofounders and owners of the Tree of Healing-LD Clinic in Herzliya, Israel, where they practice clinical TCM herbal medicine and acupuncture. Author Aliza Adar Levine is a practicing clinical TCM herbalist and associate of the Tree of Healing-LD Clinic.

Author Dr. Miriam Katz, a clinical pediatric psychiatrist, heads the Pediatric ADHD and Adaptation Clinic, Sheba Medical Center, Tel Hashomer, Israel. Dr. Katz has no past or present financial involvement, or future commercial interest in the CHP under study, in any capacity whatsoever, and received no financial remuneration.

Jeremy Kark MD PhD, who kindly provided technical guidance with analysis, interpretation, and presentation of the data, has no financial involvement in the CHP under study and received no remuneration.

The compound herbal preparations (CHP/ CHP-H) under study (registered by Tree of Healing-LD Clinic under the name “Rikuzit” in Israel, and “Nurture & Clarity” internationally) are at this time only available to Tree of Healing-LD Clinic patients undergoing therapy. The CHP has, until now, been produced in-house, using simple ethanol extraction in the pharmacy laboratory of the Tree of Healing-LD Clinic, in quantities sufficient to supply patients undergoing therapy. At this time, therefore, the CHP is not connected with any pharmaceutical or manufacturing company.

Declaration of Conflicting Interests

The authors declared that they had no conflicts of interests with respect to their authorship or the publication of this article.

Funding

The authors received no financial support for the research and/or authorship of this article.

References

- American Psychiatric Association. (2000). *Diagnostic and statistical manual of mental disorders* (DSM-IV-TR). Washington, DC: Author.
- Baynes, J., & Dominiczak, M. H. (1999). *Medical biochemistry*. London: Harcourt Brace.
- Bensky, D., & Gamble, A. (1993). *Chinese herbal medicine materia medica* (Rev., ed.). Seattle: Eastland Press.
- Benton, D., & Roberts, G. (1998). Effect of vitamin and mineral supplementation on intelligence of a sample of school children. *Lancet*, *i*, 140-143.
- Bhattacharya, S. K., Satyan, K. S., & Ghosal, S. (1997, March). Antioxidant activity of glycowithanolides from *Withania somnifera*. *Indian Journal of Experimental Biology*, *35*, 236-239.
- Bloom, B., & Cohen, R. A. (2006). *Summary health statistics for U.S. children: National health interview survey*. Division of Health Interview Statistics, U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Health Statistics, Hyattsville, Maryland.
- Blumenthal, M., Ed. (1998). *The complete german commission E monographs*. Boston, MA: American Botanical Council.
- Bornstein, R. A., Baker, G. B., Carroll, A., King, G., Wong, J. T., & Douglass, A. B. (1990). Plasma amino acids in attention deficit disorder. *Psychiatry Research*, *33*, 301-306.
- Brinkhaus, B., Lindner, M., Schuppan, D., & Hahn, E. G. (2000). Chemical, pharmacological and clinical profile of the east Asian medical plant *Centella asiatica*. *Phytomedicine*, *7*, 4274-4278.
- Bunge, S. A., Dudukovic, N. M., Thomason, M. E., Vaidya, C. J., & Gabrieli, J. D. (2002). Immature frontal lobe contributions to cognitive control in children: Evidence from fMRI. *Neuron*, *33*, 301-311.
- Carlini, E. A. (2003, June). Plants and the central nervous system. *Pharmacology, Biochemistry, and Behavior*, *75*, 501-512.
- Castellanos, F. X., Lee, P. P., Sharp, W., Jeffries, N. O., Greenstein, D. K., Clasen, L. S., et al. (2002). Developmental trajectories of brain volume abnormalities in children and adolescents with attention-deficit/hyperactivity disorder. *Journal of the American Medical Association*, *288*, 1740-1748.
- Centers for Disease Control and Prevention. (2003). Prevalence of diagnosis and medication treatment for attention-deficit/hyperactivity disorder. *Morbidity and Mortality Weekly Report*, *54*, 842-847.
- Charach, A., Figueroa, M., Chen, S., Ickowicz, A., & Schachar, R. (2006, April). Stimulant treatment over 5 years: Effects on growth. *Journal of the American Academy of Child and Adolescent Psychiatry*, *45*, 415-421.
- Charach, A., Ickowicz, A., & Schachar, R. (2004, May). Stimulant treatment over five years: Adherence, effectiveness, and adverse effects. *Journal of the American Academy of Child and Adolescent Psychiatry*, *43*, 559-567.
- Chatfield, J. (2002). AAP guideline on treatment of children with ADHD. American academy of pediatrics. *American Family Physician*, *65*, 726-728.
- Ciferri, O., & Tiboni, O. (1985). The biochemistry and industrial potential of *Spirulina*. *Annual Review of Microbiology*, *89*, 503-526.
- Coleman, M. C., Steinberg, C., Tippett, J., Bhagavan, H. N., Coursin, D. B., Gross, M., et al. (1979). A preliminary study of the effect of pyridoxine administration in a subgroup of hyperkinetic children: A double-blind crossover comparison with ethylphenidate. *Biological Psychiatry*, *14*, 741-751.
- Conners, C. K., Sitarenios, G., Parker, J. D., & Epstein, J. N. (1998a). The revised Conners' Parent Rating Scale (CPRS-R): Factor structure, reliability, and criterion validity. *Journal of Abnormal Child Psychology*, *26*, 257-268.
- Conners, C. K., Sitarenios, G., Parker, J. D., & Epstein, J. N. (1998b). Revision and restandardization of the Conners Teacher Rating Scale (CTRS-R): Factor structure, reliability, and criterion validity. *Journal of Abnormal Child Psychology*, *26*, 279-291.
- Dean, W., Morgenthaler, J., & Fowkes, S. (1993). *Phosphatidylserine smart drugs II, the next generation*. Menlo Park, CA: Health Freedom Publications.
- DuPaul, G. J., Power, T. J., Anastopoulos, A. D., & Reid, R. (1998). *ADHD Rating Scale-IV: Checklists, norms, and clinical interpretations*. New York: Guilford.
- Engert, F., & Bonhoeffer, T. (1999). Dendritic spine changes associated with hippocampal long-term synaptic plasticity. *Nature*, *399*, 66-70.
- Faries, D. E., Yalcin, I., Harder, D., & Heiligenstein, J. H. (2001). Validation of the ADHD Rating as a clinician administered and scored instrument. *Journal of Attention Disorders*, *5*, 39-47.
- Froehlich, T. E., Lanphear, B. P., Epstein, J. N., Barbaresi, W. J., Katusic, S. K., & Kahn, R. S. (2007). Prevalence, recognition, and treatment of attention-deficit/hyperactivity disorder in a national sample of US children. *Archives of Pediatric and Adolescent Medicine*, *161*, 857-864.

- Harding, K. L., Judah, R. D., & Gant, C. E. (2003, August). Outcome-based comparison of Ritalin versus food-supplement treated children with AD/HD—Original Research. *Alternative Medicine Review*, 8, 319-330.
- Hodge L., Kruger, M., Meyer, B., Morgan, W., Richardson, A., Sinclair, A., et al. (2007, September). Omega-3 fatty acids: Essential nutrients for our children. *Arbor Clinical Nutrition Updates*, 283S, 1-3.
- Hostettmann, K., Marston, A., Maillard, M., & Hamburger, M. (Eds.). (1995). *Phytochemistry of plants used in traditional medicine*. New York: Oxford Science Publications.
- Hunt, R. D., Mandl, L., Lau, S., & Hughes, M. (1991). Neurobiological theories of ADHD and Ritalin. In: L. L. Greenhill & B. B. Osman (Eds.), *Ritalin: Theory and patient management* (pp. 15-42). New York: Mary Ann Liebert.
- Jensen, P. S., Arnold, L. E., Swanson, J. M., Vitiello, B., Abikoff, H. B., Greenhill, L. L., et al. (2007, August). 3-year follow-up of the NIMH MTA study. *Journal of the American Academy of Child and Adolescent Psychiatry*, 46, 989-1002.
- Kaplan, H., & Sadock, B., Eds. (1995). *Comprehensive textbook of psychiatry* (6th ed.). Baltimore, MD: Williams & Williams.
- Kaufman, J., Birmaher, B., Brent, D., Rao, U., & Ryan, N. (1996). *Kiddie-SADS—Present and lifetime version (K-SADS-PL, version 1.0)*. Pittsburgh, PA: University of Pittsburgh School of Medicine.
- Keys, J. D. (1976). *Chinese herbs, their botany, chemistry and pharmacodynamics*. Rutland, VT: CE Tuttle.
- Kidd, P. M. (1999). A review of nutrients and botanicals in the integrative management of cognitive dysfunction. *Alternative Medicine Review*, 4, 144-161.
- Kidd, P. M. (2000, October). Attention deficit/hyperactivity disorder (ADHD) in children: Rationale for its integrative management. *Alternative Medicine Review*, 5, 402-428.
- Kozielec, T., & Starobrat-Hermelin, B. (1997). Assessment of magnesium levels in children with attention deficit hyperactivity disorder (ADHD). *Magnesium Research*, 10, 143-148.
- Kuboyama, T., Tohda, C., Zhao, J., Nakamura, N., Hattori, M., & Komatsu, K. (2002, October). Axon- or dendrite-predominant outgrowth induced by constituents from *Ashwagandha*. *Neuroreport*, 13, 1715-1720.
- Leark, R. A., Dupuy, T. R., Greenberg, L. M., Corman, C. L., & Kindschi, C. L. (1996). *Test of variables of attention professional manual* (Version 7.0). Los Alamitos, CA: Universal Attention Disorders.
- Liu, T. P., Liu, M., Tsai, C. C., Lay, T. Y., Hsu, F. L., & Cheng, J. T. (2002, May). Stimulatory effect of paeoniflorin on the release of noradrenaline from ileal synaptosomes of guinea-pig in-vitro. *Journal of Pharmacy and Pharmacology*, 54, 681-688.
- Liu, J., Lin, D. Z., Xian, L., & Zhu, X. Z. (2006, May). Paeoniflorin attenuates chronic cerebral hypoperfusion induced learning dysfunction and brain damage in rats. *Brain Research*, 1089, 162-170.
- Lozoff, B. (1989). Iron and learning potential in childhood. *Bulletin of the New York Academy of Medicine*, 65, 1050-1066.
- Makrides, M., Neumann, M., Simmer, K., Pater, J., & Gibson, R. (1995). Are long-chain polyunsaturated fatty acids essential nutrients in infancy? *Lancet*, 345, 1463-1467.
- Mehta, A. K., Binkley, P., Gandhi, S. S., & Ticku, M. K. (1991, August). Pharmacological effects of *Withania somnifera* root extract on GABAA receptor complex. *Indian Journal of Medical Research*, 94, 312-315.
- Moser, M. B. (1999). Making more synapses: A way to store information. *Cellular and Molecular Life Sciences*, 55, 593-600.
- Nalini, K., Aroor, A. R., Karanth, K. S., & Rao, A. (1992). Effect of *Centella asiatica* fresh leaf extract on learning and memory and biogenic amine turnover in albino rats. *Fitoterapia*, 63, 232-238.
- National Center for Health Statistics. (2007). Summary health statistics for U.S. adults: National Health Interview Survey, 2006. *Vital and Health Statistics*, 10, 234.
- Ohta, H., Ni, J. W., Matsumoto, K., Watanabe, H., & Shimizu, M. (1993). Paeony and its major constituent paeoniflorin, improve radial maze performance impaired by scopolamine in rats. *Pharmacology, Biochemistry, and Behavior*, 45, 719-723.
- Otles, S., & Pire, R. (2001, Nov-Dec). Fatty acid composition of *Chlorella* and *Spirulina* microalgae species. *Journal of AOAC International*, 84, 1708-1714.
- Paladini, A. C., Marder, M., Viola, H., Wolfman, C., Wasowski, C., & Medina, J. H. (1999). Flavonoids and the central nervous system: From forgotten factors to potent anxiolytic compounds. *Journal of Pharmacy and Pharmacology*, 51, 519-526.
- Poulton, A. (2005, August). Growth on stimulant medication; clarifying the confusion: A review. *Archives of Disease in Childhood*, 90, 801-806.
- Scarnati, R. (1986). An outline of hazardous side effects of ritalin (methylphenidate). *International Journal of the Addictions*, 21, 837-841.
- Schnoll, R., Burshteyn, D., & Cea-Aravena, J. (2003). Nutrition in the treatment of attention-deficit hyperactivity disorder: A neglected but important aspect. *Applied Psychophysiology and Biofeedback*, 28, 63-75.
- Shaw, P., Lerch, J., Greenstein D., Sharp, W., Clasen, L., Evans, A., et al. (2006, May). Longitudinal mapping of cortical thickness and clinical outcome in children and adolescents with attention-deficit/hyperactivity disorder. *Archives of General Psychiatry*, 63, 540-549.
- Sinn, N. (2007). Physical fatty acid deficiency signs in children with ADHD symptoms. *Prostaglandins, Leukotrienes & Essential Fatty Acids*, 77, 109-115.
- Sinn, N., & Bryan, J. (2007). Effect of supplementation with polyunsaturated fatty acids and micronutrients on learning and behavior problems associated with child ADHD. *Journal of Developmental and Behavioral Pediatrics*, 28, 82-91.
- Soumyanath A., Zhong, Y. P., Gold, S. A., Yu X., Koop, D. R., Bourdette D., et al. (2005, September). *Centella asiatica* accelerates nerve regeneration upon oral administration and contains multiple active fractions increasing neurite elongation in-vitro. *Journal of Pharmacy and Pharmacology*, 57, 1221-1229.

- Spencer, T. J., Faraone, S. V., Biederman J., Lerner M., Cooper, K. M., Zimmerman B., et al. (2006, May). Does prolonged therapy with a long-acting stimulant suppress growth in children with ADHD? *Journal of the American Academy of Child and Adolescent Psychiatry*, 45, 527-537.
- Stevenson, J. (2006, November). Dietary influences on cognitive development and behaviour in children. *Proceedings of the Nutrition Society*, 65, 361-365.
- Swanson, J. M., & Castellanos, F. X. (2002). Biological bases of ADHD—Neuroanatomy, genetics, and pathophysiology. In: P. S. Jensen & J. R. Cooper (Eds.), *ADHD State of the Science, best practices* (pp. 7-20). Kingston, NJ: Civic Research Institute.
- Tohda, C., Kuboyama, T., & Komatsu, K. (2000, June). Dendrite extension by methanol extract of Ashwagandha (roots of *Withania somnifera*) in SK-N-SH cells. *Neuroreport*, 11, 1981-1985.
- Tohda, C., Kuboyama, T. & Komatsu, K. (2005). Search for natural products related to regeneration of the neuronal network. *Neuro-Signals*, 14 (1-2):34-45.
- Toren, P., Eldar, S., & Sela, B. A. (1996). Zinc deficiency in attention-deficit hyperactivity disorder. *Biological Psychiatry*, 40, 1308-1310.
- Vaidya, C. J., Bunge, S. A., Dudukovic, N. M., Zalecki, C. A., Elliott, G. R., & Gabrieli, J. D. (2005). Altered neural substrates of cognitive control in childhood ADHD: Evidence from functional magnetic resonance imaging. *American Journal of Psychiatry*, 162, 1605-1613.
- Vinutha, B., Prashanth, D., Salma, K., Sreeja, S. L., Pratiti, D., Padmaja, R., et al. (2007, January). Screening of selected Indian medicinal plants for acetylcholinesterase inhibitory activity. *Journal of Ethnopharmacology*, 109, 359-363.
- Vitiello, B. (April 2008). Understanding the risk of using medications for attention deficit hyperactivity disorder with respect to physical growth and cardiovascular function. *Child and Adolescent Psychiatric Clinics of North America*, 17, 459-474.
- Volkow, N. D., Wang, G. J., Fowler, J. S., Gatley, S. J., Logan, J., Ding, Y. S., et al. (1998). Dopamine transporter occupancies in the human brain induced by therapeutic doses of oral methylphenidate. *American Journal of Psychiatry*, 155, 1325-1331.
- Wake, G., Court, J., Pickering, A., Lewis, R., Wilkins, R., & Perry, E. (2000). CNS acetylcholine receptor activity in European medicinal plants traditionally used to improve failing memory. *Journal of Ethnopharmacology*, 69, 105-114.
- Watanabe, H. (1997, February). Candidates for cognitive enhancer extracted from medicinal plants: Paeoniflorin and tetramethylpyrazine. *Behavioural Brain Research*, 83, 135-141.
- Wurtman, R. J. (1988). Effects of dietary amino acids, carbohydrates and choline neurotransmitter synthesis. *Mount Sinai Journal of Medicine*, 55, 75-86.
- Zachor, D. A., Roberts, A. W., Hodgens, J. B., Isaacs, J. S., & Merrick, J. (2006, March-April). Effects of long-term psychostimulant medication on growth of children with ADHD. *Research in Developmental Disabilities*, 27, 162-174.
- Zametkin, A. J., & Liotta, W. (1998). The neurobiology of attention-deficit/hyperactivity disorder. *Journal of Clinical Psychiatry*, 59, 17-23.
- Zhao, J., Nakamura, N., Hattori, M., Kuboyama, T., Tohda, C., & Komatsu, K. (2002, June). Withanolide derivatives from the roots of *Withania somnifera* and their neurite outgrowth activities. *Chemical & Pharmaceutical Bulletin (Tokyo)*, 50, 760-765.
- Zimmer, L., Vancassel, S., Cantagrel, S., Breton, P., Delamanche, S., Guilloteau, D., et al. (2002). The dopamine mesocortico-limbic pathway is affected by deficiency in n-3 polyunsaturated fatty acids. *American Journal of Clinical Nutrition*, 75, 662-667.

Bios

Dr. Miriam Katz is a clinical pediatric psychiatrist, heading the Pediatric ADHD and Adaptation Clinic, Sheba Medical Center, Tel Hashomer, Israel. As a specialized pediatric psychiatrist, Dr. Katz treats children with attentional disorders, as a clinical practitioner, as well as conducting ongoing research into attentional disorders.

Aliza Adar Levine is a practicing, clinical, Traditional Chinese Medicine (TCM) Herbalist, and RN. Ms. Adar Levine, is an associate of the Tree of Healing-LD Clinic, Herzliya, Israel, as well as treating attentional disorders for over 20 years in private clinical practice in Jerusalem, Israel. Ms. Adar Levine is involved in clinical studies focusing on biochemical analysis of traditional herbs, and herbal formulas.

Hadassa Kol-Degani is a Licensed Traditional Chinese Medicine (TCM) Practitioner of Herbal Medicine, and Acupuncture. As director of Tree of Healing-LD Clinic, Herzliya, Israel, a large TCM treatment and research center for attentional disorders, she has been in clinical practice for eight years, and has established and run an herbal research laboratory and pharmacy, conducting ongoing Herbal Medicine research on ADHD applications.

Liora Tanuri Kav-Venaki, a Licensed Traditional Chinese Medicine (TCM) Practitioner of Herbal Medicine and Acupuncture. Tanuri Kav-Venaki was co-founder of Tree of Healing-LD Clinic, Herzliya, Israel, a large TCM treatment and research center for attentional disorders, and was in clinical practice for seven years. Additionally Kav-Venaki was involved in ongoing Herbal Medicinal research studies.