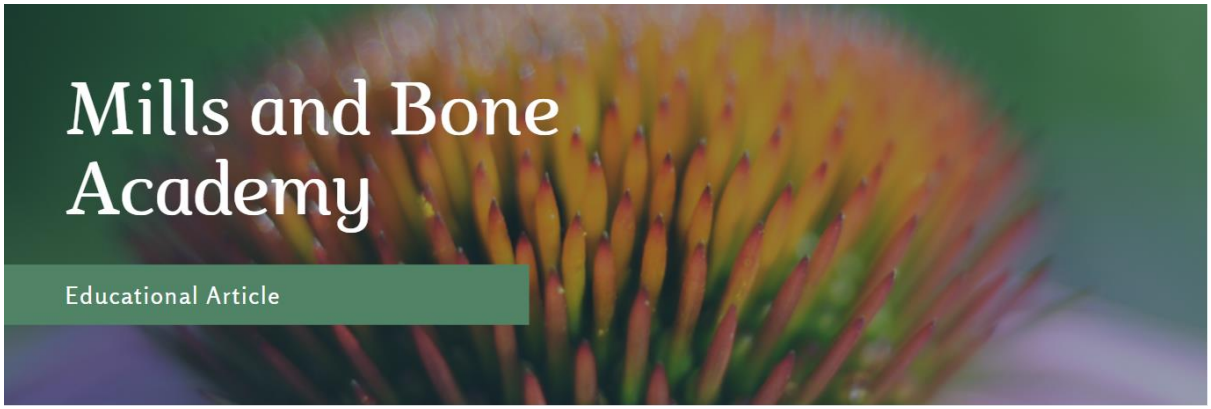

More New Herbal Developments for ADHD – Kerry Bone

Probably the largest number of recent herbal studies have examined the potential benefit of *Ginkgo biloba* extract in children suffering from ADHD (attention deficit hyperactivity disorder). The first published study was in 2001 and tested a combination of American ginseng (*Panax quinquefolium*) and Ginkgo extract (50 mg/day) in 36 children ranging in age from 3 to 17 years who met the diagnostic criteria for ADHD.[i] The design was open-label and treatment results were compared to baseline readings. After 2 weeks of treatment, the proportion of the patients exhibiting improvement ranged from 31% for the anxious-shy attribute to 67% for the psychosomatic attribute. After 4 weeks of treatment, the proportion of patients with improvement ranged from 44% for the social problems attribute to 74% for the Conners ADHD index and the DSM-IV hyperactive-impulsive attribute. Five (14%) of the 36 children reported adverse events, only two of which were considered related to the study medication.

Ginkgo had in fact already developed a reputation in ADHD, as evidenced by a survey of herbal use in children with either ADHD or depression conducted between October 2000 and July 2001 in five community health centres in Texas.[ii] Herbal medicines were given most frequently for a behavioural condition, with Ginkgo, Echinacea and St John's wort most often used.

Much later in 2010, Neiderhofer published results of a small open-label trial in six psychiatric outpatients diagnosed with attention-deficit disorder (ADD).[iii] Patients were rated at baseline and while taking Ginkgo to determine its efficacy as a treatment for ADD. Comparisons of Wender Utah ratings were used to measure behavioural changes. During Ginkgo treatment, the patients' average scores improved significantly overall, and in hyperactivity, inattention, and immaturity factors.

In the same year, an Iranian study compared Ginkgo with methylphenidate in double blind, randomized, parallel group trial conducted over 6 weeks.[iv] Fifty outpatients (39 boys and 11 girls) with a DSM-IV diagnosis of ADHD were the study population of this trial. All were randomly assigned to receive treatment using Ginkgo extract at a dose of 80 or 120 mg/day depending on weight (80 mg/day for <30 kg and 120 mg/day for >30 kg) (group 1) or methylphenidate at a dose of 20 or

30 mg/day depending on weight (20 mg/day for <30 kg and 30 mg/day for >30 kg) (group 2). The principal outcome measure was the Teacher and Parent ADHD Rating Scale-IV. Patients were assessed at baseline and at 21 and 42 days after the medication started. Results indicated that Ginkgo was less effective than methylphenidate, although the typical side effects of the drug (decreased appetite, headache and insomnia) were in evidence.

Just out in 2015 is a clinical trial from a different Iranian research center.[v] Children and adolescents with ADHD (average age around 8 years) randomly received methylphenidate (20 to 30 mg/day) plus either Ginkgo (80 to 120 mg/day) or a matching placebo for 6 weeks. Teacher and Parent forms of the ADHD Rating Scale-IV (ADHD-RS-IV) were completed at baseline, week 2, and week 6. A treatment response was defined as 27% improvement from baseline in the ADHD-RS-IV. Compared with placebo, more reduction was observed with Ginkgo in terms of the ADHD-RS-IV parent rating inattention score (-7.74 ± 1.94 vs. -5.34 ± 1.85, $p < 0.001$) and total score (-13.1 ± 3.36 vs. -10.2 ± 3.01, $p = 0.001$) as well as teacher rating inattention score (-7.29 ± 1.90 vs. -5.96 ± 1.52, $p = 0.004$). The response rate was also higher with Ginkgo compared to the placebo, based on parents' ratings (93.5% vs. 58.6%, $p = 0.002$). This trial demonstrates that not only is it safe to give Ginkgo to children with ADHD already stabilized on methylphenidate, it is also beneficial.

Just prior, in 2014, a German collaboration tested the clinical efficacy of a standardized Ginkgo extract in an open clinical pilot study in 20 children aged 6 to 13 years with ADHD.[vi] The Ginkgo was given over 3 to 5 weeks and the dosage was increased from 80 mg to a maximum of 240 mg/day if attention problems persisted. Efficacy was assessed in a multilevel approach including clinical assessment, quality of life (QoL), as well as performance and brain-electrical activity evoked during a Continuous Performance Test (CPT). This last test is also known as contingent negative variation (CNV) and uses magneto-encephalography to measure the amplitude of brain waves that correspond to attention and stimuli.

After therapy with Ginkgo extract, significant improvements were found for the parents' assessment of their children's attentiveness. Furthermore, severity of hyperactivity, impulsivity and the total score for symptom severity were decreased significantly (all $p < 0.01$). The general psychopathological profile obtained with a parent-rated assessment revealed significant improvement regarding Prosocial Behaviour ($p < 0.01$) while Peer Problems, Hyperactivity, Emotional Problems and Conduct Problems remained nearly unchanged (all $p > 0.14$). Moreover, improvements were also found in the Oppositional-Aggressive symptomatology ratings ($p < 0.01$) while Dissocial-Aggressive symptoms showed probably a floor-effect with no change ($p = 0.25$). Strains on family life also improved ($p < 0.01$), but the children's self-reported quality of life remained unchanged ($p = 0.72$). These changes in ADHD symptoms also corresponded with improved CNV measurements.

The authors concluded that their short-term, open pilot study showed that Ginkgo extract seems to be a well-tolerated complementary

medicine for treating childhood ADHD in patients who do not tolerate or are not willing to take methylphenidate. Treatment with Ginkgo over a total period of more than 700 observation days revealed an incidence rate of 0.004 adverse events per observation day without any serious side effects. They noted that following administration, interrelated improvements of behavioural ratings of ADHD symptoms and electrical brain activity were detected. However, they stressed the need for a double blind, controlled trial, such as the one just published above.

So the evidence for Ginkgo in helping children with ADHD must be regarded as promising. The correlation of symptom improvement with objective brain readings adds credibility to the observed clinical changes having a real physiological basis. The first Iranian study demonstrates that, overall, Ginkgo is not as powerful as methylphenidate, but as the German authors suggest, it may be a viable alternative in children not suited to the drug. This is especially the case now the second Iranian study found it was better than a placebo, at least in children already taking methylphenidate.

A quite small observational study from a pediatric centre in Italy pointed to a modest benefit for ginseng root (Korean or Asian ginseng, *Panax ginseng*) in ADHD. Three 14 to 17-year-old male psychiatric outpatients diagnosed with ADHD disattention type for at least 6 years were rated before and after 4 weeks of ginseng (500 mg/day extract, corresponding to about 3 g/day of original root), and compared with a period of placebo treatment.[vii] Improvement was determined using comparisons of Conners' parent ratings. For this ADHD rating scale, an improvement was observed for the inattention score (a drop from 22 to 18), the hyperactive/impulsive score (a drop from 24 to 20), and the total score (a drop from 46 to 38). Placebo showed scores similar to those of the before-treatment period: inattention score of 20, hyperactive/impulsive score of 22, and a total score of 42.

Of course, relying on a single herbal treatment in children with ADHD will probably give only limited benefits. More profound results are likely to result from a well-chosen herbal combination. In this context it is worthwhile to revisit Bacopa, which has new trial data out. Published in 2014 is an open-label study involving 31 children aged 6 to 12 years.[viii] The children received a standardised Bacopa extract at 225 mg/day for a period of 6 months. Bacopa significantly reduced the subtest scores of ADHD symptoms, except for social problems. Symptom scores for restlessness were reduced in 93% of children, whereas improvement in self-control was observed in 89%, and the attention-deficit symptoms were reduced in 85%. Similarly, symptom scores for learning problems, impulsivity and psychiatric problems were reduced for 78%, 67% and 52% of children, respectively. It was observed that 74% of the children exhibited up to a 20% reduction, while 26% of children showed between a 21% and a 50% reduction in the total subtest scores.

A combination of the herb valerian with lemon balm also seems to be helpful for restless children, according to a study from Germany. School children with restlessness, concentration difficulties and impulsiveness, but not precisely fulfilling criteria for ADHD were treated in an observational study with a combination of valerian (*Valeriana officinalis*)

root and lemon balm (*Melissa officinalis*) leaf.[ix] One hundred and sixty-nine children aged 6 to 11 years received 7 weeks of treatment. The daily dose corresponded to about 2.9 g of valerian root and 1.6 g of lemon balm. At baseline, and at two time points during the treatment, doctors rated the following symptoms: ability to concentrate, hyperactivity, impulsiveness, social behaviour, difficulties to fall asleep or to sleep through the night and morning fatigue. Problems with concentration, hyperactivity and impulsiveness were more prominent than sleep disturbances and morning fatigue. Parents also completed a questionnaire on their children's behaviour. Complete results were available for 152 children.

At the end of herbal treatment, all symptoms improved significantly from baseline ($p < 0.0001$). The proportion of children having strong or very strong symptoms of poor ability to concentrate decreased from 75% to 14%; hyperactivity decreased from 61% to 13%; and impulsiveness decreased from 59% to 22%. Difficulties to sleep through the night were reduced from 19.4% of children to 6.1%. Children having difficulties falling asleep always, very often or often decreased from 37.6% to 9.1%.

The largest improvement from the parent's perspective was found for pronounced distractibility, which decreased from a score of 4.15 to 3.35 ($p < 0.0001$). Doctors reported improvements within the family: 45% experienced reduced stress in everyday life; 30.2% experienced a more friendly atmosphere and conversation; in 13.6% of the families the frequency of common activities had increased; and 30.5% of the parents had not noticed any change in the family situation. Two children reported mild transient adverse reactions, which were judged unlikely to have been caused by the herbal treatment.

You will have noticed that many of these trials were open-label or observational. One reason for this is that it is quite difficult to recruit children for ADHD trials where there is a control group who are given only a placebo. So the better option is to use a drug control, but even here organizing such a control can be quite a challenge. A group of scientists from Israel did manage to conduct a placebo-controlled trial for a specific herbal combination. This was a randomized, double blind trial in 120 newly diagnosed children (aged 6 to 12 years) with ADHD according to the DSM-IV (80 active, 40 placebo).[x] In all, 73 patients in active group (91%) and 19 in the control group (48%) completed the 4-month trial. The herbal formulation contained white peony (*Paeonia lactiflora*), ashwagandha (*Withania somnifera*), gotu kola (*Centella asiatica*), Bacopa, lemon balm and Spirulina (*Spirulina platensis*) and the dose was 9 mL/day. According to the authors, the Spirulina was mainly present for its nutritive value.

The test of Variables of Attention (TOVA) was used to assess outcomes. There was a significant improvement in the overall TOVA score of the herbal group compared to the placebo group ($p < 0.001$). The four subscales (omission, commission, response time and variability) all demonstrated significant clinical improvement after the herbal combination, differences that were again significant from the placebo group. Hence, the treated children demonstrated improved attention, cognition and impulse control. No serious adverse events were reported and the rate of even mild adverse events among the herbal group was actually less than for placebo.

The trial did have some weaknesses and exact details of the herbal combination and doses were not provided. Also the preparation tested is not commercially available. Hence, the take-home message from this study is probably more one of principle: that a combination of herbs that are well known for improving cognitive function can exert a clinically measurable effect in children with ADHD.

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