# *Passiflora incarnata* in the treatment of attention-deficit hyperactivity disorder in children and adolescents

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**Background:** Attention-deficit hyperactivity disorder (ADHD) is a common early-onset childhood disorder that is estimated to occur in 3 to 5% of school-aged children. Stimulants are the first-line medication in the pharmacotherapy of ADHD. Nevertheless, approximately 30% of children and adolescents either do not respond to or do not tolerate stimulants. Therefore, new treatments, including alternative medicine, are still needed. Passion flower consists of the fragmented or cut, dried aerial parts of *Passiflora incarnata L.*, and is a folk remedy for anxiety and ADHD. However, there is no evidence-based document that confirms its efficacy in the treatment of ADHD. **Objectives:** We hypothesized that passion flower would be beneficial for the treatment of ADHD and report the results of a controlled trial of tablets of passion flower and methylphenidate in the treatment of this disorder. **Patients & methods:** A total of 34 children with ADHD as defined by the Diagnostic and Statistical Manual of Mental Disorders (DSM IV) were randomized to receive tablets of passiflora or methylphenidate, dosed on a weight-adjusted basis. Group 1 received passiflora 0.04 mg/kg/day (twice daily) and group 2 received methylphenidate 1 mg/kg/day (twice daily) in an 8-week, double-blind, randomized clinical trial. The principal measure of outcome was the Parent and Teacher ADHD Rating Scale. Patients were assessed by a child psychiatrist at baseline, 14, 28, 42 and 56 days after the medication was started. **Results:** No significant differences were observed between passiflora and methylphenidate on the Parent and Teacher Rating Scale scores over the course of the trial ($F = 0.007$, $df = 1$, $p = 0.93$; and $F = 0.006$, $df = 1$, $p = 0.94$, respectively). Both treatment groups demonstrated significant clinical benefit over the period of treatment as assessed by both parents and teachers. Although the number of dropouts in the methylphenidate group was higher than in the *Passiflora* group, there was no significant difference between the two protocols in terms of dropouts. In addition, decreased appetite and anxiety/nervousness were observed more often in the methylphenidate group. **Conclusions:** The results suggest that passiflora may be a novel therapeutic agent for the treatment of ADHD. In addition, a tolerable side-effect profile may be considered as one of the advantages of passiflora. Nevertheless, our study is relatively small and our results require confirmation in a larger study.

**Keywords:** alternative medicine, attention deficit hyperactivity disorder, methylphenidate, *Passiflora incarnata*

Attention-deficit hyperactivity disorder (ADHD) is a loosely defined assemblage of neuropsychiatric symptom clusters that emerge in childhood and often persist into adulthood [1]. Although the means to its diagnosis is only empiric, ADHD is increasingly being employed as a diagnostic label for individuals who display a wide range of symptoms, such as restlessness, inability to stay focused, mood swings, temper tantrums, problems completing tasks, disorganization, inability to cope with stress and impulsivity [2].

The etiology of ADHD is not understood, yet potent drugs are being employed for its medical management while safe and effective alternatives are being neglected. Neurochemical studies suggest alterations in catecholaminergic – mainly dopaminergic and noradrenergic – transmitter functions markedly contribute to the symptoms of ADHD [1–3]. The symptoms of ADHD are significantly ameliorated by agents that specifically influence these neurotransmitter systems, and animal studies implicate areas of the brain in which these neurotransmitters are most dominant [3]. ADHD is the most prevalent behavioral disorder in children, and its symptoms are frequently comingled with learning problems, oppositional conduct and depression, which altogether compound the family's emotional burden [1]. Psychostimulant medications are generally the first choice of medication for ADHD. Approximately 70% of children treated show improvement in primary ADHD symptoms and in comorbidity

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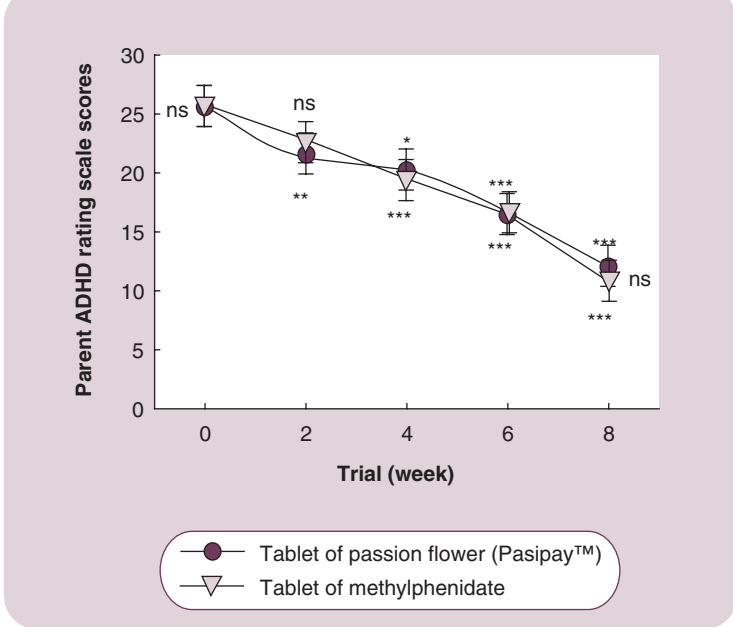
**Table 1. Baseline data.**

| | Passion flower group | Methylphenidate group |
|---|---|---|
| Girl | 6 | 5 |
| Boy | 11 | 12 |
| Age (mean ± standard deviation) | 9.58 ± 2.09 | 9.05 ± 2.53 |
| Ethnicity | All Persian | All Persian |

such as conduct disorder; although the benefits may not hold beyond 2 years [4–6]. Despite the well-established efficacy and safety of stimulants for ADHD, alternative medicines are still needed for several reasons. Approximately 30% of children and adolescents with ADHD may not respond to stimulants or may be unable to tolerate the potential adverse events, such as decreased appetite, mood lability and sleep disturbances [7–10]. Although stimulants do not increase the risk of later substance abuse in ADHD, concerns have been raised about special prescription rules, and the potential for abuse by persons other than the ADHD subject [10].

Passion flower (*Passiflora incarnata L.*) is a woody, hairy, climbing vine and is reputed to have sedative/anxiolytic properties. It has been widely used as an ingredient of herbal remedies, chiefly in the form of a liquid extract tincture [11]. Commission E approved the internal use of passion flower for nervous restlessness and the British Herbal Compendium indicates its use for sleep disorders, restlessness, ADHD, nervous stress and anxiety [11–17]. We hypothesized that passion flower would be beneficial for the treatment of ADHD, and that this could be evaluated in a double-blind, randomized, parallel group comparison of fixed daily doses of tablet of passiflora 0.04 mg/kg/day (Pasipay™, Iran Darouk, Iran) and methylphenidate.

**Figure 1. Mean ± SEM scores of two protocols on the Parent ADHD Rating Scale.**




The horizontal symbols (***) were used to express statistical significance vs. their respective baseline value.
ADHD: Attention-deficit hyperactivity disorder; ns: Nonsignificant and vertical symbols indicate the between subjects comparison. ***<0.001; **<0.01; *<0.05.

## Methods

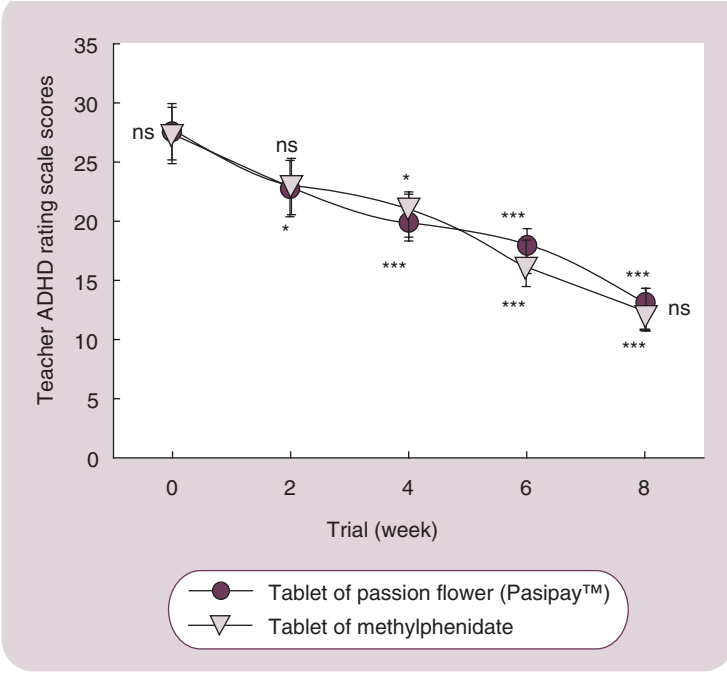
### *Trial organization*

This was an 8-week, parallel group, randomized trial undertaken in an out-patient child and adolescent clinic of Roozbeh Psychiatric Hospital, Tehran, Iran, between January 2003 and January 2004.

### *Participants*

The subjects were 34 out-patients, children (23 boys and 11 girls) between the ages of 6 and 13 years who clearly met the Diagnostic and Statistical Manual of Mental Disorders (DSM IV) diagnostic criteria for ADHD [18], and who were recruited from the out-patient child and adolescent clinic of Roozbeh Psychiatric Hospital. The diagnosis of ADHD was confirmed by a child and adolescent psychiatrist before participants were initiated into the study. All patients had a combined subtype of ADHD and were newly diagnosed. Parents were carefully interviewed and asked to rate the severity of the DSM IV inattention symptoms their children displayed. Children were excluded if they had been previously diagnosed with a psychiatric disorder or mental retardation (IQ < 70). In addition, patients were excluded if they had a clinically significant chronic medical condition, including organic brain disorder, seizures, current abuse or dependence on drugs within the last 6 months and current treatment with psychotropic medications. To participate, parents and children had to be willing to comply with all requirements of the study. After a description of the procedures and purpose of the study, written informed consent was obtained from each patient's parent or guardian. Informed consent was received before the administration of any study procedure or dispensing of study medication in accordance with the ethical standards of the investigative site's institutional review board and with the Helsinki declaration of 1975, as revised in 2000.

**Figure 2. Mean ± SEM scores of two protocols on the Teacher ADHD Rating Scale.**




The horizontal symbols (***) were used to express statistical significance vs. their respective baseline value.
ADHD: Attention-deficit hyperactivity disorder; ns: Nonsignificant and vertical symbols indicate the between subjects comparison. *** < 0.001; * < 0.05.

### *Study design*

Patients underwent a standard clinical assessment comprising a psychiatric evaluation, a structured diagnostic interview and medical history and an electrocardiogram. Patients were randomized to receive tablets of passion flower or methylphenidate in a 1:1 ratio using a computer-generated code. The assignments were kept in sealed, opaque envelopes until the point of allocation. The randomization and allocation process was carried out by the pharmacist of the Roozbeh Hospital. All study subjects were randomly assigned to one of two groups; group 1 received treatment with tablets of passion flower 0.04mg/kg/day (twice daily) and group 2 received methylphenidate 1 mg/kg/day (twice daily) in an 8-week, double-blind, randomized clinical trial. Throughout the study the person who administrated the medications, rater and patients were blind to assignments. The principal measure of the outcome was the Parent and Teacher ADHD Rating Scale that has been used extensively in Iran in school-age children, and provides valid measures of behavioral abnormality and attention [19]. Patients were assessed by a child psychiatrist at baseline, 14, 28, 42 and 56 days after the medication started. Two patients dropped out of the methylphenidate group and one from the passion flower group and were lost to follow-up, leaving 31 patients who completed the trial.

### *Statistical analysis*

A two-way, repeated-measures analysis of variance (time–treatment interaction) was used. The two groups (passion flower and methylphenidate) as a between-subjects factor (group) and the five measurements during treatment as the within-subjects factor (time) were considered. This was carried out for Parent and Teacher ADHD Rating Scale scores. In addition, a one-way, repeated-measures analysis of variance with a two-tailed post hoc Tukey mean comparison test was performed on the change in Parent and Teacher ADHD Rating Scale scores from baseline. Results are presented as mean ± standard error of the mean (SEM) differences and were considered significant with $p \leq 0.05$. To compare the demographic data and frequency of side effects between the protocols, Fisher's exact test was performed. Intention-to-treat analysis with the last-observation-carried-forward procedure was performed.

## Results

No significant differences were identified between patients randomly assigned to groups 1 and 2 with regard to basic demographic data including age, gender and ethnicity (**Table 1**).

### *Parent ADHD rating scale: tablets of passion flower versus methylphenidate*

The mean ± SEM scores of the two groups of patients are shown in **Figure 1**. There were no significant differences between the two groups at day 0 (baseline) on the Parent ADHD Rating Scale ($t = 0.05$; $df = 32$; $p = 0.95$). Both groups showed a significant improvement over the 8 weeks of treatment (Greenhouse–Geisser correction; $F = 46.51$, $df = 2.46$, $p < 0.000$) and the trend was linear. The difference between the two protocols was not significant as indicated by the effect of group; the between-subjects factor ($F = 0.007$, $df = 1$, $p = 0.93$). The behavior of the two treatment groups was homogeneous across time (groups-by-time interaction, Greenhouse–Geisser correction: $F = 0.42$, $df = 2.46$; $p = 0.69$). In addition, a one-way, repeated-measures analysis of variance showed a significant effect of both protocols on the Parent ADHD Rating Scale scores ($p < 0.000$). In both

**Table 2. Clinical complications and side effects.**

| Complications | Passion flower | Methylphenidate | p |
|---|---|---|---|
| Hallucination, delusions | none | none | none |
| Increased appetite | none | none | none |
| Decreased appetite | 1 | 7 | 0.03* |
| Palpitation | 2 | 3 | 0.39 |
| Euphoria, hypomania | none | none | none |
| Dysthymia | none | none | none |
| Anxiety, nervousness | none | 6 | 0.01** |
| Stereotypies | none | none | none |
| Weight loss | 2 | 5 | 0.39 |
| Nausea, vomiting | none | none | none |
| Dry mouth | 1 | 3 | 0.60 |
| Constipation | 1 | 2 | 1.00 |
| Diarrhea | none | none | none |
| Abdominal pain | none | none | none |
| Early awakening | 1 | 1 | 1.00 |
| Headaches | 2 | 4 | 0.65 |
| Difficulty falling asleep | 1 | 4 | 0.22 |

*$p \leq 0.05$; **$p \leq 0.01$.

groups, post hoc comparisons of the baseline Parent ADHD Rating Scale scores with the scores at day 56, by means of the Tukey procedure, revealed significant decreases from baseline ($p < 0.001$). However, post hoc testing revealed a significant reduction from baseline from week 2 in the passiflora group and from week 4 in the methylphenidate group. The difference between the two protocols was not significant at end point ($t = 0.15$, $df = 32$, $p = 0.58$).

### *Teacher ADHD rating scale: tablet of passion flower versus methylphenidate*

The mean ± SEM scores of the two groups of patients are shown in **Figure 2**. There were no significant differences between the two groups on day 0 (baseline) on the Teacher ADHD Rating Scale ($t = 0.01$; $df = 32$; $p = 0.98$). Both groups showed a significant improvement over the 8 weeks of treatment (Greenhouse–Geisser correction; $f = 39.46$; $df = 2.16$; $p < 0.000$) and the trend was linear. The difference between the two protocols was not significant, as indicated by the effect of group, the between-subjects factor ($F = 0.006$; $df = 1$; $p = 0.94$). The behavior of the two treatment groups was homogeneous across the time (groups-by-time interaction, Greenhouse–Geisser correction; $F = 0.40$, $df = 2.16$, $p = 0.68$). In addition, a one-way, repeated-measures analysis of variance showed a significant effect of both protocols on the Teacher ADHD Rating Scale scores ($p < 0.000$). In both groups, post hoc comparisons of the baseline Teacher ADHD Rating Scale scores with the scores on day 56, by means of the Tukey procedure, revealed significant decreases from baseline ($p < 0.001$). However, post hoc testing revealed a significant reduction from baseline from week 2 in the passiflora group and from week 4 in the methylphenidate group. The difference between the two protocols was not significant at end point ($t = 0.30$; $df = 32$; $p = 0.75$).

### *Retention in treatment*

In the passiflora and methylphenidate group the number of dropouts were one and two, respectively. Although the number of dropouts in the methylphenidate group was higher than the passiflora group, no significant difference was observed in the two groups ($p = 1.00$).

### *Clinical complications & side effects*

A number of probable side effects were studied (**Table 2**). Decreased appetite and anxiety/nervousness were more frequently observed in the methylphenidate group.

## Expert commentary & discussion

Current evidence supports the notion that ADHD is a brain disorder of multiple causes: genes, biologic substrates and psychosocial adversity. Despite a vast literature supporting the efficacy of stimulant treatment for ADHD, more

**Highlights**

- Attention-deficit hyperactivity disorder (ADHD) is a common early onset condition that is estimated to occur in 3 to 5% of school-aged children.
- Stimulants are the first-line medication in the pharmacotherapy of ADHD.
- Approximately 30% of children and adolescents do not respond to the stimulants or do not tolerate them.
- Such difficulties highlight the need for alternative safe and effective medications in the treatment of ADHD.
- Among alternative therapies, medicinal plants such as *Passiflora incarnata* have a special place.
- *Passiflora* may be a novel therapeutic agent for the treatment of ADHD.

efforts are needed to further develop safe and effective alternative treatments for ADHD [20–22]. Strong impetus for such efforts derives from the well-documented evidence that a substantial minority of stimulant-treated patients cannot tolerate or do not adequately respond to stimulant drugs, and the short duration of action of these drugs and their controlled status seriously limit their usefulness [7–10]. Such difficulties highlight the need for alternative safe and effective medications in the treatment of ADHD [20–22].

Among the alternative therapies, medicinal plants such as passiflora have a special place [12,13]. Our main overall finding was that tablets of passiflora and methylphenidate are effective in the treatment of ADHD. No significant difference was observed between the two protocols at the end of the trial. Nevertheless, in the passiflora group, but not the methylphenidate group, significant effects were observed by week 2 and indicates a rapid onset of action for Passiflora. In addition, the substantially lower incidence of decreased appetite and anxiety/nervousness could be an important advantage of Passiflora. However, it should be emphasized that there was no significant difference between the two treatments in terms of other side effects. To the best of our knowledge, the present study is the first double-blind, controlled trial of passiflora in the treatment of ADHD. The limitations of the present study, including the lack of a placebo group, using only a fixed dose of passiflora, the small number of participants and the short period of follow-up should be considered; therefore, further research in this area is needed. We conclude that Passiflora may be a novel therapeutic agent for the treatment of ADHD. In addition, a tolerable side-effect profile may be considered as one of the advantages of passiflora. Nevertheless, our study is relatively small and our results require confirmation in a larger study.

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