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Pharmacotherapy of Attention Deficit Hyperactivity Disorder in Children: Results of a Multicenter, Double-Blind, Placebo-Controlled Trial of Hopantenic Acid

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Objectives. To assess the efficacy and safety of hopantenic acid (Pantogam) compared with placebo in the treatment of ADHD for four months in children aged 6–12 years during a prospective, multicenter, comparative, double-blind, placebo-controlled, parallel-group trial. **Materials and methods.** The study included 100 patients constituting the safety population (50 in the Pantogam group and 50 in the placebo group). A total of 89 patients completing the study in compliance with the protocol entered the efficacy evaluation population: 45 in the Pantogam group (group 1) and 44 in the placebo group (group 2). Pantogam was given as tablets containing 250 mg at the pediatric therapeutic dose of 30 mg/kg, divided into two split doses, for four months. Assessment of patients' statements at follow-up addressed the total points scores on the DSM-IV ADHD, the CGI-S Clinical Global Impression scale, the WFIRS-P functional impairments scale, and the results of a correction test (the Toulouse–Pieron test). **Results and conclusions.** The efficacy of Pantogam in ADHD in children aged 6–12 years as compared with placebo showed a marked tendency to an increase in the proportion of patients with improvements (decreases in total points scores on the DSM-IV ADHD scale by more than 25%) by the ends of the third and fourth months of treatment: treatment responses were achieved in 66.7% and 68.9%, respectively, compared with 52.3% and 61.4% in the placebo group. Pantogam therapy also produced a decrease in disease severity from the placebo level on the CGI-S scale. At four months of Pantogam treatment, there were decreases in the severity of functional impairments on sections 4 and 6 of the WFIRES-P "Family," "School and learning," "Child's self-concept," and "Risky activities" scales. Pantogam also improved the maintenance of attention in children with ADHD, as measured using the Toulouse–Pieron test (quality and rate of performance) as compared with placebo. Treatment with Pantogam at a mean daily dose of 30 mg/kg for four months demonstrated a favorable safety profile, no different from that of placebo.

Keywords: attention deficit hyperactivity disorder, treatment, hopantenic acid (Pantogam), multicenter double-blind, placebo-controlled trial.

Attention deficit hyperactivity disorder (ADHD) is the commonest psychoneurological disorder of childhood age and is encountered in 5% of the child population [1–3]. ADHD is manifest as difficulties in concentrating and maintaining attention, with extreme movement activity (hyperactivity), and impulsivity. These symptoms do not correspond to age-normal behavioral characteristics and are consistently seen in at least two types of context: at school or in preschool establishments, at home, in leisure or sport activities, in social locations, and other situations.

The treatment of ADHD in children must start as early as possible and should be complex, including medication and various types of behavioral, educational, neuropsychological correction, and family psychotherapy [2–6]. Russian

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specialists treating ADHD traditionally use nootropic agent, which have stimulatory actions on those cognitive functions which are poorly developed in children with ADHD.

Hopantenic acid (Pantogam) is a nootropic agents with a wide spectrum of clinical applications. In terms of its chemical structure, it is close to natural compounds and is the calcium salt of D(+)-pantoyl-γ-aminobutyric acid, a higher homolog of D(+)-pantothenic acid (vitamin B_5), in which β-alanine is replaced by γ-aminobutyric acid (GABA). This homolog, as compared with other nootropic agents, is a natural metabolite of GABA in nervous tissue. Hopantenic acid, unlike GABA, crosses the blood-brain barrier and is barely metabolized in the body; its pharmacological effects are due to the actions of the whole molecule rather than its separate fragments. The nootropic effects of hopantenic acid are linked with its stimulatory action on tissue metabolism (metabolic and bioenergetic) in neurons; it enhances GABAergic inhibition via interactions with the ionotropic $GABA_A$ receptor system, has activatory actions on the dopaminergic and acetylcholinergic systems of the brain, including increasing acetylcholine synthesis, and it improves choline transport in structures supporting memory mechanisms [7].

The efficacy of hopantenic acid in the treatment of ADHD has previously been demonstrated in several trials [8–10], though in small groups of patients. This generates the need for additional controlled studies of the efficacy and safety of its use.

The influences of Pantogam syrup at doses of 30–50 mg/kg/day) were evaluated in children aged 7–8 years with neurotic reactions, 40% of whom were also diagnosed with ADHD [8]. The results indicated that significant improvements from baseline were seen in relation to the speed and quality of sensorimotor reactions, visuomotor coordination, and short-term visual memory. Children aged 6–12 years with hyperactivity disorder (inattention, hyperactivity, impulsivity) showed significant increases in cognitive productivity on the background of using Pantogam, while no such changes were seen in children receiving placebo [9]. Children with ADHD on long-term treatment with Pantogam showed decreases in the severity of illness as assessed on the DSM-IV ADHD scale (general assessment, impaired attention, and hyperactivity/impulsivity) and decreases in measures on the functional impairment scale WFIRS-P, which is evidence of a decrease in the difficulties in the behavior of children with ADHD both in the family and in society, Pantogam treatment having a significant influence on study parameters by just two months [10].

The aim of the present work was to assess the efficacy and safety of the original Russian formulation Pantogam in comparison with placebo in the treatment of ADHD for four months in children aged 6–12 years in a prospective, multicenter, comparative, double-blind, placebo-controlled, parallel-group trial.

Materials and Methods. Patients were included in the trial in compliance with the following criteria: diagnosis of ADHD in terms of the ICD-10 criteria [11], hyperdynamic (hyperkinetic) syndrome with attention deficit; age 6–12 years (inclusive); severity of ADHD on the CGI-ADHD-S scale [12] 3–6 points; total score on assessment of the clinical signs of ADHD on the ADHD-DSM-IV scale [13] at least 25 for boys and 22 for girls; informed consent form signed by parents or guardians before any trial procedures are carried out.

Exclusion criteria were as follows: age less than 6 years or greater than 12 years; body weight less than 17.5 kg or greater than 60 kg; presence of concomitant diseases which the investigator felt required treatment with barbiturates, anticonvulsants, or any other nootropic agents; malignant neoplasms of any location; benign CNS tumors or other benign tumors able to have adverse influences on the course of the main disorder; history-based indications of intolerance of components of the formulation of the hypersensitivity to any component of the formulation; presence of concomitant diseases exacerbating the course of the disorder and influencing the treatment outcome (obesity greater than grade 1, diabetes mellitus types 1 or 2, blood disorders, immunodeficiency states, infectious diseases, etc.); severe renal failure (creatinine clearance less than 30 ml/min), including in the history; liver failure in the medical history; use of any medication for the pharmacotherapy of ADHD during the month prior to the start of the trial; involvement in any other clinical drug trial during the month prior to the trial; suspected incompetence on the part of the patient, parents, or legal guardian in relation to the study procedures (as determined by the investigator); history of epilepsy or psychotic disorder.

In addition, patients were excluded from the trial in situations classified as premature withdrawal (exclusions) due to: noncompliance with the inclusion or non-inclusion criteria; adverse events requiring interruption of trial participation for the patient's safety and wellbeing; the need, for any reason, to take drugs as indicated in paragraph 3 of the non-inclusion criteria; refusal of the patient, parents, or legal guardian to continue participation in the trial for any reason or refusal to provide informed consent; inability to continue follow-up of the patient; protocol violations having significant influences on assessment of efficacy and safety.

Patients were randomized to two groups.

Patients of group 1 were given Pantogam as 250-mg tablets at a therapeutic dose of 30 mg/kg body weight divided into two split doses after meals. Treatment with Pantogam continued for four months. Doses were slowly escalated during the first week.

Patients of group 2 received placebo as tablets with external appearance, packaging, and labeling identical to those of the study drug, using the same after-meals protocol, for four months.

The trial included 100 patients in the population for the safety assessment – 50 in group 1 and 50 in group 2; 89 patients completing the study per protocol made up the pop-

TABLE 1. Characteristics of Patients Completing the Trial per Protocol and Entering the Efficacy Evaluation Population

Parameter	Group 1 (Pantogam, $n = 45$)	Group 2 (placebo, $n = 44$)
Age, years, $M \pm SD$	8.7 ± 2.1	8.24 ± 1.63
Body weight, kg, $M \pm SD$	31.9 ± 8.9	29.58 ± 8.32
Height, cm, $M \pm SD$	136.1 ± 13.6	134.11 ± 11.07
Gender		
male	39 (86.7%)	34 (77.3%)
female	6 (13.3%)	10 (22.7%)
Clinical forms of ADHD:		
combined type of ADHD	11	16
ADHD with mainly impairment to attention	31	24
ADHD with mainly hyperactivity/impulsivity	3	4
Total points score on DSM-IV ADHD	33.2 ± 5.7	35.1 ± 7.9
Assessment on CGI ADHD-S	4.4 ± 0.7	4.4 ± 0.7

ulation for assessment of efficacy – 45 in group and 44 in group 2 (Table 1).

The combined type of ADHD was diagnosed in 27 patients; 55 predominantly had impairments to attention, and seven had a predominance of hyperactivity-impulsivity.

The data presented in Table 1 show that patients in the two groups were comparable in terms of age, body weight, and height. The predominance of cases of the combined type of ADHD and ADHD mostly with impairments to attention in both groups and the mainly male gender of patients are consistent with published data on ADHD [1–3]. The two treatment groups were not significantly different in terms of gender, the proportion of patients with different clinical forms of ADHD, or the severity of ADHD symptoms.

All patients included in the population for analysis of efficacy had clinically marked signs of ADHD; there were no statistically significant ($p < 0.05$) differences between total DSM-IV ADHD scores [13] or scores on the separate subscales. Total scores on the DSM-IV ADHD scale were 25–43 in boys in group 1, 26–49 in boys in group 2, 22–44 in girls in group 1, and 24–41 in girls in group 2. In addition, the study groups were not statistically significant different in terms of the mean scores on the CGI ADHD-S scale [12].

Patients were assessed to evaluate treatment efficacy before treatment initiation and then at 1, 2, 3, and 4 months of treatment. Criteria for evaluating efficacy were:

Primary efficacy endpoint: changes in the total points scores on the DSM-IV ADHD scale [13] by at least 25% compared with baseline.

Secondary efficacy endpoints: 1) comparison of total points scores on the CGI ADHD-S scale [12] in groups compared with baseline values; 2) comparison of total points scores on the DSM-IV ADHD scale [13] in groups compared with baseline values; 3) comparison of assessment on the Weiss Functional Impairments Scale, form completed by Parents (WFIRS-P) [14] compared with baseline; 4) dynamics of results of correction test (Toulouse–Pieron test) [15].

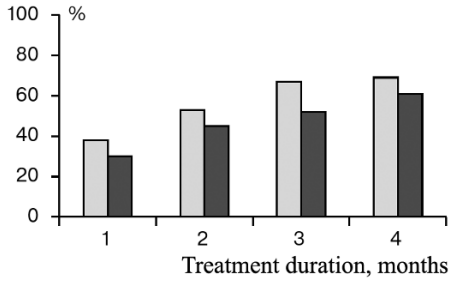

Fig. 1. Proportions of patients with clinical improvements in the two groups (decreases in total points scores on the DSM-IV ADHD scale by 25% or more from baseline) at 1, 2, 3, and 4 moths of treatment. Light columns show Pantogam, dark columns show placebo.

Results and Discussion. The proportion of patients with marked positive improvements (decreases in total scores on the DSM-IV ADHD scale by 25% or more) increased in patients of group 1 throughout the trial (Fig. 1). One month from treatment initiation, responses were seen in 17 patients (37.8%) in the Pantogam treatment group and 13 patients (29.6%) in the placebo group; at two months the number of patients with marked changes on the DSM-IV ADHD scale increased to 24 (53.3%) in group 1 and 20 (45.5%) in group 2. An analogous but more marked tendency to changes was seen at three months of treatment: 30 patients (66.7%) in group 1 and 23 patients (52.3%) in group 2. At four months of treatment, the groups, as previously, differed in terms of the study parameter: improve-

TABLE 2. Comparison of Mean Total ADHD Severity Scores on the CGI (CGI-ADHD-S) at 1, 2, 3, and 4 Months of Treatment in the Two Groups of Patients

Time point	Points, CGI-ADHD-S ($M \pm SD$)		p (Mann–Whitney test)
	Group 1, $n = 45$	Group 2, $n = 44$	
Before treatment	4.4 ± 0.7	4.4 ± 0.7	0.97
Treatment 1 month	3.2 ± 1.0	3.5 ± 0.7	0.15
Treatment 2 months	3.0 ± 1.0	3.3 ± 0.8	0.22
Treatment 3 months	2.7 ± 0.9	3.1 ± 1.2	0.07
Treatment 4 months	2.4 ± 1.2	2.9 ± 1.2	0.014*

*Statistically significant difference between the two groups.

ments were seen in 31 patients (68.9%) in group 1 and 27 patients (61.4%) in group 2. However, the difference between groups did not reach statistical significance.

Clinical improvements in children in group 2, i.e., the placebo group, could be due to the fact that the patients and their parents entered into regular contact with qualified specialists from the time of screening, promoting improvements in parents' knowledge of their children's problems and ways of overcoming them, as well as interactions between parents and children and the psychological climate in families.

Assessment of the efficacy of Pantogam was based on changes in scores on the CGI-S scale [12], which involved ranking patient status from 1 to 7 points, where 1 point corresponds to the state of "normal, not ill at all" and 7 points to the state of "patient very severely ill." Results from comparison of mean scores on the CGI-S for the severity of ADHD at 1, 2, 3, and 4 months of treatment as compared with baseline for the trial groups are shown in Table 2. Initial mean points scores in the two groups were identical and there were no statistically significant differences at 1, 2, or 3 months of treatment, though there was a tendency to a decrease in the severity of ADHD in the group of patients treated with Pantogam. Statistically significant efficacy of Pantogam was seen at four months of treatment: the mean CGI-S score in group 1 was 2.4 ± 1.2, which was significantly lower than that in group 2, at 2.9 ± 1.2, $p = 0.014$. This result corresponds to a significant difference in the distribution of individual assessments in terms of CGI-S points scores at four months of treatment in the two groups (Fig. 2). In group 1, most patients achieved maximum scores at follow-up of 1, 2, and 3 points, while most of those in group 2 achieved disease severity scores of 3, 4, and 5. Thus, at four months of Pantogam treatment, there was a statistically significant decrease in disease severity on the CGI-S scale, as compared with the placebo group.

Results obtained by individual assessment of treatment efficacy showed that not all children with ADHD who might respond positively to Pantogam treatment displayed significant regression of the main symptoms of ADHD in the first 1–2 months of treatment. This effect could need longer periods of time. In particular, the data obtained here showed that the number of patients with improvements on Pantogam treatment increased by three and four months.

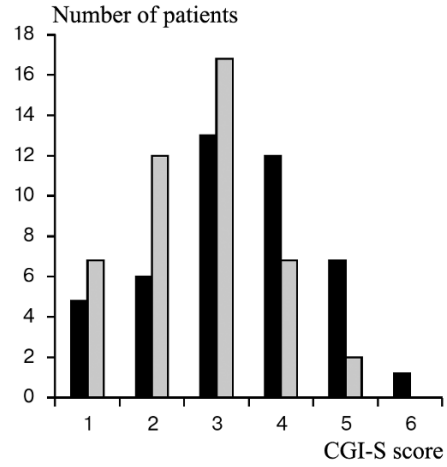

Fig. 2. Numbers of patients with different points scores on the CGI ADHD-S scale in groups 1 and 2 at four months of treatment. Light columns show group 1, dark columns show group 2.

The present study also assessed treatment responses in relation to the clinical form of ADHD (see Table 1) at 1, 2, 3, and 4 months of treatment. The most significant positive results were obtained in patients with the combined type of ADHD. At four months of treatment, total points scores on the DSM-IV ADHD scale in patients with the combined form of ADHD decreased more significantly in group 1 patients than in group 2 patients: to 19.8 ± 7.5 and 25.2 ± 11.3, respectively, though this between-group difference did not reach statistical significance ($p = 0.15$). At the same time, there was a statistically significant ($p = 0.04$) reduction in the mean score for symptoms on the "hyperactivity–impulsivity" scale of the DSM-IV ADHD scale in group 2 as compared with group 1: to 9.3 ± 3.4 and 13.1 ± 6.0 points, respectively. In patients with the combined type of ADHD, those in group 1, as compared with those in group 2, also showed a tendency to a decreased score on the "Impaired attention" scale, to 10.6 ± 5.6 and 12.7 ± 6.0, respectively, $p = 0.35$. Statistically significantly changes in ADHD

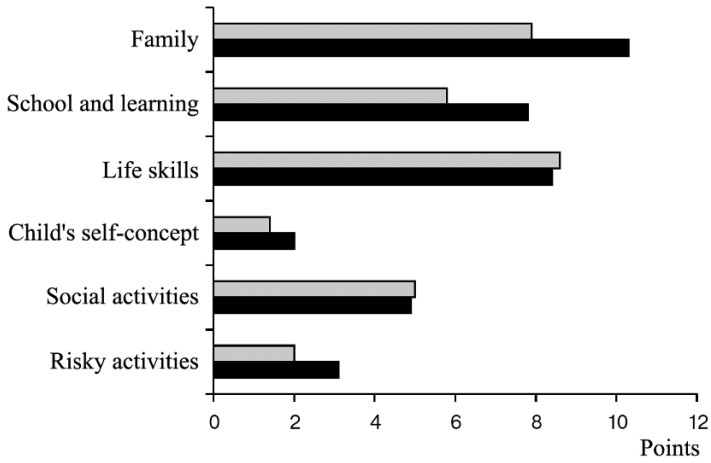

Fig. 3. Measures of functional impairments on the WFIRS-P scale at four months of treatment in two groups of boys with ADHD. Light columns show group 1, dark columns show group 2. The abscissa shows points scores.

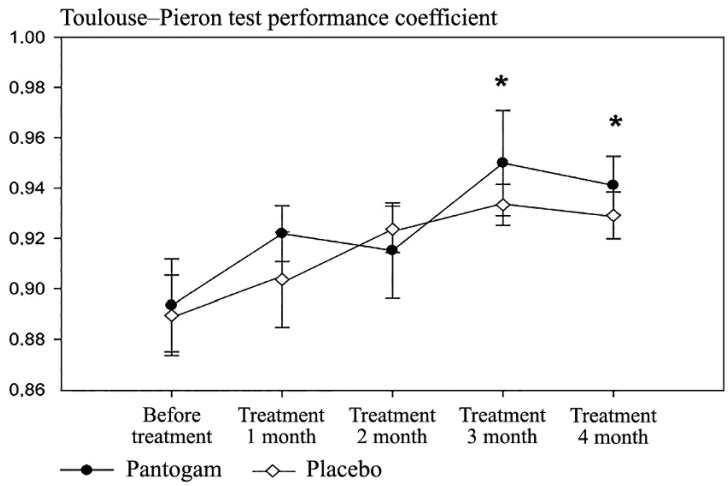

Fig. 4. Dynamics of the Toulouse–Pieron test performance coefficient in groups 1 and 2. Data are shown as means and standard errors. *Statistically significant differences between groups 1 and 2, $p < 0.05$.

symptoms compared with the pre-treatment baseline were seen in patients with this type of ADHD in both group 1 and group 2.

In contrast to the decrease in the main symptoms of ADHD, more time was needed to overcome impairments to functioning of in different areas. The WFIRS-P scale [14] was used as a sensitive and clinically significant tool for assessing the severity of functional impairments in patients with ADHD in the present study. Figure 3 shows measures of the severity of functional impairments in boys with ADHD in groups 1 and 2 at four months of treatment. The clear positive effects of Pantogam ($p < 0.01$ compared with pretreatment values), in contrast to those of placebo, were apparent as decreases in assessments on four of the six sections on the WFIRS-P: "Family" (7.9 ± 5.8 points in the Pantogam group and 10.3 ± 7.6 points in the placebo group), "School and learning" (5.8 ± 4.15 points in the Pantogam group and 7.8 ± 6.6 points in the placebo group), "Child's self-concept" (1.4 ± 1.4 points in the Pantogam group and 2.0 ± 1.9 points in the placebo group), and "Risky activities" (2.0 ± 1.5 in the Pantogam group and 3.1 ± 3.1 points in the placebo group). It should be noted that a tendency to the appearance of these between-group differences was seen by three months, though these became statistically significant by the end of treatment courses, i.e., by four months.

The influences of study drug in patients were evaluated in relation to voluntary attention, concentration, and ability to work using the Toulouse–Pieron test, a version of a correction test. Speed and accuracy were assessed (coefficient of performance). Improvements in performance speed from baseline reached statistical significance in the groups from the first month of treatment ($p < 0.001$) and then continued to the end of the study. These data indicate that performance speeds in the study groups were not statistically significant different at one month of treatment (32.5 ± 14.4 symbols in group 1 and 31.5 ± 9.8 in group 2, $p = 0.87$) or at two months

(36.3 ± 16.5 symbols in group 1 and 34.3 ± 11.1 in group 2, $p = 0.81$). At the end of treatment, the mean task performance speed was 40.2 ± 16.8 symbols in group 1 and 38.0 ± ± 13.1 in group 2, which, according to normal rates of test performance, correspond to a good age norm. At the end of the trial there was no difference between the performance speeds in the two groups ($p = 0.71$).

As regards performance quality and the number of errors, the task performance coefficient showed no between-group difference at one month (0.92 ± 0.07 and 0.90 ± 0.13 in groups 1 and 2, respectively, $p = 0.46$) or two months (0.92 ± 0.13 and 0.92 ± 0.06, $p = 0.14$). Significant differences in test performance accuracy appeared by three months of treatment: the mean performance coefficient in group 1 was 0.95 ± 0.14 and was statistically significantly ($p = 0.015$) greater than the analogous coefficient in group 2 (0.93 ± 0.05). This effect of Pantogam persisted at four months of treatment: mean performance coefficients in groups 1 and 2 were 0.94 ± 0.08 and 0.93 ± 0.06, respectively ($p = 0.008$) (see Fig. 4). Both speed and the test performance coefficient approached normal: at four months of treatment, values in group 1 corresponded to the age normal, while those in group 2 remained below normal, even though they had increased significantly from the very low pretreatment values.

Thus, Pantogam treatment promoted significant improvements in measures of maintained attention, which was confirmed by increases in the correction test performance coefficient in combination with performance speeds at three and four months of treatment.

No serious adverse events (AE) were seen in the present study, which is evidence for the favorable safety profile of this drug. A total of 49 AE were recorded in 34 patients, of which 28 AE were seen in the Pantogam treatment group and 21 in the placebo group. Of this total, 30 AE were clinically apparent, four of which – acute respiratory virus infections (ARVI), acute respiratory infections (ARI), chickenpox, and aggressive behavior – were seen in both groups; a further three – influenza, irritability, and anomalous dental enamel structure – occurred only in group 1; a further three AE – atopic dermatitis, allergic rhinitis, and bradycardia – occurred only in the placebo group. All other AE were clinically minor deviations from normal values of laboratory and instrumented investigation results. In the view of the clinical investigators, none of the AE met the criteria for being regarded as serious. In some case, the development of AE (ARVI/ARI, influenza, chickenpox, allergic rhinitis, atopic dermatitis) required the use of specific treatment in the form of medication; these AE were evaluated as clinically significant and of mild-moderate severity. Assessment using the WHO criteria and the Naranjo algorithm indicated that the significance of the cause-effect relationship between drug and AE was in most cases dubious, only five cases being regarded as possible (hyperbilirubinemia, leukopenia, thrombocytopenia, irritability, aggressive behavior). Cases of aggressive behavior were seen in the placebo group at the same rate. Overall, statistical analysis did not identify any significant differences between groups in terms of the frequency of deviations in clinical and biochemical blood tests or measures of urinalysis from normal values in the groups of patients studied.

The safety of Pantogam as compared with placebo was assessed in the present trial by clinical and neurological examination of the patients, along with dynamic assessment of vital signs at each visit. The results of clinical and neurological examination, the state of the major organs and organ systems, and the nervous system revealed no significant between-group differences at the end of the trial. This provided grounds for concluding that Pantogam is no less safe than placebo.

Thus, analysis of the therapeutic efficacy of Pantogam in ADHD in children aged 6–12 years, as compared with placebo, showed a more marked tendency to an increase in the proportion of patients with improvements (decreases in total points scores on the DSM-IV ADHD scale by more than 25%) by the ends of the third and fourth treatment months, when treatment responses were obtained in 66.7% and 68.9% of patients, compared with 52.3% and 61.4%, respectively, in the placebo group. At four months of Pantogam treatment, the severity of the disorder decreased statistically significantly on the CGI-S in children aged 6–12 years with ADHD, as compared with placebo. Pantogam decreased the severity of ADHD symptoms assessed on the DSM-IV ADHD scale in children aged 6–12 months with diagnoses of ADHD as compared with placebo. Regression of the main symptoms of ADHD started in the first 1–2 months of treatment and continued throughout the following two months of treatment, reaching a maximum level at four months of treatment in the subgroup of patients with the combined type of ADHD. As compared with placebo, Pantogam decreased the severity of functional impairments on the WFIRS-P scale in children aged 6–12 months with ADHD at four months of treatment. The clear positive effects of Pantogam were apparent as improvements in assessments on four of the six sections of the WFIRS-P: the "Family," "School and learning," "Child's self-concept," and "Risky activities" scales. Pantogam also improved measures of maintained attention on the Toulouse–Pieron test (in terms of both performance quality and speed) as compared with placebo in children aged 6–12 years with ADHD. Pantogam at a mean daily dose of 30 mg/kg for four months had a favorable safety profile, which was not significantly different from that of placebo.

The authors have no conflicts of interests.

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