

## **A randomized double blind placebo-controlled drug trial with Mentat in children with Attention Deficit Hyperactivity Disorder**

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### **SUMMARY**

*A randomized double blind placebo-controlled trial was conducted to evaluate the efficacy of Mentat, an herbal formulation, in school going children with Attention Deficit Hyperactivity Disorder (ADHD). A total of 195 children were screened, out of which 60 satisfied the DSM-IV criteria for ADHD. Among those enrolled in the study, 30 received Mentat and 30 received placebo. An assessment of academic functioning along with psychological tests was done before and after the treatment. Malin's Intelligence Scale for Indian Children (MISIC), Conner's 10 point rating scale, Kaufman Assessment Battery for Children (KABC) and brain SPECT (Simple Photon Emission Computed Tomography) scans and subtests were assessed. Six children were dropped from the study, as they were lost to follow-up and another 4 children showed variable results. Thus, statistical analysis was carried out in only 50 children. The Conner's test and Gestalt closure subtest of KABC showed a statistically significant improvement in the Mentat group as compared to the placebo group. Pre- and post-SPECT scan observations showed improvement in three children in the Mentat group as compared to one child in the placebo group. For all other tests, no significant difference was found between the Mentat and placebo groups.*

### **INTRODUCTION**

Attention Deficit Hyperactivity Disorder (ADHD) is a common neurobehavioral disorder of childhood punctuated with unacceptable behavior, restlessness, inattentiveness, excitability, impulsiveness, fidgetiness, distractedness and disruptiveness.<sup>1,2</sup> The prevalence of ADHD in the school age population, varies from 4 to 12% and estimated prevalence, based on combining studies is reported to be ~8 to 10%. With the DSM-IV criteria (APA 1994), ADHD is common in males, though more females have been diagnosed as predominantly inattentive type.<sup>3,4</sup> The etiology is multifactorial. The importance of genetic transmission of ADHD has been highlighted by recent studies.<sup>5-6</sup> Other possible factors include dysfunction of the adrenergic or serotonergic systems, high blood levels of lead,<sup>7</sup> alcohol consumption by pregnant women,<sup>8</sup> family stress and low socioeconomic status.<sup>9,10</sup>

The treatment of ADHD requires a multimodal approach. Medications are often recommended for children with marked behavioral and cognitive problems. Stimulants, which include amphetamine, methylphenidate and pemoline, are the primary pharmacological intervention. Their efficacy has been demonstrated in more than 150 controlled studies.<sup>2</sup> They have shown to be most effective in the treatment of children with disorders of activity modulation and attention regulation, resulting in significant improvement in 70-80% of affected children.<sup>11-14</sup> However, they are ineffective or even contra-indicated because of adverse side effects in 10-30% of the cases.<sup>2,15</sup>

Ancient Indian medical literature advocates the use of herbal drugs for various mental disorders. Mentat, herbal formulation of ingredients mentioned in Ayurveda, is useful to improve memory and attention span.<sup>16,17</sup> It has been found to have a tranquilizing action in mental disorders.<sup>18</sup> The aim of this pilot study was to assess the efficacy of Mentat in Attention Deficit Disorder through a double blind, randomized, placebo-controlled drug trial.

## **MATERIALS AND METHODS**

A randomized double blind placebo-controlled trial was planned to evaluate the efficacy of Mentat in school going children with ADHD diagnosed by standard diagnostic criteria.

### **Subject identification**

Contact was established with 12 public schools in Delhi, to identify children having learning and attention difficulties, performing poorly/below average in class and showing features of hyperactivity. About 195 children identified by school teachers were referred.

### **Inclusion Criteria**

The DSM-IV criteria, implies presence of atleast 6/9 of the standard questions used for ADD/ADHD. For this study, children aged 6-12 years, with an IQ ranging between 90-110 were recruited.

### **Subject selection**

Of the 195 children, 60 satisfied the DSM-IV criteria for ADHD. The sixty identified subjects were classified into three subtypes i.e. ADD inattentive type (24), ADHD-Hyperactive-impulsive type (7) and ADHD combined type (29). All the 3 types were included in the study.

### **Investigations and Work-Up Plan**

#### *Pre-trial Investigations:*

- Diagnostic assessment included a parent and patient interview to identify symptoms of ADHD and other disorders. Corroborative information from adults in other settings including teachers was obtained. Detailed history was taken and physical examination done to identify any systemic illnesses. An assessment of academic functioning was done. The following psychological tests were assessed:

- Malin's Intelligence Scale for Indian Children (MISIC)<sup>19</sup>. An Indian Adaptation of the WISC was used to assess the IQ of the children, which gives scores on Verbal IQ, Performance IQ and full scale IQ.
- Coding subtest (MISIC): This sub-test of the MISIC requires the subject to put the correct code in a jumbled sequence of numbers and figures. It tests the concentration, visual-motor co-ordination and speed of processing.
- Kaufman Assessment Battery for Children (KABC)<sup>20</sup>. Four subtests of the battery were used. These were the sequential processing subtests, which are sensitive to attention deficits and minimize language demands.
  - ◆ Gestalt closure: Gestalt closure measures the child's ability to mentally "fill in the gaps" in a partially completed inkblot drawing and to name/describe that picture. It consists of 25 items. Good performance on gestalt closure is often dependent on flexibility in perceiving or, thinking and on alertness of the environment.
  - ◆ Number recall: Number recall measures the child's ability to repeat in sequence a series of numbers spoken by the examiner. It consists of 19 items and demands good attention span. Distractibility and anxiety disrupt performance.
  - ◆ Triangles: Triangles measures the child's ability to assemble several identical rubber triangles to match a picture of an abstract design. It consists of 18 items and measures mental processing in the visual motor channel of communication.
  - ◆ Spatial memory: This measures the child's ability to recall the location of pictures arranged randomly on a page. It consists of 21 items and demands good concentration for success, and performance can be easily disrupted by a poor concentration span, distractibility, anxiety and a field dependent cognitive style.
- Conner's 10-point rating scale<sup>21</sup>. This is an assessment by the parents and is used to identify the hyperactivity of the children. Symptoms are rated on a 3-point scale (0-2: not at all, occasionally, most often). The maximum score received by a subject is 20. The 10-item scale contains overlapping parent and teacher items that are particularly useful for repeated measures in drug trials.
- Bender-Gestalt test for young children<sup>22</sup>. This test identifies any perceptual motor problems in the children.
  - ◆ Brain SPECT (single photon emission computed tomography) scan: The regional cerebral blood flow was evaluated using technetium 99m hexamethylpropylamine oxime (<sup>99m</sup>Tc-HMPAO SPECT). The SPECT images were acquired using a dual headed gamma camera system with fan beam-collimator (Elscent varicam).
  - ◆ Blood Lead levels were estimated using anodic stripping voltametry by portable lead care analyzer. *Hemoglobin and Thyroid function test (T3, T4, TSH)* were done as routine tests for all the children in the study.

## **Drug Trial Method**

Sixty children were randomized to a prospective double blind placebo-controlled drug trial using Mentat and an identical looking placebo. The drug code was revealed to the investigator at the end of the trial. Of the children enrolled into the study, 30 received Mentat and 30 received a placebo.

## **Composition of each Mentat tablet (Botanical names)**

**Extracts:** *Bacopa monnieri* (136 mg), *Centella asiatica* (70 mg), *Withania somnifera* (52 mg), *Evovulus alsinodes* (52 mg), *Nardostachys jatamansi* (52 mg), *Valeriana wallichii* (50 mg), *Embelia ribes* (50mg), *Prunus amygdalus* (50 mg), *Tinospora cordifolia* (36 mg), *Terminalia chebula* (36 mg), *Embllica officinalis* (36 mg), *Oroxylum indicum* (32 mg) and *Celastrus paniculatus* (32 mg).

**Powders:** *Bacopa monnieri* (80mg), *Orchis mascula* (18mg), *Mucuna pruriens* (18 mg), *Elettaria cardamomum* (18 mg), *Terminalia arjuna* (18 mg), *Foeniculum vulgare* (18mg), *Ipomoea digitata* (18 mg), *Zingiber officinale* (14 mg), *Terminalia belerica* (14 mg), *Myristica fragrans* (14 mg), *Syzygium aromaticum* (10 mg) and Mukta pishti (3 mg).

The total weight of Mentat tablet is 515 mg.

## **Duration of trial**

The drug/placebo was administered for 6 months at a dose of 2 tablets per day to the children. Follow-up was done besides initial assessment, when the children were without medication, bi-monthly at 2, 4 and 6 months.

## **Outcome measures**

**Clinical Measures:** Psychological tests were performed by the same observer during pre and post 6 months drug trial evaluation. The tests included Coding subtest (MISIC), four subtests of Kaufman Assessment Battery for Children (KABC), Conner's 10 point rating scale and to Bender Gestalt test for young children.

**SPECT Pre-Post:** A baseline SPECT scan (where permission was granted by the parents) before initiating the drug trial, and a repeat scan was done at the completion of the drug/placebo trial to assess the cerebral regional blood flow abnormalities.

## **Statistical Analysis**

Data was recorded on a pre-designed proforma and managed on an excel worksheet. All the entries were double-checked for any possible errors. Quantitative variables such as age and various psychological parameters were evaluated for approximate normal distribution. Age was summarized as mean and SD. Since the psychological parameters were not normally distributed, these were summarized by median and range in follow up during the trial.

Quantitative variables were summarized as frequencies. Student's t-test/Wilcoxon rank test was used to compare mean/median amongst Mentat and placebo groups. Chi<sup>2</sup> test/Fischer exact tests were used to assess the association between various category variables and the treatment groups. STATA 7.0 intercooled version (STATA Corporation, Houston, TX, USA) was used for statistical analysis. In this study, a *p* value of <0.05 was considered statistically significant.

## RESULTS

After screening 195 children referred for poor performance in class, 60 children satisfying the DSM-IV criteria with IQ between 90-110 were enrolled and randomized to a prospective double blind placebo-controlled-drug trial using Mentat and an identical looking placebo. Of the children enrolled in the study, 30 received Mentat and 30 received placebo. Of the 60 children on the trial drug, six children dropped out from the study as they were lost to follow-up and four children showed consistently variable results and therefore, analysis was carried out only in 50 children.

To test the pretest comparability of the two groups, the baseline parameters were analyzed and compared. Table 1 shows that the age and sex of the two groups was comparable, with more males in the Mentat group as compared to the placebo group. Diagnosed cases of ADHD-combined type and ADD inattentive type were comparable in both the groups. Poor fine-motor co-ordination was prevalent in more children in the placebo group as compared to the Mentat group (16 Vs 8). The pre-trial psychological tests scores, including the IQ, KABC subtests measuring attention and concentration and the Bender-Gestalt test scores in both the groups were comparable. However, Conner's rating scale scores in the Mentat group were higher than in the placebo (though not statistically significant) indicating that Mentat group subjects had more hyperactivity as compared to the placebo group.

Apart from the ADHD symptoms, other associated problems were analyzed for both the groups (Table 2). It was found that behavioral and other miscellaneous problems were present in significant numbers in both the groups.

Adverse perinatal events reported by mothers included birth asphyxia in 5/60 (8.3%) and seizures in 6/60 (10%) children. Physical examination revealed that 11/60 (18%) children had visual problems. 6/60 (10%) children were left-handed/ambidextrous. Blood lead test was done and it was found that 11/39 (28.2%) children had elevated blood levels (greater than 10 mg/dl). 3/51(5.8%) children had low hemoglobin levels. 41/42 (97.6%) children who had undergone the thyroid function test showed results within the normal range.

Baseline parameters			Mentat (n=27)	Placebo (n=27)	Statistical significance	
Age (mean± SD) years			9.1 ± 2.5	8.7 ± 2.4	t= -0.54, p=0.58	
Sex M/F			26/1	21/6		
Parents Education Status:	School level		8/27	8/27		
	Professional		19/27	19/27		
Diagnosis	ADD		13	10		
	ADHD		02	02		
	ADHD-Combined		12	15		
Poor fine-motor co-ordination			8	16		
Psychological Test scores (mean ± SD)	MISIC (Full scale IQ)		95.7 ± 7.64	95.9 ± 7.37	t= 0.09, p=0.9	
	Conner's scale		12.74 ± 2.95	10.96 ± 4.11	t= -1.8, p=0.07	
	KABC Subtests rawscores	Gestalt closure		12.74 ± 5.29	11.88 ± 4.75	t= -0.62, p=0.5
		Number recall		12.14 ± 2.5	11.44 ± 1.73	t= -1.19, p=0.23
		Triangles		10.54 ± 4.04	9.48 ± 4.21	t= -0.89, p=0.5
		Spatial memory		12.16 ± 3.33	11.96 ± 3.4	t= -0.20, p=0.83
Bender-Gestalt test			5.96 ± 3.44	6.62 ± 4.01	t= -0.15, p=0.5	

Table 3 shows percentage improvement in the various psychological test scores during follow-up and at the end of the trial. Conner's test and Gestalt closure subtest scores showed improvement in the Mentat group as compared to the placebo group. This was found to be statistically significant. For all other tests, no significant difference was found between the Mentat and placebo groups in the final follow-up of the trial.

Associated Symptoms	Mentat (n=27)	Placebo (n=27)
Enuresis	3	2
Behavior problems	7	10
Frequent medical illnesses	2	1
Emotional problems	1	1
Disturbed sleep	6	6
Miscellaneous	10	9

SPECT scan observations showed hypoperfusion in the thalamus or basal ganglia in 17/26 pre-therapy scans. Pre- and post-SPECT scan observations showed improvement in the abnormal scans of 3/9 children in the Mentat group, versus 1/8 of the placebo group, indicating the positive effect of Mentat after the 6-month drug trial period.

## DISCUSSION

Attention deficit hyperactivity disorder (ADHD) is a common neurobehavioral disorder of childhood characterized by poor ability to attend to a task, overactivity and impulsivity. Stimulant medications have shown to benefit some children with ADHD. However, they may have side effects. The benefits are often not sustained and sub-optimal and few patients may worsen following their administration. Other alternative therapies have been tried but not found to be very effective.

Parameters		% improvement [(median range)]		
		Baseline - 2 months	Baseline - 4 months	Baseline - 6 months
Conner's test	Mentat	5.5 (-37 - 50)	18.75 (-25 - 50)	38.8 (-30.30 - 88.34)
	Placebo	23.6 (-55 - 83.33)	30.95 (-25 - 100)	36.36 (-50 - 100)
		Z = 1.77, p = 0.07	Z = 2.075, p = 0.03	Z = 2.43, p = 0.015
Gestalt closure	Mentat	10.79 (-66 - 50)	19.09 (-33 - 100)	30.76 (0 - 100)
	Placebo	11.76 (-50 - 140)	15 (-100 - 160)	22.2 (-50 - 180)
		Z = -0.5, p = 0.59	Z = 0.44, p = 0.65	Z = 1.2, p = 0.22
Number recall	Mentat	7.69 (-20 - 33.3)	9.09 (-30 - 50)	9.09 (-10 - 50)
	Placebo	0 (-23.5 - 33.3)	0 (-28.57 - 36.36)	9.09 (-14.28 - 54.54)
		Z = 0.91, p = 0.35	Z = 1.04, p = 0.29	Z = 0.35, p = 0.72
Triangles	Mentat	8.01 (-18 - 100)	12.23 (-14.28 - 100)	18.18 (0 - 100)
	Placebo	0 (-11 - 125)	8.01 (-80 - 125)	14.28 (-9.09 - 200)
		Z = 0.48, p = 0.62	Z = 0.69, p = 0.94	Z = 0.19, p = 0.84
Spatial memory	Mentat	9.09 (-3.03 - 100)	14.28 (-66.6 - 53.8)	16.6 (-66.6 - 100)
	Placebo	0 (-42.85 - 75)	7.69 (-8.3 - 150)	18.18 (-28.57 - 150)
		Z = 1.41, p = 0.32	Z = 0.30, p = 0.76	Z = -0.01, p = 0.99
Bender gestalt	Mentat	22.5 (-40 - 80)	36.6 (-100 - 75)	46.1 (-300 - 100)
	Placebo	36.6 (-50 - 100)	46.4 (-100 - 100)	59 (0 - 100)
		Z = 0.98, p = 0.32	Z = -1.2, p = 0.22	Z = -0.23, p = 0.81
Coding	Mentat	18.52 (-43.75 - 450)	7.9 (-28.94 - 733)	25.8 (-19.85 - 750)
	Placebo	16.44 (-46.25 - 63.15)	14.8 (-35.7 - 84.21)	27.65 (-14.28 - 128)
		Z = 0.63, p = 0.52	Z = 0.082, p = 0.93	Z = 0.15, p = 0.87

In the present study, Mentat, a polyherbal formulation was used on children with ADHD. *Bacopa monnieri*, *Withania somnifera*, *Centella asiatica* and *Nardostachys jatamansi* in their optimum concentrations are used in Mentat. It was also found that *Nardostachys jatamansi* exhibited more potent effect than the other two drugs.<sup>18</sup> The effect of *Bacopa monnieri* on the central nervous system of mice and rats, using doses ranging from 1 to 30 g/kg has been studied. The tested parameters were motor coordination, tail-withdrawal reaction time, pentobarbiturate hypnosis, electroshock, chemoconvulsions and conditioned avoidance response. The test material exhibited a sedative effect and significantly prolonged hypnotic action of phenobarbiturate.<sup>23</sup> Based on these studies, Mentat has been tried on human subjects. In normal adults, Mentat has been reported to be useful in improving short-term memory and attention span.<sup>16,17</sup>

In the present study, the two groups were comparable in their characteristics, severity and pattern of attention deficit (Table 1). Also, comparison at 2, 4 and 6 months revealed no significant differences in the assessed parameters (Table 3). The Conner's test and Gestalt closure subtest scores showed improvement in the Mentat group as compared to the placebo group at 4 and 6 months evaluation. The Coding subtest, which measures concentration,

visual-motor co-ordination and speed of processing, shows higher percentage of improvement in the Mentat group as compared to the placebo in the 4 monthly follow-up. Spatial memory, which measures attention and concentration, shows higher percentage of improvement in the Mentat group as compared to the placebo on the 6<sup>th</sup> month follow-up. The Bender-Gestalt test, which identifies perceptual motor difficulties, found steady improvement in the Mentat group as compared to the placebo at all points of time (on the 2, 4 and 6 months follow-up). Non-significance can be attributed to a small sample size. In all other parameters there was no significant difference between the Mentat and placebo groups.

Pre-and post-SPECT scan observation revealed improvement in the abnormal scans of three out of nine children in the Mentat group in comparison to one out of eight in the placebo group, indicating the positive effect of the Mentat medicine after the 6 month drug trial period.

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