MEMORY PLUS

CLINICAL TRIALS

(SUMMARY)

MAY, 1999

CENTRAL DRUG RESEARCH INSTITUTE LUCKNOW

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MEMORY PLUS

CLINICAL TRIAL SUMMARY

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CENTRAL DRUG RESEARCH INSTITUTE
LUCKNOW
INDIA

CLINICAL TRIALS WITH MEMORY PLUS

A. Phase I clinical trail with Bacosides A&B

Dr. O.P. Asthana — Div. of Clinical & Experimental Medicine
Dr. J.S. Srivastava — C.D.R.I., Lucknow.

B. Double blind clinical study of Memory plus/Ginko biloba /placebo in elderly subjects with age associated memory Impairment.

Dr.P.S. Anklesaria — Clinical Pharmacology Unit
Dr. R.A. Kulkarni — (CPU), Deptt. Of Pharmacology
Dr. U.M. Thatte — seth G.S. Medical College,
Dr. V.J. Ashar — Bombay
Dr. N.A. Rajwade
Dr. N.K. Desai
Prof. S.A. Dahanukur
Dr. J.S. Srivastava — Div. of Clinical & Exp. Med.
Dr. O.P. Asthana — C.D.R.I., Lucknow.

C. Double blind placebo controlled efficacy study of Memory plus in Children with attention deficit hyperactivity disorder.

Dr.K.S. Negi — B.R.D. Medical College
Dr. Y.D. Singh — Gorakhpur
Dr. K.P Kushwaha
Dr. C.K. Rastogi
Dr. A.K.Rathi
Dr. S.K. Mandal — Div. of Biometry
Dr. R.C. Gupta — Div. of Pharmacokinetics
Dr. J.S. Srivastava — Div. of Clinical & Exp. Med.
Dr. O.P. Asthana — C.D.R.I., Lucknow.

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INTRODUCTION

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Biological evaluation of plants based on their use in the traditional systems of medicine is a sound and cost effective strategy to develop new drugs from plants (1,2). Since time immemorial, Ayurveda, the science of life, has provided a rationale basis for
treatment of various ailments. Based on the medicinal properties of selected plants as described in the Ayurvedic texts, our institute has in recent years developed several drugs for refractory diseases for which no effective remedy is available in the modern system of medicine. These include hypolipidaemic, hepatoprotective, macrofilaricidal etc.

Another promising lead obtained is the confirmation of the traditional claim of Bacopa monniera (Linn.) Pennel (Syn: Herpestis monniera (Linn.) HB&K) (Hindi: Brahmi, Jal Neem) (Family: Scrophulariaceae), which has been in use since times immemorial as nerve tonic for improvement of memory. Although, it has been frequently mentioned in the religious, social and medical treatises of India since the time of Athar-Ved (C 800B.C.), the first clear reference to its CNS effect is to be found in Charak Samhita written in the Ist century A.D., where Brahmi is prescribed as a cure for mental disorder (retardation) leading to insanity(10:62). The etiology of the mental disorder according to Charak is a combination of anxiety, weak intellect and lack of concentration. Another authentic Ayurvedic treatise, i.e., Susruthu Samhita describes brahmi as efficacious in loss of intellect and memory.

Bacopa monniera is a perennial creeping plant found throughout India in wet, damp and marshy areas. An infusion of the plant has also been used in Indian folklore as a nerve tonic(3). The plant has been investigated in several Indian laboratories for its neuro pharmacological effects. Central Drug Research Institute, Lucknow also initiated the evaluation of the traditional claims of brahmi by investigating its effect on the acquisition, consolidation and retention of three newly acquired behavioral responses in albino rats (4). These included foot shock motivated brightness discrimination reaction, active conditioned avoidance response and Sidman's continuous avoidance response. The results of the investigation using these three learning schedules clearly indicate that the effect of brahmi extract is manifest both in facilitating the cognitive function and augmenting the mental retention capacity.

Having confirmed the traditional claim, the next logical step was to identify the chemical constituents responsible for this activity. The identified compounds included two saponins designated as Bacosides A & B. The bacosides were found to be safe in regulatory pharmacological and toxicological studies. After obtaining the approval of the Drugs Controller General (India), clinical studies were initiated with Bacosides.

Memory plus capsules marketed by M/s Velvette International Ltd., contained 125 mg Bacosides in each capsule for adults and 50 mg Bacoside per capsule for pediatric subjects.

Clinical studies on memory plus are divided into three components:

A. Phase I clinical trial with Bacosides A&B
(active constituent of memory plus).
B. Double blind clinical study of Memory plus/Ginko biloba/placebo in elderly subjects with Age Associated Memory Impairment (AAMI).
C. Double blind placebo controlled efficacy study of Memory plus in children with Attention deficit Hyperactivity Disorder.

PHASE I CLINICAL TRIAL WITH BACOSIDES

PHASE I CLINICAL TRIAL WITH BACOSIDES

This study was carried out in two parts – single dose and multiple dose tolerance study in healthy male volunteers.

Single Dose study:

Phase I single dose tolerance study was undertaken at B.R.D. Medical College, Gorakhpur. Thirty one normal male volunteers who consented to undergo the trial as per approved protocol completed the study. The trial was double blind placebo controlled and non-crossover. The dose of bacosides A&B ranged from 20 mg to 300 mg. Six volunteers received placebo while 4 each were given 20 mg, 50 mg, 75 mg, 100 mg, 150 mg, 200 mg and 1 volunteer received 300 mg bacosides in gradually escalated manner.

In all cases Bacosides A&B was well tolerated. Recording of vital parameters (pulse, blood pressure and general condition) at 0,1,2,3,4,6, and 24 hours post medication were normal limits. The hematological parameters (Hb, TLC,DLC,PCV,ESR), biochemical parameters (blood sugar, blood urea, creatinine, bilirubin, SGOT,SGPT,AP, serum proteins, total cholesterol and triglycerides) and electrocardiogram were within normal range in +24 hours of post medication.

Multiple dose study:

Twenty healthy male volunteers who executed the written informed consent, completed the study as per approved protocol. Initially the first group of 10 volunteers was give Bacoside (100 mg) orally once a day for 4 weeks. Subsequently, the second group of 10 healthy male subjects received Bacoside (200 mg) orally for 4 weeks.

Each volunteer was subjected to a detailed history, clinical examination and laboratory investigations before the administration of first dose of Bacosides with the aim of having initial baseline pretherapy values of each parameters. Subsequently all the volunteers were closely monitored during the trail. Every volunteer was examined for vital parameters (blood pressure and pulse) and subjective experiences every week during the 4 week study. In each case all baseline clinical and laboratory investigations were repeated at the end of 4 week trail. A critical appraisal of these observations revealed that no drug related abnormalities could be detected in clinical and laboratory parameters. Thus it can be concluded that Bacosides A&B with 100 mg and 200 mg doses given orally each day for 4 weeks is will tolerated and does not produce any undesirable side effects or abnormality on these dose levels(5).

CLINICAL STUDY IN ELDERLY SUBJECTS WITH AAMI

DOUBLE BLIND CLINICAL STUDY OF MEMORY PLUS/GINKO BILOBA/ PLACEBO IN ELDERLY SUBJECTS SUFFERING FROM AGE ASSOCIATED MEMORY IMPAIRMENT.

A double blind placebo controlled randomized study was performed in elderly individuals (above the age of 45 years). Patients with subjective evidence of age associated memory loss and who satisfied the inclusion evidence of age associated memory loss and who satisfied the inclusion criteria (complaints of memory loss in everyday activities, a cut off score of < 6 on Weschler Memory Scale, score of >24 on Mini Mental State Examination and a score of >9 on Vocabulary subset of Wechsler Adult Intelligence Scale) were recruited for this study and were randomly assigned to receive either Memory plus(125 mg capsule) or (Ginko biloba (60 mg capsule) or placebo (identical capsule) twice a day for 12 week. Assessment was done on day 0, 4^{th}, 8^{th}, 12^{th}, and 16^{th} week (i.e. 4 weeks after stopping therapy). This included clinical history, laboratory investigation and psychometric tests i.e. Wechsler's Memory Scale (WMS) & Mini Mental State Examination (MMSE).

A total of thirty two patients were included in the study. Out of these 11 received memory plus, 12 received Ginko biloba and 9 were given placebo. Out of 11 patients (7 males +4 females) who received Memory plus, 2 patients dropped out and 9 completed the trail. The mean age of these patients was 62.0+10.4 years.

A detailed analysis of hematological and biochemical parameters at 0, 4, 8 and 12 and 16 weeks of drug administration (Memory plus/Ginko biloba or placebo did not reveal any significant deviation from the baseline (0 week). This establishes the safety of memory plus (125 mg BD) in nine elderly subjects after 12 weeks of drug administration.

CLINICAL STUDY IN CHILDREN WITH ADHD

STATISTICAL METHOD:

1. We have applied paired "t" Test to test the significance between the periods of visits i.e. from initial pre drug test score to subsequent values observed at 4 weekly intervals (+4, +8, +12, &+16 weeks).
2. To test the efficacy of Memory Plus as compared with Placebo, first we have subtracted the initial test score from subsequent week's values then non-parametric test, "u' Test (Mann Whitney) was applied.

RESULTS

The present study was carried out in the Department of Pediatrics, Baba Raghav Das Medical College, Gorakhpur, Lucknow, from August, 1997 to November, 1998. The study was designed to evaluate the efficacy and tolerability of Memory Plus in children suffering from Attention Deficit Hyperactivity Disorder. The treatment was assigned as per random allocation into two groups receiving Memory Plus and Placebo. The following conclusions were drawn from the present double blind controlled study.

1. Thirty six patients were selected for the study period as per Diagnostic & Statistical Manual (DSMIV) OF American Psychiatric Association Committee criteria, 19 in Memory Plus and 17 in Placebo group.

2. In this figure included drop out were, one in Memory Plus and six in Placebo group.

3. The mean age was 8.32 years and 9.3 years in Memory Plus and Placebo group respectively.

4. Maximum number of patients were in age group of 6-8 years and 10-12 years in placebo group as well as in Memory Plus group.

5. The male: female ratio was 5.3:1 and 3.3:1 in Memory Plus and placebo group respectively.
6. As per educational distribution data, most of the children 36.8% and 41.2% of Memory Plus and Placebo group respectively were studying in Class Ist whereas the minimum number of children 5.3% were in class Third in Memory Plus and 5.9% in Fifth Class from Placebo group.
7. So far the history of past illness and possible etiological factor is concerned, perinatal asphyxia and viral encephalitis dominated in Placebo group as 5(29.5%) and 4(23.53%) cases respectively, whereas in Memory Plus high grade fever 4(21.1%) and viral encephalitis 4(21.1%) were the two equal predominating possible etiological factors. There was no reported history of past illness in 7(36.8%) in Memory Plus and 5(29.4%) cases in placebo group.
8. Following tests were applied to assess memory enhancing properties and effect of Memory Plus in ADHD during study period.

(i) Personal information
(ii) Mental control
(iii) Sentence repetition
(iv) Logical memory
(v) Word recall (meaningful)
(vi) Digit span test
(vii) Word recall (non-meaningful)
(viii) Delayed response learning
(ix) Picture recall
(x) Paired associate learning

9. A significant improvement was observed in scoring of mental control, sentence repetition word recall (meaningful) picture recall, paired associate learning right from the 4th week duration of treatment trail and from 8th week onwards in personal information, digit span test, word recall (non-meaningful) and logical memory However, there was no significant change on delayed learning. (Tables 1to 11).

10. There was no significant improvement in scores in any of these tests in placebo group except for mental control, sentence repetition and picture recall, where there was an improvement at 12 weeks of study. Further, in memory plus group there was a highly significant effect on improvement in all the tests except delayed response learning from 8th week of clinical trial.

11. The effect was maintained even after drug withdrawal from beginning of 13th week to 16th week, which supports the withdrawal free effect of Memory Plus.

12. A pre and post drug monitoring of clinical hematological and biochemical parameters did not suggest any drug related abnormality in both the treatment groups. This indicates the excellent tolerability and safety of the drug, in the subjects of study.

13. In contrast to Placebo group some of the patients of memory plus group, 4(22.2%) reported improvement in their appetite at the end of 4 weeks, of the trail and 13 (72.2%) cases reported improvement in their concentration which was confirmed objectively in the memory test.

14. The data observed from the present study have confirmed the efficacy of Memory Plus in the treatment of ADHD.

15. The sample size of patients for the study was limited to only 36 instead of required 60 patients because of certain reasons beyond our control. However, the present study strongly supports the safety and efficacy tolerance of Memory Plus and it facilitates the learning process through enhancement of memory.

DOUBLE BLIND CLINICAL EFFICACY STUDY OF MEMORY PLUS IN CHILDREN SUFFERING FROM ATTENTION DEFICIT HYPERACTIVITY DISORDER:

A double blind controlled clinical efficacy study of memory plus was carried out at B.R.D. Medical College, Gorakhpur. The study was designed to evaluate the efficacy and tolerability of Memory plus in children suffering from Attention Deficit Hyperactivity Disorder.

ATTENTION DEFICIT HYPERACTIVITY DISORDER(ADHD)

It is one of the common disorder of childhood and is characterized by developmentally inappropriate level of inattentiveness, impulsivity and motoric activity that appears in at least two contexts (e.g. home and school) and has been present for at least six months before the age of 7 years.

PREVALENCE:

In India the prevalence rate of ADHD ranges from 5 to 10 percent (6,7). The ADHD children, who were diagnosed in accordance to Diagnostic and Statistical Manual 4th edition (DSMIV) showed a prevalence rate of 5 to 10% whereas those using ICD-10 (International Classification of Disease-10th revision) suggest a prevalence rate of ADHD around 1.1 to 2 percent.

CLINICAL FEATURES OF ADHD

The hall marks of ADHD are poor attention span, high impulsivity, often accompanied by hyperactivity. Some children may be inattentive, some predominantly hyperactive and impulsive and other may show mixed features. This behaviour is never restricted to one setting and is normally observable at home, at

School and on the play ground. In fact, if a child is showing features of hyperactivity, he fidgets a lot, cannot sit in one place for long, runs about or climbs excessively, cannot enjoy quiet leisure activities and talks excessively. He wears out the parents who see him almost like machine always on the run and almost tireless.

Inattention is seen in failure to give close attention to details, careless mistakes incomplete chores, forgetfulness, distractibility, a tendency to lose belongings, and an inability to organize tasks or work in sustained manner on them. By virtue of being impulsive this child often blurts out answer even before the question is complete, tends to be intrusive and often rude because be cannot wait patiently for his turn.

DIAGNOSIS OF ADHD

There are no specific tests to diagnose ADHD, but the diagnosis is based on detailed history regarding the child's behaviour in specific situations, birth and development history, interview, the complete physical and neurological examination, psychometric tests, psychosocial evaluation of the family and assessment of school environment.

CRITERIA FOR DIAGNOSIS

Two standard criteria are commonly used to diagnose
ADHD:

(I) – Diagnostic and Statistical Manual(DSMIV), 1994 developed by American Psychiatric Association Committee.

(II) – International Classification of Disease 10th revision by World Health Organization (ICD-10).

MATERIAL AND METHODS

The present study was carried out in the Department of Pediatric, B.R.D. Medical College, Gorakhpur, Lucknow. The period of study was one year four months starting from August, 1997 to November, 1998. The aim of the study was to evaluate memory enhancing properties of Memory plus in children with Attention Deficit Hyperactivity Disorder(ADHD).

SUBJECTS: The study included 36 children of ADHD fulfilling the criteria of Diagnostic and Statistical Manual, 4th Edition (DSM IV) of American Psychiatric Association Committee.

SAMPLE SELECTION: The children between the age of 6 to 12 years were selected from Out Patient Department (OPD) of Pediatrics, B.R.D. Medical College, Gorakhpur. In addition the children from nearby school were also screened and children found with ADHD were selected for the study. Each subject was evaluated for intelligence quotient (IQ) wherever possible. Those children who were found having visual, hearing impairment, seizure disorder, acute/chronic diarrhea were excluded.

ETHICS:

Prior to each study parents/guardian of each child was explained in such a manner that he/she could completely understand that chills had been treated with a new drug. Written informed consent was obtained from parent/guardian of each child enrolled in the study.

MATERIAL

Capsules of identical colour and size containing 50 mg Memory Plus powder and equal amount of placebo, were used.

DESIGN

Double blind, randomized, placebo controlled design was used.

HYPERACTIVITY

(a) Fidgets with hands or feet squirms in seat.

(b) Leaves seat in classroom or in other situations in which remaining seated is expected.

(c) Runs about or climbs excessively in situations in which it is inappropriate.

(d) Has difficulty playing or engaging in leisure activities quietly.

(e) Is: "on the go" OR ACTS AS IF "driven by motor"

(f) Talks excessively.

IMPULSIVITY

(g) Blurts out answers before questions have been completed.

(h) Has difficulty awaiting turn.

B. Some hyperactive impulsive or inattentive symptoms that caused impairment were present before age 7 years.

C. Some impairment from the symptoms is present in two or more settings(e.g., at school[or work] and at home).

D. There must be a clear evidence of clinically significant impairment in social, academic or occupational functioning.

E. The symptoms do not occur exclusively during the course of a Pervasive Developmental Disorder, Schizophrenia, or other Psychotic Disorder and are not better accounted for by an other mental disorder.

(ii) ICD-10 Criteria – Six or more from inattention, three or more from hyperactivity and one or more from impulsivity group of DSMIV criteria.

(i) DSM-IV Diagnostic Criteria for ADHD:

A. Either (1) or (2):

1. Six (or more) of the following symptoms of inattention occur often and have persisted for at least 6 months.

INATTENTION

(a) Fails to give close attention to details.

(b) Has difficulty sustaining attention in tasks or play activities.

(c) Does not seem to listen when spoken to directly.

(d) Does not follow through on instructions and fails to finish schoolwork, chores, or duties in the workplace.

(e) Has difficulty in organizing tasks and activities.

(f) Avoids, dislikes or is reluctant to engage in tasks that require sustained mental effort.

(g) Loses things necessary for tasks or activities.

(h) Is often easily distracted by extraneous stimuli.

(i) Is forgetful in daily activities.

2. Six (or more) of the following symptoms of hyperactivity/impulsivity occur often and have for at least 6 months.

TREATMENT SCHEDULE:

The children received 50 mg. Memory Plus/Placebo capsules twice a day for 12 weeks as per random allocation and from 13th week to 16th week, the children were given placebo only.

CLINICAL & MEMORY/LEARNING EVALUATION

Each child underwent a complete physical examination on each visit. Subjects who fulfilled the above stated inclusion criteria were enrolled in the trial. They were evaluated before (0 day), and thereafter at +4,+8 and +12 week of drug administration as per random allocation. One evaluation of the child was done after 4 weeks of stopping the medication, when all children were given placebo only.

Certain tests were applied to compare the response of Memory Plus and Placebo. Before undergoing the test every possible effort was done to make the child understand the test clearly. The tests applied were:

I. Personal Information **Maximum Score-5**

The following questions were asked.

1. How many people are there in your family?
2. What is the day to day?
3. When did you first join school?
4. What is the name of this month?
5. In which State are you living?

Each correct answer was given a score of one.

II. Mental Control **Maximum Score-15**

Each item of the following first sub tests were read distinctly and slowly at a steady rate. If the child failed to understand the item, it was repeated. Time taken and error/omission made by the subject on each of the five subjects were noted down.

1. Naming days of the week forward Score

All correct within 15 seconds	3
With one mistake	1
More than one mistake	0

2. Naming days of the week backward

All correct within 20 seconds	3
All correct beyond 20 seconds	2
With One mistake	1

More than one mistake 0

3. Naming months of the year forward

All correct within 25 seconds 3

All correct beyond 25 seconds 2

With One mistake 1

More than one mistake 0

4. Naming months of the year backward

All correct within 45 seconds 3

All correct beyond 45 seconds 2

With One mistake 1

More than one mistake 0

5. Deducting 5's from 60

All correct within 60 seconds 3

All correct beyond 60 seconds 2

With One mistake 1

More than one mistake 0

III. Sentence Repetition Maximum Score-9

Each of the total sentences, were presented one by one to the subject for immediate reproduction. Each sentence was read out slowly, distinctly and at a uniform rate during presentation. The subject's recall was noted and each of

the correctly recalled clause was ticked. If the subject made an error, omission, in recalling the sentence then while presenting the subsequent sentence, the subject was reminded once again to be attentive, careful and reproduce the sentence as exactly as possible. One mark was given for each clause correctly reproduced. The sentences were made in such an order to make a total maximum score of 9.

IV. Logical Memory-(Story Recall Immediate) Maximum Score 18.

A story was made and the separate items in the story were indicated by slash (/) mark, ti give one mark for each correctly recalled item. The subject was told to listen the story carefully. After reading the story the subject was told to tell the everything of

The story he could remembered. Immediately following the first trial, the subject was retold to recall whatsoever part of the story he was remembering. Then the story was re-read to subject and the subject was told to recall everything of the story he could remembered. The recall following the second reading came after 20 min. of testing involved verbal materials.

V. Word Recall (Meaningful Words) Maximum Score-10

The subject was instructed to look carefully the cards with meaningful words for 30 seconds. After sometimes (2 minutes) he was gold to point the same meaningful words from the second card. Each meaningful word correctly identified and was given score of one.

VI. Digit Span Test Maximum Score-15

The subject was told to listen some of the digits carefully, and instructed to repeat the digits in the same order-

-The numbers were read at the rate of one per second

-The incorrect or correct response of the child was noted. The digit span was the highest number of digits repeated correctly.

The child was instructed to listen the spoken digits carefully and asked to repeat them in reverse order-

1. Digit forward – Number of digits in the longest series correctly reproduced.
2. Digit backward – Number of digits in the longest series correctly reproduced in reverse order.

Summation of scores earned on digit forward and backward was the score of the sub test.

VII. Word Recall (Non-meaningful) Maximum Score-10

The subject was instructed to look carefully at a card written with some non-sense syllables for 30 seconds. After sometimes (2 minutes), he was told to point the same non-sense syllabus from the second card. Each non-meaningful word correctly identified and named was given a score of one.

VIII- Picture Recall Maximum Score-4

The subject was shown some rows of little pictures and then the pictures were covered. The subject was asked to tell the shown pictures in same order started from one end of the row.

The exposure time for each row was as follows:-

Row1:	3 Seconds
Row2:	3 Seconds
Row3:	4 Seconds
Row4:	5 Seconds

1. 2 seconds	1)	2)			
2. 3 seconds	1)	2)	3)		
3. 4 seconds	1)	2)	3)		
4. 5 seconds	1)	2)	3)	4)	5)

IX. Delayed Response Learning **Maximum Score-8**

The subject was given a small arithmetic problem and he/she was instructed to keep the result of that problem in his/her mind, to use that to solve another problem 10 seconds later.

1. 6+4 = x	Interval add x to 5+x=
2. 3+9 = x	Look at the picture 5+x=
3. 7-3=x	Interval and x to 11-4=
4. 4-4=x	Look at the picture 12-7

Giving correct answer for each problem was given a score of 1.

X. Paired Associate Learning **Maximum score -21**

The subject was instructed to listen carefully a list of words of which two words were read at a time. After that the first presentation was read at the rate of one pair at every two seconds. Then the subject was given first word of the pair and asked to tell the second in 5 seconds. On correct response, the next pair was proceeded. After the completion of first recall a 10 second interval was given and then the second list presentation proceeded as before.

One credit for correct response, if given within 5 seconds. Final score was achieved as follows:

All credits obtained on easy association in left hand column were added and divided by score by 2. Credits on hard association in the right hand column were also added. Total of each column was done. Score on entire test was sum of both easy and hard association scores.

CLINICAL HEMATOLOGICAL AND

BIOCHEMICAL MONITORING

Each child underwent a clinical examination at every visit to Pediatric O>P>D. of B.R.D. Medical College, Gorakhpur. This also included monitoring of vital parameters (B.P., Pulse rate), physical parameters (weight and height) and subjective experiences as per Dosage Record Treatment Emergent System Scale (DOTES).

The pre and post drug hematological monitoring consisted of hemoglobin, total leukocyte count, red blood cell count estimations included total protein, blood sugar (random) serum cretonne and durum bilirubin.

TABLE 1 : Effect of memory plus/placebo on personal information in children suffering from ADHD.
(Values expressed as mean _+SD)

Weeks	Memory Plus	Placebo
0	2.2 +_1.2 (19)	2.2 +1.3 (17)
4	2.8 +_2.9 (18)	2.8 +1.4 (11)
8	2.8* +_1.1 (18)	2.5 +1.4 (11)

12	**3.0* +_1.3 (18)**	**2.5 +1.4 (11)**
16	**3.0* +_1.3 (18)**	**2.5 +1.4 (11)**

Number of patients in parentheses.
*p>0.05

Note: 4 weekly observations in memory plus group showed significant improvement from baseline from 8th week onwards c.f. No such improvement is seen in patients receiving placebo treatment.

TABLE 2 : Effect of memory plus/placebo on mental control in children suffering from ADHD

(Values expressed as mean _+SD)

Weeks	Memory Plus	Placebo
0	**2.8 +_2.8 (19)**	**3.8 +_0.8 (17)**
4	**3.6* +_3.2 (18)**	**4.0 +_1.2 (11)**
8	**4.1* +_3.7 (18)**	**4.0 +_1.1 (11)**

12	**4.8***	**4.4**
	+_3.9	**+_1.1**
	(18)	**(11)**
16	**4.8***	**4.4***
	+_3.9	**+_1.1**
	(18)	**(11)**

Number of patients in parentheses.
*p>0.05

Note: 4 weekly observations in memory plus group showed significant improved from baseline from 8th week onwards c.f. A significant change in placebo group observed in 12th week.

TABLE 3 : Effect of memory plus/placebo on sentence repetition in children suffering from ADHD.
(Values expressed as mean _+SD)

Weeks	Memory Plus	Placebo
0	**2.0**	**3.8**
	+_1.9	**+_3.3**
	(19)	**(17)**
4	**2.7***	**4.5**
	+_2.1	**+_4.0**
	(18)	**(11)**
8	**3.4****	**4.6**
	+_1.9	**+_3.9**

	(18)	**(11)**
12	**4.5**** **+_2.8** **(18)**	**4.9*** **+_3.7** **(11)**
16	**4.5**** **+_2.8** **(18)**	**4.9*** **+_3.7** **(11)**

Number of patients in parentheses.

*p>0.05, **p,0.01

Note: 4 weekly observations in memory plus group showed significant improved from baseline from 8th week onwards c.f. A significant change in placebo group observed in 12th week.

TABLE 4 : Effect of memory plus/placebo on logical memory in children suffering from ADHD.

(Values expressed as mean _+SD)

Weeks	Memory Plus	Placebo
0	**4.1** **+_3.3** **(19)**	**3.8** **+_3.0** **(17)**
4	**4.7** **+_3.8** **(18)**	**3.8** **+_2.8** **(11)**
8	**6.4****	**4.3**

	+_4.4 (18)	**+_2.7 (11)**
12	**7.3** +_4.0 (18)**	**4.4 +_2.8 (11)**
16	**7.2** +_3.6 (18)**	**4.4 +_2.8 (11)**

Number of patients in parentheses.
***p<0.01**

Note: Highly significant effect of memory plus from 8th week onwards. No significant change observed in placebo group.

TABLE 5 : Effect of memory plus/placebo on word recall (meaningful) in children Suffering From ADHD.
(Values expressed as mean _+SD)

Weeks	Memory Plus	Placebo
0	**4.1 +_3.3 (19)**	**4.1 +_3.0 (17)**
4	**4.7* +_3.9 (18)**	**4.6 +_2.6 (11)**
8	**6.4** +_4.4**	**5.56 +_3.0**

	(18)	**(11)**
12	**7.3** **+_3.9** **(18)**	**6.1*** **+_3.5** **(11)**
16	**7.3** **+_3.6** **(18)**	**6.1*** **+_3.5** **(11)**

Number of patients in parentheses.
***p>0.05 **p<0.01**

Note: Highly significant effect of memory plus 8th week onwards. No significant effect Observed with placebo although an increase in test score is there in this group too.

TABLE 6 : Effect of memory plus/placebo on digit span test in children suffering from ADHD.
(Values expressed as mean _+SD)

Weeks	Memory Plus	Placebo
0	**5.6** **+_2.5** **(19)**	**5.5** **+_2.7** **(17)**
4	**6.0** **+_2.5** **(18)**	**6.1** **+_2.0** **(11)**
8	**7.1****	**7.0**

	+_2.8 (18)	**+_2.4 (11)**
12	**8.3** +_2.8 (18)**	**7.0 +_2.4 (11)**
16	**8.3** +_2.8 (18)**	**7.0 +_2.4 (11)**

Number of patients in parentheses.
****p<0.01**

Note: Significant effect was observed in memory plus group 8th week onwards. No significant change observed with placebo although on increase in the test score is there in this group also.

TABLE 7 : Effect of memory plus/placebo on word recall (non-meaningful) in Children suffering from ADHD. (Values expressed as mean _+SD)

Weeks	Memory Plus	Placebo
0	**2.8 +_2.2 (19)**	**2.4 +_0.7 (17)**
4	**3.0 +_2.4 (18)**	**2.5 +_0.6 (11)**
8	**3.8***	**2.6**

	+_2.5 (18)	+_0.8 (11)
12	4.1** +_2.8 (18)	2.6 +_0.8 (11)
16	4.2** +_2.7 (18)	2.6 +_0.8 (11)

Number of patients in parentheses.
***p<0.05 **p<0.01**

Note: A significant effect was observed in memory plus group 8th week onwards. No significant change observed in placebo group.

TABLE 8 : Effect of memory plus/placebo on delayed response learning in children suffering from ADHD.
(Values expressed as mean _+SD)

Weeks	Memory Plus	Placebo
0	1.8 +_1.4 (19)	1.5 +_1.6 (17)
4	2.2 +_1.4 (18)	2.1 +_1.7 (11)
8	2.2 +_1.6	2.4 +_1.2

	(18)	**(11)**
12	**2.3 +_1.6 (18)**	**2.5 +_1.2 (11)**
16	**2.3 +_1.6 (18)**	**2.5 +_1.2 (11)**

Number of patients in parentheses.

Note: No significant change observed in any of the group.

TABLE 9 : Effect of memory plus/placebo on picture recall in children Suffering From ADHD.
(Values expressed as mean _+SD)

Weeks	Memory Plus	Placebo
0	**2.2 +_1.1 (19)**	**2.2 +_0.8 (17)**
4	**2.5 +_1.1 (18)**	**2.4 +_0.5 (11)**
8	**3.0***	**2.6**

	+_1.1	+_0.8
	(18)	(11)
12	3.4**	2.7*
	+_1.0	+_0.8
	(18)	(11)
16	3.5**	2.7*
	+_1.0	+_0.8
	(18)	(11)

Number of patients in parentheses.
***p<0.05** ****p<0.01**

Note: A significant improvement was observed 8th week onwards in memory plus group. In placebo group, significant improvement observed in 12 weeks of the study.

TABLE 10 : Effect of memory plus/placebo on paired associate learning in children Suffering from ADHD.
(Values expressed as mean _+SD)

Weeks	Memory Plus	Placebo
0	7.9	9.4
	+_4.1	+_5.5
	(19)	(17)
4	8.9*	9.3
	+_3.9	+_5.9
	(18)	(11)
8	10.8**	9.9

	+_4.1 (18)	+_6.0 (11)
12	12.7** +_5.4 (18)	9.9 +_6.0 (11)
16	13.5** +_5.0 (18)	9.9 +_6.0 (11)

Number of patients in parentheses.
***p<0.05** ****p<0.01**

Note: A significant improvement was observed from 4th week onwards in memory plus group. No change was observed in placebo group.

TABLE 11 : Distribution of comparative change in Test score from 0 week to 12 week in Memory Plus and Placebo group. (Values expressed as mean _+SD (n)

Test	Memory Plus Group	Placebo Group	Significance
Personal Information	0.8+_0.80 (18)	0.3+_0.5 (11)	N.S.
Mental Control	1.80+_2.5 (18)	1.20+_1.6 (18)	N.S.
Sentence Repetition	2.4+_1.8 (18)	0.70+_1.0 (11)	**

Logical Memory	**3.2+_2.3 (18)**	**0.5+_1.1 (11)**	**
Word Recall (Meaningful)	**2.4+_2.1 (18)**	**2.10+_3.5 (11)**	**N.S.**
Digit Span Test	**2.7+_1.9 (18)**	**2.0+_3.4 (11)**	**N.S.**
Word Recall (Non-meaningful)	**1.5+_1.9 (18)**	**0.70+_0.9 (11)**	**N.S.**
Picture Recall	**1.05+_1.0 (18)**	**0.40+_0.5 (11)**	**N.S.**
Delayed Response Learning	**0.47+_1.1 (18)**	**0.40+_0.70 (11)**	**N.S.**
Paired Associate Learning	**4.9+_4.0 (18)**	**1.4+_2.1 (11)**	**
Total Memory Test score	**21.7+_12.5 (18)**	**6.1+_8.3 (11)**	**

**** Highly Significant (P<0.01), N.S. – Not Significant (P>0.05)**

The above table shows the highly significant change in Sentence Repetition, Logical Memory and Paired Associate Learning Test scores and Total score values of Memory Plus group as compared to Placebo group. However, in other Test score of the study, there was the tendency of increasing values as compared to Placebo group.

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