

TREATMENT OF AGE-RELATED COGNITIVE DECLINE WITH A HERBAL FORMULATION : A DOUBLE-BLIND STUDY

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ABSTRACT

There is little published research in mainstream Indian journals of the clinical psychotropic properties of herbal medicines. The present study therefore evaluated the psychotropic effects of Memorin (from a pharmaceutical house based at Maharashtra), a herbal formulation. Subjects with DSM-IV age-related cognitive decline were randomized to receive Memorin (n=22) or placebo (n=23) for three months. Before and after treatment, all subjects completed a battery of neuropsychological tests that assessed visual and verbal memory, visuospatial skills, and perceptuomotor functioning. Subjects and rater were alike blind to treatment group. The results revealed that in the Memorin group, on most tests significant improvement in performances were observed after treatment; improvement in many of the memory tasks was however confined to males; age did not significantly influence the results. In contrast, in placebo-treated subjects there was little therapeutic gain. It is concluded that irrespective of the subject's actual age, Memorin may benefit elderly persons, particularly males, who experience age-related cognitive decline.

Key words : Age-related cognitive decline, cognition, drug trial, elderly, herbal pharmacotherapy, neuropsychological changes, sex differences

India has a rich tradition in herbal medicine, and a number of herbs with psychotropic properties have been identified; these include Shankapushpi, Brahmi, Ashwagandha, Mandookaparni and others (for review, see Iyengar, 1981; Dhawan, 1995; Handa, 1995; Satyavati, 1995). While a large number of pre-clinical studies have identified potential psychotropic applications of various herbal formulations (Andrade, 1995; Andrade et al., 1994; 1995; Joseph et al., 1994; Faruqi et al., 1995; Ramteke et al., 1995), few clinical studies on these herbs and formulations have been published in mainstream Indian journals. In particular, not a single clinical study on the subject has been published in the Indian Journal of

Psychiatry since 1985.

Such a poverty of publications suggest a neglect of research into traditional strengths in Indian medicine. Allopathic science may derive much gain from herbal medical practices. Very many important allopathic drugs, such as digitalis, quinine and atropine, originated from plant sources; the Indian herbal pharmacopoeia contributed reserpine to modern medicine.

The need to study the psychotropic properties of herbal drugs is recognised even in the west; for example, clinical research on St. John's Wort (Linde et al., 1996) has recently been reviewed in the British Medical Journal. American laboratories are already screening individual herbs for psychotropic potential;

the USA efforts in this regard have been summarized by Cott (1995). By way of example, Cott et al. (1994) reported that extracts from *Withania somnifera* (Ashwagandha) show high affinity for GABA receptors, and that extracts from *Centella asiatica* (Mandookaparni) show affinity for CCK receptors. Since GABA agonism and CCK antagonism have been linked to anxiety, these findings support the recommendation in Ayurveda (a traditional system of herbal medicine in India) that Ashwagandha and Mandookaparni be used for tranquillization (Handa, 1995). Therefore the Indian psychiatrists should take a closer look at what is available at their doorstep. The present study was designed with this objective in mind.

Memorin (from a pharmaceutical house based at Maharashtra*) is a herbal formulation derived from Mandookaparni, Jatamansi, Yashtimadhu, Shankapushpi and Smruti Sagar. These ingredients have been suggested in Ayurveda to be brain tonics, anti-stress agents, and vitalizers (Iyenger, 1981; Dhawan, 1995; Handa, 1995; Satyavati, 1995). Memorin is formulated in accordance with principles laid down in Ayurveda, and the various constituents are suggested to complement each others, actions. The formulation has been commercially available since 1983.

Preliminary research on Memorin, conducted on animal models, has demonstrated that Memorin attenuates anterograde and retrograde amnesia induced by electroconvulsive shocks (Vinekar et al., 1998; Andrade et al., 1998). The present study sought to ascertain whether intermediate-term therapy with Memorin benefits normal elderly subjects who experience cognitive decline.

MATERIAL AND METHOD

The sample comprised subjects recruited from three homes for the elderly located within the boundaries of Bangalore city. To be eligible for participation in the study, all subjects had to meet the DSM-IV description of Age-related cognitive decline (American Psychiatric

Association, 1994; see appendix). The DSM description was operationalized as follows: the purpose of the study was explained to the residents of the homes, and volunteers for the study were invited; all volunteers were required to provide clear examples of forgetfulness or decreased intellectual ability in their day to day lives to be considered for inclusion. All volunteers were also required to be physically and mentally healthy, as certified by the attendant physician at the home, and as subsequently confirmed during the screening assessments. Finally, all volunteers were required to be non-smokers and teetotallers.

With these selection criteria specified, 45 volunteers were obtained. The subjects provided a clinical history and underwent physical and mental status examination to confirm their suitability for the study. All 45 candidates were found suitable. Informed consent for participation in the study was obtained in writing.

The following neuropsychological tests were administered at baseline:

1. Complex passage test (Mukundan et al., 1983 & 1991): three trials and one delayed recall assessment.
2. Complex figure test (Mukundan et al., 1983 & 1991): three trials and one delayed recall assessment.
3. Block Design Test (Andrade and Mukundan, 1996): first 5 tasks.
4. Digit Symbol Substitution Test (Andrade and Mukundan, 1996).
5. Selective Reminding Test (Buschke and Fuld, 1974).

The complex passage and complex figure tests assess verbal and visual memory respectively. The Block Design test assesses visuospatial skills and perceptuomotor speed. The Digit Symbol Substitution Test assesses scanning and perceptuomotor speed. The Selective Reminding Test assesses different aspects of verbal and visual memory: short-term storage, long-term storage, and retrieval.

Subjects were also rated on the Hamilton scales for anxiety and depression

*Phyto Pharma, Kolhapur are manufacturers of Memorin.

(Bech *et al.*, 1988). Subsequently, the subjects were randomized to receive either Memorin or placebo. Treatments were administered in the form of identical capsules, to be taken on an empty stomach in the dose of two capsules twice a day. Neither subjects nor rater knew the treatment group to which the subjects were assigned. The study were therefore double-blind.

Regular contact was maintained with the subjects to confirm compliance by pill counts and to effect troubleshooting, if required. Compliance was found to be excellent, and no distress interventions were necessary. After three months of treatment, the subjects were assessed once more on the tests and scales administered at baseline. Adverse effects with treatment were evaluated using the Systematic Assessment for Treatment Emergent Effects (SAFTEE) symptom checklist (Levine and Schooler, 1986). Subjective improvement in cognition was rated using the Clinical Global Impression scale (Guy, 1976). Finally, subjects were asked whether they wished to continue or discontinue the treatment that they were receiving.

Statistical analysis : Performances on various tests were compared before and after treatment using multivariate analyses of variance (MANOVA) based on Pillai's criterion. There were one or two repeating measures introduced, depending on the test; time (before vs after treatment with Memorin/placebo) was the invariable repeating measure, and subtest (e.g. 4 trials on each testing occasion in the visual and the verbal memory tasks; 5 tasks on each testing occasion in the block design test) was the second repeating measure, wherever applicable. Sex (male vs female) was the invariable between subjects factor.

Pearson's product moment correlation coefficients were computed to test the relationship between age and improvement on various measures on each test. Alpha for statistical significance was set at 0.05 for the MANOVAs and 0.01 for the correlations; the latter sought to attenuate the risk for type 1

errors.

Due to idiosyncratic circumstances, all subjects did not complete all tests; these variations in sample size for individual tests are reflected in the degrees of freedom.

RESULTS

A total of 45 subjects were recruited, of whom 22 received Memorin and 23 received placebo. A comparison of baseline performances on the neuropsychological tests revealed

TABLE 1
M (SD) MEMORY SCORES ON COMPLEX PASSAGE (VERBAL) AND COMPLEX FIGURE (VISUAL) MEMORY TESTS AT BASELINE AND ENDPOINT IN SUBJECTS TREATED WITH MEMORIN (N=20)*

	Trial 1	Trial 2	Trial 3	Delayed Recall
Complex passage baseline	15.3 (4.6)	19.4 (3.7)	23.1 (3.5)	16.7 (3.7)
Complex passage endpoint	18.5 (3.5)	22.1 (3.1)	25.4 (2.9)	22.1 (3.9)
Complex figure baseline	3.1 (1.8)	4.6 (2.5)	6.3 (2.9)	3.8 (2.5)
Complex figure endpoint	3.4 (1.5)	4.6 (2.4)	6.3 (2.7)	3.8 (2.5)

* values represent number of units recalled; higher scores reflect better learning/recall. Endpoint scores were significantly higher than baseline scores for the complex passage test only.

TABLE 2
M (SD) BLOCK DESIGN SCORES AT BASELINE AND ENDPOINT IN SUBJECTS TRTREATED WITH MEMORIN (N=18)*

	Baseline	Endpoint
Pattern 1	41.4 (17.1)	54.0 (13.9)
Pattern 2	74.6 (31.9)	74.5 (20.9)
Pattern 3	135.2 (54.6)	126.0 (45.1)
Pattern 4	204.8 (61.7)	261.8 (45.8)
Pattern 5	242.5 (63.1)	274.8 (43.3)

* values represent time (in secs) taken to complete task; lower scores reflect better performance.

TREATMENT OF AGE-RELATED COGNITIVE DECLINE WITH A HERBAL FORMULATION

TABLE 3
M (SD) VERBAL SELECTIVE REMINDING TEST
SCORES AT BASELINE AND ENDPOINT IN SUBJECTS
TREATED WITH MEMORIN (N=20)

	Baseline	Endpoint	Significance
Short-term storage	5.6 (1.8)	5.2 (1.5)	NS
Half long-term storage	2.4 (2.6)	3.3 (2.2)	p<0.009**
Full long-term storage	8.0 (1.9)	7.1 (3.0)	p<0.03**
Consistent long-term retrieval	3.6 (2.8)	4.8 (3.5)	p<0.001**
Total trials*	6.5 (1.4)	6.1 (1.4)	p<0.008**
Total recall at last trial	8.1 (1.5)	8.4 (1.8)	P=0.09**

*lower scores reflect better performance

**significant improvement in males but not in females

TABLE 4
M (SD) VISUAL SELECTIVE REMINDING TEST SCORES
AT BASELINE AND ENDPOINT IN SUBJECTS
TREATED WITH MEMORIN (N=19)

	Baseline	Endpoint	Significance
Short-term storage	4.8 (1.9)	4.9 (1.9)	P=0.06**
Half long-term storage	2.5 (2.6)	2.1 (3.0)	NS
Full long-term storage	7.6 (2.4)	6.9 (2.6)	p=0.06**
Consistent long-term retrieval	3.4 (2.8)	4.5 (3.8)	p=0.02**
Total trials*	6.4 (1.7)	6.3 (1.5)	p<0.006**
Total recall at last trial	8.2 (1.5)	8.4 (1.4)	p=0.013**

*lower scores reflect better performance

**significant improvement in males but not in females

that the Memorin and placebo groups were cognitively substantially different: therefore, intergroup (endpoint) statistical analyses could not be validly performed. Accordingly, only the findings with Memorin-treated subjects are highlighted, making this an uncontrolled but double-blind study. In order that the findings be placed in perspective, however, the results in the placebo-treated subjects are also

presented, albeit in summary.

Endpoint data were unavailable for two Memorin-treated subjects because they left the homes in which they had been staying. Of the remaining subjects, 8 were male and 14 were female. The age of the sample ranged from 59-86 years, with a mean (standard deviation) [M (SD)] of 72.8 (7.2) years. Males and females did not differ significantly in age. Males and females also did not differ significantly in baseline performances on any of the tests.

The Complex Passage and Complex Figure memory performances at baseline and endpoint in Memorin-treated subjects are presented in table 1. There was a significantly main effect for time in the complex passage test ($F=12.91$, $d.f.=1,18$, $p<0.002$), indicating improved learning at the treatment endpoint. In the visual memory test, however, there was no significant change at the end of the treatment period. In neither task was there a difference in performance between males and females.

The Block Design performances at baseline and endpoint in Memorin-treated subjects are presented in table 2. There was no significant change at the end of the treatment period, nor were there differences in performances between males and females.

The M (SD) time taken by Memorin-treated subjects to complete the Digit Symbol Substitution Test was 136.3 (45.0) secs at baseline, and 103.7 (25.5) secs at endpoint. The improvement was statistically significant ($F=14.61$, $d.f.=1,18$, $p<0.002$). Males and females did not differ in performances.

The performances of Memorin-treated subjects on the verbal and visual Selective Reminding Tests are presented in tables 3 and 4 respectively. For the verbal test, short-term storage scores did not improve significantly at endpoint. On the remaining elements of the verbal test, half long-term storage ($F=8.72$, $d.f.=1, 18$, $p<0.009$), full long-term storage ($F=5.71$, $d.f.=1,18$, $p<0.03$), consistent long-term retrieval ($F=15.58$, $d.f.=1,18$, $p<0.001$), total number of trials ($F=8.79$, $d.f.=1, 18$,

$p < 0.008$) and total recall at last trial ($F = 3.19$, $d.f. = 1, 18$, $p = 0.091$) improved significantly only in males.

For the visual test, short-term storage ($F = 3.48$, $d.f. = 1, 16$, $p = 0.08$), full long-term storage ($F = 3.43$, $d.f. = 1, 16$, $p = 0.084$), consistent long-term retrieval ($F = 6.88$, $d.f. = 1, 16$, $p = 0.019$), and total trials ($F = 7.90$, $d.f. = 1, 16$, $p = 0.013$), showed significant or near significant improvement only in males. There were no significant changes in half long-term storage and last trial recall scores.

In Memorin-treated subjects, for all measures on all tests, improvement scores were obtained by calculating the difference between baseline and endpoint scores. Two-tailed correlations were examined between age and each improvement score. No significant correlations emerged, indicating that the change between baseline and endpoint was independent of age.

Mean (SD) Hamilton anxiety scores in Memorin-treated subjects were 4.6 (2.2) at baseline and 3.9 (1.4) at endpoint; Mean (SD) Hamilton depression scores were 5.0 (2.1) at baseline and 3.9 (1.6) at endpoint. There were no significant changes, nor did males and females differ.

The Mean (SD) Clinical Global Impression scores in Memorin-treated subjects, rating subjective improvement in cognitive performance in day to day life at the end of the trial, was 1.6 (0.9). This indicates that the participants subjective rating of improvement was in the high mild to moderate range. SAFTEE assessments indicated no treatment-related adverse events during the course of the trial. All subjects opted to continue Memorin beyond the end of the trial.

In order that the above findings be placed in perspective, a summary of the findings in the placebo group are presented below: there were 9 males and 14 females, with Mean (SD) age of 72.8 (7.2) years. A total of 5 subjects reported a total of 6 treatment emergent adverse effects: dysphagia ($n = 2$), bowel disturbances ($n = 2$), fatigue and tiredness ($n = 1$) and tremor ($n = 1$). Two subjects discontinued

treatment because of the adverse effects. The nonspecific nature of these adverse effects however suggests that the complaints may have been due to non-treatment causes, such as a low grade intercurrent bowel or other infection.

Post-treatment improvement in the placebo group was observed in the complex passage and the digit symbol substitution tests only. No separate effects for males was observed. While all subjects who completed the trial opted to continue their medication, the overall Mean (SD) CGI rating of benefit was 1.3 (0.7), indicating subjective experience of benefit in the low mild to moderate range.

DISCUSSION

Herbal medicines are traditionally combined and administered as formulations because it is expected that such herbs exert a synergistic effect in combination. Very many patent formulations are commercially available in India; regrettably, little is known about the clinical efficacy of such formulations because the Drug Controller of India does not require clinical trials to be performed before these formulations are marketed. The present trial therefore fulfilled a felt need: it examined the benefits and adverse effects associated with the clinical use of one such formulation.

With the exception of the complex figure and the block design tests, improvement was noted at the treatment endpoint on all the tests administered. It is conceivable that the improvement was due to a placebo effect, and/or to a practice effect since parallel versions of the tests were unavailable. Two arguments, however, at least partially discredit the placebo and practice effect hypothesis. Firstly, it is hard to accept that subjects with cognitive decline will recall the elements of a task three months after its administration (this is particularly relevant with highly abstract tasks). Secondly, it is hard to understand why a practice or placebo effect should favour males more than females. These arguments are supported to a fair extent by the relative poverty of improvement in the

placebo group.

It is therefore likely that Memorin played at least some role in improving cognitive performance; this supposition is strengthened by the observation that coexisting mood disturbance was unlikely to have influenced the results because no subject at either time point experienced anxiety or depression of clinical significance, and all subjects had very low ratings of anxiety and depression.

Memorin benefited males more than females. This was a moderately consistent finding. The finding is hard to explain unless one hypothesizes that age-related cognitive decline is pathogenetically heterogeneous between the sexes. Such a hypothesis is unconfirmed but conceivable, because it is known that, for example, Alzheimer's disease is commoner in females. This may mean that females are more likely to have neuropathological changes in their brains which do not respond well to treatments, herbal or otherwise. However, the subjects' actual age did not influence outcome, even though older subjects are also more likely to show neuropathological changes.

Cognitive performance is well known to decrease with increasing age. Most elderly persons complain of a mild degree of memory impairment and subjective word or name finding disability. The prevalence of age-associated memory impairment, a more rigorously defined and restrictive diagnosis than the DSM-IV age-related cognitive decline, is 18.5% in persons above the age of 50 years (Barker et al., 1995). There is therefore a large population of persons who might benefit from the use of risk-free medication that improves cognitive performance.

In conclusion : Memorin significantly improved cognitive performance in healthy subjects with age-related cognitive decline. Males benefited from treatment more than did females. There were no treatment-related adverse events. All subjects chose to continue with their treatment at the end of the treatment period. In contrast, placebo-treated patients showed little therapeutic gain. It is therefore

concluded that Memorin may be a useful treatment for the improvement of cognitive performance in the elderly; the formulation hence merits further evaluation with a larger sample, in a controlled study. Such future studies should examine dose ranging effects to identify the ideal dose as well as to ascertain whether higher doses in women (than administered in this study) purvey clearer cognitive benefits.

APPENDIX

DSM-IV provides a description but does not specify diagnostic criteria for the category age-related cognitive decline. According to the description, the focus of clinical attention should be an objectively identified decline in cognitive functioning, consequent to the ageing process, that is within normal limits given the subject's age. Example of problems that the subjects may complain of are forgetfulness for names or appointments, or difficulties in solving complex problems. Age-related cognitive decline should be diagnosed only if the cognitive impairment is not attributable to a specific neurological or psychiatric disorder.

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