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Is chronic use of Bacopa monnieri an effective treatment to improve memory performance in healthy and aging adults?

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A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

In Partial Fulfillment of the Requirements For

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In

Health Sciences – Physician Assistant

Department of Physician Assistant Studies
Philadelphia College of Osteopathic Medicine
Philadelphia, Pennsylvania

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ABSTRACT

OBJECTIVE: The objective of the systematic review is to determine whether or not chronic use of Bacopa monnieri is an effective treatment to improve memory performance in healthy and aging adults.

STUDY DESIGN: Review of three English language primary studies published in 2006, 2008 and 2008.

DATA SOURCES: Randomized, double-blind, placebo-controlled trials comparing chronic use of Bacopa monnieri extract to placebo were found using Ovid MEDLINE, PubMed and Cochrane databases.

OUTCOMES MEASURED: Ability to recall newly learned information evaluated using the Cognitive Drug Research (CDR) cognitive assessment system, the Rey Auditory Verbal Learning Test (AVLT) and the Wechsler Memory Scale.

RESULTS: All three RCT's included in this review found significant improvement versus placebo in the realm of recalling newly learned information, specifically in spatial working memory, paired associated learning and delayed word recall memory tests.

CONCLUSIONS: The results of the RCT's reviewed demonstrate that chronic use of B monnieri extract has the potential to significantly improve cognitive function, namely the ability to recall newly learned information, in healthy as well as the elderly with age-related cognitive impairment.

KEY WORDS: Bacopa monnieri, Brahmi, cognitive, memory

INTRODUCTION

Memory, or the ability to recall information, is a common subject of complaint in healthcare as evidenced by the ADHD patient who cannot remember what he or she just read or by the aging patient who complains of an increasing inability to think of the right word to describe something. Even in the perfectly healthy individual memory has its limit. The desire to improve one's memory is near universal, and a recent study at the University of Sterling found that people with better working memory tend to be happier and more successful.¹ While memory is a multifactorial and not fully understood process, the weakening of the memory can be disabling and costly to patients. Conversely, the improvement of memory can lead to more effective living.

As many as one-third of adults will experience mild cognitive decline as they age⁴, and with an aging baby-boomer demographic beginning to enter their golden years, a desire for treatment and improvement in memory may increase in demand. While drugs such as Aricept and Namenda are being effectively used for Alzheimer's related cognitive decline, no pharmaceutical drugs or supplements are FDA approved to improve normal or age-related memory decline. Concurrently, there is a trend towards health consumers turning to complementary and alternative medicine (CAM) in the United States, with approximately \$34 billion spend on it in 2007⁷. A recent report revealed Americans spent \$107 million dollars on ginkgo biloba in hopes to improving memory.² As patients in a primary care setting increasingly inquire about supplements and herbs such as ginkgo--and indeed may be taking them without the

providers' knowledge-- it becomes important to know the evidence in order to educate patients in making informed decisions with their health.

Traditionally conservative methods such as low fat diets, regular exercise, adequate intake of fish, tight glucose control and adequate sleep of all been posited to stave off or improve memory decline.⁴ While the exact workings of memory and its decline are unknown, researchers have pointed to declining levels of neurotransmitters such as acetylcholine, serotonin and DHEA, a decrease in neurons and frequency of nerve impulses, oxidative damage to neurons (especially in the hippocampus), chronic inflammation and decreased blood flow to the brain, among others as responsible mechanisms.⁴ Many supplements ranging from B-vitamins to coffee to “smart drugs” like piracetam are marketed to improve cognitive function and enhance memory. As interest and research grows in this field, efforts must be made to evaluate the evidence to support their use. To illustrate the importance of evidence behind these therapies, a recent, federally funded study to evaluate ginkgo biloba in preventing age related cognitive decline was published in JAMA in 2009 and showed no difference versus placebo.³

Bacopa monnieri (Brahmi) is another herb—a leaf extract of water hyssop, a popular aquarium plant--has garnered recent attention for its potential in improving memory. It is being sold today in health food stores such as Whole Foods and GNC. Traditionally it has been used as far back as the 6th century in Ayurvedic medicine for enhancing memory, analgesia and treating epilepsy.⁵ Today it is being used in alternative medicine and supplement for cognition, memory, anxiety, IBS and epilepsy. The exact mechanism of action is unknown, but it is thought that saponins from B monnieri are responsible for its positive effects, hypothetically by upregulation of cholinergic regulation, GABA modulation with anxiolytic effects, antioxidant effects in the prefrontal cortex, striatum and hippocampus (as evidenced in chronic use in mice models),

altered protein synthesis in the brain, 5-HT agonism and modulation of brain stress hormone.

^{8,9,10} Early trials have not shown any significant benefit from B monnieri use in the acute setting, but small and preliminary studies have shown some promise of benefit in the arena of memory with chronic use (90 days) of B monnieri.

OBJECTIVE

The goal of this review is to determine if chronic use (of at least 3 months) of a standardized extract of B monnieri is an effective treatment to improve memory performance in healthy and aging adults.

METHODS

A search to locate RTC's that evaluated extract of B monnieri on memory performance in adults was performed. The different interventions used were 300mg standardized extract/day taken for 12 weeks; 150mg of specialized extract for twice a day for 90 days; and 125mg of standardized extract taken twice a day for 12 weeks followed by four weeks of placebo. The common denominator of these studies is administration of at least 250mg per day for at least 12 weeks (84 days). All of these interventions were compared versus placebo. Outcomes included working memory, word recall, spatial memory, anxiety and visual information processing. The studies included in this review were all randomized, double-blind placebo controlled studies.

Key words used for the search were “Brahmi” (the Indian name for B monnieri), “B monnieri”, “cognitive” and “memory”. All three studies were published and written in the English language. The Cochrane Database of Systematic Reviews, PubMed and Ovid MEDLINE—“2000 to present” were used to locate the studies published in 2006, 2008 and 2008

respectively. Criteria for selection were those published in 2000 or later, included human beings and were in the English language, dealt with POEMS and were RCT's not previously used for SRs or MAs. The researchers of the studies were from the Brain Sciences Institute from Swinburne University, KG Medical University researchers in India, and the National College of Natural Medicine in conjunction with OHSU in Portland, Oregon.

OUTCOMES MEASURED

The outcomes evaluated in the respective studies were POEMS such as the ability to recall new information, change in anxiety level, attention, working memory, spacial working memory and the ability to recall information after delay or with distraction. To evaluate these POEMS, the Wechsler Memory Scale, Cognitive Drug Research cognitive assessment system (CDR) and Rey Auditory-Verbal Learning Test (AVLT) were used. All three of the studies used very similar interventions of at least 250mg of a standardized or “specialized” B monnieri extract that included at least 50% concentration of bacosides A and B versus placebo. They were all conducted over chronic courses defined as at least 12 weeks. Two of the studies used healthy adult populations while the other study used a population of adults with complaints of insidious age-related cognitive impairments. The major characteristics of the studies under review are organized in **Table 1**.

Table of demographics of included studies: Table 1

CHARACTERISTICS OF STUDIES INCLUDED IN THE SYSTEMATIC REVIEW OF THE EFFICACY OF BACOPA MONNIERI VERSUS PLACEBO IN IMPROVING MEMORY PERFORMANCE							
Study	Type	#Pts	Age/ Yrs	Inclusion Criteria	Exclusion Criteria	W/D	Interventions
Calabrese, 2008 (1)	Double-blind, placebo controlled RCT	54	65+	Living independently, without signs of dementia	No meds other than ASA, NSAIDs, vitamins, stable doses of thyroid med, HRT, anti- HTN or cholesterol drugs	6	Standardized B. monnieri extract of 300 mg/day taken orally for 12 weeks
Stough, 2008 (2)	Double-blind, placebo controlled RCT	107	18- 60	Healthy	Hx of dementia, psychiatric or neurological disorders endocrine disorder, chronic illness or infection, pregnant or lactating, Taking anti- coagulators, ACE inhibitors, anti- Parkinson's or any other cognition enhancing drug, cigarette smoking.	35	Specialized extract of B. monnieri 300mg/day taken orally or 90 days
Raghav, 2006 (3)	Double-blind, placebo controlled RCT	40	55+	Complaints of insidious- onset memory impairment. <6 on Wechsler Memory Scale	Evidence of dementia or psychiatric disorder. > 24 on MMSE	5	Standardized B. monnieri extract 125mg BID for 12 weeks followed by 4 weeks of placebo

RESULTS

Table 2 displays a summary of results from a study conducted by Calabrese et al. in 2008. For the purpose of this analysis, results from the AVLT, or the Rey Auditory-Visual Learning Test, were chosen from the battery of measurements only if they directly related to memory. The AVLT measures short-term auditory-verbal memory among other facets of the memory such retention, retrieval accuracy and the like.⁸ The Blessed Orientation-Memory-Concentration (BOMC) and Wide Range Achievement Test (WRAT) were administered at baseline to participants and along with gender were analyzed using ANCOVA and ANOVA to determine if covariate were effecting significance. F values were all < 1 signifying that covariates did not differ between groups or gender.⁸ The ability of the bacopa group to recall words after delay had a significant increase (p 0.03) whereas placebo did not. The control group recall scores did not change significantly over 12 weeks, while the experimental arm scores increased by 1 word over 12 weeks. Significance was not seen until the 12th week interval testing.⁸

Table 2. Comparing AVLT Delayed Recall Scores Over Time in B monnieiri Versus Placebo⁸

Calabrese et al., 2008								
Means for Cognitive Measures at Baseline, 6 weeks and 12 weeks in using AVLT Delayed Recall (# of words)								
Variables	Group	Baseline M (SD)	+6 weeks M (SD)	+12 weeks M (SD)	F	df	p	η
AVLT Delayed Recall (# of words)	Placebo	6.8 (3.6)	6.6 (3.9)	6.9 (4.2)	<1			
	Bacopa	6.4 (3.1)	6.6 (3.6)	7.6 (3.9)	5.4	1,21	0.03	0.20

The results from a 2008 study conducted by Stough et al. are presented in **Table 3** and **Table 4**. The main evaluation in this experiment used the CDR computerized assessment test. The CDR assesses speed of attention, speed of memory, accuracy of attention, secondary and working memory via a variety of tests⁹. For the purpose of this analysis, only measures pertaining to secondary and working memory were examined. ANOVA conduction revealed a significance within the class of “Working Memory” tests $F(1,53) = 4.70, p = 0.035$ (**Table 4**) and specifically within in this class, “Spatial Working Memory” improved significantly $F(1,54) = 3.98, p = 0.051$ (**Table 3**).⁹ It is important to note that in the class of “Secondary Memory” there was no significant difference between groups. Note that secondary memory is also referred to as long-term memory in psychological parlance. In the specific tests of numeric-working memory, delayed-word recall, word-recognition recall and delayed-picture recall, no significant difference between placebo and the experimental arm was detected.

Table 3. Effect of B monnieri treatment on the CDR measure of spatial working memory⁹

C. Stough et al, 2008 study						
Measure	Tx group	N	Mean	SD Baseline	Mean	SD Post Tx
Spatial Working Memory (% Correct)	Placebo	28	95.67	6.91	97.97	2.53
	Bacopa	33	91.40	9.99	96.84*	5.91
Numeric Working Memory (%) correct	Placebo	28	92.94	6.34	91.89	8.26
	Bacopa	33	93.70	6.15	93.80	5.22
Delayed Word Recall (%)	Placebo	29	28.74	11.90	34.37	13.37
	Bacopa	31	31.61	14.40	34.58	14.46
Word Recognition Recall (%)	Placebo	29	81.72	11.43	84.14	8.48
	Bacopa	33	83.84	8.50	85.15	9.43
Delayed Picture Recognition (% correct)	Placebo	29	84.40	7.75	86.90	9.18
	Bacopa	33	86.29	8.73	86.82	10.94

Table 4. Baseline and Post-treatment scores for the “working memory” CDR measure⁹

C. Stough et al, 2008 study					
CDR factor	Treatment	M (baseline)	SD (baseline)	M (post-tx)	SD (post-tx)
Working Memory	Bacopa	185.11	13.16	190.64 *	9.39
	Placebo	188.71	9.50	189.85	9.08
Secondary Memory	Bacopa	246.64	33.73	254.66	39.36
	Placebo	236.93	34.75	251.49	34.53

* p < 0.05

Table 5 shows the results from a 2006 study conducted by Raghav et al., a study that used participants who have age-related cognitive impairment in contrast to the other two studies in this review. The Wechsler Memory Scale was used to evaluate memory function. Subtests of the WMS were used and are represented in **Table 5**. At 12 weeks, paired t-test analysis showed significant improvement in the Bacopa arm in the areas of mental control, logical memory, paired associate learning and total memory score ($p < 0.01$) as well as in digit forward ($p < 0.05$).¹⁰ No significant differences were seen in digit backward testing and visual reproduction measures. Moreover, no memory loss nor loss of gains was seen from week 12 to week 16 in the Bacopa arm when placebo was used in both groups for the last four weeks. When improvement of > 21% is set to define what constitutes a considerable gain, 55% of the Bacopa subjects improved considerably as opposed to none in the placebo group.¹⁰ With this dichotomous determination made, NNT would be 2 patients.

Table 5. Comparison of Wechsler Memory Scale scores of B monnieri versus placebo groups at 0, 4, 8, 12 and 16 weeks¹⁰

Raghav et al, 2006					
Variables	0 week	4 week	8 week	12 week	16 week
<i>Mental Control</i>					
Bacopa	7.4 +/- 0.9	7.8 +/- 0.7	8.2 +/- 0.9	8.6 +/- 0.6**	8.6 +/- 0.6
Placebo	7.7 +/- 0.6	7.7 +/- 0.6	8.0 +/- 0.4	8.0 +/- 0.4	8.0 +/- 0.4
't'		1.94	2.06	3.53	
<i>Logical Memory</i>					
Bacopa	4.3 +/- 1.1	5.9 +/- 1.2**	7.4 +/- 1.2**	8.7 +/- 2.1 **	8.8 +/- 2.1
Placebo	4.8 +/- 1.1	5.5 +/- 1.3	6.4 +/- 1.8*	6.7 +/- 1.6	6.7 +/- 1.4
't'		2.58	2.47	3.48	
<i>Paired Associate Learning</i>					
Bacopa	13.9 +/- 3.6	14.6 +/- 3.3	16.8 +/- 2.4 **	18.1 +/- 2.3**	18.2 +/- 2.1
Placebo	12.7 +/- 1.4	13.2 +/- 1.2	13.7 +/- 2.1*	14.5 +/- 1.8	14.5 +/- 1.7
't'		1.26	1.9	2.48	
<i>Digit Forward</i>					
Bacopa	6.3 +/- 0.5	6.8 +/- 0.7	6.6 +/- 0.7	7.0 +/- 0.7*	7.0 +/- 0.4
Placebo	6.8 +/- 0.7	6.7 +/- 0.7	6.8 +/- 0.6	6.8 +/- 0.7	6.8 +/- 0.6
't'		1.4	0.55	0.96	
<i>Digit Backward</i>					
Bacopa	5.5 +/- 0.3	5.2 +/- 0.4	5.2 +/- 0.5	5.2 +/- 0.4	5.9 +/- 0.8
Placebo	5.7 +/- 0.7	5.7 +/- 0.8	5.6 +/- 0.6	5.7 +/- 0.6	5.7 +/- 0.6
't'					
<i>Visual Reproduction</i>					
Bacopa	11.7 +/- 1.6	11.5 +/- 1.7	11.6 +/- 1.6	11.7 +/- 1.7	11.7 +/- 1.7
Placebo	12.0 +/- 1.9	12.1 +/- 1.8	12.0 +/- 2.1	12.1 +/- 2.2	12.1 +/- 2.1
't'					
<i>Total Memory Score</i>					
Bacopa	57.4 +/- 4.4	60.8 +/- 4.7*	66.9 +/- 4.7**	70.2 +/- 4.8**	70.6 +/- 4.0
Placebo	57.5 +/- 3.1	59.1 +/- 3.4	63.3 +/- 4.9	64.6 +/- 4.8	64.4 +/- 4.9
't'		2.87	10.7	4.98	
* p < 0.05 ** p < 0.01					

As mentioned previously, one study did use subjects with insidious age-related cognitive impairment (Raghav et al.) while the others used healthy participants. Exclusion criteria were similar and only one study reported compliance (Calabrese et al.), which was high with an average of 3.9 pills missed over 12 weeks with no significant difference between control and interventional arm.^{8,10} Adverse events, although not under examination in this review, are still

worth mentioning as it might affect compliance, but in all three studies no significant difference between placebo and Bacopa intervention.^{8,9,10}

DISCUSSION

Each study showed some significant improvement in a facet of memory with the most impressive gains reported in the Raghav et al. study in which participants were suffering from age-related cognitive impairment with a Wechsler score < 6 .¹⁰ It is not understood why gains would be made in one area of memory and not others, but what the statistics do bear out is that working or “short-term memory,” to put it simply, is significantly improved in the interventional group in all 3 studies. Certain subtests in the studies such “visual reproduction” (Raghav study) and “numeric working memory” (Stough study) show no difference between groups. Given the complexity of the human brain and memory, it is difficult to say why this would be. An obvious limitation of all of the studies in this review is small sample size that confers weak statistical power.

With respect to clinical use of this herb, the Natural Standard reports that palpitations, dry mouth, nausea and fatigue have been reported with use.⁵ Based on animal studies, caution should be used in patients taking drugs metabolized by the cytochrome P450 enzyme, in patients receiving treatment for thyroid disorders as it may increase levels and patients taking CCBs or sedatives to potentiation due to potential additive effects.⁵

CONCLUSION

Yes, B monnieri has the potential to be an effective treatment to improve memory performance in both the healthy and aging adults, including those suffering from age-related memory impairment. It is recommended that large scale, long duration studies are conducted to

confirm and strengthen the evidence for using this herb. Moreover, long-term studies might be explored for its potential to play a role in protecting or delaying age-related memory decline or delay Alzheimer's disease onset and/or progression. It is interesting to note that cognitive gains made in the Raghav study that involved patients with insidious age-related cognitive impairment were maintained even after discontinuing the intervention. This is a promising clinical POEM that would benefit patients if larger studies bear out similar significant evidence in the future.

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