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Efficacy of Donepezil to Enhance Cognitive and Functional Performance in Healthy, Rested Soldiers

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Table of Contents

	Page
Acknowledgements.....	iii
Introduction.....	1
Methods.....	3
Participants.....	3
Measures	4
Questionnaires.....	4
Cognitive tests.....	6
Military tasks.	7
Procedure	10
Blinding, randomization, and dosing.	12
Statistical analysis and quality control.....	12
Objective 1.....	12
Objective 2.....	12
Results.....	12
Objective 1	13
Stroop Task.	13
Digit Span Task.....	13
Rapid Visual Information Processing Task.	14
Shifting Attention Task.....	14
Standard Marksmanship Task.....	14
Change/Threat Detection Task.	14
Flight performance.....	14
Objective 2.....	15
Karolinska sleepiness scale.....	16
Profile of Mood States – Short Form.....	16
Evaluation of Risks Questionnaire.....	16
Symptom checklist.....	16
Discussion	17
Conclusion	18
References	19

List of Figures

1. EST 2000 set-up.....	8
2. Example of map and symbols in supervision task.....	9
3. Percentage of flight time above ceiling for Flight 2 by drug condition.....	15

List of Tables

1. Summary of Published Findings on Donepezil and Cognitive Enhancement in Healthy, Rested Adults	2
2. Summary of Flight Scenarios and Data Collected.....	10
3. Time Required for Each Portion of Testing Session/participant Activities of Data Collection	11
4. Frequencies of Symptoms Reported by Drug Condition.....	16

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Introduction

Pharmaceuticals like modafinil and mixed amphetamine salts have been studied extensively with respect to cognitive enhancement (Battleday & Brem, 2015; Advokat, 2010). The results have been mixed and tend to be moderated by individual differences in baseline level of function. A systematic review of cognitive enhancement techniques in healthy, rested adults identified donepezil (Kelley et al., 2019) as an alternate pharmaceutical strategy for cognitive enhancement despite having received less research focus.

Donepezil hydrochloride (Aricept) is an acetylcholinesterase inhibitor approved by the U.S. Food and Drug Administration (FDA) for the treatment of Alzheimer's dementia. Efficacy has been demonstrated in patients with mild, moderate, and severe Alzheimer's Disease. Most research looking at potential cognitive enhancements from donepezil use has focused on various aspects of memory, which coincides with the clinical use of donepezil in Alzheimer's populations. In the published literature, working memory is the most studied cognitive system, followed by attention, aspects of learning, performance retention, and general executive functioning. Much research has studied the long-term use of donepezil with a smaller subset looking at effects following administration of a single dose. Findings tend to be mixed and many alternate explanations for negative findings have been suggested, including time-dependency and task difficulty. Specifically, in a single-dose administration study of immediate effects, Zaninotto et al. (2009) concluded that some cognitive measures may be time-dependent based on dosing, citing differences in effectiveness between 90- and 210-minutes post-ingestion for a working memory task (Digit Span Task). Alternatively, Zaninotto et al. (2009) found increased episodic memory and specific improvement across post-administration test sessions for recall of objects, spatial locations, and verbal prose. Additionally, Ashare et al. (2012) found that 4-week administration of 5 milligrams (mg) of donepezil led to improved working memory, but only at higher level tasks, such that is seen with the Letter-N-Back Task. This may potentially indicate that donepezil's impact is greatest at cognitive tasks of greater difficulty compared to lower ones.

In addition to studying cognitive enhancement, two studies examined the donepezil's effects on functional performance. Rokem and Silver (2010) demonstrated that, despite an overall decrease in task performance, five days of 5 mg donepezil use was associated with improvements in perceptual learning during a visual motion direction discrimination task. Yesavage et al. (2002) administered donepezil over the course of 30 days to pilots who did not show improvements in their flight simulator performance, but instead, the donepezil administration prevented a decline in performance over the 30 days, whereas in the placebo group, a significant decline in performance was seen (Yesavage et al., 2002). Thus, the use of donepezil may help for retention of skills and abilities, instead of enhancing these skills and abilities.

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Table 1. Summary of Published Findings on Donepezil and Cognitive Enhancement in Healthy, Rested Adults

Donepezil

Main findings and take away:

1. Constructs and Measures:
 - a. Review article by Repantis et al. (2010) suggests:
 - i. There is a lack of consistent evidence for neuroenhancement effect.
 - ii. May improve retention of training on complex aviation tasks, verbal memory, and episodic memory.
 - iii. May be appropriate in instances of 24-hour sleep deprivation, whereas individuals with sleep deprivation had reduced memory and attention deficits. No improvement was seen in those who were well-rested.
 - b. Review article by Fond et al. (2015) suggests:
 - i. Most randomized-placebo-controlled trials found negative results of general psychostimulants.
 - ii. May improve some cognitive functions such as verbal episodic memory.
 - c. No studies use consistent measures/outcomes.
 - d. Consistent effects seen with:
 - i. Sustained performance
 - ii. Working memory
2. Sample size:
 - a. Findings by gender are not reported.
 - b. Between subjects design – sample sizes range from 12-27 with significant effects.

Construct	Outcomes	Reference	Sample size	Dose	Design	Population	Effects Observed
Sustained performance and task retention	Flight summary score	Yesavage et al., 2002	18 males	5 mg	Placebo, randomized, between-subjects, double-blind	Healthy non-sleep deprived pilots	Moderate retention of emergency scanning/approach to landing scores
Working memory performance	Scene/face memory task	Reches et al., 2014	18 (males and females)	5 mg	Placebo, randomized, between-subjects, double-blind	Healthy rested adults	No difference in behavioral measures
Sustained attention and working memory	Letter-N-Back and Penn Continuous Performance Task	Ashare et al., 2012	18 (6 females)	5 mg	Placebo, randomized, between-subjects, double-blind	Healthy rested adults, smokers	Improved working memory and marginal difference in attention
Attention, memory, executive	Neuro-cognitive battery:	Beglinger et al., 2004	27 (8 males)	5 mg	Placebo, randomized, between-	Healthy rested adults	No immediate difference,

functioning, language, and motor ability	Stroop color and word test, Digit symbol, trail making test, verbal fluency				subjects, double-blind		negative results with long-term use
Visual perceptual learning	Motion direction distinction task	Rokem & Silver, 2010	12 (6 males)	5 mg	Placebo, randomized, between-subjects, double-blind	Healthy rested adults	Increased performance and selectivity
Episodic memory, working memory, mood	Visuospatial tasks, object relocation tasks, digit span, corsi-block test	Zaninotto et al., 2009	24 males	5 mg	Placebo, double-blind, between-subjects	Healthy rested adults	Improved long-term recall in objects and spatial locations

Taken together, the civilian literature suggests that cognitive and performance enhancement effects of donepezil have been mixed. In addition to the suggested causes of negative findings, these mixed results may be influenced by a moderator variable, baseline intelligence. The present study is designed to establish whether this individual difference may limit application to a military population such that enhancement may prove unsuccessful for those with higher abstract reasoning skills. This is particularly important when considering enhancement in specialized sub-populations such as aviators who have a higher level of general intelligence. The secondary objective is to document any undesirable secondary effects including medically relevant side effects, increased risk-taking, and impulsivity.

Methods

This study evaluated the cognitive enhancement effects of a single dose (5 mg) of donepezil in healthy, rested Soldiers using a randomized, placebo-controlled, within-subjects, double-blind experimental design. The independent variable was the drug (donepezil 5 mg; placebo) and abstract reasoning ability was included as a moderator variable. The primary outcomes were cognitive ability (attention, visual information processing, memory), marksmanship performance, and flight performance on a subset of aviators.

Participants

Participants were 23 male, U.S. Army active-duty Soldiers. Eight participants were rated aviators and completed three simulated flights. All participants were between the ages of 21 and 45 years ($M = 31.93$ years, $SD = 5.37$). Females were excluded given that there is minimal information about how the drug administered could potentially impact the very early stages of pregnancy. Normal (or corrected to normal) vision, hearing, and cognitive function were prerequisites for eligibility. Participants were required to sleep a minimum of six hours the night before participation, refrain from consumption of stimulants (including caffeine) and over-the-counter medications that may induce drowsiness for a minimum of 16 hours prior to each test session, alcohol and sedatives for 24 hours prior, and nicotine 8 hours prior to all testing sessions, assessed by self-report. Participants were healthy such that they were free of the

following exclusion criteria:

- Currently taking medications that induce drowsiness, such as over-the-counter antihistamines (assessed through self-report).
- Current medical conditions or medications affecting cognitive function or attention as determined via screening by study physician or medical practitioner.
- Current or recent use (as determined by study physician or medical practitioner) of medications that may interact with the test articles. Determined by self-report and exclusion at the discretion of the study physician or medical practitioner.
- Any history of any attention deficit condition requiring medication. A history of any attention deficit condition requiring medication is disqualifying as the potential interactions with testing are unknown and would therefore produce a potential source of confound or bias into the results of the study.
- Any history of psychological/psychiatric disorder.
- Any history of addiction or substance abuse as assessed through self-report.
- Any history of metabolic disorder such as dysthyroidism.
- Any history of significant cardiovascular disease or hypertension.
- Any history of hepatic or renal disorder.
- Any history of circulatory disorders given that mixed amphetamine salts can cause peripheral constriction of blood vessels.
- Any history of circulatory disorders.
- Any history of peptic ulcer disease or gastrointestinal bleeding. Current and regular use of aspirin or other nonsteroidal anti-inflammatory drug medications.
- Any history of seizures or neurological conditions.
- Any history of lung disorders such as asthma or chronic obstructive pulmonary disease.

Measures

Instruments and tasks used in this study are divided in three categories: Questionnaires, cognitive tests, and military functional tasks.

Questionnaires.

All instruments were administered electronically with the exception of the Shipley Institute of Living scale, which was administered in hardcopy.

Adult Attention Deficit/Hyperactive Disorder (ADHD) Self Report Scale Symptom Checklist (ASRS).

The ASRS contains 18 items and requires 2 minutes for completion. It was developed in conjunction with the World Health Organization (WHO) and the Workgroup on Adult Attention Deficit Hyperactivity Disorder (ADHD) (Kessler et al., 2005) and is used as a screening tool with adult patients. The items are consistent with the Diagnostic and Statistical Manual of Mental Disorders, version IV criteria (American Psychiatric Association, 2000). For the purposes of this study, the scores were used to screen for symptoms associated with ADHD that could

potentially confound the results. These data are not reported as they were only used for screening purposes.

Sleep Timing Questionnaire (STQ).

The STQ is an 18-item self-report measure of sleep habits shown to be valid (such that it correlates with sleep diary information) and reliable across repeated administrations (Monk et al., 2003). This information was used in this study to identify any potential confounds pertaining to sleep disturbances or otherwise insufficient rest. These data are not reported as they were only used for screening purposes.

Karolinska Sleepiness Scale (KSS).

The KSS is a well-validated single-item questionnaire that asks subjects to rate how sleepy they feel in the moment (Kaida et al., 2006). The KSS measures daytime sleepiness with higher scores indicating greater daytime sleepiness. This information was used to identify potential confounding factors. The KSS was administered twice on each test day, pre-dosing and post-testing. Thus, for each test day, difference scores were calculated and analyzed in order to evaluate any changes in daytime sleepiness associated with each test article.

Beck's Depression Inventory (BDI).

Depression symptoms were measured using the Beck Depression Inventory- II (BDI-II; Beck et al., 1996). The BDI-II is a commonly used 21-item, multiple-choice self-report questionnaire that captures affect, cognition, and physical symptoms of depression over the most recent two-week period. Higher scores indicate greater endorsement of depression symptoms. For the purposes of this study, the scores were used to screen for symptoms associated with depression and anxiety that could potentially confound the results. These data are not reported as they were only used for screening purposes.

Shipley Institute of Living Scale (SILS).

The SILS was designed to assess general intellectual functioning in adults and adolescents and to aid in detecting cognitive impairment in individuals with normal original intelligence. The SILS yields three major summary scores: Vocabulary, abstract reasoning, and combined total scores. The vocabulary sub-scale consists of 40 multiple-choice verbal reasoning questions, and primarily taps crystallized intelligence. The abstract reasoning subscale includes 20 series-completion items of inductive reasoning that tap fluid ability (Zachary, 1986). Convergent validity of both the vocabulary and abstraction measures with crystallized and fluid intelligence, respectively, has been assessed and confirmed in a general population (Matthews et al., 2011). For our purposes, the abstract reasoning subscore is the only outcome reported.

Profile of Mood States – Short Form (POMS-SF).

The POMS-SF is a valid and reliable short version of the POMS, a measure of psychological distress and mood (McNair et al., 1981). The POMS-SF contains 35 items; in each, an adjective is provided and the subject rates how much it describes them using a 5-point

Likert scale format (Curran et al., 1995). The POMS-SF was administered to evaluate the degree to which the test articles impacted mood states. The scale outputs seven subscale scores: Tension, anger, vigor, esteem-related affect, fatigue, depression, and confusion. Additionally, a total mood disturbance score is computed by summing the scores for the “negative” affect subscales (tension, anger, fatigue, depression, and confusion) and subtracting the “positive” affect subscales (vigor and esteem-related affect). The POMS-SF was administered twice on each test day: Pre-dosing and post-testing. Thus, for each test day, difference scores were calculated and analyzed in order to evaluate any mood disturbances associated with each test article.

Evaluation of Risks Scale (EVAR).

The EVAR is a 24-item questionnaire that has been used effectively to measure individual variability in risk assessment in previous research with Special Operations Forces (Sicard et al., 2001). Individuals mark a point along a 100-millimeter (mm) bipolar visual analogue scale to indicate their preference for various types of risky activities. The scale yields five subscores: Impulsiveness, self-control, energy, invisibility, and danger-seeking. This scale is included to evaluate the effect of the test articles on secondary outcomes.

Symptom Checklist.

A brief questionnaire was developed in-house to assess the presence, severity, and onset of any side effects. Twelve possible symptoms are listed in the checklist as well as space to write in any additional symptoms.

Cognitive tests.

All tests were administered electronically.

Stroop Task.

The Stroop task is a well-established cognitive test of selective attention (Macleod, 1991). In this task, participants are presented with color words and must name the color that the word is printed in and ignore the meaning of the word. Participants complete 10 trials of each congruent and incongruent color-word pair. Stroop effect interference is the key outcome measure and is the mean difference in reaction time between congruent and incongruent trials.

Digit Span Task.

The Digit Span task is a well-established cognitive test of working memory (Miller, 1956). Participants are presented strings of numbers in increasing length and must recall them. The task is complete when a participant cannot accurately recall the string of numbers of a particular length twice. The dependent measure is the longest string length accurately recalled.

Rapid Visual Information Processing Task (RVIP).

The RVIP is a well-validated measure of sustained attention (Bakan, 1959). In each trial, participants are presented with a sequence of digits ranging from 2 to 9 in length and must detect “target” sequences within those presented. Difficulty is manipulated using the length of the “target” sequence as well as the speed of the sequence presentation (2 levels: slow [1,200 milliseconds (ms)], fast [600 ms]). Participants complete six blocks of trials.

Shifting Attention Task.

The Shifting Attention task (digit symbol substitution task) requires participants to “code” a set of digits with the provided symbols in 90 seconds (a total of 98 digits to code). The number of correctly coded digits is the dependent measure. This is a well-established measure of executive function, set shifting, and attention (Royer, 1971).

Military tasks.

Tasks were simulated using validated assessments.

Standard Marksmanship Task.

In the standard marksmanship qualifying task, participants shoot at 40 targets presented sequentially using a rifle. The targets vary in distance, from 50 to 300 meters. The scenario entails the participant firing from three positions: Prone supported, prone unsupported, and kneeling. The key dependent variables for these tasks are accuracy, reaction time, and throughput (accurate shots per second). The weapons simulator used for this task is the Engagement Skills Trainer (EST) 2000. The EST 2000 is a United States Army small arms training device. This system allows for weapons training in a controlled (simulated) environment. As can be seen in Figure 2, a participant fires from a lane (the U.S. Army Aeromedical Research Laboratory [USAARL] EST 2000 has a five-lane configuration) at “targets” which appear on a projection screen at a distance of 26 feet 3 inches from the firing line. The weapons have been modified to use with the EST 2000 but maintain their form, fit, feel, and function. At the onset of this task, participants familiarized themselves with the weapons simulator and zeroed their weapon (i.e., aligned the laser sensor to the equivalent of the mechanical weapon zero).

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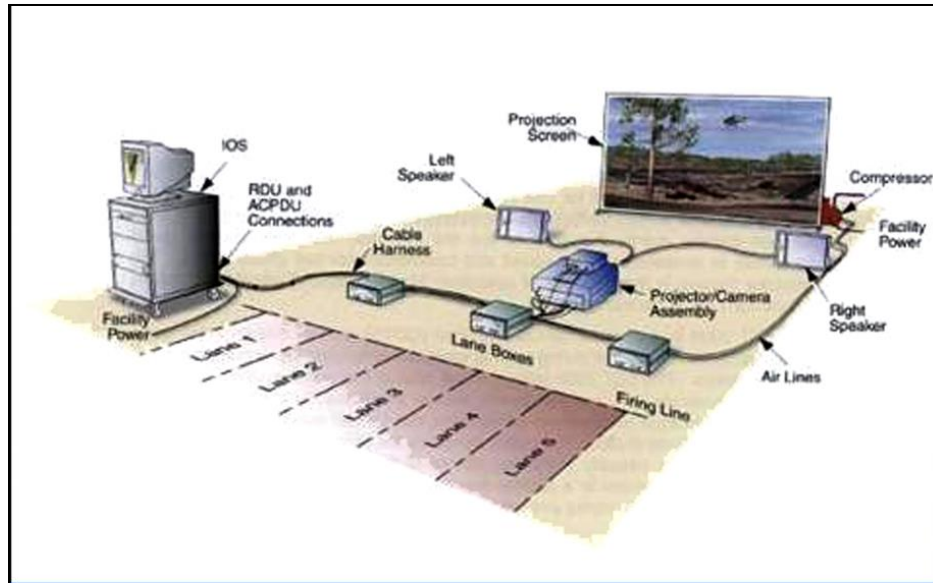


Figure 1. EST 2000 set-up.

Change/Threat Detection Task.

The change/threat Detection task is administered on a tablet and simulates an Unmanned Aerial Systems (UAS) operator supervision task. In the task, a map is presented with symbols denoting friendly or foe targets (identical to those employed in actual UAS operations; Figure 2). Subjects were instructed to monitor the map and respond with the left arrow key when a symbol change is detected and a right arrow key when a threat (foe) symbol appears in the monitored space. The workload level was considered “high,” displaying 2 events per minute (120 events per hour) (a valid manipulation demonstrated by Lin [2017]). Performance was measured in response time to threats (measured in ms from onset of threat) and targets (measured in ms from onset of target appearance) and correct responses to threats and identification of targets.

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Figure 2. Example of map and symbols in supervision task.

Flight simulator and flight tasks.

Data was collected using USAARL's full-motion NUH-60 research flight simulator. The NUH-60 consists of a simulator compartment containing a cockpit, instructor/operator station, and observer station and a six-degree-of-freedom motion system. It is equipped with six Dell precision 450 personal computer visual image generator systems that simulate natural helicopter environment surroundings for day, dusk, or night, and with blowing sand or snow. A Dell Precision laptop receives information concerning changes in the aircraft/simulator state parameters at a 60 hertz (times per second) capture rate. The spatial resolution is 1/256 of a foot, and data files are reported to two decimal places. The flight tasks and variables measured are described in Table 2.

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Table 2. Summary of Flight Scenarios and Data Collected

Primary Flight Task	Duration (minutes [min])	Conditions/Description	Variables Measured
Terrain Flight	10	Low visibility and precipitation	Altitude and airspeed deviations
Respond to emergency	10	Introduction of an emergency event, such as a fuel filter bypass or engine failure	
Perform rescue hoist	10	Day time; high winds	
Total Flight time			30 minutes

Note. LZ = Landing zone; ALT = Altitude.

Procedure

Participants completed a total of four sessions: Consent/screening, baseline, test session 1, test session 2, and test session 3. Prior to each session (except consent/screening), participants were required to: Abstain from medication inducing drowsiness, stimulants, and alcohol within the prior 16 hours; abstain from nicotine within the prior 8 hours; and sleep for a minimum of 6 hours. Sleep was estimated with the use of wrist-worn actigraphy device. In each session (except the consent/screening), the order of the cognitive tasks was randomized and target stimuli in the cognitive tasks were varied in order to minimize carryover and order effects. The four test sessions were separated by a minimum of two days to eliminate the possibility of drug carryover effects. Participants arrived at the laboratory at 0800 hours on each test day at which time they confirmed (or denied) adherence to the study criteria and a study team member checked the actigraphy device data. Participants then completed the symptom checklist, Karolinska Sleepiness Scale, and the POMS-SF to determine whether any physical symptoms were present prior to dosing (e.g., headaches) and any mood disturbances. At the two active test sessions (excluding baseline), participants were then administered a single, oral dose of donepezil (5 mg), or placebo. Participants were monitored/supervised at all times following dosing until the study physician or medical practitioner released them for the day. Three hours and 30 minutes following dosing, participants began testing. Activities and times associated for each session are outlined in Table 3.

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Table 3. Time Required for Each Portion of Testing Session/participant Activities of Data Collection

Session	Participant Activity	Data collected	Approximate Time to Complete
1: Test scheduling, informed consent, and screening procedures	Informed Consent	Not Applicable (N/A)	30 minutes
	SILS	Abstraction quotient score, vocabulary score, total score	15 minutes
	Screening	N/A	10 minutes
	Actiwatch administration	N/A	2 minutes
Total time for Session 1			Approximately 1 hour
2: Baseline test session	BDI	Total symptom score	2 minutes
	STQ	Sleep quantity, wake after sleep onset	3 minutes
	ADHD scale	Total scores (Part A and B)	2 minutes
	EVAR	Total and 3 subscale scores	5 minutes
	Marksmanship	Performance measures	40 minutes
	Cognitive tasks	Performance measures	17 minutes
	Simulated flight (aviators only)	Performance measures	30 minutes
	Change/threat detection task	Performance measures	20 minutes
Total time for Session 2			Approximately 1.5 - 2 hours
3-4: Drug administration test sessions	Dosing	N/A	10 minutes
	Recreational time	N/A	210 minutes
	POMS-SF	Total and 6 subscale scores	3 minutes
	Symptom Checklist	Symptom ratings	2 minutes
	Karolinska Sleepiness Scale	Sleepiness score	1 minute
	Marksmanship	Performance measures	40 minutes
	Patrol exertion task	Performance measures	20 minutes
	Cognitive tasks	Performance measures	35 minutes
	Simulated flight (aviators only)	Performance measures	30 minutes
	Change/threat detection task	Performance measures	20 minutes
	EVAR	Total and 3 subscale scores	5 minutes
	Meet with study physician or medical practitioner to release for the day	N/A	10 minutes
Total time for Sessions 3-4 (per session)			Approximately 5.5 - 6 hours

Blinding, randomization, and dosing.

Participants and the research team were both blind to the drug administered at each test session. All test medications and placebo were administered orally in capsules that had been rolled in sugar, to mask any potential taste, shape, size, or color differences. A web-based randomization system was used to create a random order of the test articles unique to each participant. After test articles were prepared (put in capsules and rolled in sugar to mask taste), they were put into bags labeled by participant number and test session by an individual otherwise unaffiliated with the study. For safety purposes, a master drug list was maintained and stored in a password protected file in the event of a medical emergency (e.g., seizure) or adverse event (e.g., rash).

Statistical analysis and quality control

All data were inspected for impossible values and technical errors prior to analyses.

Objective 1.

The effect of donepezil was evaluated using repeated measures analyses of covariance (ANCOVAs) and multivariate ANCOVAs (MANCOVAs). Six models were run, one per cognitive test (Stroop, digit span, RVIP, shifting attention) and military task (marksmanship, change detection task). For the aviator participant subset, flight performance data (deviations from specified airspeed and altitude) were analyzed using repeated measures ANCOVAs. All outcome measures were independent of each other. Abstract reasoning was included as a covariate in order to control for baseline intelligence. Planned comparisons were used to evaluate differences between drug conditions.

Objective 2.

In order to document any undesirable secondary effects, two multivariate, repeated measures, analyses of covariance (MANCOVAs) were run: 1) POMS, and 2) EVAR subscale scores. All outcome measures were independent of each other. Abstract reasoning was included as a covariate in order to control for baseline intelligence. Planned comparisons were used to compare the donepezil conditions to the placebo condition. Frequencies of symptoms for each condition are reported.

Results

One participant did not complete both drug conditions and thus was removed from analyses ($n = 22$). Outliers (standardized values exceeding 3) were removed listwise from the individual analyses. Missing data were also removed from analysis of respective tasks or instruments, thus ensuring that the repeated measures design maintained balanced samples.

Abstract reasoning scores were considered for inclusion in the analyses as a covariate ($M = 33.87$, $SD = 3.77$). Published normative data (Harnish et al., 1994) for the age groups represented in this study are mean abstract reasoning scores of 29.47 ($SD = 7.46$) for those 20-29 years and 29.64 ($SD = 6.52$) for those 30-39 years.

Objective 1

Planned analysis originally included each participant's Shipley abstract reasoning score as a covariate. However, this covariate was removed from the analysis because none of the outcome variables met the underlying assumptions of (1) linear relationships between the covariate and each dependent variable with (2) homogenous regression slopes across treatment levels.

Prior to conducting ANOVA on the digit span data and MANOVAs on the other outcome variables, conventional distributional assumptions were checked. Most of the sets of variables failed to meet multiple assumptions, e.g., correlated dependent variables, multivariate normality, and/or homogeneity of variance-covariance matrices. As a result, analysis was conducted using Pillai's trace and Hotelling's T^2 (converted to F statistics) as test statistics since these are generally robust to departures from distributional assumptions when sample sizes are balanced across treatment combinations (Smith, 2018).

Stroop Task.

For analysis of performance on the Stroop task, congruence level was included as an additional factor potentially affecting the outcome variables. Results from a two-way MANOVA indicate a significant interaction effect between Drug and congruence level (Pillai's Trace, $F(1, 21) = 0.268, p = 0.044$) on the vector of two Stroop outcome variable means. As a result, post-hoc two-way repeated measures ANOVAs were run to determine whether this interaction effect was present for each individual outcome.

Post-hoc results indicate a significant interaction effect between Drug and congruence level on mean response time ($F(1, 21) = 7.642, p = 0.0116$) and no interaction effect on the sum of correct responses ($F(1, 21) = 0.042, p = 0.84$). Congruence was found to exert a significant main effect on the sum of correct responses ($F(1, 21) = 8.091, p = 0.00971$), with no significant main effect of Drug level ($F(1, 21) = 1.272, p = 0.272$).

Further post-hoc pairwise t -tests were administered to test the effect of Drug level on mean response time at each congruence level. When the Stroop congruence level is "congruent," Drug has no significant effect on mean response ($t(21) = -1.3949, p = 0.1776$). Likewise, when the Stroop congruence level is "incongruent," Drug has no effect on mean response time ($t(21) = 0.823, p = 0.4199$). The conditional effect of congruence on mean response time was not investigated further since it is not of substantive interest for this study.

Digit Span Task.

Since outcome data from the digit span task are non-normally distributed, for counts with a very small range (min = 2; max = 7), a non-parametric within-subjects approach was used to compare the effect of Drug on digit length. Wilcoxon's signed-rank test for paired samples was used since it can accommodate non-continuous ordinal data. Results from the Wilcoxon signed-rank test do not support an effect of Drug on recalled digit length ($V = 45, p = 0.059$).

Rapid Visual Information Processing Task.

For analysis of performance on the RVIP task, task speed was included as an additional factor potentially affecting the outcome variables. Two participants' data were excluded from the analysis due to extreme values (outliers) ($n = 20$). Two-way MANOVA results indicate a significant main effect of task speed on the vector of two RVIP outcome variable means (Pillai's Trace, $F(2, 18) = 47.35, p < 0.001$), with no significant interaction between task speed and Drug (Pillai's Trace, $F(2, 18) = 0.86, p = 0.44$) and no effect of Drug treatment (Pillai's Trace, $F(2, 18) = 0.54, p = 0.59$). Pairwise comparisons showed that slower reaction times ($p < 0.001$) were seen in the slow condition ($M = 490.59, SD = 12.87$) than the fast condition ($M = 415.94, SD = 9.74$). Conversely, accuracy (d' values) was greater ($p = 0.036$) in the slow condition ($M = 3.91, SD = 0.13$) than the fast condition ($M = 3.54, SD = 0.18$).

Shifting Attention Task.

One outlier was excluded from analysis ($n = 21$). Results from a one-way MANOVA (Hotelling's $T^2(1, 20) = 0.101, p = 0.399$) show no significant effect of Drug treatment on Shifting Attention outcome variables.

Standard Marksmanship Task.

Three subjects were removed from the analysis of EST task results due to missing data. Results from a one-way MANOVA (Hotelling's $T^2(1, 18) = 0.081, p = 0.516$) indicate that Drug treatment has no significant effect on the vector of EST outcome variable means.

Change/Threat Detection Task.

Two participants' data were removed due to outliers. Results from a one-way MANOVA (Hotelling's $T^2(1, 19) = 0.143, p = 0.300$) showed no significant effect of Drug treatment on change/threat detection outcome variables.

Flight performance.

Data were analyzed by flight. In flight one, participants completed a terrain flight and were instructed to maintain an altitude above ground level (AGL) of 500 feet and an airspeed of 100 knots. The primary variable of interest was the mean AGL deviation from 500 feet and the secondary variable was the mean airspeed deviation from 100 knots. A paired-samples t -test did not show a difference in performance between drug conditions for altitude deviation ($t(7) = 0.09, p = 0.93$) or airspeed deviation ($t(7) = 0.09, p = 0.93$).

During flight two, participants responded to an emergency event while maintaining an AGL at or below 150 feet and an airspeed of 100 knots. One participant's data was excluded due to a technical error ($n = 7$). The variable of interest was the mean percent of time at an AGL above 150 feet. A paired-samples t -test showed a difference in performance between drug conditions ($t(6) = -5.48, p = 0.001$) such that altitude deviations were greater in the placebo condition ($M = 0.38$, standard error of the mean $[SE] = 0.04$) than in the donepezil condition ($M = 0.26, SE = 0.04$). Figure 3 shows a scatterplot by drug conditions.

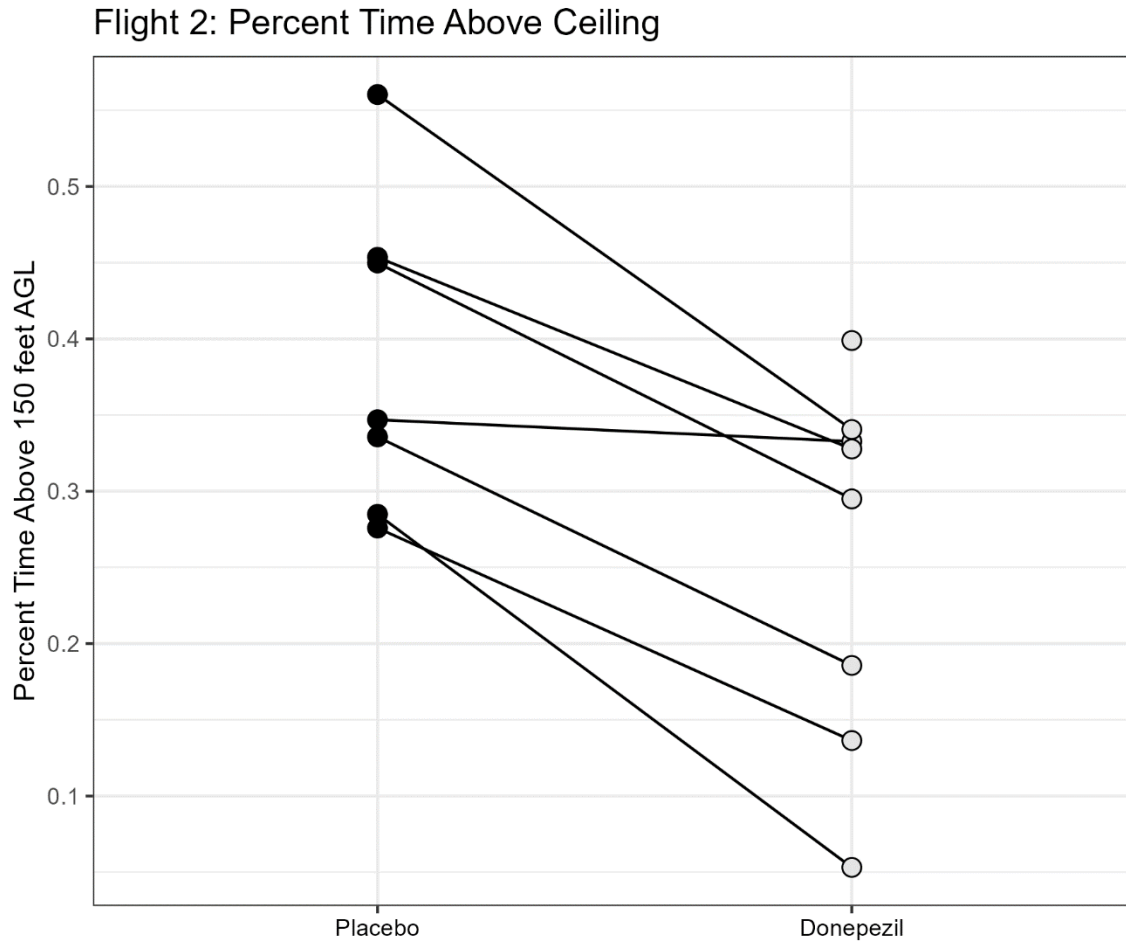


Figure 3. Percentage of flight time above ceiling for flight two by drug condition. Lines are drawn between observations from individual participants in each condition.

In flight three, participants completed a rescue hoist and were instructed to maintain an AGL at 300 feet or below. The variable of interest was the mean percent of time at an AGL above 300 feet. One participant's data was excluded due to technical error ($n = 7$). A paired-samples t -test did not support a difference in performance between drug conditions ($t(6) = 1.06, p = 0.33$).

Objective 2

Prior to conduct of MANOVAs on the EVAR and POMS-SF scores, conventional distributional assumptions were checked. The variable sets failed to meet multiple assumptions, e.g., correlated dependent variables, multivariate normality, and/or homogeneity of variance-covariance matrices. As a result, analysis was conducted using Pillai's trace and Hotelling's T^2 (converted to F statistics) as test statistics as was done for analyses to meet Objective 1.

Karolinska sleepiness scale.

The scale was administered pre- and post-testing to assess any changes in sleepiness by drug condition. Difference scores were calculated by subtracting the post-score from the pre-score. Two participants' data were excluded due to missing values ($n = 20$). A paired-samples t -test did not support a difference between drug conditions ($t(19) = 0.66, p = 0.52$).

Profile of Mood States – Short Form.

The POMS-SF outputs seven subscale scores: Tension, anger, vigor, esteem-related affect, fatigue, depression, and confusion. Three participants' data were excluded due to outliers. Results from a one-way MANOVA (Hotelling's T^2 , $F(1, 18) = 0.649, p = 0.415$) show no significant effect of Drug treatment on POMS subscores.

Evaluation of Risks Questionnaire.

The EVAR yields five subscores: Impulsiveness, self-control, energy, invisibility, and danger-seeking. Results from a one-way MANOVA (Hotelling's T^2 , $F(5, 17) = 0.19, p = 0.96$) show no significant effect of Drug treatment on EVAR subscores.

Symptom checklist.

The symptom checklist was administered at pre-dosing and during testing. Here we report the symptoms reported during testing only if the symptom was not reported also at pre-dosing. Table 4 shows the frequency of each symptom reported by drug condition.

Table 4. Frequencies of Symptoms Reported by Drug Condition

Symptom	Donepezil	Placebo
Nervousness	0	0
Excitation	0	1 (mild)
Feelings of aggression	0	0
Headache	2 (one mild, one moderate)	0
Feelings of happiness or elation	1 (moderate)	2 (mild)
Pain in abdomen or stomach area	0	0
Dry mouth	0	1 (mild)
Pounding heart	0	0
Racing heartbeat	0	0
Tremor	0	0
Nausea	0	0
Jitteriness	0	1 (mild)

Discussion

The purpose of this study was to evaluate enhancements on cognitive and military functional tasks that were evident following a single administration of donepezil (5 mg) compared to a placebo. Results of past research have been mixed. Some studies have shown positive cognitive enhancement effects following single administration (e.g., Zaninotto et al., 2009) and multiple doses over a period of time (e.g., Ashare et al., 2012) whereas others have not seen significant differences (e.g., Reches et al., 2014). This study measured both cognitive performance as well as performance on functional tasks including marksmanship, change/threat detection (similar to that performed by UAS operators), and simulated flight. The findings overall do not support efficacy of a single, 5 mg dose of donepezil for enhancement purposes.

Out of nine tasks (including three simulated flights), only one significant difference between drug conditions was found. The effect was seen on one of the simulated flights, which were only completed by rated aviators, approximately 36 percent of participants who completed the study ($n = 8$). The scatterplot presented in Figure 3 shows the percentage of time above AGL by drug condition and suggests that the effect is likely not driven by values from one or two participants. This finding may be attributed to workload level. Specifically, maintaining a lower altitude in flight two than in flights one and three may have driven up the perceived workload. Unfortunately, perceived workload was not measured, thus this is merely speculation. However, if this were true, then perhaps donepezil's utility is in maintaining performance when experiencing high workload rather than enhancing performance on less demanding tasks. Ultimately, this data is insufficient to answer this question and may be worthwhile to explore in future research. It is imprudent to find this one significant outcome to be truly meaningful in the context of the many other tasks of varying difficulty that did not yield significant effects.

The secondary objective of the study was to evaluate any negative side effects of the drug administration. Again, the findings are not supportive of any effects, and reported side effects were minimal. Note that two participants did report a headache during testing following donepezil administration. Symptoms were reported at the start of the testing session so as not to be confounded by any effects of the testing itself (e.g., eye strain from extended exposure to a computer screen). Permitted activities between dosing and testing (approximately 3.5 hours) included, but were not limited to, watching movies on a television or phone, using a mobile phone, ping pong, reading, video games, and the like. Many of these activities could also reasonably contribute to a headache. Severity was reported as mild by one participant and moderate by the other.

The results of this study should be considered in the context of its limitations and unique participant population. Differences between this study and past studies with respect to participants may contribute to the difference in findings. The sample population in this study was limited to Soldiers whereas many other studies used college students as participants. This leads to a slightly older population in our study than studies with student participants in addition to the many other factors that distinguish these populations (e.g., education level). Also, use of functional tasks is limited in the literature and participants may be less invested in conducting computerized cognitive assessments. Intrinsic motivation to perform well and susceptibility to boredom are important factors to consider yet not measured here. Finally, the sample size, while comparable to past studies, is small with respect to the aviator subset.

Conclusion

This study evaluated the efficacy of a single, 5 mg dose of donepezil to enhance cognitive and military functional performance in Soldiers. Overall, the findings did not support enhancement efficacy. The negative findings may be attributed to the participant population, the complexity of the tasks, or the lack of true enhancement properties. Further research, particularly focused on the role cognitive workload and intrinsic motivation may play, is required prior to recommendation regarding donepezil and its enhancement properties.

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