

Cognition Enhancement by Modafinil: A Meta-Analysis

AMANDA M. KELLEY, CATHERINE M. WEBB, JEREMY R. ATHY, SANITA LEY, AND STEVEN GAYDOS

KELLEY AM, WEBB CM, ATHY JR, LEY S, GAYDOS S. *Cognition enhancement by modafinil: a meta-analysis*. *Aviat Space Environ Med* 2012; 83:685–90.

Introduction: Currently, there are a number of pharmaceuticals available that have potential to enhance cognitive functioning, some of which may ultimately be considered for such use in military operations. Some drugs with potential for cognition enhancement have already been studied for use in military operations specific to their primary effect in sleep regulation (i.e., dextroamphetamine, modafinil, caffeine). There is considerable information available on many of these drugs. However, considerations for military appropriateness must be based on proficient research (e.g., randomly controlled trial design). **Methods:** A meta-analysis was conducted to summarize the current state of knowledge of these potentially cognition-enhancing drugs. The analysis only included studies which met inclusion criteria relevant to military research. **Results:** The results of the literature review reveal a gap in research of the enhancement properties of the drugs of interest. The results yielded three studies (all of which studied modafinil) that met the criteria. The meta-analysis of these three studies revealed a relatively weak pooled effect of modafinil on some aspects of cognitive performance in normal, rested adults. **Discussion:** While the results of this study support the efficacy of modafinil, the main finding is the large literature gap evaluating the short- and long-term effects of these drugs in healthy adults.

Keywords: performance enhancement, pharmaceuticals, cognition.

THE U.S. MILITARY is constantly striving for optimal physical and mental performance from its soldiers. One strategy to improve cognitive performance involves the use of pharmaceuticals. Currently, there are a number of pharmaceuticals available that have potential to enhance cognitive functioning. Available drugs include, but are not limited to, beta-blockers, typically prescribed for cardiac arrhythmia; methylphenidate, prescribed for attention-deficit disorder; modafinil, a wake-promoting agent for those with sleep disorders; and donepezil, an acetylcholinesterase inhibitor typically prescribed for those with Alzheimer's disease. All of these medications are prescribed for a therapeutic effect not related to cognition enhancement. Caffeine, on the other hand, is available without a prescription and is frequently used specifically for its stimulant properties which impact attention. Pharmaceutical companies are also researching more substances to be used as "smart drugs" which could arrive on the market over the next few years.

It is important to note that while operational risk mitigation and soldier performance are regular considerations for commanders, pharmacologic agents are not considered optimal solutions. In fact, they are most often employed when nonpharmacologic measures (e.g., work hour policies, napping) have been exhausted or

are simply not feasible. The concerns also vary depending on the population receiving the medication. For instance, any performance-enhancing medication taken by aircrew needs to be free of side effects of aeromedical concern. For example, modafinil can cause mild side effects including dizziness, headache, and nausea, as well as severe side effects like confusion, irregular heartbeat, and shortness of breath. There is also the concern of abuse potential with certain stimulant medications.

A number of ethical concerns are raised with regard to off-label prescribing of medications (16). Despite these concerns, drugs inevitably will be considered for use in military operations for enhancement purposes. There is historical precedent for the use of pharmaceuticals for sustainment in aviation crews during combat. Some drugs with potential for cognition enhancement have already been studied for use in military operations and some are already included in Army policy in terms of their recommended use (e.g., dextroamphetamine). An initial, cursory review of the current literature revealed a wealth of research on the therapeutic uses of the above-mentioned drugs. However, there was comparatively little information available regarding their potential for cognition enhancement. In order to understand the potential risks and benefits associated with the use of these drugs for enhancement purposes, well-designed experiments using healthy, normal adults need to be conducted. The goal of this study was to conduct an in-depth review of the existing literature and conduct a meta-analysis to determine what is currently known about the effects of these drugs on cognitive performance under normal conditions. The results of this study have implications for future experimental research on the effects of cognition enhancing drugs on performance in military operations and on the immediate suitability of these agents for use by aviators and ground troops. Research has shown that cognitive function is related to performance

From the U.S. Army Aeromedical Research Laboratory, Fort Rucker, AL.

This manuscript was received for review in October 2011. It was accepted for publication in February 2012.

Address correspondence and reprint requests to: Amanda M. Kelley, U. S. Army Aeromedical Research Laboratory, P.O. Box 620577, Fort Rucker, AL 36362-0577; amanda.m.kelley@us.army.mil.

Reprint & Copyright © by the Aerospace Medical Association, Alexandria, VA.

DOI: 10.3357/ASEM.3212.2012

on military tasks. Specifically, visuospatial abilities and attention predict performance on marksmanship (9) while spatial disorientation negatively affects working memory and mathematical processing performance (18).

The use of cognition enhancement drugs has attracted much attention over recent years. In April of 2008, the journal *Nature* published results of an informal survey polling readers regarding use of three specific cognition enhancement agents (13). The results indicated that approximately 20% of the respondents reported use of the agents for nontherapeutic enhancement purposes. The majority of the respondents (69%) agreed that healthy adults should have the option to use cognition enhancement agents. While these results are interesting and suggest a growing favorable opinion of enhancement drugs, the limitations of this methodology, such as selection bias, prohibit statistical inference. Rigorous scientific research is needed to fully analyze the costs and benefits.

Soldiers must perform under conditions of stress including fatigue, thermal extremes, altitude, and nutritional deprivation. The U.S. Army is continuously working to determine techniques and countermeasures to sustain performance under these conditions. Considerable amounts of research have shown that these stressors are decrements to both cognitive and physical performance. Both pharmacologic and nonpharmacologic interventions have been identified and approved for use in operations to diminish these negative effects. However, this is a continuous effort and pharmacologic interventions to sustain and enhance cognitive performance may be applicable for these purposes in both aviation and ground troops.

The effectiveness of cognition-enhancing pharmaceuticals is variable and dependent on factors such as baseline performance and dosage. For example, some drugs are shown to enhance performance for individuals who perform at a "low" baseline level and do not enhance or may even hinder performance for individuals who perform at a "high" baseline level. Also, a dose that is under or above the manufacturer's recommendations may alter performance (4). Many of the currently available substances with potential to enhance cognitive performance are discussed in Army policies in terms of their approved therapeutic use, which is highly regulated and monitored (6). A few of the potential cognition enhancement agents that are currently used in military operations are discussed below (11).

The U.S. Army currently approves two agents for fatigue management: dextroamphetamine, a stimulant used to treat ADHD and sleep disorders such as narcolepsy, and caffeine, a stimulant available over-the-counter in various forms, including chewing gum and beverages. Dextroamphetamine is a dopamine agonist and has been shown to increase wakefulness and alertness (1). Caffeine increases vigilance and alertness by leading to increased cyclic adenosine monophosphate levels (5). A third agent pending approval for fatigue management is modafinil, a wake agent often used to treat sleep disorders. At present, modafinil's mechanism of action is

unclear, but it promotes wakefulness and is associated with increased extracellular dopamine levels (3).

Modafinil, dextroamphetamine, and caffeine have been the focus of much research and have been shown to restore and sustain cognitive performance during sleep deprivation (19). The U. S. Army Aeromedical Research Laboratory recently completed an assessment of 100 mg modafinil and 5 mg dextroamphetamine throughout 40 h of continuous wakefulness (8). Results showed that the stimulants maintained alertness, cognitive function, judgment, and risk assessment in sleep deprived aviators better than placebo without evidence of any side effects of aeromedical concern at that dosage level. While this cursory review of the literature suggests cognitive function may be affected by these agents, it is important to base pharmacological treatment of soldiers only on well-designed and relevant research studies. Thus, a systematic and critical review of the available literature (e.g., a meta-analysis) was undertaken. There were two objectives of the present study: 1) to conduct a meta-analysis to determine the pooled effect of enhancement drugs on cognitive function in healthy, rested adults relevant to aviation and ground military operations; and 2) to identify gaps in the literature and areas for future research.

METHODS

Literature Search and Study Eligibility

Literature searches were conducted in mainstream databases, including the Defense Technical Information Center, PubMed/Medline, clinicaltrials.gov, and PsycInfo. The literature search included "gray" (difficult to locate) literature, which required the assistance of a professional librarian.

Eligibility: The inclusion criteria were set to be conservative in order to increase homogeneity and to ensure only well-designed and controlled experiments were included in the analysis. The criteria were such that an included study must have the following characteristics: 1) randomly controlled trial design, 2) between-subjects design, 3) healthy human subjects ages 18 to 50 yr, 4) assessments of cognition-enhancement using valid and reliable cognitive performance measures, and 5) were published in the English language. Studies not meeting these criteria were excluded. Details regarding keywords used in literature searches and study inclusion/exclusion criteria can be found in the published technical report available in the Defense Technical Information Center (10).

Procedure

The analysis was carried out according to published guidelines for systematic reviews and meta-analyses (12). A summary of the literature search and review process is presented in the following list:

- 449 search results
- 147 duplicate citations
- 171 citations judged irrelevant by title and abstract
- 131 full text retrievals

11 judged ineligible (reviews)

120 relevant reports

91 excluded due to irrelevant populations, design, noncognitive outcome measures, or unavailable data

16 excluded due to incomplete design

10 excluded due to incomparable outcome measures

3 included studies

The librarian first located potentially relevant studies using specified search criteria (10). All eligible studies were independently read and reviewed for inclusion (as defined by the inclusion criteria) by the first three authors of this report. The investigators collectively determined which studies met our criteria and were to be included in the analysis. Minor discrepancies were settled through discussion and the investigators came to absolute agreement. The studies which met our inclusion criteria were then reviewed for comparability. Data for these studies were extracted and maintained in a database for statistical analysis. The review results can be found in the published technical report (10) as well as a complete list of references and full descriptions of the tasks used to assess cognition in the three included studies.

Statistical Analysis Approach

Effect size was calculated for each study for each dependent measure using an unstandardized mean difference (standardization was not necessary since the same cognitive tests were used across all studies). The inverse variance weight was calculated for each study and, finally, tests for overall effect and homogeneity (Q-statistic) were conducted.

RESULTS

The results of the literature search, eligibility assessment (e.g., healthy adults under normal conditions), and study quality (e.g., randomly controlled trial design) assessment yielded three modafinil studies for inclusion in the meta-analysis. Of the relevant reports retrieved, a majority of the reports were excluded based on outcome measures and populations irrelevant to our objectives despite the large body of literature on substances such as caffeine and dextroamphetamine. A summary of the test population and study design characteristics for the three studies is presented in **Table I**. All of the included articles (14,15,17) were published as full publications (rather than abstract format only).

Given the similarities of the studies (two of three studies included were conducted by the same research team/personnel) and populations tested, as well as nonsignificant Q-statistics (thus suggesting homogeneity of studies), a fixed-effects model was fit to the data. Even though only three small sample studies were included (thus few effect sizes based on relatively small samples used to compute the Q-statistics), which lends to low statistical power for rejecting homogeneity, the similarity of the studies supported the use of a fixed-effects model. Two sets of analyses were conducted: one comparing placebo to a modafinil dose of 100 mg and one comparing placebo to a modafinil dose of 200 mg. The statistically significant

TABLE I. INCLUDED STUDY CHARACTERISTICS.

Characteristics	Randall et al. (14)	Randall et al. (15)	Turner et al. (17)
Drug: modafinil	Y (yes)	Y	Y
Doses: 100 mg, 200 mg, placebo	Y	Y	Y
Double-blind assignment	Y	Y	Y
Random Assignment	Y	Y	Y
Sample Size	30 (10 per group)	60 (20 per group)	60 (20 per group)
Age Range	20-22	19-22	20-29
Gender	19 male, 11 female	29 male, 31 female	All male
Healthy	Y	Y	Y
Cognitive Tests:			
Trail Making Test A	Y	Y	
Rapid Visual Information Processing*	Y	Y	Y
Digit Span		Y	Y
Spatial Working Memory*		Y	Y
Logical Memory	Y	Y	
Trail Making Test B	Y	Y	
Stockings of Cambridge*	Y	Y	
Stroop	Y	Y	
Clock Drawing	Y	Y	
Controlled Oral Word Association Test	Y	Y	
Association Test			
Intra/extra Dimensional Set Shift*	Y	Y	Y
Delayed Matching to Sample*	Y		Y

*Subtest from Cambridge Neuropsychological Test Automated Battery. The included studies did not indicate whether the authors controlled for factors influencing metabolism (e.g., dose to bodyweight). They did, however, prohibit caffeine and alcohol use prior to testing.

results of the first and second sets of analyses are displayed in Forest plots as **Fig. 1 and 2**, respectively.

In the first set of analyses comparing the efficacy of a modafinil dose of 100 mg to enhance cognition to that of placebo, there was a significant overall effect for the rapid visual information processing test ($Z = -9358.17$, $CI = 95\%$, $P < 0.05$), backward digit span test ($Z = 49.42$, $CI = 95\%$, $P < 0.05$), Stockings of Cambridge task ($Z = 13.33$, $CI = 95\%$, $P < 0.05$), and clock drawing test ($Z = -2.49$, $CI = 95\%$, $P < 0.05$). All tests for overall effect favored treatment (100 mg of modafinil) over control (placebo). These cognitive tests measure sustained attention, working memory, spatial planning, and executive function.

In the second set of analyses comparing the efficacy of a modafinil dose of 200 mg to enhance cognition to that of placebo, there was a significant overall effect for backward digit span test ($Z = 17.06$, $CI = 95\%$, $P < 0.05$), Stockings of Cambridge ($Z = 9.42$, $CI = 95\%$, $P < 0.05$), Stroop ($Z = 28,864.92$, $CI = 95\%$, $P < 0.05$), and clock drawing test ($Z = -17.46$, $CI = 95\%$, $P < 0.05$). The test for overall effect that favored treatment (200 mg dose of modafinil) over control (placebo) was the clock drawing test. All other tests for overall effect favored control (placebo) over treatment (200 mg dose of modafinil). These cognitive tests measure working memory, attentional interference, spatial planning, and executive function. It should be noted that one study (14) reported significant effects only for the 100 mg

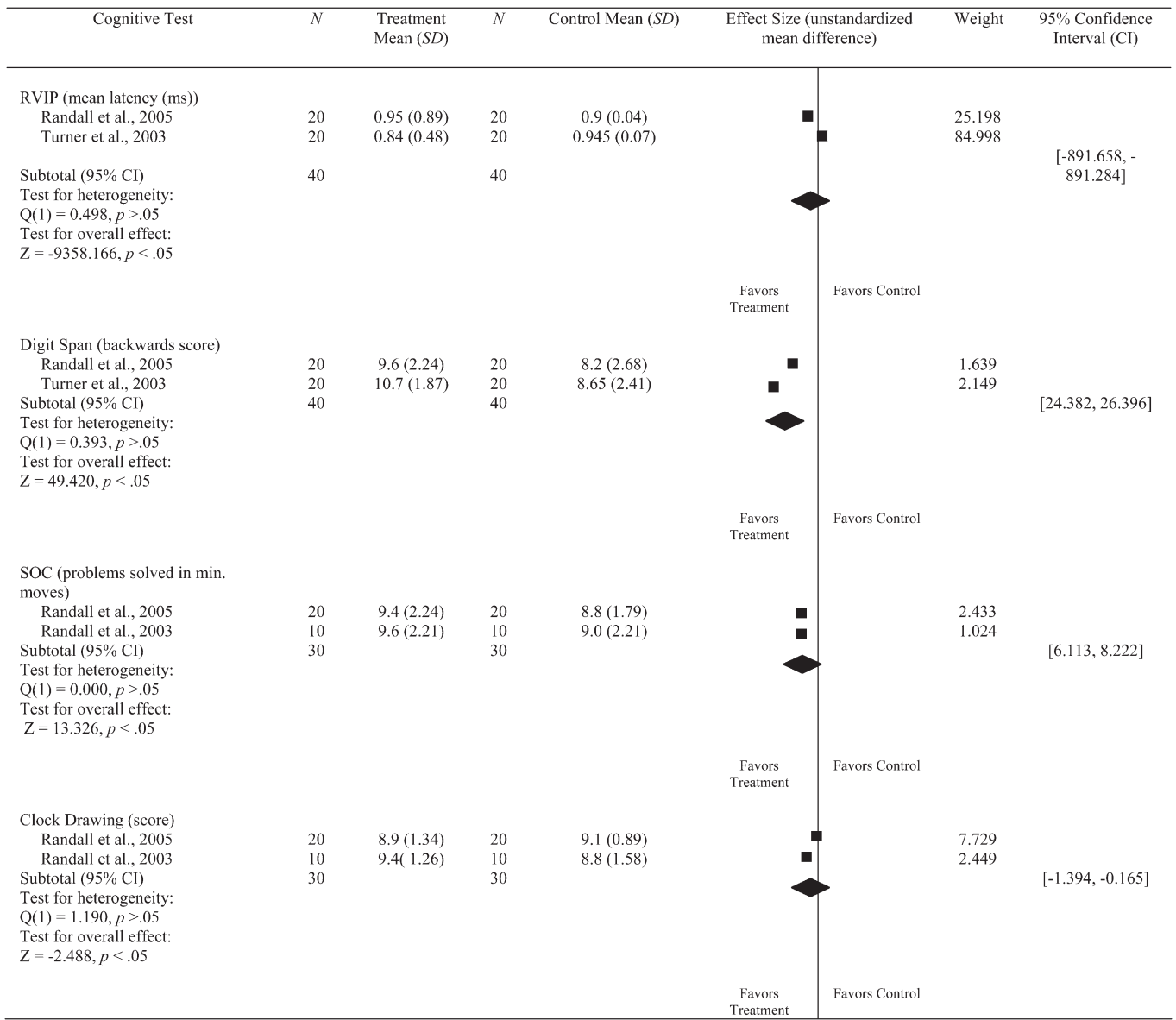


Fig. 1. Forest plot displaying significant results for analysis of modafinil (100 mg). The black squares represent the effect size for each individual study and the diamond represents the overall effect.

dose of modafinil (low dose) and no significant effects for the 200 mg dose of modafinil (high dose), which is inconsistent with results reported by another study (15), which showed significant effects of both doses.

DISCUSSION

There were two main objectives of this study: to conduct a meta-analysis of cognition enhancement pharmaceuticals in healthy volunteers and to review the literature to identify research gaps for future study. The results of this meta-analysis suggest that modafinil may have limited cognition enhancing properties (particularly limited to sustained attention, attentional interference, working memory, spatial planning, and executive function) in healthy young adults under normal conditions. (Note that this analysis does not have implications for cognition enhancement under conditions of operational stress.) The two studies conducted by the same research team reported

slightly different results, which may be attributed to the increased sample size and statistical power in the latter of the two studies. The results also suggest differences in the effectiveness of a low dose (100 mg) versus a high dose (200 mg) of modafinil such that a low dose promotes cognition to a greater extent than a high dose. This finding is likely driven by one study employing a 200-mg dose of modafinil not reporting any significant effects on cognitive performance, which is inconsistent with the other two studies. Largely, modafinil research focuses on restoring performance or attenuating performance deficits under conditions of fatigue and sleep deprivation; such studies were excluded from this analysis. Under sleep deprivation conditions, modafinil is effective at maintaining an acceptable level of performance in both cognitive and aviator performance (2,20). Thus, the results of this meta-analysis suggest lower dosages of modafinil may enhance and restore or maintain cognitive function.

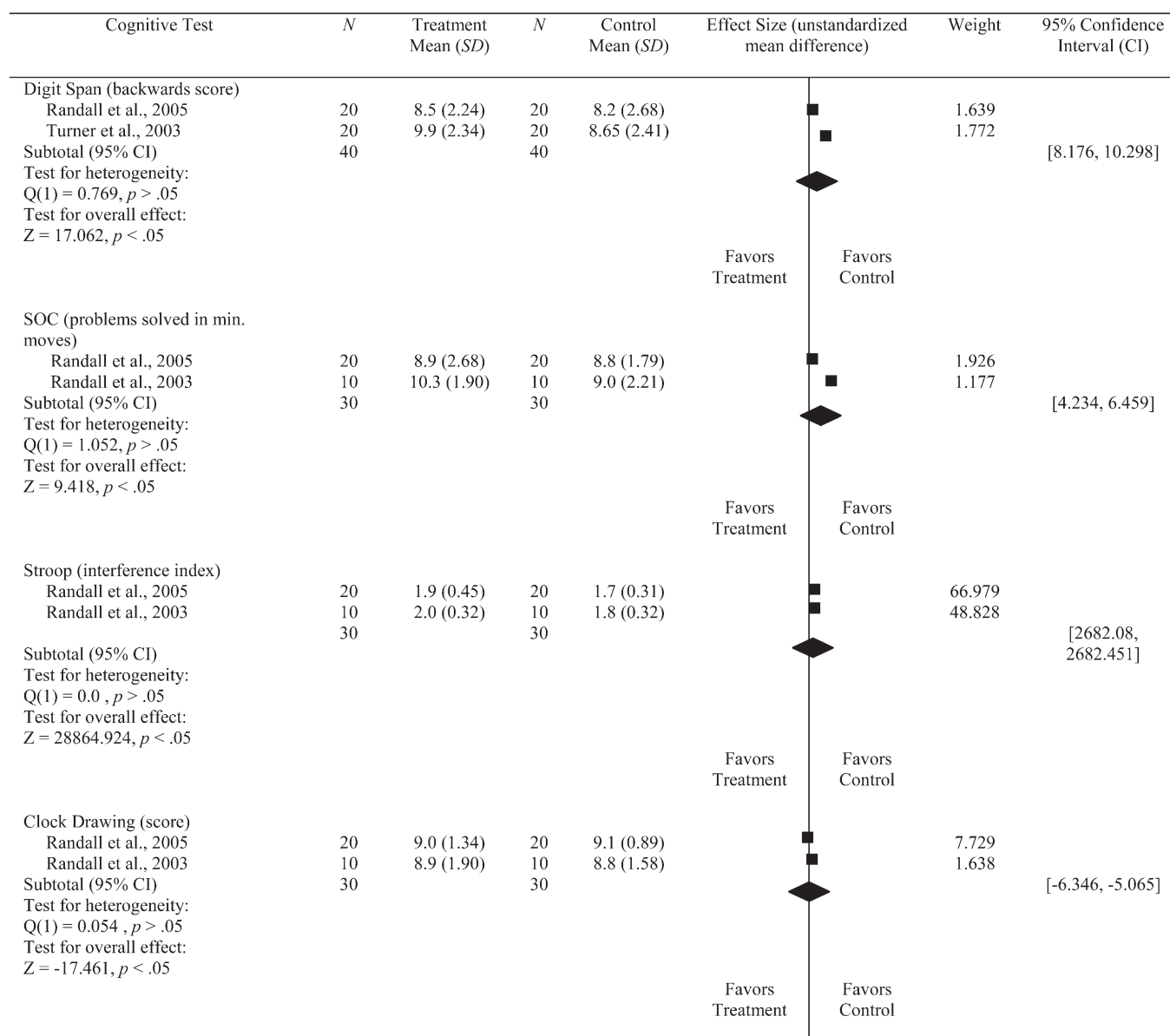


Fig. 2. Forest plot displaying significant results for analysis of modafinil (200 mg). The black squares represent the effect size for each individual study and the diamond represents the overall effect.

As the primary goal of this review is to provide interpretation of the appropriateness of cognition-enhancing pharmaceuticals in military contexts, careful consideration must be given to ethical concerns. It should be noted that although the results of this study show promise for modafinil as a cognition-enhancing agent, its use in this capacity for otherwise healthy, well-rested individuals is not approved by the Food and Drug Administration (FDA). Current indications include narcolepsy, obstructive sleep apnea/hypopnea syndrome, and shift work sleep disorder (3). Medication prescription or use for an indication other than that approved by the FDA is considered “off-label.” This practice is common and legal. Whether it is safe or appropriate depends on its judicious application.

The position of prescribing drugs for “enhancement” for an individual in a non-pathological condition is up for debate. Perhaps a perspective from the discipline of

aerospace medicine is appropriate whereby health promotion, disease prevention, and even treatment often entails a normal patient operating in a very abnormal environment—hypobaria, hypoxia, acceleration, radiation, and others. On the contrary, traditional medicine most often addresses a patient’s pathological condition in a normal environment.

Russo (16) frames the ethical considerations regarding such use citing issues of individual choice, safety, and necessity. He provides a logical, compelling argument for ethical application of cognition enhancement within the military with the following provisos: 1) the decision to use a performance-enhancing/sustaining medication rests freely with the individual; 2) the use of the drug is safe within the context in which it is used; 3) the manner of the substance’s use remains consistent with its dosage and pharmacologic function;

and 4) in general, the military employs medication options only after exhausting nonpharmacologic alternatives.

The literature search indicated that there is limited research conducted on cognition enhancement in healthy, young adults and even less under conditions of operational stress with the exception of sleep deprivation. One drug of particular interest for cognition enhancement is methylphenidate. Despite the growing popularity of this drug in civilian populations [e.g., a survey study at the University of Kentucky in which 34% of undergraduate students reported taking ADHD stimulants without a prescription (7)], the efficacy of this drug in a healthy population has not been adequately studied nor has it been studied under conditions of sleep deprivation (or other operational stressors). Given the popularity and social acceptance of pharmaceutical cognition enhancement, it is rather alarming that this large gap in the literature exists.

One limitation of this study is the relatively small number of studies that met the conservative inclusion criteria for the meta-analysis. The authors chose to adopt a conservative approach for two reasons: 1) to ensure the proficiency of the studies included in the analysis, and 2) to minimize the degree of heterogeneity between studies. There is much controversy in the literature regarding whether a more inclusive, liberal approach or a less inclusive, conservative approach is ideal for conducting a meta-analysis. While the authors recognize that a more liberal approach would have allowed for the inclusion of more studies, the results of this analysis have implications for pharmaceutical use in military populations, which is a sensitive topic that deserves and requires a high level of scrutiny. A second limitation is that the study was restricted to only some drugs/drug classes. Subsequently, potential cognition enhancing drugs/stimulants were excluded (e.g., dextroamphetamine). Therefore, this meta-analysis cannot be considered comprehensive in terms of drugs included. Finally, the authors chose to limit included research designs to between-subjects designs given that it is not advisable to combine effect sizes from both designs (within- and between- subjects).

The fact remains that much is asked of soldiers—dangerous missions under very difficult circumstances and extreme environments. The use of cognitive enhancing agents in a manner that is voluntary, safe, scientifically valid, controlled, and part of a comprehensive plan does have a role. The findings of this analysis suggest that modafinil (at both low and high doses) shows promise as an enhancement agent; however, further research on its efficacy in healthy individuals under normal conditions is needed. Likewise, much research is needed on other pharmaceuticals that show promise of cognition enhancement in healthy adults under normal and operational stress conditions. Finally, a systematic review of the excluded studies from this meta-analysis would be a beneficial addition to the literature.

ACKNOWLEDGMENTS

The views expressed in this manuscript are those of the authors and do not necessarily represent the official policy or position of the Department of Defense (paragraph 4-3, AR 360-5) or the U. S. Army Medical Command.

Authors and affiliation: Amanda M. Kelley, M.A., Ph.D., Catherine M. Webb, B.A., M.S., Jeremy R. Athy, B.A., M.S., Sanita L. Ley, B.S., and Steven J. Gaydos, M.D., M.P.H., U.S. Army Aeromedical Research Laboratory, Fort Rucker, AL.

REFERENCES

1. Caldwell JA, Caldwell JL, Crowley JS. Sustaining female helicopter pilot performance with dexedrine during sleep deprivation. *Int J Aviat Psychol* 1997; 7:15–36.
2. Caldwell JA, Smythe NK, Caldwell JL, Hall KK, Norman DN, et al. The effects of modafinil on aviator performance during 40 hours of continuous wakefulness: a UH-60 helicopter simulator study. Fort Rucker, AL: United States Army Aeromedical Research Laboratory; 1999. USAARL Technical Report No. 99-17.
3. Cephalon. Provigil Medication Guide. 2010; Retrieved 27 June 2011 from http://www.provigil.com/media/PDFs/prescribing_info.pdf.
4. de Jongh R, Bolt I, Schermer M, Oliver B. Botox for the brain: enhancement of cognition, mood, and pro-social behavior and blunting of unwanted memories. *Neurosci Biobehav Rev* 2008; 32:760–76.
5. Department of the Army. Combat and operation stress control manual for leaders and soldiers. Washington, DC: U.S. Army; 2009.
6. Department of the Army. Aeromedical policy letters. Washington, DC: U.S. Army; 2006.
7. DeSantis AD, Webb EM, Noar SM. Illicit use of prescription ADHD medications on a college campus: a multi-methodological approach. *J Am Coll Health* 2008; 57:315–24.
8. Estrada A, Kelley AM, Webb CM, Athy JR, Crowley JS, et al. A comparison of the efficacy of modafinil and dextroamphetamine as alertness promoting agents in aviators performing extended operations. Fort Rucker, AL: United States Army Aeromedical Research Laboratory; 2011. USAARL Technical Report 2011-05.
9. Kelley AM, Athy JR, King M, Erickson B, Chiamonte J, et al. Think before you shoot: the relationship between cognition and marksmanship. Fort Rucker, AL: U.S. Army Aeromedical Research Laboratory; 2011. USAARL Technical Report No. 2011-23.
10. Kelley AM, Webb CM, Athy JR, Ley S, Gaydos SJ. Cognition-enhancing drugs and their appropriateness for aviation and ground troops: a meta-analysis. Fort Rucker, AL: U.S. Army Aeromedical Research Laboratory; 2011. USAARL Technical Report No. 2011-06.
11. Lanni C, Lenzken SC, Pascale A, Vecchio ID, Racchi M, et al. Cognition enhancers between treating and doping the mind. *Pharmacol Res* 2008; 57:196–213.
12. Littell JH, Corcoran J, Pillai V. Systematic reviews and meta-analysis. New York: Oxford University Press; 2008.
13. Maher B. Poll results: look who's doping. *Nature* 2008; 452:674–5.
14. Randall DC, Schneerson JM, Plaha KK, File SE. Modafinil affects mood, but not cognitive function, in healthy young volunteers. *Hum Psychopharmacol* 2003; 18:163–73.
15. Randall DC, Viswanath A, Bharania P, Elsabagh SM, Hartley DE, et al. Does modafinil enhance cognitive performance in young volunteers who are not sleep deprived? *J Clin Psychopharmacol* 2005; 25:175–9.
16. Russo MB. Recommendations for the ethical use of pharmacologic fatigue countermeasures in the U.S. military. *Aviat Space Environ Med* 2007; 78(5, Suppl.):B119–27.
17. Turner DC, Robbins TW, Clark L, Aron AR, Dowson J, Sahakian BJ. Cognitive enhancing effects of modafinil in healthy volunteers. *Psychopharmacology (Berl)* 2003; 165:260–9.
18. Webb CM, Estrada A, Kelley AM, Ramiccio JG, Rath E, et al. The effects of spatial disorientation on working memory and mathematical processing. Fort Rucker, AL: U.S. Army Aeromedical Research Laboratory; 2010. USAARL Technical Report No. 2011-08.
19. Wesensten NJ, Killgore WD, Balkin TJ. Performance and alertness effects of caffeine, dextroamphetamine, and modafinil during sleep deprivation. *J Sleep Res* 2005; 14:255–66.
20. Whitmore J, Doan B, Heintz T, Hurtle W, Kinsner J, Smith J. The efficacy of modafinil as an operational fatigue countermeasure over several days of reduced sleep during a simulated escape and evasion scenario. Brooks City-Base, TX: United States Air Force Research Laboratory; 2004. Report No. AFRL-HE-BR-TR-2004-0021.