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## A systematic review of performance-enhancing pharmacologicals and biotechnologies in the Army

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## ABSTRACT

**Introduction:** In 2015, the Australian Army commissioned a systematic review to assess the evidence on effectiveness and safety of pharmacological and biotechnological products for cognitive enhancement specifically in Army personnel.

**Methods:** Searches for studies examining biotechnological and pharmacological products in Army populations were conducted in December 2015. Cochrane CENTRAL, MEDLINE, EMBASE, CINAHL and PsycINFO were searched; no date or language restrictions were applied. WHO's International Clinical Trials Registry Platform and ClinicalTrials.gov were searched to identify ongoing trials. Studies meeting inclusion criteria were evaluated for risk of bias using the Cochrane Risk of Bias tool. Due to heterogeneity of findings, meta-analysis could not be conducted. Findings were synthesised narratively and by vote-counting method.

**Results:** Sixteen pharmacological enhancement products were evaluated in 22 RCTs, involving 1,284 personnel in aggregate. Only 3 of the studies were published since 2010. The interventions evaluated were varied, including supplements (e.g. carbohydrate), stimulants (e.g. caffeine), and hormones (e.g. melatonin). Generally, caffeine provided an improvement in performance compared to placebo on 5 of 7 reported cognitive outcomes, followed by levothyroxine (4 cognitive outcomes) and prazosin (3 cognitive outcomes). Performance results were mixed (finding an improvement but also no effect in comparison to placebo) for caffeine and melatonin on 2 outcomes. No evidence was found pertaining to biotechnological products. Studies rarely reported safety outcomes (e.g., adverse events and addiction).

**Conclusion:** Findings from this review need to be interpreted with considerable caution. Future studies should include outcome such as acute and long-term adverse events, and should evaluate cognitive performance using cognitive tests that are specific to the Army population.

**Keywords:** pharmacological, biotechnological, performance-enhancement, army, systematic review

## **WHAT THIS PAPER ADDS**

### **What is already known on this subject?**

- Availability and use of cognitive enhancers in the form of pharmacologicals and biotechnologies is increasing
- Substantial investment is being made in funding research involving pharmacologicals and biotechnologies to enhance the performance of service personnel

### **What important gaps in knowledge exist on this topic?**

- The effectiveness, safety and other impacts of using cognitive enhancers in the Army population is unclear

### **What this study adds**

- Evidence on the impacts of use of cognitive enhancers in the Army population is limited, inconsistent, and frequently poorly reported, precluding the ability to make recommendations
- Harms such as acute and long-term effects of enhancers need to be more frequently assessed and reported when conducting studies in Army personnel

# Performance-enhancing pharmacologicals and biotechnologies in the Army: a systematic review of the evidence

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## INTRODUCTION

Military combat and highly-intense military training requires resistance to physical and cognitive stress, as extended times of these operations and training exercises are associated with considerable physical and cognitive fatigue.(1) Therefore, substantial investment is being made in funding research involving biotechnological and pharmacological applications including *in vitro* therapeutic systems, *in vivo* therapies, and hybrid biological/device treatment systems to enhance the performance of service personnel. For example, the Defence Advanced Research Projects Agency (DARPA) in the USA has proposed to invest just under \$US3 billion into developing enhancement technologies.(2) Based on publicly available information, one focus of DARPA appears to be on developing cognitive enhancers such as pharmacological products and biotechnologies.

Pharmacological products (pharmacologicals) take the form of drugs, supplements, nutraceuticals, or functional foods. They include, for example, nootropic drugs (sometimes referred to as “smart drugs”), nootropic nutraceuticals, and other drugs and molecules. Specific nootropic drugs may include, but are not limited to, racetams (piracetam; pramiracetam; oxiracetam; coluracetam; aniracetam), stimulants (amphetamines, caffeine, methylphenidates, eugeroics, xanthins, nicotine), drugs for managing symptoms related to Alzheimer’s disease (acetylcholinesterase inhibitors, meclofenoxate / cenrophenoxine), and others (phosphatidylserine; tianeptine; L-theanine; valproate; phenylalanine). Nootropic nutraceuticals may include, for example, creatine, omega 3 and various antioxidants. These pharmacologicals are thought to work directly on the receptors in the brain (e.g. N-methyl-D-aspartate – NMDA – receptors), increasing the release of particular neurotransmitters that can transiently or in the short-term change the function of brain connections. They are mainly taken orally, but may also be injected, inhaled, or administered topically.(3, 4)

Biotechnology can be defined as the use of living organisms, or their products, to create new ways to improve human health (medical biotechnology) and the environment. Performance-enhancing biologicals / biopharmaceutical engineered products thus could include NMDA (NR2B) expression, oxygen (O<sub>2</sub>) enhancers (such as blood doping and erythropoietin (EPO)), and manufactured growth factors. Cell therapies, including tissue engineering, could be used to produce various growth factors for use as performance enhancers.(5)

As performance-enhancing pharmacologicals and biotechnologies proliferate, it was considered necessary to consider the evidence of the products' effects on the well-being and cognitive performance of service personnel. The Australian Army therefore commissioned a systematic review to assess the available evidence on the pharmacological and biotechnological products used for cognitive enhancement specifically in the Army population. The findings of this systematic review are presented here.

## **METHODS**

### **Protocol**

A protocol for the systematic review was prepared by the authors, submitted for feedback to the Australian Army, and revised accordingly.

### **Searches**

In December 2015, a systematic search was conducted of the following medical databases: The Cochrane Central Register of Controlled Trials (CENTRAL, Issue 12, 2015), MEDLINE (via OVID SP), EMBASE (via EMBASE.com), CINAHL (via EBSCOhost) and PsycINFO (via OVID SP). The search strategy is provided in Appendix 1.

To identify ongoing trials, the World Health Organization's International Clinical Trials Registry Platform (WHO ICTRP) and ClinicalTrials.gov were searched in June 2016.

### **Inclusion and exclusion criteria**

The search results were screened for inclusion by four authors (in pairs of two). Any differences were resolved by consensus and consultation with a third author. The following inclusion and exclusion criteria were applied:

**Studies:** only comparative interventional studies were included – randomised controlled trials (RCTs) and quasi-RCTs.

**Participants:** The study population had to include Army personnel. Army personnel could be at any position or professional level within the Army (e.g. junior officers, senior officers, engineers). There were no restrictions on sex, age, or ethnic background. All settings were

included, ranging from training activities to active combat. The baseline status of the Army personnel included relatively healthy/stable individuals who may be under physical, mental, and/or emotional stress. Although physical, mental, and/or emotional stress may result in injury and impairment, studies where personnel had chronic, sustained, or serious injury or impairment that took them out of active duty were excluded.

**Interventions:** Pharmacological products could take the form of drugs, supplements, nutraceuticals, or functional foods. Biologicals / biopharmaceutical engineered products could include NMDA (NR2B) expression, oxygen (O<sub>2</sub>) enhancers (such as blood doping and erythropoietin (EPO)), and manufactured growth factors. Cell therapies, including tissue engineering, could be used to produce various growth factors for use as performance enhancers. Excluded interventions were: genetic engineering technologies (e.g. gene therapy and genetic testing), biosensors and biomolecular sensors, biomedical devices, educational programmes, and computer hardware and software systems (this may include a whole range of decision aides, decision-making software, and analytical software).

**Comparators:** Studies needed to compare the intervention(s) to either a different intervention(s), or the same intervention(s) at a different dose, placebo, or no treatment.

**Outcomes:** Army-relevant cognitive performance measures were sought, and were grouped under the following 10 domains:

1. Alertness (arousal / sleepiness)
2. Attention (selective / focused / divided)
3. Action control (action selection / initiation / maintenance / completion)
4. Decision-making (perception / diagnosis / selection)
5. Self-regulation and executive function (working memory / switching / inhibitory control)
6. Memory (long term / procedural / declarative / working)
7. Vigilance (threat detection / discrimination - response time / bias / sensitivity)
8. Communication (language processing / implicit perception)
9. Co-action (mental modelling / coordination)
10. Stress resistance (threat appraisal)

Other outcomes of interest included: safety (e.g. mortality, morbidity, addiction, and any adverse events), quality of life, and ethical issues (e.g., issues pertaining to autonomy, the right to object, dignity, etc.).

## Data extraction

Data from included studies was extracted and entered into evidence tables by three authors. The evidence tables collected the following information for each study: study design, country where the study was conducted, participant population (including sex and age), health status of the participants, condition of testing, intervention used (dose, frequency), comparator (dose, frequency), outcomes measured (including outcome definitions), cognitive tests used to assess the outcomes and associated results, adverse events, and any reporting of ethical issues in the studied populations.

To link the outcomes reported in the included studies to the 10 cognitive outcome domains of interest, one author mapped each cognitive test to one or more cognitive outcome domains. For example, one cognitive test known as the Walter Reed Performance Assessment Battery was judged as measuring performance on 5 cognitive domains: alertness, attention, self-regulation and executive function, memory and vigilance. Given the considerable variability in the cognitive tests used, this approach of mapping tests to cognitive outcomes was viewed as the most pragmatic approach to synthesise the breadth of information.

## Risk of bias

One author assessed and rated the risk of bias of each study across seven domains using Cochrane's risk of bias tool.<sup>(6)</sup> These domains included: (1) random sequence generation, (2) allocation concealment, (3) blinding of participants and personnel, (4) blinding of outcome, (5) incomplete outcome data, (6) selective outcome reporting and (7) any other potential sources of bias. Within each study, a domain was judged as having low risk of bias, high risk of bias or unclear risk of bias (e.g., due to a lack of information or uncertainty over the potential for bias).

## Synthesis

Owing to the breadth of interventions used and variations in outcome measures, and in some cases poor reporting of the results, this review did not explicitly extract numerical data from dichotomous variables (e.g. correct or incorrect answer) or continuous variables (e.g. reaction time). In lieu of this, a summary of the direction of the results for each cognitive outcome was done by a vote-counting method.

For a particular cognitive outcome, a study that reported a superior performance result in the intervention group compared to the comparison group was given a score of either +2 (meaning the results strongly favoured the intervention) or +1 (meaning the results favoured the intervention). This categorisation system was extended to include circumstances where a study would report all the sub-measure results for a particular cognitive test. If all of the sub-measure results were positive then the study was given a +2 on the cognitive outcome domain.

Studies reporting no significant or meaningful difference between the effects of the intervention compared to the comparator were given a score of 0.

In studies where the effect of the intervention was worse than the comparator for a particular outcome (or sub-measures of an outcome), the outcome was given a score of -1 (meaning the results favoured the comparator) or -2 (meaning the results strongly favoured the comparator).

This categorisation system does not assign weightings to studies, and does not differentiate between those studies that reported one overall cognitive test result and those studies that reported many test results from the one cognitive battery. However, given the varied quality of study data, as well as the wide range of interventions evaluated by the included studies, this was deemed to be the most pragmatic method to convey a general overview of the results.

## **RESULTS**

### **Results of the search**

The search yielded 3910 references. On de-duplication and screening of the references on title and abstract, 364 references were identified as potentially relevant and reviewed in full-text. Of these, 22 studies (RCTs) met the inclusion criteria.

### **General characteristics of the relevant studies**

The 22 included RCTs included 1,284 Army personnel in aggregate. The majority of the RCTs (19 out of 22) were conducted in the United States (994 personnel) and recruited males (over 75%). Only three studies were published since 2010, 10 between 2000 and 2009, and the remaining were all published prior to 2000. The majority of the studies were

small – only four RCTs had a sample size greater than 100. One RCT evaluated an intervention (phenformin) that was removed from the market in 1978 by the Food and Drug Administration (FDA) in the United States. Sixteen pharmacological enhancement products were evaluated by the included studies; none of the included studies evaluated biotechnological products.

### **Risk of bias assessment**

The quality of the included studies was assessed using the Cochrane risk of bias tool. This involved judging a study's risk of bias (serious, uncertain or no risk) on a particular domain. Each domain had been selected based on epidemiological evidence that, if at risk, the believability of the result would be less certain (see Figure 3 in Appendix 2).

In general, for the random sequence generation domain (i.e. whether the method of generating a random sequence was adequate or not), 20 out of 22 RCTs were deemed to be at uncertain risk of bias. Similarly, all 22 RCTs were at uncertain risk of bias for allocation concealment because none of the studies reported their methods. For the blinding of participants and personnel domain, 16 of 22 RCTs were at low or no risk of bias because the participants and investigators were unlikely to know the allocated treatment group. For blinding of outcome assessors, only 13 of 22 RCTs were judged at low risk of bias for outcomes such as self-reported mood profiles and 15 of 22 RCTs were judged at low risk of bias for outcomes that were 'objective' (meaning that there was little room for misinterpreting of the results). Three studies were at high risk of bias for failing to adequately analyse data, substantial missing data and selective reasoning for excluding participants. In terms of reporting all the outcomes intended, 20 RCTs reported the results for the outcomes listed in the methods section but 2 RCTs omitted to report outcome data.

### **Interventions studied**

Sixteen unique interventions were used to assess cognitive performance on a range of cognitive tests. The interventions were broad-ranging, including benzodiazepines (for insomnia and anxiety), hormones (such as melatonin), stimulants (such as caffeine), steroids, tropane alkaloids (medication for motion sickness) and anti-diabetic medication (phenformin) which had been removed from the market by the FDA in 1978.

The most frequently studied *class* of interventions was supplements, such as: carbohydrate supplements, creatine, iron, multivitamin/minerals, and protein (Table 1).

In terms of the total number of participants enrolled, the three most studied interventions for assessing cognitive performance were: (1) carbohydrate supplementation (302 personnel across 3 studies), (2) multivitamin and mineral supplementation (240 personnel in 1 study) and (3) iron supplementation (219 personnel in 1 study).

Out of the 16 interventions, only 4 (25%) were investigated by more than one study: caffeine (2 studies in the past 10 years), carbohydrate supplements (3 studies in the past 20 years), dexamethasone (2 studies in the past 20 years), and scopolamine (3 studies in the last 30 - 40 years).

### **Outcomes investigated**

Ten cognitive outcomes were investigated by the included studies: alertness, attention, vigilance, self-regulation and executive function, memory, action control, co-action, decision making, stress resistance and communication. The 5 most studied cognitive domains were: alertness, attention, self-regulation and executive function, memory, and vigilance (Figure). Each of these is discussed in more detail below.

[insert figure 1 here]

**Figure 1: Randomised controlled trials comparing total sample sizes, total number of studies, and number of interventions contributing to the evidence for each of the 10 cognitive outcomes**

### **Alertness**

Seventeen RCTs, involving 1,115 participants, reported results on one or more cognitive tests relevant to alertness (Figure 2).

Three interventions showed an improvement in alertness, when compared to placebo: prazosin, multivitamin and mineral supplementation, and levothyroxine. A study in active-serving Army personnel with PTSD found that performance on four cognitive tests (Cognitive Affective Processing System or CAPS, CAPS hyperarousal cluster, global function, and sleep data) strongly favoured prazosin over placebo.(7) In general Army personnel during sustained training, there was increased alertness (less sleepiness) after multivitamin and mineral supplementation than placebo.(8) Levothyroxine showed better performance on the Profile of Mood States (POMS) test than the placebo group, amongst Army personnel in setting of cold exposure.(9)

Studies of five interventions – carbohydrate supplements,(10-12) caffeine,(13, 14) melatonin,(15) dexamethasone,(16, 17) and montelukast sodium(18) – showed mixed results, e.g. an improvement in performance when assessed by one cognitive test (e.g. Stroop test), but no improvement when assessed on another cognitive test (e.g. POMS).

Three interventions showed no change in performance on alertness-related tests when compared to placebo: iron supplements,(19) creatine supplements,(20) and triazolam.(21)

[insert Figure 2 here]

**Figure 1: Distribution of favourable, neutral, or unfavourable results from RCTs for cognitive tests for alertness, attention, self-regulation and executive function, memory and vigilance.**

## **Attention**

Fourteen RCTs, involving 888 participants, reported results on one or more cognitive tests relevant to attention (Figure 2).

Three interventions showed an improvement on attention-related cognitive tests, compared to placebo or control: prazosin, protein supplement, and levothyroxine. In a study of 67 active-serving Army personnel with PTSD, performance on a global function cognitive test strongly favoured prazosin over placebo.(7) A study of general Army personnel in simulated mountain skirmishes strongly favoured protein supplementation over carbohydrate supplementation (active control) in performance on choice visual reaction time test.(22) Finally, a study of general Army personnel in a cold exposure setting favoured levothyroxine group over the placebo group for performance on POMS test.(9)

Studies of 3 interventions showed mixed results – that is, improvement or no change in performance on attention-related cognitive tests: temazepam,(23) caffeine,(13, 14), and melatonin.(15)

Five interventions showed no change in performance on attention-related cognitive tests, when compared to either placebo or control: iron supplements;(19) carbohydrate supplements;(10-12) pyridostigmine bromide, diethyltoluamide, and permethrin;(24) creatine supplements;(20) and triazolam.(21)

## **Self-regulation and executive function**

Twelve RCTs, involving 492 participants, reported results relevant to self-regulation and executive function (Figure 2).

In comparison to placebo, three interventions showed an improvement in self-regulation and executive function: levothyroxine, prazosin, and caffeine. In a study of general Army personnel in cold exposure setting, levothyroxine group performed better on a matching-to-sample task than placebo group.(9) In active-serving Army personnel with PTSD, the prazosin group performed better on a global function cognitive test than the placebo group.(7) General Army personnel under sustained training and sleep deprivation who were assigned to the caffeine group, had better marksmanship performance than the placebo group.(13)

Studies of triazolam(21) and dexamethasone(16) showed conflicting results – improvement, no change, or decline in performance (in comparison to placebo) – depending on the cognitive test used to assess performance.

Carbohydrate supplements;(11, 12) pyridostigmine bromide, diethyltoluamide, and permethrin;(24) and creatine supplements(20) showed no change in performance on self-regulation and executive function tests, when compared to placebo.

When compared to placebo, scopolamine showed reduced performance on self-regulation and cognitive function tests.(25, 26)

## **Memory**

Nine RCTs, involving 448 participants, reported results on one or more cognitive tests relevant to memory (Figure 2).

Only one intervention – levothyroxine – showed an improvement in performance on a cognitive test assessing memory (matching-to-sample task), when compared to placebo; the study assessed the performance of general Army personnel in a cold exposure setting.(9)

A study of triazolam showed either an improvement or no change in terms of performance on memory tests, when compared to placebo.(21)

Studies comparing carbohydrate supplements to placebo found no difference in performance on memory tests.(10-12)

Studies of dexamethasone(16) and scopolamine(25, 26), on the other hand, found reduced performance on memory-assessing tests, when compared to placebo.

## **Vigilance**

Eleven RCTs, involving 673 participants, reported results relevant to vigilance (Figure 2).

Temazepam, multivitamin and mineral supplement, caffeine, and melatonin studies showed an improvement in performance on vigilance tests, when compared to placebo. A study of temazepam, conducted on Army personnel, showed improved performance on psychomotor vigilance test.(23) A study comparing the performance of Army personnel taking multivitamin and mineral supplements to placebo, found better performance on the visual acuity test in the intervention group.(8) Caffeine group performed better than placebo group on marksmanship, psychomotor recognition test, urban operation vigilance task, and vigilance task/obstacle course.(13, 14) A study of Army personnel found that melatonin group performed better than placebo group on dual vigilance task, and simple visual reaction time test.(15)

When compared to placebo, carbohydrate supplementation showed either an improvement, or no change, depending on the cognitive test used to assess performance in three studies.(10-12)

Studies of dexamethasone,(16) creatine supplementation,(20) and triazolam,(21) showed no change in performance on vigilance tests when compared to placebo.

## **DISCUSSION**

Sixteen interventions were studied across 22 RCTs. Of those, 7 interventions showed an improvement in performance on a cognitive outcome, when compared to either a control or placebo: caffeine, levothyroxine, prazosin, multivitamin and mineral, protein, melatonin, temazepam. Overall, caffeine provided the most consistent results with an improvement in performance compared to placebo on five cognitive domains: action control, decision-making, self-regulation and executive function, vigilance and co-action. Levothyroxine showed improvement on 4 cognitive domains: alertness, attention, self-regulation and

executive function, and finally, prazosin showed improvement in 3 cognitive domains: alertness, attention, and self-regulation and executive function. In most of these cases, the conditions under which the Army personnel were tested can help to explain the results. In the two studies reporting on caffeine included in this review, Army personnel had experienced sustained periods of sleep deprivation while undertaking combat tasks. It is well-established that caffeine has a beneficial effect on performing tasks over a long period of time (i.e. vigilance), reaction times and executive skills such as decision making in sleep-deprived conditions.(27) Caffeine acts by blocking adenosine to its receptors (in the brain and peripheral tissue) thereby reducing drowsiness.(27) In the one study suggesting positive effects from levothyroxine (a synthetic replacement of the thyroid hormone T<sub>4</sub>), Army personnel were enduring extreme conditions in Antarctica. People living in Antarctica have reported experiencing symptoms characteristic of hypothyroidism with changes in mood (including depression) and cognition. An elevation in T<sub>4</sub> via levothyroxine seemed to improve mood and cognition. Similarly, prazosin provides a therapeutic benefit for people with PTSD. In this review, the study that tested prazosin showed a benefit in mood outcomes for Army personnel diagnosed with PTSD.

Multivitamin and mineral supplements appeared to provide some improvement on two cognitive domains (alertness, vigilance) when compared to placebo.(8) This finding was derived from one study and viewed cautiously because the authors of the study failed to take into account training effects and poorly described the results and tools used to assess sleepiness. A similar result was observed with protein supplements (attention, decision-making).(22) Melatonin and temazepam both showed improvement in one cognitive domain – vigilance. (15, 23) In this case, Army personnel were tested under sleep-deprived conditions, such as shift-work and sleep-wake challenges. As melatonin and temazepam are drugs known to induce sleepiness and muscle relaxation, the studies showed that those personnel receiving the drugs during the allocated sleep time were able to perform better during test time than those without the drugs. The remainder of interventions studied showed improvement in no cognitive domains: phenformin/lactose, triazolam, pyridostigmine bromide, montelukast sodium, dexamethasone, carbohydrate, creatine, iron, scopolamine.

It needs to be emphasised that the findings of this systematic review are not unequivocal – interventions that showed improvement on one domain, often showed no difference or mixed results in other cognitive domains. For example, whilst caffeine showed improvement in performance on five cognitive domains (action control, decision-making, self-regulation and executive function, vigilance and co-action), it also showed mixed results – that is, showing improvement and no difference in performance – in alertness and attention. Similarly,

although melatonin showed improvement in vigilance, it showed mixed results in attention and alertness domains. In addition, the results for each intervention were summarised using a vote-counting method which is recognised as a suboptimal way to synthesise information.(6) However, as the data in the included studies were poorly reported, counting the number of ‘positive’ and ‘negative’ results was seen as the most pragmatic solution to synthesise and present highly heterogeneous information.

Additionally, many of the 16 interventions have not been investigated in the past 10 years, raising questions about their popularity, utility, or effectiveness as cognitive enhancement tools in the Army population. However, the lack of peer-reviewed publications on pharmacologicals and biotechnologies on cognitive performance in Army personnel does not necessarily mean that these interventions have not been investigated – it may, instead, suggest that the results are not available in the public domain.

Study findings are derived from cognitive testing that was neither consistent nor comprehensive. The use of individual cognitive tests was poor, with often only a single test, or a sub-scale of a test, used to generate conclusions about a cognitive outcome. The cognitive tests utilised to evaluate the interventions studied were also generally aimed at a general population – studies did not use Army population-specific cognitive tests, such as the Automated Neuropsychological Assessment Metrics (ANAM), for example. It is unclear whether the findings of non-Army-specific – or at least military-specific – tests are fully generalisable to the Army population.

Studies also generally did not systematically report safety outcomes. Where the safety outcomes were reported, they included both physical and mental adverse events, and ranged from relatively minor (e.g., discomfort, dry mouth) to serious (e.g., suicidal ideation or attempt).(7, 8, 16, 17, 24, 28) Because the popularity of enhancers is growing, and the adverse events have a negative impact on individual health – and the more serious adverse events on unit cohesion – a more systematic approach to the collection of this information should be considered.

Finally, the included studies did not address the ethical issues around their use – such as individual autonomy, consent, benefit to the army, and so forth. The paucity of search results of articles on ethics issues pertaining to pharmacologicals and biotechnologies around enhancement in general, and their use in the Army population in particular, may be due to several reasons. These may include: existence of the research but its unavailability to the

public due to the research being classified; lack of interest from researchers (Army or civilian) in publishing such articles; non-indexing of the journals which publish such articles in the databases searched; or gaps in search strategy. In light of the popularity of enhancers, questions will continue to arise about the ethical acceptability of their adoption. Collaborations between Army and civilian researchers may be an ideal approach towards filling this knowledge gap.

## **CONCLUSIONS**

The inconsistency of results, variety of interventions studied, paucity of reporting on adverse events, ethical considerations, and lack of long-term follow-up, preclude positive recommendations for any of the enhancers evaluated in the included studies. The findings also need to be interpreted with considerable caution. Future studies should include outcome such as acute and long-term adverse events, and evaluate cognitive performance using cognitive tests that are specific to the Army population.

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## **COMPETING INTERESTS**

None declared.

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**Table 1: Characteristics of included studies**

Author & year	Population	Country	Sample size	Setting / Indication (coded test condition)	Intervention	Comparator	Cognitive measures used	Safety outcomes	Ethics of the use of the intervention
<b>ANTI-DIABETIC (NB. Removed from the market in 1978 by the FDA)</b>									
<b>Phenformin / lactose</b>									
Stamper 1973 (28)	Army	USA	30	High altitude / acute mountain sickness (i.e. environmental challenge)	Phenformin / lactose	Placebo	Arousal levels	Somatic discomfort symptoms	NR
<b>ANTI-HYPERTENSIVE (treats high blood pressure, anxiety and post-traumatic stress disorder (PTSD))</b>									
<b>Prazosin</b>									
Raskind 2013 (7)	Army	USA	67	NR / PTSD (i.e. other)	Prazosin	Placebo	Sleep quality; Global function; Clinician Administered PTSD Scale; hyperarousal cluster	Serious Adverse Events (suicide attempts); other Adverse Events	NR
<b>BENZODIAZEPINES (short-term mediation for insomnia and anxiety, and has muscle relaxant properties)</b>									
<b>Temazepam</b>									
Caldwell 2003 (23)	Army - Air	USA	16	Shift (night) work (i.e. sleep-wake challenges)	Temazepam	Placebo	PVT; POMS; Flight performance (simulated); EOG; EMG-sleep data	NR	NR
<b>Triazolam</b>									
Penetar 1989 (21)	Army - Air	USA	68	Long range air flight (i.e. sleep-wake challenges)	Triazolam	Placebo	Symbol digit modalities test; trail making test; letter cancellation test; logical memory portion of the Wechsler Memory Scale; five-item map recall test; POMS; Stanford sleepiness scale	NR	NR
<b>CHOLINESTERASE INHIBITOR (reversible, treats muscle weakness)</b>									
<b>Pyridostigmine bromide, diethyltoluamide, and permethrin</b>									
Roy 2006 (24)	Army	USA	64	Under both stress and rest conditions in a supervised clinical research unit (i.e. other)	Pyridostigmine bromide, diethyltoluamide, and permethrin	Placebo	Neurocognitive battery: NASA-1 Spaceflight Cognitive Assessment Tool for Windows (WinSCAT) measuring code	Adverse Events	NR

							memory, code matching, running memory, matching, and math		
<b>HORMONES</b>									
<b>Melatonin</b>									
Comperatore 1996 (15)	Army - Air	USA	29	Maintaining stable sleep/wake cycles during a training mission involving rapid deployment to the Middle East (from USA) and night operations (i.e. sleep-wake challenges)	Melatonin	Placebo	Sleep-wake cycle; Sleep duration; POMS; Simple reaction time; Four choice reaction time; Vigilance test	NR	NR
<b>Levothyroxine</b>									
Reed 2001 (9)	Army	USA	12	Antarctic residence (i.e. environmental challenges)	Levothyroxine	Placebo	Matching-to-sample task (test of attention, spatial and short-term memory, and pattern recognition); POMS	NR	NR
<b>LEUKOTRIENE RECEPTOR ANTAGONIST (commonly used for asthma)</b>									
<b>Montelukast sodium</b>									
Muza 2004 (18)	Army	USA	12	High altitude - Acute Mountain Sickness (i.e. environmental challenges)	Montelukast sodium	Placebo	Environmental Symptoms Questionnaire, Lake Louise Acute Mountain Sickness Scoring System	NR	NR
<b>STEROIDS</b>									
<b>Dexamethasone</b>									
Jobe 1991 (16)	Army	USA	16	High altitude (i.e. environmental challenges)	Dexamethasone	Placebo	Affect (Clyde Mood Scale; multiple affect adjective check list); Cognitive performance: coding; addition; pattern comparison; Tower of Hanoi; computer interaction tasks	Dizziness	NR
Rock 1989 (17)	Army	USA	28	Simulated altitude / prophylaxis for acute mountain sickness (i.e.	Dexamethasone	Placebo	Environmental Symptoms Questionnaire; Acute Mountain Sickness - Cerebral symptoms;	Adrenal suppression at 48 hours post	NR

				environmental challenges)			headache; nausea; dyspnea; sleep disturbances	exposure to steroids	
<b>STIMULANTS</b>									
<b>Caffeine</b>									
McLellan 2005 (13)	Army	Canada	30	Sustained 55-hour field exercise + sleep deprived. (i.e. combat tasks)	Caffeine	Placebo	PVT; marksmanship; urban operation vigilance test	NR	NR
McLellan 2007 (14)	Army - Special Forces	Canada	20	Sustained operations training - sustained wakefulness and restricted daytime sleep (i.e. combat tasks)	Caffeine	Placebo	Vigilance task	NR	NR
<b>SUPPLEMENTS</b>									
<b>Carbohydrate supplements</b>									
Lieberman 2002 (10)	Army - SEAL	USA	143	Simulated military mission (i.e. combat tasks)	Carbohydrate supplement	Placebo	Vigilance (reaction time); POMS (vigour-activity; fatigue-inertia; confusion-bewilderment)	NR	NR
Montain 1997 (11)	Army	USA	27	Field training in hot, humid conditions (i.e. combinations)	Carbohydrate supplement	Placebo	Marksmanship; POMS	NR	NR
Morgan 2009 (12)	Army - Special Forces	USA	132	Sustained psychological and physical stress during Survival School Training. (i.e. combat tasks)	Carbohydrate supplement	Placebo	Complex figure copy and recall task; digit symbol task; Stroop task; letter cancellation tasks; Rey auditory verbal learning task; California verbal learning task	NR	NR
<b>Creatine supplement</b>									
Warber 2002 (20)	Army	USA	26	Military training and obstacle course (i.e. combat tasks)	Creatine supplement	Placebo	Marksmanship; POMS (Confusion, etc)	NR	NR
<b>Iron supplement</b>									
McClung 2009 (19)	Army	USA	219	Basic combat training (i.e. combat tasks)	Iron supplement	Placebo	POMS (vigour, fatigue, confusion)	NR	NR
<b>Multivitamin and mineral supplement</b>									
Li 2013 (8)	Army	China	240	Endurance military training (i.e. combat tasks)	Multivitamin and mineral supplement	Placebo	Psychological assessment: sleepiness; tiredness; visual fatigue; total stress	Somatisation; Obsessive-Compulsive behaviour: phobic anxiety	NR

								(amongst other psychological sequelae)	
<b>Protein supplement</b>									
Jimenez-Flores 2012 (22)	Army	USA	35	Simulated mountain skirmishes (i.e. combat tasks)	Protein supplement	Carbohydrate supplement	Choice reaction time test	NR	NR
<b>TROPANE ALKALOIDS (treats motion sickness)</b>									
<b>Scopolamine</b>									
Petersen 1977 study 1 (25)	Army - Medical	USA	24	Evaluating amnesic effects of scopolamine - information storage and retrieval (i.e. none)	Scopolamine	Placebo	Recall - 10 lists of words	NR	NR
Petersen 1977 study 2 (25)	Army - Medical	USA	18	Evaluating amnesic effects of scopolamine - information acquisition and retrieval (i.e. none)	Scopolamine	Placebo	Recall - list of 20 high frequency nouns	NR	NR
Petersen 1979 (26)	Army	USA	28	State-dependent memory and learning (i.e. none)	Scopolamine	Placebo	Context-Cued Recall task; Free recall; Category recall task without cues; Category recall task with cues	NR	NR

PVT = psychomotor vigilance test; NR = not reported; POMS = Profile of Mood States; PTSD = post-traumatic stress disorder; EOG = electrooculography; EMG = electromyography; SAE: Serious Adverse Event

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		<p>Beta blocker*  brahmi  cordyceps  Creatine*  Dietary protein*  eurycoma  Fatty acid*  Flavonoid*  ginkgo  Isoflavone*  Melatonin*  omega 3  panax  Propranolol*  Resveratrol*  rhodiola  salvia officinalis  valerian</p> <p>Alzheimer drug*  anti-anxiety agent* OR anti anxiety agent* OR  antianxiety agent*  Antidepressive agent* OR ant-depressive agent*  Eugeroic*  Hypnotic*  Stimulant*</p> <p>Acetylcholinesterase inhibitor*  Adrenergic beta-antagonist*  Amphetamine* OR methylphenidate*  Azabicyclo compound*  Benzhydryl compound*  Bupropion*  Caffeine*  Centrophenoxine*  Meclofenoxate*  Memantine*  Nicotine*  NMDA receptor agonist*  NMDA receptor antagonist*  NMDA receptor modulator*  Pemoline*  Phenylalanine*  Phosphatidylserine*  Piperazine*  Piperidine*  Propranolol*  Racetam* OR piracetam* OR pramiracetam* OR  oxiracetam* OR coluracetam* OR aniracetam* OR  phenylpiracetam*  Temazepam*  Theanine*  tianeptine*  valproate*  Valproate*  Xanthine*</p>	<p>MH "Hallucinogens+"  MH "Medicine, Herbal"  MH "Nootropic Agents+"  MH "Orthomolecular  Medicine"  MH "Plants, Medicinal+"  MH "Resveratrol"</p> <p>MH "Adrenergic Beta-  Antagonists+"  MH "Amphetamines+"  MH "Antianxiety  Agents+"  MH "Caffeine"  MH "Central Nervous  System Stimulants+"  MH "Cholinesterase  Inhibitors+"  MH "Dopamine Uptake  Inhibitors+"  MH "Melatonin"  MH "Memantine"  MH "Methylphenidate"  MH "Nicotine"  MH "Phenylalanine"  MH "Propranolol"  MH "Xanthines"</p>
<b>STUDY TYPES</b>	Systematic reviews	SIGN SEARCH FILTER FOR SR'S: 1: MH "Meta analysis"	

<p>Randomised controlled trials Controlled trials Cohort studies</p>	<p>2: Meta analys* 3: Metaanaly* OR meta-analy* 4: MH "Literature review" 5: systematic n1 (review or overview) 6: Or/1-5 7: PT Commentary 8: PT Letter 9: PT Editorial 10: MH "Animals+" 11: Or/7-10 12: 6 NOT 11</p> <p>SIGN SEARCH FILTER FOR RCTS: 1: MH "Clinical Trials+" 2: PT Clinical trial 3: TX clinic* n1 trial* 4: TX ((singl* n1 blind*) or (singl* n1 mask*) ) or TX ((doubl* n1 blind*) or (doubl* n1 mask*)) or TX ((tripl* n1 blind*) or (tripl* n1 mask*)) or TX ((trebl* n1 blind*) or (trebl* n1 mask*)) 5: TX randomi* control* trial* 6: MH "Random Assignment" 7: TX random* allocat* 8: TX placebo* 9: MH "Placebos" 10: MH "Quantitative Studies" 11: TX allocat* random* 12: 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11</p> <p>SIGN SEARCH FILTER FOR OBSERVATIONAL STUDIES: 1: MH "Prospective studies+" 2: MH "Case control studies+" 3: MH "Correlational studies" 4: MH "Nonconcurrent prospective studies" 5: MH "Cross sectional studies" 6: cohort N1 (study or studies) 7: observational N1 (study or studies) 8: OR/1-7</p>		
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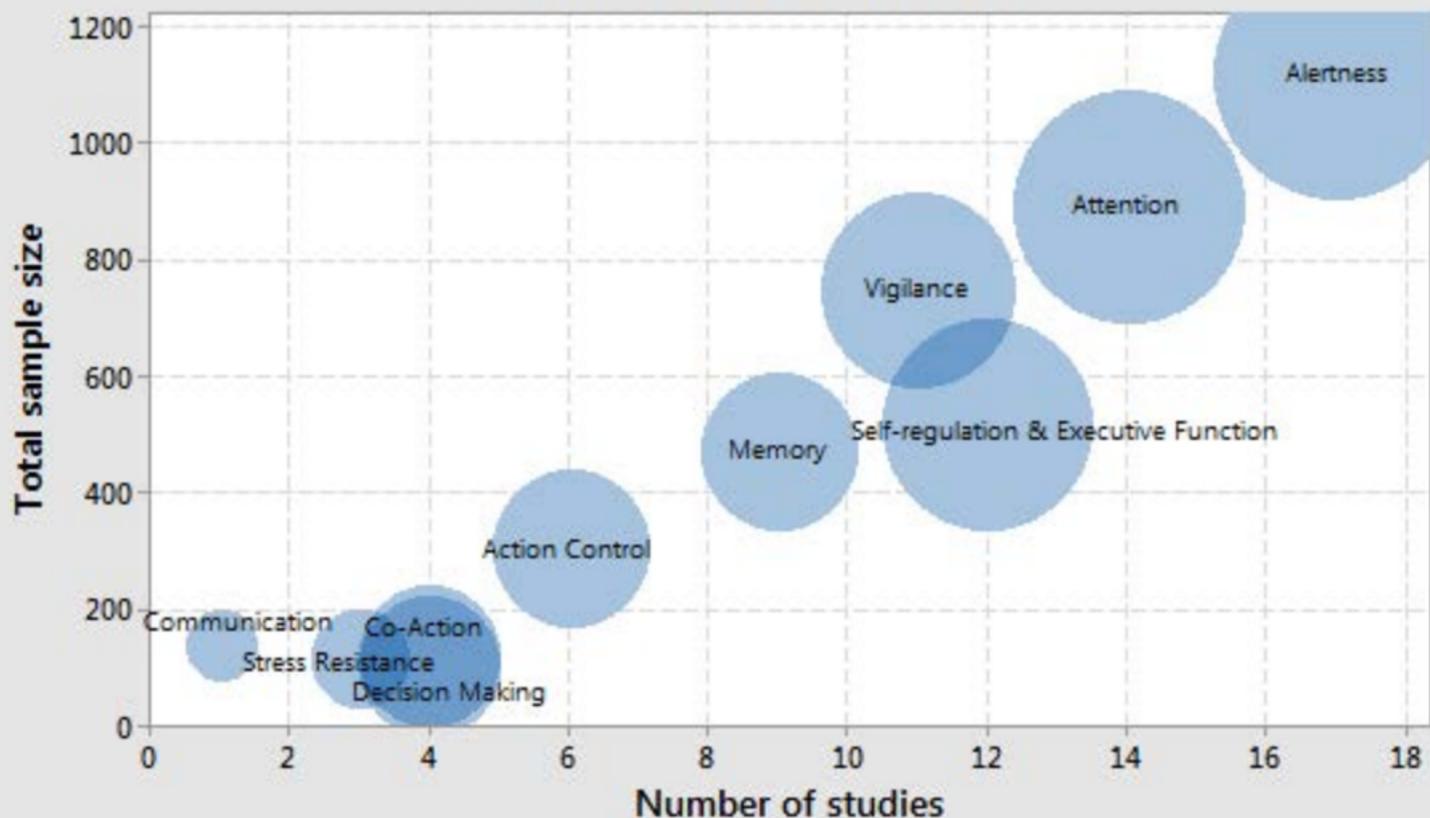
## Appendix 2 – Risk of Bias assessment

[insert figure 3 here]

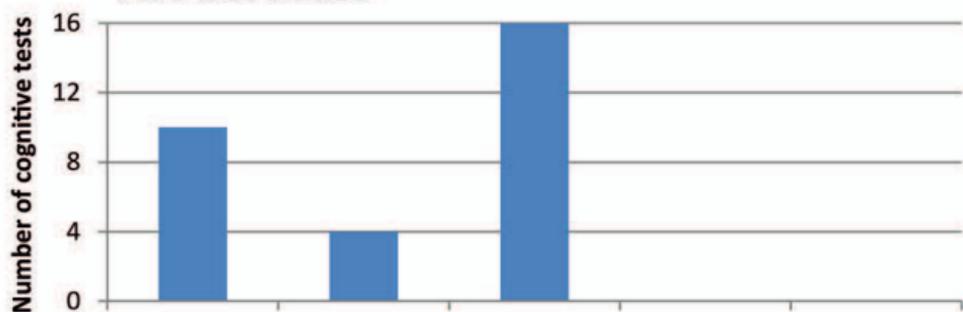
**Figure 3: The Risk of Bias assessment summary for randomised controlled trials included in the systematic review. (A white bar represents those studies for which a 'subjective' or 'objective' outcome was not assessed)**

# RCTs for cognitive performance: sample size vs number of studies

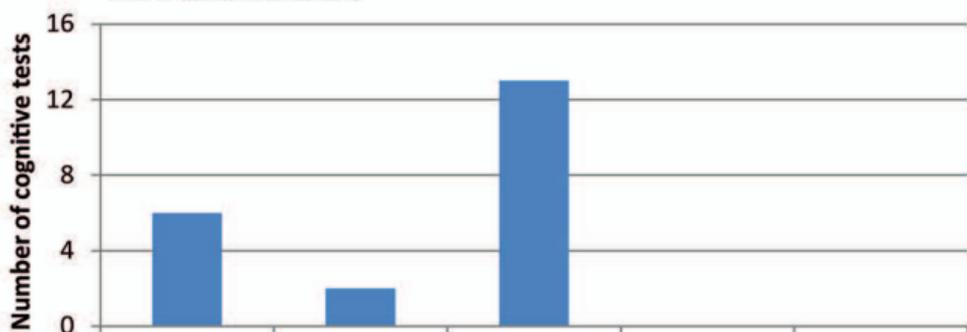
Bubble size: Number of interventions



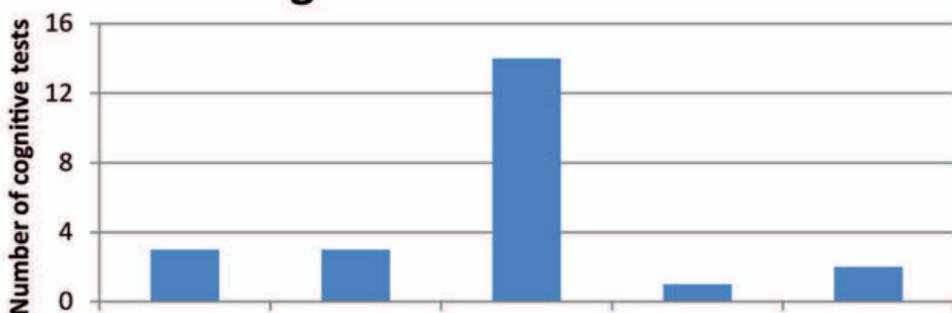
## A. Alertness



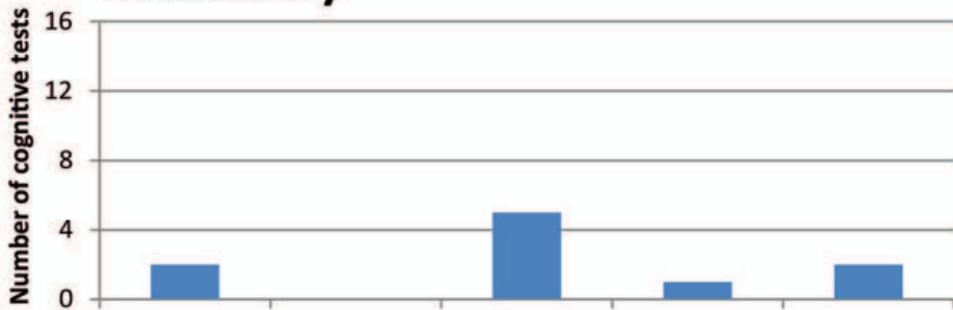
## B. Attention



## C. Self regulation & executive function



## D. Memory



## E. Vigilance

