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Modafinil to optimize the performance of cold-stressed sleep-deprived personnel

Submission date	**Recruitment status**	[_] Prospectively registered
16/07/2024	No longer recruiting	[_] Protocol
Registration date	**Overall study status**	[_] Statistical analysis plan
01/08/2024	Ongoing	[_] Results
Last Edited	**Condition category**	[_] Individual participant data
14/08/2024	Other	[X] Record updated in last year

Plain English summary of protocol

Background and study aims
Environmental and workplace stressors are common and often unavoidable in military operations. Two critical stressors are cold stress and sleep loss. They both can substantially degrade operational effectiveness. Various countermeasures are available to mitigate the adverse effects of these stressors, but due to operational requirements many are of limited use in the field. Modafinil is a drug that mitigates the effects of sleep deprivation and potentially cold stress, and modafinil may prevent performance degradation due to the combination of these stressors. This study will help determine if modafinil alters body-heat production and prevents cognitive and physical performance degradation due to cold stress in rested and sleep-deprived volunteers.

Who can participate?
Active-duty U.S. Army Soldiers aged 18-39 years

What does the study involve?
Volunteers will be tested in two 2-day testing cycles consisting of one day under well-rested conditions (the “run-in” to sleep deprivation) and one day in sleep-deprived conditions (the period following the run-in) while exposed to cold temperatures. During one of the testing cycles, they will receive one 200-mg dose of modafinil during the well-rested period and two 200-mg doses of modafinil during the sleep-deprivation period. They also will be crossed over (in a counterbalanced fashion) so that identical testing occurs in another testing cycle with four one-placebo doses during the well-rested period and two-placebo doses during the sleep-deprivation period.

What are the possible benefits and risks of participating?
There are no direct health or other benefits related to participating in this study. Information gathered from this research may benefit other people in the future. There are several risks that associated with the protocol. There may be skin irritation during the cold exposure. Overexposure to cold may lead to freezing injuries of the skin and generalized hypothermia. In some cases, cold exposure can produce asthma-like symptoms. There may be fatigue from the multiple test sessions and long hours of wakefulness. Total sleep deprivation potentially increases the risk of cold weather injuries. Possible headache, nausea, nervousness, stuffy nose,

diarrhea, pack pain, anxiety, trouble sleeping, dizziness, and upset stomach are the most common side effects from the modafinil. Serious side effects such as chest pain, mental problems, and rash can also occur. Local muscle discomfort and fatigue during and shortly after physical exercise, with possible muscle soreness afterwards. Magnetic resonance imaging can cause overheating of the temperature pill. Body composition tests will use a small amount of radiation that can cause harm to the unborn fetus in pregnant females. Fingerstick blood samples may cause pain, dizziness, fainting, infection, bruising, tenderness, or edema at the puncture site, skin irritation, nausea, and vomiting.

Where is the study run from?
United States Army Research Institute of Environmental Medicine (USA)

When is the study starting and how long is it expected to run for?
October 2022 to August 2025

Who is funding the study?
Defense Health Program (USA)

Who is the main contact?
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Contact information

Type(s)
Public, Scientific, Principal Investigator

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Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
M-11048

Study information

Scientific Title
Modafinil to optimize the performance of cold-stressed sleep-deprived personnel

Study objectives
Primary Hypothesis 1: Modafinil compared to placebo (methylcellulose) will ameliorate fatigue; improve vigilance, memory, reaction time, executive function and mood; and reduce inappropriate angry/aggressive thoughts and risky thinking in well-rested and sleep-deprived, cold-stressed volunteers.

Secondary Hypothesis 2: Modafinil compared to placebo (methylcellulose) will increase (or maintain) body temperature, improve exercise tolerance, enhance lower-body muscular power, and reduce perceived ratings of physical exertion in well-rested and sleep-deprived, cold-stressed volunteers.

Ethics approval required
Ethics approval required

Ethics approval(s)
Approved 27/04/2024, Intramural Research Review (504 Scott St, Fort Detrick, 21702-9218, United States of America; +1 (0)217 417 6269; USArmy.Detrick.MEDCOM-USAMRMC.Other.IRB-Office@health.mil), ref: M-11048

Study design
Randomized double-blind placebo-controlled crossover trial

Primary study design
Interventional

Secondary study design
Randomised cross over trial

Study setting(s)
Laboratory

Study type(s)
Efficacy

Participant information sheet
Not available in web format, please use the contact details to request a participant information sheet

Health condition(s) or problem(s) studied
Prevention of cognitive and physical performance decline associated with multi-stressor conditions (i.e., sleep-deprivation, cold exposure)

Interventions
Administration of 200 mg of modafinil every 12 hours during a continuous 33-hour data collection period in an environmental chamber to simulate cold weather operations.

Sixteen volunteers will be tested in two 2-day testing cycles consisting of 1 day under well-rested conditions (the “run-in” to sleep deprivation) and 1 day in sleep-deprived conditions (the period following the run-in) while exposed to cold temperatures. During one of the testing cycles, they will receive one 200-mg dose of modafinil during the well-rested period and two 200-mg doses of modafinil during the sleep-deprivation period. They also will be crossed over (in a counterbalanced fashion) so that identical testing occurs in another testing cycle with four one-placebo doses during the well-rested period and two-placebo doses during the sleep-deprivation period.

The code for treatment administration to the volunteers and the doses will be prepared by a qualified third party not associated with the conduct of the research. The treatment order will be balanced so that an equal number of volunteers receive modafinil or placebo first. Two separate containers will be provided to a blinded staff member for each volunteer labeled A or B (for example). These drug and placebo containers will state for research use only and include the assigned protocol identification number, the volunteer number and the order of administration of the treatment (for example A or B treatment first). Since this is a crossover study each volunteer will receive both drug and placebo in a counterbalanced order. A sealed envelope containing the order of administration and dose schedule for each volunteer will be provided to local medical staff who will remain blinded but could act in the best interest of the subject’s safety in case of an emergency. During data collection, the Principal Investigator (or Acting Principal Investigator) will also have access to each volunteer’s code (in a sealed envelope) in the event of an emergency if the medical staff is not immediately available. A password-protected electronic file (and a sealed backup paper copy) of the code will be stored on a secure server until data collection is complete.

Intervention Type
Drug

Pharmaceutical study type(s)
Not Applicable

Phase
Not Applicable

Drug/device/biological/vaccine name(s)
Provigil (modafinil)

Primary outcome measure
1. Body composition will be measured using dual x-ray absorptiometry (DXA) as well as via stadiometer (height) and calibrated electronic scale (weight) at baseline.
2. Cognitive performance and mood will be measured using the following cognitive tests during baseline and every 4 hours during the in-laboratory 2-day testing cycles: Scanning Visual Vigilance, Psychomotor Vigilance Task, Match-to-Sample, Grammatical Reasoning, N-back, Balloon Analogue Risk Task, Profile of Mood States, Buss-Perry Aggression Scale
3. Physical performance will be measured using the following tests during baseline and every 4 hours during in-laboratory 2-day testing cycles: Critical Power, Vertical Jump, Finger Tapping Test
4. Core and skin temperature will be measured continuously throughout each cold exposure; core temperature will be measured using a telemetric thermometer capsule (e-Celsius® Performance Capsule, BodyCap, Saint-Clair, France, or similar); skin temperature will be measured using sensors (thermistor or thermocouple type) attached at the volunteer’s chest, triceps, hand, thigh, calf, and foot.

5. Physical activity and sleep duration will be recorded with a wrist actigraphy monitoring system (Actiwatch Spectrum Plus, Koninklijke Philips N.V., Amsterdam, NL or equivalent device). An actigraph will be placed on the volunteer's wrist during the baseline period and will be worn continuously through each testing cycle and through the final washout period.

Secondary outcome measures
There are no secondary outcome measures

Overall study start date
01/10/2022

Completion date
30/08/2025

Eligibility

Key inclusion criteria
1. Active-duty U.S. Army Soldiers 18-39 years old
2. Willing to refrain from the use of caffeine – including dietary supplements that contain caffeine – alcohol, and nicotine 24 hours prior to data collection
3. Willing to refrain from vigorous physical activity 24 hours prior to data collection
4. Willing to from any dietary supplement use within one week of initial screening and at any time while enrolled in the study (except a multi-vitamin containing up to 100% RDA
5. Willing to consume study diets throughout the course of the study
6. Supervisory approval for participation

Participant type(s)
Healthy volunteer

Age group
Adult

Lower age limit
18 Years

Upper age limit
39 Years

Sex
Both

Target number of participants
16

Key exclusion criteria
1. Use of modafinil or armodafinil in the last 3 months
2. Known allergy to modafinil or armodafinil
3. Current medical profile, or condition (i.e., musculoskeletal injury), that limits or compromises physical activity/exercise capability
4. Individuals taking medication known to interact with modafinil such as methylphenidate,

dextroamphetamine, clomipramine, MAO inhibitors, ethinyl estradiol, phenytoin, cyclosporine (or other drugs that depend on CYP1A2, CYP2B6, and CYP3A4 for their clearance), tricyclic antidepressants, selective serotonin reuptake inhibitors, inducers of CYP3A4 (e.g., carbamazepine, phenobarbital, rifampin) or inhibitors of CYP3A4 (e.g., ketoconazole, itraconazole),
5. Females who are pregnant or breastfeeding, have a positive- pregnancy test, or plan on becoming pregnant in the next 3 months
6. Individuals currently taking/using contraceptives (i.e., oral contraceptive pill, intrauterine device, contraceptive implant, contraceptive injection, etc.) other than condoms.
7. Current or history of mental health issues, illness, or condition (i.e., attention deficit hyperactivity disorder, autism spectrum disorder, diagnosed depression or anxiety disorders).
8. Current or history of psychosis
9. History of cold injuries or cold-induced asthma
10. Raynaud's syndrome
11. Previous hand/finger injuries that impair dexterity and hand function
12. Metal hardware (plates/screws) in the upper extremities (arms/hands)
13. Abnormal blood count (For example: hemoglobin (Hb) outside of the typical normal values reported by LabCorp in accordance with OMSO (Normal [Hb] Males = 12.6-17.7 g/dL; Females = 11.1-15.9 g/dL) or hematocrit (Hct) outside of the normal ranges (Normal Hct Males = 37.5-51.0%; Females = 34.0-46.6%) levels, presence of abnormal blood laboratory measures (e.g., hemoglobin S or sickle cell traits)
14. Current or history of alcohol abuse (defined as Harmful Use by the World Health Organization), those who meet criteria for alcohol abuse disorder (as outlined in the DSM-5), or other substance abuse (i.e., the use of illegal drugs or the use of prescription or over-the-counter drugs for purposes other than those for which they are meant to be used, or in excessive amounts)."
15. Diagnosed sleep disorders (i.e., sleep-apnea, narcolepsy, etc)
16. Diagnosed medical condition, such as diseases and disorders impacting metabolic, cardiovascular, neurological, gastrointestinal, or muscular systems
17. A medical diagnosis of high blood pressure (hypertension)
18. Heart problems or prior heart attack
19. Regular daily use of medication that may significantly interfere with the study drug or outcomes, as determined by physician/healthcare provider.
20. Known allergies to medical adhesives
21. Difficulty swallowing large pills (self-reported) for those individuals unwilling to utilize the rectal suppository of the telemetric pill.
22. History of obstructive disease of the gastrointestinal tract including (but not limited to) diverticulosis, diverticulitis and inflammatory bowel disease, peptic ulcer disease, Crohn's disease, ulcerative colitis, or previous gastrointestinal surgery, etc. that OMSO physician /healthcare provider believes puts the volunteers at increased risk.

Date of first enrolment
10/01/2024

Date of final enrolment
01/08/2025

Locations

Countries of recruitment
United States of America

Study participating centre
United States Army Research Institute of Environmental Medicine
10 General Greene Ave
Natick
United States of America
01760-2612

Sponsor information

Organisation
United States Army Medical Research and Development Command

Sponsor details
810 Schreider St
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Sponsor type
Research organisation

Website
http://mrmc.amedd.army.mil/

ROR
https://ror.org/03cd02q50

Funder(s)

Funder type
Government

Funder Name
Defense Health Agency

Alternative Name(s)
Department of Defense Health Agency, U.S. Defense Health Agency, US Defense Health Agency, DHA

Funding Body Type

Government organisation

Funding Body Subtype
National government

Location
United States of America

Results and Publications

Publication and dissemination plan
The findings from the investigation will be published in an open-access peer-reviewed journal.

Intention to publish date
01/07/2026

Individual participant data (IPD) sharing plan
The datasets generated and/or analysed during the current study will be published as a supplement to the results publication. Participants will be able to request their data, which will be securely delivered to them upon completion of the study.

IPD sharing plan summary
Available on request, Published as a supplement to the results publication