Pol J Aviat Med Bioeng Psychol 2022; 28(2): 5-18
DOI: 10.13174/pjambp.23.05.2025.01

ORIGINAL ARTICLE

FLIGHT PERFORMANCE FOLLOWING ADMINISTRATION OF AN ANTI-FATIGUE STIMULANT DURING 27 HOURS OF CONTINUOUS WAKEFULNESS

Rafał LEWKOWICZ[1], Anna PRZEWODZKA[1], Joanna ŁASZCZYŃSKA[1]
1 Military Institute of Aviation Medicine, Warsaw, Poland

Source of support: This work was supported by the National Centre for Research and Development (Poland) under Grant [No. OR00004208], titled: "Improving the psychophysical fitness of a soldier during combat tasks by means of pharmacological stimulation"

Author's address: R. Lewkowicz; Military Institute of Aviation Medicine, Krasinskiego 54/56 Street, 01-755 Warsaw, Poland, email: rlewkowicz@wiml.waw.pl

Introduction: In the context of military aviation, aircrew members are required to perform a range of complex and cognitively demanding tasks under a variety of conditions, including irregular work schedules, insufficient rest periods, and disrupted circadian rhythms. This study investigates the impact of sleep deprivation on flight performance in a controlled simulator environment and examines whether the pharmacological agents modafinil and galantamine can restore flight performance to baseline levels following 27 hours of wakefulness.

Method: A group of 12 male volunteers, with a mean age of 24 ± 2.5 years, was tested in three separate sessions during which the participants were randomly assigned to receive either 100 mg of modafinil, 10 mg of galantamine, or a placebo. During the continuous wakefulness period, the participants completed three tests in a flight simulator involving a simple flight control task performed under varied conditions (flight over land and sea).

Results: Galantamine showed significant differences across flight conditions, with improved performance in maintaining altitude under the land and sea conditions ($p<0.001$). Under the same flight conditions, galantamine had a significant effect on speed, resulting in slower speeds compared to placebo. Additionally, it demonstrated a significant improvement in maintaining a stable heading under sea conditions. Across all parameters, the stimulants did not restore flight accuracy to baseline levels under control conditions.

Conclusions: The effects of both modafinil and galantamine on sleep deprivation-induced fatigue and flight performance were minimal, with results comparable to those of the placebo in most scenarios. Neither agent was able to restore baseline performance after a single dose administered following 27 hours of wakefulness. However, due to several limitations of the study, further research is warranted, with a focus on physiological assessments to strengthen the evidence base for anti-fatigue guidelines.

Keywords: flight performance, stimulant, sleep deprivation, fatigue, military aviation

Cite this article: **Lewkowicz R, Przewodzka A, Łaszczyńska J. Flight Performance Following Administration Of An Anti-Fatigue Stimulant During 27 Hours Of Continuous Wakefulness. Pol J Aviat Med Bioeng Psychol 2022; 28(2): 5-18. DOI: 10.13174/pjambp. 23.05.2025.01**

INTRODUCTION

Fatigue is a significant and persistent challenge in the field of aviation, particularly for pilots operating under demanding schedules and in high-stakes environments. It is defined as a state of mental and physical exhaustion that diminishes an individual's ability to perform effectively. Fatigue has been shown to impair cognitive and psychomotor functions essential for safe piloting, including attention [17,25], reaction time [40,41], situational awareness [19,43], and decision-making [9,39]. The effects of fatigue are particularly pronounced during long-haul and nocturnal flights, where the lack of natural light and extended hours spent in the cockpit exacerbate the cognitive decline associated with prolonged wakefulness. Research has also demonstrated that sleep deprivation and circadian rhythm disruptions are primary contributors to pilot fatigue, with measurable declines in operational performance occurring after 19 hours of sustained wakefulness [14,37,50]. Sleep deprivation-induced deficiencies are typically most severe in the early morning hours (approximately 6:00 to 8:00 AM) [1].

As fatigue continues to pose risks in aviation, pharmacological interventions — specifically psychostimulants — have been explored and implemented to counteract its effects [51]. Psychostimulants such as modafinil, a wakefulness-promoting agent, have shown promise in alleviating fatigue symptoms and enhancing alertness during long-haul or nocturnal flights [48,49,52]. Unlike traditional stimulants like amphetamines, modafinil presents a lower risk of dependency and fewer side effects, making it a viable option for mission-critical operations where sustained performance is necessary [11]. Studies have documented that modafinil can help maintain cognitive performance and reduce subjective sense of sleepiness in pilots engaged in extended flight missions, potentially mitigating the hazards associated with fatigue-induced errors [6,21,26,45].

The mechanism by which modafinil promotes alertness involves the inhibition of the dopamine reuptake transporter, resulting in increased dopamine levels in the synaptic cleft. Modafinil also affects the histamine systems, thereby regulating sleep–wake rhythms. Additionally, the psychostimulant inhibits the release of another neurotransmitter — gamma-aminobutyric acid, lowering its extracellular concentration, enhancing the action of glutamic acid, which increases neuronal activity in the cortex and cerebellum [53]. In contrast, other stimulants like caffeine, exert its stimulatory effect primarily by binding to adenosine receptors, thereby blocking the action of adenosine, which is responsible for central nervous system inhibition [44]. However, under conditions of prolonged sleep deprivation (54 hours of wakefulness), the effect of modafinil at doses of 200–400 mg was comparable to that of 600 mg of caffeine [48]. Psychomotor task speed improved. reaction time in ten-choice tests was shortened, and the ability to maintain wakefulness in a sleep-conducive environment increased. Although no statistically significant differences were found, 400 mg of modafinil was found to be slightly more effective than caffeine [48].

Modafinil has been approved as a fatigue countermeasure by the air forces of the United States, India, France, and Singapore [10,30], while certain other the air forces of countries, including the Royal Netherlands Air Force, are considering permitting its use [29,50], although its adverse effects in aviation studies remain not fully understood. Research indicates that modafinil enhances psychomotor performance [5,16], cognitive functions [24,47], reaction time, executive control [22], and mood [8], and has no negative impact on G-force tolerance [34]. Modafinil has also been shown to have beneficial effects on flight performance [5,8,24]. When administered at a dose of 200 mg every 4 hours, modafinil enabled flight performance in a simulator to be maintained close to baseline levels, i.e., a normal state, without sleep deprivation, despite 40 hours of continuous wakefulness [5]. However, at this high dose, side effects such as nausea and vertigo were reported. In another study [11], pilots who received three 100-mg doses of modafinil, administered every 5 hour,) were able to maintain flight performance within 27% of baseline during 37 hours of wakefulness, compared to an 82% decline without the stimulant treatment. In this study, no adverse effects of taking modafinil were observed, likely due to its lower dose.

Despite their benefits, and due to the lack of conclusive confirmation of stimulant effectiveness in real-world operational aviation scenarios [5,7,8,10], ethical and operational considerations regarding the routine use of stimulants in aviation remain. These also include the potential long-term impact on pilot health and safety. Although modafinil shows promise in reducing fatigue, its effectiveness in operational military aviation remains insufficiently studied [50,52]. Therefore, this study aims to extend the scope of knowledge regarding the impact of this stimulant on pilot performance.

While the effects of sleep deprivation on cognitive and motor performance are well-documented [2,22,32,46,48], the use of specific stimulants to mitigate fatigue-induced decrements in flight simulation performance is underexplored, particularly in settings with varying environmental conditions. By synthesizing recent findings, this article aims to provide a comprehensive understanding of the efficacy and impact of pharmacological countermeasures in enhancing pilot flight performance under fatigued conditions. The effect of a single dose of modafinil (100 mg) on flight performance in a simulator during a limited period of sleep deprivation, i.e., (>24 h, was examined, a condition that has not been widely studied [11,33]). The 100 mg dose of modafinil was administered after a 22 hours of sleep deprivation, following with the methodology employed by Caldwell et al. [11], but omitting the two additional doses administered after 17 and 27 hours. The rationale for this intervention was to determine whether the administration of modafinil after 22 hours would be equally effective when the dose after 17 hours was omitted.

The effect of modafinil was also compared with that induced by a single dose of galantamine (10 mg) and placebo (control trial). Galantamine was included in the study as preliminary data suggests its potential benefits in sustaining performance during sleep deprivation, such as improvements in memory and attention [28]. Galantamine acts as a reversible acetylcholinesterase inhibitor, enhancing cholinergic neurotransmission [3,12]. Evidence indicates its role in modulating cholinergic neurotransmission, which is critical for attention and memory processes. These mechanisms facilitate the suppression of distractors [18], the shifting of attention [13], and disengagement between spatial locations or features [4]. By enhancing cholinergic neurotransmission, galantamine strengthens the neuronal circuits underlying these functions, contributing to improved cognitive flexibility and attentional control. Galantamine has demonstrated cognitive-enhancing properties in clinical populations and possesses a relatively long half-life, potentially providing sustained effects [27]. However, side effects of this drug include nausea and vomiting, significant fluctuations in blood levels, and poor patient compliance [55]. It was expected that, compared with placebo, both galantamine and modafinil would counteract the effects of fatigue on flight performance. However, due to limited understanding of galantamine's effects on complex task performance under sleep deprivation, there was no reason to expect it to be more effective than modafinil.

This research was part of a project exploring pharmacological stimulation aimed at improving soldier performance in combat scenarios [23,35]. The project also addressed the critical need for evidence-based pharmacological interventions to manage fatigue in aviation. It focused on the limited understanding of the impact of modafinil and galantamine on complex task performance under the conditions of sleep deprivation, presenting an opportunity to explore innovative approaches for sustaining an aircrew performance.

METHODS

Participants

The study involved 12 healthy male participants aged 20–25 years (M=24; SD=2.5), with heights ranging from 172 to 186 cm (M=179; SD=7), body weight from 71 to 88 kg (M=80; SD=8.43), BMI between 23.5 and 26.5 kg/m2 (M=25; SD=1.5) and VO2max between 41 and 53 (M=47; SD=5.8). All participants had current medical clearance from the Regional Military Aviation Medical Commission. The participants, who were students of the Academy of Physical Education in Warsaw, were qualified for the study based on medical assessments. These evaluations were part of a broader testing protocol related to research on pharmacological stimulation aimed to enhancing soldiers' performance in combat scenarios [23,35]. The medical examinations included, i.a., internal medicine, ophthalmology, laryngology, neurology, electrocardiography, electroencephalography, tonal audiometry, cardiopulmonary exercise testing, maximal aerobic capacity (VO2max), and blood and urine analyses. Additionally, participants were screened (self-assessment) for any pre-existing sleep disorders and did not report any abnormal sleep patterns. The purpose of these examinations was to confirm the participants' good health status and to rule out any contraindications to their participation in the study.

Exclusion criteria focused on potential side effects or interactions of the medications under study — modafinil and galantamine. Individuals with conditions such as bronchial asthma, epilepsy, severe liver, kidney, or heart failure, and bradycardia were excluded. Prior to participation, subjects were instructed to avoid alcohol and excessive use of stimulants (e.g., coffee, cigarettes) the day before testing. They were also prohibited from engaging in intensive physical activity, i.e., gym workouts, running, swimming, team sports,

to avoid increasing oxidative stress levels in the body. The participants were also asked to report any health issues (e.g., mood changes, anxiety, irritability) or discomfort, both before and during the experiment, directly to the attending physician.

The research was conducted at the Military Institute of Aviation Medicine (WIML) in Warsaw, Poland, and adhered to the principles of the Declaration of Helsinki. Ethical approval was granted by the WIML Ethics Committee in accordance with requirements for research involving human subjects. The participants were informed of the known side effects of each study agent, and each signed an informed consent form.

Study design

This randomized, double-blind, crossover, active- and placebo-controlled clinical trial was conducted at consistent, repeated intervals. The study employed a within-subjects 3 × 4 design: treatment (modafinil, galantamine, placebo) × test time (T = 08:00 PM, T = 08:00 AM, T = 11:30 AM, T = 02:00 PM). Each participant completed three non-consecutive trial sessions, during which modafinil, galantamine, and placebo were administered once at 10:30 AM (Fig. 1). The interval between the sessions was seven days.

Participants remained awake for 13 hours prior to each trial, having completed a full day of regular activities followed by a sleepless night. On test days, the median wake-up time was 07:00 AM, resulting in a median period of wakefulness of 27 hours at the time of medication administration (range: 25.5–29.0 hours).

Each participant was subjected to three experimental conditions, which differed only in the type of drug administered: (1) Vigil® (100 mg modafinil), (2) Nivalin® (10 mg galantamine), and (3) a placebo (Fig. 1). The experiment began at 07:00 PM and finished at 04:00 PM the following day. During the tests (Fig. 1, Tests A-D), the participants performed a light stimulus detection task ('flicker' test), flying a flight simulator, and psychomotor and attention tests. Additionally, between 12:30 PM and 2:00 PM, participants were exposed to heat in a climate chamber at stable parameters: temperature Ta=30 ± 0,5 deg C and 35 ± 1% humidity (Fig. 1). The exposure profile included three 20-minute sessions of exercise on a Monark cycloergometer (at 30% VO2max), with 5-minute rest intervals. With the exception of the flight simulator test, results from the remaining tests were not included in the present analysis. The analysis focused exclusively on the effects of pharmacological stimulation on flight performance.

The sequence of pharmacological agents (modafinil, galantamine) and the control trial (placebo) was randomized. Measurements for Tests C and D were consistently conducted at 11:00 AM and 2:00 PM, following administration of either a stimulant or placebo (Fig. 1). Heart rate, blood pressure, core body temperature, and hydration status were measured every 3 hours during the night starting at 07:00 PM and every 2 hours the following day. Body mass, blood pressure, and energy expenditure (measured using Polar Watch RS 800 heart rate monitor) were assessed at 8:00 PM, 8:00 AM, 11:30 AM, and 2:00 PM. Meals were provided in the evening at 10:00 PM and the morning at 9:30 AM.

In each of the three experimental conditions, participants were tasked with performing a flight simulation using the Hyperion simulator (Fig. 2) at 08:00 PM, 08:00 AM, and 02:00 PM, following

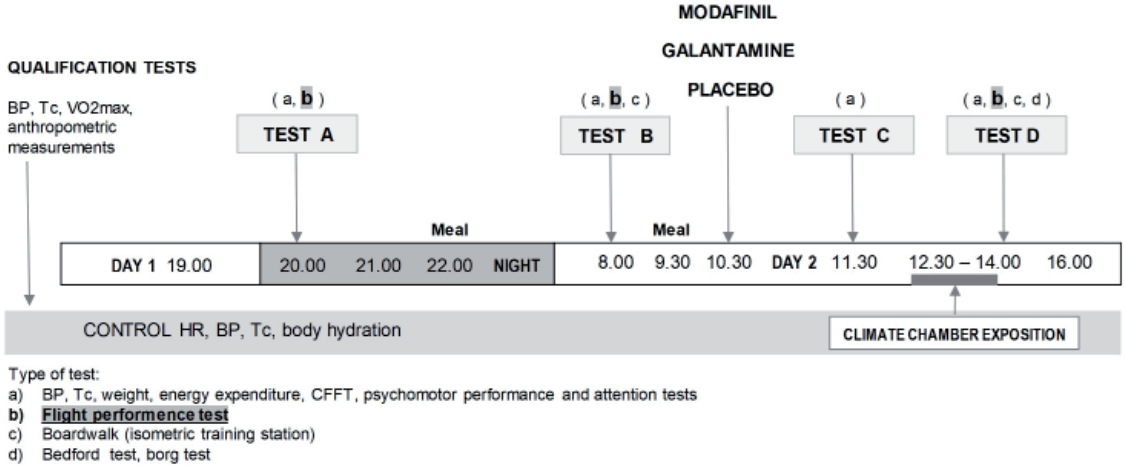

Fig. 1. Scheme of the study design (the study session). HR: heart rate, BP: blood pressure, Tc: core temperature, CFFT: Critical Flicker Fusion Threshold test, V02max: maximal aerobic capacity.

a defined flight scenario. An instructor supervised each entire simulation session, briefing the participants on procedures and safety guidelines prior to the experiment.

Psychostimulants and dosage

Two psychoactive substances, modafinil and galantamine, approved for use in the European Union, were selected for the study. The pharmacological agents containing these substances were Vigil® (100 mg modafinil) by Torres Chiesi Polska Sp. z o.o. and Nivalin® (10 mg galantamine) by Janssen-Cilag Polska Sp. z o.o., each administered in a single dose. The 100 mg dose of modafinil is recognized as an effective measure of counteracting fatigue in military aviation [5,10], with optimal effects observed at doses of 100-200 mg administered every 4–5 hours [8,16]. Its beneficial impact begins within 30–60 minutes, peaks at 2–4 hours, and has a half-life of 12–15 hours [38,50,52].

For galantamine, a 10 mg dose is considered moderate yet effective, reaching maximum efficacy within 0.5–2 hours and having an elimination half-life of 5.5 hours [42]. Psychostimulant pills were visually and physically similar to placebo pills, which contained powdered lactose as the control. Pills were swallowed whole with water, and administration timing was standardized according to the study protocol (Fig. 1). The order of stimulant and placebo administration was randomized for each participant. The properties of modafinil and galantamine are detailed in a previously published paper [35].

Equipment

A fixed-base flight simulator at the Military Institute of Aviation Medicine (WIML), Warsaw, Poland, was used to evaluate the impact of stimulants on flight performance (Fig. 2A). The simulator was equipped with a collimated visual system providing a wide-angle (horizontal ~180° and vertical ~30°), high-fidelity out-the-window (OTW) view of the simulated environment. A mirror-based collimated display was employed in the visual system, with a schematic diagram of its operational principles presented in Fig. 2B.

A monitor is located above and forward of the observer's position and is pointed down (Fig. 2B). The image is reflected away from the observer by a partially reflective beam splitter (silvered glass that reflects about half the light, and allows the remaining to pass through). The image is then reflected back toward the pilot by a large concave spherical-section collimating mirror, which enlarges the image and makes it appear as though it is generated at a great distance from the observer.

The flight simulator featured basic flight controls (stick, rudder pedals, thrust lever) and

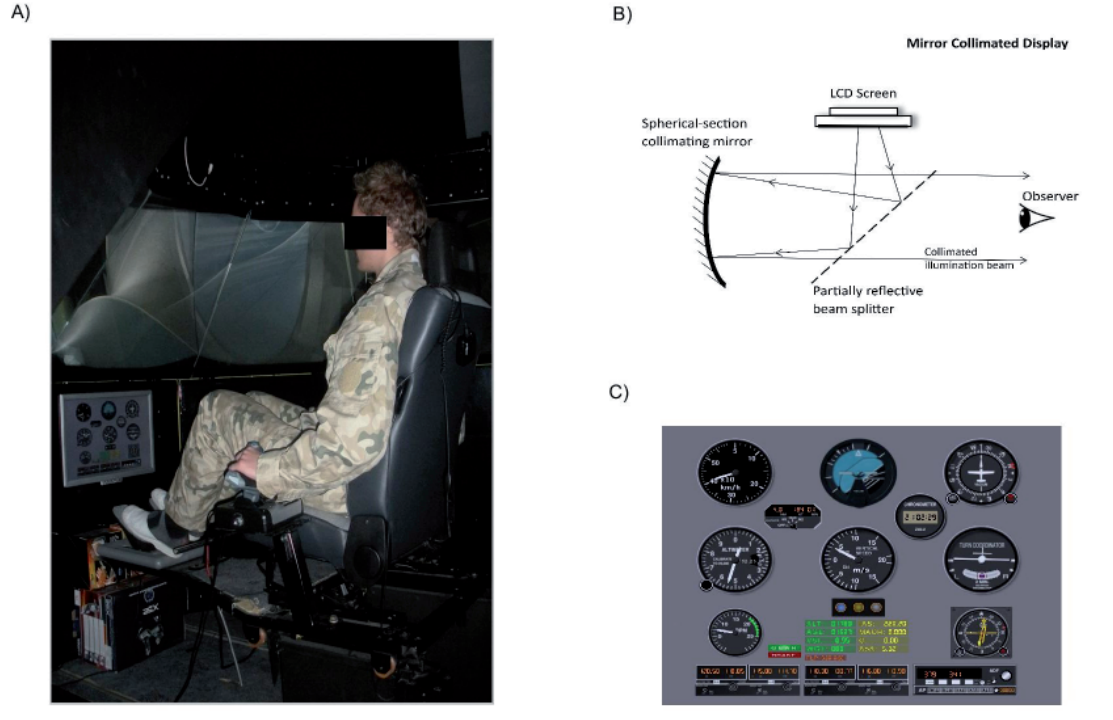

Fig. 2. A participant in a fixed-base flight simulator (A) equipped with a mirror-based collimated visual system (B), and display with primary flight instruments (C).

a primary instrument panel displaying altitude, airspeed, vertical speed, and heading. The simulation, including OTW imagery, was developed using FlightGear (Version 0.9.8, https://www.flightgear.org). The software was also used to record flight parameters for subsequent analysis. Finally, a one-way visual and two-way audio system enabled participant-operator communication and allowed researchers to monitor the participant.

Flight scenario

The flight route took place over varied terrain that included land and water (Fig. 3). The over-water flight session was conducted without any additional visual cues in the OTW display that could be employed to ascertain the flight altitude. The flight took place during daytime hours in windless conditions. The participant was instructed to maintaining horizontal flight at a speed of 400 km/h, altitude of 200 m MSL, and a heading of 280 for the entirety of the flight, which lasted approximately 480 seconds. The flight began and ended at the same altitude, speed and heading that the participants were required to maintain during the test.

During the test, the simulator software continuously recorded several flight parameters, three of which were selected to evaluate flight performance: speed, heading and flight altitude. As part of their post-processing, their average values were calculated for the entire flight as well as separately for the two flight conditions: over land and over water.

Procedure

Prior to the study, the participants were briefed on the methods and safety procedures. The known side effects of the stimulants were also explained to them. All participants completed the same tests in three sessions (Fig. 1), each time with a different randomly selected stimulant. A one-week interval separated each session.

To eliminate the influence of circadian rhythms on psychophysiological functions, all three sessions (modafinil, galantamine, placebo) were always initiated at the same time in the evening, according to the study schedule (Fig. 1). Prior to the first test (Test A) in the first of the three test sessions, the participants were instructed on how to operate the aircraft (flight simulator) and subsequently undertook an approximately 10-minute familiarization flight. This preliminary training was intended to minimize the effect of pilot performance improvement with the number of flights (so-called 'learning effect'), which could distort the analyzed results. The debriefing was conducted by an aviation specialist (flight instructor), who was also responsible for supervising the flight simulator tests.

From the flight data recorded, three parameters were selected for flight performance analysis: altitude, speed and heading. The flight route was divided into three sections of similar duration, differing in terrain conditions. These sections were designated as follows: land and sea, in which the flight took place in varying conditions over both land and water; land, in which the flight took place exclusively over land; and sea, in which the flight was performed exclusively over water. The analysis of the results was performed on the extracted relevant segments of the recorded flight, segments such as takeoff and flight over elevated terrain were eliminated.

Statistical analysis

To assess the effect of the stimulant, the results collected in Test D, following the administration of the anti-fatigue agent, were compared (Fig. 1). Additionally, data from Test A were compared with the data from Test D to assess whether flight accuracy could be restored to baseline levels after stimulant administration.

The Friedman test, a non-parametric repeated measures test, was employed to evaluate the impact of stimulant type (modafinil, galantamine, and placebo) in three distinct flight conditions

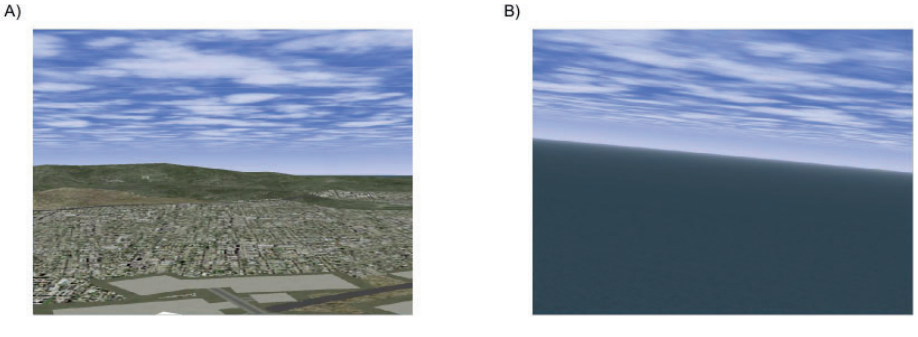

Fig. 3. Flight scenery (out of the window) with land (A) and sea (B) conditions viewed from the pilot perspective.

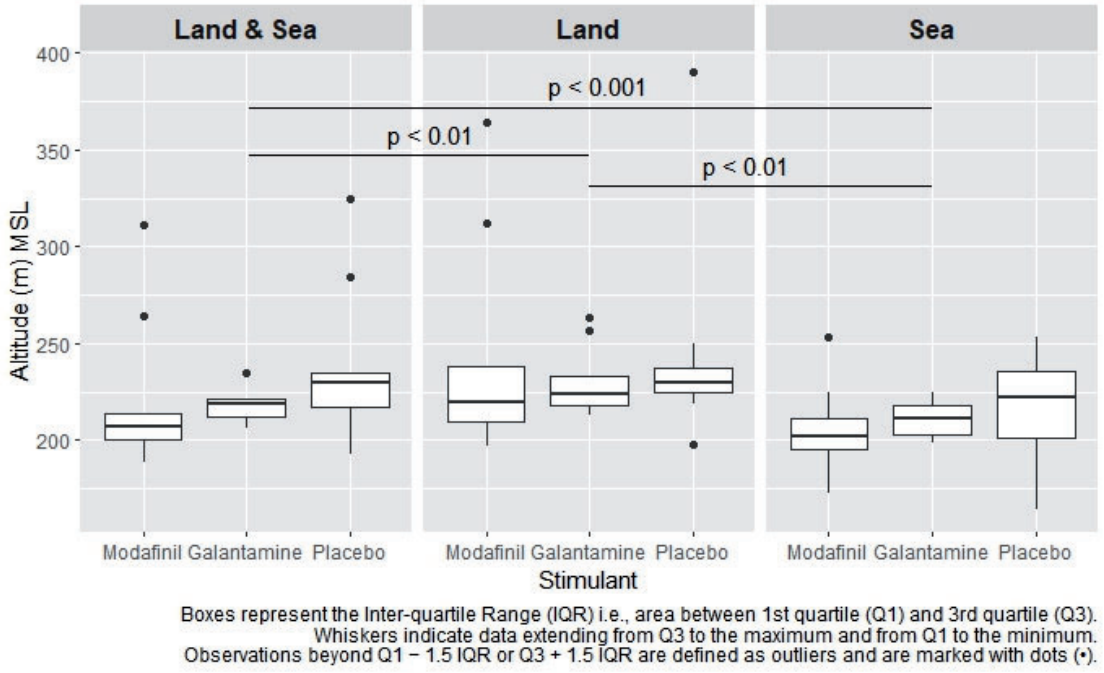

Fig. 4. Median flight altitude in two flight conditions (land, sea) following a dose of stimulant (modafinil, galantamine, or placebo).

(land and sea, land, and sea) on flight performance, as measured by three dependent variables (altitude, speed, and heading). This test was selected due to the presence of deviations from normality in all analyzed dependent variables. When necessary, Wilcoxon signed-rank tests with Bonferroni corrections were applied to identify specific pairwise differences between stimulants and conditions. Effect sizes were calculated using Kendall's W to provide insight into the magnitude of differences. Statistical significance was assumed to be $p<0.05$. All analyses were performed using R statistical software version 4.4.2 [36].

RESULTS

A total of 36 measurements were recorded during the study, with three tests (Test A, B, D) conducted for each participant in each session. Each subject completed a full flight profile. Very few and minor side effects following the administration of modafinil or galantamine administration were observed. Additionally, none of the participants reported any concerning side effects during the week following the conclusion of the study. The results of the comparative analysis of the data collected following the administration of the antifatigue agent (Test D) are presented below.

Altitude. The Friedman test revealed no significant differences in flight altitude across stimulants under each of the flight conditions (Fig. 4). Significant differences in altitude were observed across flight conditions. For galantamine, the difference was substantial and reached $\chi2(2)=10.9$ $p=0.004$, while for modafinil, it was marginal ($\chi2(2)=5.88$, $p=0.053$). For galantamine, post-hoc pairwise Wilcoxon signed ranked tests with Bonferroni correction indicated that flight conditions significantly affected performance in maintaining altitude (Fig. 4). The stimulant's effect size (Kendall's W) across conditions were large for galantamine ($W=0.605$) and moderate for modafinil ($W=0.327$).

Speed. The data analysis detected significant stimulant effects on flight speed under land and sea condition ($\chi2(2)=8.63$, $p=0.013$) with moderate effect sizes (Kendall's $W=0.479$). Post-hoc Wilcoxon pairwise comparisons identified a significant difference between galantamine and placebo ($p<0.001$) (Fig. 5). The analysis conducted to evaluate differences in speed across flight conditions revealed no significant differences for any individual stimulant.

Heading. No statistically significant differences in heading deviation were observed across stimulants in any condition (Fig. 6). Significant differences were detected across conditions for galantamine ($\chi2(2)= 11.5$, $p = 0.003$). Post-hoc com-

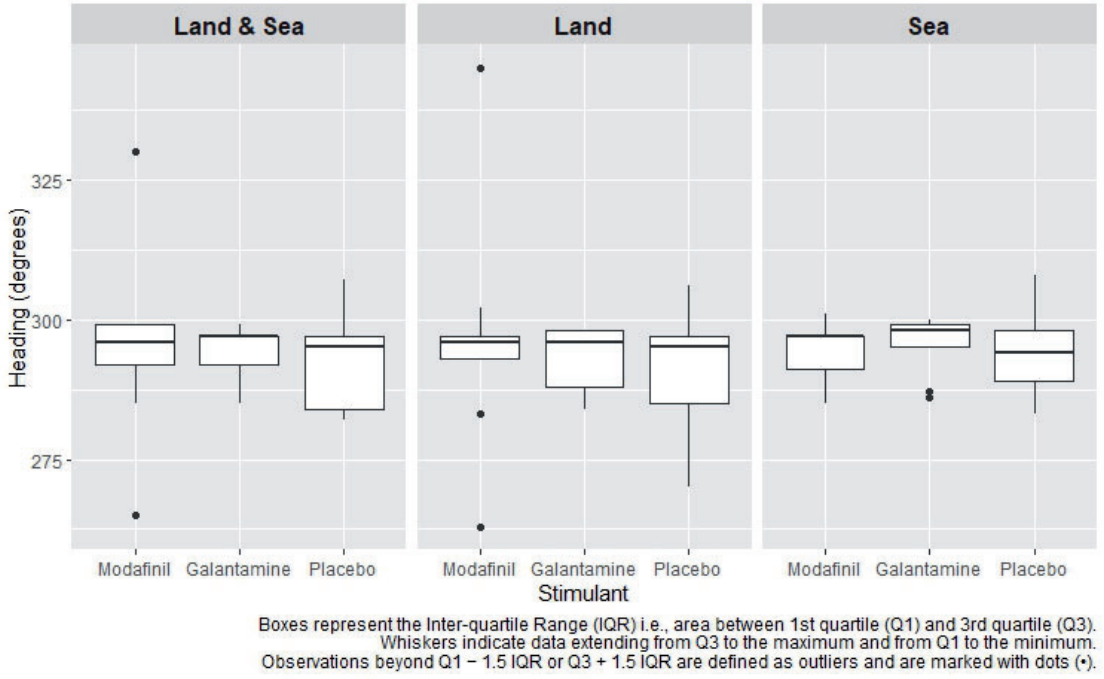

Fig. 5. Median flight speed in different flight conditions following a dose of stimulant (modafinil, galantamine, or placebo).

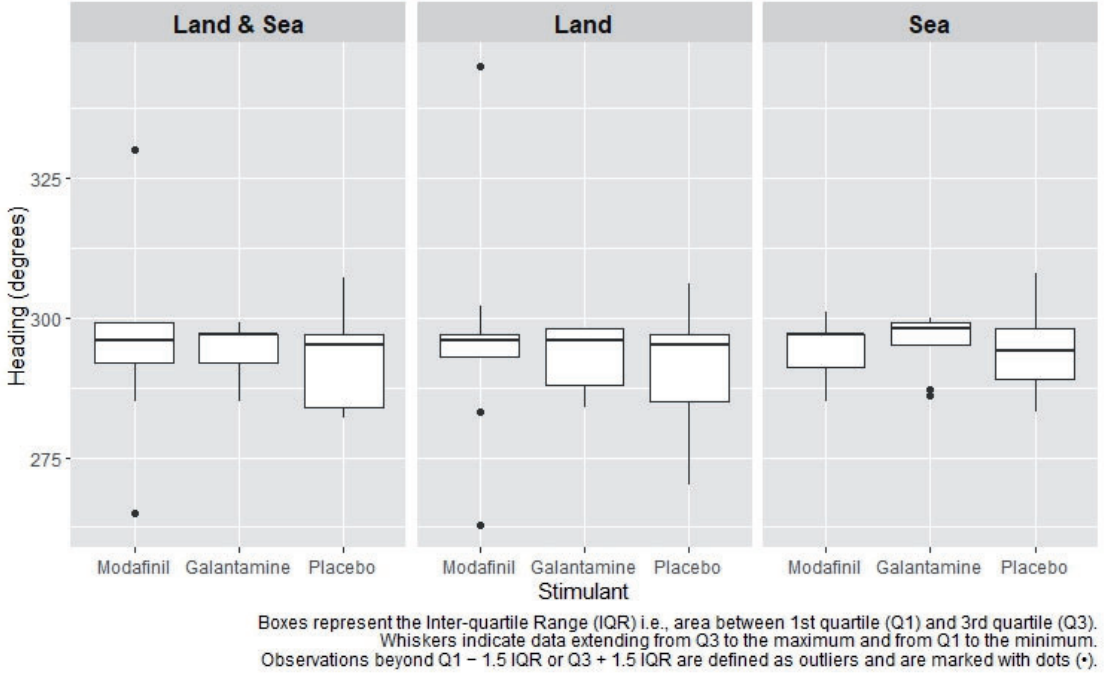

Fig. 6. Median flight heading in three flight conditions following a dose of stimulant (modafinil, galantamine, or placebo).

parisons, however, did not identify any significant differences between conditions.

The results of comparing the flight data (altitude, speed and heading) measured in Test A (control condition with no stimulants administered) with the data from Test D (following stimulant administration; Fig. 1) are shown in Fig. 7. The Friedman test revealed no significant differences in all analyzed flight parameters for either stimulant across all flight conditions.

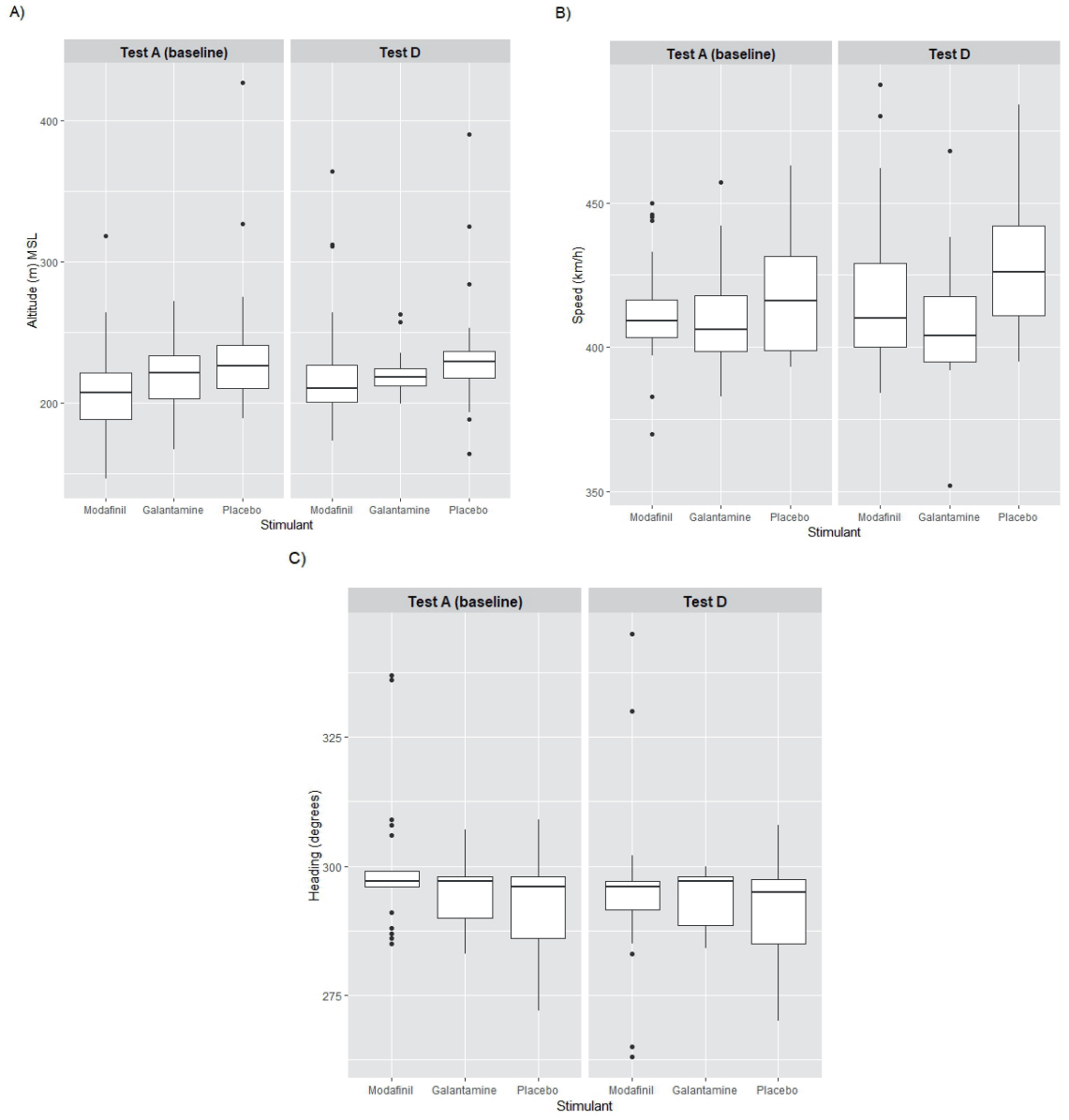

Fig. 7. Median flight altitude (A), speed (B), and heading (C) in the Test A (baseline) and Test D (following stimulant administration: modafinil, galantamine, or placebo). Box represents the Inter-quartile Range (IQR), i.e., area between 1st quartile (Q1) and 3rd quartile (Q3). Whiskers indicate data extending from Q3 to the maximum and from Q1 to the minimum. Observations beyond Q1 – 1.5 IQR or Q3 + 1.5 IQR are defined as outliers and are marked with dots (•).

DISCUSSION

The study revealed no significant differences in altitude performance between the stimulants within any single condition. However, differences emerged when comparing performance across flight conditions, particularly following galantamine administration(Fig. 4), which exhibited significant condition-specific differences. It can be observed that sea flight conditions consistently yielded a lower flight altitude, likely due to the absence of additional visual cues (references to terrain features), that could have assisted in maintaining flight altitude. In contrast, the effects of modafinil were marginal, with only a trend toward significance. A previous study [27] indicated that galantamine enhances cholinergic activity, which is associated with improved attention and task performance. Although the dopaminergic mechanism of modafinil may provide broader cognitive benefits [2,11,16,21,51,52], it may lack the same task-specific enhancements seen with cholinergic modulation provided by galantamine. These results suggest that galantamine may offer targeted benefits for tasks requiring sustained precision, particularly in challenging environments, such as piloting an aircraft. However, it is important to

note that, in addition to the desired effects, cholinergic stimulation can disrupt normal stimulus- and task-dependent activity patterns in the healthy brain [3], including those induced by galantamine.

The analysis highlighted also a significant effect of galantamine vs. placebo on speed in the land and sea conditions (Fig. 5), with moderate effect sizes. Galantamine was associated with slower speeds compared to placebo. This effect is consistent with findings from similar studies, in which cholinergic agents enhanced cautiousness and attention [3,28]. In contrast, no significant effect on speed was observed for modafinil, which likely reflects its general arousal-promoting effects rather than task-specific modulation.

With regard to the restoration of pre-sleep deprivation performance, the findings indicate that neither modafinil nor galantamine fully restored flight performance to baseline levels (Fig. 7). This is consistent with previous studies suggesting that while stimulants mitigate performance declines, they may not fully counteract the substantial cognitive and motor impairments associated with extended wakefulness [46,48]. Nonetheless, a study conducted in an aviation context [5] demonstrated that modafinil (administered in three 200 mg doses) was capable of sustaining simulator flight performance at near-rested levels despite over 30 hours of sleep deprivation. Similarly, the administration of modafinil in three doses of 100 mg resulted in the effective attenuation of fatigue-related decrements in simulator flight performance over a comparable time period [8]. The primary difference between these studies and ours is the dose size, which was several times higher. This likely explains why a similarly strong effect of modafinil on flight performance was not observed in the present study. Therefore, the inability of either agent (modafinil or galantamine) to fully restore baseline performance highlights the limitations of pharmacological interventions alone and underscores the importance of adequate sleep management in operational settings. The absence of a notable impact of stimulants in comparison to the baseline (control) measurement may have been influenced by a learning effect, as measurements repeated three times in one research session. It is also worth noting that the control measurement (Test A) was conducted at nighttime, at 08:00 PM (Fig. 1), at a time when the participants may have already exhibited some degree of fatigue. To assess the impact of this fatigue on flight performance and the threshold of information-processing speed, the Stanford Sleepiness Scale [20] would have been a valuable tool [31,49], however, it was not employed in the present study.

The slight stimulant-driven differences in flight performance in this study may also have been attributable to other factors. It is possible that the primary contributing factor was the dosage of the stimulant administered. Research [54] has highlighted the dose-dependent effects of galantamine on improving sustained attention and short-term memory. In the present study, a single dose of 10 mg galantamine and 100 mg modafinil were administered. In another study [8], the maintenance of flight accuracy within a range of 15%–30% of baseline levels was observed in pilots who were administered three doses of 100 mg modafinil at 17, 22 and 27 hours of continuous wakefulness (sleep deprivation). The authors of that study speculate that three doses of 200 mg could restore flight accuracy to baseline levels.

Another factor may be related to the level of difficulty of the task performed by the participants in the flight simulator. This task involved maintaining a constant altitude, speed and heading, an activity that requires fewer cognitive resources than, for example, the approach to landing or landing itself. The present study was conducted in controlled laboratory conditions using relatively simple flight control tasks. In real military operations, shift work, high-stress environments, and the complex, time-pressured nature of cockpit tasks impose greater demands on a pilot's mental and physical endurance [15]. Therefore, it is essential to replicate this study in a high-fidelity flight simulator or an actual flight settings to determine whether the benefits of the stimulants observed in the study translate to real-world operational conditions [50].

A further factor that may have influenced the results of the study is the individual differences in susceptibility to fatigue and response to the stimulant administered, which could lead to variations in the observed increase in performance. It has been found that the efficacy of modafinil depends on baseline fatigue vulnerability [6]. Individuals who demonstrated high performance showed minimal benefit from modafinil compared to placebo, whereas those with lower performance demonstrated significant cognitive performance improvements, particularly in vigilance and sustained attention tasks. These findings suggest that modafinil may be more beneficial for individuals with greater susceptibility to fatigue-related performance decrements. Unfortunately, it is not known whether there were participants in the present study, who exhibited a differential propensity to reduce performance due to fatigue. Therefore, the lack of expected significance of the effect of the stimulants used may also be attributable to this factor. Further studies should account for individual

differences in susceptibility to fatigue-related performance declines.

Finally, it is possible that the relatively small effect of stimulants compared to placebo may have been due to the additional thermal and physical stress to which the participants were subjected before the flight simulator test. Before Test D, each participant was subjected to thermal exposure in a climate chamber with a temperature of 30°C and 35% humidity (Fig. 1). The exposure profile included three 20-minute sessions of exercise on a cycloergometer (at 30% VO2max) with 5 minutes of rest between sessions. Differences in mean heart rate and change in energy expenditure following exposure were similar between groups (modafinil, galantamine, placebo) and were not statistically significant. Therefore, the impact of this exposure may have caused excessive psychophysical stress on the body and affected the results of the simulator test.

The use of the selected drugs in a group of individuals performing tasks in an environment with specific labor conditions (i.e., piloting an aircraft in a fatigued state) goes beyond the registered indications, i.e., the treatment of excessive sleepiness in patients with narcolepsy or cognitive impairment in neurodegenerative diseases. Nevertheless, the present study extends the current state of knowledge about the effects of drugs on the human body.

Study limitation

The study has several limitations. While the findings highlight the potential role of stimulants in managing alertness and fatigue in military aviation, the relatively small sample size limits the generalizability of these results. Further research with larger sample sizes may help clarify marginal trends and explore interactions between analyzed variables. Additionally, the exclusive focus on flight simulation tasks limits the generalizability of findings to other operational settings.

In the present study, participants were instructed to abstain from caffeine consumption during the test sessions. While this approach was intended to minimize the potential influence of caffeine on the study results, it does not reflect typical military practice, as the majority of aircrew members consume caffeine on a regular basis, as it was rightly pointed out by the authors of a previous study [50]. Consequently, the combined effect of modafinil or galantamine with caffeine on flight performance may differ from the outcomes observed in the study.

Furthermore, the lack of significant baseline-versus post-treatment restoration raises questions about the stimulants' efficacy over prolonged wakefulness. Future research could expand on these findings by examining other cognitive and motor tasks under similar conditions, and exploring dose-dependent effects and combinations of pharmacological and behavioral interventions.

CONCLUSIONS

The present study investigated the impact of fatigue on pilot flight performance, with a particular focus on the potential role of psychostimulants in mitigating these effects during long-haul and nocturnal missions. This is of particular relevance in countering the risks associated with fatigue in aviation.

The study demonstrated minimal stimulant-driven effects in mitigating sleep deprivation-induced fatigue on flight performance. Modafinil, galantamine, and placebo yielded comparable results in most scenarios, suggesting limited efficacy in enhancing performance under the tested conditions. Neither agent was able to restore baseline performance. It is also noteworthy that none of the drugs tested, when administered in a single dose after 27 hours of wakefulness, had a negative effect on flight performance.

Despite the limitations of the study and factors that may have negatively affected the results, i.e., stimulant dose, task-induced level of cognitive load, or individual differences in susceptibility to fatigue-related performance decrements, the findings indicate that the use of galantamine may prove advantageous in enhancing cognitive performance after sustained wakefulness. However, future studies should consider assessing physiological parameters in a larger sample following modafinil or galantamine administration to gather stronger evidence for the development of guidelines on fatigue countermeasures.

AUTHORS' DECLARATION:

Concept of the article: Rafał Lewkowicz. **Theoretical input:** Rafał Lewkowicz, Anna Przewodzka. **Research methods:** Rafał Lewkowicz, Joanna Łaszczyńska. **Execution of research:** Rafał Lewkowicz, Anna Przewodzka. **Data processing:** Rafał Lewkowicz, Anna Przewodzka. **Analysis and interpretation of the results:** Rafał Lewkowicz. **Manuscript preparation:** Rafał Lewkowicz, Anna Przewodzka. **Project administration:** Joanna Łaszczyńska. The Authors declare that there is no conflict of interest.

REFERENCES

1. Angus RG, Heslegrave RJ. Effects of sleep loss on sustained cognitive performance during a command and control simulation. Behav Res Methods, Instruments, Comput. 1985; 17(1):55–67.
2. Batéjat DM, Lagarde DP. Naps and modafinil as countermeasures for the effects of sleep deprivation on cognitive performance. Aviat Space Environ Med. 1999; 70(5):493–8.
3. Bentley P, Driver J, Dolan RJ. Cholinesterase inhibition modulates visual and attentional brain responses in Alzheimer's disease and health. Brain. 2008; 131(Pt 2):409–24.
4. Bucci DJ, Holland PC, Gallagher M. Removal of Cholinergic Input to Rat Posterior Parietal Cortex Disrupts Incremental Processing of Conditioned Stimuli. J Neurosci. 1998; 18(19):8038 LP – 8046.
5. Caldwell JAJ, Caldwell JL, Smythe NK 3rd, Hall KK. A double-blind, placebo-controlled investigation of the efficacy of modafinil for sustaining the alertness and performance of aviators: a helicopter simulator study. Psychopharmacology (Berl). 2000; 150(3):272–82.
6. Caldwell JL, Schroeder VM, Kunkle CL, Stephenson HG. Differential effects of modafinil on performance of low-performing and high-performing individuals during total sleep deprivation. Pharmacol Biochem Behav. 2020; 196:172968.
7. Caldwell JA. Efficacy of stimulants for fatigue management: the effects of Provigil® and Dexedrine® on sleep-deprived aviators. Transp Res Part F Traffic Psychol Behav. 2001; 4(1):19–37.
8. Caldwell JA, Caldwell JL, Smith JK, Brown DL. Modafinil's effects on simulator performance and mood in pilots during 37 h without sleep. Aviat Space Environ Med. 2004; 75(9):777–84.
9. Caldwell JA, Caldwell JL, Thompson LA, Lieberman HR. Fatigue and its management in the workplace. Neurosci Biobehav Rev. 2019; 96:272–89.
10. Caldwell JA, Mallis MM, Caldwell JL, Paul MA, Miller JC, Neri DF. Fatigue countermeasures in aviation. Aviat Space Environ Med. 2009; 80(1):29–59.
11. Caldwell J, Caldwell L, Smith J, Alvarado L, Heintz T, Mylar J, et al. The Efficacy of Modafinil for Sustaining Alertness and Simulator Flight Performance in F-117 Pilots During 37 Hours of Continuous Wakefulness. Brooks City-Base, TX; 2004.
12. Cheng B, Wang Q, An Y, Chen F. Recent advances in the total synthesis of galantamine, a natural medicine for Alzheimer's disease. Nat Prod Rep. 2024; 41(7):1060–90.
13. Davidson MC, Marrocco RT. Local Infusion of Scopolamine Into Intraparietal Cortex Slows Covert Orienting in Rhesus Monkeys. J Neurophysiol. 2000; 83(3):1536–49.
14. Dawson D, Reid K. Fatigue, alcohol and performance impairment. Nature. England; 1997; 388(6639):235.
15. Ehlert AM, Wilson PB. Stimulant Use as a Fatigue Countermeasure in Aviation. Aerosp Med Hum Perform. 2021; 92(3):190–200.
16. Estrada A, Kelley AM, Webb CM, Athy JR, Crowley JS. Modafinil as a replacement for dextroamphetamine for sustaining alertness in military helicopter pilots. Aviat Space Environ Med. 2012; 83(6):556–64.
17. Ghaderi A, Saghafi F. Enhancing pilot vigilance assessment: The role of flight data and continuous performance test in detecting random attention loss in short IFR flights. J Air Transp Manag. 2024; 120:102673.
18. Gill TM, Sarter M, Givens B. Sustained Visual Attention Performance-Associated Prefrontal Neuronal Activity: Evidence for Cholinergic Modulation. J Neurosci. 2000; 20(12):4745 LP – 4757.
19. Grugle NL. Understanding the Effects of Sleep Deprivation on Executive Function, Complex Task Performance and Situation Awareness. Virginia Tech; 2005.
20. Hoddes E, Zarcone V, Smythe H, Phillips R, Dement WC. Quantification of Sleepiness: A New Approach. Psychophysiology. 1973; 10(4):431–6.
21. Kelley AM, Webb CM, Athy JR, Ley S, Gaydos S. Cognition enhancement by modafinil: a meta-analysis. Aviat Space Environ Med. 2012; 83(7):685–90.
22. Killgore WDS, Rupp TL, Grugle NL, Reichardt RM, Lipizzi EL, Balkin TJ. Effects of dextroamphetamine, caffeine and modafinil on psychomotor vigilance test performance after 44 h of continuous wakefulness. J Sleep Res. 2008; 17(3):309–21.
23. Łaszczyńska J, Janusińska A, Biernacki M. Enhance the psychophysical state of the soldier during combat sentences through pharmacological stimulation. [Poprawa stanu psychofizycznego żołnierza w czasie zdań bojowych przez stymulację farmakologiczną]. In: Kocik J, editor. Żołnierz jako broń precyzyjna – pakiety i zestawy: ochrona przed NBC i zagrożeniami środowiskowymi; żywienie i farmakoterapia – przetrwanie w trudnych warunkach i optymalizacja wydolności psychofizycznej; medyczny – opatrunki aktywne biologicznie. Warszawa: WIHE; 2012. p. (in Polish).
24. LeDuc P, Rowe T, Martin C, Curry I, Wildzunas R, Schmeisser E, et al. Performance Sustainment of Two Man Crews during 87 Hours of Extended Wakefulness with Stimulants and Napping. Fort Rucker (AL); 2009.

25. Lopez N, Previc FH, Fischer J, Heitz RP, Engle RW. Effects of sleep deprivation on cognitive performance by United States Air Force pilots. J Appl Res Mem Cogn. 2012; 1(1):27–33.

26. McCarty DE. Ready for takeoff? A critical review of armodafinil and modafinil for the treatment of sleepiness associated with jet lag. Nat Sci Sleep. 2010; 2:85–94.

27. Metz CN, Pavlov VA. Treating disorders across the lifespan by modulating cholinergic signaling with galantamine. J Neurochem. John Wiley & Sons, Ltd; 2021; 158(6):1359–80.

28. Meziou L, Haubrick K. A Systematic Review of the Effectiveness of Acetylcholinesterase Inhibitors on Cognition for Patients with Alzheimer's Disease. Res Rev. 2024; 5(6).

29. Military Aviation Authority. Medicatie En Luchtvaart. Soesterberg, The Netherlands: Royal Netherlands Air Force; 2021.

30. Ooi T, Wong SH, See B. Modafinil as a Stimulant for Military Aviators. Aerosp Med Hum Perform. 2019; 90(5):480–3.

31. Perelli LP. Fatigue Stressors in simulated long-duration flight. Effects on performance, information processing, subjective fatigue, and physiological cost. Report SAM-TR-80-49. Brooks Air Force Base, TX; 1980.

32. Pigeau R, Naitoh P, Buguet A, McCann C, Baranski J, Taylor M, et al. Modafinil, d-amphetamine and placebo during 64 hours of sustained mental work. I. Effects on mood, fatigue, cognitive performance and body temperature. J Sleep Res. 1995; 4(4):212–28.

33. Previc FH, Lopez N, Ercoline WR, Daluz CM, Workman AJ, Evans RH, et al. The effects of sleep deprivation on flight performance, instrument scanning, and physiological arousal in pilots. Int J Aviat Psychol. 2009; 19(4):326–46.

34. Przewodzka A, Łaszczyńska J, Czerwińska A, Kowalczuk K, Biernacki M, Lewkowicz R. How do modafinil and galanthamine affect heart rate during +Gz stress. Polish J Aviat Med Bioeng Psychol. 2023; 28(3).

35. Przewodzka A, Czerwińska A, Łaszczyńska J. Influence of Selected Pharmacological Agents on the Psychophysical Efficiency of a Human in Conditions of the Extended Alert Period in Association with the Hypoxia Stimulus at High Altitude. Polish J Aviat Med Bioeng Psychol. 2018; 24(4):5–19.

36. R Core Team. R: A language and environment for statistical computing. R Foundation for Statistical Computing. Vienna, Austria; 2016.

37. Reis C, Mestre C, Canhão H, Gradwell D, Paiva T. Sleep complaints and fatigue of airline pilots. Sleep Sci (Sao Paulo, Brazil). 2016; 9(2):73–7.

38. Robertson PJ, Hellriegel ET. Clinical pharmacokinetic profile of modafinil. Clin Pharmacokinet. 2003; 42(2):123–37.

39. Rosa E, Eiken O, Grönkvist M, Kölegård R, Dahlström N, Knez I, et al. Effects of Fatigue on Cognitive Performance in Long--Duration Simulated Flight Missions. Aviat Psychol Appl Hum Factors. 2020; 10(2):82–93.

40. Russo MB, Kendall AP, Johnson DE, Sing HC, Thorne DR, Escolas SM, et al. Visual perception, psychomotor performance, and complex motor performance during an overnight air refueling simulated flight. Aviat Space Environ Med. 2005; 76(7 Suppl):C92-103.

41. Russo M, Sing H, Kendall A, Johnson D, Santiago S, Escolas S, et al. Visual Perception, Flight Performance, and Reaction Time Impairments in Military Pilots During 26 Hours of Continuous Wake: Implications for Automated Workload Control (Meeting Proceedings RTO-MP-HFM-124). In: Strategies to Maintain Combat Readiness during Extended Deployments – A Human Systems Approach. Neuilly-Sur-Seine, France: NATO Research and Technology Organisation; 2005. p. 27–1 – 27–16.

42. Scott LJ, Goa KL. Galantamine. Drugs. 2000; 60(5):1095–122.

43. Silva Gomes V, Cardoso Júnior MM. The effect of sleepiness in situation awareness: A scoping review. Work. Netherlands; 2024; 78(3):641–55.

44. Siwek R, Witkowska-Banaszczak E, Szymański M. Caffeine in medicines and food supplements - relevance to treatment. [Kofeina w lekach i suplementach diety - znaczenie w lecznictwie]. Farm Pol. 2013; 69:541-549 (in Polish).

45. Walsh JK, Randazzo AC, Stone KL, Schweitzer PK. Modafinil improves alertness, vigilance, and executive function during simulated night shifts. Sleep. 2004; 27(3):434–9.

46. Wesensten N. Effects of modafinil on cognitive performance and alertness during sleep deprivation. Curr Pharm Des. 2006; 12(20):2457–71.

47. Wesensten NJ, Killgore WDS, Balkin TJ. Performance and alertness effects of caffeine, dextroamphetamine, and modafinil during sleep deprivation. J Sleep Res. 2005; 14(3):255–66.

48. Wesensten NJ, Belenky G, Kautz MA, Thorne DR, Reichardt RM, Balkin TJ. Maintaining alertness and performance during sleep deprivation: modafinil versus caffeine. Psychopharmacology (Berl). 2002; 159(3):238–47.

49. Wingelaar-Jagt YQ, Bottenheft C, Riedel WJ, Ramaekers JG. Effects of modafinil and caffeine on night-time vigilance of air force crewmembers: A randomized controlled trial. J Psychopharmacol. 2023; 37(2):172–80.

50. Wingelaar-Jagt YQ, Wingelaar TT, Riedel WJ, Ramaekers JG. Fatigue in Aviation: Safety Risks, Preventive Strategies and Pharmacological Interventions. Front Physiol. 2021; 12:712628.

51. Wingelaar-Jagt YQ, Wingelaar TT, Riedel WJ, Ramaekers JG. Modafinil Subjectively Does Not Impair Sleep in Aviators After a Period of Extended Wakefulness. Aerosp Med Hum Perform. 2024; 95(6):290–6.

52. Wingelaar-Jagt Y, Wingelaar T, Riedel W, Ramaekers J. Subjective Effects of Modafinil in Military Fighter Pilots During Deployment. Aerosp Med Hum Perform. 2022; 93(10):823.

53. Wisor JP, Nishino S, Sora I, Uhl GH, Mignot E, Edgar DM. Dopaminergic role in stimulant-induced wakefulness. J Neurosci Off J Soc Neurosci. 2001 Mar; 21(5):1787–94.

54. Yu I, Jenkins AR, Kangas BD, Desai R. Effects of Nerve Agent Analogs on Memorial, Attentional, and Interoceptive Processes: Insights into the Cognitive Consequences of Chemical Warfare. J Pharmacol Exp Ther. 2024; 389(S3):109.

55. Zhou H, Yao W, Shan Q, Zhang X, Zhang D, Che J, et al. Hierarchical adhesive hydrogel microparticles with galantamine hydrobromide encapsulation for the treatment of Alzheimer's disease. Mater Des. 2024; 246:113322.