Stimulant Use as a Fatigue Countermeasure in Aviation

Alex M. Ehlert; Patrick B. Wilson

INTRODUCTION: Fatigue is a common problem in aviation. The identification of efficacious fatigue countermeasures is crucial for sustaining flight performance during fatigue-inducing operations. Stimulants are not recommended for consistent use, but are often implemented during flight operations with a high risk of fatigue. As such, it is important to evaluate the efficacy of approved stimulants for sustaining flight performance, alertness, and mood.

METHODS: Four electronic databases (PubMed, PsycInfo, SPORTDiscus, Web of Science) were systematically searched to identify research on the effects of caffeine, dextroamphetamine, and modafinil during simulated or in-flight operations.

RESULTS: There were 12 studies identified that assessed the effects of at least 1 stimulant. Overall, dextroamphetamine and modafinil were effective for sustaining flight performance and pilot mood during extended wakefulness. Results with caffeine were inconsistent.

DISCUSSION: Dextroamphetamine and modafinil appear to sustain flight performance and mood during extended wakefulness. However, most studies have used flight simulators and short operation durations. Additional research is needed in realistic settings and during longer duration operations. Caffeine's effects were inconsistent across studies, possibly due to differences in study methodology or individual caffeine responses. Despite fatigue being a common problem in civilian aviation as well, only one study in this review included civil aviators. More research should be conducted on the effects of caffeine during civil operations.

CONCLUSION: Dextroamphetamine and modafinil appear to be effective fatigue countermeasures but should be further evaluated in more ecologically valid settings. The effects of caffeine are unclear at this time and should continue to be evaluated.

KEYWORDS: caffeine, dextroamphetamine, modafinil, human factors, alertness.

Ehlert AM, Wilson PB. *Stimulant use as a fatigue countermeasure in aviation*. Aerosp Med Hum Perform. 2021; 92(3):190–200.

Fatigue is a prevalent and significant problem in military and civilian aviation.[46,55] In civilian aviation, long-haul and executive pilots have attributed in-flight fatigue to factors such as scheduling issues (night flights, multiple flight legs, and insufficient recovery) and high workload.[5,52] Although military pilots have different demands and tasks than civilian aviators, their beliefs are similar, citing poor sleep, around-the-clock operations, long flights, and variable scheduling as contributors to fatigue.[3] Many pilots also believe fatigue impacts their job performance.[2,43]

There are several reported consequences of pilot fatigue. Studies have shown changes in central nervous system function, including an increase in slow-wave electroencephalogram (EEG) activity[6,53] and the appearance of microsleeps during flights.[55,61] Further, surveys suggest that many civil aircrew have "nodded off" during a flight.[21,52] As a result, a review of recent National Transportation Safety Board reports found that fatigue was a contributing factor in 23% of civil aviation investigations.[40] Similarly, a review of U.S. Air Force reports suggested that ~3.9% of mishaps were fatigue-related, with nearly a quarter of these classified in the severe mishap category.[30] Notably, fatigue-related mishaps were associated with $2.1 billion of medical or property damage. Implementation of evidence-based fatigue management strategies is critical to sustaining performance during flight operations that induce fatigue.[17] This typically includes a variety of in-flight countermeasures such as cockpit napping, activity breaks, bunk sleep, adjusting cockpit lighting to mitigate circadian disruption, and the use of stimulants.[17] It is strongly suggested that quality preflight sleep and strategic naps be used before relying on stimulants or other alertness-promoting strategies. However, when pilots must

From Human Movement Sciences, Old Dominion University, Norfolk, VA, USA.

This manuscript was received for review in June 2020. It was accepted for publication in December 2020.

Address correspondence to: Alex Ehlert, M.S., 2003 Student Recreation Center, Norfolk, VA 23529, USA; aehle003@odu.edu.

DOI: https://doi.org/10.3357/AMHP.5716.2021

carry out sustained operations, the strategic use of caffeine or prescription stimulants (dextroamphetamine, modafinil) could sustain performance.[17]

Caffeine was first discovered and isolated in 1819 by German chemist Friedlieb Ferdinand Runge, though caffeine-containing plants were used for psychoactive purposes for centuries earlier.[58] Caffeine intake in a variety of forms can increase alertness and sustain performance during fatiguing events, particularly when sleep deprived.[41] The effects of caffeine are thought to be driven primarily by adenosine antagonism, which elicits numerous effects such as enhanced neurotransmitter release and central nervous system stimulation.[28] Notably, caffeine has been used as a psychostimulant to sustain performance during numerous military operations[29] and has been demonstrated to improve or sustain performance of military personnel during operational tasks.[42,57] In addition to caffeine, several prescription stimulants are authorized for use during select aviation operations under strict regulation.[17] Dextroamphetamine was developed in the 1930s and was used extensively (largely without oversight) by soldiers, aircrew, and naval personnel during World War II to sustain performance.[29,51] Dextroamphetamine is a potent psychostimulant and is thought to sustain alertness by binding to dopaminergic receptors and blocking dopamine reuptake, ultimately resulting in widespread dopaminergic activity and activation of reward centers in the brain.[47,50] Numerous studies have also demonstrated that dextroamphetamine sustains alertness and vigilance when sleep deprived,[47,59] and it has been used successfully as a fatigue countermeasure during numerous combat aviation operations.[26,56] Modafinil is the most recently developed stimulant that is authorized for use during aviation operations.[17] It is thought to promote alertness through increased extracellular dopamine concentration and inhibition of dopamine reuptake transporters,[60] though its precise mechanism of action requires further clarification.

The use of dextroamphetamine and other stimulants during aviation operations has been a topic of controversy for decades. For example, some believe dextroamphetamine could compromise pilot judgment, induce side effects such as tunnel vision, or lead to substance abuse.[33,44,50] Further, in-flight dextroamphetamine use was implicated as a contributing factor to friendly fire casualties during the Tarnak Farms Incident, despite a subsequent investigation suggesting it did not play a significant role.[25] Others have supported the use of prescription stimulants during fatiguing military operations, citing successful use during numerous conflicts and a lack of evidence indicating negative effects.[9,22] Despite the contrasting views on their use, dextroamphetamine and modafinil are currently authorized by the U.S. military for select aviation operations under strict regulations.[17]

Caffeine, dextroamphetamine, and modafinil can each promote alertness and vigilance in healthy individuals, particularly during periods of sleep deprivation.[59] However, it is important to determine whether these findings generalize to specific military operational environments such as pilot performance and alertness during aviation operations. Several papers have highlighted the efficacy of various stimulants for sustaining alertness, cognition, and flight performance,[8,17] yet none of these have reviewed the literature systematically, or they were published greater than 10 yr ago. Therefore, the purpose of this systematic review was to identify and summarize the results of experimental studies on the efficacy of stimulants for sustaining or improving flight performance, as well as other relevant factors such measures of alertness or mood, during simulated or in-flight operations.

METHODS

This systematic review was developed using the recommendations from the Preferred Reporting Items for Systematic Review and Meta-Analysis Statement.[45] Peer-reviewed articles and government technical reports were eligible for inclusion if they evaluated the effects of at least one isolated stimulant on alertness, mood, side effects, and cognitive or flight performance during simulated or in-flight aviation tasks. Conference abstracts, theses, and dissertations were not included. Specific inclusion criteria included:

- Types of studies: Experimental or quasi-experimental investigations.
- Participants: Aviators, aviation students, or other relevant flight personnel.
- Outcomes: Measures of flight performance and/or related variables (mood, alertness, etc.).

Articles were excluded if they did not meet the inclusion criteria, did not include data about an individual stimulant, were review articles, or if a full text was unavailable in English. Additionally, articles were excluded if they did not involve measurement of direct (e.g., subjective or objective measurements of maneuver performance) or secondary (e.g., alertness, mood) measures of performance during a simulator or in-flight operation.

Four electronic databases (Pubmed, Web of Science, PsycInfo, SPORTDiscus) were electronically searched with no restrictions on date. The following keyword combination was used: (military pilot OR flight crew OR aviator OR aerospace OR aircrew OR aviation) AND (stimulant OR psycho stimulant OR caffeine OR amphetamine OR dextroamphetamine OR Dexedrine OR modafinil OR ephedrine OR dimethylamylamine). Duplicate articles were removed, followed by screening of titles and abstracts. Articles deemed relevant were read in full and a decision was made regarding whether they fit the inclusion criteria. Reference lists of included articles were searched and titles that appeared to be relevant were retrieved for consideration of inclusion. Data extracted included research design, sample size, participant characteristics, stimulants assessed, stimulant dosages, independent and dependent variables, and results.

RESULTS

Search Overview

The literature search resulted in 425 total articles. After removal of duplicates and screening for relevance, 12 articles met the

inclusion criteria. A detailed overview of the search results is available in **Fig. 1**.

Of the included articles, six were part of a series of studies conducted at the U.S. Army Aeromedical Research Laboratory. The first study evaluated the effects of dextroamphetamine administration on pilot flight performance, mood, and alertness during repeated simulated flights across 37 h of sustained wakefulness.[11] Subsequent studies with similar methodology were then conducted to evaluate the effects of dextroamphetamine in female pilots,[10] when sustained wakefulness was extended to 64 h,[19] and when in-flight operations were used instead of simulated operations.[12] The remaining two studies from the U.S. Army Aeromedical Research Laboratory evaluated the effects of modafinil administration instead of dextroamphetamine.[14,15] In addition to the U.S. Army Aeromedical Research Laboratory's investigations, one study compared the effects of dextroamphetamine and modafinil,[27] while four studies assessed the effects of caffeine during simulated flight operations in civilian pilots,[20] military pilots,[24,38] and military pilot students.[35] Finally, one study compared the effects of dextroamphetamine, modafinil, and caffeine.[36] Most studies recruited military pilots or pilot students with the exception of one study which recruited civilian aviators.[20]

The studies included a total of 164 pilots, with a mean sample size of 13.7 participants (range: 6 to 32). Of the included pilots, 10 were women and 124 were men, while Caska and Molesworth[20] did not specify the gender of 30 civilian pilots in their study. Most studies conducted testing in simulators except for one study that performed all testing in flight,[12] and another that used a combination of in-flight and simulator testing.[27] All but two studies[24,35] evaluated direct measures of performance (e.g., subjective or objective ratings of performance during specific maneuvers or overall flight performance). The effects of stimulants on direct measures of performance are displayed in **Table I**. All 12 studies included secondary measures relevant to the performance of aviators, including measures of mood, alertness, and cognitive performance. The results from these studies are subsequently summarized by stimulant type, followed by the results of those that compared multiple stimulants.

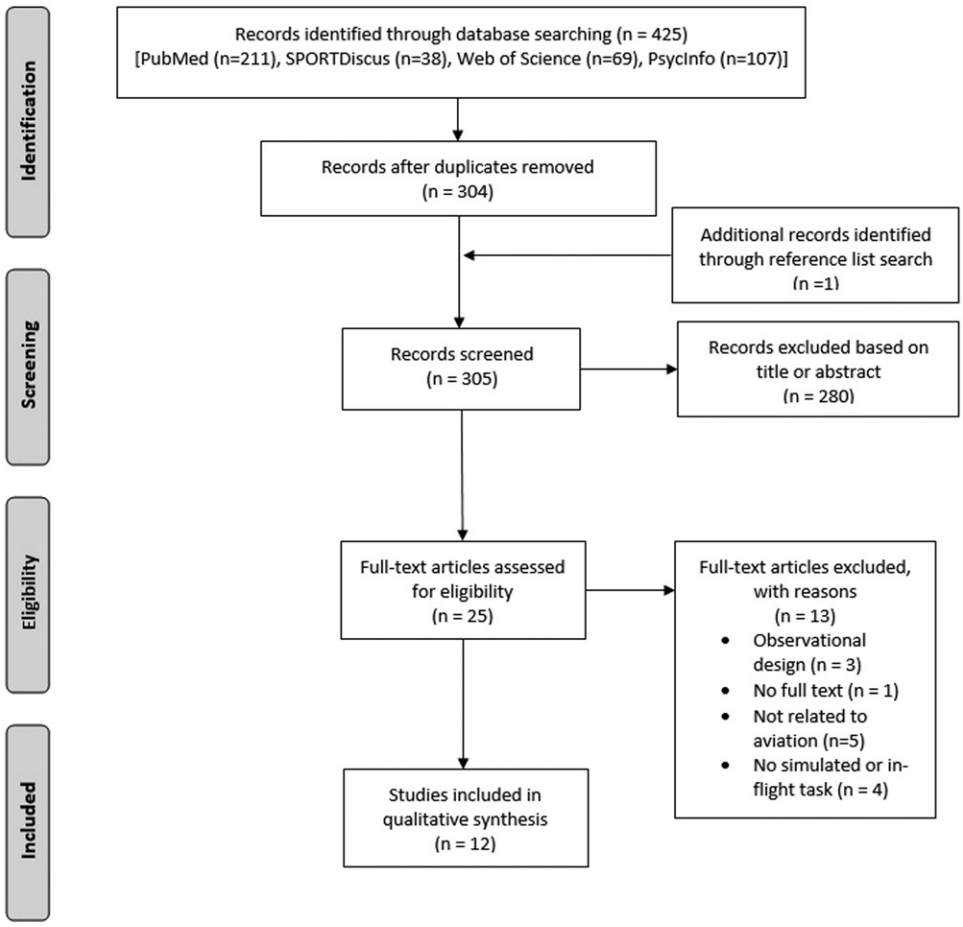

Fig. 1. Overview of the literature search.

Dextroamphetamine

Four studies assessed the effects of dextroamphetamine on either simulated[10,11,19] or in-flight[12] UH-60 helicopter maneuver performance. All four studies were part of a series of efficacy studies conducted at the U.S. Army Aeromedical Research Laboratory using nearly identical methodologies. Subjects arrived at the laboratory on Sunday night for screening. Three training sessions were performed throughout the day on Monday, and subjects were given a 2.5-mg test dose of dextroamphetamine. The remainder of the week was divided into two identical testing cycles (Tuesday/Wednesday and Thursday/Friday). Tuesday and Thursday served as control days during which testing was performed throughout the day to identify baseline performance in a rested state following a full night's sleep. Wednesday and Friday served as the sleep-deprivation testing days with sessions at 0100, 0500, 0900, 1300, and 1700, during which flight performance, electroencephalogram (EEG), and the Profile of Mood States (POMS) were assessed. During each sleep deprivation day, subjects were administered either 10 mg of dextroamphetamine or lactose placebo pills with orange juice at 0000, 0400, and 0800. All studies induced 37 h of sleep restriction per condition, other than one that was extended to 64 h.[19] The studies used a double-blind, randomized, counterbalanced

Table I. Efficacy of Stimulants on Simulator or In-Flight Performance.

ARTICLE	DESIGN	SUBJECT CHARACTERISTICS	TREATMENT	TESTING	RESULTS ($P < 0.05$)
Caldwell et al.[11]	DBRCO	Six male UH-60 helicopter pilots. Age: 27.8 yr (25–32).	3 × 10 mg DEX or placebo at 0000, 0400, and 0800	UH-60 simulator flights at 0100, 0500, 0900, 1300, and 1700. 37 h of sustained wakefulness with each treatment.	• Main drug effects: DEX > placebo for straight and levels, right standard-rate turns, descents, and left-descending turns. • Drug × session effects: DEX > placebo for straight and levels at 0900 and 1700, descents at 0500 and 0900, and left-descending turns at 0500, 0900, and 1700.
Caldwell et al.[12]	DBRCO	10 male UH-60 helicopter pilots. Age: 31.9 yr (28–36). Total flight experience: 1278 h, 839 h in UH-60.	3 × 10 mg DEX or placebo at 0000, 0400, and 0800	UH-60 in-flight sessions at 0100, 0500, 0900, 1300, and 1700. 37 h of sustained wakefulness with each treatment.	• Main drug effects: DEX > placebo for straight and levels, left standard rate turns, climbs, descents, left descending turns, and instrument landing system approach. • Drug × session effects: DEX > placebo for left-descending turns at 0500 and 0900 and instrument landing system approach at 0500 and 0900.
Caldwell et al.[10]	DBRCO	Six female UH-60 helicopter pilots. Age: 29.5 yr. Mean flight experience: 748 h.	3 × 10 mg DEX or placebo at 0000, 0400, and 0800	UH-60 simulator sessions at 0100, 0500, 0900, 1300, and 1700. 37 h of sustained wakefulness with each treatment.	• Main drug effects: DEX > placebo for GPS navigation, climbs, right standard rate turns, descents, and left descending turns. • Drug × session effects: DEX > placebo for straight and levels at 0900 and 1300, climbs at 0500 and 0900, and descents at 0500 and 0900.
Caldwell et al.[19]	DBRCO	Five male and one female UH-60 helicopter pilots. Age: 33.3 yr (27 to 40). Mean flight experience: 1245 h (200 to 2700).	3 × 10 mg DEX or placebo at 0000, 0400, and 0800.	Back-to-back UH-60 simulator sessions at 0100, 0500, 0900, 1300, and 1700. 64 h of sustained wakefulness with each treatment.	Main drug effects: DEX > placebo for overall flight performance and across all maneuvers (straight and levels, standard-rate left and right turns, standard-rate climbs, and descents, left-descending turn).
Caldwell et al.[15]	DBRCO	Six male UH-60 helicopter pilots. Age: 37.3 yr (29–46). Mean flight experience: 2173 h (900–5500), with 493 h in UH-60 helicopter.	3 × 200 mg MOD or placebo at 0000, 0400, and 0800.	UH-60 simulator sessions at 0100, 0500, 0900, 1300, and 1700. Total of 40 h sustained wakefulness with each treatment.	• Main drug effects: MOD > placebo for left-standard rate turns and left-descending turns. • Drug × session effects: MOD > placebo for straight and levels at 0900, descents at 1300, and left standard-rate turns at 0500 and 0900.
Caldwell et al.[14]	Single-blind cross over	10 male U.S. Air Force fighter pilots. Age: 36.6 yr (30–43). Mean flight experience: 2730 h (800–5800), with 432 h in F-117 (140–890).	3 × 100 mg MOD or placebo at 0000, 0500, and 1000.	F-117A simulator sessions at 2100 (baseline), 0400, 0900, 1400, and 1900. Total of 37 h sustained wakefulness with each treatment.	• Main drug effects: MOD > placebo for straight climbs, left 720° turns, left-climbing turns, right 360° turns, and straight and levels. • Drug × session effects: MOD > PLA for left 720° turns at 0900 and 1400.
Caska & Molesworth[20]	DBRCT	30 civilian pilots. Age: 23.1 ± 4.2 yr. Mean flight experience: 704.5 ± 1125.9 h. Randomly assigned to placebo, 1 mg · kg^{-1} caffeine, or 3 mg · kg^{-1} caffeine.	Placebo, 1 mg · kg^{-1}, or 3 mg · kg^{-1} caffeine administered before second of two flight simulator tasks.	Two instrument landing system approaches on personal computer aviation training device with X-Plane flight simulator software.	• No significant group differences for mean horizontal or vertical deviation on glide path. • Group × sleep interactions suggested that 1 mg · kg^{-1} and 3 mg · kg^{-1} improved horizontal deviation in pilots with least amount of sleep in the past 24 h. • Group × sleep interactions suggested that 1 mg · kg^{-1} improved vertical deviation in pilots with least amount of sleep, but 3 mg · kg^{-1} had an even larger effect.
Estrada et al.[27]	Double-blind, balanced, incomplete block	17 male, 1 female UH-60 helicopter pilots. Age: 29.5 yr (22–38). Mean flight experience: not reported. Randomly assigned to one of six conditions to encompass all six potential combinations of treatments across two testing cycles.	Administered one of the following during each of two testing cycles: 3 × 100 mg MOD, 3 × 5 mg DEX, or placebo at 2300, 0300, and 0700.	15 UH-60 flight sessions (12 in-flight, 3 simulator) across 2 d. Divided into three periods: drug administration, postdrug administration, and recovery. 40 h of sustained wakefulness with each treatment.	No significant drug or drug × time effects on flight performance.

Table I, *Continued.*

ARTICLE	DESIGN	SUBJECT CHARACTERISTICS	TREATMENT	TESTING	RESULTS ($P < 0.05$)
LeDuc et al.[36]	Double-blind, repeated measures between-group design	30 male, 2 female UH-60 pilots. Age: N/A. Mean flight experience: N/A. Pseudo-randomly assigned to a placebo, caffeine, DEX, or MOD treatment condition.	3 × 200 mg caffeine, 3 × 100 mg MOD, 3 × 5 mg DEX, or placebo at 0000, 0400, or 0800 during sleep-deprivation period.	11 UH-60 simulator sessions over a 68-h sleep deprivation period. Provided a 2-h nap followed by four more simulator sessions before a 10-h recovery sleep period.	• Main drug effects for hovers and climbs, but post hoc analyses suggested that MOD > DEX for hovers, and DEX > placebo for climbs. • No drug × session effects.
Lohi et al.[38]	DBRCT	13 male Finnish military pilot students. Age: 23–24 yr. Mean flight experience: 190 h (170–210). Randomly assigned to caffeine ($N = 7$) or placebo ($N = 6$).	4 × 200 mg caffeine taken 60 min before each simulator session	Four simulated flights in BAE Hawk Mk 51 simulator over 2 d. Total of 30 h of sustained wakefulness.	No significant differences between caffeine and placebo for situational awareness, instrument flight procedure, emergency procedure, or overall flight performance.

DBRCO, double-blind randomized crossover; DBRCT, double-blind randomized control trial; DEX, dextroamphetamine; MOD, modafinil.

crossover design. Because of the standardized measures across studies, the key results will be organized by outcome.

Flight performance. In each of the dextroamphetamine efficacy studies, standardized maneuvers were performed such as straight and levels, straight climbs and descents, right and left standard-rate turns, and descending turns. Computerized flight information was collected on headings, altitudes, and airspeeds during each maneuver and used to assess performance for each maneuver during each session. An overview of the main drug effects for each study are displayed in **Table II**.

Caldwell et al.[11] reported better performance in male UH-60 pilots during the dextroamphetamine condition for several maneuvers including straight and levels, right standard-rate turns, straight descent, and left descending turns. Additionally, there were drug × time interactions for straight and levels, straight descents, and left descending turns. Performance tended to be sustained with dextroamphetamine compared to placebo early in the day (0500 and 0900) and toward the end of the day (1700). Caldwell et al.[12] used identical procedures, but evaluated in-flight UH-60 performance rather than in a simulator environment. Dextroamphetamine was again effective compared to placebo, with reported benefits such as less heading error during straight and levels, more heading and slip control during climbs, better heading, airspeed, and vertical speed control during descents, and more vertical speed control during left descending turns. Again, drug × session interactions tended to support better performance for dextroamphetamine than placebo during morning sessions (0500 and 0900). Caldwell et al.[10] again used identical procedures, but recruited female UH-60 pilots instead of men. Overall, women appeared to respond similarly, as dextroamphetamine resulted in better overall performance for GPS navigation tasks, straight climbs, right standard-rate turns, straight descents, and left descending turns. They also found a variety of drug × time interaction effects, with dextroamphetamine tending to sustain performance earlier in the day (0500 and 0900) for several maneuvers compared to placebo. Finally, Caldwell et al.[19] evaluated dextroamphetamine for sustaining performance over 64 h of wakefulness rather than 37 h. Overall flight performance was calculated by averaging scores for each maneuver for each session. Performance during the dextroamphetamine condition was better than placebo overall and across all maneuvers. Additionally, drug × session interactions suggested that dextroamphetamine resulted in better performance throughout the day, but especially at 0500, 0900, and 1300.

EEG responses. All four studies evaluated EEG responses after each testing session. Delta activity was the slowest wave EEG evaluated and its appearance in awake subjects is suggestive of

Table II. Overview of Main Drug Effects for Each Flight Performance Maneuver from the Standardized U.S. Army Aeromedical Research Lab Studies Except for Caldwell et al.[14] Due to Differences in the Maneuvers Assessed.

	FLIGHT MANUEVER					
AUTHOR	STRAIGHT AND LEVEL	LEFT STANDARD-RATE TURN	RIGHT STANDARD-RATE TURN	STRAIGHT CLIMB	STRAIGHT DESCENT	LEFT DESCENDING TURN
Caldwell et al.[11] (D)	+	=	+	=	+	+
Caldwell et al.[12] (D)	+	+	=	+	+	+
Caldwell et al.[10] (D)	=	=	+	+	+	+
Caldwell et al.[19] (D)	+	+	+	+	+	+
Caldwell et al.[15] (M)	=	+	=	=	=	=

D = dextroamphetamine, M = modafinil. A plus sign (+) is indicative of a benefit for the stimulant compared to placebo ($P < 0.05$). An equal sign (=) is indicative of no or minimal difference between the placebo and stimulant conditions.

fatigue or sedation.[48] Two studies found greater delta activity under placebo compared to dextroamphetamine.[11,19] Theta activity is the second slowest wave assessed and tends to increase during sleep deprivation.[48] Theta activity was greater under the placebo condition compared to dextroamphetamine in all four studies. Alpha activity is usually the primary wave detected in rested, waked subjects.[48] Two studies found alpha activity was greater with dextroamphetamine compared to placebo.[10,12] Finally, none of the studies found any drug-related effects on beta activity, the fastest wave evaluated in these studies.

POMS, physiological responses, and side effects. The 65-item POMS questionnaire[49] was completed after each flight session and was used to assess six transient mood states: tension-anxiety, anger-hostility, vigor-activity, fatigue-inertia, depression-dejection, and confusion-bewilderment. An overview of main drug effects from all studies that evaluated POMS is displayed in **Table III**. Caldwell et al.[11] found benefits of dextroamphetamine in comparison to placebo for anger-hostility, fatigue-inertia, confusion-bewilderment, and vigor-activity. This finding was supported by Caldwell et al.[12] and Caldwell et al.[19], who found benefits of dextroamphetamine on vigor-activity, fatigue-inertia, and confusion-bewilderment. Caldwell et al.[19] also found slightly lower anger-hostility for dextroamphetamine compared to placebo. In contrast, Caldwell et al.[10] did not find any main drug effects on POMS. There were drug × time interactions, however, suggesting that dextroamphetamine may have preserved vigor-activity and attenuated fatigue-inertia and confusion-bewilderment during earlier testing sessions with differences dissipating as the day progressed.

Additionally, two of the efficacy studies evaluated effects on vital signs. Caldwell et al.[12] found statistically significant differences between conditions, with dextroamphetamine resulting in higher heart rate (72.0 vs. 67.4 bpm; $P < 0.001$), systolic pressure (135.8 vs. 127.7 mmHg; $P < 0.001$), and diastolic pressure (77.3 vs. 71.5 mmHg; $P < 0.001$) vs. placebo. Similarly, Caldwell et al.[19] found greater heart rate (68 vs. 62 bpm; $P = 0.009$), systolic pressure (129 vs. 125 mmHg; $P = 0.019$), and diastolic pressure (73 vs. 69 mmHg; $P = 0.024$) with dextroamphetamine compared to placebo.

Modafinil

Two studies examined the efficacy of modafinil for sustaining flight performance during continuous wakefulness.[14,15] These studies were continuations of the U.S. Army Aeromedical Research Laboratory efficacy trials. Caldwell et al.[15] used nearly identical procedures to the dextroamphetamine studies described above, except that three doses of 200 mg of modafinil were administered rather than dextroamphetamine. Caldwell et al.[14] used a lower dose (three doses of 100 mg), recruited fighter pilots to fly in a F-117A simulator rather than helicopter aviators in a UH-60 simulator, and used a slightly altered design. Of the 10 aviators, 5 had already performed one cycle of sleep deprivation testing sessions with no drug administration for a previous project, while five had not. The aviators that had previously performed the testing were rerecruited for one additional cycle, were given modafinil, but were told they could receive either treatment to maintain blindness. Their original testing served as their baseline control and the second cycle as the modafinil condition. The newly recruited aviators performed two cycles in same manner as the dextroamphetamine studies. They were told they would receive the treatments in a random order, but were given modafinil first. This resulted in a single-blind, nonrandomized crossover trial, while the other studies had been double-blinded.

Flight performance. Because Caldwell et al.[15] used nearly identical flight procedures as the dextroamphetamine studies, Table II displays the main drug effects for this study as well. Caldwell et al.[15] found differences between conditions for left standard-rate turns, while effects on right standard-rate turns and left descending turns did not reach statistical significance ($P = 0.066$ and 0.052, respectively). Caldwell et al.[14] evaluated different maneuvers due to flight sessions being in a F117A (not shown

Table III. Overview of Main Drug Effects During Each Experimental Study for the Profile of Mood States (POMS).

	DRUG EFFECTS					
AUTHOR	TENSION-ANXIETY	DEPRESSION-DEJECTION	ANGER-HOSTILITY	VIGOR-ACTIVITY	FATIGUE-INERTIA	CONFUSION-BEWILDERMENT
Caldwell et al.[11] (D)	=	=	+	+	+	+
Caldwell et al.[12] (D)	=	=	=	+	+	+
Caldwell et al.[10] (D)	=	=	=	=	=	=
Caldwell et al.[19] (D)	=	=	+	+	+	+
Caldwell et al.[15] (M)	=	=	=	=	+	+
Caldwell et al.[14] (M)	=	=	+	+	=	=
Doan et al.[24] (C)	=	=	=	=	+	=
Estrada et al.[27] (D)*	=	=	=	=	=	=
Estrada et al.[27] (M)*	=	=	=	=	=	=
Kilpelainen et al.[35] (C)	=	=	=	=	=	=
LeDuc et al.[36] (D)*	=	=	=	=	+	=
LeDuc et al.[36] (M)*	=	=	=	=	=	=
LeDuc et al.[36] (C)*	=	=	=	=	=	=

D = dextroamphetamine, M = modafinil, C = caffeine. A plus sign (+) is indicative of a benefit for the stimulant compared to placebo ($P < 0.05$). An equal sign (=) is indicative of no or minimal difference between the placebo and stimulant. *One condition of multiple within a study.

in Table II). They found greater performance during the modafinil condition for straight climbs, left 720° turns, left climbing turns, right 360° turns, and straight and levels. Additionally, differences between conditions for right descending turns trended toward significance ($P = 0.059$).

EEG response. Both modafinil efficacy studies evaluated EEG responses following testing sessions,[14,15] although the EEG data for Caldwell et al.[14] was located in the full technical report.[13] Like the dextroamphetamine trials, aviators presented greater slow wave (delta and theta) activity with placebo compared to modafinil in both studies.

POMS and subjective measures. Both studies administered the POMS after flight sessions (Table III). Caldwell et al.[15] found modafinil resulted in less fatigue-inertia and confusion-bewilderment compared to placebo. Additionally, drug × session effects suggested that modafinil resulted in greater vigor-activity and lower fatigue-inertia during the early part of the day (0335–1135) versus placebo. Caldwell et al.[14] also assessed subjective measures using visual analog scales. Alertness decreased over time, with a large decline during the morning (0330–0830), and energy levels declined linearly with time awake. However, modafinil sustained alertness, confidence, and energy compared to placebo.

Physiological and side effects. Caldwell et al.[15] found no differences in oral temperature between conditions, but did find increases in heart rate from modafinil at various time points. Blood pressure was only elevated at one time point (1615) compared to placebo. Caldwell et al.[14] did not assess vital signs. Both studies evaluated side effects to determine if modafinil was a suitable alternative to dextroamphetamine. Caldwell et al.[15] reported several side effects with modafinil, including nausea, vertigo, jitteriness or nervousness, dizziness, heartburn, and headaches. The authors suggested this was due to the dose (3 × 200 mg). In a later trial, Caldwell et al.[14] prescribed a lower dose (3 × 100 mg) and found similar benefits with very few side effects.

Caffeine

Four studies assessed caffeine's effects on outcomes of interest in civilian pilots,[20] military pilot students,[35] or military pilots.[24,38] The study with civilian pilots evaluated two different doses of caffeine (1 mg · kg^{-1} or 3 mg · kg^{-1}) on simulated horizontal and vertical deviation during instrument landing system approaches.[20] The studies by Lohi et al.[38] and Kilpeläinen et al.[35] assessed the effects of 200-mg doses on a variety of performance measures in military pilots or students during training sessions and sleep deprivation. The final study compared two doses of caffeinated pudding tube food (200 mg each) with a placebo on simulated nighttime U-2 missions in male U.S. Air Force pilots.[24]

Caska and Molesworth[20] did not find any significant main effect differences between the two caffeine groups and placebo group. However, to evaluate the moderating effects of sleep, they also conducted a series of paired repeated measures analyses with sleep as a covariate. The results suggested that pilots in the 1 mg · kg^{-1} and 3 mg · kg^{-1} caffeine groups with the least amount of sleep tended to have improved performance.

Kilpeläinen et al.[35] reported minor differences between caffeine and placebo groups. There was a greater performance in sustained attention for the caffeine group at the fourth measurement point, but not at any other time point. Additionally, the number of incorrect responses during the sustained attention task increased over time with placebo but not caffeine. However, no other differences were found in cognitive performance or vigilance. Additionally, fatigue increased and vigor significantly decreased over time in both groups, with no difference between them. Interestingly, the placebo group perceived their performance as getting worse while the caffeine group believed it remained stable as sleep deprivation duration increased. Similar results were reported by Lohi et al.[38] There were no differences between groups for flight performance. However, the caffeine group tended to evaluate their performance higher than the placebo group after about 20 h of sleep deprivation, despite no differences in actual performance. There were no group differences for sleepiness or body temperature.

The results from Doan et al.[24] run in opposition to the other trials. There were significant treatment effects for performance on an adaptive tracking test, a code substitution test, and a match-to-sample test. Significant drug × time interactions for each of these tests suggested that performance rapidly degraded over time with placebo while performance remained relatively stable for most or all the testing with caffeine. The POMS was also completed throughout each session. Fatigue-inertia was greater with placebo and a drug × time effect was also detected, suggesting that fatigue-inertia increased over time with placebo, while it remained lower in the caffeine trial until the final session. There was no main drug effect for vigor-activity, but there was a drug × time interaction effect, with a dramatic decrease in vigor that remained low in the placebo condition, while the caffeine condition gradually declined. There were no reports of moderate or severe symptoms in either group and minor symptoms were not different between groups.

Comparison Between Stimulants

One study assessed the effects of both dextroamphetamine and modafinil on physiological measures, symptomology, flight performance, and a variety of cognitive assessments using a double-blind, balanced, incomplete block design.[27] Eighteen UH-60 pilots were assigned to two of three available treatments in random order (3 × 100 mg of modafinil, 3 × 5 mg of dextroamphetamine, and 3 doses of placebo). This resulted in six total combinations of condition × order encompassing each possible combination of treatments. Three aviators were assigned to each of the six combinations. They then performed two identical testing cycles, one with each of their assigned treatments. Each cycle involved a series of tests and treatment dosages during continual wakefulness. At the end of each cycle, they were allowed recovery sleep and given their second treatment condition for identical testing the following day. The results were

compared between three time windows: drug administration period, postdrug administration period, and recovery period.

They found no evidence of main or treatment × time interaction effects on flight performance. The only drug main effect for POMS was depression; however, post hoc simple effect analysis revealed no significant differences. There was also no significant main effect for drug for the fatigue-inertia scale, but placebo led to greater fatigue-inertia during the drug administration period. Tension scores were greater with modafinil compared to placebo during recovery. Additionally, vigor was greater at the drug administration period for modafinil compared to placebo. Subjective measures assessed using visual analog scales revealed only significant findings for a couple of measures. There was no main drug effect for talkativeness, but talkativeness was greater for modafinil conditions when compared to dextroamphetamine at drug administration. Placebo led to greater sleepiness than modafinil and the interaction suggested this was mostly due to higher sleepiness scores at the drug administration period. Finally, there were no differences between conditions for risk propensity.

LeDuc et al.[36] compared the effects of dextroamphetamine, modafinil, and caffeine to placebo on two-man crew UH-60 flight performance, crew coordination, and other relevant effects (e.g., side effects, cognitive performance, etc.) during a 68-h period of sleep deprivation and testing, as well as after a 2-h nap. There were significant drug main effects for performance during hover and climb maneuvers, with post hoc analysis suggesting enhanced hover performance in the modafinil group compared to dextroamphetamine, and better climb performance in the dextroamphetamine group compared to placebo. They also found a variety of other effects, such as lower ratings of fatigue, irritability, and sleepiness, with dextroamphetamine compared to placebo. Similarly, subjective alertness was higher with modafinil and dextroamphetamine compared to placebo. Interestingly, simulator sickness symptoms and side effects were significantly more severe with caffeine and placebo than either dextroamphetamine or modafinil; caffeine elicited high levels of nausea, jitteriness, and nervousness specifically ($P < 0.05$).

DISCUSSION

Due to the pervasiveness and potential ramifications of fatigue in aviation, there is a need for evidence-based strategies to counteract its effects on flight performance when adequate recovery sleep cannot be obtained.[17] A variety of countermeasures are approved for use, including strategic naps, bunk rest, and activity breaks.[17] Although these are preferred methods for sustaining performance, certain operations may require the use of stimulants to maintain alertness and performance.[17] Three stimulants (caffeine, dextroamphetamine, and modafinil) are commonly used and approved for use by military aviation personnel, while caffeine can be used in civil operations. This systematic review aimed to synthesize available data on their effects on flight performance and related variables.

Twelve studies evaluated the effects of at least one stimulant. In totality, the studies on dextroamphetamine support its efficacy for sustaining flight performance and mood state during simulator or in-flight training sessions with sleep deprivation. The dextroamphetamine efficacy studies generally reported benefits to performance and mood state and, oftentimes, the effects sustained performance during late night or early morning. These studies also showed consistent benefits to certain aspects of mood, particularly vigor-activity, fatigue-inertia, and confusion-bewilderment, and resulted in less slow wave EEG activity. Considering that dextroamphetamine and other stimulants are thought to improve flight performance through sustainment of alertness and vigilance,[17] this is not overly surprising.

There are a limited number of studies available on modafinil use during flight operations, but the findings were comparable to the dextroamphetamine studies. Indeed, one article[7] aggregated and compared the results from two studies within this review that used identical testing procedures to evaluate potential differences between dextroamphetamine and modafinil.[11,15] The only difference between the studies was that one that administered dextroamphetamine,[11] and the other administered modafinil.[15] Overall, both drugs were considered effective and the effects of dextroamphetamine and modafinil only differed on two variables, and, in those cases, one favored dextroamphetamine, the other modafinil. This analysis provides evidence to suggest that both dextroamphetamine and modafinil can be effective fatigue countermeasures for military aviators. Given the totality of evidence, it is not surprising that Kenagy et al.[34] found that 97% of B-2 bomber pilots who used dextroamphetamine perceived a benefit, while Emonson and Vanderbeek[26] found that 61% of stimulant users reported it as essential and another 35% as beneficial during combat operations.

One major limitation of the current research on dextroamphetamine and modafinil is that only one study has been conducted in flight.[12] Indeed, in another post hoc analysis, Caldwell and Roberts[18] aggregated the data from two dextroamphetamine efficacy studies within this review that were identical other than one used a UH-60 simulator[11] and the other performed testing in flight.[12] Both studies demonstrated that dextroamphetamine sustained performance during periods of sustained wakefulness, but the effects were more pronounced in the simulator environment for five of the six evaluated maneuvers (e.g., in Caldwell et al.[11]). This analysis led Caldwell and Roberts[18] to suggest that dextroamphetamine has, at best, a modest effect on in-flight performance during sustained wakefulness. Studies that have evaluated other pharmaceutical interventions in both simulator and in-flight environments have found similar results.[4,16] There are several potential reasons for why effects are lessened in an actual flight environment, including more chaotic conditions due to weather turbulence, highly variable environmental conditions, and potentially increased arousal of the pilots when operating an aircraft compared to simulated flight.[18] As such, while tightly controlled laboratory studies have consistently demonstrated benefits of

dextroamphetamine and modafinil, it is unclear how well these findings truly generalize to actual operational environments, particularly during combat operations when arousal and stress are even higher than in typical in-flight training operations. Additionally, the flight times during these studies were an hour or less, which may not reflect many real-world operations. For example, stimulants are used more often when flight durations are beyond 8 h,[32] and in most cases dextroamphetamine and modafinil will not be authorized during short duration operations.[17] Therefore, future research should determine the efficacy of dextroamphetamine and modafinil in more ecologically valid contexts. Finally, the studies in this review provided minimal information about previous stimulant use by the recruited pilots; therefore, future studies should consider reporting previous usage and whether it moderates responses during flight operations.

The results with caffeine were mixed and inconclusive, though two studies were based on samples of only 6–8 participants per group,[35,38] meaning they may have been statistically underpowered. Despite a lack of clear evidence of objective benefit, pilots receiving caffeine tended to perceive their performance as better than those in placebo groups. This may be a result of increased confidence and it is unclear whether this would be a net positive or negative effect. As an example, an overconfident pilot could take unnecessary risks, which may be particularly problematic when they are sleep deprived. Doan et al.[24] found contrasting results, finding sustainment of cognitive performance, vigilance, and mood state when Air Force pilots consumed caffeinated tube food during long, nighttime flight simulations. Additionally, Caska and Molesworth[20] provided some evidence that caffeine could be more effective for pilots who had less sleep leading up to the operation. The mixed results are somewhat surprising considering the well-established benefits of caffeine on cognition[39] and positive findings from other military contexts.[23,37] The disparate findings could be due to differences in subject characteristics, study procedures, or sample sizes and statistical power. Clearly, more research should be conducted on caffeine's efficacy during sustained aviation operations. In particular, studies should be conducted using different dosages of caffeine and results should be compared between habitual and nonhabitual consumers.

Finally, only one study to date has evaluated the effects of stimulants in civilian pilots.[20] Fatigue is a common occurrence in many civilian operations and, as such, it is important to identify countermeasures for aviators in the civilian sector as well.[17,31] Caffeine is the only feasible stimulant option for civilian aviators, as prescription stimulants such as dextroamphetamine and modafinil are generally prohibited.[17] Caffeine is commonly used during civilian flight operations, with recent studies finding relatively high caffeine usage during air medical missions[1] and in both long-haul and short-haul pilots.[54] Future research should strive to identify the efficacy of caffeine for sustaining performance and alertness during operations that are a high risk for fatigue, such as long-haul international flights or overnight cargo transport pilots.[31]

In conclusion, given the risks of fatigue during aviation operations, it is important that countermeasures and fatigue management strategies be based on quality scientific evidence. The results of this review have largely supported the efficacy of dextroamphetamine and modafinil for sustaining flight performance and mood state during continuous wakefulness. Additionally, these stimulants have relatively comparable effects based on current data. However, most of these studies used small samples, conducted sessions with flight simulators rather than in flight, and used short flights. More studies should be implemented in flight to determine if the benefits extend to more ecologically valid situations than a simulator flight in a lab setting. Finally, the results with caffeine have been largely mixed and, given its high prevalence of use among pilots, more research should be conducted to elucidate the effectiveness of caffeine as a fatigue countermeasure in aviation contexts.

ACKNOWLEDGMENTS

Financial Disclosure Statement: The authors have no competing interests to declare.

Authors and affiliation: Alex M. Ehlert, B.S., M.S., and Patrick B. Wilson, Ph.D., R.D., Old Dominion University, Norfolk, VA, USA.

REFERENCES

1. Amann U, Holmes A, Caldwell J, Hilditch C. Sleep and sleepiness of pilots operating long-range airplane emergency medical missions. Aviat Space Environ Med. 2014; 85(9):954–959.
2. Belland KM, Bissell C. A subjective study of fatigue during Navy flight operations over southern Iraq: Operation Southern Watch. Aviat Space Environ Med. 1994; 65(6):557–561.
3. Bendak S, Rashid HSJ. Fatigue in aviation: a systematic review of the literature. Int J Ind Ergon. 2020; 76:102928.
4. Billings CE, Gerke RJ, Wick RL Jr. Comparisons of pilot performance in simulated and actual flight. Aviat Space Environ Med. 1975; 46(3):304–308.
5. Bourgeois-Bougrine S, Carbon P, Gounelle C, Mollard R, Coblentz A. Perceived fatigue for short- and long-haul flights: a survey of 739 airline pilots. Aviat Space Environ Med. 2003; 74(10):1072–1077.
6. Cabon P, Coblentz A, Mollard R, Fouillot JP. Human vigilance in railway and long-haul flight operation. Ergonomics. 1993; 36(9):1019–1033.
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. Dextroamphetamine and modafinil are effective countermeasures for fatigue in the operational environment. Strategies to Maintain Combat Readiness During Extended Deployments—A Human Systems Approach. Neuilly-sur-Seine (France): NATO Research and Technology Organization; 2005:1–31.
9. Caldwell JA. Go pills in combat: prejudice, propriety, and practicality. Air & Space Power Journal. 2008; 2(3):97–104.
10. Caldwell JA, Caldwell JL, Crowley JS. Sustaining female helicopter pilot performance with Dexedrine during sleep deprivation. Int J Aviat Psychol. 1997; 7(1):15–36.
11. Caldwell JA, Caldwell JL, Crowley JS, Jones HD. Sustaining helicopter pilot performance with Dexedrine during periods of sleep deprivation. Aviat Space Environ Med. 1995; 66(10):930–937.
12. Caldwell JA, Caldwell JL, Lewis JA, Jones HD, Reardon MJ. An in-flight investigation of the efficacy of dextroamphetamine for the sustainment of

helicopter pilot performance (Report No.: USAARL-97-05). Fort Rucker (AL): Army Aeromedical Research Laboratory; 1996.
13. Caldwell JA, Caldwell JL, Smith J, Alvarado L, Heintz T. The efficacy of modafinil for sustaining alertness and simulator flight performance in F-117 pilots during 37 hours of continuous wakefulness (Report No. AFRL-HE-BR-TR-2004-0003). Brooks City-Base (TX): Air Force Research Laboratory, Human Effectiveness Directorate Biosciences and Protection Division, Fatigue Countermeasures Branch; 2004.
14. 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):777–784.
15. Caldwell JA, Caldwell JL, Smythe NK, 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):272–282.
16. Caldwell JA, Jones HD. A comparison of computerized measurement of helicopter pilot performance with atropine sulfate during actual and simulated flight. Fort Rucker (AL): Army Aeromedical Research Lab; 1990.
17. Caldwell JA, Mallis MM, Caldwell JL, Paul MA, Miller JC, Neri DF. Aerospace Medical Association Fatigue Countermeasures Subcommittee of the Aerospace Human Factors Committee. Fatigue countermeasures in aviation. Aviat Space Environ Med. 2009; 80(1):29–59.
18. Caldwell JA, Roberts KA. Differential sensitivity of using simulators versus actual aircraft to evaluate the effects of a stimulant medication on aviator performance. Mil Psychol. 2000; 12(4):277–291.
19. Caldwell JA, Smythe NK, Leduc PA, Caldwell JL. Efficacy of Dexedrine for maintaining aviator performance during 64 hours of sustained wakefulness: a simulator study. Aviat Space Environ Med. 2000; 71(1):7–18.
20. Caska TJ, Molesworth BR. The effects of low dose caffeine on pilot performance. Int J Appl Aviat Stud. 2007; 7(2):244–255.
21. Co EL, Gregory KB, Johnson JM, Rosekind MR. Crew factors in flight operations. 11; A survey of fatigue factors in regional airline operations (Report no: NASA/TM – 1999-208799). Moffett Field (CA): NASA Ames Research Center; 1999.
22. Cornum K, Cornum R, Storm W. Use of psychostimulants in extended flight operations: a Desert Shield experiment. AGARD conference proceedings 579. Neuilly-sur-Seine (France): AGARD; 1996:37-1–37-4. Report No. AGARD-CP-579.
23. Crawford C, Teo L, Lafferty L, Drake A, Bingham JJ, et al. Caffeine to optimize cognitive function for military mission-readiness: a systematic review and recommendations for the field. Nutr Rev. 2017; 75(suppl_2):17–35.
24. Doan BK, Hickey PA, Lieberman HR, Fischer JR. Caffeinated tube food effect on pilot performance during a 9-hour, simulated nighttime U-2 mission. Aviat Space Environ Med. 2006; 77(10):1034–1040.
25. Dungan CP. Rules of engagement and fratricide prevention: lessons from the Tarnak Farms Incident. UCLA Journal of International Law & Foreign Affairs. 2004. [Accessed January 2021]. Available at: https://ssrn.com/abstract=612021.
26. Emonson DL, Vanderbeek RD. The use of amphetamines in U.S. Air Force tactical operations during Desert Shield and Storm. Aviat Space Environ Med. 1995; 66(3):260–263.
27. 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):556–564.
28. Fredholm BB, Bättig K, Holmén J, Nehlig A, Zvartau EE. Actions of caffeine in the brain with special reference to factors that contribute to its widespread use. Pharmacol Rev. 1999; 51(1):83–133.
29. Friedl KE. U.S. Army research on pharmacological enhancement of soldier performance: stimulants, anabolic hormones, and blood doping. J Strength Cond Res. 2015; 29(Suppl 11):S71–S76.
30. Gaines AR, Morris MB, Gunzelmann G. Fatigue-related aviation mishaps. Aerosp Med Hum Perform. 2020; 91(5):440–447.
31. Gander PH, Rosekind MR, Gregory KB. Flight crew fatigue VI: a synthesis. Aviat Space Environ Med. 1998; 69(9, Suppl):B49–B60.
32. Gore RK, Webb TS, Hermes ED. Fatigue and stimulant use in military fighter aircrew during combat operations. Aviat Space Environ Med. 2010; 81(8):719–727.
33. Hurst PM. The effects of d-amphetamine on risk taking. Psychopharmacologia. 1962; 3(4):283–290.
34. Kenagy DN, Bird CT, Webber CM, Fischer JR. Dextroamphetamine use during B-2 combat missions. Aviat Space Environ Med. 2004; 75(5):381–386.
35. Kilpeläinen AA, Huttunen KH, Lohi JJ, Lyytinen H. Effect of caffeine on vigilance and cognitive performance during extended wakefulness. Int J Aviat Psychol. 2010; 20(2):144–159.
36. LeDuc P, Rowe T, Martin C, Curry I, Wildzunas R, et al. Performance sustainment of two man crews during 87 hours of extended wakefulness with stimulants and napping. Fort Rucker (AL): Army Aeromedical Research Lab; 2009. Report No. USAARL-2009-04.
37. Lieberman HR, Tharion WJ, Shukitt-Hale B, Speckman KL, Tulley R. Effects of caffeine, sleep loss, and stress on cognitive performance and mood during U.S. Navy SEAL training. Psychopharmacology (Berl). 2002; 164(3):250–261.
38. Lohi JJ, Huttunen KH, Lahtinen TM, Kilpeläinen AA, Muhli AA, Leino TK. Effect of caffeine on simulator flight performance in sleep-deprived military pilot students. Mil Med. 2007; 172(9):982–987.
39. Lorist MM, Tops M. Caffeine, fatigue, and cognition. Brain Cogn. 2003; 53(1):82–94.
40. Marcus JH, Rosekind MR. Fatigue in transportation: NTSB investigations and safety recommendations. Inj Prev. 2017; 23(4):232–238.
41. McLellan TM, Caldwell JA, Lieberman HR. A review of caffeine's effects on cognitive, physical and occupational performance. Neurosci Biobehav Rev. 2016; 71:294–312.
42. McLellan TM, Kamimori GH, Bell DG, Smith IF, Johnson D, Belenky G. Caffeine maintains vigilance and marksmanship in simulated urban operations with sleep deprivation. Aviat Space Environ Med. 2005; 76(1):39–45.
43. Miller JC, Melfi ML. Causes and effects of fatigue in experienced military aircrew. Brooks City-Base (TX): Air Force Research Laboratory, Human Effectiveness Directorate Biosciences and Protection Division, Fatigue Countermeasures Branch; 2006. Report no. AFRL-HE-BR-TR-2006-0071.
44. Mills KC, Spruill SE, Kanne RW, Parkman KM, Zhang Y. The influence of stimulants, sedatives, and fatigue on tunnel vision: risk factors for driving and piloting. Hum Factors. 2001; 43(2):310–327.
45. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst Rev. 2015; 4(1):1.
46. Neville KJ, Bisson RU, French J, Boll PA, Storm WF. Subjective fatigue of C-141 aircrews during Operation Desert Storm. Hum Factors. 1994; 36(2):339–349.
47. Newhouse PA, Belenky G, Thomas M, Thorne D, Sing HC, Fertig J. The effects of d-amphetamine on arousal, cognition, and mood after prolonged total sleep deprivation. Neuropsychopharmacology. 1989; 2(2):153–164.
48. Oken BS, Salinsky MC, Elsas SM. Vigilance, alertness, or sustained attention: physiological basis and measurement. Clin Neurophysiol. 2006; 117(9):1885–1901.
49. Pollock V, Cho DW, Reker D, Volavka J. Profile of Mood States: the factors and their physiological correlates. J Nerv Ment Dis. 1979; 167(10):612–614.
50. PubChem. PubChem Compound Summary for CID 5826, Dextroamphetamine. Bethesda (MD): National Library of Medicine (US), National Center for Biotechnology Information; 2004. [Accessed 2020 Oct. 23]. Available from: https://pubchem.ncbi.nlm.nih.gov/compound/Dextroamphetamine.
51. Rasmussen N. Medical science and the military: the Allies' use of amphetamine during World War II. J Interdiscip Hist. 2011; 42(2):205–233.
52. Rosekind MR, Co EL, Gregory KB, Miller DL. Crew factors in flight operations XIII: a survey of fatigue factors in corporate/executive aviation operations. Moffett Field (CA): NASA Ames Research Center; 2000. Report No.: NASA/TM-2000-209610.
53. Rosekind MR, Graeber RC, Dinges DF, Connell LJ, Rountree MS, et al. Crew factors in flight operations IX: effects of planned cockpit rest on crew performance and alertness in long-haul operations. Moffett Field (CA): NASA Ames Research Center; 1994. Report No.: NASA Technical Memorandum 108839.

54. Sallinen M, Sihvola M, Puttonen S, Ketola K, Tuori A, et al. Sleep, alertness and alertness management among commercial airline pilots on short-haul and long-haul flights. Accid Anal Prev. 2017; 98:320–329.
55. Samel A, Wegmann HM, Vejvoda M. Jet lag and sleepiness in aircrew. J Sleep Res. 1995; 4(S2):30–36.
56. Senechal PK. Flight surgeon support of combat operations at RAF Upper Heyford. Aviat Space Environ Med. 1988; 59(8):776–777.
57. Tharion WJ, Shukitt-Hale B, Lieberman HR. Caffeine effects on marksmanship during high-stress military training with 72 hour sleep deprivation. Aviat Space Environ Med. 2003; 74(4):309–314.
58. Weinberg BA, Bealer BK. The world of caffeine: the science and culture of the world's most popular drug. New York: Routledge; 2001.
59. Wesensten NJ, Killgore WD, Balkin TJ. Performance and alertness effects of caffeine, dextroamphetamine, and modafinil during sleep deprivation. J Sleep Res. 2005; 14(3):255–266.
60. Wisor JP, Nishino S, Sora I, Uhl GH, Mignot E, Edgar DM. Dopaminergic role in stimulant-induced wakefulness. J Neurosci. 2001; 21(5):1787–1794.
61. Wright N, McGown A. Vigilance on the civil flight deck: incidence of sleepiness and sleep during long-haul flights and associated changes in physiological parameters. Ergonomics. 2001; 44(1):82–106.