Subjective Effects of Modafinil in Military Fighter Pilots During Deployment

Yara Q. Wingelaar-Jagt; Thijs T. Wingelaar; Wim J. Riedel; Johannes G. Ramaekers

INTRODUCTION: Fatigue has negative effects on flight safety, especially in military aviation, where missions are often performed under challenging conditions. Modafinil is a relatively new pharmaceutical able to counter the symptoms of fatigue, but efficacy has not yet been studied in operational military aviation. This study aims to establish effectiveness and safety of modafinil in military operations.

METHODS: This field study was conducted during deployment in the Middle East by the Royal Netherlands Air Force fighter pilots. Prior to use operationally, pilots had to complete a 24-h ground test in which modafinil was administered during a nonflying period using a questionnaire to screen for duty-relevant side effects. If no side effects were reported, operational usage was allowed. In addition to registration of modafinil's effects, relevant data prior to and after administration were recorded, including caffeine consumption and sleep afterwards.

RESULTS: Of the 75 pilots who completed ground testing, only one experienced duty-relevant side effects. Modafinil was used in 192 operational flights, mostly during nighttime. In 128 (67%) of the flights, modafinil was used preventively, in 64 (33%) because of fatigue. In 182 (95%) of the flights, positive effects of modafinil were reported, with a maximum effect 2–3 h after administration. There was no statistical correlation between modafinil's beneficial effects and prior administration of caffeine or sleep medication, nor was sleep afterwards negatively affected.

DISCUSSION: This study indicates modafinil is a suitable pharmaceutical countermeasure to minimize the effects of fatigue during real-life fighter operations, without signs of negative impact on flight safety or sleep quality afterwards.

KEYWORDS: aviation, fatigue, wakefulness-promoting agents, sleep, human performance.

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Military flight operations have increased in length, in part due to technological advances, such as fifth-generation fighter aircraft. This increase in mission length can influence pilots' emotional state and cause fatigue, particularly at the end of a mission.[18] Fatigue is an important risk factor for aircraft incidents and accidents, both in civil and military aviation, thus negatively affecting aviation safety.[21] Although having sufficient sleep is regarded as the optimal method of avoiding fatigue, this is often difficult to achieve, especially during military deployments, because sleep in the field is often of poorer quality and shorter duration than sleep at home.[10] Moreover, for tactical reasons, military operations are often performed at night, thereby disrupting normal sleep patterns and increasing the risk of fatigue.[2] Further, the deployment itself, including both the mission and potential threats associated with it, may induce stress, which may also contribute to fatigue.

Similar to many military aviation authorities, the Royal Netherlands Air Force (RNLAF) allows for the use of caffeine as a stimulant, i.e., a medication that increases vigilance and reduces fatigue.[13] Unfortunately, aircrew members have reported that caffeine supplements are not sufficiently effective in reducing fatigue, which may be due to the high normal daily consumption of caffeine by many of these individuals.[5,15] Additionally, caffeine

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has a relatively short half-life (T1/2) of 4–6 h, making it less effective during longer periods requiring vigilance, such as during long night-time operations. Moreover, concerns have been raised about the diuretic effect of caffeine and its impact on the pilot's hydration status and the need to void in flight. However, the majority of research has shown that this diuretic effect is small and possibly even nonexistent when caffeine is taken prior to exercise.[22] As military flying is considered to be comparable to exercising, this possible drawback might be less relevant.

Flight missions during their upcoming deployment to the Middle East were expected to be particularly demanding of RNLAF pilots of F16 aircraft, due to the long duration of these missions and the frequency of nighttime flights. Thus, an operational risk management session within the RNLAF was organized to study and assess alternative pharmacological countermeasures against fatigue. The agent dextroamphetamine was deemed unsuitable because of its possible impairing side effects, its narrow therapeutic window, and its significant potential for addiction and abuse. The possibilities of using modafinil, a relatively new wakefulness-promoting stimulant, were therefore explored.

Modafinil has been approved as an agent to counter fatigue by the air forces of Singapore, the United States, India, and France.[16] At the time of its evaluation in 2015, however, no studies had been published on its safety and efficacy in actual flight operations.[6] Although the exact mechanism of action of modafinil remains undetermined, it is thought to exert a stimulating effect by altering the levels of several neurotransmitters, including serotonin, noradrenalin, dopamine, and gamma-aminobutyric acid.[1,12] Modafinil has a time to reach peak concentration (T_{max}) of 2 to 4 h and a T1/2 of 12 to 15 h, which are longer than the T_{max} (30–120 min) and T1/2 (4–6 h) of caffeine.[17,21] Evaluations of its efficacy showed that modafinil is a promising fatigue countermeasure. At the beginning of 2015, the Surgeon General of the Royal Netherlands Armed Forces authorized the use of modafinil 200 mg, but only for the fighter pilots deployed on this specific mission. Prior to usage in-flight, pilots had to complete a 24 h ground test in which modafinil was administered during a nonflying period to screen for duty-relevant side effects, with in-flight modafinil allowed only for pilots who did not experience interfering side effects. Modafinil use was completely voluntary, and its administration could not be used to expand flight time limitations.

To evaluate the efficacy of modafinil in real-life missions and to validate its acceptance as a standard fatigue countermeasure, the use of modafinil was scientifically evaluated in RNLAF pilots. The present study tested the subjective effects, both positive and negative, encountered by pilots after administration of modafinil 200 mg during ground testing and operational flights.

METHODS

Subjects

This field study was conducted during the deployment of RNLAF pilots of F16 aircraft to the Middle East. The study procedure was in accordance with the Declaration of Helsinki and was approved by the Surgeon General of the Netherlands Armed Forces.

All F16 pilots deployed during Air Task Force Middle East between 2015 and 2019 were eligible for inclusion. Pilots with contraindications for the administration of modafinil (such as pregnancy or breastfeeding; current use of a medication metabolized through CYP3A4/5, CYP2C19, or CYP2C9; and/or a history of psychiatric illness, including sleep disorders) were excluded from this study. Participants were fully informed, both verbally and in writing, about the use of modafinil and its possible side effects, as well as the aims, consequences, and constraints of the study, with all providing written consent. This informed consent was voluntary and could be retracted at any time with no consequences.

Ground tests screening for duty-relevant side effects were administered to 75 pilots, all of whom were included in the study. All were male and underwent regular medical screening every 6–12 mo as part of their flight medicals. All were considered fit to fly according to the guidelines of the European Union Aviation Safety agency (EASA) and the RNLAF Military Aviation Regulations.[8,14]

Procedure

Ground tests were administered to pilots during a 24-h nonflying period, either at their home base or in the operational theater. Pilots were instructed to report to the flight surgeon approximately 2 h after awakening. The flight surgeon took a thorough medical history from each pilot to detect any possible contraindications to modafinil. If none were present, the pilot was administered two tablets of 100 mg modafinil, which were to be orally ingested with water. Pilots remained at the medical center for 15 min to monitor for any immediate reactions to the modafinil. Afterward, pilots were able to continue their daily routine, which had to include reading and participation in sports. Driving and flying were prohibited, as was the consumption of alcohol and sleep medication. Subjects were instructed to record any effects they experienced and to immediately consult the flight surgeon if they experienced any side effects. Pilots were evaluated by the flight surgeon 8 and 24 h after modafinil administration, with the latter period including the previous night's sleep. Pilots were subsequently administered a ground test questionnaire, after which they were declared fit to fly. Pilots who experienced side effects during the ground test discussed with the flight surgeon whether those effects would interfere with their flying duties, with the flight surgeon determining whether the pilot was allowed to use modafinil operationally.

Pilots who did not experience substantial side effects during the ground test were provided with two tablets of 100 mg modafinil to use of their own accord. Because the landing phase has been identified as a risk factor for aviation accidents, the pilots were advised to take the tablets at least 2 h before the planned landing, such that modafinil would be effective during the landing phase.[9] The obligatory crew rest period after a flight mission was extended from 12 h to 16 h in pilots who took

modafinil. Before being cleared to resume flying duties, pilots had to report to the flight surgeon and complete the operational questionnaire. Pilots taking modafinil were allowed use of caffeine and sleep medication, within RNLAF's regulations. Temazepam (10 or 20 mg) or zolpidem (10 mg) were allowed as sleep medication, with respective grounding periods of 12 and 6 h. Caffeine tablets of 300 mg were available to be taken at the pilot's own discretion, but with the advice to minimize their overall caffeine consumption, so they would benefit most from its effect when needed.

Materials

Each pilot completed two complementary questionnaires, one after the ground test and one after operational use. The ground test questionnaire consisted of four sections, and the operational questionnaire consisted of five sections.

The first section of both questionnaires included questions about the characteristics of the subjects, including the names of the pilot and flight surgeon, the pilot's squadron, and the date and time of modafinil administration. This section in the operational questionnaire also included questions about time of takeoff, duration of the flight, and whether modafinil had been taken preventively or because of fatigue symptoms.

The next section of the two questionnaires consisted of questions about the period prior to modafinil administration, including important aspects of the pilot's medical history, use of caffeine and other fatigue countermeasures during the previous 24 h, and use of medications and sleeping aids. The third section of the two questionnaires consisted of questions about the effects of modafinil experienced by the pilot, including the nature and times of the first and optimal effects. Participants were asked to indicate if they had experienced any of the most common side effects of modafinil, including "Headaches," "Dizziness," "Nausea," "Sleepiness," and "Mood swings," and to indicate the intensity of these side effects as "Severe," "Moderate," "Mild," or "None." Subjects were also asked if they had experienced any other side effects. The operational questionnaire included an additional section, which asked whether the participant had taken any caffeine tablets in addition to modafinil; subjects who had taken caffeine were queried as to their reasons for doing so and the effects experienced. The final section in both questionnaires asked participants about sleep after modafinil administration, including questions about the use of sleep medication, the time and duration of the sleep period, and the quality of the sleep.

All questionnaire results were collected and stored in a database. Inferential statistical analysis was performed using SPSS statistical software (IBM Corp; Armonk, NY: 2020, version 27.0). Fisher's exact tests were used to determine differences in the incidence of beneficial and side effects after ground testing and operational use and to evaluate the relationship between beneficial and side effects after operational modafinil administration and prior use of sleep medication. Statistical significance was defined as $\alpha < 0.05$.

RESULTS

Of the 75 pilots who completed the ground tests, only 1 experienced duty-relevant side effects and therefore failed his ground test. Of the remaining 74 pilots who were authorized for modafinil use operationally, 55 (74%) actually used modafinil during operational flights. These 55 pilots completed a total of 192 questionnaires after operational use of modafinil, one after each mission. Most pilots reported taking modafinil several times operationally, with these pilots taking modafinil a median of three times (range: 1–13, IQR: 1.5–4.5).

These questionnaires were completed after real-life missions, most of which were surveillance or armed overwatch missions. **Fig. 1** illustrates the time frames of the 143 missions of which timing was reported. Most flights took off at night, including 56 (39%) during the Window of Circadian Low (WOCL)

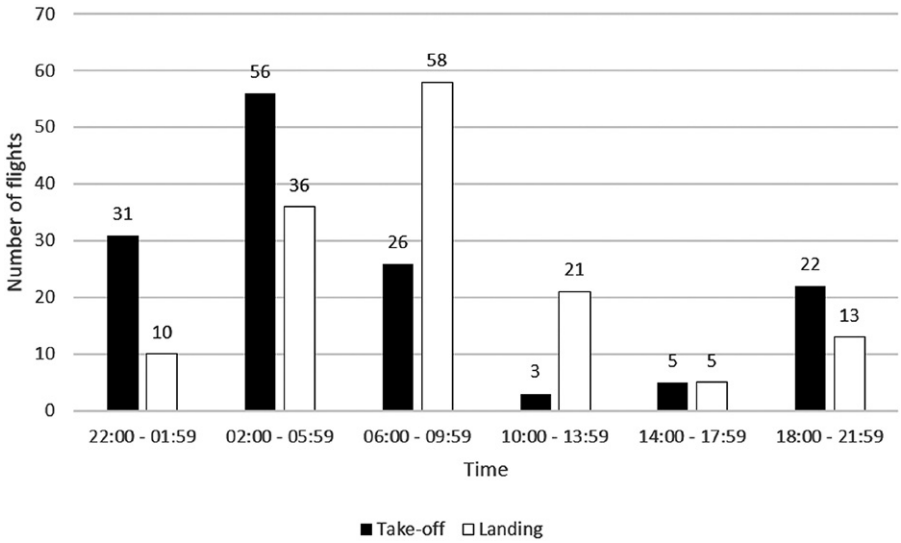

Fig. 1. Timings of takeoffs and landings of included flights ($N = 143$).

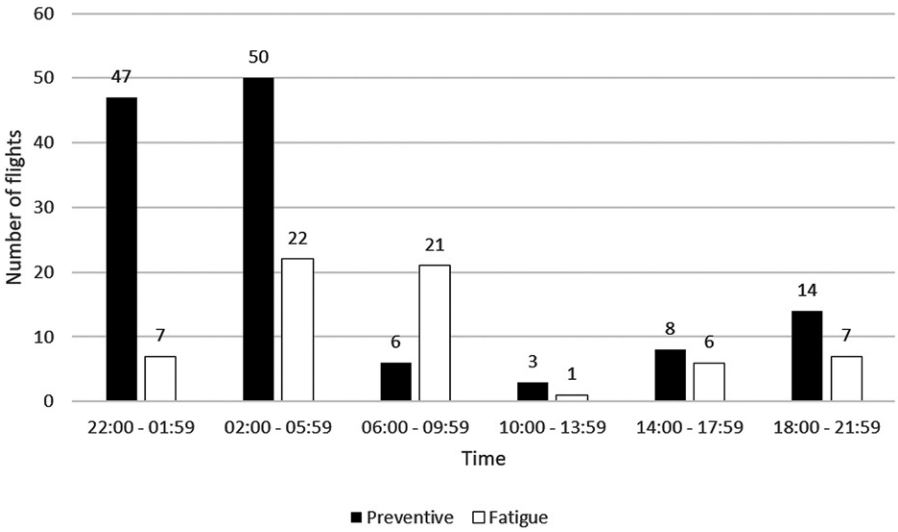

Fig. 2. Relationships between timing of modafinil administration and reasons for using modafinil (N = 192).

between 2:00 and 6:00 a.m. Most landings occurred early in the morning, including 36 (25%) during the WOCL. Median mission duration was 5.5 h (range: 2–8 h). Only 16 (8%) of the total of 192 flights lasted less than 5 h, whereas 35 (18%) were longer than 5 h.

When asked about the reason for taking modafinil during the 192 operational flights, pilots of 128 (67%) of the flights reported taking modafinil for preventive reasons, whereas pilots of the other 64 (33%) flights reported already experiencing some level of fatigue. This is consistent with the percentages of missions in which modafinil was taken before (N = 130, 68%) and during (N = 60, 31%) flights. A comparison of the reason for modafinil administration with the timing of administration showed that most instances of fatigue were late at night and early in the morning (**Fig. 2**).

Evaluation of the medical history of the pilots before the ground test identified no clinically relevant facts. Apart from some pilots who were taking vitamin pills and three pilots using omeprazole, quinapril, and finasteride, respectively, there was no medication use, including no use of sleep medications. No ailments were noted, except from some pre-existing fatigue, as several of the pilots took the ground tests after their first night in the operational theater.

No anomalies were encountered in the medical history of these pilots prior to operational modafinil use. Pilots took sleep medication prior to 89 (46%) of the missions, with 13 (7%) not responding to this question. Of those 80 pilots, 70 (79%) took zolpidem 10 mg; 13 (15%) and 6 (7%) used temazepam 10 mg and 20 mg, respectively; and 3 (3%) took both zolpidem and temazepam during the 24 h period before modafinil administration. The median wakeful time prior to operational modafinil administration was 3.5 h, with only 17 (9%) reporting having been awake for more than 10 h, with outliers being awake for 19 and 24 h.

The amount of caffeine consumed prior to modafinil administration was similar before the ground tests and operational use (**Table I**). Only 24 (13%) pilots reported moderate to high caffeine consumption during operations, with most adhering to the RNLAF advice to minimize caffeine consumption, to benefit most when needed.

The one pilot with major side effects during the ground test experienced a severe headache and moderate nausea. Of the 75 pilots, 58 (77%) experienced no side effects, and 16 (21%) experienced (very) mild side effects, which were not considered to interfere with the performance of flight duties and were often attributed to other causes, such as headaches due to dehydration on the first day in the operational theater. The recorded side effects are shown in **Table II**. Uncategorized side effects included a minor stomachache around mealtime in one pilot, a very limited period of "cold sweat" in one, and a slight increase in heart rate in three.

Only 2 of the pilots of the 192 operational flights experienced side effects, with one experiencing mild sleepiness and an undefined effect on mood, and the other experiencing slight impatience. Although the side effect rate was significantly lower after operational use than during ground testing ($P < 0.001$), there was no statistically significant relationship between the incidence of side effects and the use of sleep medication prior to operational modafinil use ($P = 1.000$).

When asked about the positive effects experienced after modafinil administration during ground testing, only 15 (20%) pilots reported no notable effects. Of the 60 (80%) pilots who experienced positive effects, 29 (48%) reported less fatigue, 24 (40%) reported increased alertness, and

Table I. Amount of Caffeine Consumption Before Modafinil Administration.

	GROUND TRIALS	IN FLIGHT
None	23%	27%
Low (< 200 mg · d^{-1})	45%	34%
Moderate (200–500 mg · d^{-1})	16%	9%
High (> 350 mg · d^{-1})	9%	4%
Not reported	7%	27%

Table II. Side Effects Encountered During Ground Tests.

	HEADACHES	DIZZINESS	NAUSEA	SLEEPINESS	MOOD	OTHER
Severe	1	0	0	0	0	0
Moderate	0	0	1	0	0	0
Mild	7	0	1	4	3	5
None	67	75	73	71	72	70
Total	75	75	75	75	75	75

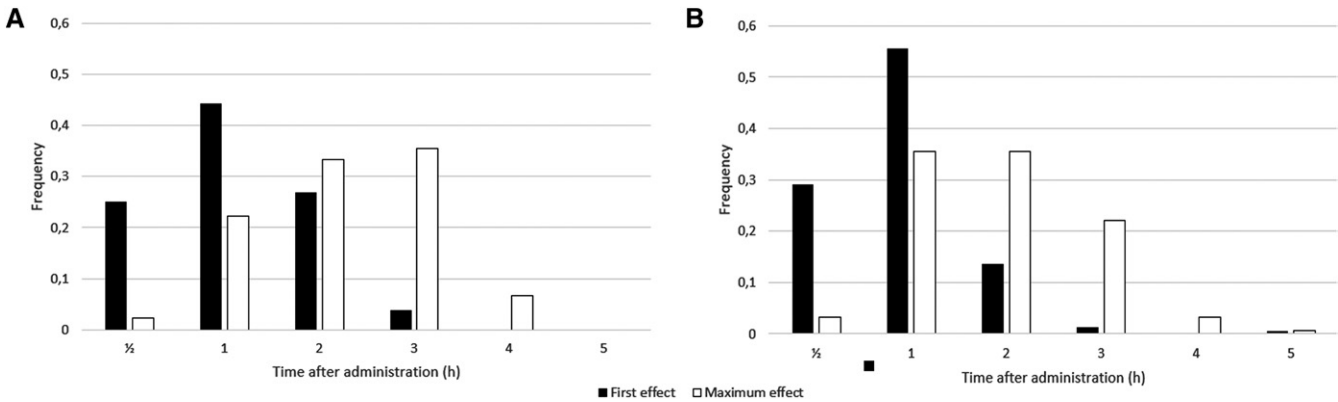

Fig. 3. Reported onset of effects after modafinil administration: A) during ground tests; and B) after operational use.

14 (23%) reported a better ability to concentrate, with 16 (27%) experiencing a combination of these effects. Beneficial side effects of modafinil intake were experienced by 183 (95%) pilots after 192 operational flights, however, only in 74 (40%) of these 183 reports were the pilots able to specify this beneficial effect. This included 45 (61%) who reported feeling less fatigued, 35 (74%) who felt more alert, and 11 (15%) who were able to concentrate better. In contrast, pilots failed to experience beneficial side effects after 9 (5%) of the 192 operational flights, a percentage significantly lower than the percentage of pilots who experienced no positive effects during ground testing ($P < 0.001$). There was no statistically significant relationship between positive effects after operational modafinil administration and the prior use of sleep medication ($P = 0.747$).

The onset times of positive effects of modafinil during the ground test and after operational use showed a similar pattern (**Fig. 3**). Most pilots experienced the initial effects of modafinil within the first 2 h after administration and the maximal effects after 2–3 h.

Operational modafinil administration was combined with 300 mg caffeine tablets during only 2 of the 192 missions. One pilot reported a good synergistic effect between modafinil and caffeine, whereas the other found that caffeine had no effects. The latter pilot had taken caffeine tablets because of their faster onset of effects.

Due to a fair number of only partially filled out ground test questionnaires, only little information was available about the timing and duration of sleep period after modafinil administration. However, as the ground tests were planned during nonflying periods, the sleep periods likely conformed to these participants' normal sleep patterns.

The median time from operational modafinil administration to the next sleep period was 12 h (range: 4.5–21.5 h, IQR: 8.5–17 h). Following the 192 operational flights, 101 (53%) of the pilots reported a sleep duration longer than 6 h, 35 (18%) reported a sleep duration of 4–6 h, and 29 (15%) reported naps of 3 h or less; sleep durations after 27 (14%) flights were not recorded.

Sleep medication was prohibited during the ground tests and was rarely used after operational administration of modafinil. Pilots took sleep medications after 13 missions, including 9 who took zolpidem (10 mg), and 3 and 1 who took temazepam (10 mg and 20 mg, respectively).

Sleep quality after modafinil administration was generally scored as good (**Fig. 4**). Sleep described as less than optimal was generally attributed to the sleeping circumstances, such as noise, heat, or light. Only in five of the ground test questionnaires and six of the operational questionnaires were sleep difficulties ascribed to modafinil use.

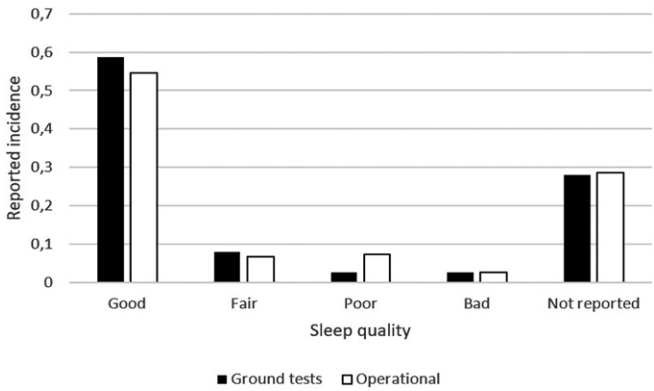

Fig. 4. Reported sleep quality after modafinil administration.

DISCUSSION

To our knowledge, this is the first study to analyze the effects of a single dose of modafinil during real-life military flight operations. The present study demonstrates that modafinil is a safe and effective fatigue countermeasure for use by pilots during military flight operations. Few side effects were reported, during both ground testing and operational use. Most pilots used modafinil several times operationally and regarded their performance as being subjectively enhanced. Although no objective parameters of performance were measured, the pilots described feeling less fatigued and more alert after taking modafinil. Most pilots reported taking modafinil operationally for preventive purposes, allowing them to maintain their performance during long flights at often-challenging times. Moreover, most pilots reported that modafinil administration did not impair the duration or quality of subsequent sleep.

During the ground tests, only 1 of the 75 pilots experienced duty-relevant side effects, i.e., severe headaches and moderate nausea. This is in agreement with previous results, including a study of pilots in the Republic of Singapore Air Force, which found that only 6 of their study group of 243 pilots failed the modafinil ground tests.[16] Headaches were found to be the most frequently reported side effect of modafinil. Because headaches may interfere with flying duties, it is strongly recommended that pilots be subjected to ground testing before operational use of modafinil is authorized.[21] Of our 75 pilots, 16 (21%) experienced (very) mild side effects, and 58 (77%) experienced no side effects. During operational use, the incidence of side effects was significantly lower, being observed after only two of these flights. This finding is consistent with previous reports, showing a very low side effect rate after modafinil use.[6] The higher incidence of reported side effects during ground testing than during operational use may be due to observation bias, as pilots were specifically instructed to report any symptoms during ground testing. Additionally, most side effects reported during ground testing were attributed to other causes.

The majority 55 (74%) of the pilots who passed the ground tests used modafinil operationally, with most using it several times. This is also seen in the study from Schallhorn, in which 57 (72%) of 79 pilots were found to have used modafinil during 386 combat sorties.[19] In that study, however, modafinil use was allowed only if pilots were experiencing symptoms of fatigue. In the present study, two-thirds of the pilots who took modafinil operationally did so for preventive reasons, whereas one-third took modafinil only after experiencing some level of fatigue.

Fatigue-related risk in the aviation industry has been reported to be substantially higher when one or more of the following criteria are met: the workday is longer than 16 h; preduty sleep duration is shorter than 6 h; and the workday coincides with the crew's usual sleep hours.[2] The average flight duration in the present study was 5.5 h, with most of the flights taking off during the evening and at night, thus fitting the third criterion. Additionally, many takeoffs and landings took place during the WOCL, i.e., between 2:00 and 6:00 a.m., defined as the period during which levels of attention are at their lowest, further increasing the risks of fatigue and lower performance.[21] Because this study did not assess the median duration of preduty sleep in pilots, conclusions could not be drawn about whether these pilots met the second criterion. Evaluation of the length of the workday in these pilots showed that the period of wakefulness prior to the mission was limited, at a median 3.5 h, although pilots on 17 (9%) missions reported having been awake for more than 10 h. When combined with a median flight duration of 5.5 h, pilots of at least 17 flights had a workday longer than 16 h, matching the first criterion. Thus, most of the missions flown by these pilots fulfilled at least one fatigue-increasing criterion, several had two, and some may have met all three. This finding emphasizes the importance of countermeasures and fatigue management strategies that can enable military pilots to perform their duties safely during these often-challenging situations.

Although no objective parameters of performance were recorded, most of the pilots reported feeling less fatigued, more alert, and/or more able to concentrate after taking modafinil. This finding is in agreement with previous studies in which both the objective and subjective parameters of performance were evaluated.[3,7] The frequency during which pilots reported no notable positive effects of modafinil during ground testing (20%) and operational use (5%) differed significantly. This was understandable, as the test settings differed markedly; ground testing was performed during the daytime and usually after a normal night's sleep, whereas operational testing was performed following in-flight use, often during fatiguing circumstances. The positive effects of modafinil reported by the majority of pilots during ground testing may have been due to sleep deficits after their first night in the operational theater. Alternatively, these effects may be an indication of the cognition-enhancing properties of modafinil under normal sleep conditions.[1] Most pilots reported that modafinil had positive effects within the first 2 h after administration, and most experienced optimum benefits after 2–3 h, in agreement with its T_{max} of 2–4 h.[17]

Sleep after modafinil use was generally scored as good, with few pilots attributing sleep difficulties to modafinil administration. The absence of effect on recovery sleep may be due to the median time between modafinil administration and the subsequent sleep period of 12 h, similar to the T1/2 of modafinil of 12–15 h.[17] However, the time between modafinil administration and recovery sleep was frequently less than 12 h, providing further evidence that recovery sleep is not impaired by modafinil administration.[11,20]

Despite this study being the first to document the experiences of pilots with modafinil administration during actual flight operations, it had several limitations. The most important was likely the use of subjective parameters and the lack of objective parameters. Although objective parameters would likely substantiate these, the subjective experiences of pilots may be equally important for flight safety. For example, less experienced pilots were found to be more likely to use modafinil, possibly because it gave them some sense of security, allowing them to safely perform challenging missions.[19] Second, some of the questionnaires were only partially filled out, resulting in missing information. The percentage of missing data varies between

0% and 40%, with most data missing from the sleeping sections on the ground test questionnaires. Although more data would be beneficial to this study, there were no indications of reporting bias. Finally, it would have been advantageous to determine the baseline susceptibility of these pilots to sleep loss, as the benefits of modafinil are more pronounced in subjects who are more susceptible to the effects of sleep loss.[4]

In conclusion, the present study showed that modafinil is a suitable pharmacological countermeasure to minimize the effects of fatigue during real-life fighter operations. The reported flight planning, with its subsequent risk of fatigue, underlines the importance of providing pilots with adequate and scientifically proven fatigue management strategies, enabling them to perform their duties safely. Ground testing is strongly recommended to identify pilots who might experience duty-related side effects of modafinil. The positive effects of modafinil were reported to occur as early as 30 to 60 min after administration, with optimal benefits after 2 to 3 h, a finding congruent with the T_{max} of modafinil. Therefore, to maximize the benefits of modafinil, it should be taken at least 3 h before its effect is needed. Subsequent sleep was not affected after modafinil administration, not even within the first 12 h. Evaluation of objective parameters after operational administration of modafinil may provide pilots with better guidance about the use of this fatigue countermeasure.

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