A State-of-the-Art Review on the Use of Modafinil as A Performance-enhancing Drug in the Context of Military Operationality

Martine Van Puyvelde, PhD[*,†,‡]; *Jeroen Van Cutsem, PhD*[*,§]; *Emilie Lacroix, PhD*[*]; *Med Maj Nathalie Pattyn, PhD*[*,§]

ABSTRACT

Introduction:

Modafinil is an eugeroic drug that has been examined to maintain or recover wakefulness, alertness, and cognitive performance when sleep deprived. In a nonmilitary context, the use of modafinil as a nootropic or smart drug, i.e., to improve cognitive performance without being sleep deprived, increases. Although cognitive performance is receiving more explicit attention in a military context, research into the impact of modafinil as a smart drug in function of operationality is lacking. Therefore, the current review aimed at presenting a current state-of-the-art and research agenda on modafinil as a smart drug. Beside the question whether modafinil has an effect or not on cognitive performance, we examined four research questions based on the knowledge on modafinil in sleep-deprived subjects: (1) Is there a difference between the effect of modafinil as a smart drug when administered in repeated doses versus one single dose?; (2) Is the effect of modafinil as a smart drug dose-dependent?; (3) Are there individual-related and/or task-related impact factors?; and (4) What are the reported mental and/or somatic side effects of modafinil as a smart drug?

Method:

We conducted a systematic search of the literature in the databases PubMed, Web of Science, and Scopus, using the search terms "Modafinil" and "Cognitive enhance*" in combination with specific terms related to the research questions. The inclusion criteria were studies on healthy human subjects with quantifiable cognitive outcome based on cognitive tasks.

Results:

We found no literature on the impact of a repeated intake of modafinil as a smart drug, although, in users, intake occurs on a regular basis. Moreover, although modafinil was initially said to comprise no risk for abuse, there are now indications that modafinil works on the same neurobiological mechanisms as other addictive stimulants. There is also no thorough research into a potential risk for overconfidence, whereas this risk was identified in sleep-deprived subjects. Furthermore, eventual enhancing effects were beneficial only in persons with an initial lower performance level and/or performing more difficult tasks and modafinil has an adverse effect when used under time pressure and may negatively impact physical performance. Finally, time-on-task may interact with the dose taken.

Discussion:

The use of modafinil as a smart drug should be examined in function of different military profiles considering their individual performance level and the task characteristics in terms of cognitive demands, physical demands, and sleep availability. It is not yet clear to what extent an improvement in one component (e.g., cognitive performance) may negatively affect another component (e.g., physical performance). Moreover, potential risks for abuse and overconfidence in both regular and occasional intake should be thoroughly investigated to depict the trade-off between user benefits and unwanted side effects. We identified that there is a current risk to the field, as this trade-off has been deemed acceptable for sleep-deprived subjects (considering the risk of sleep deprivation to performance) but this reasoning cannot and should not be readily transposed to non-sleep-deprived individuals. We thus conclude against the use of modafinil as a cognitive enhancer in military contexts that do not involve sleep deprivation.

INTRODUCTION

Modafinil or 2-([diphenylmethyl]sulfinyl)acetamide, commercially known as Provigil, is an eugeroic (i.e., wakefulness-promoting) drug that was approved in 1998 by the Food and Drug Administration and the European Medicines Agency for the treatment of narcolepsy, excessive sleepiness during the day due to obstructive sleep apnea, and shift work sleep disorder (e.g.,[1,2]). Eugeroic drugs mimic the effects of d-amphetamines by producing high-quality wakefulness, while said to lack the typical unwanted side effects associated with amphetamines (e.g.,[3–5]). As a result, modafinil has quickly

[*]VIPER Research Unit, Department of LIFE, Royal Military Academy, Brussels 1000, Belgium

[†]Brain, Body and Cognition, Department of Psychology, Vrije Universiteit Brussel, Brussels 1050, Belgium

[‡]Clinical & Lifespan Psychology, Department of Psychology and Educational Sciences, Vrije Universiteit Brussel, Brussels 1050, Belgium

[§]MFYS-BLITS, Department of Human Physiology, Vrije Universiteit Brussel, Brussels 1050, Belgium

doi:https://doi.org/10.1093/milmed/usab398

© The Association of Military Surgeons of the United States 2021. All rights reserved. For permissions, please e-mail: journals.permissions@oup.com.

Downloaded from https://academic.oup.com/milmed/article/187/1-2/52/6386431 by guest on 02 August 2022

been used in a nonmedical context for other reasons than the previously cited sleep disorders with an estimated 90% off-label use in 2004[6]. In the meantime, these tendencies even increased.[7–9] Based on the Health Social Care Information Centre (2015), Brunyé et al. reported that prescription rates of stimulants in general in the UK rose from about 220,000 in 1998 to 1,160,000 in 2014 (on a population of 54 million people).[7] The second large increase considered modafinil with a proportional raise of 212%.[7] Modafinil has found its way to a variety of users such as personnel exposed to sleep deprivation (e.g., military personnel, nurses, and medical doctors, being on-call jobs)[3,10] or persons functioning in a highly cognitive competitive context (e.g., students, academics, or corporate executives).[11–13] In the former, modafinil is used to counteract the impact of sleep deprivation on wakefulness and cognition. In the latter, it is used as a nootropic or smart drug, i.e., a drug that aims at improving cognitive performance in healthy subjects in the absence of any medical indication.[14]

The first publicly available documented use of modafinil in a military context occurred before the approvement of the European Medicines Agency, to counteract sleep deprivation and fatigue during the Gulf War in 1991.[1] Indeed, sleep loss is recognized to negatively impact not only attention and[15,16] executive functioning[15–17] but also decision-making[18] and emotion regulation[19–21] (see Alhola and Polo-Kantola for a review[22]). However, military reports on modafinil applications remain rather rare. For instance, except a recent study by Ooi et al.[23] no study on modafinil in a military context has been published for the last 10 years certainly not outside a context of sleep deprivation.[24] Nevertheless, besides sleep deprivation[25] and an overall increased operational tempo,[26,27] mental fatigue among military personnel is becoming a pressing aspect of sustained operationality as well.[28–30] Moreover, it is now widely accepted that mental fatigue can decrease performance on sustained physical tasks.[31,32] Therefore, it is not surprising that in military personnel the interest in modafinil as a smart drug is also present.[33] This may, however, raise questions regarding efficacy, safety, and ethics of such use.[34]

Hence, knowing that there is a 10-year gap in studies on modafinil in function of military operational performance, that cognitive demands in military personnel are high, and that the interest in modafinil as a smart drug is increasing, we reviewed the literature on the use of modafinil as a smart drug. On this backdrop, we thus aimed at presenting a state-of-the-art and a future research agenda in function of military operationality. To structure our research questions, we used the existing knowledge on modafinil in sleep-deprived contexts and the relevant safety issues, in both military and civilian investigations.

Investigations in Sleep-Deprived Populations

As stated by Babkoff and Krueger, studies in a military context on the impact of modafinil in sleep-deprived subjects can be divided into two categories, that is, either studies in a preventive (maintenance) paradigm, designed to maintain behavior over longer periods of time; or studies in a recovery paradigm, designed to offset the effects of sleep deprivation and/or sustained performance.[35] In maintenance studies, the participants receive several smaller doses of 100-200 mg every few hours to test performance maintenance throughout a sleep deprivation period. In recovery paradigms, the participants receive a single larger dose (e.g., 300-400 mg) after a period of sleep deprivation to measure restoration capacity in comparison with initial baseline levels.[35]

In a military sleep deprivation context, we found three experimental maintenance flight simulation studies. Caldwell et al. reported attenuated flight performance decrements in 10 Air Force F-117 pilots after three doses of 100 mg modafinil intake over 37 h of sleep deprivation, whereas placebo led to a decline of 60-100%.[36] Similarly, three doses of 100 mg modafinil at 4 h intervals over 40 h of sleep deprivation enabled the maintenance of alertness, feelings of well-being, cognitive function, judgment, risk perception, and situation awareness, compared to placebo.[37] However, the objectively measured improvement after the first dose was not subjectively experienced by the participants, which may mean a risk for escalation and abuse. Another study by Caldwell et al. showed that three 200 mg doses at 4-h intervals over 40 h of sleep deprivation improved performance, alertness, and mood compared to placebo; however, side-effects were reported (i.e., vertigo, nausea, and dizziness).[3] In a nonmilitary population, however, a meta-analysis by Repantis et al. concluded that repeated administration is successful to maintain wakefulness up to 4 days of sleep deprivation, but that there is no reliable support for a beneficial impact on attention or executive functioning.[38]

There might be several reasons for the conclusion of Repantis et al.,[38] Firstly, modafinil's efficiency may be dose dependent. For instance, Baranski et al. showed that a repeated intake of three doses 100 mg every 8 h over 24 h of sleep deprivation maintained cognitive performance near to baseline. However, this effect decreased substantially with 50 mg; and the 16.7 mg dose did not show significant differences when compared to placebo.[39] Increasing doses to 300 mg and 400 mg appears to be pointless and only increases the risk of side effects such as nervosas,[40] negative mood,[41] and—important in military operations—overconfidence.[42,43] Secondly, dose dependency would interact with the targeted variable of performance. For instance, working memory, executive functioning, and attention showed less improvement with 100 mg than with 150 mg[18,36,39,44]; with an exception in Stivalet et al., who found a positive effect of recurrent 100-mg doses on attention.[45] From 200 mg onwards, the impact of modafinil on cognitive performance in sleep-deprived subjects is more convincing and congruent over different cognition variables. These studies all showed a beneficial effect of modafinil on executive functioning,[5,36,43,46–50]

Downloaded from https://academic.oup.com/milmed/article/187/1-2/52/6386431 by guest on 02 August 2022

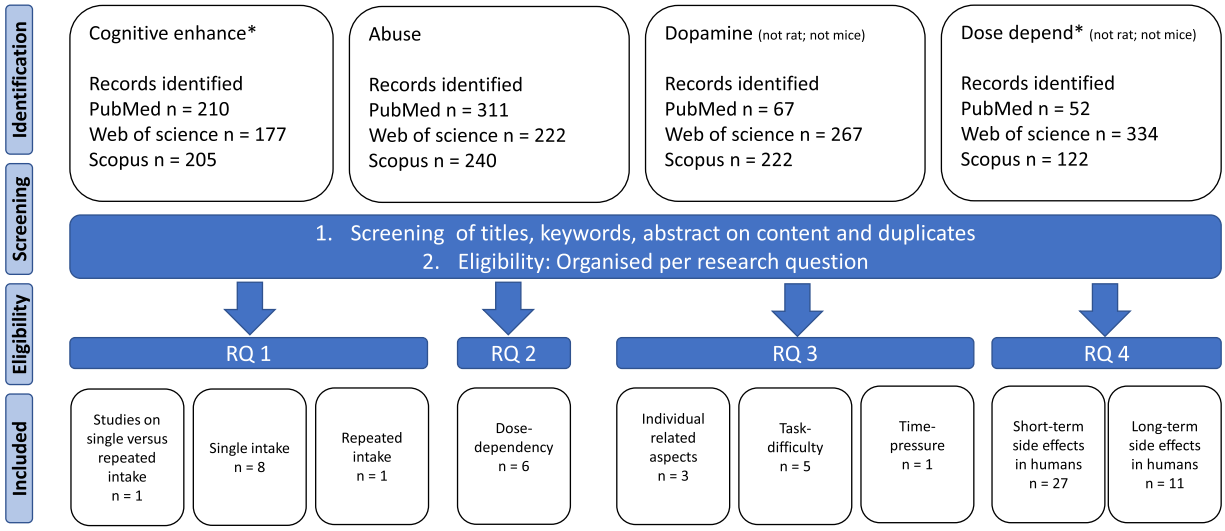

FIGURE 1. Overview of the identified, screened, and selected articles based on the "Preferred Reporting Items for Systematic Reviews and Meta-Analyses" (PRISMA) method. In the eligibility process, we performed an extra screening in function of the four assumed research questions.

memory,[39,45,47,51] and attention.[18,39,45,49–52] The only exception was the study by Li et al., who found mixed results with 200 mg.[53] However, in this study, the interval of administration was more than 12 h, whereas it was maximum 8 h in other studies.[53]

Hence, based on the literature in sleep-deprived subjects, we can conclude that a single-dose modafinil intake enhances recovery after sleep loss, but that the impact of a repeated modafinil intake may be dependent on the interaction between the administered dose and the targeted performance variable. Moreover, somatic side effects may occur in higher doses and overconfidence was reported in initial studies. Based on these results, and taking into account the importance of individually tailored approaches when researching fatigue-related topics in extreme operational contexts,[54,55] we selected the following four research questions to investigate the current state of the art: (1) Is there a difference between the effect of modafinil as a smart drug when administered in repeated doses versus one single dose? (2) Is the effect of modafinil as a smart drug dose-dependent? (3) Are there individual-related and/or task-related impact factors? (4) What are the reported mental and/or somatic side-effects of modafinil as a smart drug?

METHODS

We performed a systematic search of the literature in the databases PubMed, Web of Science, and Scopus, using the search terms "Modafinil" and "Cognitive enhance*", in combination with "dose depend*", "abuse," and "side-effects" (based on "Preferred Reporting Items for Systematic Reviews and Meta-Analyses", PRISMA[56]). Since "individual factors" "personality" and "task difficulty" gave no new hits, we screened the content of the selected articles to find an answer on research question 3 (see Fig. 1). We included only studies on healthy human subjects with quantitative cognitive outcomes. For those studies that tested other cognitive enhancers than modafinil as well, only the results for modafinil were reported. We found only one publication on modafinil use as a nootropic within a military population, despite the widespread use of the molecule as an accepted and validated strategy to counteract sleep deprivation. Therefore, all literature matching the inclusion criteria was considered relevant, as we could not target solely military populations.

RESULTS

Research Question 1: Is There a Difference Between the Effect of Modafinil as a Smart Drug When Administered in Repeated Doses Versus One Single Dose.

Only two studies reported a repeated intake.[57,58] However, the first study focused on the impact on mood (3×400 mg) and not on cognitive performance.[57] The second study (2×200 mg) presented the results as a single intake[58] and will be discussed under the paragraph "time-pressure." The studies on the impact of modafinil in single dose (200 mg) showed contradictive findings.

Attention and Vigilance

Ikeda et al. found improved accuracy and reaction times in attention tasks[59] and Lees et al. reported a small improvement in sustained attention.[60] Other single-dose studies[61,62] did not evidence an effect.

Executive Functioning

Fernández et al. reported less mistakes on the Stroop test after 200 mg intake[63] and Rattray et al. reported better reaction times with 400 mg when taking into account time on task.[64] However, Rattray et al. observed a negative impact on physical performance in physically active participants.[64] Schmidt et al. found a positive impact of 600 mg on inhibition response

Downloaded from https://academic.oup.com/milmed/article/187/1-2/52/6386431 by guest on 02 August 2022

tasks.[65] Furthermore, no other single-dose study evidenced improved executive functioning.[59,60,62,66]

Memory

No effects were found for short-term, visual, or verbal memory.[38,59,60,63,65]

Conclusion

We found no clear answer to the first research question. No repeated intake studies are available, and the results of single-dose intakes on cognitive performance are unclear and not comparable with repeated intake. Moreover, a negative impact of modafinil on physical performance was reported (see Table I).

Research Question 2: Is the Effect of Modafinil as a Smart Drug Dose-Dependent?

Attention and Vigilance

Cope et al. found no difference between 200 and 400 mg.[67] Both doses increased attention on a continuous performance task without providing other cognitive advantages. Dose dependency was however observed by Makris et al. when taking into account the posttreatment interval.[68] The authors examined the course of the impact of a single dose on attention and memory 30 min after drug administration and at hourly intervals for 5 hours. The used doses were either 1.75 mg/kg (low), 3.5 mg/kg (medium), or 7 mg/kg (high) (equivalent to 130, 262, and 525 mg). The results showed dose by posttreatment interval interaction effects for sustained attention. Medium and higher doses were related with better performances over time compared to lower ones.[68]

Executive Functioning

Turner et al. found a dose–response effect in an inhibition stop-signal paradigm but not in other variables.[69] They concluded that modafinil is a reducer of impulsive response tendencies and that only a response inhibition effect might be dose-dependent. The abovementioned improved response inhibition with 600 mg in Schmidt et al. might support this hypothesis.[65] However, no further dose dependency benefits were found in other studies.[67,70–73] On the contrary, some authors reported participants made more errors with higher doses.[73]

Memory

Based on a range of studies, Randall and colleagues concluded against dose dependency when using modafinil as a smart drug.[70,71,73] No significant cognitive improvements were found (100/200 mg) in students,[70] healthy middle-aged volunteers,[73] or young volunteers.[71] Moreover, in the event of a small benefit, the participants showed slower response latencies,[72] certainly with 200 mg intake.[66] Makris et al. found an improvement on working memory in the three modafinil doses but no dose dependency.[68]

Conclusion

No study showed a clear dose–response effect for modafinil. Moreover, in cases of improved alertness, accuracy was not guaranteed, and more errors occurred, suggesting a speed-accuracy trade-off effect. However, it may be that time-on-task interacts with dose administration. The fact that the effects in Makris et al. occurred in function of the duration of the posttreatment intervals may be the expression of a vigilance effect, i.e., to sustain attention and/or performance over time. Hence, this may raise the question whether fatigue related to time-on-task may play a moderating role. Besides, modafinil as a smart drug may be beneficial in inhibition tasks (see Table II).

Research Question 3: Are there individual-related and/or task-related impact factors?

Attention and Vigilance

Task difficulty

Marchant et al. reported an improvement of rapid attention switching only in the most difficult switching tasks.[74] However, other studies did not evidence this improvement.[75,76]

Executive Functioning and Memory

Task difficulty

An impact of 200 mg on executive functioning such as planning and decision-making was present, but only for the most difficult tasks in Müller et al.[75] Winder-Rhodes et al. found a beneficial effect of 300 mg of modafinil on spatial planning accuracy and working memory, again only at the most difficult task level.[77] A study by Esposito et al.[78] showed that a beneficial impact of 100 mg modafinil on the Raven's Advanced Progressive Matrices II was only significant for the medium difficulty level. However, when inspecting raw data, a ceiling effect might have been present. The baseline levels were very low, which may indicate that the medium level was the limit of the participants' capacities in IQ and thus, possibly, the highest level that still allowed for improvement. Finally, both Makris et al. and Müller et al. found a positive impact in delayed and possibly more difficult conditions of test designs.[68,76]

Time pressure

In Franke et al., modafinil significantly decreased the number of victorious games by chess players when playing under time pressure, due to an increased response latency. However, an enhancement occurred when no time pressure was present.[58]

Individual ability and personality aspects

Randall et al. conducted a meta-analysis on their former studies, dividing their participants in a low- and high-performing IQ group.[71] The results showed that previously reported improvements only appeared in the lower IQ group. A small

Downloaded from https://academic.oup.com/milmed/article/187/1-2/52/6386431 by guest on 02 August 2022

TABLE I. Summary of Studies Assessing the Use of Modafinil as a Smart Drug for Cognitive Enhancement in a Single Dose Vs. Repeated Intake

Study	Design and sample size	Modafinil intake protocol	Evaluated cognitive domain	Results
Single dose				
Mohamed et al. 2014[66]	Parallel 31 M 33 F ~25 years (19-36)	200 mg	Hayling Sentence Completion Test.	No impact of modafinil compared to placebo.
Fernandez et al. 2015[63]	Crossover 52 M 76 F ~21 years	200 mg	Battery of cognitive tests: • Stroop Test: selective attention • Forward and Backward Digit Span (short-term memory) • Biber Cognitive Estimation Test	Impact on Stroop: improvement in congruent conditions and decreased latency in incongruent conditions. No advantage of Modafinil over placebo for short-term memory or other executive function.
Bellebaum et al. 2016[61]	Parallel 40 M	200 mg	Alertness task: tonic and phasic alertness. Feedback learning task: tests the choice of previously rewarded or punished (approach/avoidance) behavior.	No effect of Modafinil on alertness.
Ikeda et al. 2017[59]	Crossover 14 M 9 F ~29.5 years	200 mg	Attention network test task: measures three distinct attentional networks, i.e., alerting, orienting, and executive attention.	Impact on attention tasks: Significantly faster reaction times in flanker tasks in modafinil vs. placebo. Higher accuracy in modafinil vs. placebo. Modafinil decreased the orienting effect. No difference in executive control effect between modafinil and placebo.
Lees et al. 2017[60]	Parallel 15 M 13 F (healthy volunteers) ~25 years	200 mg	MATRICS Consensus Cognitive Battery. CANTAB Schizophrenia Battery.	No clear impact: only improvement on rapid visual processing task (sustained attention).
Schmidt et al. 2017[65]	Crossover 21 M 24-39 years	600 mg	Go/no-go functional magnetic resonance imaging paradigm: measures; execution/inhibition of a motor response after a visual stimulus.	High-dose impact on inhibition task: modafinil significantly improved inhibition performance.
Rattray et al. 2019[64]	Crossover 13 M ~23.5 years	400 mg	AX-Continuous Performance Task (AX-CPT): cognitive control task examining context processing and goal maintenance. Incongruent Stroop 90 min. Brunel mood scale. Situational motivation scale. National Aeronautics and Space Administration Task Load Index (NASA-TLX) fatigue scale. Physical performance electronically braked cycle ergometer.	Improved incongruent Stroop with time on task. (Remark: negative impact on physical performance).
Repantis et al. 2021[62]	Three-arms study: placebo and one of three stimulants (caffeine, methylphenidate, and modafinil) 84 M ~27 years (21-36)	200 mg	Battery of cognitive tests: • Declarative memory • Logical reasoning • Working memory • Speed of information processing • Implicit and explicit verbal memory Creativity and divergent thinking. Sustained attention: Psychomotor Vigilance Test (PVT).	No effective impact of modafinil on cognitive tasks.

(continued)

Downloaded from https://academic.oup.com/milmed/article/187/1-2/52/6386431 by guest on 02 August 2022

TABLE I. (Continued)

Study	Design and sample size	Modafinil intake protocol	Evaluated cognitive domain	Results
Repeated intake				
Franke et al. 2017[58]	Crossover 39 M ~37 years	2 × 200 mg but not analyzed as repeated intake	See Table III "time pressure".	

Abbreviations: M = male; F = female.

TABLE II. Summary of Studies Assessing the Usage of Modafinil as a Smart Drug for Cognitive Enhancement to Test Dose Dependency

Study	Design and sample size	Modafinil intake protocol	Evaluated cognitive domain	Results
Turner et al. 2003[69]	Parallel 60 M ~25 years	Placebo vs. 100 mg vs. 200 mg Single oral dose	Battery of cognitive tests: • Visual memory • Working memory and planning • Executive functioning: stop signal Vigilance.	No clear dose dependency: except in the stop-signal paradigm (i.e., better performance with 200-mg dose).
Randall et al. 2003[70]	Parallel 19 M 11 F 19-23 years	Placebo vs. 100 mg vs. 200 mg Single oral dose	Battery of cognitive tests: • Visual memory • Mental flexibility • Spatial planning • Vigilance/sustained attention • Verbal memory Test response inhibition.	No dose dependency and no effect of modafinil on any of the cognitive tests.
Randall et al. 2004[73]	Parallel 20 M 25 F 50-67 years	Placebo vs. 100 mg vs. 200 mg Single oral dose	Battery of cognitive tests: • Visual memory • Mental flexibility • Spatial planning • Vigilance/sustained attention • Verbal memory Test response inhibition.	No clear dose dependency and no effect of modafinil on most of the cognitive tests. 200 mg group was faster in the color naming of dots and showed better constructional ability. They made more errors in the shift task.
Randall et al. 2005a[71]	Parallel 29 M 31 F 19-22 years	Placebo vs. 100 mg vs. 200 mg Single oral dose	Battery of cognitive tests: • Visual memory • Mental flexibility • Spatial planning • Vigilance/sustained attention • Verbal memory Test response inhibition.	No clear dose dependency and no effect of modafinil in some tests. 200 mg group performed better in simple color naming of dots and in the vigilance task. 100 mg group performed better in digit span test.
Makris et al. 2007[68]	Cross-over 5 M 6 F 21-35 years	Placebo vs. modafinil (1.75 mg/kg vs. 3.50 mg/kg vs. 7.00 mg/kg) vs. d-amphetamine (0.035 mg/kg vs. 0.070 mg/kg vs. 0.140 mg/kg) Single oral dose	Battery of cognitive tests: • Working memory • Psychomotor activity • Learning efficiency Temporal discrimination.	Subjective indications of dose dependency: Visual Analogue Scale (VAS) scores of stimulations were increased in a dose-related manner. Objectively: increased correct responses working memory; dose × time effect for psychomotor activity and learning efficiency.
Cope et al. 2017[67]	Parallel 26 M 36 F	Placebo vs. 200 mg vs. 400 mg modafinil Single oral dose	Five-choice continuous performance task Wisconsin Card Sort Task.	No dose dependency.

Abbreviations: M = male; F = female.

Downloaded from https://academic.oup.com/milmed/article/187/1-2/52/6386431 by guest on 02 August 2022

TABLE III. Summary of Studies Assessing the Usage of Modafinil as a Smart Drug for Cognitive Enhancement regarding Task-related and Individual-related Factors

Study	Design and sample size	Modafinil intake protocol	Evaluated cognitive domain	Results
Task difficulty				
Müller et al. 2004[76]	Crossover 10 M 6 F 20-29 years	Placebo vs. 200 mg Single oral dose	Working memory. Maintenance processes. Attention. Different difficulty levels were included.	Task difficulty appears to be a moderator: Modafinil did not affect attention. Improved maintenance processes and challenging working memory.
Marchant et al. 2009[74]	Parallel 7 M 17 F ∼22 years	Placebo vs. 200 mg Single oral dose	Task requiring rapid switching of attention vs. task requiring rapid switching of attention + working memory vs. task requiring prospective memory.	Type of attentional shifting appears to be a moderator: Modafinil improved accuracy in both types of cognitive tasks, but only in the most challenging trials. No effect on prospective memory.
Winder-Rhodes et al. 2010[77]	Crossover 12 M 18-39 years	Placebo vs. 300 mg modafinil vs. 3 mg prazosin vs. 300 mg modafinil + 3 mg prazosin Single oral dose	Battery of cognitive tests different difficulties: • Working memory • Pattern recognition memory • Rapid visual information processing • Response inhibition	Task difficulty appears to be a moderator: Modafinil improved planning and working memory at the most difficult levels.
Müller et al. 2013[75]	Parallel 31 M 33 F ∼25 years	Placebo vs. 200 mg Single oral dose	Battery of cognitive tests—different difficulties • Working memory • Planning and decision making • Visuospatial declarative memory Nonverbal creative problem solving.	Task difficulty appears to be a moderator: Modafinil improved spatial working memory, planning, and decision-making at the most difficult levels.
Esposito et al. (2013)[78]	Parallel 26 M 25-35 years	Placebo vs. 100 mg Single oral dose	Fluid intelligence and abstract reasoning with different levels of difficulty.	Task difficulty appears to be a moderator: Modafinil improved fluid intelligence in those subjects that were low performing at baseline and only in items of a medium difficulty level.
Time pressure				
Franke et al. 2017[58]	Crossover 40 M ∼37 years	2 × 200 mg but not analyzed as repeated intake	Chess match against Fritz chess computer. Sustained attention (PVT). Battery of cognitive tests: • Visual attention, psychomotor speed • Working memory • Selective attention, cognitive flexibility and processing speed • Set-shifting Risk-taking behavior. Problem-solving capacity.	Significant decrease of winning chess games/events under time pressure due to a response latency. When not under time pressure, there was an enhancement. No further improvements in other cognitive domains.

(continued)

Downloaded from https://academic.oup.com/milmed/article/187/1-2/52/6386431 by guest on 02 August 2022

TABLE III. (Continued)

Study	Design and sample size	Modafinil intake protocol	Evaluated cognitive domain	Results
Individual-related factors				
Randall et al. 2005b[72]	Parallel 47 M 42 F 19-23 years Low-IQ group (≤110) vs. high-IQ group (≥111) Based on NARTII	Placebo vs. 100 mg vs. 200 mg Single oral dose	Battery of cognitive tests: • Attention • Mental flexibility • Vigilance • Working memory • Verbal memory • Spatial planning Response inhibition.	IQ level appears to be a moderator: Modafinil-related improvements were greater in the low-IQ group. Modafinil improved vigilance and response time, but the overall pattern of cognitive improvement was difficult to classify.
Finke et al. 2010[79]	Crossover 9 M 9 F 20-35 years Low performers vs. high performers Based on baseline performance	Placebo vs. 400 mg modafinil vs. 40 mg methylphenidate Single oral dose	• Visual perceptual processing speed • Visual short-term memory storage capacity	Baseline performance appears to be a moderator: Modafinil both enhanced perceptual processing speed and short-term memory storage capacity in low performers.

Abbreviations: M = male; F = female; PVT = Psychomotor vigilance test; NART = National Adult Reading Test-II.

benefit in the high IQ group was only present when taking 200 mg and not with 100 mg. Hence, low IQ profiles benefited already from 100 mg and higher IQ profiles only from 200 mg onwards, but this benefit was rather small. A study by Finke et al. supported these results.[79] They showed that 400-mg modafinil enhanced perceptual processing speed and short-term memory in low-performing participants only. Finally, Mohamed et al. showed that only low-scoring persons on convergent thinking benefited afterward from 200-mg modafinil.[80] We did not encounter any study on personality aspects as a potential moderator.

Conclusion

Individual ability, task difficulty, and time pressure appear to play a role in mitigating the effect of modafinil. Persons with an initial lower test performance benefit more from modafinil than those with higher levels and the latter show dose-dependent results. Higher task difficulty was related with a more consistent positive impact of modafinil. However, modafinil may have detrimental outcomes for tasks under time pressure (see Table III).

Research Question 4: What are the Reported Mental and/or Somatic Side Effects of Modafinil as a Smart Drug?

Short-term Effects

Baranski et al.[42] reported a trend toward mild overconfidence in task-level estimates in non-sleep-deprived persons using modafinil and thus advised further investigation with a higher number of participants. Franke et al.[58] evidenced a significant decreased "fear of failure" scale. A series of studies reported somatic anxiety after 100 mg[70], 400 mg,[57] and 600 mg,[81] sometimes documented by increased amygdala activity.[81] Hence, anxiety occurs—certainly in higher doses[82]—and the negative effects of modafinil may outweigh the cognitive benefit.[70]

On a somatic level, the largest part of the reviewed studies did not investigate side effects,[42,68–74,77,79,80,83,84] except for Ooi et al.,[23] who examined side effects of 100 mg in military aviators. Ooi et al. followed 243 aircrew members (Republic of Singapore Air Force) for 7 years from 2011 to 2018 but only reported short-term effects.[23] In their study, only 2.5% of the exposed population reported side effects during ground testing (headache, anxiety, diarrhea, and insomnia), which was considered a counterindication for operational use. In other studies, side effects were reported to be absent[66,76,78] (100/200 mg) or minimal.[82] Two studies[58,75] reported headaches, three studies mentioned problems falling asleep,[58,62,64] and an investigation in students described flushes, headaches, thirstiness, reduced appetite, and sleep problems as reported complaints.[85] In Repantis et al., the impact of 200 mg on heart rate and blood pressure remained within normal ranges.[62] However, in Taneja et al., the intake of three doses of 400 mg over 3 days induced a heightened sympathetic outflow, characterized by increased heart rate (+9.2 bpm), systolic (+7.3 mm Hg) and diastolic (+5.3 mm Hg) blood pressure, and excretion of urinary catecholamines (increase of 33% norepinephrine and 81% epinephrine).[86] The authors concluded that modafinil substantially altered autonomic cardiovascular regulation.

Long-term Effects

A psychophysiological long-term effect that should be considered is the risk for abuse. A drug has a potential for abuse when it acts on the dopaminergic system, inducing dopamine release in the mesoaccumbens.[87] Due to dopaminergic mesoaccumbens, plasticity, sensitization, effects of

Downloaded from https://academic.oup.com/milmed/article/187/1-2/52/6386431 by guest on 02 August 2022

reinforcement incentive salience, and craving are experienced by the user.[88,89] Although sensitization is a long-term process, in laboratories, it can be induced and examined by short-term protocols as well.[90] Initially, modafinil was considered to have low abuse potential, suggesting that it was acting on non-dopaminergic systems[91,92] or by a different interaction[93] than other performance-enhancing drugs. However, recent indications point to an activation of dopamine networks too.[68,94–96] Wuo-Silva et al.[95,96] showed that modafinil impacted a rapid-onset sensitization in mice within a few hours from drug administration. A fast neuroplastic change was evidenced in these studies, which may pave the way for later drug abuse.[95,96] Nevertheless, in mice, some studies[97,98] argued against a dopamine-dependent mechanism. In healthy humans, based on a positron emission tomography investigation, dopaminergic affinity of modafinil was shown to be close to that of methylphenidate, indicating that both are comparable in relation to abuse liability related to dopaminergic transmission.[99] Moreover, imagery showed involvement of the nucleus accumbens.[100,101] In clinical literature, case studies of modafinil dependence in patients with a previous drug abuse history are reported,[102–107] which supports the observations that 200 mg of modafinil, but not placebo, induced a significant bias toward approach behavior[61] and induced reinforcement effects.[108]

Conclusion

There is no research into long-term effects of regular modafinil use. However, there are indications that modafinil does work on the same neurobiological mechanisms as other addictive stimulants. Hence, the risk for abuse should be investigated, not only on a neurobiological level but also on the level of the subjective user. Both abuse and escalation may lead to higher intakes, likely to induce short-term side effects on top. Regarding short-term effects, on a somatic level, higher doses induce sympathetic arousal and on a mental level, the risk for overconfidence should be systematically examined in future studies.

DISCUSSION

Whereas many studies to date report significant effects of modafinil on mental performance, the current review intended to answer four specific research questions, aiming to formulate a current state-of-the-art for a military context. We examined potential moderating factors in the impact of modafinil as a nootropic in non-sleep-deprived subjects, such as the dose–response effect, individual-related and task-related characteristics, repeated or single dose administration, and the prevalence of short-term and long-term mental and somatic side effects.

Firstly, it is salient that until now, no study has investigated the impact of modafinil as a smart drug in a military context. The studies we encountered were all laboratory experimental studies in a nonmilitary context except for Ooi et al.,[23] who investigated side effects in military aviators flying in their circadian trough; hence still in the context of sleep deprivation. Knowing that pressure on military personnel is ever increasing[28–30]—also in terms of cognitive load[31,32]—and that there is interest to use the drug among military personnel,[33] research in function of the demands of military operationality is highly recommended before the use of modafinil can be deemed acceptable as a cognitive enhancer outside of a sleep deprivation context.

Regarding our research questions, the first one remained unanswered. There is no research on the impact of a repeated intake of modafinil as a smart drug on cognitive or operational performance. Nevertheless, when considering how a smart drug is used in nonmilitary contexts, this should be one of the first tracks to follow. People who use, use frequently. A recent international survey[109] reported that 20% of the modafinil users took the drug on a daily base and about 66% of them at least three times a week. These statistics teach us that, by the time there is sufficient research available to make evidence-based decisions on the topic, our target audience may very well have performed their own personal trial-and-error investigations regarding dose, side effects, and protocol with online-purchased molecules. This brings us immediately to the last research question, namely that side effects are insufficiently examined and/or reported so far. Moreover, in contradiction to what has been claimed before,[3–5] there are mounting indications that modafinil comprises a risk for abuse.[95,96,108] Furthermore, objective improvements of modafinil do not always correspond with the subjective perceptional awareness, which may interact with abuse or escalation risk.[36] Hence, although it remains unclear to what extent this risk for abuse poses a problem in function of operational use, until this uncertainty is lifted, caution is strongly advised. This issue is especially relevant for the use as a cognitive enhancer. Whereas the use of a eugeroic drug will be dictated by the circumstances of sleep deprivation, hence being *de facto* constrained to a certain time and place; the use of a cognitive enhancer leaves a much broader scope for application and thus potential for abuse.

Besides abuse, to preserve military safety, future research should investigate the risk for overconfidence in a much more rigorous manner. A significant increase in overconfidence was previously reported in a sleep-deprived population[43] and a tendency towards overconfidence in non-sleep-deprived subjects.[42] Until now—considering the risk of sleep deprivation to performance—a trade-off between user-benefits and unwanted side effects has been deemed acceptable for sleep-deprived subjects, but this cost–benefit analysis cannot and should not be readily transposed to non-sleep-deprived individuals without any ethical consideration. It has already been reported how people tend to choose medicalized solutions to meet professional requirements, rather than change behaviors, or in operational context, leadership decisions.[110] The responses on research questions 2 and 3 showed that there are several indications that low-performance persons on

Downloaded from https://academic.oup.com/milmed/article/187/1-2/52/6386431 by guest on 02 August 2022

baseline tasks benefit more from modafinil than initial high performers—certainly on difficult tasks.[75–78] Hence, stretching the argument without ethical considerations to a military context, one could fear that—considering the current recruitment issues of military all over the world—a "wonder drug" may trigger the acceptance of a "quantity-over-quality" gap in recruitment procedures, losing track of the long-term consequences on the required operationality of military personnel. Lastly, an issue receiving very little attention in the scientific literature, yet of paramount importance for our population, is the effect of modafinil on exercise tolerance. The reported sympathetic effects do not bode well in this regard. As suggested by an operationally relevant investigation,[64] a gain in executive functioning due to modafinil was at the cost of physical endurance. Hence, the interaction between the impact of modafinil on cognitive and physical performance should be examined before using in a military context, certainly outside of sleep deprivation issues.

Final Conclusion: Current Position Statement and Research Agenda

Despite the usefulness of modafinil in operational sleep-deprived contexts, its use as a smart drug (i.e., outside of an occasional sleep deprivation constraint) should be banned in military contexts considering the current gaps in knowledge and the existing cost–benefit profile.

Further research on modafinil in function of military profiles is needed. Individual abilities, cognitive and physical task demands, and sleep availability may all contribute to the impact of modafinil intake. Moreover, it is not yet clear to what extent an improvement on one component (e.g., cognitive performance) may have a negative effect on another component (e.g., physical performance). Finally, a potential risk for abuse and overconfidence in both regular and occasional intake should be thoroughly investigated.

ACKNOWLEDGMENTS

This article was funded by Belgian Defence Grant HFM-1908.

FUNDING

None declared.

CONFLICT OF INTEREST STATEMENT

None declared.

REFERENCES

1. Billiard M, Broughton R: Modafinil: its discovery, the early European and North American experience in the treatment of narcolepsy and idiopathic hypersomnia, and its subsequent use in other medical conditions. Sleep Med 2018; 49: 69–72.
2. Minzenberg MJ, Carter CS: Modafinil: a review of neurochemical actions and effects on cognition. Neuropsychopharmacology 2008; 33(7): 1477–502.
3. Caldwell JA, Caldwell JL: Fatigue in military aviation: an overview of U.S. military-approved pharmacological countermeasures. Aviat Space Environ Med 2005; 76(7 II).
4. Lyons TJ, French J: Modafinil: the unique properties of a new stimulant. Aviat Space Environ Med 1991; 62(5): 432–5.
5. Lagarde D, Batejat D, Van Beers P, Sarafian D, Pradella S: Interest of modafinil, a new psychostimulant, during a sixty-hour sleep deprivation experiment. Fundam Clin Pharmacol 1995; 9(3): 271–9.
6. Vastag B: Poised to challenge need for sleep, "Wakefulness Enhancer" rouses concerns. J Am Med Assoc 2004; 291(2): 167–70.
7. Brunyé TT, Brou R, Doty TJ, et al: A review of US army research contributing to cognitive enhancement in military contexts. J Cogn Enhanc 2020; 4(4): 453–68.
8. Vargo EJ, James RA, Agyeman K, et al: Perceptions of assisted cognitive and sport performance enhancement among university students in England. Perform Enhanc Heal 2014; 3(2): 66–77.
9. Vargo EJ, Petróczi A: "It was me on a good day": exploring the smart drug use phenomenon in England. Front Psychol 2016; 7(MAY): 1–12.
10. Eliyahu U, Berlin S, Hadad E, Heled Y, Moran DS: Psychostimulants and military operations. Mil Med 2007; 172(4): 383–7.
11. Dietz P, Striegel H, Franke AG, Lieb K, Simon P, Ulrich R: Randomized response estimates for the 12-month prevalence of cognitive-enhancing drug use in university students. Pharmacotherapy 2013; 33(1): 44–50.
12. Franke AG, Bagusat C, Dietz P, et al: Use of illicit and prescription drugs for cognitive or mood enhancement among surgeons. BMC Med 2013; 11(1): 1–9.
13. Maher B: Poll results: look who's doping. Nat Poll Results 2008; 452: 674–5.
14. Frati P, Busardo F, Cipolloni L, De Dominicis E, Fineschi V: Anabolic androgenic steroid (AAS) related deaths: autoptic, histopathological and toxicological findings. Curr Neuropharmacol 2015; 13(1): 146–59.
15. Van Dongen HPA, Maislin G, Mullington JM, Dinges DF: Erratum: the cumulative cost of additional wakefulness: dose-response effects on neurobehavioral functions and sleep physiology from chronic sleep restriction and total sleep deprivation (Sleep [March 2003] 26, 2 [117-126]). Sleep 2004; 27(4): 600.
16. Van Dongen HPA, Baynard MD, Maislin G, Dinges DF: Systematic interindividual differences in neurobehavioral impairment from sleep loss: evidence of trait-like differential vulnerability. Sleep 2004; 27(3): 423–33.
17. Choo WC, Lee WW, Venkatraman V, Sheu FS, Chee MWL: Dissociation of cortical regions modulated by both working memory load and sleep deprivation and by sleep deprivation alone. NeuroImage 2005; 25(2): 579–87.
18. Killgore WDS, Balkin TJ, Wesensten NJ: Impaired decision making following 49 h of sleep deprivation. J Sleep Res 2006; 15(1): 7–13.
19. Dinges DF, Pack F, Williams K, et al: Cumulative sleepiness, mood disturbance, and psychomotor vigilance performance decrements during a week of sleep restricted to 4-5 hours per night. Sleep 1997; 20(4): 267–77.
20. Philibert I: Sleep loss and performance in residents and nonphysicians: a meta-analytic examination. Sleep 2005; 28(11): 1392–402.
21. Yoo -S-S, Gujar N, Hu P, Jolesz FA, Walker M: The human emotional brain without sleep — a prefrontal amygdala disconnect. Curr Biol 2007; 17(20): R877–8.
22. Alhola P, Polo-Kantola P: Sleep deprivation: impact on cognitive performance. Neuropsychiatr Dis Treat 2007; 3(5): 553–67.
23. Ooi T, Wong SH, See B: Modafinil as a stimulant for military aviators. Aerosp Med Hum Perform 2019; 90(5): 480–3.
24. Ehlert AM, Wilson PB: A systematic review of stimulant use in civilian and military aviation. Int J Aerosp Psychol; 2021: 1–21.
25. Campbell JS, Markwald R, Chinoy ED, et al: A sleep primer for military psychologists. In: Bowles S, Bartone PT, eds. *Handbook of Military Psychology*. Springer International Publishing; 2017: 239–58.

Downloaded from https://academic.oup.com/milmed/article/187/1-2/52/6386431 by guest on 02 August 2022

26. Castro CA, Adler AB, Castro CA, Adler AMYB: OPTEMPO: effects on soldier and unit readiness. The US Army War College Quarterly: Parameters. US Army War College Carlisle United States 1999; 29: 3.
27. Miller NL, Shattuck LG, Matsangas P: Sleep and fatigue issues in continuous operations: a survey of U.S. Army officers. Behav Sleep Med 2011; 9(1): 53–65.
28. Vrijkotte S, Roelands B, Meeusen R, Pattyn N: Sustained military operations and cognitive performance. Aerosp Med Hum Perform 2016; 87(8): 718–27.
29. Vrijkotte S, Roelands B, Pattyn N, Meeusen R: The overtraining syndrome in soldiers: insights from the sports domain. Mil Med 2019; 184(5–6): e192–200.
30. Weeks SR, McAuliffe CL, DuRussel D, Pasquina PF: Physiological and psychological fatigue in extreme conditions: the military example. PM&R 2010; 2(5): 438–41.
31. Van Cutsem J, Marcora S, De Pauw K, Bailey S, Meeusen R, Roelands B: The effects of mental fatigue on physical performance: a systematic review. Sport Med 2017; 47(8): 1569–88.
32. Marcora SM, Staiano W, Manning V: Mental fatigue impairs physical performance in humans. J Appl Physiol 2009; 106(3): 857–64.
33. 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.
34. Löken LS, Wessberg J, Morrison I, McGlone F, Olausson H: Coding of pleasant touch by unmyelinated afferents in humans. Nat Neurosci 2009; 12(5): 547–8.
35. Babkoff H, Krueger GP: Use of stimulants to ameliorate the effects of sleep loss during sustained performance. Mil Psychol 1992; 4(4): 191–205.
36. 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.
37. 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): 556–67.
38. Repantis D, Schlattmann P, Laisney O, Heuser I: Modafinil and methylphenidate for neuroenhancement in healthy individuals: a systematic review. Pharmacol Res 2010; 62(3): 187–206.
39. Baranski JV, Cian C, Esquivié D, Pigeau RA, Raphel C: Modafinil during 64 Hr of sleep deprivation: dose-related effects on fatigue, alertness, and cognitive performance. Mil Psychol 1998; 10(3): 173–93.
40. Eddy D, Gibbons J, Storm W, et al: An assessment of modafinil for vestibular and aviation-related effects. NTI INC BROOKS CITY-BASE TX. Published online 2005:1–58.
41. Pigeau R, Naitoh P, Buguet A, 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.
42. Baranski JV, Pigeau R, Dinich P, Jacobs I: Effects of modafinil on cognitive and meta-cognitive performance. Hum Psychopharmacol 2004; 19(5): 323–32.
43. Baranski JV, Pigeau RA: Self-monitoring cognitive performance during sleep deprivation: effects of modafinil, d-amphetamine and placebo. J Sleep Res 1997; 6(2): 84–91.
44. Whitmore J, Hickey P, Doan B, et al: *A double-blind placebo-controlled investigation of the efficacy of Modafinil for maintaining alertness and performance in sustained military ground operations*. Air Force Research Lab Brooks AFB TX Human Effectiveness DIR/Biodynamics and Protection DIV, 2006.
45. Stivalet P, Esquivié D, Barraud PA, Leifflen D, Raphel C: Effects of modafinil on attentional processes during 60 hours of sleep deprivation. Hum Psychopharmacol 1998; 13(7): 501–7.
46. Bard EG, Sotillo C, Anderson AH, Taylor MM: DCIEM map task corpus: spontaneous dialogue under sleep deprivation and drug treatment. Proc Int Conf Spok Lang Process ICSLP 1996; 3: 1958–61.
47. Batéjat D, Coste O, Van Beers P, Lagarde D, Piérard C, Beaumont M: Prior sleep with zolpidem enhances the effect of caffeine or modafinil during 18 hours continuous work. Aviat Space Environ Med 2006; 77(5): 215–25.
48. Dagan Y, Doljansky JT: Cognitive performance during sustained wakefulness: a low dose of caffeine is equally effective as modafinil in alleviating the nocturnal decline. Chronobiol Int 2006; 23(5): 973–83.
49. Whitmore J, Doan B, Fischer J, French J, Heintz T: *The efficacy of modafinil as an operational fatigue countermeasure over several days of reduced sleep during a simulated escape and evasion scenario*. Air Force Research Lab Brooks AFB TX Human Effectiveness DIR/Biodynamics and Protection DIV, 2004.
50. 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.
51. Hart CL, Haney M, Vosburg SK, Comer SD, Gunderson E, Foltin RW: Modafinil attenuates disruptions in cognitive performance during simulated night-shift work. Neuropsychopharmacology 2006; 31(7): 1526–36.
52. Gill M, Haerich P, Westcott K, Godenick KL, Tucker JA: Cognitive performance following modafinil versus placebo in sleep-deprived emergency physicians: a double-blind randomized crossover study. Acad Emerg Med 2006; 13(2): 158–65.
53. Li YF, Zhan H, Xin YM, Tang GX, Wei SH, Li T: Effects of modafinil on visual and auditory reaction abilities and subjective fatigue level during 48 h sleep deprivation. Space Med Med Eng 2003; 16(4): 277–80.
54. Mairesse O, MacDonald-Nethercott E, Neu D, et al: Preparing for Mars: human sleep and performance during a 13 month stay in Antarctica. Sleep 2019; 42(1): 1–12.
55. Van Puyvelde M, Neyt X, McGlone F, Pattyn N: Voice stress analysis: a new framework for voice and effort in human performance. Front Psychol 2018; 9(1994): 1–25.
56. Tricco A, Lillie E, Zarin W, et al: PRISMA extension for scoping reviews (PRISMA-ScR): checklist and explanation. J Phys A Math Theor 2011; 44(8): 1689–99.
57. Taneja I, Haman K, Shelton RC, Robertson D: A randomized, double-blind, crossover trial of modafinil on mood. J Clin Psychopharmacol 2007; 27(1): 76–9.
58. Franke AG, Gränsmark P, Agricola A, et al: Methylphenidate, modafinil, and caffeine for cognitive enhancement in chess: a double-blind, randomised controlled trial. Eur Neuropsychopharmacol 2017; 27(3): 248–60.
59. Ikeda Y, Funayama T, Tateno A, Fukayama H, Okubo Y, Suzuki H: Modafinil enhances alerting-related brain activity in attention networks. Psychopharmacology (Berl) 2017; 234(14): 2077–89.
60. Lees J, Michalopoulou PG, Lewis SW, et al: Modafinil and cognitive enhancement in schizophrenia and healthy volunteers: the effects of test battery in a randomised controlled trial. Psychol Med 2017; 47(13): 2358–68.
61. Bellebaum C, Kuchinke L, Roser P: Modafinil alters decision making based on feedback history – a randomized placebo-controlled double blind study in humans. J Psychopharmacol 2016; 31(2): 243–9.
62. Repantis D, Bovy L, Ohla K, Kühn S, Dresler M: Cognitive enhancement effects of stimulants: a randomized controlled trial testing methylphenidate, modafinil, and caffeine. Psychopharmacology (Berl) 2021; 238(2): 441–51.
63. Fernández A, Mascayano F, Lips W, Painel A, Norambuena J, Madrid E: Effects of modafinil on attention performance, short-term

Downloaded from https://academic.oup.com/milmed/article/187/1-2/52/6386431 by guest on 02 August 2022

memory and executive function in university students: a randomized trial. Medwave 2015; 15(5): e6166.
64. Rattray B, Martin K, Hewitt A, Cooper G, McDonald W: Effect of acute modafinil ingestion on cognitive and physical performance following mental exertion. Hum Psychopharmacol 2019; 34: 4.
65. Schmidt A, Müller F, Dolder PC, et al: Comparative effects of methylphenidate, modafinil, and mdma on response inhibition neural networks in healthy subjects. Int J Neuropsychopharmacol 2017; 20(9): 712–20.
66. Mohamed AD, Lewis CR: Modafinil increases the latency of response in the hayling sentence completion test in healthy volunteers: a randomised controlled trial. PLoS One 2014; 9: 11.
67. Cope ZA, Minassian A, Kreitner D, et al: Modafinil improves attentional performance in healthy, non-sleep deprived humans at doses not inducing hyperarousal across species. Neuropharmacology 2017; 125: 254–62.
68. Makris AP, Rush CR, Frederich RC, Taylor AC, Kelly TH: Behavioral and subjective effects of d-amphetamine and modafinil in healthy adults. Exp Clin Psychopharmacol 2007; 15(2): 123–33.
69. Turner DC, Robbins TW, Clark L, Aron AR, Dowson J, Sahakian BJ: Cognitive enhancing effects of modafinil in healthy volunteers. Psychopharmacology (Berl) 2003; 165(3): 260–9.
70. Randall DC, Shneerson JM, Plaha KK, File SE: Modafinil affects mood, but not cognitive function, in healthy young volunteers. Hum Psychopharmacol 2003; 18(3): 163–73.
71. Randall DC, Viswanath A, Bharania P, et al: Does modafinil enhance cognitive performance in young volunteers who are not sleep-deprived? J Clin Psychopharmacol 2005; 25(2): 175–9.
72. Randall DC, Shneerson JM, File SE: Cognitive effects of modafinil in student volunteers may depend on IQ. Pharmacol Biochem Behav 2005; 82(1): 133–9.
73. Randall DC, Fleck NL, Shneerson JM, File SE: The cognitive-enhancing properties of modafinil are limited in non-sleep-deprived middle-aged volunteers. Pharmacol Biochem Behav 2004; 77(3): 547–55.
74. Marchant NL, Kamel F, Echlin K, Grice J, Lewis M, Rusted JM: Modafinil improves rapid shifts of attention. Psychopharmacology (Berl) 2009; 202(1–3): 487–95.
75. Müller U, Rowe JB, Rittman T, Lewis C, Robbins TW, Sahakian BJ: Effects of modafinil on non-verbal cognition, task enjoyment and creative thinking in healthy volunteers. Neuropharmacology 2013; 64: 490–5.
76. Müller U, Steffenhagen N, Regenthal R, Bublak P: Effects of modafinil on working memory processes in humans. Psychopharmacology (Berl) 2004; 177(1-2): 161–9.
77. Winder-Rhodes SE, Chamberlain SR, Idris MI, Robbins TW, Sahakian BJ, Müller U: Effects of modafinil and prazosin on cognitive and physiological functions in healthy volunteers. J Psychopharmacol 2010; 24(11): 1649–57.
78. Esposito R, Cilli F, Pieramico V, et al: Acute effects of modafinil on brain resting state networks in young healthy subjects. PLoS One 2013; 8(7): 1–10.
79. Finke K, Dodds CM, Bublak P, et al: Effects of modafinil and methylphenidate on visual attention capacity: a tva-based study. Psychopharmacology (Berl) 2010; 210(3): 317–29.
80. Mohamed AD: The effects of modafinil on convergent and divergent thinking of creativity: a randomized controlled trial. J Creat Behav 2016; 50(4): 252–67.
81. Schmidt A, Müller F, Dolder PC, et al: Acute effects of methylphenidate, modafinil, and MDMA on negative emotion processing. Int J Neuropsychopharmacol 2018; 21(4): 345–54.
82. Rasetti R, Mattay VS, Stankevich B, et al: Modulatory effects of modafinil on neural circuits regulating emotion and cognition. Neuropsychopharmacology 2010; 35(10): 2101–9.
83. Theunissen EL, Elvira JDLA, Van Den Bergh D, Ramaekers JG: Comparing the stimulant effects of the H1-antagonist fexofenadine with 2 psychostimulants, modafinil and methylphenidate. J Clin Psychopharmacol 2009; 29(5): 439–43.
84. Pringle A, Browning M, Parsons E, Cowen PJ, Harmer CJ: Early markers of cognitive enhancement: developing an implicit measure of cognitive performance. Psychopharmacology (Berl) 2013; 230(4): 631–8.
85. Steward A, Pickersgill M: Developing expertise, customising sleep, enhancing study practices: exploring the legitimisation of modafinil use within the accounts of UK undergraduate students. Drugs Educ Prev Policy 2019; 26(4): 347–55.
86. Taneja I, Diedrich A, Black BK, Byrne DW, Paranjape SY, Robertson D: Modafinil elicits sympathomedullary activation. Hypertension 2005; 45(4): 612–8.
87. Alcaro A, Huber R, Panksepp J: Behavioral functions of the mesolimbic dopaminergic system: an affective neuroethological perspective. Brain Res Rev 2007; 56(2): 283–321.
88. Robinson TE, Berridge KC: The incentive sensitization theory of addiction: some current issues. Philos Trans R Soc B Biol Sci 2008; 363(1507): 3137–46.
89. Vézina J, Hébert M: Risk factors for victimization in romantic relationships of young women: a review of empirical studies and implications for prevention. Trauma, Violence, Abus 2007; 8(1): 33–66.
90. Valjent E, Bertran-Gonzalez J, Aubier B, Greengard P, Hervé D, Girault JA: Mechanisms of locomotor sensitization to drugs of abuse in a two-injection protocol. Neuropsychopharmacology 2010; 35(2): 401–15.
91. Jasinski DR: An evaluation of the abuse potential of modafinil using methylphenidate as a reference. J Psychopharmacol 2000; 14(1): 53–60.
92. Zhang HY, Bi GH, Yang HJ, et al: The novel modafinil analog, JJC8-016, as a potential cocaine abuse pharmacotherapeutic. Neuropsychopharmacology 2017; 42(9): 1871–83.
93. Schmitt KC, Reith MEA: The atypical stimulant and nootropic modafinil interacts with the dopamine transporter in a different manner than classical cocaine-like inhibitors. PLoS One 2011; 6: 10.
94. Vargas I, Nguyen AM, Muench A, Bastien CH, Ellis JG, Perlis ML: Acute and chronic insomnia: what has time and/or hyperarousal got to do with it? Brain Sci 2020; 10(2): 71–83.
95. Wuo-Silva R, Fukushiro-Lopes DF, Fialho BP, et al: Participation of Dopamine D1 and D2 receptors in the rapid-onset behavioral sensitization to modafinil. Front Pharmacol 2019; 10(Mar): 1–9.
96. Wuo-Silva R, Fukushiro DF, Hollais AW, et al: Modafinil induces rapid-onset behavioral sensitization and cross-sensitization with cocaine in mice: implications for the addictive potential of modafinil. Front Pharmacol 2016; 7(Nov): 1–10.
97. Deroche-Gamonet V, Darnaudéry M, Bruins-Slot L, Piat F, Le Moal M, Piazza P: Study of the addictive potential of modafinil in naive and cocaine-experienced rats. Psychopharmacology (Berl) 2002; 161(4): 387–95.
98. Mereu M, Hiranita T, Jordan CJ, et al: Modafinil potentiates cocaine self-administration by a dopamine-independent mechanism: possible involvement of gap junctions. Neuropsychopharmacology 2020; 45(9): 1518–26.
99. Kim WC, Tateno A, Arakawa R, et al: In vivo activity of modafinil on dopamine transporter measured with positron emission tomography and [18F]FE-PE2I. Int J Neuropsychopharmacol 2014; 17(5): 697–703.
100. Funayama T, Ikeda Y, Tateno A, et al: Modafinil augments brain activation associated with reward anticipation in the nucleus accumbens. Psychopharmacology (Berl) 2014; 231(16): 3217–28.

Downloaded from https://academic.oup.com/milmed/article/187/1-2/52/6386431 by guest on 02 August 2022

101. Volkow ND, Fowler JS, Logan J, et al: Effects of modafinil on dopamine and dopamine transporters in the male human brain clinical implications. JAMA 2009; 301(11): 1148–54.
102. Alacam H, Basay O, Tumkaya S, Mart M, Kar G: Modafinil dependence: a case with attention-deficit/hyperactivity disorder. Psychiatry Investig 2018; 15(4): 424–7.
103. D'Souza PD, Mascarenhas JJ: A case report on modafinil dependence. Galore Int J Health Sci Res 2019; 4(3): 8–11.
104. Jerry JM, Shirvani N, Dale R: Addiction to armodafinil and modafinil presenting with paranoia. J Clin Psychopharmacol 2016; 36(1): 98–100.
105. Kate N, Grover S, Ghormode D: Dependence on supratherapeutic doses of modafinil: a case report. Kate, Natasha al "Dependence supratherapeutic doses modafinil a case report". Prim Care Companion CNS Disord 2012; 14(5): PCC11l01333.
106. Krishnan R, Chary KV: A rare case modafinil dependence. J Pharmacol Pharmacother 2015; 6(1): 49–50.
107. Cengiz Mete M, Ö Ş, Ö S, Atasoy N, Atik L: Compulsive modafinil use in a patient with a history of alcohol use disorder. Gen Hosp Psychiatry 2015; 37(2): e7–8.
108. Stoops WW, Lile JA, Fillmore MT, Glaser PEA, Rush CR: Reinforcing effects of modafinil: influence of dose and behavioral demands following drug administration. Psychopharmacology (Berl) 2005; 182(1): 186–93.
109. Teodorini RD, Rycroft N, Smith-Spark JH: The off-prescription use of modafinil: an online survey of perceived risks and benefits. PLoS One 2020; 15(2): 1–17.
110. Coveney CM, Nerlich B, Martin P: Modafinil in the media: metaphors, medicalisation and the body. Soc Sci Med 2009; 68(3): 487–95.

Downloaded from https://academic.oup.com/milmed/article/187/1-2/52/6386431 by guest on 02 August 2022