Effect of Pharmacological Enhancement on the Cognitive and Clinical Psychomotor Performance of Sleep-Deprived Doctors

A Randomized Controlled Trial

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Objectives: To investigate the effect of modafinil 200 mg on the performance of a cohort of healthy male doctors after 1 night of supervised sleep deprivation.

Summary Background Data: Sleep-deprived and fatigued doctors pose a safety risk to themselves and their patients. Yet, because of the around-the-clock nature of medical practice, doctors frequently care for patients after periods of extended wakefulness or during circadian troughs. Studies suggest that a group of substances may be capable of safely and effectively reversing the effects of fatigue. However, little work has been done to investigate their role within our profession.

Methods: We conducted a parallel, double-blind, randomized, and placebo-controlled study to investigate the effect of pharmacological enhancement on performance doctors. Thirty-nine healthy male resident doctors received either lactose placebo (n = 19) or modafinil 200 mg (n = 20) after 1 night of sleep deprivation. A selection of CANTAB neuropsychological tests was used to assess higher cognitive function. Clinical psychomotor performance was assessed using the Minimally Invasive Surgical Trainer Virtual Reality. Assessments were carried out between 6.00 AM and approximately 8.00 AM.

Results: Modafinil improved performance on tests of higher cognitive function; participants in the modafinil group worked more efficiently when solving working memory ($F_{1,38} = 5.24$, $P = 0.028$) and planning ($F_{1,38} = 4.34$, $P = 0.04$) problems, were less-impulsive decision makers ($F_{1,37} = 6.76$, $P = 0.01$), and were more able to flexibly redirect their attention ($F_{1,38} = 4.64$, $P = 0.038$). In contrast, no improvement was seen in tests of clinical psychomotor performance.

Conclusions: Our results suggest that fatigued doctors might benefit from pharmacological enhancement in situations that require efficient information processing, flexible thinking, and decision making under time pressure. However, no improvement is likely to be seen in the performance of basic procedural tasks.

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The link between fatigue and human performance impairment is well established; we now know that the effects of extended wakefulness on certain aspects of human cognition, closely mirror those of alcohol intoxication.[1] Consequently, fatigued doctors risk making poor judgments[2] and committing serious medical errors.[3] Reduced working hours have now been implemented for training grade doctors working in both the United States and Europe. However, shift work manipulation suffers from important limitations including pressure to balance service and education needs and the uncertain relationship that exists between shift work requirements, sleep patterns, and sleep quality.[4,5]

Thus, although methods to promote good-quality sleep must remain the focus of research efforts, it is important to acknowledge that alternative measures to reduce fatigue exist and should not be overlooked.[6] In this regard, some evidence exists to support the use of stimulants such as caffeine, found in coffee, tea, and energy drinks, to temporarily counteract the effects of fatigue.[7] Importantly, the strategic use of such a substance might allow doctors to remain alert until the opportunity for sleep naturally presents itself. Although minimal research has been executed to investigate the use of stimulants by doctors, other industries such as aviation and the military in which fatigue poses a safety risk have published encouraging findings.[8]

Caffeine is widely available, effective, and in common use; however, we do not believe that it is ideally suited to this task—wakefulness-promoting effects are transient and, at the dose required for maximum effect (around 600 mg), side effects including tremor, anxiety, and nausea are common.[9] We have therefore carried out a study—the first of its type—to investigate the effects of modafinil 200 mg on the cognitive and clinical psychomotor performance of a cohort of sleep-deprived doctors. This agent is effective in the treatment of shift work sleep disorder,[10] has few reported side effects, and has been shown to ameliorate the cognitive effects of fatigue in sleep-deprived healthy individuals.[11]

METHODS

Participants

Eligible candidates were defined as healthy resident doctors taking no regular medication and with an experience of less than 10 laparoscopic cases as primary operator. Candidates were not eligible if they had a history of psychiatric illness; suffered from visual, auditory, or motor impairment; had a cardiac or neurological illness; scored greater than 10 on the Epworth Sleepiness Scale[12]; answered yes to more than 2 questions on the CAGE questionnaire[13]; had a history of drug or alcohol addiction; drank more than 8 cups of coffee per day; or were unable to complete standardized psychomotor skills training. Female doctors were excluded from participation to eliminate the possibility of harm to a pregnancy.

Potential candidates were identified through their affiliation with St Mary's Hospital or Imperial College London and recruited via e-mail or in person. Detailed information sheets were provided to participants, all of whom provided written consent before their inclusion in the study.

Study Design and Conduct

The study followed a parallel, double-blind, randomized, and placebo-controlled design—we chose not to use a crossover design to avoid the confounding influence of practice effects. A sample size of 40 was chosen on the basis of the results of previous pharmacological enhancement studies. Ethical approval was granted by Cambridgeshire Research Ethics Committee 1 on June 22, 2009 (Ref: 09/H0304/24). Site-specific approval, sponsorship, and funding for the study were provided by Imperial College London. Candidates, recruited between August 2009 and February 2010, were allocated to 1 of 2 study arms (modafinil 200 mg or lactose placebo) according to a computer-generated random number sequence (performed by a third party) held by the Pharmacy Clinical Trials Department. This was only made available to the research team upon formal request after completion of data analysis.

Before the study, participants undertook a 3- to 5-day period of psychomotor training during which they agreed to maintain their habitual sleep-wake cycle. Participants also agreed to abstain from alcohol and caffeine for 48 hours before the study. On the study day, participants reported at 8.00 AM, committed to remain awake for the duration of the day, and attended the study center (St Mary's Hospital, Praed Street, London) for the overnight session at 8.00 PM. Between this time and the conclusion of the study at 8.00 AM the following day, participants were awake and supervised at all times by a member of the research team. Nonstrenuous activities, including watching TV, reading books, and playing video games, were permitted.

Identical black gelatin capsules containing the allocated substance were administered at 3.00 AM and counterbalanced cognitive and psychomotor assessments were carried out at 6.00 AM (peak plasma concentration occurs between 2 and 4 hours postadministration)[14] for approximately 2 hours. Assessments were performed in a designated research laboratory on a one-to-one basis and were administered by a trained member of the research team.

Visual analog scales[15] were completed by participants at 3.00 AM, 6.00 AM, approximately 7.00 AM, and approximately 8.00 AM and physiological measurements (blood pressure and heart rate) were taken at 3.00 AM, 6.00 AM, and approximately 8.00 AM.

Upon completion of the study, participants agreed not to undertake clinical work for 48 hours.

Assessment Tools

Cognition (CANTAB)

Cognitive tests from CANTAB (Cambridge Cognition Limited, Cambridge, United Kingdom)[16] were chosen to assess cognitive performance. This battery of extensively validated computerized neurocognitive tests has a bibliography of more than 650 peer-reviewed journal papers. Tasks are delivered using a tablet computer and participants register their responses via a touch-screen interface or response key depending on the task.

Tasks relevant to the study of sleep deprivation and modafinil and conceptually relevant to effective performance within the medical profession were chosen (Table 1).

Psychomotor Skill (MIST VR)

The MIST-VR (Minimally Invasive Surgical Trainer Virtual Reality) simulator (Mentice, Gothenberg, Sweden) was chosen to assess clinical psychomotor performance. This system is composed of a conventional PC computer and a virtual laparoscopic interface consisting of 2 instruments held in a fixed position, sensing apparatus, and foot pedal to apply electrocautery. Tasks are abstract (spherical and cylindrical objects are manipulated in a 3-dimensional environment) and participants must use both their left and right hands to complete the task. A range of metrics (economy of movement, time taken, and the number of errors committed) is automatically recorded by the simulator. The MIST-VR is thoroughly validated[17] and sensitive to the effects of acute sleep deprivation.[18]

Simulator Training

With the objective of reducing preexisting group variance, candidates were required to complete a standardized device-specific psychomotor training curriculum.[19] In the final part of the curriculum, candidates performed the 2 most complex tasks-–stretch diathermy (SD) and manipulate diathermy (MD)—at the hardest difficulty setting. Successful completion was defined as the attainment of proficiency benchmarks (derived from the performance of 10 experienced laparoscopic surgeons) for each construct valid metric on 2 consecutive occasions.

TABLE 1. Cognitive Tasks

Task	Description	Reference	Important Measures
Working memory and planning			
Reverse SSP	A test of spatial working memory span to recall the reverse order in which a series of boxes was highlighted.	Owen et al[31]	Span length Total errors
OTS	A spatial planning test, involving planning a sequence of moves to make an arrangement of colored balls achieve a goal arrangement without moving the balls.	Baker et al[32]	Mean attempts Latency to correct (ms)
Cognitive flexibility			
IED	Rule acquisition and reversal learning testing the ability to selectively attend to and set shift between shape and color stimulus	Rogers et al[33]	Stages completed
Impulsivity, decision making, and risk taking			
CGT	A decision-making task, involving deciding under which colored box a token will be hidden. Points can be bet on whether the right choice has been made.	Rahman et al[34]	Probability of choosing the most likely outcome Percentage bet placed on decision Delay aversion (impulsivity) Overall proportional bet Deliberation time (ms)

Assessment Procedure

After the overnight session, performance was assessed using the same 2 complex tasks (MD and SD) on which candidates had demonstrated proficiency. In this phase, participants were asked to perform 8 repetitions of each task in an alternating fashion.

Questionnaires

Epworth Sleepiness Scale

The Epworth Scale[12] was completed by all participants upon recruitment to the study. With respect to the recent past, participants were asked to "rate their chance of dosing" on a scale of 0 to 3 in a range of conditions.

Visual Analog Scales

Participants rated how they felt by making a mark on a continuous 10-cm line linking 2 opposing conditions. Sixteen dimensions include alert-drowsy, attentive-dreamy, and incompetent-proficient.[15]

Safety Measures

Physiological measurements were taken using a validated automated blood pressure monitoring (MX2 Basic, Omron, Milton Keynes, United Kingdom) device placed around the upper arm.[20] Participants were asked to report adverse effects at the conclusion of the overnight session and at a subsequent follow-up session.

Statistical Analysis

Demographics and baseline measurements were compared using 1-way, between-groups analysis of variance (ANOVA) as were cognitive task parameters (Intra-Extra-Dimensional Set Shift, One Touch Stockings of Cambridge, and Reverse Spatial Span,) with the exception of the Cambridge Gamble Task, which was analyzed using a repeated-measures ANOVA (probability and direction of bets as within-subject factors). Data were normally distributed with the exception of the Intra-Extra-Dimensional Set Shift and One-Touch Stockings of Cambridge variables, which were log transformed before analysis.

Psychomotor data were also analyzed using 1-way ANOVAs. Analyses were performed using both the raw simulator metrics (time, economy of movement, and error rate) and data dichotomized according to whether or not benchmarked criteria had been met. As psychomotor data were found to be skewed, log transformations were performed before analysis.

Visual analog scales and physiological parameters were analyzed using repeated-measures ANOVAs (with time as a within-subjects factor). Where a significant group × condition interaction was identified, post hoc F tests were performed as appropriate.

For all analyses, a $P < 0.05$ was considered significant whereas $0.05 < P < 0.1$ was considered a trend toward significance. Untransformed values are presented in the tables and figures for clarity.

RESULTS

Participants

Fifty-five doctors were asked to participate in the study of which 6 did not meet the inclusion criteria and 9 refused to take part. Of the remaining 40 participants who underwent pretrial training and randomization, 1 failed to meet the required psychomotor training criteria and was excluded from further participation (Fig. 1).

The 39 included participants (placebo, n = 19; modafinil, n = 20) were well matched on all measured baseline parameters (Table 2)

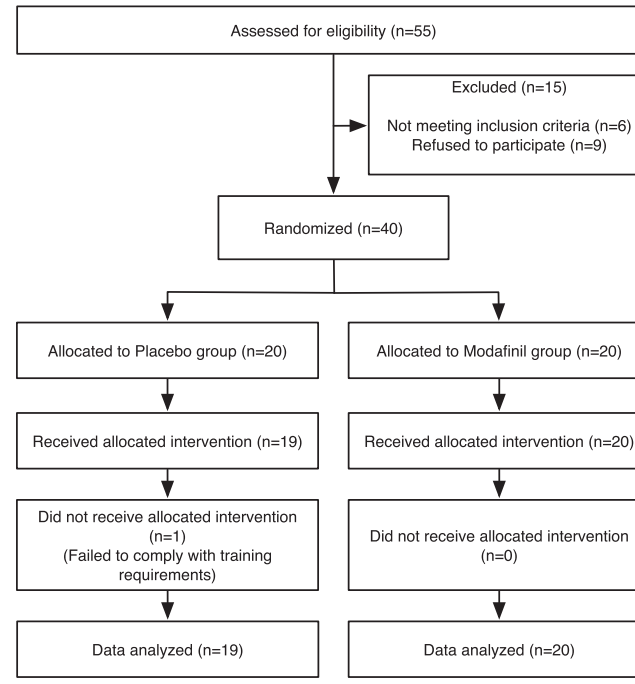

FIGURE 1. Flow chart.

Cognition

Modafinil improved participants' performance on at least 1 important measure for each of the administered cognitive tasks (Table 3).

Intra-Extra-Dimensional Shifting

Participants in the modafinil group were more likely to pass the final extra-dimensional shifting stage of the task ($F_{1,38} = 4.64$, $P = 0.038$).

Cambridge Gamble Task

The probability of choosing the most likely outcome ($F_{1,37} = 0.57$, $P = 0.46$), the percentage bet placed ($F_{1,37} = 0.39$, $P = 0.54$), deliberation time ($F_{1,37} = 0.39$, $P = 0.54$), and overall proportional bet ($F_{1,37} = 0.01$, $P = 0.92$) did not differ between groups. However, differences were seen in the impulsivity metric (delay-aversion)—the modafinil group made smaller bets than the placebo group in the descending condition and larger bets in the ascending condition ($F_{1,37} = 6.76$, $P = 0.01$, Fig. 2).

TABLE 2. Demographics and Baseline Measures

	Placebo	Modafinil	*P*
Age, yr	28.16 (0.77)	28.68 (0.94)	0.67
NART	117.84 (0.90)	116.14 (1.05)	0.24
PGY	3.74 (0.49)	3.05 (0.39)	0.28
ESS	5.42 (0.67)	4.5 (0.53)	0.28

Values shown are given as mean (standard error of the mean).

The reported P values were derived from one-way ANOVAs, with group (placebo vs Modafinil) as a between-subjects factor.

NART indicates National Adult Reading Test IQ score; PGY, postgraduate year; and ESS, Epworth Sleepiness Scale score.

TABLE 3. Cognitive Task Results

		Placebo	Modafinil	*F* Statistic	*P*
IED	Stages completed	8.6 (0.17)	9.0 (0.00)	4.64	0.04
OTS	Mean latency	21198.1 (322.53)	17414.9 (1598.96)	2.42	0.13
	Mean latency to correct, 5 move problems	36555.5 (10971.61)	25589.8 (3236.40)	4.34	0.04
	Mean attempts	1.2 (0.02)	1.2 (0.06)	0.05	0.83
CGT	Probability of choosing the most likely outcome	0.98 (0.01)	0.97 (0.01)	0.57	0.46
	Percentage bet placed on decision	0.61 (0.02)	0.63 (0.02)	0.39	0.54
	Overall proportional bet	0.57 (0.02)	0.58 (0.02)	0.01	0.92
	Deliberation time	2234.5 (140.9)	2128.1 (232.2)	0.39	0.71
	Delay aversion	0.24 (0.04)	0.10 (0.03)	6.76	0.01
Reverse SSP	Errors	2.68 (0.32)	1.6 (0.34)	5.24	0.03
	Span length	6.05 (0.27)	6.8 (0.37)	2.58	0.12

Values shown are given as mean (standard error of the mean).
The reported P values were derived from one-way ANOVAs, with group (placebo vs modafinil) as a between-subjects factor.
IED = Intra-extra-dimensional set shift; OTS = One-touch stockings of Cambridge; CGT = Cambridge gamble task; and SSP = spatial span.

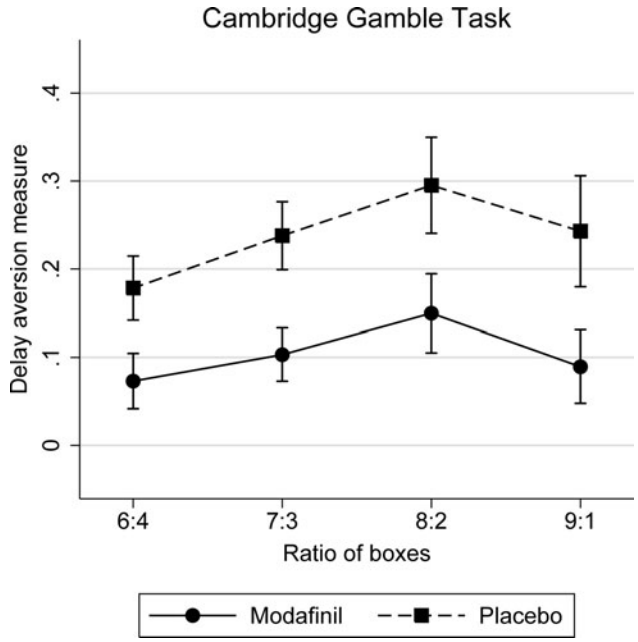

FIGURE 2. Cambridge gamble task. The modafinil group was less impulsive and therefore made smaller bets in the ascending condition and larger bets in the descending condition than the placebo group.

Reverse Spatial Span

The groups did not differ according to span length ($F_{1,38} = 2.58$, $P = 0.12$). However, the modafinil group made fewer errors (touching boxes not in the highlighted sequence) than the placebo group ($F_{1,38} = 5.24$, $P = 0.028$).

One-Touch Stockings of Cambridge

Overall mean latency ($F_{1,38} = 2.42$, $P = 0.13$) and mean number of attempts ($F_{1,38} = 0.05$, $P = 0.82$) did not differ between groups. However, for the more difficult 5 move problems, the modafinil group took less time to provide a correct answer ($F_{1,38} = 4.34$, $P = 0.04$).

Psychomotor Skill

No psychomotor performance differences were found between the placebo and modafinil groups (Table 4). Groups were compared on time taken to complete the MD ($F_{1,38} = 0.46$, $P = 0.5$) and SD tasks ($F_{1,38} = 1.20$, $P = 0.28$), the number of errors committed on the MD ($F_{1,38} = 0.04$, $P = 0.84$) and SD tasks ($F_{1,38} = 0.02$, $P = 0.88$) and the economy of movement recorded during performance of the MD ($F_{1,38} = 0.29$, $P = 0.59$) and SD tasks ($F_{1,38} = 0.81$, $P = 0.38$).

In addition, the placebo and modafinil groups satisfied benchmark performance criteria on a similar number of task attempts for both the MD ($F_{1,38} = 0.9$, $P = 0.35$) and SD tasks ($F_{1,38} = 0.03$, $P = 0.87$).

Visual Analog Scales

No overall group differences (main effects) were found for any of the 16 visual analog scale dimensions. However, interaction effects were found for the following: alert-drowsy, strong-feeble, incompetent-proficient, withdrawn-gregarious, and attentive-dreamy. Post hoc analysis of these dimensions between groups at each time point revealed that, at 6.00 AM, the modafinil group felt more alert ($F_{1,36} = 6.41$, $P = 0.016$), stronger ($F_{1,36} = 8.89$, $P = 0.005$), more proficient ($F_{1,36} = 3.39$, $P = 0.074$, trend level), more gregarious ($F_{1,36} = 5.45$, $P = 0.025$), and more attentive ($F_{1,36} = 9.36$, $P = 0.004$) than the placebo group. These differences were no longer present at 7.00 or 8.00 AM.

Safety Measures

No differences were found between groups for HR ($F_{1,36} = 0.03$, $P = 0.86$), systolic blood pressure ($F_{1,36} = 0.68$, $P = 0.42$), or diastolic blood pressure ($F_{1,36} = 0.19$, $P = 0.66$) measurements. The following side effects were reported by participants: modafinil group—headache (2), nausea (2), and diarrhea (1); and placebo group—headache (1), nausea (1), and dizziness (1).

DISCUSSION

Sleep deprivation and fatigue have now been firmly linked with cognitive dysfunction and impaired clinical performance.[3,21] Despite this, our profession remains engaged in an almost perpetual debate about how to reconcile a need for reduced working hours with the inherently inflexible, demanding, and unpredictable nature of medical practice.

In this randomized placebo-controlled study, modafinil 200 mg given to a cohort of sleep-deprived doctors was found to improve cognitive processes critical for efficient information processing, flexible thinking, and decision making under time pressure but was not effective in improving clinical psychomotor performance. Although no

TABLE 4. Psychomotor Task Results

	Placebo	Modafinil	*F* Statistic	*P*
Manipulate diathermy				
Mean time taken	38.54 (2.93)	36.03 (1.61)	0.46	0.5
Mean error rate	82.63 (8.19)	82.25 (6.22)	0.04	0.84
Mean economy of movement	3.39 (0.19)	3.35 (0.09)	0.29	0.59
No. of attempts satisfying all benchmarked performance criteria	5.9 (0.51)/8	5.3 (0.47)/8	0.9	0.35
Stretch dithermy				
Mean time taken	45.13 (2.67)	42.08 (1.44)	1.20	0.28
Mean error rate	8.84 (2.77)	6.73 (0.88)	0.02	0.88
Mean economy of movement	4.90 (0.39)	4.64 (0.27)	0.81	0.38
No. of attempts satisfying all benchmarked performance criteria	6.0 (0.43)/8	6.1 (0.49)/8	0.03	0.89

Values shown are given as mean (standard error of the mean).
The reported P values were derived from one-way ANOVAs, with group (placebo vs Modafinil) as a between-subjects factor.

difference was found in the "risk-taking" metrics of the Cambridge Gamble decision-making task, participants in the modafinil group behaved less impulsively than the placebo group placing lower bets in the descending condition and higher bets in the ascending condition. The modafinil group also solved complex 5-move one-touch stockings of Cambridge problems in less time and solved reverse spatial span tasks with greater accuracy than the placebo group suggesting improved working memory and planning ability. Strikingly, although all participants in the modafinil group successfully completed the intra-extra-dimensional set shift task, a proportion of participants in the placebo group were unable to progress beyond the final extra-dimensional set shift stage. This pattern of perseverative errors is similar to that seen in patients with lesions to the prefrontal cortex.[22]

Previous research has established that modafinil, taken at the conclusion of an overnight shift, can improve the subjective alertness and attention of emergency department physicians.[23] However, the data presented in this study are the first evidence of improved higher-order thinking, also known as "executive functions." Although focused attention acts like a spotlight illuminating salient sensory information, intact higher-order functions are required for this to be successfully integrated, manipulated, and processed.[24] These processes, largely subserved by the prefrontal cortex,[25] where metabolic activity is substantially reduced after extended wakefulness,[26] are often found to be impaired in sleep-deprived individuals.[27] Modafinil's cognitive effects are, in part, thought to be mediated by increased activation in this area of the brain.[28]

Complex cognitive challenges occur ubiquitously within our profession, but subgroups of doctors in specialties such as surgery and cardiology also rely heavily upon on a set of specialized practical techniques. The psychomotor assessments carried out in this study represent core components of laparoscopic skill required for a broad range of minimally invasive procedures.[19] The performance of these tasks has been found previously to be susceptible to the effects of fatigue.[18] In this study, as expected, the control group performed suboptimally under conditions of fatigue—failing to achieve performance benchmarks on an approximately 25% of task attempts. Importantly, however, modafinil administration did not improve basic laparoscopic psychomotor performance: no differences were found in the number of errors made, the time taken to perform the tasks or the economy of movement between groups. Because practiced psychomotor tasks are thought to place little demand on higher-cognitive centers,[29] it is likely that the attenuation of impulsivity and enhancement of working memory and cognitive flexibility conferred no advantage with respect to the performance of basic laparoscopic tasks. Although this is an important finding, further work will be required to investigate the effect of enhancement in older participants, participants with poor baseline performance and using tasks that require the integration of cognitive and psychomotor skill.

The fact that participants reported transient feelings of alertness at peak plasma concentrations but not throughout the testing regimen suggests that cognitive effects occur independently of subjective feelings of alertness. From a clinical perspective, because self-monitoring of performance is an important requirement of medical practice, a drug with less-prominent subjective effects is also likely to be safer and therefore more desirable. In line with previous work, participants in this study tolerated modafinil very well[30]—no serious side effects were reported and no adverse events occurred.

In the interest of patient safety, field studies investigating pharmacological enhancement will not be sanctioned until sufficiently detailed favorable laboratory evidence is available. Yet, if and when they are eventually performed, it would be reasonable to expect cognitive deficits similar to those found in functionally impaired clinical populations[22] and psychomotor findings anchored to validated performance benchmarks to translate into clinically meaningful effects. Most notably, less-impulsive doctors are likely to be more thorough in their approach to patient assessment and doctors exhibiting enhanced flexibility are likely to respond more dynamically to rapidly changing clinical circumstances. Although this can be said with some degree of certainty, further research will be required to prove it empirically.

Until more detailed laboratory and field evidence is accrued, the use of pharmacological agents to enhance performance in the workplace cannot be recommended. However, we do believe that the continuing discourse regarding the interplay between work hours, service provision, graduate education, fatigue, and patient safety strongly suggests that novel solutions, orthogonal to the traditional working-hours debate, might ultimately be required.

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