

The Use of Stimulants to Modify Performance During Sleep Loss: A Review by the Sleep Deprivation and Stimulant Task Force of the American Academy of Sleep Medicine

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INTRODUCTION

SLEEP DEPRIVATION IS BOTH COMMON AND CRITICALLY RELEVANT IN OUR SOCIETY.¹ AS A CLINICAL ENTITY, SLEEP DEPRIVATION IS RECOGNIZED BY the diagnosis of insufficient sleep syndrome (International Classification of Diseases [ICD] #307.49-4). However, sleep loss is also common in a broad range of occupations and in many normal healthy individuals. About a third of normal young adults can be considered too sleepy by various criteria (see review²). Significant sleepiness is also associated with a number of sleep disorders, night shift work, and jet lag. Sleepiness poses an increased risk when driving and during other safety-sensitive activities. For some of these individuals, an appropriate course of action is recognition and treatment of an underlying sleep disorder. Others may be unaware that they have adopted a sleep-wake schedule that does not allow sufficient time for sleep, and this results in chronic partial sleep deprivation.³ For these sleepy individuals, an appropriate course of action is to modify their schedule to allow appropriate time for sleep. However, in those for whom sleep loss is inevitable (eg, in emergencies when public health and safety personnel are responding to a disaster or when military personnel must engage in prolonged operations), judicious voluntary use of a stimulant under appropriate medical supervision may be warranted. In such

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situations, the use of a stimulant to maintain alertness and performance should be the result of informed decisions in which the potential risks and benefits are understood and accepted.

Concerns about the potential reliance of healthy, sleep-deprived persons on stimulants to prevent the effects of sleep loss on alertness and performance have led the American Academy of Sleep Medicine to examine the evidence for the efficacy and safety of stimulant use during sleep loss and to review other risks associated with stimulants as a means of defining parameters for the appropriate use of stimulants during sleep loss. This evidence-based review summarizes current knowledge of the performance effects of the stimulants caffeine, amphetamine, methylphenidate, pemoline, and modafinil in sleep-deprived healthy humans.

METHODS

An initial MEDLINE search was performed on August 29, 2003. The following string of search terms was used: Sleep deprivation and caffeine, or modafinil (or Provigil[®]), or methylphenidate (or Ritalin[®]), or amphetamine, or pemoline (or Cylert[®]). The search was limited to human research. This generated 181 references. Review of the bibliographies of the initial references (pearling) resulted in the inclusion of several additional papers. In addition, the purview of the committee was extended to include review of papers that focused on performance after administration of these compounds following normal sleep (ie, in the non-sleep-deprived state). It was also decided to include some supplementary information on effects of the stimulants on sleep, as well as other physiologic effects, safety, tolerance, and withdrawal. As a result, a total of 239 papers were obtained and made available to all of the committee members.

Papers were sorted by compound, and committee members were assigned to review 1 of 4 areas: caffeine, amphetamine, modafinil, or methylphenidate and pemoline (the latter 2 combined). Inclusion criteria for the performance section of the paper required presentation of empirical data relevant to the compound under review. Exclusion criteria included abstracts, reviews, theoretical papers, editorials, and case studies. However, these sources were considered for the general sections of the paper that dealt with physiology, safety, and general discussion. In a few instances, abstracts were considered for inclusion in the review section, and these instances are all specifically indicated as "abstract."

A data extraction sheet was developed prior to review of the articles. It included the following information: study design,

number and sex of subjects, types of performance measures, drugs and doses utilized, length of sleep deprivation and placement of stimulant during sleep loss, results, and miscellaneous notes.

There were 134 papers identified for evaluation under the topic of caffeine and sleep loss; 100 papers were identified under the topic of amphetamine and sleep loss; 32 articles were identified under the topic of modafinil and sleep loss; 17 articles were identified under the topic of methylphenidate and sleep loss; and 7 papers were identified under the topic of pemoline and sleep loss. The papers that dealt with 2 or more stimulants were included in each stimulant area. The great majority of the published studies reviewed in the performance sections involved administration of a given stimulant in a double-blind, placebo-controlled trial. Studies that did not involve all of these design factors are noted in the text by an asterisk next to the citation number.

Caffeine

Caffeine is arguably the most commonly ingested stimulant. Caffeine is not sold as a medication and, therefore, does not have specific indications or limitations. Caffeine is used regularly by 80% of adults in the United States,⁴ and per capita intake has been estimated at greater than 200 mg per day.⁴ The caffeine content of a few common foods is presented in Table 1. One 10-year-old review of caffeine cites 656 references⁵ related to the effects of caffeine in humans. An Institute of Medicine review of the use of caffeine to sustain mental task performance was published in 2001.⁶ A large number of studies have also examined the specific effect of caffeine upon a wide range of variables after restricted sleep and after periods of sleep deprivation ranging from 1 to 3 nights.

The efficacy of caffeine as a countermeasure to sleep deprivation can be examined as a function of several parameters, including length of sleep deprivation; dose of caffeine; type of measure; and, potentially, previous experience with, or tolerance to, caffeine. The doses of caffeine administered in the studies evaluated here ranged from 32 to 600 mg in single doses and up to 1200 mg per day in divided doses. Multiple formulations, including liquid, chewing gum, and tablets or capsules (some in time-release formulation) have been studied. A wide range of performance measures have been used to measure caffeine effects. Because caffeine is widely used in society, many studies have been limited to subjects who have relatively low habitual caffeine intake (usually less than 200-300 mg per day). As such, reported dose and time-course effects may not generalize to individuals with greater habitual caffeine use. In addition, tolerance to the effects of caffeine may develop within a few days in some circumstances^{7*} but apparently not in others.^{8*} However, because most sleep-loss studies have been acute, few address the development of tolerance during periods of sleep deprivation.

Caffeine Formulation Information

Caffeine has been examined in a number of formulations, including liquid (often in coffee), chewing gum, and in capsule or tablet form. Caffeine decreases adenosine transmission from both A(1) and A(2A) receptors in the brain. These receptors may be involved in a number of processes, including regulation of dopamine.⁹

In 1 study that examined the availability of caffeine from Stay

Table 1—Caffeine Content of Common Foods¹⁵⁴

Food Item	Size	Caffeine Content, mg
Nō-Dōz™	1 tablet, maximum strength	200
Brewed coffee	8 oz	134-217
Instant coffee	8 oz	95
Red Bull™	8.3 oz	80
Tea (bag)	8 oz	50
Common soft drinks	12 oz	34-55
Hershey™ bar	1.5 oz	10
Hot chocolate	8 oz	5

Alert® chewing gum compared with a capsule formulation,¹⁰ higher plasma concentration was seen for the first 10 to 40 minutes after administration, and an overall shorter time to maximum blood level (0.73-1.34 hours versus 1.4-2.0 hours for the capsule) was identified. There was a trend toward a lower maximum blood concentration from the gum formulation (less than 100% availability from the gum). In another study,¹¹ ingestion of an aqueous solution of 350 mg of caffeine resulted in a time to maximum blood level of 0.78 hours, with a maximum blood concentration of 8.3 µg/mL. Half-life typically ranged from 3 to 6 hours.¹² The slow-release formulation of caffeine (capsule) at 400 mg revealed a time to maximum blood level of 4 hours and a maximum blood concentration of 5.5 µg/mL.¹² The 600-mg dose of slow-release caffeine revealed a time to maximum blood level of 4.4 hours and a maximum blood concentration of 7.7 µg/mL. Elimination half-life (average of 4.4 hours in this study) was significantly shorter in habitual smokers compared with nonsmokers but was not shorter in habitual caffeine users compared with occasional users.¹² The slow-release caffeine data are consistent with the assertion that this formulation remains active for a longer period with a lower peak level than other forms of caffeine at comparable doses. The data from the liquid formulation suggest that the reported difference in onset attributed to the caffeine gum may be more related to digestion of a capsule in the stomach because the time to maximum blood level for the liquid caffeine solution was comparable with that of the gum.

Caffeine Psychomotor Performance Effects by Task

An examination of the sleep-deprivation and caffeine literature revealed several objective measures that have been widely employed in empirical studies. The most commonly reported objective measure, while not a psychomotor performance measure as strictly defined, is the ability to remain awake, as measured either by latency to physiologic sleep in a stay-awake paradigm—the Maintenance of Wakefulness Test (MWT)—or by latency to physiologic sleep in a fall-asleep paradigm—the Multiple Sleep Latency Test (MSLT). Fourteen of 15 studies of sleep-deprived subjects have shown significant increases in wakefulness measured by sleep-latency tests after the use of caffeine at several dose levels, as compared with placebo.^{13-20*,21-27} Additional studies have revealed significant increases in sleep latency when caffeine has been administered after normal nights of sleep.^{7*,28}

Reaction time from several different types of tests is a frequently reported performance outcome in caffeine trials. The

most commonly used test has been a choice reaction time (usually 4-choice) paradigm. Various aspects of performance on this task, including reaction time,^{26,27,29-32} accuracy,²⁵ and response failures,¹³ were improved significantly after caffeine administration compared with placebo in sleep-deprived subjects. In an unblinded, non-placebo-controlled study of more than 7000 adults who were not sleep deprived, simple reaction time decreased in a linear fashion as a function of habitual caffeine consumption for amounts ranging from 0 to 7 or more cups of coffee per day, with the greatest effect seen in older individuals (aged 55+ years).^{8*}

Short-term memory has been examined with several types of task, including the Digit Symbol Substitution Task (DSST). During sleep loss, significant beneficial effects of caffeine relative to placebo have been found in several studies^{13,15,19,29,33} but not all³⁴ (the latter was significant for DSST but not digit recall performance). In 1 study specifically designed to test the interaction of sleep loss with caffeine on memory performance,³⁵ it was found that 350 mg of caffeine had no significant effect on temporal memory (recency) after normal sleep but significantly improved this aspect of memory compared with placebo after 35 hours of sleep loss.

A number of caffeine studies have included measures of auditory or visual vigilance. Eight studies that included well-defined vigilance tasks all showed decreases in vigilance performance during sleep deprivation that were significantly reduced after administration of caffeine, as compared with placebo.^{14,15,22,29-31,34,36}

In 7 studies, grammatical reasoning ability has been examined during sleep loss after administration of caffeine or placebo.^{13-15,19,29,32,34} All found a significant improvement in grammatical reasoning after administering caffeine in sleepy individuals.

Several studies have specifically examined the effect of caffeine during simulated driving after sleep restriction.³⁷⁻⁴² All of these studies measured lane drifting (ie, the number of times the simulated car drifted across a lane marker), and all found a significant reduction when caffeine, as compared with placebo, was administered after a night of restricted sleep. However, in 1 study after a full night of sleep deprivation, the beneficial effects of 200 mg of caffeine (relative to placebo) were not maintained after 30 minutes.⁴⁰

Two studies followed Navy SEAL trainees through 72 hours of sleep deprivation prior to administration of caffeine and measurement of marksmanship. In 1 study,³¹ no significant effect of caffeine was found on marksmanship. In a second study that specifically concentrated on marksmanship parameters,⁴³ accuracy did not change after caffeine administration, but there was a significant reduction in sighting time. A third study of marksmanship measured during a 3-hour tour of sentry duty in non-sleep-deprived soldiers showed an interaction of caffeine or placebo use with time on duty.⁴⁴ There was little difference in time to respond to a new target at the beginning of the tour, but response time stayed constant for the 3 hours after administration of caffeine, whereas it increased by 400 milliseconds at the end of 3 hours in the placebo condition. A similar relationship was seen when “failure to fire” (ie, percentage of times that the soldier simply did not detect a target) was measured. About 10% of targets were not seen in each 30-minute period after caffeine. After placebo, failures increased from 12% at the beginning of the tour to 20% at the end (a statistically significant increase), but accuracy did not change.

Caffeine Psychomotor Effects by Dose

The effects of caffeine during sleep loss have been examined over a dose range from 75 to 1200 mg (divided doses) per 24 hours. Several studies have looked at a range of caffeine doses within a single administration study.^{17,19,31,43} All of these studies included a low dose (100 mg-150 mg), a medium dose (200 mg-300 mg), and a high dose (300 mg-600 mg). Two of the studies examined performance when 100 mg, 200 mg, or 300 mg of caffeine was administered after about 72 hours with 1.5 hours of sleep.^{31,43} After 72 hours, no significant improvement in marksmanship or psychomotor performance was found for the 100-mg dose. Performance was significantly improved for sighting time (marksmanship) and time to complete a memory/motor-learning task at 1 and 8 hours after administration for the 200-mg and 300-mg doses (200 mg only for the learning task). On a vigilance task, hits were increased and false alarms reduced in a dose-dependent fashion, with significantly improved performance at the 300-mg dose 1 hour after administration, as compared with placebo. However, the authors of these studies recommended the 200-mg dose as the most efficacious.

The other 2 dose studies examined the efficacy of caffeine administered after either 20 hours¹⁹ or 49 hours¹⁷ of wakefulness. After 20 hours of wakefulness, slow-release caffeine produced significant improvement on MSLT and 7 performance tasks for 13 hours (last test point). For the 150-mg dose, performance was significantly improved for 2 (of 7) tests at 9 hours and for 1 test at 13 hours after administration. For the 300-mg dose, alertness was improved at 2 hours, and performance was improved on 3 tests at 9 hours and 2 tests at 13 hours. For the 600-mg dose, performance was increased for 3 tests at both 9 and 13 hours. The second study¹⁷ reported reaction time and objective alertness for 12 hours after the same doses of caffeine (normal caffeine in a lemon drink). Significant improvement in ability to stay awake, as measured by the MSLT, was found for 6 hours after administration of 300-mg and as long as 10 hours after the 600-mg dose (the report of “significance” was estimated from data presented in a table). No significant change in alertness was apparent after the 150-mg dose. Reaction-time performance was significantly improved at 8 hours after administration in the 600-mg group but was not obviously improved at lower doses. The 300-mg dose was cited as preferable because side effects (shivering or tachycardia) were more prominent at the 600-mg dose, particularly in women.¹⁹ There is a probable interaction of caffeine dose with degree of sleep loss when the caffeine is administered—as a result, further dose effects will be discussed in the following section on varying lengths of sleep loss.

Caffeine Effects by Length of Sleep-Deprivation Period

The impact of caffeine on various tests of alertness and psychomotor performance has been documented following normal sleep, sleep restriction, during night work (usually involving 5-20 hours of sleep loss), after short periods of sleep deprivation (24-36 hours), and after extended sleep deprivation (64-72 hours).

Caffeine Following Normal Sleep

There is a common perception that caffeine has little beneficial effect on the performance of individuals who are not sleep deprived.⁴⁵ Three studies specifically compared the effect of caf-

feine on performance following normal nights of sleep versus periods of sleep loss.^{32,33,46} Two of the studies found similar (main effect only for caffeine) improvement in performance on visual search, reasoning, and reaction time after caffeine administration on the baseline day and during a single night of total sleep loss.^{32,46} Another study found a significant interaction that demonstrated superior improvement on a memory task during sleep loss but worse performance after caffeine consumption during a normal day.³³

One study⁴⁷ reported performance effects from a wide range of caffeine doses (32 mg-256 mg) administered to groups of habitual, high (314 mg/day) and low (0 mg/day) caffeine users following normal sleep. Performance on vigilance and 4-choice reaction time was significantly improved after all doses of caffeine in both groups. Significant changes were not found on a pegboard task, tapping, fine finger movement, DSST, and a simple reaction time task after any dose of caffeine. In a different type of study, Jarvis^{8*} interviewed a large sample of people, noted habitual caffeine use, and measured psychomotor performance. A linear relationship was found, indicating that reaction time reliably decreased as habitual caffeine consumption level (cups of coffee per day) increased.

Three studies have looked at the effects of single doses of caffeine on MSLT after normal sleep. In 2 of 3 reports, significantly increased sleep latency (increased alertness) was found after caffeine administration.^{7*,16,48} In 1 study,⁴⁸ sleep latency averaged 17 minutes on the first day of caffeine consumption (250 mg b.i.d.) and 14.6 minutes on the second day compared with a placebo group average of 5 minutes. A second within-subjects study^{7*} found that sleep latency was significantly increased from 10.7 to 17.8 minutes on the first day following caffeine (400 mg t.i.d.). Daytime sleep latency was 13.4 minutes after a week of caffeine administration (the withdrawal value was 11.3 minutes). A third study reported a nonsignificant increase in sleep latency after a single dose of caffeine (250 mg).¹⁶

Many studies have looked at psychomotor performance with various doses of caffeine after normal sleep periods. One study of caffeine doses ranging from 32 mg to 256 mg found significantly increased vigilance and reaction-time performance at all doses compared with placebo.⁴⁷ Two studies^{49,50} have reported significant improvement in performance (reaction time and DSST) after moderate doses of caffeine (250 mg or 300 mg) but not higher doses (500 mg or 600 mg). Another study⁴⁴ found that administration of caffeine (200 mg) prevented a linear increase in time taken to respond over 3 hours of sentry duty that occurred in control and placebo conditions. As such, response time was about 100 milliseconds faster 40 minutes after caffeine ingestion, but the difference increased to 400 milliseconds after 3 hours. Another study⁵¹ found a decrease in performance time at first exposure to an embedded-figures task following caffeine administration but a significant improvement on the task during a second exposure (explained as a novelty effect).

In contrast with the positive effects on performance from caffeine after a normal night of sleep, 2 studies found no improvement on any performance task when caffeine was administered to higher caffeine users (3 to 5 caffeine beverages per day^{45,52}), but 1 study reported significant decreases in performance when subjects were withdrawn from caffeine.⁵² The author of the study suggested that the positive effects of caffeine administration on performance found in other studies might be the result of comparing caffeine conditions to baseline levels where subjects were ac-

tually in withdrawal during the baseline period.⁵² However, some of the other studies are based upon between-groups comparisons, in which any withdrawal might be assumed to be equivalent,⁴⁸ and other studies have examined subjects who habitually use little caffeine. Several reviews of the effects of caffeine upon performance after normal sleep have concluded that beneficial effects exist.^{5,53} However, there is also evidence that large numbers of individuals suffer from some level of chronic partial sleep deprivation. It is possible that the observed benefits of caffeine in these individuals were at least partially attributable to reversal of the effects of unrecognized partial sleep deprivation.

Caffeine and Sleep Restriction

Acute sleep restriction, typically between 4.5 hours and 5 hours in bed for 1 night, has been a common manipulation prior to evaluating the effects of caffeine on driving simulator performance. Three studies using common methodology have looked at performance on a 1- or 2-hour drive after consumption of an energy drink (containing 80 mg of caffeine), or after 150 mg of caffeine, or after 200 mg of caffeine.⁴⁰⁻⁴² In all studies, fewer “incidents” of a driver crossing a lane-marker line were found for the entire hour or first 90 minutes of the 2-hour drive following caffeine versus placebo. In a third study,³⁷ incidents of lane drifting were decreased for 45-minute simulated drives at 9:00 AM and 1:00 PM following administration of 300 mg of slow-release caffeine versus placebo at 8:00 AM. One study found significant improvement on reaction time and MSLT when caffeine, 75 mg or 150 mg, was administered after 5 hours of sleep.²²

Several studies have looked at caffeine as an aid during night-shift work. In 5 investigations, approximately 300 mg of caffeine was administered at about 11:00 PM.^{21,23,34,36,54} These studies reported significant beneficial effects of caffeine relative to placebo throughout the test periods (that ranged from 6-10 hours after administration) on outcomes that included sleep-latency tests,^{21,23} simulated assembly line, vigilance, memory, and reasoning.^{32,33,46} However, at this dose level, alertness and performance continued to deteriorate during the night as a function of circadian rhythm and increasing sleep loss in both the placebo and caffeine groups. Addition of a 4-hour prophylactic nap prior to the administration of 200 mg of caffeine at 1:30 AM and 7:30 AM was sufficient to maintain vigilance and objective alertness at baseline levels throughout the night and until 10:00 PM on the next evening.¹⁴

Caffeine Following 1 Night of Total Sleep Loss

A few studies have examined the beneficial effects of caffeine following 1 night of total sleep loss. Significant improvement on a range of tasks, including memory, logical reasoning, vigilance, math, and reaction time, at 1.5 and 5.5 hours after drug administration was found when caffeine (300 mg/70 kg) was compared with placebo after 1 night of sleep loss.²⁹ Two studies of slow-release caffeine showed improvement in reaction time (including recognition time) and sustained attention for 21 hours after administration at 9:00 pm⁵⁵ and improvement on memory search and tracking tasks for 13 hours after administration.¹⁹

Caffeine Following 2 or More Nights of Total Sleep Loss

Several studies have examined the efficacy of caffeine during sleep-deprivation periods that extended for 2 or more nights. One

group of studies placed a single administration of caffeine during either the second night (after 41.5-64 hours of wakefulness) or third night (after 72 hours of wakefulness with a 1.5-hour nap). In 1 study, 600 mg of caffeine was administered after 41.5 hours of wakefulness.²⁵ Performance on the psychomotor vigilance task (PVT), the serial addition/subtraction task, a 4-choice task, and sleep latency improved for 11 hours, as determined by significant main effects without time interactions in the analyses of variance. Performance after 600 mg of caffeine was similar to that seen after 200 mg to 400 mg of modafinil administered at the same time and significantly better at some points than 100 mg of modafinil.²⁵ In another study,²⁷ 600 mg of caffeine was administered after 64 hours of wakefulness, and PVT response time was improved until 6 hours later. Performance after 600 mg of caffeine remained improved as long as performance after 20 mg of d-amphetamine but not as long as the improvement seen with 400 mg of modafinil.

Kamimori et al¹⁷ administered either 150 mg, 300 mg, or 600 mg of caffeine after 49 hours of wakefulness. Significant improvement on the MSLT was evident for 6 hours after administration of the 300-mg and for as long as 10 hours after the 600-mg dose. No significant change on the MSLT was apparent after the 150-mg dose. Reaction-time performance was significantly improved at 8 hours after administration in the 600-mg group but was not improved at lower doses.

In 2 other single-dose studies,^{31,43} 100 mg, 200 mg, or 300 mg of caffeine was administered after 72 hours of sleep loss (including one 1.5-hour nap), and performance was tested 1 and 8 hours later. Relative to placebo, performance after 100 mg of caffeine was not significantly improved on any measure. Performance on response-time measures (from 4-choice and repeated acquisition) and on marksmanship sighting times was significantly improved after 200 mg of caffeine. The repeated-acquisition improvement remained significant after 8 hours. Similar results were found for the 300-mg dose.^{31,43}

Another group of studies has examined the effects of multiple caffeine doses across 2 nights of sleep deprivation. These studies allowed comparison of doses of caffeine at 2 graded levels of sleep loss. Wright et al²⁶ administered caffeine 200 mg twice a day (at 8:00 PM and 2:00 AM) on each night and found significant main effects for caffeine (no significant interaction by night) for performance tasks, including PVT, Thurstone word generation, and switching tasks. A significant caffeine-by-night interaction was found for the MWT, with a significantly greater effect on the second night. However, this difference could have been caused by ceiling effects during the first night (the MWT was only 15 minutes long). Using a similar design, 2 studies provided 400 mg of caffeine at 1:30 AM on each of 2 consecutive sleep-loss nights.^{15,18} Performance on vigilance, additions, DSST, logical reasoning tasks, and alertness, as measured by the MSLT and MWT, was significantly improved compared with baseline at test sessions 3 to 4 hours after caffeine was administered and, in the case of logical reasoning, for 12 hours after administration on the first night of sleep deprivation. Performance and MSLT measures showed significant improvement 3 to 4 hours after administration on night 2 but not during later test sessions. In a final multnight study,¹³ slow-release caffeine was administered at 300 mg twice each day (at 9:00 PM and 9:00 AM). In this paradigm, sleep latency (MSLT) was significantly increased throughout the entire sleep-deprivation period (until 4:00 PM following the second night of sleep loss). Psychomotor performance was significantly improved on

a wide variety of tasks, including reaction time (night 1), mathematical processing (elements throughout), memory scanning (throughout), symbol cancellation (throughout), tracking (until the final test), and grammatical reasoning (night 1).

In summary, many studies have provided evidence for improved performance following caffeine administration. Some studies have shown increased sleep latency and, occasionally, improved performance when caffeine has been administered under baseline sleep conditions. Beneficial effects of caffeine upon performance variables have been found at doses as low as 32 mg with no sleep loss, for moderate doses (75-150 mg) after sleep restricted to 5 hours for 1 night, and at higher doses (200-600 mg) for at least 8 hours after a third night of deprivation. With 1 possible exception,³³ none of the papers reported significantly decreased alertness or performance on any measure at any point following caffeine administration as compared with placebo groups. One study did report longer reaction time in infrequent caffeine users after a 400-mg dose with no sleep loss, whereas higher caffeine users were found to have decreased reaction time in the same paradigm.⁵⁶ Caffeine administration typically improves performance during sleep loss as compared with placebo, but performance and alertness continue to decline as a function of sleep loss, circadian rhythm, and caffeine half-life so that participants may still have escalating sleepiness and diminishing performance over time.

Caffeine Subjective Effects

Many studies of psychomotor performance after caffeine administration have also monitored the effect of caffeine upon subjective alertness and mood. It is common to find significant decreases in subjective alertness and increases in fatigue and sleepiness during sleep deprivation. Studies that monitor mood typically show that caffeine ameliorates these subjective changes, with a time course similar to that seen for performance variables.^{15,31,57}

However, there are several situations in which subjective response results may not parallel the typical performance results. For example, in a study of low doses of caffeine given after normal sleep, Lieberman, et al⁴⁷ found no significant changes in subjective report while finding significant positive performance change. In 2 studies that examined repeated caffeine administration (125 mg or 400 mg t.i.d for 6 or 7 days), the typical increase in subjective alertness/vigor after initial administration was found, but significantly decreased alertness/vigor compared with predrug baseline developed after 6 or 7 days of use.^{7*,52} As a comparison, MSLT was significantly increased at initial caffeine use and significantly lower than the initial caffeine value after 7 days of use but still significantly increased when compared with baseline.^{7*} The implication of this pattern of results is that some "subjective tolerance" (as measured here by mood scales) to the caffeine developed over the week and that this subjective tolerance was greater than the physiologic tolerance (as measured here by the MSLT). In a recent study of hourly low-dose (0.3 mg/kg) caffeine administration, increased sleepiness was reported compared with placebo in a second (but not the first) 28-hour administration period,⁵⁸ again supporting subjective tolerance after repeated administration. This more-rapid development of subjective versus objective tolerance might predispose individuals to increase caffeine consumption more rapidly than indicated by physiologic tolerance and could help to explain the previously described find-

ings that reaction time decreases in a linear fashion with increasing habitual dose of caffeine.^{8*}

Caffeine Effects on Sleep and Other Physiologic Effects

A number of studies have documented that caffeine administered within 2 hours of bedtime in doses of 100 mg or greater can produce degraded sleep, usually evidenced by increased sleep latency and decreased amounts of slow-wave sleep and total sleep time (reviewed by Bonnet and Arand⁷). Effects on sleep are related to dose and probably to individual tolerance to caffeine. Such effects may be of concern in some sleep-deprivation paradigms, such as night-shift work, in which individuals may use caffeine to help maintain alertness at work or during the commute home shortly before initiating sleep. One study²¹ reported no significant difference in daytime sleep parameters after administration of caffeine (2 doses of about 140 mg at 10:20 PM and 1:20 AM on the prior night). However, there was interindividual variability in response to caffeine, and the mean total sleep time after the first night of caffeine administration was an hour less in the caffeine group when compared with the placebo group. A second study reported a significant decrease in slow-wave sleep during a day sleep period following administration of 300 mg of caffeine at 11:15 PM on the previous night, as compared with placebo.³⁴ There was also a 35-minute reduction in total sleep time, but this was not statistically significant. These studies suggest that there can be some effects of caffeine on sleep periods that begin about 8 hours after caffeine administration. In a study of sleep 16 hours after administration of 200 mg of caffeine at 7:00 am, Landolt et al⁵⁹ reported no statistically significant difference in sleep latency (8.5 vs 13 minutes for placebo and caffeine, respectively) but a significant decrease in sleep efficiency. However, when sleep efficiency was calculated as total sleep divided by time in bed (from data in the manuscript), sleep efficiency following both placebo and caffeine was 96%.

A number of physiologic changes have been reported following caffeine consumption. Acute effects include increased metabolic rate,⁷ increased blood pressure,⁶ increased gastric secretion,⁴ diuresis,⁴ increased secretion of epinephrine and norepinephrine,⁶⁰ increased body temperature,⁶¹ and possible increase in heart rate.⁴ Some individuals suffering from anxiety disorders may have increased anxiety or panic attacks following caffeine administration. Although there is no evidence that any of these physiologic effects are further exacerbated by the combination of caffeine and sleep loss, few published studies of caffeine either measure or report physiologic outcomes.

Caffeine Safety and Side Effects

The safety of caffeine as a food and beverage additive has been evaluated several times.⁶ In 1987, the United States Food and Drug Administration (FDA) concluded that caffeine added to beverages at a level of 0.02% or less did not present a health risk. In 1992, another FDA review concluded that there was no evidence of a human health hazard from the consumption of caffeine in cola beverages at 100 mg per day or less (but this should not imply risks or safety at higher doses).

Caffeine has been shown to produce a transient increase in blood pressure, but a number of studies have failed to link caffeine with cardiovascular disease. The possible effect of caffeine on reproduction, bone mineral density, and fluid homeostasis was

reviewed in a report from the Institute of Medicine.⁶ The report concluded that caffeine might be associated with a small increase of spontaneous abortion in the first trimester of pregnancy and that caffeine can significantly increase 24-hour urine output. These effects were not seen as limitations on the military use of caffeine, though increased urine output, for example, could provide practical problems under some operational conditions. It was recommended that doses should not exceed 600 mg due to possible negative effects on mood and performance at higher doses. The Institute of Medicine report did not note the shift in effective dose related to degree of sleep loss that has become evident in this review.

Because caffeine is not a prescription medication, standard dosing and side-effect information are not available. The information in the Physicians Desk Reference for Nonprescription Drugs and Dietary Supplements for the product Nō-Dōz[®], which contains 200 mg of caffeine, indicates that the product may cause “nervousness, irritability, sleeplessness and, occasionally, rapid heart beat.” Few research studies report carefully controlled side-effect data from matched caffeine and placebo groups. One of 3 studies adopting such an approach²⁵ found a significant increase in heart pounding and nausea about 3 hours after administration of 600 mg of caffeine but not at later time points. Two instances of vomiting were also reported.²⁵ Another study found significant increases in jitteriness, nausea, tremor, and racing heartbeat for as long as 6 hours after administration of 600 mg of caffeine.²⁷ In the final study,³¹ an 8% incidence of nervousness and blurry vision, a 6% incidence of dizziness, and a 4% incidence of tiredness/crash after administration of 200 mg or 300 mg of caffeine was reported, but these rates of occurrence were not statistically significant. De Valck et al³⁷ reported 1 subject (of 12) with gastrointestinal upset, nervousness, and sweating after administration of 300 mg of slow-release caffeine. In a study of 300 mg and 600 mg of slow-release caffeine, 8 (of 24) subjects suffered from minor “numbness, shaking, muscular pains, palpitations, and/or headache” (19p658). Finally, an abstract reported 2 cases of nausea and 1 case of palpitation (in the same 12 subjects at multiple doses) after administration of doses of slow-release caffeine ranging from 300 mg to 1200 mg.⁶² At 2400 mg, 3 subjects had vomiting. Both subjects given 3600 mg had frequent severe vomiting lasting up to 24 hours.

Some investigators estimate that as many as 10% of adults develop the syndrome of caffeinism,⁴ which is defined as the daily consumption of large amounts of caffeine (usually in excess of 500 mg/day). Symptoms of caffeinism or caffeine intoxication include restlessness, nervousness, excitement, insomnia, flushed face, diuresis, gastrointestinal disturbance, muscle twitching, rambling speech, tachycardia, and agitation.⁴ The lethal acute adult dose of caffeine is about 5 to 10 grams (about 75 cups of coffee).

Caffeine Conclusions

Caffeine is a readily available, short-acting stimulant that has been shown to reduce some of the deficits associated with sleep loss. Studies suggest that caffeine can provide improved alertness and performance at doses of 75 to 150 mg after acute restriction of sleep and at doses of 200 to 600 mg after a night or more of total sleep loss. Caffeine is unlikely to have major disruptive effects on the sleep that follows 8 hours or longer after administration.

However, frequent use of caffeine can lead to tolerance and negative withdrawal effects.

Amphetamine

Amphetamines, first discovered in 1887, are anorexic/stimulant compounds, with a current FDA indication for the excessive hypersomnolence associated with narcolepsy and attention-deficit/hyperactivity disorder (ADHD).⁶³ Due to their high abuse potential, risk of dependence, and side effects, they are listed in Schedule II of the Controlled Substances Act of the Drug Enforcement Administration (DEA). In addition to their FDA-approved indications, amphetamines have been sanctioned for use since 1960 during some military flight operations⁶⁴ to mitigate the adverse behavioral effects of sleep loss. The effects of amphetamines have been widely studied in healthy adults.

Amphetamine Formulation Information

The most commonly administered form of amphetamine in human research studies is dextroamphetamine (d-amphetamine), which is almost 2 times more potent for promoting alertness and waking functions than the l-isomer, l-amphetamine.⁶⁵ The use of d-amphetamine has been reported to produce greater improvement on a vigilance task^{66*} and greater disturbance in sleep continuity⁶⁷ compared with l-amphetamine.

Amphetamine's mode of action involves rapid diffusion directly into neuronal terminals. The substance enters vesicles via dopamine and norepinephrine transporters (DATs and NETs), causing release of the corresponding neurotransmitters. The actual mechanism, however, appears to be more complex than merely promoting neurotransmitter release. In knockout mice lacking an intact DAT, dopamine is not released into the synaptic cleft in response to amphetamine exposure, showing the DAT to be the rate-limiting step. The dopaminergic effects of amphetamines are the reverse of the effects found for NETs. Knockout mice lacking an intact NET were actually supersensitive to amphetamines, since, in the absence of norepinephrine transport, there is no feedback control on amphetamine-induced dopaminergic function.⁶⁵

Following oral administration, peak levels of d-amphetamines in the plasma are achieved after approximately 2 hours, with a half-life of approximately 16 to 30 hours. The most frequent route of d-amphetamine administration in experimental reports on its effects in healthy individuals is oral administration, with doses of 10 or 20 mg most commonly studied. One of 33 studies reviewed here administered d-amphetamine in liquid form.⁶⁸ One double-blind, randomized study examined the difference in effect of 20 mg of (free base) d-amphetamine in salt (phosphate) versus a cationic resinate form, with both forms administered orally.^{69*} Significantly lower plasma and blood cell levels were seen with the resinate form 90, 120, and 240 minutes after administration compared with the salt form. In both of these (non-sleep-deprivation) studies, d-amphetamine induced brief increases of systolic and diastolic blood pressure, with salt effects significantly greater than those of resin.^{69*}

Methamphetamine differs from amphetamine by an additional methyl group attached to the amine, making it a secondary substituted amine. Methamphetamine also possesses l and d stereoisomers, with the dextro form more widely studied. A small number of studies have examined the stimulant effects of methamphetamine; however, this compound is less widely studied or

administered, due to its significant neurotoxic effects, resulting in destruction of basal ganglia dopaminergic neurons,⁷⁰ and adverse effects on the cardiovascular system.⁷¹ Methamphetamine appears to increase free radicals, decrease adenosine triphosphate synthesis, and cause mitochondrial damage.⁶⁵

Methamphetamine and its effects will be briefly addressed first, but the focus of this section will be on d-amphetamine.

Methamphetamine Psychomotor Performance Effects

One placebo-controlled study investigated the effects of 3 consecutive days of methamphetamine administration (10 mg/day and 20 mg/day) under normal sleep conditions (no sleep deprivation) on a performance battery that included tests of working memory (DSST, repeated acquisition task), short- and long-term memory (immediate and delayed digit recall), divided attention, and information processing.^{72*} The report concluded that methamphetamine had no consistent effects on task performance.^{72*}

Another study examined vigilance and tracking task performance over 13.5 hours of sustained performance during 1 night of sleep loss with methamphetamine given at a dose of 5 mg per 70 kg of body weight or 10 mg per 70 kg of body weight.⁷³ Both doses reduced the detrimental effects of sustained performance on vigilance, and efficiency returned to 78% of its initial level approximately 2 hours after the drug was ingested. After 2 hours, efficiency in the 10-mg group actually continued to increase slightly, whereas the efficiency of the 5-mg group decreased slightly. Performance lapses also occurred less frequently at both drug doses. These results contradict the experimental hypothesis that methamphetamine would induce faster, but less careful, responses. Both doses also reduced the negative effects of sustained performance on tracking errors.⁷³

A third study examined methamphetamine as an aid to increasing performance during night-shift work.⁷⁴ A single dose of either 5 mg or 10 mg of methamphetamine or placebo was administered to subjects 1 hour after waking for 3 consecutive days under 1 of 2 shift conditions: during the day shift, participants performed tasks from 8:30 AM to 5:30 PM and went to bed at midnight for an 8.25-hour sleep period; during the night shift, participants performed tasks from 12:30 AM to 9:30 AM and went to bed at 4:00 PM for an 8.25-hour sleep period. Following drug administration, an improvement in performance measures was evident during the night-shift condition. Specifically, significant decreases were observed in both methamphetamine dose conditions (relative to the placebo condition) on the number of errors on the repeated acquisition task, the mean hit latency on the divided attention task, and the number of false alarms on the rapid information task. In contrast, methamphetamine produced few significant effects on performance during the day-shift condition.⁷⁴

A final methamphetamine study involved 25 naval aviators undergoing 60 hours of sleep deprivation and various performance tasks. Subjects were given either placebo or methamphetamine at 10 mg per 70 kg body weight 50.3 hours into the study. The drug significantly improved performance during the Manikin and pattern recognition tasks. Throughout the 60 hours of sleep deprivation, subjects given placebo appeared to shift from a conservative to a more risky response strategy (resulting in an increase in error rate as well as hit rate), and methamphetamine appeared to decrease this risky behavior.⁷⁵

Methamphetamine Subjective Effects

In the absence of sleep deprivation, subjects reported “good drug effects” and a “high” on the first day of 20 mg of methamphetamine administration per day.^{72*} However, these effects were no longer evident by the third day, and this suggested development of tolerance to the drug.^{72*} An increase in subjective reports of positive drug effects was observed under methamphetamine administration of 7.5 mg, 15 mg, and 30 mg per 70 kg of body weight with no sleep deprivation.⁷⁶ In addition, subjects reported a higher incidence of nervousness and reduced sleep duration following administration of drug compared with placebo.⁷⁶

One study had subjects rate their sleepiness using the Stanford Sleepiness Scale during a 13.5-hour sustained-performance session throughout a night of sleep loss.⁷³ Methamphetamine (5 mg/70 kg or 10 mg/70 kg) or placebo was administered at 1:16 am. It was found that mean sleepiness ratings in the methamphetamine groups were higher than mean ratings in the placebo group, but this was due primarily to a paradoxical decrease in sleepiness ratings in the placebo group rather than to a large increase in the drug groups.

In the study described above of a single daily dose of either 5 mg or 10 mg of methamphetamine or placebo administered during 3 days of day shifts (with nocturnal sleep) and during 3 days of night shifts (with diurnal sleep),⁷⁴ both 5-mg and 10-mg doses of the drug increased ratings of “alert” and “self-confident” on the first night and decreased ratings of “tired” across the first 2 nights, but only the 10-mg dose increased ratings of “alert” on the second night and ratings of being “self-confident” on the third night. However, these improvements in subjective alertness from methamphetamine did not prevent decreases across all 3 night shifts in all 3 conditions.

In a study involving 60 hours of sleep loss with administration of 10 mg of methamphetamine per 70 kg of body weight, reported fatigue and sleepiness (Stanford Sleepiness Scale) were decreased.⁷⁵

Methamphetamine Sleep Effects

Only 1 study that examined the effects of methamphetamine administration on sleep physiology was found, and it involved no sleep deprivation. Following the first day of 10 mg of methamphetamine administration at 10:00 AM and 6:00 pm, total sleep time, sleep efficiency, and total minutes of non-rapid eye movement (NREM) sleep were significantly decreased, and the number of movements and awakenings were increased, compared with placebo.^{72*} Furthermore, subjective sleep quality, assessed using visual analog scales, decreased on the first night, and subjective sleep quantity decreased on the first and second nights. On the third night, however, these detrimental effects on both objective and subjective sleep measures were no longer present,^{72*} and this suggests that tolerance had developed to the 10-mg dose of methamphetamine. However, improved sleep during the third night would also have been a response to partial sleep loss on the first 2 nights.

Methamphetamine Safety and Side Effects

One study examined the physiologic and neurobehavioral effects of methamphetamine (15 mg/70 kg, 30 mg/70 kg) under sleep-satiated conditions, compared with placebo.⁷⁶ All doses of

methamphetamine and d-amphetamine produced dose-related increases in blood pressure. Increases in respiratory rate, core body temperature, pupillary dilation, tachycardia, and adrenaline levels and decreased appetite were also observed with both drugs. The higher dose of methamphetamine was also associated with increased urine production.⁷⁶ In a simulated night-shift work condition, 5 and 10 mg of methamphetamine produced an anorexigenic effect, resulting in a significantly reduced caloric intake.⁷⁴

Several adverse experiences have been reported by non-sleep-deprived subjects following daily administration of 10 mg or 20 mg of methamphetamine for 3 days.^{72*} These included dizziness, jitteriness, anxiety, depression, difficulty concentrating, confusion, insomnia, chills, sweating, flu-like symptoms, numbness in the extremities, heart pounding, nausea, vomiting, and decreased appetite or hunger. A decrease in caloric intake also occurred during the drug condition. On the final day of drug administration, there were increased reports of “bad drug effects,” that included a decreased rating of desire to take the drug again when compared with reports on the first day of administration. In addition, following the end of drug administration, subjects experienced hangover effects, including irritability, jitteriness, misery, and heavy limbs.

Performance Effects of d-Amphetamine by Task

Relative to methamphetamine, d-amphetamine has been more extensively studied. A total of 20 peer-review papers on the effects of d-amphetamine on performance measures were identified and evaluated. Four were published in the 1970s,^{66,77-79} one in 2003,²⁹ and the remaining 15 reports derive from 3 military laboratories and were published between 1989 and 2001.^{66,80-93} It is not entirely clear whether these 15 reports represent 15 unique experiments or different facets of a smaller number of experiments. Among these 20 publications, a range of performance measures has been reported relative to the effects of administration of d-amphetamine.

The effects of d-amphetamine on reaction-time performance have been assessed using a 4-choice serial reaction-time task.^{29,80} Following administration of 20 mg of d-amphetamine after 40.5 hours of wakefulness, an improvement in visual reaction time was evident.²⁹ Similarly, 20 mg of d-amphetamine increased accuracy in a visual reaction time task following 60 hours of sleep deprivation.⁸⁰

Two studies included measures of auditory or visual vigilance. On an auditory reaction time task completed after 63 hours of total sleep deprivation,⁸¹ performance improvements were found following administration of 20 mg of d-amphetamine compared with placebo. Improved performance was also found after 20 mg of d-amphetamine, compared with placebo, on a visual vigilance task after 40.5 hours of total sleep deprivation.²⁹

The effects of d-amphetamine on both short- and long-term memory also have been examined. In 3 studies, memory performance was significantly improved after use of d-amphetamine relative to placebo. Following administration of 20 mg of d-amphetamine, digit span memory was improved after 64 hours of total sleep deprivation,⁸² and performance on a running memory task was improved after 40.5 hours of total sleep deprivation.²⁹ Ten milligrams of d-amphetamine given 1 hour before a short-term memory task improved performance in a study involving

no sleep deprivation.⁹² In contrast, administration of 10 mg of d-amphetamine was reported to have had no significant effect on a nonsense syllable learning memory test after 20 hours of total sleep deprivation, despite positive subjective effects.⁷⁷

Mathematical reasoning ability during sleep loss after administration of d-amphetamine has been tested with addition/subtraction tasks. Three studies showed significant improvement in performance on these tasks after administration of 20 mg of d-amphetamine per day during 40 hours to 64 hours of total sleep deprivation.^{29,83,84} In a fourth study, performance on psychomotor and cognitive tasks was not altered by the 10-mg dose of d-amphetamine during 20 hours of total sleep deprivation,⁷⁷ despite positive subjective effects.

Five published reports by the same military-based investigators have assessed the effectiveness of d-amphetamine during sleep loss in helicopter flight simulators^{85-87,93} or in actual helicopter operations.^{88*} One study reported that three 10-mg doses of d-amphetamine administered during two 41-hour periods of total sleep deprivation (during 1 of the sleep-deprivation periods, subjects were provided with d-amphetamine, whereas in the other, placebo was administered) were associated with improved performance in 6 of 9 helicopter flight simulator maneuvers, as compared with placebo.⁹³ Another study reported an overall increase in performance on UH-60 helicopter flight simulators following three 10-mg doses of d-amphetamine during two 41-hour periods of total sleep deprivation (again, during 1 of the sleep-deprivation periods, subjects were provided with d-amphetamine, whereas, in the other, placebo was administered). However, this effect was not consistent across all time points; amphetamine's benefits were most apparent at the times during which the homeostatic- and circadian-driven decrements in alertness and performance were most severe.⁸⁵ This finding was replicated in subsequent studies using the same experimental protocol⁸⁷ and in actual helicopter flight operations.^{88*}

Two studies from army investigators used the Performance Assessment Battery to measure performance effects of 20 mg of d-amphetamine during 40.5 to 64 hours of total sleep deprivation.^{29,80} Tests included visual scanning, running memory, logical reasoning, mathematical processing, Stroop reaction time, time wall, pursuit tracking, visual vigilance, Trails, and long-term memory tasks. Both placebo-controlled, double-blind studies showed improvement with drug for every measure within the test battery.^{29,80}

Motor task performance was also assessed in a number of experiments. Tasks included a kinesthetic arm-position replication task with arm-movement apparatus,⁹⁴ the Grunberger fine motor activity test,⁸⁹ the O'Connor test (metal pins inserted in holes),^{69*} a tapping speed task,⁷⁷ and an aiming task.⁷⁷ The kinesthetic task, administered after 63 hours of total sleep deprivation, was significantly improved by administration of 20 mg of d-amphetamine.⁹⁴ In 1 study under normal sleep conditions, 10 mg of d-amphetamine enhanced tapping speed on a 2-handed tapping task⁹²; however, in another study, tapping speed and aiming tasks were unaffected by 10 mg of d-amphetamine after 20 hours of total sleep deprivation.⁷⁷

Four studies used tracking tasks to measure performance following d-amphetamine administration or placebo. A dose of 10 mg of d-amphetamine improved tracking and alertness in subjects undergoing no sleep deprivation⁷⁸ and in subjects undergoing 34 hours to 55 hours total sleep deprivation.^{95*} A dose of

20 mg of d-amphetamine also improved tracking performance during 40.5 to 60 hours of total sleep deprivation.^{29,84}

Effects of d-Amphetamine by Dose

The effects of d-amphetamine during sleep loss have been examined over a dose range of 1 mg to 40 mg per 24 hours. Six studies have looked at a range of d-amphetamine doses within a single-administration study.^{68,76,79,80,89,96} However, only 1 of these reports⁷⁴ involved performance outcomes during sleep deprivation. Most of these studies included a low dose of 5 mg or 10 mg and a high dose of 10 mg to 40 mg, with some studies including intermediate doses of 15 mg to 20 mg.

One study examined 5 mg, 10 mg, and 20 mg of d-amphetamine administered after 48 hours of wakefulness during a 60-hour period of sleep loss⁸⁰; d-amphetamine produced a significant dose-related improvement in accuracy on a mathematical task, with a significant dose-by-time interaction for accuracy score. The 20-mg dose rapidly improved accuracy, and the 10-mg dose produced results of a similar magnitude, but only the 20-mg dose was able to maintain such levels. Performance accuracy after the 10-mg dose declined slightly after 2.5 hours and was not significantly different from placebo by 4.5 hours after drug administration. The 5-mg dose had no significant effects on performance.⁸⁰ Six of 7 studies found performance effects associated with 2 to 3 different doses of d-amphetamine without sleep deprivation.^{68,76,78,79,89,96} The physiologic effects of 10 mg of d-amphetamine differed significantly from those of the 1-mg dose at 1.5, 2, 2.5, and 3 hours after administration, with the 10-mg dose producing significantly larger effects.⁹⁶ Without sleep deprivation, a dose of 10 mg of d-amphetamine produced feelings of restlessness and agitation, palpitations, dry mouth, and difficulty sleeping in some subjects; the higher dose also caused a significant reduction in hunger ratings. These effects were not evident following administration of 1 mg of d-amphetamine.

Higher doses of 10 mg or 15 mg of d-amphetamine per 77 kg of body weight⁷⁹ and 7.5, 15, and 30 mg per 70 kg body weight⁷⁶ were administered in 2 studies, neither of which involved sleep deprivation. In a study conducted under normal sleep conditions,⁷⁹ performance on a coding task and a letter-checking task did not differ as a function of dose. In contrast, verbal production during a writing task showed a strong initial drug effect. Average word count on the first day was increased significantly by 10-mg and 15-mg doses, but there was no significant increase for either dose on the second day. The 7.5-mg, 15-mg, and 30-mg doses of d-amphetamine in the second study,⁷⁶ also conducted without sleep deprivation, produced dose-related increases in blood pressure and body temperature.

Effects of d-Amphetamine by Length of Time Awake

Of the 33 d-amphetamine studies reviewed, 9 compared d-amphetamine to placebo following normal nights of sleep,^{67-69*,76,79,89,96,97} 1 examined drug effects during partial sleep loss (subjects were allowed to sleep only between 10:00 PM and 2:00 AM for 1 night),⁷⁸ and the remaining 23 studies involved various intervals of sleep deprivation.

Nearly all studies investigating the effects of d-amphetamine on alertness and/or neurocognitive performance reported a positive effect of drug administration. One early study reported that 20 mg of d-amphetamine improved performance, in the absence

of sleep deprivation.^{69*} Vigilance performance under normal sleep conditions was better after 10 mg of d-amphetamine than after placebo.⁶⁷ The 1971 Hurst et al study⁷⁹ reported increases in performance on an editorial composition task following administration of 10 mg per 70 kg or 15 mg per 70 kg of body weight following a full night of sleep. Ten milligrams of d-amphetamine improved performance on tapping and short-term memory tasks in a study involving normal sleep.⁹²

The effect of d-amphetamine on performance generally has been found to be positive in subjects deprived of sleep for up to 64 hours. In a study of partial sleep loss, with subjects sleeping 4 hours for 1 night, an increase in performance on a critical tracking task was observed following administration of 10 mg of d-amphetamine.⁷⁸ However, in a study involving 20 hours of total sleep deprivation, 10 mg of d-amphetamine was reported to have no significant effect on performance of a nonsense syllable learning memory test, a tapping speed task, or an aiming task.⁷⁷ In contrast, a study involving 34 hours to 55 hours total sleep deprivation found that 10 mg of d-amphetamine significantly improved tracking performance.^{95*}

The effects of 20-mg doses of d-amphetamine have typically been studied in experiments involving sleep loss beyond 24 hours. Positive effects of d-amphetamine administered after 32.5 hours of sleep deprivation were observed on a range of neurobehavioral tasks that were detrimentally affected by sleep deprivation.²⁹ During the sleep-loss protocol, deficits in performance on running memory reaction time, math processing reaction time, logical reasoning response time, tracking errors, visual vigilance task reaction time, and visual vigilance hits occurred. At 1.5 hours following administration of 20 mg of d-amphetamine, these deficits were reduced on all measures except logical reasoning response times. At 5.5 hours after administration, all deficits induced by sleep deprivation were reduced by d-amphetamine.

Four published studies reported that 20 mg of d-amphetamine, administered after 40.5 to 64 hours of sleep deprivation, significantly improved reaction-time performance.^{29,80,81,89} In addition, performance on a running memory task and a visual vigilance task were improved by 20 mg of d-amphetamine after 40.5 hours of total sleep deprivation.²⁹ In 2 studies, UH-60 helicopter simulator performance was improved by three 10-mg doses of d-amphetamine during two 41-hour periods of total sleep deprivation, though the effect was not consistent across all time points.^{85,93} Performance on the Performance Assessment Battery tests of serial addition/subtraction,^{24,27} logical reasoning,^{27,74} choice reaction time,⁷⁴ running memory,²⁷ and tracking and visual vigilance²⁷ during 40.5 hours and 64 hours of total sleep deprivation was reported to be improved by 20 mg of d-amphetamine in 2 studies.^{29,80}

In 3 studies, 20 mg of d-amphetamine significantly improved mathematical reasoning during 40 to 64 hours of total sleep deprivation.^{29,83,84} During 63 to 64 hours of total sleep deprivation, 20 mg of d-amphetamine improved memory task performance,⁸² auditory vigilance,⁸¹ and kinesthetic task performance,⁹⁴ as compared with placebo.

One potentially important factor in the effectiveness of stimulants in optimizing alertness and performance levels during periods of sleep loss is the duration of wakefulness prior to administration of the medication. In 1 study, 20 mg of d-amphetamine was administered after 48 hours of wakefulness and produced a significant increase in performance on a sustained-attention reaction-time task.⁸¹ In another study in which 10 mg of d-amphet-

amine was administered at 55 hours of wakefulness, decreases in performance errors on both dynamic and static tracking tasks were observed.^{95*}

Baranski and Pigeau compared prior studies involving 20 mg of d-amphetamine and 300 mg of modafinil during 64 hours of sleep deprivation to a similar protocol with one 2-hour nap on either the first night of deprivation or the second night of deprivation.^{82, 83} Based on performance on a logical reasoning task, a short-term memory task, and subjective measures, it was concluded that both d-amphetamine and modafinil were more effective in promoting performance on the first night of sleep deprivation than was a 2-hour nap. However, one 2-hour nap taken at the circadian nadir of the second night without sleep was judged by these investigators as more effective than modafinil or d-amphetamine. In 1 study, 20 mg of d-amphetamine was administered to subjects following 65 hours of an 85-hour period of total sleep loss. The use of d-amphetamine was effective in improving performance on the PVT for several hours after administration. Improvement on performance of the PVT was greatest during the daily performance circadian nadir.

d-Amphetamine Subjective Effects

In 22 of 33 d-amphetamine studies, some method of subjective evaluation such as the Profile of Mood States^{66*,80,85-88*,93} was employed. Positive appraisals of fatigue, vigor, and confusion-bewilderment were reported during the morning (as opposed to the afternoon and evening) over 40 hours of total sleep deprivation following administration of 30 mg of d-amphetamine (administered in 3 doses of 10 mg each).⁸⁵ The use of d-amphetamine increased alertness⁹³ and reduced fatigue, confusion, and depression while increasing feelings of vigor,^{86,88*,98} even with a dose as low as 10 mg over 24 hours of sleep deprivation.^{66*}

In a study by Rush et al.,⁹⁰ 10 mg and 20 mg of d-amphetamine increased ratings of 2 questions on a subject-rated drug-effect questionnaire: "Did the drug have any effects," and "Did you like the drug?" Both doses of d-amphetamine also significantly increased ratings of feeling "high," above levels found with placebo. Both doses of d-amphetamine also increased "good effects" and "willing to take again" ratings on an end-of-the-day questionnaire. Subjects' awareness of these kinds of effects raise questions about the maintenance of the blind in double-blind studies of amphetamine.

An amplification effect on subjective measures of the Addiction Research Center Inventory, such as stimulant (amphetamine - A) and euphoric (morphine-benzedrine—MBG) scores, was evident following 15 mg of d-amphetamine administration during normal sleep⁹⁷ and 10 and 20 mg of d-amphetamine following normal sleep.⁹⁰ One study found that self-ratings of alertness showed a significant main effect of dose after 20 mg of d-amphetamine was administered under normal sleep conditions.⁸⁰ Another experiment utilized the Scheier and Cattell 8-Parallel-Form Anxiety Battery and the Clyde Mood Scale for subjective measurement, with 10 mg of d-amphetamine over 20 hours of sleep deprivation ameliorating many fatigue effects.⁷⁷ A decrease in attention variability measured by the Grunberger AD test was reported following administration of either 10 mg or 20 mg of d-amphetamine during 40.5 hours of total sleep deprivation.²⁴ It is noteworthy that only 1 of 33 publications failed to report significant subjective effects following d-amphetamine administration. In that study, the

effects of 1 and 10 mg of d-amphetamine were examined under normal sleep conditions,⁹⁶ and subjective effects were assessed using a novel sleep-pattern and side-effects questionnaire.

In 1 study in which 10 mg of d-amphetamine was administered after 20 hours of wakefulness, there was no significant effect of drug administration on several performance measures that included an aiming task, reading comprehension, learning and memory, and addition/subtraction tasks.⁷⁷ In contrast to the lack of effects on performance, subjects reported a decrease in feelings of fatigue, sleepiness, and clumsiness. There was also a reversal of the slowing and confusion of thought processes and reading comprehension induced by sleep deprivation. Subjective levels of happiness were increased, and subjects felt more involved in their environments and physically reactive and faster.

In conclusion, the ubiquitous finding of positive subjective effects,^{66,84-86,88*,90,98} including increased feelings of being “high”⁹⁰ and mildly euphoric,⁷⁷ following commonly studied dosages of d-amphetamine, suggests that the drug has psychological effects that go beyond its effects on cognitive performance. Such subjective effects would likely make it more attractive to subjects than a stimulant with less-potent experiential effects or effects that do not extend to feelings of “high.” However, such effects are not beneficial in allowing individuals to introspect their level of sleep loss and obtain recovery sleep as soon as practical.

The Effects of d-amphetamine on Sleep and Other Physiology

The administration of d-amphetamine has been associated with a number of effects on objectively measured sleep physiology and sleep variables. Effects on sleep continuity have been examined in 5 studies. One study found that subjects who ingested 10 mg of d-amphetamine 20 minutes before bed experienced decreased total sleep duration and increased duration of wakefulness during sleep.⁶⁷ A study of 20 mg of d-amphetamine administered 4.5 hours before bedtime also found decreased total sleep time and sleep efficiency, increased duration of wake during sleep and number of awakenings, and early termination of sleep. This study also reported a decrease in awakening threshold.²⁴ Another study in which 20 mg of d-amphetamine was administered 6 hours before bedtime reported that total sleep time was decreased, latency to sleep and number of awakenings were increased, and there was early termination of sleep.^{69*} In 2 studies, 10 mg of d-amphetamine ingested 15 hours before bedtime was associated with decreased sleep efficiency,⁸⁷ increased latency to sleep^{87,88*} increased duration of wakefulness during sleep,^{88*} and increased movements.^{88*}

Administration of d-amphetamine also has produced significant changes in sleep architecture. In a 1997 study, minutes of stage 1 and stage 2 sleep decreased after administration of 10 mg of d-amphetamine 15 hours before bedtime, relative to placebo.⁸⁶ Rapid eye movement (REM) sleep was decreased as well, and there was increased latency to REM.⁸⁶ The drug was associated with suppression of the first REM episode of the sleep period.⁸⁶

In a recently published study, 20 mg of d-amphetamine ingested 4.5 hours before bedtime was associated with decreased minutes of stage 2 sleep, slow-wave sleep, and REM sleep; increased percentage of stage 1 sleep; decreased percentage of slow-wave sleep and REM sleep; increased number of sleep-stage changes; and increased latency to REM sleep.²⁴ In some subjects, d-amphetamine administration was associated with a complete suppression

of REM sleep.²⁴

A double-blind, randomized study conducted in 1976 showed that 20 mg of d-amphetamine administered 6 hours before bedtime was associated with decreased minutes of stage 2 sleep, decreased percentage of REM sleep, and increased latency to REM sleep.^{69*} In another 1976 placebo-controlled study, 15 mg of d-amphetamine was associated with decreased minutes of slow-wave sleep and REM sleep.^{99*}

Effects of d-amphetamine on sleep are not always limited to the first night following administration. Increased sleep latency has been reported on the second night following the administration of 20 mg of d-amphetamine 4.5 hours before bedtime during 40.5 hours of sleep deprivation.²⁴ In addition, on the second night of recovery sleep following 64 hours of sleep loss, 20 mg of d-amphetamine ingested 40.5 hours prior to bedtime produced an increase in the number of sleep-stage changes, increased minutes and percentage of REM sleep, and decreased percentage of stage 2 and slow-wave sleep, compared with subjects receiving placebo.⁹¹ Increased minutes and percentage of REM sleep were evident in subjects administered d-amphetamine compared with subjects administered 3 doses of 300 mg of modafinil.⁹¹

Moreover, in subjects administered 20 mg of d-amphetamine, the second night of recovery sleep was characterized by increased minutes of stage 1 and percentage of REM sleep; decreased minutes of stage 2, stage 4, slow-wave, and NREM sleep; and decreased percentage of stage 2 and NREM sleep⁹¹ compared with the first night of recovery sleep.

The administration of d-amphetamine has also been reported to produce parallel negative effects on subjectively assessed sleep parameters. Subjects have reported decreased sleep quality with 20 mg of d-amphetamine.²⁴ A study in which 10 mg of d-amphetamine was administered reported increased sleep latencies or difficulty falling asleep and increased sleep disruption or awakenings.⁹⁶

Changes in cardiovascular function are also commonly reported following d-amphetamine administration. For example, increases in systolic,^{69*,77,80, 87,90,97} diastolic,^{69*,87,90, 97} and total²⁴ blood pressure have been observed to be associated with 10-mg to 20-mg doses of d-amphetamine over 0 to 64 hours of total sleep deprivation in most but not all studies.⁹⁶ In addition, changes in pulse rate^{24, 80, 87} body temperature^{80, 82} and pupil dilation have been reported following 10 to 15 mg of d-amphetamine administration over 0 to 64 hours total sleep deprivation.⁷⁷

The use of d-amphetamine is also associated with an anorexic effect following administration of 10-mg and 15-mg doses in subjects without sleep deprivation.^{96, 97} Alterations in a limited number of peripheral neuroendocrine variables have been reported following administration of d-amphetamine. For example, decreases in cortisol and adrenaline have both been reported following 20-mg of d-amphetamine administration after 40.5 hours of total sleep deprivation.²⁴

The effects of d-amphetamine on thyroid activity were examined in a 1976 paper.^{99*} After amphetamine administration, there was a marked inhibition of the nocturnal increase in thyrotropin, and nocturnal T₄ levels were reduced and delayed. Total excretion of free T₄ was slightly increased, and its correlation with serum variables was lost. Upon withdrawal of amphetamine, there was a trend to regain the original hormonal circadian profile, and nocturnal changes in both thyrotropin and T₄ exhibited a phenomenon resembling a rebound effect in some subjects. A decrease in

total T_4 became significant. Thyroid hormones tended to recover their usual levels after drug withdrawal.

d-Amphetamine Safety and Side Effects

A wide range of adverse experiences has been reported following d-amphetamine administration. One study provided a comprehensive report of physiologic and psychologic adverse experiences associated with escalating doses from 5 mg to 10 mg of d-amphetamine given each hour until the drug could no longer be tolerated.⁶⁸ This study included 9 adult men who were not sleep deprived. The paper lacks specific information on the cumulative dose at which the following adverse physiologic reactions occurred: increased blood pressure, postural hypotension, tachycardia, increased oral temperature, premature ventricular contractions, decreased appetite/anorexia, pin-and-needle paresthesias, and sleep disturbances. Psychologic adverse experiences included depression, hypochondria, no interest in surroundings or activities, irritability, fault finding, dependence on clinical staff, negativity, paranoia, denial of paranoia, and delusions, but again, the doses at which these were seen were not indicated in the paper. At some point in dose escalation, all subjects refused to continue their participation in experimental data collection, including psychologic testing and electroencephalogram recordings.⁶⁸

Many of these adverse experiences have been observed in other studies following the administration of lower doses of d-amphetamine. A dose of 20 mg of d-amphetamine has consistently been reported to produce an increase in blood pressure after 40.5 hours of sleep deprivation²⁴ and nausea, headaches, anxiety, stomach cramps, dry mouth, pounding heart, muscle twitches, and hangover effects after no sleep deprivation.^{69*} A dose of 15 mg of d-amphetamine after normal sleep also increased blood pressure and produced headaches.⁹⁷ Finally, 10 mg of d-amphetamine after normal sleep produced increased restlessness, agitation, palpitations, and dreaming.⁹⁶

Amphetamine Conclusions

Amphetamines are anorexic/stimulant compounds that have been found to increase a wide range of psychomotor performance in both non-sleep-deprived and sleep-deprived individuals. The most commonly administered form of amphetamine in human research studies is d-amphetamine. At both 10-mg and 20-mg doses, d-amphetamine has been found to promote alertness and many forms of psychomotor performance in sleep-deprived subjects, with effects lasting longer at the higher dose. At these doses, d-amphetamine produces subjective feelings of alertness and positive mood and, occasionally, feeling "high." These effects can occur even when performance effects are not seen.

Administration of d-amphetamine at 10 mg to 20 mg has consistently been reported to have adverse effects on sleep physiology, continuity, and duration; cardiovascular measures; and metabolic neuroendocrine responses. These doses can also produce a range of adverse experiences. Although amphetamines have been sanctioned for use since 1960 during some military flight operations⁶⁴ to mitigate the adverse behavioral effects of sleep loss, they are typically used by the military in single doses lower than 20 mg. Nevertheless, their high abuse potential and risk of dependence and side effects has resulted in the FDA listing them as Schedule II drugs. The benefits of amphetamines for psychomo-

tor performance in sleep-deprived healthy adults must be carefully weighed against their unwanted effects on subjective state, disruptions of sleep physiology, cardiovascular and metabolic dysregulation, and abuse liability. More studies are needed to determine if other stimulants with fewer side effects and lower abuse potential can be as effective as 20 mg of d-amphetamine in promoting psychomotor performance.

Methamphetamine has not been shown to be superior to d-amphetamine in any study and may be associated with more side effects. For these reasons, methamphetamine is not recommended for use during sleep deprivation.

Methylphenidate Introduction and Formulation Information

Methylphenidate, a piperidine derivative, is a central nervous system-acting psychomotor stimulant with pharmacokinetics and pharmacologic mechanisms similar to those of amphetamine. Methylphenidate is a FDA Schedule II medication that has indications for the treatment of narcolepsy and ADHD.⁶³ In an immediate-release formulation, its plasma concentration peaks within 2 hours, and its half-life is 2.5 to 3.5 hours. There are sustained- and extended-release formulations and combination formulations with both immediate and extended release. These formulations increase the duration of activity of the drug to approximately 8 to 12 hours, and this allows once-a-day dosing as opposed to the 2 or 3 daily doses necessary with the immediate-release formulations. Methylphenidate is a dopamine reuptake blocker that also enhances dopamine and norepinephrine release.

Methylphenidate Psychomotor Performance Effects

Studies of the performance and alerting effects of methylphenidate in healthy normal subjects during sleep loss are limited. The performance-enhancing effects of methylphenidate have been studied using standard tests that assess simple attention, divided attention, and protracted attention (eg, vigilance). In 1 study of 12 healthy adults undergoing a 64-hour sleep deprivation, administration of a single 10-mg dose of methylphenidate did not result in significant effects on a simple reaction time task.¹⁰⁰ In contrast, when 10 mg of methylphenidate was given twice a day to 9 healthy adults after 8 hours or 0 hours in bed the previous night, improved performance was found on a divided-attention task and an auditory vigilance task after the sleep deprivation but not after the 8 hours of time in bed. In a follow-up study, administration of 10 mg of methylphenidate after 4 hours but not 8 hours of time in bed in 6 healthy normal subjects improved divided-attention performance as compared with placebo.¹⁰¹

The daytime alerting effects of methylphenidate have been studied in normal subjects and in patients with narcolepsy using the MSLT and the MWT. Methylphenidate, 60 mg, was shown to increase sleep latency on the MWT in narcoleptics.¹⁰² The 2 studies cited above also included MSLT assessments in healthy normal subjects after 8 hours of time in bed versus no sleep the previous night. Administration of 10 mg of methylphenidate twice a day increased sleep latency on the MSLT after both the 8 hours and 0 hours of previous time in bed.¹⁰³ In the follow-up study comparing the single 10-mg dose after 8 or 4 hours of time in bed, methylphenidate administration again increased MSLT sleep latencies for both bedtimes.¹⁰¹

Methylphenidate Effects in Patients

The 2 clinical indications for methylphenidate are for treatment of ADHD and narcolepsy. In a randomized clinical trial of methylphenidate at doses of 10, 30, and 60 mg conducted in patients with narcolepsy, the 60-mg dose improved daytime alertness as measured by the MWT.¹⁰² There have been no other studies in patients with narcolepsy.

The literature on the effects of methylphenidate in patients with ADHD is extensive. A systematic review of the more than 1000 articles is beyond the scope of this review. However, several studies of methylphenidate effects on different behavioral domains in adults assessed in the laboratory can be cited to illustrate this literature.¹⁰⁴ These patients have poorer automobile driving performance than their peers. A double-blind, placebo-controlled study of 10 mg of methylphenidate in 7 adults with ADHD assessed driving performance in a driving simulator.¹⁰⁵ Compared with healthy controls, the patients' driving-simulator performance was worse, and it was significantly improved with methylphenidate. The patients also rated their driving performance as improved. Effortful continuous learning tests are particularly challenging to patients with ADHD. A double-blind, placebo-controlled study of 5, 10, and 20 mg of methylphenidate was conducted in 17 adult patients with ADHD.¹⁰⁶ Doses were adjusted within patients until the learning performance, defined as more correct responses and less variability, was improved, and, in 15 of the 17 patients, methylphenidate improved continuous learning. Of the 88% who were responders, the optimal dose for 41% of patients was 5 mg, for 12% of patients was 10 mg, and for 35% of patients was 20 mg.

In clinical use, 2 to 3 daily doses are typically used. A recent meta-analysis of the efficacy of methylphenidate in treatment of adult ADHD was conducted.¹⁰⁷ Physician and self-ratings of ADHD symptoms were used to assess efficacy, and the meta-analysis reported average daily doses of 44 mg produced improvement relative to placebo with medium effect sizes, but higher daily doses, average of 63 mg, produced greater effect sizes (0.9). Thus, as in the laboratory studies, the 10- to 20-mg dose range was optimal for improving the clinical symptoms of ADHD.

Methylphenidate Effects on Physiology and Adverse Effects

As expected of a sympathomimetic drug, intravenous administration of 0.3 mg/kg of methylphenidate in healthy adults produces increases in blood pressure and heart rate.¹⁰⁸ Consistent with this hemodynamic effect, plasma concentrations of epinephrine are elevated. Additionally, plasma concentrations of cortisol and growth hormone are elevated, and concentrations of prolactin are reduced. The side effects reported with methylphenidate use include insomnia, diminished appetite, irritability, weight loss, abdominal pain, and headaches.¹⁰⁹ The incidence of psychosis is very rare in clinical use.

Methylphenidate Conclusions

These few studies do show that methylphenidate, 10 to 20 mg, improves psychomotor performance in healthy normal subjects who have been screened for normal sleep and daytime alertness and are experiencing sleep loss. The performance improvement is seen after sleep loss but not after a standard 8 hours of time in bed. At an appreciably higher dose, 60 mg, the excessive daytime sleepiness of patients with narcolepsy is improved. It is at single

doses of 5 and 10 mg that laboratory performance improvement in adult patients with ADHD has been demonstrated. But, in clinical use, average daily doses of 63 mg (given in divided doses 2-3 times per day) produce the greatest improvement in ADHD symptoms.

Pemoline Introduction and Formulation Information

Pemoline, unlike methylphenidate and amphetamine, is an oxizolidine with stimulant properties. It reaches peak plasma concentration within 2 to 4 hours, and its half-life is about 12 hours. The pharmacology of pemoline is not well understood, but it probably acts as a presynaptic releaser and a reuptake blocker of dopamine. Pemoline is a FDA Schedule IV medication that has indications for the treatment of ADHD.⁶³ Due to the risk of hepatotoxicity, its clinical use is severely limited,¹¹⁰ and the FDA advises that patients be asked to sign an informed consent regarding this risk.

Pemoline Psychomotor Performance Effects

Study of the stimulant effects of pemoline during sleep deprivation is very limited. A double-blind study compared pemoline, 37.5 mg, to placebo administered to healthy normal subjects at hour 40 in a 64-hour sleep deprivation.¹¹¹ The study found improved performance on a tapping task and a pattern-recognition task. In another study, pemoline, 37.5 mg, or placebo was administered to healthy naval volunteers every 12 hours during a 64-hour continuous work period.¹¹² Pemoline improved 4-choice reaction-time performance during this sleep deprivation, as compared with placebo. A double-blind placebo-controlled crossover study of pemoline at doses of 10, 20, 30, and 40 mg during a 12-hour overnight work period was conducted.¹¹³ Performance on a range of tasks, assessed every 1.5 hours, was improved for all active drug doses on all but 2 tasks. The onset of improvement was first seen 4.5 hours after drug administration when performance impairment first appeared in the placebo condition.

Pemoline Studies in Patients

Studies of the alerting effects of pemoline have been done in patients with narcolepsy using the MSLT and the MWT. Doses from 20 to 75 mg did not improve alertness, as measured with the MWT, in narcoleptics; it was only at a 112.5-mg dose that improvement was seen.¹⁰² In another study of narcoleptics, pemoline dosing was pushed to the maximum tolerated dose, 87.5 mg on average. Relative to the pretreatment scores, MSLT scores were improved in 7 of the 9 patients at this dose.¹¹⁴

There have been very few studies of pemoline for treatment of ADHD. One chart review of pemoline treatment in college students with ADHD reported that 37% of the 43 students failed to respond.¹¹⁵ Among the nonresponders, one-third reported lack of efficacy and two-thirds reported side effects. The mean daily dose of the treatment responders was 56 mg, and the dose of the nonresponders was 38 mg per day (due to side effects).

Pemoline Conclusions

Although these studies show that pemoline does have the capacity to improve performance and alertness, its hepatotoxicity¹¹⁰ limits its use as an agent to improve performance in healthy normal subjects undergoing sleep deprivation.

Modafinil

Modafinil (dl-2-[(diphenyl-methyl)-sulfinyl]acetamide) is a FDA Schedule IV medication that is approved for treatment of the daytime sleepiness associated with narcolepsy, shift-work sleep disorder, and obstructive sleep apnea/hypopnea syndrome (when residual sleepiness remains after successful treatment with continuous positive airway pressure).⁶³

Modafinil Formulation Information

Modafinil is available in 100-mg and 200-mg tablets. The precise mechanism or mechanisms by which modafinil exerts its wakefulness-promoting effects and performance-enhancing effects are not yet known or agreed upon. There is some evidence to suggest that modafinil requires the DAT gene to promote wakefulness,¹¹⁶ but its effects are not exclusively or primarily mediated by dopaminergic mechanisms involved in the effects of amphetamine and other dopamine-receptor agonist stimulants (eg, methylphenidate). Following oral administration, peak plasma concentrations are reached in 2 to 4 hours, and elimination half-life is 13 to 14 hours. Modafinil is metabolized mainly via the CY-P450 enzyme CYP3A4. Its major metabolites are modafinil acid (CRL 40467) and modafinil sulfone (CRL 41056), and the main route of elimination is through urine. Modafinil acid (the main metabolite) is pharmacologically inactive, but another metabolite, modafinil sulfone, is pharmacologically active, with a half-life of approximately 12 hours.

Modafinil Psychomotor Performance Effects by Task

An examination of the sleep-deprivation and modafinil literature revealed several objective measures that have been used in empirical studies. Reaction time from several different types of tasks has been frequently reported. Reaction time or response time was significantly improved after modafinil administration (50 to 400 mg per 24 hours) during sleep-deprivation periods of 36 to 88 hours, compared with placebo, in 9 of 10 studies.^{25,27,117-124}

Five of 5 studies have shown significant increases in objective alertness measured by sleep-latency tests (both MSLT and MWT) after the use of modafinil during sleep deprivation at several dose levels, compared with placebo.^{25,27,122,125,126}

Short-term memory has been examined with tasks, including the DSST and memory search. During sleep loss, significant beneficial effects of modafinil relative to placebo have been found in 3 studies^{119,120,122} but not in a fourth.¹¹⁷

Mathematic ability, usually measured by numbers of correct addition or subtraction problems completed in a given period of time, was significantly improved during sleep loss after administration of modafinil compared with placebo in 3 studies^{83,117,119} but not in a fourth.²⁵

Two studies both found improved grammatical reasoning ability during sleep loss after administration of modafinil compared with placebo.^{118,123}

A study of simulated flight performance in helicopter pilots during 40 hours of sleep loss found that performance was improved on maneuvers, including “left standard-rate turn,” “straight and level,” and “descent” after administration of 200 mg of modafinil, relative to placebo.⁹⁸ In another study of simulated flight performance in F-117 pilots, 100 mg of modafinil admin-

istered at 17, 22, and 27 hours of sleep deprivation maintained flight accuracy (straight climb; left 720-degree turn; left climbing turn; right descending turn; right 360-degree turn; straight and level).¹²⁷

Although, as reviewed above, modafinil has been shown to improve performance on simple psychomotor tasks, its effect on executive functions during sleep deprivation has received less attention. One study¹²² found improved performance after modafinil, compared with placebo, on creative-thinking and sentence-completion tasks during a night-shift paradigm. Another study showed decreased errors in complex estimation during sleep loss after modafinil, 400 mg, compared with placebo.²⁷

In summary, 100 to 300 mg of modafinil, administered repeatedly over extended sleep deprivation (eg, 64 hours) or once over the course of shorter periods of sleep deprivation (eg, 36 hours), was found to improve performance on tasks involving reaction time, alertness, memory, mathematical ability, and logical/grammatical reasoning. In some studies, a return to baseline (pre-sleep-deprivation) performance was noted, but, in other studies, performance did not appear to be restored to baseline levels. The effects of different doses of modafinil were not directly compared in these studies, and it is therefore difficult to determine whether failures to find statistically significant differences were dose related. In 1 study, modafinil appeared to impair performance on a map-reading/reconstruction task; however, the relevance of this finding to other aspects of operational performance is unclear.

Modafinil Effects by Dose

Few studies have been published in which the effects of different doses of modafinil have been directly compared. In the first such study to be published, Saletu et al¹²⁸ examined the effects of modafinil, 200, 400, or 600 mg, on tests of reaction time and attention (administered at 0, 2, 4, 6, and 8 hours after medication) in a non-sleep-deprived, elderly, subject sample (mean age, 66 years). All doses of modafinil improved reaction-time and attention-task performance, with positive effects evident as early as 2 hours after administration. Although the effects appeared to be dose dependent, statistical evidence was not presented.

Performance following several doses of modafinil (16.7 mg, 50 mg, or 100 mg administered every 8 hours across 64 hours of wakefulness—ie, after 16, 24, 32, 40, 48, and 54 hours of continuous wakefulness) was evaluated in 6 healthy men in a crossover design.¹¹⁷ Significant drug-by-session interactions for 4-choice reaction time and mental addition suggested that modafinil, 300 mg per 24 hours, improved performance compared with placebo, and performance was generally reported to be maintained at or near baseline levels with this dose. For low-dose modafinil (16.7 mg every 8 hours or 50 mg per day), performance was comparable to that found with placebo, and the intermediate dose (50 mg every 8 hours or 150 mg per day) produced intermediate levels of performance, in a dose-dependent manner.

A single administration of modafinil, 100 mg, 200 mg, or 400 mg, was compared with caffeine, 600 mg, after 41 hours of sleep deprivation during a 54-hour sleep-deprivation period in a parallel-groups study (N = 50).²⁵ The PVT³ and a modified MWT were administered every 2 hours prior to drug administration and hourly thereafter. Response speed on the PVT was maintained for 11 hours after administration of both 200 mg and 400 mg of

modafinil. Differences between the 200-mg and 400-mg dose of modafinil were not statistically significant.

In summary, results suggest some dose-response effects, but these were more consistently found between 50 mg and 200 mg than between other doses. Early studies involving multiple administrations of a single dose of modafinil have generally utilized the 200-mg dose,¹²⁶ perhaps based on the report that higher doses produce no additional improvements in performance. However, it is possible that practical benefits can be realized with doses higher than 200 mg, especially in those instances in which circadian and homeostatic factors converge to produce poor performance (eg, after 2 or more nights of sleep loss and near the trough of the circadian rhythm of performance).

Modafinil Effects by Length of Time Awake

As the duration of continuous wakefulness is extended, the effectiveness and/or duration of the effect of modafinil on performance appears to be reduced. For example, 1 study⁸² found that both modafinil (300 mg) and d-amphetamine (20 mg) significantly improved performance on 4-choice serial reaction time for 9 hours when administered at 17.5 hours of sleep deprivation, but the performance-enhancing effects of modafinil were significant (compared with placebo) for only 6 hours after a subsequent administration at 47.5 hours of sleep deprivation. A similar effect was reported for the group administered 20 mg of d-amphetamine. Statistically significant effectiveness was maintained for only 8 hours when administered at 47.5 hours of sleep deprivation. However, for both medications, the drug administrations occurred at different times of day and different phases of circadian rhythm of alertness, and the duration of effects might also have been related to circadian time.

Despite the relatively small numbers of volunteers used in most studies to date, modafinil, in single^{25,120} or repeated doses^{82, 98} ranging from 200 mg to 400 mg, has been shown to improve performance and objective alertness (increasing latency to sleep). In most of these studies, short-duration tasks that tap some specific cognitive function (eg, memory, grammatical reasoning) were used, and the effects of modafinil on reaction time and/or accuracy were reported. Many of these tasks had previously been shown to be sensitive to sleep deprivation (particularly those with a reaction-time component), and thus were appropriately sensitive for testing the efficacy of modafinil for reversing the effects of sleep loss. Results from some studies suggest that modafinil at doses of 200 mg or greater restore performance to pre-sleep-deprivation levels,^{98,123} although this does not appear to be the case in all studies, or for all performance measures (for example, see results reported in).^{82,83} In some studies, it was difficult to determine whether modafinil restored performance to baseline levels because of the statistical techniques reported.

Few studies of modafinil have employed tasks that are thought to reflect higher-order mental processes (ie, “executive functions”) or employed tasks with high face validity in combination with sleep deprivation. One exception was the study in which a UH-60 helicopter simulator was utilized.⁹⁸ However, in that study, only the pilots’ ability to perform specific, well-practiced, flight maneuvers in a simulator was evaluated—thus restricting the generality of the findings. Another study, which evaluated the ability to verbally describe a map for reconstruction by another subject, reported decreased performance following administration of modafinil.⁸⁴

Modafinil Subjective Effects

Studies have shown that modafinil improves subjective alertness^{25,82} and mood^{82,98,126,128} at doses that also improve psychomotor performance. In non-sleep-deprived volunteers, both impairments¹²⁹ and improvements¹³⁰ in mood have been reported.

It has been reported that modafinil impairs subjects’ ability to self-assess performance on 2 tasks.⁸³ In the first task (perceptual comparison), subjects determined which of 2 parallel horizontal lines was either longer or shorter (depending on instructions provided just before the stimulus). In the second task, subjects mentally added 8 numbers that were presented sequentially. Subjects provided an estimate of (a) the percentage of trials they anticipated that they would get correct just prior to performing each task and (b), immediately following each task, the percentage of trials they thought they had answered correctly. Feedback was not provided for either task. The difference between actual and estimated percentages of correct responses was analyzed separately for pretask and posttask estimates. For both tasks, results for both pretask and posttask estimates suggested an overconfidence effect with modafinil but not with d-amphetamine or placebo. Results from 2 recent studies from the same laboratory suggest that the overconfidence effects associated with modafinil occur only under sleep-deprived conditions¹³¹ and that modafinil does not induce overconfidence when the same absolute dose (300 mg) is divided into smaller, spaced doses (100 mg every 8 hours).¹¹⁸ Nonetheless, the results suggest that modafinil impairs some aspects of self-appraisal of performance and warrant replication.

Modafinil Effects on Sleep and Other Physiology

In 1 study,⁹¹ modafinil reduced total sleep time (sum of stages 2, slow-wave, and REM sleep; 9.78 hours) relative to placebo (11.43 hours) on the first night of recovery sleep but not on the second night. Another study showed a reduction in total sleep time and sleep efficiency when modafinil 200 mg but not 100 mg was administered 30 minutes prior to bedtime (no sleep deprivation).⁸⁹ Modafinil also impairs recovery sleep, as recorded subjectively via sleep logs; and it delays rebound recovery sleep. Lagarde et al¹²⁶ reported that sleep duration increased on the first recovery sleep night for the placebo group but not for the modafinil group (10.0 hours vs 8.5 hours, respectively), compared with baseline. On the second night, the reverse was found—placebo subjects reported 8.1 hours of sleep, whereas modafinil subjects reported sleeping 10 hours. These results suggest that modafinil delays recovery sleep but, like all other stimulants, does not reduce sleep need.

The extent to which poor sleep following modafinil administration could impair performance has received little attention. In those studies in which performance after recovery sleep was measured,^{27,82,119,126,132} statistical results were not provided. However, the results appear to indicate that performance after recovery sleep did not differ between modafinil and placebo, and that, for both groups, performance was restored to pre-sleep-deprivation levels. A recent study²⁷ showed that performance was restored to pre-sleep-deprivation levels; however, in that study, 400 mg of modafinil did not impair sleep during a 12-hour recovery period following 85 hours of total sleep deprivation (also, recovery sleep commenced 20 hours after the dose was given).

The degree to which the physiologic effects of modafinil are unique to sleep deprivation are unclear, since few published stud-

ies have addressed these same effects in non-sleep-deprived individuals. However, administration of modafinil at doses exceeding 400 mg in non-sleep-deprived adults has been shown to produce increased heart rate and blood pressure,¹³³ with milder effects at lower doses.¹³⁰

Modafinil increases core body temperature in both non-sleep-deprived and sleep-deprived adults. During sleep deprivation, these effects are most apparent during the circadian trough in body temperature, at which time modafinil suppresses the normal nocturnal decline.^{82,123,134,135} Two studies also reported that modafinil increased core body temperature during exercise in sleep-deprived adults.^{118,136} At least 1 investigator has suggested that this could place individuals at greater risk for heat injury if they are performing heavy work and/or wearing protective clothing that inhibits the body's ability to dissipate heat.¹³⁶ Modafinil was also reported to increase heat production in non-sleep-deprived, cold-exposed humans.¹³⁷ In the only published study addressing the effect of modafinil on hormones,¹²³ 300 mg of modafinil administered during sleep deprivation had no effect on plasma melatonin, cortisol, or growth hormone.

Modafinil Safety and Side Effects

Safety data specific to the use of modafinil during sleep deprivation in otherwise normal, healthy adults is lacking. In the above-reviewed studies, however, no serious adverse events were reported. For modafinil, the LD-50 (ie, the dose that is fatal for 50% of animals administered the drug) is 1250 mg/kg in mice and rats and 200 mg/kg in dogs. Assuming identical dosing, the LD-50 for dogs would be comparable to 14 grams in a 70-kg human. In humans, there have been 2 cases of reported high-dose ingestion of modafinil. In 1 case, 4.0 gm of modafinil was ingested, and, in the second case, 4.5 gm of modafinil was ingested. Both cases resulted in excitation/agitation, insomnia, and "slight or moderate elevations in hemodynamic parameters" (modafinil package insert). Both patients fully recovered within 24 hours. In clinical studies, effects observed at elevated doses included confusion, nervousness, tremor, palpitations, anxiety, irritability, aggressiveness, sleep disturbances, nausea, diarrhea, and decreased prothrombin time. In comparison to placebo-treated patients, the most commonly observed adverse events associated with modafinil include headache, infection, nausea, nervousness, anxiety, and insomnia. In 2 multicenter studies, 5% of patients (19 of 369) discontinued modafinil due to an adverse event. Reasons for discontinuation included headache (most common), cataplexy, nausea, depression, and nervousness. Since few studies exist in which different doses of modafinil have been compared within the same study, it is unclear whether side effects are dose related. Results indicate a dose-response relationship for incidence of adverse events;¹³³ however, in that study, data for specific adverse events were not provided, and, of the doses tested (200 mg, 400 mg, 600 mg, and 800 mg administered as a single dose), the 600-mg and 800-mg doses exceeded those administered in normal, healthy adults in the above-reviewed sleep-deprivation studies.

Side effects similar to those reported by sleep-deprived volunteers (eg, shaking, palpitations, dizziness, restlessness, irritability) were reported by non-sleep-deprived volunteers receiving comparable modafinil doses,¹²⁹ and this suggests that the side effects of modafinil are a direct effect and not due to an interaction with sleep deprivation.

There is one report that modafinil caused vertigo in helicopter

pilots flying in a simulator.⁹⁸ In that study, vertigo was attributed to either the simulator, movement of the simulator, modafinil dosage (600 mg total, administered as 3 doses of 200 mg each every 8 hours), or some combination of these 3 factors. However, in a more recent study by the same authors in which volunteers (F-116 pilots flying an F-116 simulator) were specifically asked about vertigo,¹²⁷ this symptom was reported by both modafinil and placebo groups. The latter finding suggests that vertigo was caused by an interaction between sleep deprivation and the simulator but was unrelated to modafinil. Likewise, in another study in which volunteers were specifically queried about vertigo-like symptoms (no simulator was used in this study), volunteers did not report an increased incidence of this side effect following the use of modafinil.²⁵

Modafinil Conclusion

The evidence suggests that modafinil, in repeated doses ranging from 100 mg to 300 mg per dose, and in single doses ranging from 100 mg to 400 mg, improves psychomotor performance, objective and subjective alertness, and mood during sleep-loss periods of up to 85 hours, in comparison with placebo, in otherwise normal, healthy adults. In some studies, it was clear that modafinil improved performance and alertness beyond levels seen in the placebo group, but, in other studies, the findings were less clear due to lack of appropriate statistical analyses. Two notable exceptions to the general performance-enhancing effects of modafinil were negative effects on the verbal map-reconstruction task⁸⁴ and negative effects on self-assessment of performance that could be interpreted as "overconfidence."⁸³ However, the failure to fully report statistical analyses in the latter study makes this finding difficult to assess.

Modafinil reduced recovery sleep initiated within 14 hours of administration; however, with sufficient recovery-sleep periods (eg, at least 10 hours), the minimal loss in total sleep time did not appear to affect performance after recovery sleep. Modafinil also raised core body temperature, a physiologic effect that may be relevant under certain operational conditions.

Multiple Drug Comparison Studies

Relatively few studies have directly compared the effects of different stimulants during sleep loss. One study resulting in 2 publications compared 300 mg of caffeine with 20 mg of amphetamine and 37.5 mg of phentermine administered at 3:30 PM after 1 night of sleep loss.^{24,29} Performance was measured 1.5 hours and 5.5 hours later. Statistical comparisons were not made between the drugs. However, rank-order-of-performance values across memory, logical reasoning, math, tracking, and 2 vigilance tasks showed that (with best performance as 1.0) caffeine yielded average ranks of 2.0 and 2.2 at 1.5 and 5.5 hours after administration, amphetamine yielded average ranks of 2.3 and 2.2 respectively, phentermine yielded average ranks of 1.8 and 2.0, and placebo had average ranks of 4.5 and 5. Two independent studies have used a similar design to evaluate d-amphetamine at doses of 5, 10 and 20 mg⁸⁰ and caffeine at doses of 100, 300, and 600 mg.⁵⁷ Sleep latency, as measured by the MSLT, was significantly increased, as compared with placebo, for 7 hours after administration of 20 mg of amphetamine versus 4.5 hours after administration of 600 mg of caffeine. This difference may reflect the somewhat longer half-life of amphetamine.

Wesenstein et al²⁵ measured alertness and performance for 12 hours after administration of 600 mg of caffeine and 3 doses of modafinil (100 mg, 200 mg, and 400 mg) with medication administered at about midnight just prior to the second night of sleep loss. Many differences were found relative to placebo, but only 1 drug/drug comparison for performance and alertness measures was significant. On the MWT, average latencies for the 400-mg modafinil (8.8 minutes) and caffeine (9.2 minutes) groups were significantly longer than latency for the 100-mg modafinil group (4 minutes).

The use of d-amphetamine has been compared with modafinil. One study⁸² evaluated the effects of d-amphetamine, 20 mg, and modafinil, 300 mg. Performance- and alertness-restoring effects were similar between the 2 drugs. Likewise, reductions in total sleep time during the first night of recovery sleep were similar for modafinil, 300 mg, and d-amphetamine, 20 mg, (9.78 vs 9.37 hours respectively, compared with 11.43 hours for placebo).⁹¹ The same study⁸³ reported that 20 mg of d-amphetamine did not impair the ability to self-monitor to the same extent as did 300 mg of modafinil, although the medications were shown to produce comparable preventative and recuperative effects on cognitive task performance during 64 hours sleep deprivation.⁸³

Several other stimulants have also been compared with d-amphetamine, including fencamfamin (a central nervous system stimulant that increases alertness and drive, used in the treatment of depressive fatigue),⁷⁷ phentermine (the most commonly prescribed appetite suppressant),^{24,29} and caffeine.^{24,29} Overall, it was observed that d-amphetamine and caffeine produced the greatest improvements in performance and produced the fewest side effects among these drugs.²⁴

In a recently completed study,²⁷ the performance- and alertness-enhancing effects of 400 mg of modafinil, 600 mg of caffeine, and 20 mg of d-amphetamine were compared during 85 hours of sleep deprivation. Doses of each drug were chosen based on results from previous studies, indicating roughly comparable performance-enhancing efficacy.^{25,57,80} Drug or placebo was administered at 64 hours of sleep deprivation (just prior to midnight). All 3 drugs improved PVT speed and increased sleep latency for several hours after the dose was given (most notably during the hours of 7:00 AM and 11:00 AM), with modafinil and d-amphetamine effects lasting longer than those of caffeine (which the authors attributed to caffeine's shorter half-life). Probe tasks of executive function also were administered after the drug was given, and results suggested that impairments on these tasks were most effectively countered by 600 mg of caffeine, followed by 400 mg of modafinil, and less so by 20 mg of d-amphetamine. None of the drugs significantly impaired recovery sleep compared with placebo, and performance after recovery sleep and alertness were restored to baseline levels. Side effects were also assessed with a standard questionnaire. Modafinil was associated with a significant increase in excitation at 1 time point compared with placebo. The use of d-amphetamine was associated with significantly increased excitation, pounding heart, and jitteriness compared with placebo, and the use of caffeine was associated with a significant increase in jitteriness, nausea, tremors, and racing heartbeat, as compared with placebo.

Differences in sleep-related variables have been reported in comparisons between modafinil and d-amphetamine. One study showed that 300 mg of modafinil had less effect on the human waking electroencephalogram than did 20 mg of d-amphetamine when both drugs were administered during 64 hours of total sleep deprivation,¹²⁵ but these medications exerted comparable perfor-

mance and alertness-restoring effects.⁸² Another non-sleep-deprivation study showed a decrease in total sleep time and sleep efficiency after 20 mg of d-amphetamine compared with placebo and 100 or 200 mg of modafinil.⁸⁹ In the same study, there was a reduction in stage 2 and REM sleep with d-amphetamine but not with modafinil, and subjective sleep quality was significantly better after either dose of modafinil than after 20 mg of d-amphetamine. A third study reported that, on the first recovery night after deprivation, sleep efficiency and REM sleep were lower, whereas REM latency was increased in the 20-mg d-amphetamine group compared with the 300-mg modafinil group.⁹¹

Stimulant Abuse Liability

Table 2 presents the DEA drug scheduling presents the FDA schedule for each stimulant according to the Controlled Substances Act of 1970 and lists the current approved indications for each stimulant. A number of central nervous system-acting compounds are known to have high abuse liability (ie, the likelihood of developing physiologic and/or behavioral dependence with use).¹³⁸ Physiologic dependence is a state induced by repeated drug use that results in a withdrawal syndrome when the drug is discontinued or an antagonist is administered. Many central nervous system-active drugs produce physiologic dependence, although the syndrome intensity, relationship to dose, and necessary duration of use for development of physiologic dependence varies among drugs. In the sleep field, the phenomenon suggestive of physiologic dependence is a REM rebound.¹³⁹ When drugs that suppress REM sleep are administered repeatedly, tolerance to the REM suppression develops, and, when discontinued, a REM rebound occurs (characterized by a reduced REM latency and an increase in REM time and REM density).

Physiologic dependence may be a component of, but not a necessary or sufficient condition for, behavioral dependence. Behavioral dependence is a pattern of behavior characterized by repetitive and compulsive drug seeking and consumption.¹³⁸ Drug taking, whether in a therapeutic and socially accepted recreational form or in an excessive, socially unacceptable, and physically hazardous form, is a behavior that can be analyzed to determine those factors important to the initiation and maintenance of drug taking. A drug can be viewed as a reinforcer if it promotes and maintains drug-seeking and drug self-administration behaviors.

Assessment of the abuse liability of drugs in humans is done with mood scales,⁹⁸ visual analog scales of drug effects, validated drug-effect questionnaires (ie, Addiction Research Center Inventory), and drug-discrimination procedures. The ultimate measure of abuse liability is assessment of drug self-administration—the conditions under which the drug is self-administered and the characteristics of that self-administration behavior. All drugs that are known to be drugs of abuse in society are self-administered in nonhuman and human laboratory studies. When it is ethically questionable to expose humans to drug self-administration procedures, subjective drug-discrimination assessments provide a means of estimating the abuse liability of a drug. In such assessments, drugs that are discriminated as being similar to drugs with known abuse liability are identified as likely to be drugs of abuse.

However, the fact that a drug acts as a reinforcer, promoting and maintaining drug self-administration behaviors, does not necessarily imply that the drug self-administration behavior is drug abuse. The conditions under which the drug is self-admin-

istered and the characteristics of that self-administration behavior must be considered. Drug-seeking or drug abuse must be distinguished from therapy-seeking behaviors.¹⁴⁰ In the latter case, the focus of the drug self-administration is disease or symptom reversal, whereas, in the former case, non-disease effects of the drug (sometimes referred to as a drug's "euphorogenic" effects) are the focus of the behavior. In the present context, self-administration of a stimulant to reduce the effects of sleep deprivation is not drug abuse. However, dose escalation and self-administration outside of the therapeutic context (ie, when not sleep deprived) would be suggestive of drug abuse.

Amphetamine

Amphetamine is the prototypical stimulant drug of abuse (see review).¹⁴¹ Tolerance to amphetamine develops rapidly, and the development of physical dependence is evident in the appearance of a withdrawal syndrome during abstinence. For example, in an early sleep laboratory study, individuals who were currently abusing amphetamine took their last dose on the first day in the hospital and then abstained.¹⁴² During abstinence, self-rated depression was increased; urinary excretion of 3-methoxy-4-hydroxy-phenylglycol (MHPG), a major metabolite of norepinephrine, was decreased; and total sleep time and REM sleep were increased.¹⁴²

Administration of amphetamine produces increases in the Profile of Mood States vigor, elation, and arousal scales and increases in Addiction Research Center Inventory scales: amphetamine (A); the benzedrine group (BD), another amphetamine sensitive scale; and the morphine-benzedrine group (MBG), a scale associated with euphoria.¹⁴¹ Subjects can be trained to discriminate amphetamine versus placebo and will correctly identify amphetamine 83% to 93% of the time.¹⁴¹ Not all subjects learn such a discrimination, and those unable to learn a discrimination have lower scores on subjective-effects scales, although no specific subjective-effect scale is singularly predictive of the ability to learn a drug discrimination. In drug self-administration studies of healthy normal subjects, amphetamine, 5 to 10 mg, is chosen on 60% or more of opportunities and more frequently than placebo. Visual-analog ratings of drug "liking" are consistent with the choice behavior of these healthy volunteers.

Methylphenidate

The abuse liability of methylphenidate is not as clear as that of amphetamine, although it shares pharmacologic mechanisms of action with amphetamine. This literature was recently reviewed.¹⁴³ The extent to which tolerance develops to the therapeutic effect of methylphenidate in the treatment of ADHD is disputed. Some of the studies suggest the absence of tolerance development to the clinical effects during long-term use.¹⁴⁴ On the other hand, studies carefully accounting for the pharmacokinetics of this drug do show acute tolerance.¹⁴⁵ Little systematic work has assessed tolerance development in the treatment of narcolepsy. The issue of physical dependence is complex and determined by the pharmacokinetics of the drug and the pattern of use.

The subjective effects experienced with methylphenidate are quite similar to those for amphetamine. Typically, the A, BG, and MBG scales of the Addiction Research Center Inventory are increased, and the Profile of Mood States vigor and fatigue scales are improved with methylphenidate in doses of 7.5 to 60 mg.¹⁴³

In drug-discrimination studies, subjects trained on cocaine or amphetamine versus placebo discriminations find methylphenidate to be similar to the training stimulus.¹⁴² However, self-administration studies have not been as strongly supportive of the abuse liability of methylphenidate. In 1 study, healthy volunteers, in a discrete-choice methodology, chose methylphenidate (20–40 mg), placebo, or neither after having established an individualized discriminable dose versus placebo.¹⁴⁶ Methylphenidate, at the average discriminable dose of 31 mg, was chosen on 28% of opportunities. Another study used a modified progressive-ratio methodology in which, after sampling 20 mg and 40 mg of methylphenidate, the volunteers pressed a response key on an increasing ratio schedule for drug and placebo.⁹⁰ The break point (ie, the highest ratio value completed) was increased relative to placebo for the 40-mg dose only, while in the same study, d-amphetamine, 10 mg and 20 mg, increased the break point above placebo levels. A third study of the reinforcing effects of methylphenidate in non-drug-abusing volunteers used a forced-choice methodology to assess reinforcing effects, and, like an earlier study,¹⁴⁶ found that 10 mg of methylphenidate was chosen on 29% of opportunities.¹⁰¹ However, after only 4 hours in bed on the previous night, subjects chose methylphenidate on 88% of opportunities. These laboratory studies suggest that the self-administration of these volunteers is therapy-seeking behavior to reverse the impact of partial sleep deprivation.

Caffeine

The abuse liability of caffeine has been evaluated.^{147,148} Tolerance development to the subjective effects of caffeine was shown in a study in which caffeine was administered at 300 mg twice each day for 18 days.¹⁴⁸ Tolerance to the daytime alerting effects of caffeine, as measured by the MSLT, was shown over 2 days on which 250 mg of caffeine was given twice each day⁴⁸ and to the sleep-disruptive effects (but not REM percentage) over 7 days of 400 mg of caffeine given 3 times each day.^{7*} In humans, placebo-controlled caffeine-discontinuation studies have shown physical dependence on caffeine, as evidenced by a withdrawal syndrome.¹⁴⁷ The most frequently observed withdrawal symptom is headache, but daytime sleepiness and fatigue are also often reported. The withdrawal-syndrome severity is a function of the dose and duration of prior caffeine use.

Subjective effects of caffeine are positive at low and intermediate doses and include a sense of well-being, alertness, clear-headedness, and an improved ability to concentrate.¹⁴⁷ At higher doses, negative effects such as dysphoria, anxiety, and nervousness are experienced. The subjective-effect profile of caffeine is similar to that of amphetamine,¹⁴⁷ with the exception that dysphoria/anxiety is more likely to occur with higher caffeine doses than with higher amphetamine doses. Caffeine can be discriminated from placebo by the majority of participants, and correct caffeine identification increases with dose.¹⁴⁷ Caffeine is self-administered by about 50% of normal subjects who report moderate to heavy caffeine use. In posthoc analyses of the subjective effects reported by caffeine choosers versus nonchoosers, the choosers report positive effects and the nonchoosers report negative effects. Interestingly, choosers also report negative effects such as headache and fatigue with placebo, and this suggests that caffeine-withdrawal syndrome, secondary to placebo choice, contributes to the likelihood of caffeine self-administration. This implies that physical dependence potentiates behavioral dependence to caffeine.

Table 2—United States Drug Enforcement Administration Classifications and Food and Drug Administration Labeling Indications

	Half-life, h	Schedule*	Approved for	Typical dose, mg	Abuse potential
Amphetamine	16-30	II	ADHD, narcolepsy	5-20	Box warning
Methylphenidate	2.5-3.5	II	ADHD, narcolepsy	20-30	Box warning
Modafinil	12-14	IV	Excessive daytime sleepiness associated with narcolepsy, treated sleep apnea, or shift work sleep disorder	200	Reinforcing in primates
Pemoline	12	IV	ADHD	56.25-112.5	Not reinforcing in primates
Caffeine	3-6	Not scheduled	Not applicable	100-200	Reinforcing in humans

*Category II—HIGH POTENTIAL FOR ABUSE: Use may lead to severe physical or psychological dependence. Prescriptions must be written in ink or typewritten and signed by the practitioner. Verbal prescriptions must be confirmed in writing within 72 hours and may be given only in a genuine emergency. No renewals are permitted.

Category III—SOME POTENTIAL FOR ABUSE: Use may lead to low-to-moderate physical dependence or high psychological dependence. Prescriptions may be oral or written. Up to 5 renewals are permitted within 6 months.

Category IV—LOW POTENTIAL FOR ABUSE: Use may lead to limited physical or psychological dependence. Prescriptions may be oral or written. Up to 5 renewals are permitted within 6 months.

Category V—SUBJECT TO STATE AND LOCAL REGULATION: Abuse potential is low; a prescription may not be required.

Modafinil

The studies conducted to assess the abuse liability of modafinil conclude that it does not show a pattern of effects indicative of a drug likely to be abused.^{149,150} However, development of tolerance and physiologic dependence have not been as thoroughly assessed for modafinil as for other stimulants, such as d-amphetamine and caffeine. As reviewed in the modafinil section, studies have not shown tolerance development with repeated administration over a 60-hour period of sleep deprivation. Studies of subjective effects in individuals with a history of stimulant abuse indicate that 200 to 400 mg of modafinil is experienced differently than 45 to 90 mg of methylphenidate.¹⁴⁹ Methylphenidate increased Addiction Research Center Inventory A scale scores, but modafinil did not. In another study of stimulant abusers, the discriminative-stimulus effects of modafinil in cocaine-trained individuals showed that 200 to 600 mg of modafinil was readily discriminated from cocaine.¹⁵⁰ These few studies suggest that modafinil is less likely to be a drug of abuse than is amphetamine or methylphenidate.

Pemoline

No studies of the abuse liability of pemoline in humans have been conducted. The FDA scheduling (see Table 2) reflects an estimated low abuse liability.

Summary

The abuse liability of stimulant drugs range from high to low. This is reflected in the FDA scheduling of these drugs that is presented in Table 2. Amphetamine is considered the prototypical stimulant for its abuse liability. Its high abuse liability has been well documented in laboratory studies and is reflected in its history of abuse in society. Although methylphenidate is generally considered safe by the public and the general medical community, its potential abuse liability in laboratory studies does not appear to differ much from that of amphetamine, although it is not self-administered under normal conditions. Caffeine is not a controlled substance, but its abuse liability can be considered moderate,

based on the laboratory assessments. Finally, the available laboratory studies of modafinil thus far suggest that it has a low abuse liability, but further assessment is needed.

DISCUSSION

Sleep loss in healthy individuals is a common and sometimes unrecognized risk factor that can result in performance failure. Individuals deal with sleep loss in many ways, including increased activity levels, increased exposure to external stimulation, naps, or the use of stimulants. These alternatives may mask sleep-loss-associated deficits to some extent for a limited period of time, but they do not substitute for the daily need for sleep of sufficient quantity and quality to maintain alertness, performance, and mood. Use of stimulants, including, in some cases, consideration of possible off-label use of prescription stimulants, should be regarded as an occasional stop-gap measure against temporarily inadequate sleep only on a volunteer basis when other alternatives are not feasible. However, the effects of sleep loss on alertness and performance are consistent, accumulating with either continued wakefulness or chronic shortening of sleep, and, eventually, are overwhelming. In certain situations in which sleep will not be possible, treatment with medications may become a necessity.

Each of the stimulants reviewed can reduce many of the major effects of sleep loss to some extent with a duration of action related to pharmacokinetics and dose. However, they do not always restore alertness and performance to non-sleep-deprived levels and may be associated with a number of side effects, adverse experiences, and risks. Additionally, each stimulant has a unique onset and metabolic profile. Appropriate use involves attention to initiation of benefit and eventual loss of efficacy, with the secondary awareness that these factors are related to dose and degree of sleep loss. There large interindividual differences in sensitivity to each of the stimulants and in response to sleep loss as well. Recommended doses of these medications, typically as used to treat narcolepsy, are listed in Table 2, along with other formulary information. Studies of extended sleep deprivation have examined higher doses of caffeine (up to 600 mg) and modafinil (up to 400 mg) but similar doses of the other medications.

Two previous papers have reviewed the use of stimulants during sleep loss.^{6,151} The reviews have consistently emphasized the role of adequate sleep to maintain alertness and performance. There is also evidence that provision of a longer-than-normal sleep period prior to a period of sleep deprivation (prophylactic nap) can decrease some of the negative performance and alertness effects.^{14,152} The effectiveness of prophylactic sleep is related to the total amount of sleep that can be obtained prior to sleep deprivation.¹⁴ Sleep during a period of sleep loss can also provide benefits, but such benefits are increased by naps taken in the early part of the sleep-loss episode.¹⁵² When short periods of sleep are allowed later during sleep loss, subjects may be difficult to awaken and may display considerable sleep inertia after awakening.¹⁵³ Other research has shown that the beneficial effects of naps and caffeine may be additive, and that the combination of a nap prior to sleep deprivation with caffeine use during sleep deprivation can provide improved alertness over a longer period and perhaps with lower doses of caffeine.¹⁴

The relative risks and benefits associated with the stimulants can be assessed in a number of ways, including previous recommendations in the literature, side-effect profiles, development of tolerance or withdrawal effects, or attention to scheduling guidelines provided by the FDA. Each of these methods provides an independent method to use in the selection of a stimulant that is independent of information about overall effectiveness.

Previous Recommendations

After examination of the available stimulants, previous reviewers have typically suggested caffeine as an initial stimulant of choice^{6,151} for the following reasons:

1. It is easily available in many forms.
2. Most individuals have previous experience with caffeine and already have an idea of personally effective dose levels and possible side effects.
3. It is not a restricted substance.
4. It has been used for many years and has been thought to have limited abuse potential.
5. It has relatively little impact on sleep in sleep periods that follow administration by several hours.

There are too few published experiments with adequate statistical power to compare the effects and side effects of caffeine with other stimulants in sleep-deprived adults and draw conclusions about the extent to which caffeine should be recommended over these controlled substances beyond the 5 points listed above. Also, additional information concerning several of the stimulants has appeared since these reviews were published.

Recommendations Based upon Tolerance

Evidence from tolerance and dependence studies suggests that there is significant potential for development of tolerance and dependence with the use of amphetamine (see Section 4AI). There is evidence for the development of tolerance with methylphenidate, but abuse liability does not appear to be as great as with amphetamine (see Section 4BI). Evidence for moderate abuse liability and the development of moderate physical dependence has been shown for caffeine (see Section 4CI). Such evidence indicates that care should be used in chronic administration of

caffeine and that withdrawal effects after extended use need to be considered. There is limited evidence concerning abuse potential for modafinil because of relatively recent availability. Although studies of modafinil have not shown a pattern of adverse effects similar to those of drugs of abuse, additional studies of possible side effects, tolerance, and withdrawal are needed. Based upon this tolerance data, it is recommended that all stimulants be used only on an acute basis to maintain effectiveness.

Recommendations Based upon Side Effects

Although stimulants differ in activity, all have the potential to produce negative effects, depending upon dose and individual sensitivity. The FDA has concluded that caffeine at 100 mg per day or less presents no evidence of human health hazard. However, the Institute of Medicine⁶ has recommended that caffeine doses should not exceed 600 mg per day to avoid negative effects. Negative effects upon acute administration of higher doses of caffeine include heart pounding, nausea, tremor, and jitteriness.^{27,31} One study has reported vomiting after a 600-mg dose of caffeine administered during sleep deprivation.²⁵ The diuretic effect may make caffeine a less-desirable alternative in some operational settings. Anxiety may be increased and sleep disturbance has been reported for sleep periods beginning within 8 hours of administration. With repeated use, development of subjective tolerance might precipitate dose escalation.

In studies of modafinil, participants have discontinued participation because of headache, nausea, depression, and anxiety. Modafinil has some adverse effects on sleep periods that follow administration within 14 hours. These effects appear to be less than those found for amphetamine but may be dose related. In general, modafinil appears to have a less-severe side-effect profile or overdose risk than do amphetamines. Although it has been suggested that modafinil may distort (inflate) subjects' estimates of their performance,⁸³ this effect needs replication.

Amphetamine at the 20-mg dose has been reported to increase blood pressure and may produce nausea, headaches, anxiety, stomach cramps, dry mouth, pounding heart, excitement, or jitteriness.²⁷ Amphetamine impairs sleep periods that follow administration within 15 hours. It may also impair sleep on the following night (28.5 hours after administration). Subjects may report a pleasant feeling ("high") that drives repeated use. Current evidence of neurotoxic effects of methamphetamine^{65,70,71} suggests that methamphetamine not be used in preference to d-amphetamine. The history of amphetamine use for performance enhancement by healthy individuals is a mixed lesson. The longstanding tradition of using d-amphetamine during sleep deprivation in some military operations dates back to World War II and continues to this day. However, drug testing for amphetamine in the Olympic games began in 1968, in response to illness and death caused by widespread amphetamine use in prior decades.

Current evidence from side-effect data suggests that pemoline should not be used because of unpredictable potential for liver damage.¹¹⁰ It should be noted that, at one point in time, pemoline was designated as the "drug of choice for enhancement of alertness" for the British Royal Air Force prior to knowledge of its potential liver effects.^{151p153} This is a cautionary note that the ultimate utility of stimulants may become apparent only after extended experience. As such, toxicity from long-term use or high-dose use should remain an important issue for monitoring in all

new stimulants.

None of these compounds is benign. As all may produce side effects, consideration for usage should be based on necessity (sleep is not an option) and for the minimal amount of time until normal sleep is possible. As prescription medications, all of the stimulants require physician approval to justify need and length of use.

Recommendations Based Upon Abuse Scheduling From the FDA

FDA recommendations for the stimulants reviewed here are quite disparate, primarily due to the historic use of caffeine and its nonscheduled status. Availability has led to publication of large amounts of data, and these indicate that the central nervous system effects and side effects of caffeine may be underappreciated. Modafinil is a FDA Schedule IV medication approved for use for excessive daytime sleepiness in several conditions. Amphetamine and methylphenidate are Schedule II medications approved for use in narcolepsy and ADHD. Pemoline remains available for use as a Schedule IV medication with an indication for ADHD, but the FDA advises that patients sign a separate informed consent acknowledging risks.

If one considers only the drug scheduling according to the Controlled Substances Act of 1970, enforced by the DEA, then amphetamine and methylphenidate have the highest abuse potential. They are classified as Schedule II drugs, which means that they have high abuse potential and may lead to severe physical and/or psychologic dependence. Other examples of drugs in this category include opium, morphine, hydromorphone, codeine, and oxycodone. Based upon the FDA scheduling, one might recommend caffeine for acute use in large groups (troops in deployment) during which careful medical observation is not available. Modafinil, as a Schedule IV medication, may have less abuse potential and might therefore be considered for prescription before d-amphetamine and methylphenidate, as the latter medications are both Schedule II. However, use of any of these medications during sleep deprivation is considered an “off-label” use based upon data originally submitted to the FDA for the use of these compounds.

Future Research

Many studies have shown that the stimulants reviewed here can provide benefits for alertness and performance during sleep loss. However, it is often difficult to compare studies because many parameters, including length of sleep loss, time of stimulant administration, dose of stimulant, formulation of stimulant, schedule of repetition of stimulant, and history of stimulant use by subjects may vary from study to study. The only way to directly compare stimulants is by including more than 1 stimulant in head-to-head empirical studies that are adequately powered to detect differences between substances. Such studies will be difficult to design due to dose-response and pharmacokinetic differences between the stimulants. It is important to evaluate relative abuse potential and tolerance effects within such studies.

Compared with caffeine and amphetamine, modafinil is a relatively new stimulant. Based on current data, modafinil appears to be a somewhat safer alternative to other prescription stimulants for promoting cognitive performance during sleep deprivation in healthy individuals. The fact that it has generally lower abuse potential and/or a less-serious side-effect profile than amphetamine,

methylphenidate, and pemoline may reflect either fewer underlying problems or less accumulated use by a relatively smaller number of individuals. Only additional study can resolve this issue.

Historically, most studies of sleep deprivation have concentrated on basic cognitive tasks involving sustained attention, reaction time, short-term memory, or arithmetic. As a result, less is known about the impact of sleep loss on complex judgment abilities. Additional investigations are needed on the effect of these stimulants on executive-function tasks.

As a stimulant, caffeine, because of its nonprescription status, is in a unique class that gives it significant benefits and liabilities. Benefits include easy access, extensive research findings, and broad familiarity with effects. One liability is that caffeine use is already so high in society that many individuals have developed some degree of tolerance. For caffeine, in particular, more information is needed concerning the development of tolerance, withdrawal, and ability to reestablish sensitivity. Many individuals may use caffeine from habit rather than necessity, and this may interfere with the ability of caffeine to be used effectively by those individuals during sleep loss. For such individuals, more-judicious and informed use of caffeine may be appropriate. Caffeine tolerance may also make the other stimulants less effective (cross-tolerance), although there is little research in this area. The level of caffeine use and the level of sleep deprivation in society justify additional research to understand these issues and to educate the public concerning appropriate use of caffeine.

CONCLUSIONS

In situations in which extended wakefulness is necessary and sleep must be curtailed, limited use of stimulant medication may be appropriate on a voluntary basis. Important considerations in treatment include the length of the proposed period of additional wakefulness, the level and type of activity during the additional wakefulness, and the availability of medical supervision during the period of sleep loss.

In most situations that involve limited sleep loss, caffeine, in liquid, tablet, or gum form, can provide significantly improved alertness and performance starting with doses as low as 75 mg. In situations involving extended sleep loss (more than 2 nights), available data indicate that caffeine administered as a single dose of 600 mg is roughly comparable to (but not as long lasting as) a single 20-mg dose of d-amphetamine or a single 400-mg dose of modafinil. However, all of these doses and medications may be associated with side effects that could limit use under certain operational conditions.

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