

# Chapter 4

## PERFORMANCE-MAINTAINING AND PERFORMANCE-ENHANCING DRUGS AND FOOD COMPONENTS

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## INTRODUCTION

This chapter discusses drugs and food constituents that could potentially enhance mental performance on the battlefield or in other intense military operations. Other strategies to enhance cognitive performance, such as behavioral techniques (including training and behavior modification), are not addressed, nor is physical performance enhancement. Psychoactive substances have been used in combat for thousands of years. Alcohol has a long history of use on the battlefield, probably as a result of the euphoric feeling and loss of inhibition it can produce. In modern times, the most extensive, officially sanctioned use of drugs to enhance performance in combat has been the use of amphetamines by most armies, including the US Army, during World War II. These stimulants prevented fatigue and drowsiness, and improved concentration and memory.<sup>1</sup> According to a psychiatrist assigned to the 25th Infantry Division during the Vietnam War, Long-Range Reconnaissance Patrol (LRRP) soldiers used methylphenidate and dextroamphetamine regularly.<sup>1</sup> He stated that these compounds were standard

issue and that—other than mild rebound depression and fatigue when the drugs were discontinued—no adverse effects were reported. In addition, he noted that the LRRPs found that such drugs were particularly useful when a rapid return to base camp was necessary after completing a mission.<sup>1</sup> Amphetamines and caffeine have been the most studied performance enhancers in the military, with significant research programs focused on fatigue countermeasures in aviators conducted by the Naval Aviation Medical Research Laboratory (NAMRL; Pensacola, Fla), the US Army Aeromedical Research Laboratory (USAARL; Fort Rucker, Ala), and the Human Performance Effectiveness Division (School of Aerospace Medicine, Brooks Air Force Base, San Antonio, Tex).

The medical literature contains few published reports on the use of performance-enhancing or performance-sustaining drugs in combat or in combat-like conditions. To illustrate some of the issues associated with the use of drugs during military combat operations, a detailed discussion of one report is presented



**Fig. 4-1.** These technologically advanced aircraft permit long duration missions that push the limits of human endurance, requiring special consideration to fatigue countermeasures for the aircrew.

Photograph: Reproduced from the US Air Force. Image ID: 060214-F-6911G-135. Available at: <http://www.af.mil/photos>.

to provide a frame of reference for the reader. This report, which provided considerable valuable (albeit anecdotal) information on the use of drugs during a combat mission, appeared in the 1988 issue of *Aviation, Space, and Environmental Medicine* as the first “Operational Note” ever published in that journal.<sup>2</sup> It was written by a US Air Force flight surgeon who provided support to an EF-111A Raven unit that was responsible for electronic warfare during an air strike on Libya in April 1986 (Figure 4-1). The mission originated in the United Kingdom and lasted approximately 13 hours, with the aircraft departing at 1800 hours and returning the next morning. Even though it was only a single 12-hour flight, the anticipated fatigue and stress of this combat mission were sufficient enough for the unit commander to request pharmacological support for his pilots. The flight surgeon was asked to provide go/no-go medications to the unit. Thus, he issued secobarbital (Seconal, 100 mg [Eli Lilly and Company, Indianapolis, Ind]) and dextroamphetamine sulfate (Dexedrine, 5 mg [GlaxoSmithKline, Philadelphia, Pa]) to all crew members. Operational requirements of the one-time mission provided a striking illustration of the complex and difficult physiological and behavioral factors associated with even a single combat mission. Many problems that occur in short duration missions are exacerbated during sustained operations. The severe decrements in cognitive performance associated with sustained, combat-like operations are much greater than those produced by alcohol intoxication or clinical hypoglycemia.<sup>3,4</sup> For a detailed discussion of fatigue, sleep, and cognitive performance, see Chapter 3 (Measuring and Predicting Sleep and Performance During Military Operations) in this volume.

Before the Libya mission, almost all aircrew members reported an inability to sleep for 24 hours because of the high level of physical and mental stress associated with preflight preparations. However, none of the crew used the secobarbital reportedly because they did not have confidence in it, although all of them had documented ground testing with the drug in their medical records. Perhaps their prior experience with the drug convinced the crew members that it could have adverse effects on their next-day performance. Indeed, some crew members explicitly reported that they did not trust using the medication before such a

crucial mission. This may have been an appropriate decision because barbiturates can impair performance the day after they are used as hypnotics. During the prestrike portion of the mission, the crew members reported nervousness (including gastrointestinal distress), but had no problem staying alert. However, on the return leg of the mission, after their final in-flight refueling, the crew definitely noticed the fatigue and stress of the previous 24 hours. All of them took the dextroamphetamine and reported benefiting from it. This may have occurred at the nadir of the crews’ circadian cycle because they landed between 0600 and 0700 hours. No definitive conclusions should be drawn from this illustration, but military physicians must be prepared to consider the issues associated with the use of drugs and other performance-enhancing strategies in combat.

Similar reports regarding the use of go/no-go medications by aviation units during the sustained, high-intensity air operations of the Persian Gulf War have also appeared in the literature, although they have only been published as abstracts.<sup>5-7</sup> One report concluded that approximately 60% of US Air Force Tactical Air Command aircrew occasionally used dextroamphetamine during operations in the Persian Gulf War.<sup>7</sup> Dextroamphetamine was also used by the US Air Force during Operation Enduring Freedom in Afghanistan. Its use was widely publicized because several pilots were using it when they were involved in a friendly fire incident, and there was some concern that the pilots’ judgment may have been impaired by the drug.<sup>8</sup>

This chapter is not intended as a comprehensive review of all the literature available on each class of drugs or food constituents of interest nor has every compound that could potentially enhance performance been reviewed. Rather, classes of compounds that are likely to be considered for use or that have previously been used on the battlefield or in intense, stressful military operations will be discussed. The improvement in our understanding of structure–function relationships of these drugs and advances in neurophysiology should enable a more systematic modeling of when and how drugs and nutritional supplements can most effectively optimize performance (see Chapter 3, Measuring and Predicting Sleep and Performance During Military Operations).

### SEDATIVE-HYPNOTICS AND ANTIANXIETY AGENTS

The use of compounds that are generally categorized as central nervous system (CNS) depressants to enhance or sustain performance would, at first glance, seem to be a paradox. However, such compounds have repeatedly been studied and used in military opera-

tions to promote sleep at desired times<sup>9</sup> (Figure 4-2). By ensuring that soldiers sleep at appropriate times, subsequent mental performance will be preserved or improved. A number of studies have been conducted to induce or maintain sleep at desired times with



**Fig. 4-2.** Marines sleeping on a transport aircraft. Pharmacological fatigue countermeasures must not interfere with opportunities for restorative sleep because this is the best available fatigue countermeasure.

Photograph: Reproduced from the US Marine Corps, Defense Visual Information. Image ID: DM-SD-05-11545. Photographer: LCPL Andrew Williams, US Marine Corps. Available at: <http://www.dodmedia.osd.mil>.

the use of drugs, as well as other compounds with sedative-like properties (eg, the dietary amino acid tryptophan and the hormone melatonin). Hypnotics or sedatives have also been used in attempts to speed reentrainment of circadian rhythms when military units cross multiple time zones or shift from day to night operations.<sup>10-12</sup> Many drugs with hypnotic or sleep-inducing properties also have potent antianxiety effects. Such properties could, in theory, also be useful on the battlefield or in other high-intensity, stressful operations. However, the hypnotic-sedative effects of these compounds, including their adverse effects on mental performance, generally exclude their use as antianxiety agents in combat.

Sedative-hypnotic drugs are used to treat anxiety and insomnia, and in some cases to prevent epileptic seizures. Although each drug has its preferred clinical usage, sedative-hypnotics are often capable of inducing various states of sedation, ranging from mild relief to deep sedation, depending on the dose. Thus, a drug commonly prescribed for its antianxiety effects may induce lethargy and sleep at higher doses. The decision regarding which drug to prescribe for a particular clinical condition is often based on its elimination half-life and side-effect profile.

Many of the older sedative-hypnotics, such as the barbiturates, produce widespread depression of the CNS. However, the benzodiazepine sedative-hypnotics—that interact with  $\gamma$ -aminobutyric acid (GABA)-benzodiazepine receptor sites—are potent

antianxiety agents, have excellent utility as hypnotics, and rarely produce nonspecific CNS depression when used in appropriate doses. Zolpidem (Ambien [Sanofi-Aventis U.S., Bridgewater, NJ]), an imidazopyridine, and similar compounds such as zaleplon (Sonata [King Pharmaceuticals, Inc, Bristol, Tenn]) also act at these sites, although these compounds have a higher affinity for benzodiazepine type 1 receptor sites than the type 2 sites. The traditional benzodiazepines are nonselective, binding with equal affinity to both type 1 and type 2 receptors. The azaspiron compound, buspirone—an antianxiety agent not pharmacologically related to the benzodiazepines, barbiturates, or any other sedating hypnotic—does not seem to have potent hypnotic properties and could, at least in theory, be used for its antianxiety properties in military operations. Although its precise mechanism of action is unknown, it has a high affinity for serotonin receptors, but not GABA receptors. There is a low incidence of nonspecific depression when buspirone is used appropriately.

The following sections are subdivided by class of drug discussed. Barbiturates, benzodiazepines and related compounds, and buspirone are discussed in detail. Melatonin, which has hypnotic properties, will also be reviewed. For practical purposes, a key question for ongoing review is, “What are the residual effects when a sedative-hypnotic is used to promote sleep the night before an important activity?” Another issue is whether the compound impairs performance during the period of time when it is being used to induce and maintain sleep. This is an important issue in military applications, because emergencies may arise even when personnel are off duty. Of course, the answer to these questions varies among drugs, dosages, and even individual subjects; but experimental examples are given to illustrate the most probable effects. From the hundreds of relevant articles, special consideration was given to those with applicability to military situations. Another key issue that has rarely been addressed is whether the use of such compounds in an operational setting actually improves next-day performance in addition to enhancing sleep.

### Barbiturates

Barbiturates are fat soluble and are thus rapidly and completely absorbed in the stomach. Therefore, they are usually administered by mouth, with the exception of intravenous use of a very short-acting compound as a general anesthetic. Their duration of action is determined by the drugs’ metabolism and excretion. For example, a short-acting drug such as thiopental is extremely fat soluble. It is very rapidly absorbed, but

it is also very quickly redistributed from the CNS to muscle and fat tissue. Then, it is slowly metabolized by the liver and excreted by the kidneys. This explains why individuals who have been sedated or anesthetized by thiopental wake up within a few minutes, but remain groggy for several hours.

A long-acting barbiturate such as phenobarbital, however, is only slowly absorbed by fat tissue and muscle. Thus, the barbiturate circulates in the blood in concentrations sufficient to keep the individual sedated until it can be metabolized by the liver or excreted by the kidneys.<sup>13</sup> Barbiturates are no longer generally used as hypnotics. They have been replaced by benzodiazepines and related compounds, and are a particularly poor choice in situations in which next-day performance is important.

McKenzie and Elliott<sup>14</sup> studied the effects of secobarbital on the performance of 48 pilots on a simulated air mission. The goal was to investigate the effect of premission sedation, prescribed in instances in which the pilot must retire in late afternoon and be awakened 8 hours later for an early morning flight. The subjects were given 200 mg secobarbital when they retired at 2100 hours. They were awakened for breakfast at 0545 hours. As previously noted, secobarbital was issued by a flight surgeon before an actual combat mission, but a dose of 100 mg was used.<sup>2</sup> The simulated mission designed by McKenzie and Elliott<sup>14</sup> began at 0700 hours and lasted 12 hours, with two meals given en route. The 200-mg dose produced performance decrements not only at the start of the mission, which was 10 hours postdosage, but also throughout the entire 12-hour simulation.

A thorough review of 23 studies on the effects of barbiturates on performance indicated that administration of these drugs produced impairment in 29.9% of the placebo-barbiturate comparisons. The tasks most sensitive to barbiturate-induced impairment were those involving tracking, concentrated visual searching, and sorting. Tasks that were least affected were those involving manual dexterity, arithmetic, and choice reaction time.<sup>15</sup> Although only a limited number of studies tested performance at standardized intervals after dosage, available data for the 7- to 10-hour postadministration period showed a 32% decrement in overall performance, compared with 36% at 11 to 14 hours and 24% at 15 to 22.5 hours. The magnitude and duration of the deficits were not necessarily consistent with the half-lives of the drugs. Overall, these are very substantial and sustained adverse effects on performance. There seems to be little reason to use barbiturates as sleep enhancers in military operations; other compounds (eg, the benzodiazepines) are generally preferred as hypnotics. Furthermore, the adverse

effects of the barbiturates on next-day mental performance are probably greater at equipotent doses than those of the benzodiazepines.

### **Benzodiazepines and Related Compounds**

All benzodiazepines are lipid soluble. However, the pharmacokinetic activity of the benzodiazepines varies widely because their solubility can differ by as much as a factor of 50.<sup>13</sup> Many benzodiazepine metabolites are also pharmacologically active, effectively prolonging clinical effects. Thus, in choosing an appropriate benzodiazepine, a physician must consider both the desired speed of onset and the overall duration of action.

Typically, chronic anxiety and epilepsy are best treated using a drug with a long duration of action, whereas induction of sleep is optimally achieved with a rapid-onset, short-acting agent. Rapid-onset drugs minimize morning hangover effects, although early morning awakening has been reported when short-duration benzodiazepines are used.<sup>16</sup> Benzodiazepines are widely used for their antianxiety, sedative, and hypnotic properties. Zolpidem, a nonbenzodiazepine, acts at the same GABA receptor sites as the benzodiazepines and has nearly identical effects. Adverse effects of these compounds include daytime sedation, motor incoordination, and cognitive impairments, especially anterograde amnesia. Long-term use has additional risks, including physical dependence, withdrawal, and rebound insomnia.<sup>17</sup> Buspirone, which acts at serotonergic receptor sites, is widely used as an antianxiety agent and may have advantages over the benzodiazepines and zolpidem for this indication because its sedative effects seem to dissipate when used for several days.<sup>18</sup>

### ***Benzodiazepines in Operational Scenarios***

Cluydts and colleagues<sup>19</sup> investigated the effects of the benzodiazepines—lormetazepam and zolpidem—in operational scenarios. Twelve subjects were given either 2 mg lormetazepam or 10 mg zolpidem when they went to bed at 2245 hours. For the next 8 hours, traffic noise ranging from 32 to 77 dB was played continuously. Such disruptions of sleep produced by external stimuli are very likely to occur in operational situations and combat. Although both hypnotics significantly increased total sleep time, lormetazepam had the most profound effects, with a mean increase of 24 minutes, compared with 16 minutes for zolpidem. Although lormetazepam produced a significant decrease in the number of sleep-stage transitions, arousals, and awakenings throughout the night, there was no difference between the drugs on subjective measures of sleep quality, mood, or morning alertness. Behavioral

testing the following morning showed significant adverse effects of lormetazepam, but not zolpidem, on the four-choice reaction test, particularly a significant increase in overall reaction time.

### ***Benzodiazepines and Memory Impairments***

O'Donnell et al<sup>20</sup> investigated the effects of triazolam (Halcion [Pfizer, Inc, New York, NY]), another short half-life benzodiazepine, on performance and sleep after exposure to a stressful movie. At 0930 hours, 49 subjects watched a short movie titled "Subincision," which was used in previous studies to increase autonomic arousal. The subjects were then given 0.125 mg, 0.25 mg, or 0.5 mg triazolam and instructed to try to sleep in an environment that was similar to that experienced by airline passengers. The 0.5-mg dose of triazolam significantly increased the continuity and duration of sleep. However, at 90 minutes post-administration, that same dosage was also associated with slowed performance and impairments in learning new material. This impairment of short- and long-term memory is a classic side effect of the benzodiazepines. Deficits were no longer apparent at 6 hours post-administration, and no deficits were seen with the lower doses at either time period. In other studies, similar doses of triazolam have been shown to impair performance the next day.

In one of the few military field studies of benzodiazepines, Penetar and colleagues<sup>21</sup> administered 0.5 mg triazolam or placebo to 68 airborne soldiers on the first leg of a flight from the United States to the Middle East. During a refueling stop 8 hours later, the soldiers' mood and performance were assessed. Triazolam did not improve the duration or continuity of sleep as measured by wrist-worn activity monitors, nor did it alter mood or sleepiness. However, significant impairments in memory function were observed when behavioral testing was conducted. The authors concluded that this dose of triazolam was not suitable for use when unimpaired cognitive function was essential immediately on arrival. (For a review of the effects of the benzodiazepines on memory and mood, see the study by Curran.<sup>22</sup>)

### ***Benzodiazepines and the Sleep-Rest Cycle***

Seidel and colleagues<sup>23</sup> tested the effects of triazolam and flurazepam on sleepiness, objective performance, and mood during a forced shift in the sleep-rest cycle. For three 24-hour periods, subjects were shifted 12 hours in their sleep-wake cycle by postponing sleep until noon. At that time, they received either 0.5 mg triazolam or 30 mg flurazepam, then went to bed for

an 8-hour interval. Triazolam has an elimination half-life of 2 to 5 hours, whereas the major metabolite of flurazepam has a half-life of 50 to 100 hours. Postsleep testing showed that, although both drugs produced similar increases in sleepiness and mood disturbance, subjects receiving flurazepam displayed deficits in vigilance and visual tracking. Triazolam, however, maintained or improved performance on all tests. The authors stated that, by facilitating good sleep, the compound with a shorter half-life—triazolam—was able to preserve daytime performance despite the 12-hour phase shift. Subjects receiving the long half-life hypnotic showed decrements greater than those seen in placebo controls.<sup>23</sup>

### ***Benzodiazepines and Military Duty***

Caldwell et al<sup>24</sup> conducted a study at the US Army Aeromedical Research Laboratory (Fort Rucker, Ala) to determine whether aviators who had taken a benzodiazepine as a sleep aid before bedtime could adequately perform their duties the following day. The authors also investigated whether the volunteers could perform their duties if they were awakened in the middle of the night (if, for example, an urgent mission unexpectedly arose). Ten Army helicopter pilots were given 0.25 mg triazolam or placebo 15 minutes before retiring to bed at 2200 hours. Sleep was monitored, and the subjects were assessed on subjective sleepiness, cognitive function, and simulated helicopter flight performance the morning and afternoon following drug administration. Testing occurred after an 8-hour sleep period on one night and after 2 hours of sleep on another night.

Triazolam produced decrements in five of nine simulated flight maneuvers the morning following the full night of sleep.<sup>24</sup> Three of these maneuvers were less affected during the afternoon test session. Although testing 2 hours after the dose was taken revealed decrements in only two maneuvers, compared with the placebo, performance at this hour was poorer overall than for all groups in the afternoon sessions. Some subjects who received triazolam were difficult to awaken for this "emergency" test session, but all subjects were able to return to sleep faster than those who had received placebo. There were no differences between triazolam and placebo on subjective sleepiness, but two of the ten pilots were unable to recall portions of the midnight flight following triazolam. Based on these results, the authors state that performance following 8 hours of sleep with triazolam is affected, but not to the extent that an aviator cannot control an aircraft. They suggest that, before triazolam is used as a sleep aid, it should be administered in a controlled trial to determine how long it would take a subject to awaken

and whether any other negative effects would occur. In general, preoperational testing of compounds that may alter cognitive performance is recommended, because this gives personnel an opportunity to experience the effects of the drug prior to its operational use and may reveal any idiosyncratic adverse effects.

In a study conducted by Caldwell et al,<sup>25</sup> temazepam (30 mg; Restoril [Mallinckrodt Medical, Inc, Hazelwood, Mo]) was tested on helicopter pilots to determine if it would enhance daytime sleep and prevent the deterioration in performance seen during the subsequent night shift. Temazepam is rapidly eliminated and has no long-acting metabolites. The drug clearly improved daytime sleep, as well as cognitive performance that night, as measured by a computerized reaction time task. However, performance in a flight simulator was not clearly improved by enhanced daytime sleep.<sup>25</sup>

The US Air Force School of Aerospace Medicine conducted a study with FB-111A aircrew members who used 30 mg temazepam as a sleep aid before either a simulated or a real training mission.<sup>26</sup> The study was designed to simulate surge operations requiring two consecutive nighttime missions with daytime sleep periods interspersed. Temazepam enhanced sleep duration and continuity, as measured with activity monitors. However, 12 hours after administration, there were some subtle, adverse effects of the drug on cognitive performance.

This study was motivated by a report that, during the Falkland Islands War in 1982, temazepam was extensively and successfully used by British aviators who were required to fly very long flights with limited rest periods.<sup>9</sup> Typically, aircrews took 20 mg temazepam at least 8 hours before flying missions. Crew members reported that they could fly as soon as 6 hours after taking the drug without ill effects. It is difficult to interpret this and similar observational reports regarding the use of drugs in actual combat. Obviously, rigorous studies cannot be conducted in such situations, and they are difficult, if not impossible, to adequately simulate in the laboratory.

A number of studies have been conducted by military laboratories comparing various sleep-inducing compounds. For example, Paul and colleagues<sup>27</sup> compared the effect of a single dose of zaleplon (10 mg), zopiclone (7.5 mg), temazepam (15 mg), and melatonin (6 mg in a timed-release preparation) on psychomotor performance and attempted to quantify the postingestion time required for return to normal performance. They determined that, "The recovery time to baseline subjective sleepiness levels for zaleplon, zopiclone, temazepam, and melatonin were 4.25, >6.25, 5.25, and >4.25 hours, respectively. However, they noted that, "[i]n spite of a

prolonged period of perceived sleepiness, melatonin was superior to zaleplon in causing no impact on performance."<sup>27</sup> The remaining drugs listed in increasing order of performance impact duration are zaleplon, temazepam, and zopiclone. The hormone melatonin is discussed later. A study by Whitmore et al<sup>28</sup> also indicates that zaleplon is a useful sleep aid that has few residual effects, which is consistent with its relatively short half-life, compared with benzodiazepines and similar compounds. However, it is reasonable to anticipate that a drug with a shorter half-life will maintain sleep for a shorter period of time, compared with one with a longer half-life. Melatonin also has an extremely short half-life<sup>29</sup> unless it is administered in a time-release preparation, as done by Paul and colleagues.<sup>27</sup>

### **Risks and Benefits**

Overall, the documented adverse effects of many of the benzodiazepines and related compounds, even those that are widely used with shorter half-lives (eg, triazolam [Halcion] and zolpidem [Ambien]), on performance the day after they are administered makes their use in combat or other intense operations a difficult medical /operational judgment. These compounds, like any drug, may sometimes have greater risks than benefits. As demonstrated in a study by Paul and colleagues,<sup>27</sup> the shortest-acting compounds (eg, zaleplon) probably have the lowest risk. Although the value of sleep cannot be overestimated, the adverse effects that these compounds have the next day could be potentially life-threatening in combat conditions. For a discussion of the importance of sleep and the effects of sleep deprivation, see Chapter 3 (Measuring and Predicting Sleep and Performance During Military Operations) in this volume. Unfortunately, there is limited evidence demonstrating that the use of benzodiazepines to improve sleep also improves subsequent military performance, although it does appear that short-acting benzodiazepines speed reentrainment to new daily schedules of activity. The benzodiazepines and related compounds are particularly useful when it is likely that duty the next day will not be required. When military physicians consider the use of these drugs operationally, they must consult official doctrine and carefully weigh the risks and benefits.

Belenky<sup>30</sup> has advanced a possible solution to the problem of next-day hangover effects induced by the benzodiazepines, as well as the issue of emergency awakening soon after benzodiazepine administration. He has suggested that an antagonist of the benzodiazepines, flumazenil, could be used operationally to rapidly reverse the effects of the benzodiazepines.<sup>30</sup> Although flumazenil is a US Food and Drug Adminis-

tration (FDA)-approved drug, it is currently available only as an injectable formulation. It has been shown to reverse the adverse effects of both triazolam and zolpidem on memory.<sup>31</sup>

### **Antihistamines**

Antihistamines are another class of compounds that can clearly have sedative effects and are sometimes used as mild sleep aids. These drugs are most commonly used to treat allergic rhinitis and other allergic symptoms. Newer forms that have little or no sedative effects (eg, loratadine and terfenadine) have been developed. Several of the older antihistamines (eg, doxylamine and diphenhydramine) are sold as over-the-counter (OTC) sleep aids, but they do not appear to have the potency of the barbiturates or benzodiazepines. These antihistamines may be useful in military operations as substitutes for more potent sleep-inducing compounds; however, even in low doses, antihistamines with sedative properties can impair performance.<sup>32</sup>

### **Melatonin**

One compound that may provide an alternative to the use of traditional hypnotic drugs to enhance sleep, and thereby improve performance, is the hormone melatonin.<sup>33</sup> In humans, melatonin is secreted by the pineal gland, predominantly at night in the dark. Its function is unknown. When administered in pharmacologic doses, it has sedative-like properties and rapidly induces sleep.<sup>33-35</sup> Melatonin is extremely potent and has a very short half-life.<sup>29,36</sup> This hormone has sleep-inducing properties even when it is administered in doses (0.1 mg) that produce plasma levels not much greater than human nocturnal plasma levels.<sup>36</sup> Melatonin is sold as a dietary supplement in the United States, as permitted by the Dietary Supplement Health and Education Act of 1994 (DSHEA). However, from a scientific perspective, it should be considered a drug. Because of its unique regulatory status, sufficient data are not currently available to conclude with certainty that it is an effective hypnotic or to determine its optimal dose, although evidence-based reviews conclude that melatonin is effective as a sleep aid and circadian synchronizer.<sup>37-40</sup> Although it can be sold as a dietary supplement in the United States, the FDA does not require any demonstration of efficacy or safety. Doses of melatonin ranging from 0.3 to 10 mg have been suggested as appropriate for inducing and maintaining sleep.<sup>11,36</sup> It is typically sold in doses of 3 or 5 mg.

Several studies suggest that melatonin may be useful in operational scenarios as a potential treatment for

transmeridian desynchronization (ie, jet lag). In a study with an operational US Army Special Forces aviation unit deploying across multiple time zones to evaluate melatonin as an operational anti-jet-lag treatment, administration of 10 mg melatonin each day before the sleep period significantly improved vigilance and sleep, as measured indirectly with activity monitors.<sup>11</sup> Unlike the benzodiazepines, melatonin does not seem to impair memory and has considerably fewer adverse effects on cognitive performance, even when administered in much higher doses than required to enhance sleep.<sup>27,33</sup> Paul and colleagues<sup>12</sup> conducted a study that compared sustained release melatonin (2 mg) with 5 mg zopiclone, a benzodiazepine-like drug, in aircrews who were flying transatlantic missions. They found that both compounds were equally effective. A systematic review of the literature addressing the utility of melatonin for circadian resynchronization was conducted.<sup>37</sup> It concluded that: "Melatonin is remarkably effective in preventing or reducing jet-lag, and occasional short-term use appears to be safe." However, its classification as a dietary supplement in the United States is an obstacle to its sanctioned operational use, because legally such products are not approved for specific medical uses. It should also be noted that, even when melatonin is administered in very low doses, it does acutely impair certain aspects of cognitive performance.<sup>34,36</sup>

### **Buspirone**

As described previously, buspirone is an antianxiety agent not pharmacologically related to the benzodiazepines, barbiturates, or any other sedative hypnotic. It exerts its effects by binding with high affinity to 5-HT<sub>1A</sub> (5-hydroxytryptamine [serotonin] receptor 1A) receptors. Although its precise mechanism of action has not been conclusively demonstrated, a number of studies have found that buspirone rarely produces nonspecific depression, unlike the other traditional sedative hypnotics. Buspirone is a water-soluble compound, it is rapidly absorbed and metabolized, and its average elimination half-life is 2 to 3 hours.

Buspirone is used primarily as an antianxiety agent to treat various psychiatric disorders, especially generalized anxiety disorder. Like many drugs used in psychiatry, buspirone has a very slow onset of action, requiring several weeks of administration before its therapeutic actions are maximal. Even before it was available in the United States, Jones<sup>1</sup> suggested that it might be useful on the battlefield because of its antianxiety properties and lack of adverse effects on cognitive performance. To date, studies have not been conducted to determine whether this compound would be useful

as an antianxiety agent during intense military operations. The high frequency of psychiatric casualties from battlefield stress seen in intense military operations<sup>41</sup> suggests that a compound with such properties could, in theory, be of great benefit to soldiers. However, the optimal level of anxiety on the battlefield is a matter of some debate. Very low levels of anxiety in the face of danger are not desirable and could be fatal. It is difficult to envision how appropriate studies to assess the utility of buspirone as an antianxiety agent for use on the battlefield could be conducted in the laboratory or clinic, given the practical and ethical constraints of human research. Several studies have demonstrated that buspirone lacks many of the adverse effects of the benzodiazepines.

Moskowitz and Smiley<sup>42</sup>—in a study of 48 subjects—administered 20 mg buspirone, 15 mg diazepam, or a placebo for 9 days. On the ninth day, the volunteers were also given alcohol to produce a peak blood alcohol level of 0.10%. On days 1, 8, and 9, subjects were tested on a driving simulator using a divided attention task before and 1 hour after dosage. The divided attention test was also administered at 3 and 5 hours after dosage. Diazepam impaired driving performance

and attention performance after both a single day of treatment and following 8 days of treatment compared to placebo. There was no evidence of the development of tolerance to the impairments, as performance decrements were more severe and longer lasting on day 8 as opposed to day 1. However, treatment with buspirone slightly improved performance after the first day of treatment, with an increase in benefits by day 8. Although alcohol potentiated the deficits of diazepam, buspirone offset some of the alcohol-induced impairments. The authors concluded that buspirone could be used effectively as an antianxiety agent for 8 days with little fear of impaired performance.

Lader,<sup>18</sup> who conducted a similar study, found some initial increase in drowsiness induced by buspirone (5 or 10 mg three times a day) that wore off by the end of the week, in contrast to diazepam. Because of this relative absence of side effects, buspirone has achieved widespread use since its introduction in 1987. However, caution is warranted. LeWitt and colleagues<sup>43</sup> have reported instances of dyskinesia and dystonia associated with prolonged buspirone use. Whether buspirone induced or exacerbated an existing movement disorder is unknown.

## STIMULANTS

CNS stimulants are drugs that increase alertness and improve mental performance. Several types of drugs are referred to as stimulants, and they vary widely in their structure and mechanism of action. The most important compounds with potential for use on the battlefield are amphetamines and drugs with similar actions.<sup>13</sup> Another well-known stimulant-like compound, caffeine, is found in a variety of foods and is consumed on a daily basis by millions of people.<sup>44</sup> The stimulant-like action of caffeine is from its effects on central adenosine receptors. The drug theophylline—even though similar in structure and mechanism of action to caffeine—is not typically used for its stimulant-like actions, but rather to treat asthma. Newer stimulant-like compounds, which include modafinil and armodafinil, are now available for operational use; but, to date, only modafinil has been used operationally.

The following sections describe the effects of stimulants on various aspects of performance by using examples from the scientific literature. From hundreds of relevant studies, those with performance measures that generalize to military operations were selected. The discussion is limited to behavioral stimulants and does not include drugs such as strychnine, which is also classified as a stimulant.

Amphetamines and related drugs are sympatho-

mimetic amines that structurally resemble the neurotransmitter norepinephrine. They are typically used in the treatment of narcolepsy and attention-deficit hyperactivity disorder (ADHD). Amphetamines exert their central effects by increasing central norepinephrine and dopamine, although each stimulant may do so by a different mechanism.<sup>45</sup> The most common amphetamine derivatives are dextroamphetamine and methamphetamine. Comparatively, dextroamphetamine has a greater effect on the CNS, with less pronounced effects on the cardiovascular system than the *l*-isomer or the racemic mixture. Methamphetamine and dextroamphetamine are essentially equivalent in their effects.

The stimulants methylphenidate and pemoline, which are used primarily in the treatment of children with ADHD, are classified as “nonamphetamines.” Methylphenidate and pemoline are structurally similar to amphetamines and affect the same brain receptors. Thus, although they are technically not amphetamines, their pharmacological effects are quite similar.<sup>13</sup> Several OTC drugs or dietary supplements, such as phenylpropanolamine (PPA) and ephedra, are also stimulants with structural similarities to amphetamines and they, too, seem to increase alertness. However, in recent years, there has been increasing concern about their safety. PPA was removed from the market, and

ephedra/ephedrine cannot be sold as a dietary supplement, although it is available as an OTC drug to treat asthma.

Modafinil and armodafinil have been evaluated as potential performance enhancers. Both compounds are novel stimulants that are pharmacologically distinct from the amphetamines and methylphenidate. A number of studies demonstrate that modafinil enhances mental performance and wakefulness, without sympathomimetic side effects.<sup>46-53</sup> The following sections discuss the most common amphetamine derivatives dextroamphetamine and methamphetamine, the closely related compounds methylphenidate and pemoline, and the atypical stimulant modafinil.

### **Dextroamphetamine and Methamphetamine**

Medical applications of amphetamines are primarily related to the treatment of attention deficit disorders in children and adults or as an alternative to methylphenidate in patients with narcolepsy.<sup>45</sup> Although these agents have been used as appetite suppressants, this practice has been strongly discouraged because of the rapid development of tolerance and the high potential for abuse.<sup>45</sup> Amphetamines are readily absorbed after oral ingestion and are excreted by the kidney. Their half-lives can range from 7 to 30 hours.<sup>45</sup> At therapeutic doses, the amphetamines produce increases in blood pressure, relaxation of bronchial muscle, increased plasma glucose and blood flow to skeletal muscle with a concomitant decrease in blood flow to internal organs, and pupillary dilation.<sup>13</sup> Typically, administration of an amphetamine will increase alertness, elevate mood, and improve concentration. However, adverse behavioral side effects can include increased irritability, restlessness, anxiety, and perhaps aggression.<sup>13</sup> At higher doses, the drug effects are exaggerated. A slight tremor may be induced, respiration and motor activity increase, and insomnia occurs. Although amphetamines prevent fatigue, sleep cannot be postponed indefinitely, and rebound increases in sleep time will occur.<sup>13</sup> The limits of this effectiveness have never been tested in controlled military studies, although an elegant study was proposed in the 1990s by Dr John Caldwell that would have continued amphetamine dosing and attempted sustainment of wakefulness out to 105 hours; ultimately, the greatest challenge was in the establishment of an effective placebo control group for comparison of effects produced by continued wakefulness and the effects produced by the drug.

In an effort to determine whether dextroamphetamine could overcome the effects of sleep loss on

arousal, mood, and cognitive functioning, investigators at Walter Reed Army Institute of Research<sup>54-56</sup> gave 5, 10, or 20 mg dextroamphetamine to 36 male subjects who had been deprived of sleep for 48 hours. The subjects were then deprived of sleep for an additional 12 hours for testing. Dextroamphetamine, in a dose-related manner, reversed the decrements in cognitive performance and self-rated vigor produced by sleep deprivation. The drug also antagonized the decrease in sleep latency produced by sleep deprivation. A dose of 20 mg dextroamphetamine returned subjects to normal levels of performance on arithmetic and verbal reasoning tasks, and normalized sleep latency for several hours. Effects of the 10-mg dose were smaller and briefer, whereas the 5-mg dose produced no significant changes.

Although these performance-enhancing effects are significant, this study also provided evidence of the residual effects of amphetamine administration on subsequent sleep.<sup>56</sup> When the test subjects were permitted to sleep 14 hours after amphetamine administration, there was a significant decrease in total sleep time following the 20-mg dose of amphetamine, largely because of a significant decrease in time spent in rapid eye movement (REM) sleep. The 20-mg dose reduced total sleep time from 8.1 hours on placebo to 7 hours. Latency to REM sleep was shortened after the 5-mg dose and the 10-mg dose, but not with the highest dosage. Latency to sleep, however, was not affected by any dosage. The authors suggest that these effects on sleep more than 15 hours after drug ingestion indicate a prolonged drug effect.<sup>56</sup>

Shappell and colleagues<sup>57</sup> studied the effects of methamphetamine on simulated sustained flight operations and performance. Twenty-five subjects simulated extended operations by following a schedule of 9 hours of work and 4 hours of rest, followed by 14 hours of work. Then they rested for 6 hours before repeating the work-rest-work schedule. Thirteen subjects were given 0.14 mg methamphetamine per 70 kg of body weight approximately 4 hours and 20 minutes into the second work period. Cognitive performance was assessed with a test battery that included four-choice reaction time, pattern recognition, serial addition/subtraction, grammatical reasoning, and time estimation. Various mood states were assessed, including fatigue and self-rated sleepiness. As the simulated mission progressed, reaction time decreased, but response accuracy was stable. This resulted in an overall increase in the number of correct responses, but also an increase in errors. According to the authors, subjects adopted a more risky response strategy. Methamphetamine reduced subjective fatigue and improved perfor-

mance on two tasks: (1) pattern recognition and (2) mental rotation.

Stanny and colleagues<sup>58</sup> investigated the effects of the same dose (0.14 mg/70 kg body weight) of methamphetamine on vigilance, tracking, and long- and short-term memory during a night without sleep. Thirteen subjects were tested every 90 minutes, from 1930 hours to 0900 hours. Seven subjects received methamphetamine at about 0100 hours, whereas the remaining six subjects received a placebo. Memory, vigilance, tracking, and decision speed worsened through the night, but methamphetamine reversed these effects within approximately 2 hours of administration. Furthermore, analysis of the vigilance data showed no tendency toward increased impulsive responses. Thus, the improved performance seen in the methamphetamine treatment group was in all probability the result of a genuine increase in accuracy rather than a change in response strategy. The authors concluded that methamphetamine was effective in counteracting the effects of sleep loss during sustained operations.

Caldwell et al<sup>49</sup> have conducted a series of studies to determine whether dextroamphetamine is an effective fatigue countermeasure for use by military pilots who are sleep deprived. In one study, they examined the ability of dextroamphetamine to maintain flight simulator performance during 64 hours without sleep. Dextroamphetamine (10 mg) was administered 3 times a day: (1) at midnight, (2) at 0400 hours, and (3) at 0800 hours. Simulator flight performance, mood, and cognitive performance were assessed and electroencephalographic evaluations conducted. It was concluded that dextroamphetamine "sustained aviator performance and alertness during periods of extended wakefulness, but its use should be well controlled."<sup>49</sup> Recovery sleep was somewhat less restful following dextroamphetamine administration.

In another study, Caldwell and colleagues<sup>59</sup> selected data from several controlled aviation studies on dextroamphetamine to substantiate the efficacy of this drug as a fatigue countermeasure. They observed that dextroamphetamine was "effective for maintaining flight skills, psychological mood, and physiological activation (measured via electroencephalograph data) in sleep-deprived pilots."<sup>59</sup> It was concluded that dextroamphetamine was an appropriate intervention for fatigue in aviation-sustained operations, but not a substitute for proper crew-rest scheduling because there is no replacement for adequate restful sleep.<sup>56</sup> Dextroamphetamine (Dexedrine) is approved by the US Air Force for management of aircrew fatigue, but "only after all other nonpharmacologic countermeasures have been exhausted."<sup>60</sup>

## Methylphenidate

Methylphenidate (Ritalin [Novartis Pharmaceuticals, Basel, Switzerland]) is a stimulant primarily used in the treatment of narcolepsy in adults and ADHD in children. (Although concerns are periodically raised about the safety, efficacy, and appropriateness of using this medication with children, it has remained on the market and is extensively used, as is amphetamine.) Rapidly absorbed in oral form, peak plasma levels are attained in 1 to 2 hours, with a 4- to 6-hour duration. About 80% of methylphenidate is metabolized into ritalinic acid, which is excreted in the urine.<sup>45</sup> The physiological effects of this compound are similar to those produced by the amphetamines. For example, Oken and colleagues<sup>61</sup> investigated the effects of methylphenidate on alertness and attention. Twenty-three subjects completed various behavioral and cognitive tasks, which included tests of spatial attention and visual search. Objective measures included analysis of electroencephalogram results and measurement of sleep onset. The authors found that performance on cognitive tasks improved with methylphenidate. Babkoff et al<sup>62</sup> also studied this compound, and their results are discussed in the next section.

## Pemoline

Pemoline is an oxazolidine used for the treatment of ADHD in children. It is similar to other stimulants, except that it seems to have minimal sympathomimetic effects. Taken orally, pemoline is rapidly absorbed, with peak serum levels occurring within 2 to 4 hours postdosage. It is primarily metabolized by the liver, and its half-life is approximately 12 hours.<sup>63</sup> It has, however, been reported by the National Institutes of Health that "pemoline can cause serious and sometimes deadly liver damage,"<sup>64</sup> and thus careful monitoring of liver function must accompany the use of this drug in children.

Babkoff and colleagues<sup>62</sup> investigated the effects of both methylphenidate and pemoline on cognitive performance, subjective and objective sleepiness, and mood after 64 hours of total sleep deprivation in adults. Unlike many other sleep deprivation studies with stimulants, they repeatedly administered the two drugs throughout the period of sleep deprivation in an effort to maintain, rather than recover, predeprivation levels of performance. Pemoline was administered in 37.5-mg doses every 12 hours, and methylphenidate was administered in 10-mg doses every 6 hours. Overall, pemoline was more effective than methylphenidate at offsetting the effects of sleep loss. Pemoline significantly reduced both subjectively and objectively

measured sleepiness throughout the deprivation period on all but one test, the tapping test, which showed drug effectiveness dropping off 32 hours after the drug was first administered. Methylphenidate was not effective in reducing sleepiness on any measures. On performance tasks, subjects receiving pemoline performed more rapidly than the placebo group on one or more sessions on five of six measures. However, analysis of accuracy showed significant benefit of pemoline on only the four-choice reaction test and a trend toward benefit on digit symbol substitution. Performance on digit span memory, a matrix test, and pattern recognition showed no drug effects. Drug performance was worse than with the placebo in one quarter of the instances in which there was a significant difference between groups. The authors suggested that methylphenidate might have a greater beneficial effect at a higher dosage. It should be noted that comparisons across drugs when based on studies conducted using single doses can be difficult to interpret because optimal doses of each drug may not have been tested. Additional research with these compounds is necessary before clear conclusions can be made regarding their potential utility in combat.

### **Other Amphetamine-Like Stimulants**

As noted previously, several OTC medications and dietary supplements that have been used to treat colds, asthma, or to induce weight loss are sympathomimetic amine stimulants, which resemble the amphetamines in mechanism of action and structure. Amphetamine was synthesized based on the naturally occurring compound ephedrine, which had been used for thousands of years in traditional Chinese herbal medicine in the form of the herb ephedra.<sup>65</sup> Ephedrine and its analogs, as well as PPA, share many properties with amphetamines. Although it has been noted that ephedrine's effects on the CNS are less pronounced than those of the amphetamines,<sup>66</sup> it has been demonstrated that this compound antagonizes the hypnotic effect of sedatives.<sup>67</sup> Ephedrine also enhances cognitive performance,<sup>68</sup> although only a few studies have investigated its behavioral effects. (For a review, see Lieberman.<sup>65</sup>)

Alone or in combination with caffeine, ephedrine is a potent ergogenic aid that enhances aerobic performance.<sup>69-71</sup> Ephedrine, in the form of the herb ephedra, was an extremely popular dietary supplement in the United States that was used to enhance physical performance and increase weight loss. However, the FDA banned its sale as a dietary supplement in 2004 because of the large number of adverse events thought to be attributable to this drug.<sup>72</sup> Many of these reported adverse events were serious, including myocardial infar-

tions, cerebrovascular accidents, seizures, and death.

PPA, which has fewer peripheral effects than ephedrine, has also been reported to improve cognitive function<sup>73</sup> and antagonize the adverse effects of environmental stress.<sup>74</sup> However, based on evidence that it could increase the risk of stroke, PPA was taken off the market in 2000.

The prescription drug fenfluramine is used to induce weight loss, and it resembles amphetamine in structure. However, it was reported to have significant cardiovascular side effects and was withdrawn from the US market in 1997.<sup>75-77</sup>

### **Summary of Traditional Stimulants**

There is little doubt that amphetamines enhance some aspects of mental performance in sleep-deprived subjects. Other stimulants, such as pemoline, also enhance cognitive performance, but their effects are not as well documented as those of amphetamines. The effects of amphetamines have been demonstrated not only in laboratory tests of cognitive performance, but also in flight simulators. Unfortunately, these drugs have significant adverse effects. Amphetamines interfere with subsequent sleep and significantly increase blood pressure. They have considerable abuse potential; therefore, medical professionals must carefully supervise amphetamine use (see Roehr<sup>78</sup> for a discussion of amphetamine abuse in the United States). Amphetamines have been used in combat, and anecdotal reports from several operations<sup>1,2,5-7</sup> suggest that it was effective at preventing deterioration in cognitive performance when military personnel were severely fatigued from sustained sleep loss and stress. Amphetamines improve aerobic physical performance, an additional benefit in combat. There are difficult socio-political issues associated with the officially sanctioned use of amphetamines in combat, and these would be greatly magnified if widespread use of the compound occurred in US military operations. The ethical and command issues regarding its use are discussed herein; however, the use of any performance-enhancing drug in military operations must be approved by the chain of command. The previously noted friendly fire incident in Afghanistan is an example of the kind of issues arising from the use of such compounds. In that incident, the potential side effects of amphetamines were used in the legal defense of the pilots who were involved.<sup>8</sup>

### **Modafinil**

Modafinil (Provigil [Cephalon, Inc, Frazer, Pa]) is a novel stimulant that, unlike the amphetamines, appears to have minimal peripheral side effects, has

a low abuse potential, may not induce tolerance, and does not interfere with normal sleep.<sup>47,51</sup> Its behavioral effects in healthy, sleep-deprived volunteers are of the same approximate magnitude as those of amphetamines, depending, of course, on dose. Modafinil was initially approved by the FDA for the treatment of narcolepsy, and has been approved to treat excessive sleepiness-associated obstructive sleep apnea/hypopnea syndrome and shift work sleep disorder. Its use in a variety of other disorders that impair daytime alertness is under investigation. A similar compound, armodafinil (Novigil [Cephalon, Inc, Frazer, Pa]), which is reportedly more potent, was also approved by the FDA in 2007 for the treatment of various sleep disorders.<sup>79</sup>

Saletu and colleagues<sup>80</sup> investigated the effects of a morning dose of 200, 400, or 600 mg modafinil on performance and mood. They found that all three doses enhanced concentration, mood, and cognitive function. In another study, Saletu and colleagues<sup>81</sup> investigated the effects of 100 or 200 mg modafinil, given at bedtime, and assessed self-rated and polysomnographic sleep parameters over the course of five nights. They found that, unlike dextroamphetamine, modafinil did not induce a reduction in the amount of stage 2 and REM sleep. In addition, subjective sleep quality was rated significantly better when subjects received modafinil, compared with the reference compound. Subjective awakening quality and morning well-being showed no significant decrements following modafinil administration. The authors emphasized the need to differentiate the effects of modafinil and amphetamine, with modafinil having greater benefits and fewer side effects.<sup>81</sup>

In another modafinil study using a recovery paradigm, Lagarde and Batejat<sup>46</sup> tested the effects on performance of 200 mg modafinil given three times a day. Eight healthy subjects were deprived of sleep for 60 hours, during which time they were given part of the STRESS (Standardized Tests for Research with Environmental Stressors) battery of tests, which includes reaction time, memory, spatial processing, and divided attention tasks. When modafinil was administered, the cognitive performance of sleep-deprived volunteers was equivalent to the performance observed in non-sleep-deprived control trials. Furthermore, performance while taking modafinil remained constant until the 44th hour of sleep deprivation, when it began to deteriorate somewhat toward placebo levels (hours 44–60). The authors concluded that modafinil appears to be a vigilance-promoting substance capable of maintaining psychomotor performance during 60 hours of sleep deprivation.<sup>46</sup> Like amphetamines, modafinil also enhances physical

aerobic performance.<sup>82</sup>

In a study conducted at a Canadian military laboratory, 41 military subjects received either 300 mg modafinil, 20 mg dextroamphetamine, or a placebo on three separate occasions during 64 hours of continuous cognitive work and sleep loss. Both modafinil and amphetamine improved cognitive performance and mood state, compared with placebo; however, modafinil had fewer side effects. The authors concluded that modafinil was a good alternative to amphetamines for counteracting mood and cognitive effects of sleep loss during sustained operations.<sup>48,83</sup>

A number of additional studies have been conducted in military laboratories, or with the support of military organizations, to examine the effects of modafinil in militarily relevant scenarios. For example, Wesensten and colleagues<sup>52,53</sup> conducted a laboratory study in which 50 healthy young adults were sleep deprived for 54.5 hours. They reported that 400 mg modafinil attenuated fatigue in a manner comparable with that seen with 600 mg caffeine and that the effects were particularly salient during the circadian nadir of performance (0600 through 1,000 hours); 200 mg modafinil also reversed fatigue, but was less effective than 400 mg modafinil or 600 mg caffeine.

Caldwell and colleagues<sup>84</sup> have studied the effects of modafinil in several studies. In one study, conducted in a helicopter simulator, they demonstrated that modafinil was a promising countermeasure for sleep loss, but noted that additional studies of possible side effects were needed before it could be recommended for aviators. In a second study, conducted with F-117 Nighthawk (a stealth ground attack aircraft) pilots in a simulator, it was demonstrated that modafinil had beneficial effects on simulator performance and mood state. However, because the dose tested (100 mg) did not have subjectively salient effects, the authors stated that personnel should be cautioned regarding this characteristic of the drug, since they might mistakenly perceive the drug was not working. In particular, they were concerned that the dosage might be escalated by crew members without flight surgeon approval.<sup>50</sup>

It can be concluded, based on evidence from a number of military and civilian laboratories, that modafinil has considerable potential as an operational performance enhancer because it appears to have the benefits of amphetamines without the adverse risks of abuse potential, increased blood pressure, and interference with sleep. In December 2003, modafinil was approved by the US Air Force for management of aircrew fatigue in dual-piloted bombers only after all other nonpharmacological countermeasures had been exhausted (Exhibit 4-1).<sup>60</sup>

**EXHIBIT 4-1**

**COMPARATIVE EFFECTS OF STIMULANTS IN SLEEP-DEPRIVED SOLDIERS**

In World War II, amphetamines (eg, Benzedrine, metamphetamine) were extensively used by armies to combat fatigue, depression, and to enhance endurance performance.<sup>(1)</sup> Some of the earliest evaluations were conducted by A C Ivy from the Harvard Fatigue Laboratory and involved caffeine comparisons with Benzedrine.<sup>(1,2)</sup> This interest was stimulated by the use of methamphetamine by the Germans during the early years of the Blitzkrieg.<sup>(1)</sup> The US Army continued to use amphetamines even after other countries like Germany and the United Kingdom were beginning to recognize problems associated with unrestricted use of the drugs.<sup>(1,3)</sup> Both pill and inhaler forms were available (Exhibit Figures E1-1 and E1-2). The Army and Navy evaluated the benefits in fatigued men, published in numerous technical reports.<sup>(1)</sup> Other studies published after the war noted concerns about impaired judgment and willingness to continue nonproductive or dangerous performance.<sup>(4)</sup>

Other options have become available, notably two products that originated from French military medical researchers, modafinil (Cephalon, Frazer, Pa; as discussed in this chapter) and sustained release caffeine. The field was substantially advanced by important sleep, fatigue, and jet lag studies by Alain Buguet, Didier Lagarde, and their colleagues in the French military medical research laboratories, in ad-



**Figure E1-1.** Smith, Kline & French Laboratories (Philadelphia, Pa) advertised their Benzadrine sulfate tablets to demonstrate their support for the warfighter. This advertisement originally appeared in *Minnesota Medicine*. Data source: *Minnesota Medicine*. 1944;27(October). Photograph: Courtesy of the Minnesota Medical Association, Minneapolis, Minnesota.



**Figure E1-2.** Amphetamines taken by inhaler were also widely used by US troops in World War II. This advertisement originally appeared in the *Journal of the American Medical Association*. Data source: *Journal of the American Medical Association*. 1943;123. Photograph: Courtesy of the American Medical Association, Chicago, Illinois.

(Exhibit 4-1 continues)

**Exhibit 4-1** *continued*

dition to several collaborations with Ross Pigeau at the Defence and Civil Institute of Environmental Medicine (North York, Ontario, Canada) and Paul Naitoh at the Naval Health Research Center (San Diego, Calif). Their studies with modafinil identified this drug as a preferred option for emergency conditions when adequate sleep is not feasible.<sup>(5,6)</sup> Advantages include reduced side effects, such as behavioral effects, and an improved ability to sleep when sleep opportunities occur.<sup>(7,8)</sup> Another pharmacological option is sustained release caffeine (“Caffeine LP” or “Libération Prolongée,” 300-mg caplets), studied in a series of transatlantic time zone experiments by Didier Lagarde and his colleagues in collaborations with Jon French from the Human Effectiveness Directorate performance laboratory at Brooks Air Force Base.<sup>(9-11)</sup> Caffeine LP is produced in the French military bioproduction facility and is available only for military use. Caffeine and modafinil were also shown to have a beneficial interaction with zolpidem in enhancing performance.<sup>(12)</sup>

A series of research studies led by W Scott Killgore at the Walter Reed Army Institute of Research (WRAIR; Washington, DC) provided important insights into drug-specific actions and their interaction with the effects of extending periods of sleeplessness.<sup>(13-15)</sup> These studies expanded on some of the earlier comparative studies conducted at WRAIR and by John Caldwell at the US Army Aeromedical Research Laboratory and later at the Air Force Research Laboratory (described in this chapter). Killgore identified different effects of modafinil, high-dose caffeine, and amphetamine in healthy subjects with 2 days of sleep deprivation. The many published studies resulting from this work included effects of drug-sustained and placebo-treated sleep deprivation on higher order mental functions, such as moral judgment, executive function, and subtleties of humor appreciation; psychomotor performance; olfactory memory and detection; and personality effects on response to stimulants.

A very significant finding in the work of Killgore and colleagues is the finding that amphetamine, differently than caffeine and modafinil, increased risk-taking at the same time that prolonged wakefulness increasingly impaired judgment.<sup>(15)</sup> Optimal modafinil dosing for sustained human performance is still being refined for use in combat conditions (French military medical research, private communication, 2011).

Data sources: (1) Rasmussen N. *On Speed: The Many Lives of Amphetamine*. New York, NY: New York University Press; 2008. (2) Ivy AC, Krasno LR. Amphetamine (Benzedrine) sulfate: a review of its pharmacology. *War Med*. 1941;1:15–42. (3) Davis DR. Psychomotor effects of analeptics and their relation to “fatigue” phenomena in air-crew. *Br Med Bull*. 1947;5:43–45. (4) Tyler DB. The effect of amphetamine sulfate and some barbiturates on the fatigue produced by prolonged wakefulness. *Am J Physiol*. 1947;150:253–262. (5) Lagarde D, Batejat D, van Beers P, Sarafian D, Pradella S. Interest of modafinil, a new psychostimulant, during a sixty-hour sleep deprivation experiment. *Fundam Clin Pharmacol*. 1995;9:271–279. (6) Pigeau R, Naitoh P, Buguet A, et al. Modafinil, d-amphetamine and placebo during 64 hours of sustained mental work. I. Effects on mood, fatigue, cognitive performance and body temperature. *J Sleep Res*. 1995;4:212–228. (7) Lagarde D. Effects of modafinil on the nocturnal activity and behavioural sleep of Rhesus monkeys (*Macaca mulatta*). *Med Sci Res*. 1990;18:397–399. (8) Chapotot F, Pigeau R, Canini F, Bourdon L, Buguet A. Distinctive effects of modafinil and d-amphetamine on homeostatic and circadian modulation of the human waking EEG. *Psychopharmacology*. 2003;166:127–138. (9) Lagarde D, Batejat D, Sicard B, et al. Slow-release caffeine: a new response to the effects of a limited sleep deprivation. *Sleep*. 2000;23:651–661. (10) Beaumont M, Batejat D, Pierard C, et al. Slow release caffeine and prolonged (64-h) continuous wakefulness: effects on vigilance and cognitive performance. *J Sleep Res*. 2001;10:265–276. (11) Lagarde D, Chappuis B, Billaud F, Ramont L, Chauffard F, French J. Evaluation of pharmacological aids on physical performance after a transmeridian flight. *Med Sci Sports Exerc*. 2001;33:628–634. (12) Batejat D, Coste O, Van Beers P, Lagarde D, Pierard C, Beaumont M. Prior sleep with zolpidem enhances the effect of caffeine or modafinil during 18 hours continuous work. *Aviat Space Environ Med*. 2006;77:515–525. (13) Wesensten NJ, Killgore WDS, Balkin TJ. Performance and alertness effects of caffeine, dextroamphetamine, and modafinil during sleep deprivation. *J Sleep Res*. 2005;14:255–266. (14) Killgore WDS, Lipizzi EL, Kamimori GH, Balkin TJ. Caffeine effects on risky decision making after 75 hours of sleep deprivation. *Aviat Space Environ Med*. 2007;78:957–962. (15) Killgore WDS, Grugle NL, Killgore DB, et al. Restoration of risk-propensity during sleep deprivation: caffeine, dextroamphetamine, and modafinil. *Aviat Space Environ Med*. 2008;79:867–874.

## FOOD CONSTITUENTS THAT MAY ENHANCE OR SUSTAIN PERFORMANCE

The relationship between nutrition and behavior is a relatively new and understudied area, although there are many popular and often unsubstantiated beliefs about the behavioral effects of foods. Recent research has shown that relationships between nutrition and behavior are complex, and certain food constituents have acute effects on behavior. There can also be unanticipated consequences of changes in the diet, such as the adverse symptoms that occur in heavy users

of caffeine when it is suddenly withdrawn from their diet.<sup>85,86</sup> Interested readers are directed to comprehensive reviews of the militarily relevant literature in this area.<sup>87</sup>

For many years, it was believed that the blood–brain barrier protected the CNS from the effects of most peripheral metabolic events, such as changes in plasma concentrations of food constituents or metabolites after meal consumption. This assumption was not

correct. The blood–brain barrier is selectively permeable, allowing a wide variety of biologically relevant substances to enter the brain.<sup>44</sup> Not only is the blood–brain barrier permeable to both endogenous and exogenous behaviorally active, lipid-soluble compounds (eg, melatonin),<sup>33</sup> but also a number of non-lipid-soluble substances can enter the brain via special transport mechanisms.<sup>88</sup> One such transport system conveys the large neutral amino acids—tryptophan, tyrosine, phenylalanine, and others—into the brain; another mechanism transports choline. Furthermore, under certain circumstances, many of these food constituents can affect central neurotransmitter synthesis and, potentially, behavior.<sup>44,88</sup> Nutrients such as tryptophan, tyrosine, phenylalanine, and choline are precursors for neurotransmitters, and their availability can, under certain conditions, influence the levels of specific neurotransmitters. Tryptophan is converted to the neurotransmitter serotonin, and tyrosine and phenylalanine are converted to the catecholamines—dopamine, norepinephrine, and epinephrine. The nutrient choline is a precursor of acetylcholine.

### **Tryptophan**

One of the neurotransmitter precursors that most clearly influences behavior, with effects similar to the sedative-hypnotic drugs, is the large neutral amino acid tryptophan. Tryptophan is an essential amino acid found in nearly all protein-containing foods and is the precursor of the neurotransmitter serotonin. Serotonin is believed to have a variety of functions in the brain, including a role in the regulation of mood state, particularly alertness and depression. Serotonin-containing neurons in the CNS also participate in the regulation of pain sensitivity, aggression, and food consumption.<sup>87,89,90</sup>

Although tryptophan is not approved for use as a hypnotic in the United States, it has sedative-like effects on humans when it is administered in pure form and in sufficient quantity. When tryptophan is administered in doses of several grams, subjects report feeling less vigorous and more fatigued.<sup>91</sup> However, tryptophan does not seem to affect performance even immediately after its administration.<sup>10,88,89</sup> A number of investigators<sup>92,93</sup> have consistently detected the effects of tryptophan on sleepiness, reporting it to be a useful hypnotic, although this is a subject of considerable controversy.<sup>87,94–96</sup>

Even though tryptophan seems to lack the potency of many hypnotic drugs, it may be useful as a mild sleep aid in operational scenarios when sleep is desired (eg, when soldiers are suffering from jet lag). In a study of US Marines, tryptophan administration

was reported to hasten the reentrainment of circadian rhythms of performance following air deployment from California to Okinawa.<sup>10</sup> As discussed previously, more potent sedatives (eg, benzodiazepines) impair many types of performance, not only immediately after administration, but also when subjects are tested the day following bedtime administration.<sup>15</sup>

Unfortunately, ingestion of tryptophan supplements has been associated with a rare disorder termed eosinophilia-myalgia syndrome (EMS).<sup>97</sup> EMS was caused by a contaminant found in the tryptophan produced by one manufacturer.<sup>98</sup> When EMS was first linked to consumption of tryptophan, public health officials learned that millions of Americans had been taking this amino acid for its reputed therapeutic benefits (as opposed to its nutritional benefits). Because it is a nutrient and, therefore, less stringently regulated than drugs in the United States, tryptophan had been readily available at pharmacies and health food stores without prescription. Because of the association of tryptophan and tryptophan-containing supplements with EMS, the FDA withdrew these compounds from the market. Individuals who were taking tryptophan typically used it as a sleep aid, but it also has been recommended as an antidepressant and for treatment of premenstrual syndrome. The FDA has not approved tryptophan for any of these uses. Melatonin, also sold in the United States as a dietary supplement (as discussed previously), apparently has replaced tryptophan as a widely used, supposedly “natural,” dietary sleep aid, although it is not found in foods.

### **Tyrosine**

The behavioral effects of another amino acid, tyrosine, the precursor of the catecholamines, have also been examined because administration of this amino acid may antagonize many of the adverse cognitive changes associated with severe acute stress. The synthesis and release of central catecholamines, especially norepinephrine, increase when animals are subjected to a variety of stressors. Pretreatment with tyrosine seems to mitigate some of the adverse effects of acute stress in animals<sup>74,99,100</sup> and possibly humans.<sup>101–104</sup> Tyrosine appears to affect the same neurotransmitter systems as the amphetamines and related drugs and has similar effects in animal models of acute stress.<sup>74</sup> A number of studies have been conducted with volunteers—including soldiers, Navy SEALs, and pilots—to determine whether tyrosine may reduce some of the adverse behavioral consequences of exposure to severe stress. To date, tyrosine has been shown to have beneficial effects under a variety of adverse environmental conditions, including cold, hypoxia, and psychologi-

cal stress. (For a recent review, see the report by the Committee on Military Nutrition Research/Institute of Medicine<sup>105</sup> and the summary by Lieberman.<sup>87</sup>)

For example, in a study conducted at the US Army Research Institute of Environmental Medicine (USARIEM; Natick, Mass), tyrosine (100 mg/kg body weight) was tested during acute exposure to cold and high altitude, and significantly improved cognitive performance and the symptoms associated with both cold and hypoxia.<sup>101</sup> Another study conducted by the US Army Natick Soldier Research, Development and Engineering Center (Natick, Mass), in collaboration with USARIEM, used cold-water immersion to induce physiological and psychological stress. Beneficial effects of 300 mg/kg tyrosine, administered in food bars (twice in 150 mg/kg doses), were observed, including significant improvements in the match-to-sample task, a test of working memory (short-term memory).<sup>106</sup> Simulated marksmanship was also significantly improved by tyrosine in that study.<sup>107</sup> A study conducted by the Naval Medical Research Laboratory (Silver Spring, Md) demonstrated that tyrosine improved learning and memory in volunteers exposed to the cold.<sup>103</sup>

Tyrosine (100 mg/kg of body weight) has also been tested in pilots who were required to fly a difficult, all-night mission in a flight simulator. Overall, flight performance was significantly improved when tyrosine (versus a placebo) was administered.<sup>102</sup> In a study conducted during a very stressful military training course, tyrosine had beneficial effects on cognitive performance.<sup>104</sup> Because tyrosine has no detectable effects when individuals are not exposed to significant stressors and it is normally found in protein foods, it may have a variety of benefits compared with drugs. However, like most or all nutrients, the magnitude of its effects cannot be expected to be as substantial as drugs with similar mechanisms of action. For example, in a recent study of tyrosine conducted in sleep-deprived volunteers, it was found to enhance cognitive performance, but was not as effective as caffeine or amphetamines.<sup>108</sup> A review of the literature regarding the use of tyrosine as a component in performance-enhancing rations is available,<sup>105</sup> and another review of this literature was also published in 2003.<sup>87</sup>

## Caffeine

In many countries, caffeine is the preeminent legal stimulant. Caffeine—a xanthine—is a behaviorally active, natural food constituent that is present in only a few foods. For comprehensive reviews of the mechanisms of action of caffeine and its behavioral effects, see

Lieberman et al<sup>109</sup> and Smith.<sup>110</sup> However, these foods are regularly consumed by a large part of the world's population. Coffee, tea, and colas are particularly popular in the industrialized world. Many individuals mistakenly believe that the primary stimulant in tea is theophylline, another xanthine compound. In fact, caffeine, not theophylline, is the principal, behaviorally active component found in tea.<sup>111</sup> Theophylline also improves cognitive performance when administered in clinically effective doses.<sup>112</sup> A number of investigators have recommended the use of caffeine as a stimulant in military operations when it is desirable to optimize cognitive and physical performances and prevent the

**TABLE 4-1**  
**CAFFEINE CONTENT OF SELECTED**  
**BEVERAGES AND FOODS**

Item	Caffeine Content (mg)
Coffee (5-oz cup)	
Drip method	90–150
Percolated	64–124
Instant	40–108
Decaffeinated	2–5
Instant decaffeinated	2
Tea, loose or bags (5-oz cup)	
1-min brew	9–33
3-min brew	20–46
5-min brew	20–50
Tea products	
Instant (5-oz cup)	12–28
Iced tea (12-oz can)	22–36
Chocolate products	
Hot cocoa (6 oz)	2–8
Dry cocoa (1 oz)	6
Milk chocolate (1 oz)	1–15
Baking chocolate (1 oz)	35
Sweet dark chocolate (1 oz)	5–35
Chocolate milk (8 oz)	2–7
Chocolate-flavored syrup (2 tbsp)	4
Cola beverages (12 oz)	36–48
Other soft drinks*	12–54
(Dr Pepper, Mountain Dew, Mellow Yellow, Mr. Pibb, etc)	

\*Dr Pepper: Dr Pepper Snapple Group, Plano, Tex; Mountain Dew: PepsiCo, Inc, New York, NY; Mellow Yellow and Mr. Pibb: Coca-Cola Company, Atlanta, Ga.

Source: Reproduced with permission from Lieberman HR. Caffeine. In: Jones D, Smith A, eds. *Factors Affecting Human Performance*. Vol II. *The Physical Environment*. London, England: Academic Press; 1992: 49–72.

degradation in performance associated with sleep loss.<sup>1,3,30,52,105,113–116</sup>

Although the levels of caffeine in foods vary greatly, coffee typically contains the most caffeine (about 65–110 mg per cup), whereas tea contains an intermediate amount (about 40–60 mg per cup), and cola and some other soft drinks contain about 40 mg per serving (Table 4-1).<sup>65,114</sup> Recently, two new categories of caffeine-containing beverages and dietary supplements have become very popular; these are energy drinks and energy shots. An example is the popular energy drink Red Bull (Red Bull North America, Inc, Santa Monica, Calif), which contains 80 mg of caffeine per serving.

Caffeine appears to exert its effects on the brain via modulation of the putative inhibitory neuromodulator, adenosine.<sup>111,117,118</sup> Adenosine, a cyclic nucleotide, can be found in many brain regions. Functional adenosine receptors have been localized to specific brain regions, some of which are involved in the regulation of arousal level. Caffeine, which readily crosses the blood–brain barrier, blocks the effects of adenosine on brain neurons.<sup>109,111</sup>

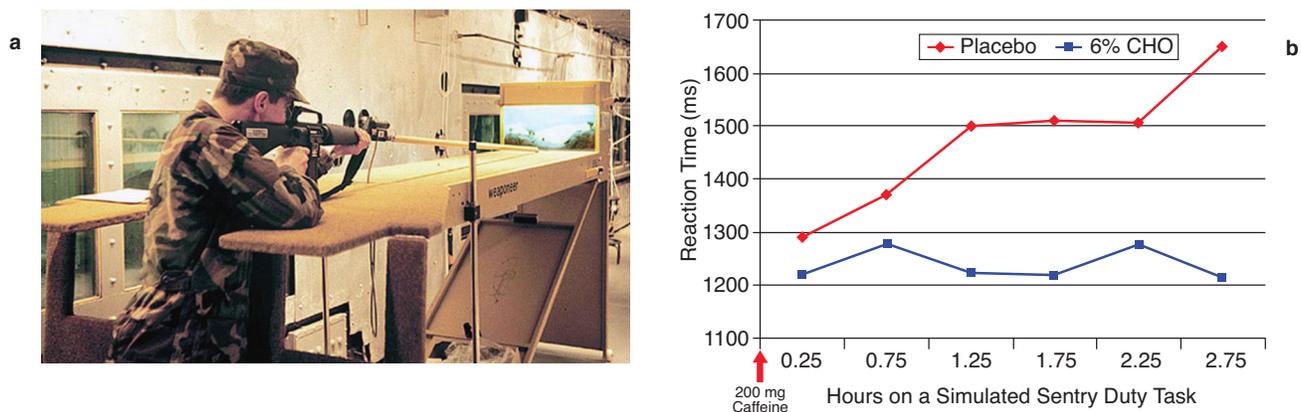
The beneficial effects of caffeine on specific types of performance in well-rested volunteers are well documented. In particular, it seems that tasks that require sustained vigilance are sensitive to the effects of caffeine in low and moderate doses. Sustained vigilance is a key element of a wide variety of essential military activities, such as performing sentry duty, monitoring surveillance equipment, and operating vehicles. Both auditory and visual vigilance tasks reliably detect the effects of caffeine in doses of 32 to 300 mg.<sup>44,87,119–122</sup>

In addition, caffeine’s effects on vigilance have been documented in both young and elderly men and women.<sup>123</sup> The foods with equivalent doses range from just a single serving of a cola beverage to several cups of coffee.

In a series of studies of direct relevance to potential military applications of caffeine, Johnson and colleagues<sup>121,124,125</sup>—using an M16 assault rifle marksmanship simulation task—have demonstrated that caffeine in a dose of 200 mg improves marksmanship when there is a substantial vigilance component included in the task (Figure 4-3). Caffeine administration does not increase errors in marksmanship or decrements in other tests of cognitive performance, including those requiring fine motor skills, when it is administered in single doses equivalent to, or slightly higher than, those consumed in foods and beverages.<sup>3,120,126</sup>

Performance of tasks that do not require sustained vigilance (eg, memory and complex cognitive function) appears less likely to be affected by moderate doses of caffeine, except when volunteers are sleep deprived.<sup>3,44,87,113,114,122,123</sup> Caffeine also has effects on self-reported mood states, most notably decreasing fatigue and increasing alertness.<sup>87,123</sup> These changes are consistent with the stimulatory effects of caffeine observed in vigilance and other performance tests. Of course, individuals vary in their sensitivity to this substance, apparently because of both innate differences and daily level of consumption.<sup>109,127</sup>

In military operations, caffeine is likely to be particularly useful when soldiers are sleep deprived, as illustrated by a study conducted at Walter Reed



**Fig. 4-3.** (a) Sentry duty performance assessed using the Weaponeer M16 rifle marksmanship simulator. (b) Speed of Weaponeer marksmanship target detection in rested volunteers given 200 mg caffeine or a placebo in pill form.

CHO: carbohydrate

Data source: McLellan TM, Bell DG, Lieberman HR, Kamimori GH. The impact of caffeine on cognitive and physical performance and marksmanship during sustained operations. *Can Mil J.* 2003–2004;4:47–54.



**Fig. 4-4.** Navy SEAL trainees in boats attempt to cross the surf line during Hell Week. The boats frequently capsized, thus soaking the trainees. Navy SEAL trainees are subjected to a variety of stressors designed to simulate combat. Hell Week (1 week of training) is especially intense and includes near continuous exposure to environmental, physical, and psychological stressors.

Army Institute of Research using doses of 150, 300, and 600 mg per 70 kg of body weight.<sup>128</sup> In that study, volunteers were deprived of sleep for 49 hours. Caffeine was administered, and a series of behavioral and polysomnographic tests were given. Caffeine at various doses significantly reduced sleepiness and improved several aspects of cognitive performance, including choice reaction time, serial addition/subtraction, and logical reasoning.

Caffeine also seems to be effective in circumstances designed to simulate combat. We conducted a study with Navy SEAL trainees who were exposed to severe environmental, physical, and psychological stress and were deprived of sleep for 3 days (Figure 4-4). In this study, caffeine in doses of 200 and 300 mg had significant positive effects on both vigilance and more complex cognitive tasks. Caffeine did not impair any aspect of marksmanship in this study, including measures designed to detect any caffeine-induced degradation in fine motor control (Figure 4-5).<sup>3,126</sup> In fact, caffeine improved certain aspects of marksmanship in this study,<sup>116</sup> a finding that has been replicated by another laboratory.<sup>129</sup>

A study discussed previously compared 600 mg caffeine with 200 and 400 mg modafinil in sleep-deprived volunteers.<sup>52,53</sup> It was observed that caffeine was as effective as 400 mg and more effective than 200 mg modafinil with regard to its ability to attenuate fatigue. However, this high a bolus dose of caffeine may have adverse effects on certain aspects of performance and mood. (See reviews by Lieberman et al,<sup>87,109</sup> the 1994



**Fig. 4-5.** Navy SEAL trainees during marksmanship testing in a caffeine study.

report by the Committee on Military Nutrition Research,<sup>105</sup> and Smith.<sup>130</sup>) Lieberman et al<sup>3</sup> conducted a study in a sustained combat-like scenario with Navy SEAL trainees in which the effects of caffeine seemed to be optimal at the 200-mg dose level. The Committee on Military Nutrition Research recommended that caffeine be administered in 100-mg increments with a maximum dose of 600 mg. (See reviews by Lieberman<sup>89,109</sup> and the 2001 report by the Committee on Military Nutrition Research.<sup>131</sup>)

A series of studies have been conducted with caffeine-containing gum (Figure 4-6) to determine if it would enhance a variety of militarily relevant functions in sleep-deprived volunteers.<sup>115,116,129</sup> Caffeine was formulated in gum to help speed entry



**Fig. 4-6.** Caffeine-containing gum has been developed and tested in a series of studies and is currently in the DoD supply system.



**Fig. 4-7.** U-2 reconnaissance aircraft in flight. Photograph: Reproduced from the US Air Force. Image ID: 091021-F-2185F-970. Available at: <http://www.af.mil/photos>.

into the circulation.<sup>132</sup> These studies demonstrate unequivocally that caffeine in moderate doses improves both physical and cognitive performance. Caffeine is currently used operationally by U-2 pilots in a specially formulated tube food suitable for use by encapsulated personnel (Figures 4-7 and 4-8). This product has been tested and shown to enhance cognitive performance in simulated overnight aviation missions.<sup>133</sup> A five-piece pack of chewing gum, which contains 200 mg of caffeine per piece, is included in the US Army's assault-type First Strike Rations.

## Carbohydrate Foods

The scientific literature addressing the effects of macronutrients—protein, carbohydrate, and fat—on cognitive function is quite limited.<sup>82</sup> If clearly beneficial behavioral effects of particular macronutrients could be documented, this would be of great use to the military. Parametric studies to address the cognitive consequences of consuming foods varying in protein, carbohydrate, and fat content have not been conducted, and many other studies in this area appear contradictory.<sup>87,134,135</sup>

We conducted a study with important military implications in which unequivocally beneficial behavioral effects of providing supplemental energy, in the form of a carbohydrate beverage, were observed.<sup>124</sup> The study used a double-blind, placebo-controlled design and was conducted with a US Army Special Operations unit. It was designed to assess the effects of a specially formulated carbohydrate beverage, the ERGO (Energy Rich, Glucose Optimized) drink, on physical and cognitive performance<sup>136</sup> (Figure 4-9). Although the beneficial effects of carbohydrate supplementation on physical performance are well documented, the effects of such supplementation on cognitive performance are quite controversial.<sup>87</sup> The beverage was formulated at the US Army Natick Soldier Center (Natick, Mass), the food developer for the Department of Defense (DoD). Unlike commercial carbohydrate sport drinks, the ERGO drink was



**Fig. 4-8.** (a) Pressure suit worn by U-2 pilots prevents consumption of ordinary food. (b) Tube foods currently used in U-2 operations.

Photographs: (a) Reproduced from the US Air Force. Image ID: 060905-F-7441T-035. Available at: <http://www.af.mil/photos>. (b) Reproduced from the US Air Force. Image ID: 060905-F-7441T-016. Available at: <http://www.af.mil/photos>.

predominately composed of maltodextrin, a complex carbohydrate, in contrast to the simple sugars used in typical commercial products. For the purposes of the study, the military unit that the authors tested was engaged in a training exercise we designed in collaboration with their officers to simulate a typical light infantry combat operation. The exercise—lasting about 10 hours—included marching, running, and a live fire rifle marksmanship test (Figure 4-10). During the study, the authors continuously assessed auditory vigilance with custom-designed and custom-constructed ambulatory vigilance monitors<sup>137</sup> (Figure 4-11). Vigilance is the ability to sustain attention to boring stimuli for relatively long periods of time. Many operational duties require sustained vigilance, such as sentry duty. Regular meals provided during the exercise were not sufficient to meet the energy needs of the study volunteers—a typical situation during such training exercises and actual operations.<sup>138</sup> The 143 male volunteers were randomly divided into three groups who received, on six occasions over the test day, either (1) a placebo beverage, (2) a 6% carbohydrate beverage, or (3) a 12% carbohydrate beverage (Figure 4-12). These beverages were identical in taste and appearance, and provided equal fluid volumes to the volunteers. In this situation, carbohydrate supplementation not only enhanced physical performance—a well-known benefit of such beverages—but also significantly improved vigilance<sup>136</sup> (Figure 4-13). The effects of energy / carbohydrate supplementation were robust and dose-related: the moderate (6%) dose of carbohydrate (35 kJ/kg) had effects on vigilance that



**Fig. 4-9.** The ERGO drink is a 12% carbohydrate beverage base designed by the US Army Natick Soldier Center (Natick, Mass) to act as an ergogenic aid. It is 2% glucose, 9% maltodextrin (a complex carbohydrate), and 1% fructose. It is available in orange, lemon, raspberry, lemon-lime, and tropical punch flavors. A 12% base carbohydrate concentration can deliver more calories and provides flexibility to make less concentrated mixtures for different requirements.

were intermediate between the placebo condition (0 kJ/kg) and the higher (12%) dose treatment (70 kJ/kg). Positive changes in mood state—specifically increased vigor and decreased confusion among volunteers receiving the ERGO drink—corroborated the vigilance results. Additional research to extend this work by determining whether other foods have similar effects is necessary.<sup>87,136</sup>



**Fig. 4-10.** US Army Rangers (a) marching during the ERGO drink study and (b) on a typical extended patrolling exercise where a convenient carbohydrate supplement, such as the ERGO drink, provides specific physical and mental performance enhancements.

Photograph (b): Reproduced from the US Army, Fort Benning. Image ID: 1189641511-TZ2hB-L.



Fig. 4-11. The latest version of the ambulatory vigilance monitor with all sensors, output devices, and push buttons identified. LED: light-emitting diode.



Fig. 4-12. US Army ranger ingesting the ERGO drink.

### POTENTIAL APPLICATIONS OF CAFFEINE

The food constituent with the most definitive, widely replicated ability to enhance cognitive and aerobic physical performance consistently and to be useful in operational scenarios is caffeine<sup>3,52,62,66,103,108,113,115,122,126</sup> (Exhibit 4-2). Under many conditions, caffeine can improve specific aspects of performance, most notably vigilance. When individuals are deprived of sleep, caffeine's beneficial effects appear to be more pervasive, and a number of critically important aspects of cognitive function are substantially enhanced by its administration. Furthermore, decrements in performance attributable to caffeine are not usually observed unless caffeine is administered in pharmacological doses.<sup>87</sup>

Sudden withdrawal of caffeine from the diet of individuals who regularly consume caffeine can produce adverse psychological and physiological consequences, including headache, impaired performance, and negative changes in mood.<sup>85,86</sup> This should be taken into consideration when soldiers who consume caffeine in garrison do not have the opportunity to continue its use in the field, or when physicians or others recommend significant reduction in caffeine consumption. It seems that gradual withdrawal of caffeine-containing foods and beverages would be preferable to a sudden halt in all caffeine consumption. In addition to its documented beneficial effects on cognitive performance, caffeine also improves certain aspects of aerobic performance, although the optimal doses for this purpose have not been established and

may be greater than the optimal dose required to enhance cognitive function.<sup>139</sup>

Overall, it is clear that caffeine can improve key aspects of cognitive performance, especially vigilance. Lapses in vigilance during critical military duties—such as oper-

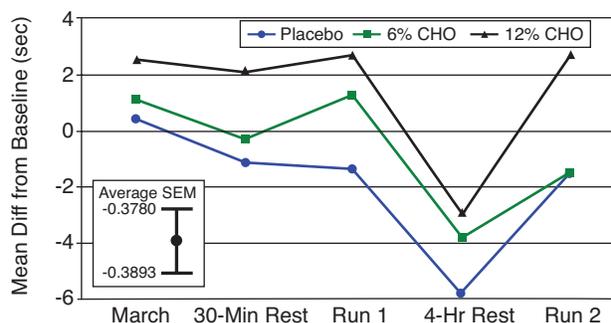


Fig. 4-13. Mean differences from baseline in auditory vigilance reaction times over the 10 hours of the ERGO drink study. Each subject's vigilance was tested continuously by the ambulatory monitor that was worn on the nonpreferred wrist. Each subject's performance was summed over five time periods: (1) march, (2) 30-min rest, (3) run 1, (4) 4-hour rest, and (5) run 2. Because the values plotted are the differences from baseline values, the higher the number on the y axis, the better the performance.

CHO: carbohydrate; Diff: differences; SEM: standard error of the mean

ating vehicles, performing sentry duty, and monitoring electronic surveillance equipment or communications devices—can have devastating effects on a unit. For a discussion of injuries and accidents in a military environment, see Chapter 12 on Injury Control. When individuals are sleep deprived, caffeine's effects generalize to a wide variety of cognitive functions, including learning, memory and reasoning, as well as militarily relevant

activities (eg, marksmanship).<sup>3,52,53,115,126</sup> The amino acid tyrosine also has significant potential as a unique performance enhancer that exerts its effects only when individuals are subjected to stressful situations. In addition, the use of liquid carbohydrate supplementation when soldiers are not consuming adequate amounts of food, a situation that typically occurs in the field,<sup>138</sup> appears to improve both cognitive and physical performance.<sup>3</sup>

## ETHICAL ISSUES ASSOCIATED WITH THE SANCTIONED USE OF DRUGS IN THE MILITARY

Historically, drugs and other stimulants have been used during many conflicts. The legal use of substances that may enhance performance or alter behavior, such as caffeine or alcohol, is common in our culture. US forces are also facing enemies who may use drugs to alter their behavior. Although some individuals will continue to debate the issue of the use of performance-enhancing drugs in military operations, it is apparent that such use will continue. Therefore, it is not a question of absolute prohibition, but of assigning and defining responsibility and setting limits/boundaries. Should use be limited to a strong cup of coffee and easily assimilated carbohydrates, or should US soldiers be

given an advantage over enemy combatants by using a sophisticated regimen of potent prescription drugs? The Byrd amendment (see Exhibit 4-3) reflects an effort to address the use of drugs that have not been approved for a particular application, such as performance enhancement in times of military necessity. It is unlikely that this will ever be used to gain blanket approval of performance-enhancing drugs during military operations. It is important that medical officers are aware of the ethical questions related to the use of performance-enhancing substances that, in some ways, parallel the concerns raised for informed consent in human research. There are four parties involved in the transaction:

### EXHIBIT 4-2

#### MILITARY COFFEE USE THROUGH THE ERAS

In his text summarizing medical research studies on Union soldiers during the Civil War, Dr Benjamin Apthorp Gould described observations on soldier road march performance during campaigns to Gettysburg and elsewhere that included an attempt to quantify energy intake and coffee consumption.<sup>(1)</sup> Coffee has been a key element of soldier provisioning throughout the US Army's existence (Exhibit Figure E2-1). It has provided a morale boost in addition to the specific benefits of the caffeine component (eg, countermeasure to fatigue and depression). In 2001, the standing Committee on Military Nutrition Research of the Institute of Medicine issued recommendations for the Department of Defense on appropriate use and safe upper limits of caffeine supplementation to counter fatigue in military operations.<sup>(2)</sup> This permitted the fielding of caffeine gum, with appropriate labeling for use by service members. Additional benefits of caffeine to soldiers have been discovered since that report and are covered, in part, in a new report from the committee on neuroprotective nutrition.<sup>(3)</sup> Several studies funded through the Army Neurotoxin Exposure Treatment (Parkinson's) Research (NETPR) program contributed to the finding that coffee consumption and, specifically caffeine, has a neuroprotective action associated with reduction in long-term neurodegenerative disease risk.<sup>(4,5)</sup> Thus, coffee drinking and caffeine consumption may be an effective intervention to reduce long-term health risks in soldiers from head impact and other brain injury (no randomized controlled study of this specific benefit has yet been conducted). There are also a wide range of noncoffee caffeine products commercially available today (Exhibit Figure E2-2).

Data sources: (1) Gould BA. *Investigations in the Military and Anthropological Statistics of American Soldiers*. Hurd and Houghton, Cambridge: Riverside Press; 1869: 603–610. (2) Committee on Military Nutrition Research, Food and Nutrition Board, Institute of Medicine. *Caffeine for the Sustainment of Mental Task Performance—Formulations for Military Operations*. Washington, DC: National Academy Press; 2001. (3) Erdman J, Oria M, Pillsbury L, eds. *Nutrition and Traumatic Brain Injury: Improving Acute and Subacute Health Outcomes in Military Personnel*. Washington, DC: National Academy Press; 2011. (4) Ross GW, Abbott RD, Petrovitch H, et al. Association of coffee and caffeine intake with the risk of Parkinson's disease. *JAMA*. 2000;283:2674–2679. (5) Chen JF, Xu K, Petzer JP, et al. Neuroprotection by caffeine and A2a adenosine receptor inactivation in a model of Parkinson's disease. *J Neurosci*. 2001;21:RC143.

(Exhibit 4-2 continues)

Exhibit 4-2 continued



**Figure E2-1.** Coffee use through four US military eras, including (a) the Spanish-American War (roasting coffee beans), (b) World War I, (c) World War II soldiers in the field, (d) World War II aviator, and (e) Operation Enduring Freedom. Photographs: Reproduced from the National Archives and Records Administration, Washington, DC.

(Exhibit 4-2 continues)

Exhibit 4-2 continued



**Figure E2-2.** Examples of the plethora of caffeine products available today. Clockwise from the upper left-hand corner: Jolt Caffeine Energy Gum (GumRunners LLC, Jersey City, NJ; 50 mg / chiclet); Stay Alert Caffeine Supplement Gum (Mastix Medica LLC, Hunt Valley, Md; 100 mg / stick); Shock-A-Lots candy (Extreme Coffee, Redwood City, Calif; 300 mg / oz candy); CLIF Bar–nutrition bar (Clif Bar & Company, Emeryville, Calif); CLIF Bar–nutrition bar (Clif Bar & Company, Emeryville, Calif); Penguin caffeinated mints (www.peppermints.com; 7 mg / mint); Caffeine Kicks candy (Caffeine Kicks, Santa Ynez, Calif); UpTime Energy and Diet POWder! fizzy crystals (UpTime Nutrition Company, Inc, Minneapolis, Minn; 150 mg / packet); Ripped Fuel chewing gum (Twinlab, New York, NY; caffeine and ephedra—the ephedra component is now banned in the United States); Black Black chewing gum (Lotte Confectionery, Hangul, South Korea; 5 mg / stick); Warp Energy Mints (Big Sky Brands, Inc, Toronto, Ontario, Canada); XTZ Herbal Energy Mints (XTZ Industries, Inc, Edmond, Wash); chewable Metabo Mints (Metabo Corporation, West Chester, Pa); mocha-flavored HooAH! Nutritious Booster Bar (D’Andrea Brothers LLC, Los Angeles, Calif); Taster’s Choice packet (Nescafé Taster’s Choice, Wilkes-Barre, Pa; consumed dry by Ranger students with dry creamer and sugar, washed down with water); No Doz caffeine pills (Novartis Consumer Health, Inc, Parsippany, NJ; 200 mg / pill); and Celestial Seasonings Morning Thunder Tea (Celestial Seasonings, Boulder, Colo; matte tea).

1. the *soldier* as the recipient, who may be naive or informed;
2. the *commander*, who has the responsibility to optimize the tactical situation, preferably by achieving tactical victory, and ensuring the health and survival of his or her subordinates;
3. *society*, which as a whole may be technologically inexperienced and unaware of its collective responsibility; and
4. the *medical officer or scientist*, who is the best informed about the effects and will probably bear the most immediate responsibility for the use of drugs on the battlefield.

**EXHIBIT 4-3**

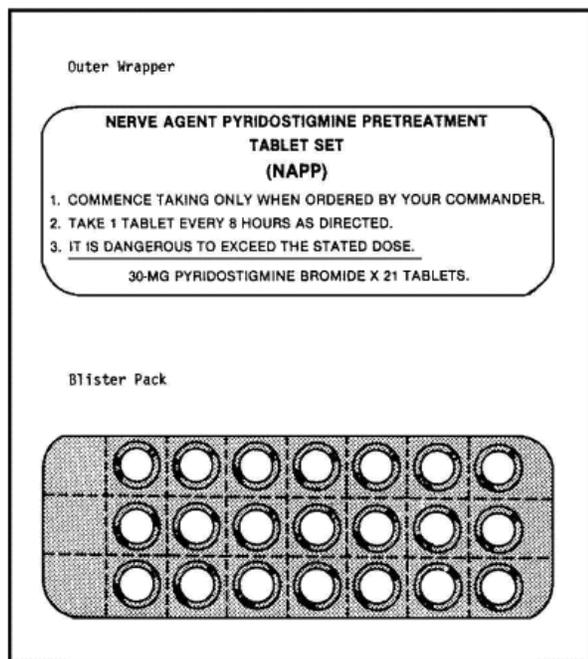
**SPECIAL PROVISIONS FOR THE MILITARY USE OF DRUGS—THE BYRD AMENDMENT**

In Operations Desert Shield / Desert Storm (the first Gulf War, 1990–1991), the Department of Defense (DoD) distributed pyridostigmine bromide (PB; Duphar B.V., Amsterdam, Holland) tablets as part of the system of protection against chemical agent attack by the Iraqi forces (Exhibit Figures E3-1 and E3-2). On a more limited basis, a vaccine to botulinum toxin was used to protect soldiers against the threat of a biological weapon. The US Food and Drug Administration (FDA) had not approved these products for these indications even though they were approved as safe and effective for other uses. The products were still designated as Investigational New Drugs (INDs) for these military applications. This urgent military need created a regulatory issue that was resolved with the issuance of the “Interim Rule” by the FDA Commissioner and the Secretary of Health and Human Services. The FDA would allow the use of an IND if (a) informed consent was not feasible; (b) there was an impending combat urgency; and (c) the use would likely protect health and lives, with no alternative protective strategy available. The FDA granted time-limited waivers for PB and botulinum toxin in January 1991.

This highlighted the issue of off-label use of a drug for military emergencies, but the Interim Rule was never finalized by the FDA. This was eventually addressed by the Byrd Amendment (Section 731, National Defense Authorization Act, FY 1999; Public Law 105-261, October 17, 1998), which was titled “Process for Waiving Informed Consent Requirement

for Administration of Certain Drugs to Members of the Armed Forces for Purposes of a Particular Military Operation.” This provided rules for the use of an IND or a drug unapproved for its applied use with service members. These rules include that only the President can waive prior consent for the use of the drug. To grant a waiver, the President is required to determine that obtaining consent is (a) not feasible, (b) contrary to the best interests of the member, or (c) not in the interests of national security.

In addition to these overarching considerations, there is an extensive list of requirements and thresholds that must be met, including such things as (a) the evidence for safety and effectiveness relative to medical risk associated with a military operation; (b) the high risk to military personnel of an operational threat, such as



**Figure E3-1.** During the 1990–1991 Gulf War, PB was classified by the FDA as an IND for use as a pretreatment for soman poisoning. Many veterans reported stopping PB use because they found the side effects unpleasant (eg, nausea, abdominal cramps, urinary urgency, headache). This illustration shows the instructions for use that appear on the blister pack of 21 tablets. NAPP: nerve agent pyridostigmine pretreatment. Illustration: Reproduced from *Field Manual 4-02.285*, “Multi-service Tactics, Techniques, and Procedures for Treatment of Chemical Agent Casualties and Conventional Military Chemical Injuries.” Washington, DC: Headquarters, Department of the Army; September 18, 2007. FM 8-285.



**Figure E3-2.** Scud missile downed by Patriot. These missiles imposed the threat of chemical weapon attacks. Photograph: Reproduced from Defense Visual Information. VIRIN: DD-ST-92-07786. Available at: <http://www.defenseimagery.mil>.

(Exhibit 4-3 continues)

**Exhibit 4-3** *continued*

from chemical, biological, nuclear, or other exposures; (c) the lack of an available satisfactory alternative treatment or protection; (d) justification for mandatory requirement for individual use or voluntary participation—review of off-label experimental use by an institutional review board; (e) explanation of how, when, and why the product will be used and how its administration to individuals will be tracked, including in the medical records of individual members; (f) provisions for an information sheet to be given to each service member prior to administration of the new drug; (g) a plan for follow-up for any adverse health consequences; and (h) other provisions, such as assurances that the DoD is pursuing full FDA approval for the intended application with all due diligence. These steps are detailed in the Code of Federal Regulations (21CFR50.23), “Informed Consent of Human Subjects—Exception from General Requirements.”

The FDA approved combat use of PB to prevent death from exposure to soman in 2003. As a result of the Gulf War experience of undiagnosed chronic multisymptom illnesses at the same time that PB was in use ahead of FDA approval, the DoD gained new understanding of the impact of this use of PB on health risk communication, disease, and morale.<sup>(1)</sup> It is less likely that the DoD will seek permission in the future to use IND products ahead of FDA approval, although the Byrd Amendment now provides a regulatory approach for that option. This puts the burden of seeking full FDA approval for new applications of drugs, such as performance-enhancing stimulants, on DoD researchers. Individual care providers can still prescribe a drug for off-label use for an individual, but not for blanket administration to a group of individuals.

Data source: (1) Friedl KE, Grate SJ, Proctor SP. Neurological issues in modern military deployments—investigation of exposures in the DoD Gulf War illnesses research program. *Mil Med.* 2009;174:335–346.

The medical officer may be expected to provide guidance to the commander concerning the use of drugs and stimulants on the battlefield, and may have more direct involvement by prescribing the specific agents.

The ethical questions regarding the use of drugs and stimulants to improve or modify alertness, cog-

nitive function, and behavior and to counter fatigue and anxiety during war are part of a larger ethical debate over the role of the physician in the military. An entire two-volume set in the *Textbooks of Military Medicine* series (titled *Military Medical Ethics*) is devoted to ethical issues.

## SUMMARY

The appropriate use of psychopharmacological and nutritional interventions on the battlefield provides a significant benefit to combat soldiers. A variety of critical situations occur during intense military operations in which preservation of cognitive function is essential, not only for the successful completion of the mission, but also for the very survival of the soldier. An adequate body of knowledge and definite doctrine regarding the use of psychotropic compounds in severely stressful environments does not always exist. Therefore, when an operational requirement calling for the use of such compounds arises, the unit physician should determine if an official doctrine is in place and seek the advice of experts in the field. Unfortunately, there is little motivation for pharmaceutical, nutrition, or biotechnology companies to actively engage in research of direct military applicability. A number of

excellent studies, which provide critical information regarding the beneficial effects of various interventions, have been conducted at various DoD laboratories. However, these studies have just begun to address the numerous issues in this complex research area. In addition, political and ethical considerations may preclude the use of performance-enhancing or performance-preserving compounds on the battlefield, especially the use of stimulant drugs. Those considerations will certainly limit the resources committed to this area of research. As noted previously, preoperational testing of compounds that may alter cognitive performance is highly recommended and may be required by official policy, in some instances, because this gives personnel an opportunity to experience the effects of the drug prior to its operational use and may reveal any idiosyncratic adverse effects.

### Acknowledgments

The authors thank Lauren Thompson and Karen Speckman for their excellent editorial assistance. This chapter was originally written in 2004. It has been periodically updated since then, but not rewritten or fully updated.

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