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# HETEROCYCLIC AMPHETAMINE DERIVATIVES AND CAFFEINE ON SLEEP IN MAN

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**1** Effects of the heterocyclic amphetamine derivatives, pemoline (20 and 40 mg), prolintane hydrochloride (5 and 10 mg), methylphenidate hydrochloride (10 and 20 mg) and fencamfamine hydrochloride (10 and 20 mg), and of caffeine anhydrous (100, 200 and 300 mg) on sleep, were compared with placebo in six young adults (20–31 years) using electroencephalography for sleep measures and analogue scales for subjective assessments of well-being and sleep quality. The study was double-blind.

**2** No consistent effect was found with pemoline.

**3** With prolintane there were no changes in sleep latencies, or in slow wave sleep (SWS). Rapid eye movement (REM) sleep was reduced during the first 2 h after sleep onset.

**4** With methylphenidate and fencamfamine latencies to sleep onset and to stage 3 sleep were unchanged. The higher dose of each drug delayed the first and subsequent REM periods. Both drugs reduced the duration of REM sleep, and the higher dose of each drug reduced the percentage REM sleep. Methylphenidate also reduced total sleep time (TST). There was no evidence of reduced SWS with either drug. Impairment of sleep was reported with each drug.

**5** With caffeine there were no changes in latencies to sleep onset or to the first REM period, though in one study with 300 mg subsequent REM periods were delayed. Awake activity and drowsy sleep were increased and TST and SWS were decreased. With 300 mg only, REM sleep was decreased though percentage REM sleep was not altered. Impaired sleep was reported with all doses of caffeine.

## Introduction

Amphetamine has cardiovascular, central stimulant and anorexigenic properties, and variation of the molecule can selectively modify the pharmacological profile. The basic $\beta$-phenethylamine moiety is essential to its activity, but an $\alpha$-methyl group (phentermine), substitution of the terminal amine (furfurylmethylamphetamine, diethylpropion), $\alpha$-phenyl substitution (fenfluramine) and cyclization of the side chain (phenmetrazine) attenuate the stimulant and cardiovascular effects, but preserve the anorexigenic activity. On the other hand modifying the aminoalkyl side chain into heterocyclic structures, as in methylphenidate hydrochloride, prolintane hydrochloride, pemoline and fencamfamine hydrochloride, still preserves the basic $\beta$-phenethylamine structure and retains the central stimulant activity without marked anorexigenic and cardiovascular side effects (Biel, 1970).

The stimulant activity of amphetamine on sleep has been studied by Rechtschaffen & Maron (1964) and by Lewis (1970). It increases wakefulness and delays the onset and duration of REM sleep. Some of its anorexigenic derivatives have similar actions, though others such as fenfluramine may have limited effects (Oswald, 1970). There is, however, less information available on the heterocyclic derivatives, and it is in this context that we have investigated their effects, and those of caffeine, on sleep.

## Methods

The study was carried out in two parts. Caffeine anhydrous (100, 200 and 300 mg) and prolintane hydrochloride (5 and 10 mg), diazepam (10 mg) as an active control and placebo were administered to a group of healthy male volunteers aged between 20 and 30 years (mean 26 years). Methylphenidate hydrochloride (10 and 20 mg), fencamfamine hydrochloride (10 and 20 mg), pemoline (20 and 40 mg), caffeine (300 mg) as an active control and placebo, were studied in a similar group of subjects aged between 21 and 31 years (mean 24 years). The structures of the drugs are shown in Figure 1. From a week preceding each study subjects drank decaffeinated coffee (Boots Pure Drug Company), and continued with this beverage throughout the experiment. Subjects, all non-smokers, were required

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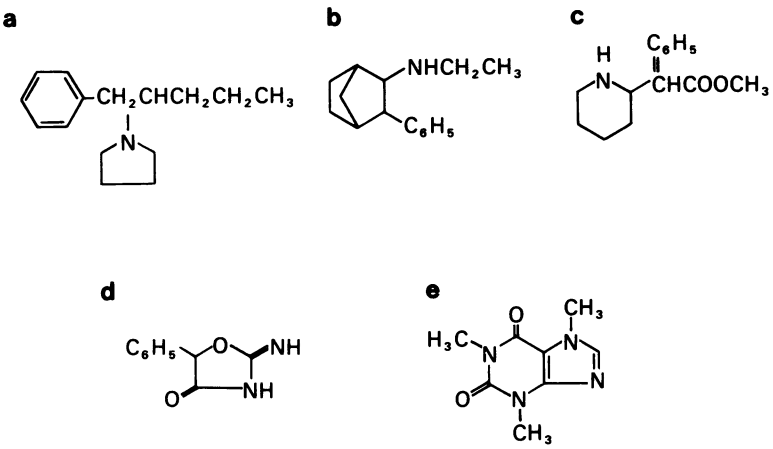


**Figure 1** (a) Prolintane: 1-[1-(phenyl methyl) butyl] pyrrolidine. (b) Fencamfamine: N-Ethyl-3-phenyl bicyclo [2.2.1]-heptan-2-amine. (c) Methylphenidate: α-Phenyl-2-piperidine acetic acid methyl ester. (d) Pemoline: 2-Imino-5-phenyl-4-oxazolidinone. (e) Caffeine: 3,7-Dihydro-1,3,7-trimethyl-1H-purine-2,6-dione.

to refrain from napping and undue exercise, and to abstain from alcohol on the days preceding sleep recordings.

The subjects were familiar with sleep recording. They reported at the laboratory 1.5 h before their usual time to retire, and the experiments were carried out in individual, sound attenuated rooms which were controlled for temperature and humidity. Two adaptation nights with ingestion of placebo only were separated by a week, but were not included in the analysis. The subsequent assessments of drug effect in which each active compound was ingested with matching placebos of the other drugs in the group also included a placebo only ingestion. The tablets were taken at 'lights out', and the drugs and placebos were arranged in a random order with seven days separating each experiment. The trial was double-blind.

Details of recording techniques and analyses are given elsewhere (Nicholson & Stone, 1979). The coefficient of variability (s.d. × 100/mean) of each measure (C/V) was used as a preliminary criterion to decide whether an analysis of variance was appropriate. If the value was above 50% the Friedman two-way analysis was used. In addition the latency, interval between, and duration of the first three REM periods were also analysed. REM sleeps separated from each other by an interval less than 10 min were taken as a single period of activity.

In the morning, 0.5 h after awakening, the subjects completed four assessments. The assessments and the extremes of the 100 mm analogue scales were, A: I slept, *Very poorly—Very well;* B: Now I feel, *Very sleepy—Wide awake;* C: I fell asleep, *Never—Immediately;* and D: After I fell asleep, I slept, *Very badly—Very well.* In each case a favourable response tended toward the 100 extreme of the scale.

## Results

*First study* (Tables 1, 2, 3, 4, 5, 6 and 7)

The effect of diazepam (10 mg) was similar to that reported previously in a comparable group of subjects (Nicholson & Stone, 1978), except that it delayed the first REM period ($P<0.001$), and decreased the duration of REM sleep in the first 2 h of the night ($P<0.05$). In the previous study these changes were seen only as trends.

With caffeine there were no changes in latencies to sleep onset, stage 3 or REM sleep. Total sleep time (TST) and duration of slow wave sleep (SWS) were decreased with 100 mg caffeine ($P<0.05$), and there were increases in duration of awakenings and percentage of drowsy sleep ($P<0.05$). Effects with 200 mg caffeine were less marked. No effect on TST could be established, but duration and percentage of SWS related to the early part of the night were reduced ($P<0.05$). Duration of awakenings ($P<0.05$), and the duration and percentage of drowsy sleep ($P<0.05$ and $<0.01$) were increased. The effect of caffeine appeared to be well established with the 300 mg dose. TST and SWS were decreased ($P<0.001$), with the latter related to the early part of the night ($P<0.05$). REM sleep was reduced from the second to the sixth hour of sleep ($P<0.05$ and $<0.01$), but percentage of REM sleep in the first 6 h was unchanged. The onsets of the second and third REM periods were delayed, but the duration of and

**Table 1** Effect of drugs on various sleep measures (means for six subjects)

| *Measure* | *C/V* | *Placebo* | *Diazepam (mg)* | *Prolintane (mg)* | | *Caffeine (mg)* | | |
|---|---|---|---|---|---|---|---|---|
| | | | *10* | *5* | *10* | *100* | *200* | *300* |
| Total sleep time (min) | 14.2 | 433.3 | 451.5 | 426.0 | 426.8 | 356.7* | 387.3 | 305.2*** |
| Stage shifts in first 6 h | 18.0 | 108.0 | 91.5 | 106.7 | 110.0 | 106.3 | 116.8 | 93.8 |
| Sleep onset latency (min) | 37.6 | 17.8 | 16.8 | 17.1 | 16.0 | 21.8 | 15.0 | 15.3 |
| Latency (min) to stage 3 | 38.8 | 14.3 | 16.3 | 14.5 | 13.6 | 16.9 | 18.8 | 18.8 |
| Latency (min) to stage REM | 29.1 | 61.4 | 114.5*** | 75.8 | 65.8 | 64.3 | 63.3 | 71.7 |
| REM/NREM ratio | 20.9 | 0.28 | 0.29 | 0.29 | 0.29 | 0.27 | 0.28 | 0.24 |
| TST/TIB | 9.1 | 0.90 | 0.93 | 0.89 | 0.90 | 0.78* | 0.86 | 0.78* |

C/V Coefficient of variability = (s.d. × 100/mean) of each measure
Significance levels *$P<0.05$; ***$P<0.001$.

**Table 2** Effect of drugs on duration (min) of sleep stages in first 6 h of sleep from sleep onset latency (means for six subjects)

| *Sleep stage* | *C/V* | *Placebo* | *Diazepam (mg)* | *Prolintane (mg)* | | *Caffeine (mg)* | | |
|---|---|---|---|---|---|---|---|---|
| | | | *10* | *5* | *10* | *100* | *200* | *300* |
| Awake | 173.3 | 6.3 | 5.2 | 9.3 | 6.8 | 46.6 | 18.4 | 48.0 |
| 1 | 34.4 | 19.9 | 14.0 | 21.3 | 20.4 | 26.0 | 31.3* | 24.8 |
| 2 | 12.8 | 174.5 | 187.5 | 188.8 | 175.2 | 151.9 | 175.5 | 151.1 |
| 3 | 32.6 | 34.5 | 46.1 | 29.3 | 37.9 | 31.7 | 37.4 | 23.9 |
| 4 | 30.6 | 48.6 | 38.8 | 46.8 | 48.2 | 37.3 | 26.6** | 26.3** |
| 3+4 | 15.2 | 83.1 | 84.8 | 76.1 | 86.1 | 68.9* | 64.0** | 49.3*** |
| REM | 25.9 | 73.4 | 67.0 | 62.8 | 69.3 | 53.7 | 69.9 | 46.2 |

C/V Coefficient of variability = (s.d. × 100/mean) of each measure.
Significance levels *$P<0.05$; **$P<0.01$; ***$P<0.001$.

**Table 3** Effect of drugs on two hourly distribution (min) of sleep stages from sleep onset latency (means for six subjects)

| *Sleep stage* | *Interval* | *C/V* | *Placebo* | *Diazepam (mg)* | *Prolintane (mg)* | | *Caffeine (mg)* | | |
|---|---|---|---|---|---|---|---|---|---|
| | *(h)* | | | *10* | *5* | *10* | *100* | *200* | *300* |
| Awake | 0–2 | 91 | 1.3 | 2.4 | 1.8 | 0.6 | 3.1 | 4.3 | 5.4 |
| | 2–4 | 196 | 2.2 | 0.4 | 2.7 | 2.8 | 14.4 | 6.4 | 18.9 |
| | 4–6 | 217 | 2.9 | 2.3 | 4.9 | 3.4 | 29.1 | 7.8 | 23.7 |
| 1 | 0–2 | 55 | 3.3 | 2.8 | 3.0 | 3.3 | 6.4 | 8.0 | 8.4 |
| | 2–4 | 49 | 6.4 | 3.3 | 6.2 | 7.3 | 7.8 | 10.1 | 8.6 |
| | 4–6 | 59 | 10.2 | 7.8 | 12.1 | 9.9 | 11.8 | 13.2 | 7.8 |
| 2 | 0–2 | 16 | 48.6 | 56.4 | 48.8 | 44.3 | 58.8* | 53.1 | 59.1* |
| | 2–4 | 15 | 68.0 | 68.8 | 66.0 | 70.0 | 55.9 | 71.9 | 53.5 |
| | 4–6 | 32 | 57.9 | 62.3 | 74.0 | 60.8 | 37.3* | 50.5 | 38.5* |
| 3 | 0–2 | 41 | 18.2 | 25.0 | 17.6 | 22.0 | 18.1 | 19.5 | 13.4 |
| | 2–4 | 66 | 9.8 | 16.7 | 8.2 | 11.3 | 9.0 | 8.7 | 6.8 |
| | 4–6 | 122 | 6.6 | 4.4 | 3.5 | 4.6 | 4.6 | 9.3 | 2.8 |
| 4 | 0–2 | 43 | 36.8 | 30.0 | 40.1 | 41.9 | 23.9 | 19.1* | 18.2* |
| | 2–4 | 123 | 7.6 | 8.3 | 6.7 | 6.2 | 11.1 | 4.6 | 6.3 |
| | 4–6 | 221 | 4.2 | 0.5 | 0.8 | 0.8 | 2.3 | 2.9 | 1.8 |
| REM | 0–2 | 55 | 11.1 | 2.8* | 8.1 | 7.1* | 8.9 | 16.0 | 15.3 |
| | 2–4 | 36 | 25.0 | 21.8 | 29.6 | 21.3 | 21.0 | 17.9 | 13.8* |
| | 4–6 | 39 | 37.3 | 42.3 | 25.2 | 40.9 | 23.8 | 36.0 | 17.2** |

C/V Coefficient of variability = (s.d. × 100/mean) for each measure.
Significance levels *$P<0.05$; **$P<0.01$.

**Table 4** Effect of drugs on percentage occupied by each sleep stage during first 6 h (means for six subjects)

| *Sleep stage* | *C/V* | *Placebo* | *Diazepam (mg)* | *Prolintane (mg)* | | *Caffeine (mg)* | | |
|---|---|---|---|---|---|---|---|---|
| | | | *10* | *5* | *10* | *100* | *200* | *300* |
| Awake | 173.3 | 1.03 | 1.5 | 2.7 | 1.9 | 7.8 | 3.1 | 18.0 |
| 1 | 28.2 | 5.7 | 3.9 | 6.1 | 5.8 | 8.7* | 9.2** | 8.9** |
| 2 | 8.1 | 49.4 | 52.7 | 53.8 | 49.7 | 50.8 | 51.4 | 56.7 |
| 3 | 30.2 | 9.7 | 13.0 | 8.4 | 10.7 | 10.2 | 11.1 | 8.3 |
| 4 | 30.2 | 13.7 | 10.9 | 13.3 | 13.6 | 12.6 | 7.7 | 10.6 |
| 3+4 | 13.5 | 23.5 | 23.9 | 21.7 | 24.4 | 22.8 | 18.8** | 18.9** |
| REM | 22.3 | 20.8 | 18.9 | 17.9 | 19.6 | 17.0 | 20.4 | 15.0 |

C/V Coefficient of variability = (s.d. × 100/mean) of each measure.
Significance levels *$P<0.05$; **$P<0.01$.

**Table 5** Effect of drugs on number and duration (min) of awakenings to 0 + 1 during the first 6 h of sleep (means for six subjects)

| *Measure* | *C/V* | *Placebo* | *Diazepam (mg)* | *Prolintane (mg)* | | *Caffeine (mg)* | | |
|---|---|---|---|---|---|---|---|---|
| | | | *10* | *5* | *10* | *100* | *200* | *300* |
| Number | 43.8 | 6.0 | 3.8 | 8.8 | 5.8 | 8.2 | 7.5 | 9.5 |
| Duration (min) | 106.1 | 14.7 | 9.3 | 19.3 | 15.6 | 61.9* | 35.7* | 31.6* |

C/V Coefficient of variability = (s.d. × 100/mean) of each measure.
*Significant ($P<0.05$) by non-parametric analysis.

**Table 6** Effect of drugs on subjective assessments (100 mm analogue scale) (means for six subjects)

| *Assessment* | *Placebo* | *Diazepam (mg)* | *Prolintane (mg)* | | *Caffeine (mg)* | | |
|---|---|---|---|---|---|---|---|
| | | *10* | *5* | *10* | *100* | *200* | *300* |
| A | 61.8 | 72.0 | 49.8 | 47.7 | 29.3*** | 46.3* | 30.0*** |
| B | 62.0 | 59.8 | 59.7 | 64.5 | 48.0 | 62.5 | 51.5 |
| C | 70.9 | 58.8 | 71.5 | 64.5 | 50.0 | 59.8 | 63.3 |
| D | 61.5 | 72.0 | 50.0 | 42.3* | 33.0*** | 54.7 | 32.2*** |

Significance levels *$P<0.05$; **$P<0.01$; ***$P<0.001$.
Assessments:—A: I slept, *Very poorly—Very well;* B: Now I feel, *Very sleepy—Wide awake;* C: I fell asleep, *Never—Immediately:* D: After I fell asleep I slept, *Very badly—Very well.*

**Table 7** Effect of caffeine and prolintane on REM sleep (means for six subjects)

| | *Placebo* | *Caffeine (mg)* | | | *Prolintane (mg)* | |
|---|---|---|---|---|---|---|
| | | *100* | *200* | *300* | *5* | *10* |
| *First period* | | | | | | |
| Onset | 61.6 | 64.3 | 63.3 | 71.7 | 77.3 | 65.8 |
| Duration | 10.1 | 9.0 | 17.3 | 12.6 | 14.7 | 8.4 |
| *Second period* | | | | | | |
| Onset | 141.6 | 148.7 | 146.9 | 238.5*** | 183.5 | 164.7 |
| Duration | 22.5 | 21.5 | 10.8 | 13.5 | 27.3 | 22.3 |
| *Third period* | | | | | | |
| Onset | 240.1 | 273.6 | 226.0 | 309.0* | 288.9 | 269.0 |
| Duration | 23.5 | 21.3 | 21.3 | 23.6 | 28.4 | 30.6 |

Analysis of intervals between REM periods was not significant.

interval between REM periods were not changed. Duration of awakenings was increased ($P<0.05$) and percentages of drowsy and slow wave sleep decreased ($P<0.01$). The subjects as a group reported that they slept less well with caffeine, but assessments of sleep onset and wakefulness the next morning were not altered. The subjective effect with 200 mg was less pronounced than that with 100 and 300 mg.

Prolintane reduced REM activity in the first 2 h of sleep ($P<0.05$), but there were no other changes in sleep. The subjects as a group reported that they slept less well with the higher dose, but estimations of sleep onset and wakefulness the next morning were not altered.

*Second study* (Tables 8, 9, 10, 11, 12, 13 and 14)

Caffeine (300 mg) has a similar effect on TST to that observed in the first study. It was not possible to establish an effect on SWS, but this may have been due to the low placebo value. Further, delays in the onset of the second and third REM periods were not observed.

Pemoline (40 mg) reduced TST ($P<0.05$). This effect was related to disturbed sleep in one subject, but there was no evidence of such an effect in that subject with the lower dose (20 mg). There were no other changes with pemoline. The subjects as a group assessed their sleep as impaired with the higher dose, but this was related to the assessment by the subject with disturbed sleep.

With fencamfamine and methylphenidate there were no changes in latencies to sleep onset or stage 3 sleep, though with the higher dose of each drug REM latency was increased ($P<0.05$ and $<0.001$ respectively). Fencamfamine (10 and 20 mg) increased awake activity ($P<0.05$), and the higher dose reduced duration and percentage of REM sleep ($P<0.05$). The higher dose of methylphenidate reduced TST ($P<0.01$), with increased awake activity and drowsy sleep ($P<0.05$ and $<0.001$ respectively), related to the early part of sleep. Percentages of awake and drowsy sleep were also increased ($P<0.05$). Duration of REM sleep was reduced by 10 and 20 mg methylphenidate ($P<0.05$ and $<0.001$ respectively), and the percentage of REM sleep was reduced ($P<0.001$) by the higher dose. There were delays in the latencies to each of the first three REM periods with 20 mg methylphenidate and 20 mg fencamfamine, but it was not possible to establish a change in their duration or in the interval between the first and second and the second and third periods. The subjects as a group reported impaired sleep with methylphenidate and fencamfamine, but there were no changes in assessments of sleep onset latency or in wakefulness the next morning.

**Table 8** Effect of drugs on various sleep measures (means for six subjects)

| *Measure* | *C/V* | *Placebo* | *Caffeine (mg)* | *Methylphenidate (mg)* | | *Pemoline (mg)* | | *Fencamfamine (mg)* | |
|---|---|---|---|---|---|---|---|---|---|
| | | | *300* | *10* | *20* | *20* | *40* | *10* | *20* |
| Total sleep time (min) | 18.04 | 435.38 | 355.58* | 405.25 | 301.08** | 411.00 | 349.33* | 418.67 | 413.00 |
| Stage shifts in first 6 h | 18.41 | 107.75 | 117.67 | 124.00 | 118.50 | 109.33 | 97.33 | 109.67 | 113.17 |
| Sleep onset latency (min) | 81.21 | 20.67 | 32.58 | 20.58 | 24.00 | 16.17 | 26.67 | 18.42 | 19.00 |
| Latency (min) to stage 3 | 183.15 | 15.92 | 54.42 | 12.92 | 66.83 | 14.92 | 18.08 | 15.50 | 16.42 |
| Latency (min) to stage REM | 46.74 | 80.50 | 103.25 | 102.83 | 190.58*** | 92.92 | 71.50 | 103.33 | 157.75* |
| REM/NREM ratio | 24.60 | 0.31 | 0.25 | 0.26 | 0.23 | 0.25 | 0.25 | 0.25 | 0.20 |
| TST/TIB | 12.56 | 0.89 | 0.74*(*) | 0.82 | 0.61*** | 0.86 | 0.80 | 0.87 | 0.84 |

C/V Coefficient of variability = (s.d. × 100/mean) of each measure.
Significance levels $*P<0.05$; $**P<0.01$; $***P<0.001$.

**Table 9** Effect of drugs on duration (min) of sleep stages in first 6 h of sleep from sleep onset latency (means for six subjects)

| *Sleep stage* | *C/V* | *Placebo* | *Caffeine (mg)* | *Methylphenidate (mg)* | | *Pemoline (mg)* | | *Fencamfamine (mg)* | |
|---|---|---|---|---|---|---|---|---|---|
| | | | *300* | *10* | *20* | *20* | *40* | *10* | *20* |
| Awake | 105.93 | 7.88 | 29.58 | 31.92* | 107.83* | 10.25 | 12.92 | 15.58* | 24.75* |
| 1 | 38.23 | 24.29 | 45.67*(*) | 35.83 | 58.58*** | 29.83 | 27.83 | 30.08 | 35.67 |
| 2 | 18.33 | 196.96 | 166.67 | 183.08 | 119.67*** | 197.58 | 178.00 | 206.33 | 197.08 |
| 3 | 38.74 | 28.75 | 22.17 | 24.25 | 19.67 | 30.17 | 25.08 | 25.67 | 24.42 |
| 3+4 | 26.73 | 56.17 | 46.50 | 57.58 | 44.00 | 62.50 | 46.83 | 51.50 | 55.75 |
| REM | 33.46 | 73.88 | 62.25 | 50.17* | 29.58*** | 56.25 | 60.33 | 56.08 | 45.58* |

C/V Coefficient of variability = (s.d. × 100/mean) of each measure.
Significance levels *$P<0.05$; **$P<0.01$; ***$P<0.001$.

**Table 10** Effect of drugs on two hourly distribution (min) of sleep stages from sleep onset latency (means for six subjects)

| *Sleep stage* | *Interval (h)* | *C/V* | *Placebo* | *Caffeine (mg)* | *Methylphenidate (mg)* | | *Pemoline (mg)* | | *Fencamfamine (mg)* | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | *300* | *10* | *20* | *20* | *40* | *10* | *20* |
| Awake | 0–2 | 208.86 | 1.33 | 15.00* | 2.50 | 22.33* | 1.75 | 4.58 | 1.92 | 10.33 |
| | 2–4 | 162.15 | 2.92 | 4.58 | 12.58 | 53.42 | 5.25 | 2.67 | 2.58 | 6.67 |
| | 4–6 | 163.16 | 3.63 | 10.00 | 16.83 | 32.08 | 3.25 | 5.67 | 11.08 | 7.75 |
| 1 | 0–2 | 64.56 | 4.54 | 20.17* | 6.50 | 17.58* | 5.50 | 6.67 | 7.08 | 8.17 |
| | 2–4 | 87.95 | 8.50 | 12.92 | 11.50 | 20.25 | 13.42 | 7.58 | 10.25 | 14.67 |
| | 4–6 | 44.14 | 11.25 | 12.58 | 17.83 | 20.75 | 10.92 | 13.58 | 12.75 | 12.83 |
| 2 | 0–2 | 19.86 | 67.50 | 54.83 | 59.00 | 52.25 | 65.08 | 69.58 | 66.42 | 59.25 |
| | 2–4 | 26.90 | 65.04 | 58.42 | 65.50 | 28.83*** | 64.75 | 55.67 | 71.92 | 78.42 |
| | 4–6 | 33.88 | 64.42 | 53.42 | 58.58 | 38.58 | 67.75 | 52.75 | 68.00 | 59.42 |
| 4 | 0–2 | 57.49 | 17.75 | 10.00 | 30.58 | 15.08 | 21.25 | 18.17 | 20.67 | 20.92 |
| | 2–4 | 136.02 | 7.46 | 8.92 | 1.58 | 0.67 | 6.92 | 3.50 | 4.67 | 6.83 |
| | 4–6 | 176.40 | 2.21 | 5.42 | 1.17 | 8.58 | 4.17 | 0.08 | 0.50 | 3.58 |
| REM | 0–2 | 99.33 | 9.25 | 10.50 | 5.42 | 0.33 | 9.58 | 9.67 | 8.08 | 2.75 |
| | 2–4 | 59.67 | 30.88 | 28.58 | 24.17 | 13.33 | 21.58 | 23.42 | 24.33 | 10.67 |
| | 4–6 | 54.09 | 33.75 | 23.17 | 20.58 | 15.92 | 25.08 | 27.25 | 23.67 | 32.17 |

C/V Coefficient of variability = (s.d. × 100/mean) of each measure.
Significance levels *$P<0.05$; ***$P<0.001$.

**Table 11** Effect of drugs on percentage occupied by each sleep stage during first 6 h (means for six subjects)

| *Sleep stage* | *C/V* | *Placebo* | *Caffeine (mg)* | *Methylphenidate (mg)* | | *Pemoline (mg)* | | *Fencamfamine (mg)* | |
|---|---|---|---|---|---|---|---|---|---|
| | | | *300* | *10* | *20* | *20* | *40* | *10* | *20* |
| Awake | 157.79 | 2.28 | 9.93* | 10.13* | 56.82 | 2.98 | 5.97 | 4.65 | 7.73 |
| 1 | 60.73 | 6.94 | 14.57* | 10.93* | 25.03* | 8.63 | 9.77 | 8.85 | 10.83* |
| 2 | 10.88 | 55.93 | 51.57 | 55.78 | 44.98** | 56.92 | 57.30 | 59.92 | 58.58 |
| 3 | 32.78 | 8.17 | 6.80 | 7.33 | 7.68 | 8.67 | 7.75 | 7.37 | 7.27 |
| 4 | 42.16 | 7.72 | 7.40 | 10.28 | 12.37 | 9.22 | 7.85 | 7.62 | 9.35 |
| 3+4 | 26.00 | 15.90 | 14.20 | 17.63 | 20.05 | 17.87 | 15.58 | 15.03 | 16.65 |
| REM | 31.49 | 21.00 | 19.40 | 15.23 | 9.80*** | 16.27 | 17.28 | 16.12 | 13.60* |

C/V Coefficient of variability = (s.d. × 100/mean) of each measure.
Significance levels $*P<0.05$; $**P<0.01$; $***P<0.001$.

**Table 12** Effect of drugs on number and duration (min) of awakenings to 0+1 during the first 6 h of sleep (means for six subjects)

| *Measure* | *C/V* | *Placebo* | *Caffeine (mg)* | *Methylphenidate (mg)* | | *Pemoline (mg)* | | *Fencamfamine (mg)* | |
|---|---|---|---|---|---|---|---|---|---|
| | | | *300* | *10* | *20* | *20* | *40* | *10* | *20* |
| Number | 59.54 | 7.50 | 12.50 | 11.83 | 11.50 | 10.00 | 8.17 | 9.33 | 12.00 |
| Duration (min) | 77.86 | 18.17 | 61.33* | 53.25* | 154.00* | 25.83 | 26.67 | 32.75 | 45.58 |

C/V Coefficient of variability = (s.d. × 100/mean) of each measure.
Significance levels $*P<0.05$.

## Discussion

In the present study with doses covering the usual therapeutic range the heterocyclic derivatives of amphetamine had very different effects on sleep. Pemoline (20–40 mg) and prolintane (10–20 mg) had minimal activity, whereas methylphenidate (10–20 mg) and fencamfamine (10–20 mg), like amphetamine (Rechtschaffen & Maron, 1964; Lewis, 1970), increased wakefulness and depressed REM sleep. Pemoline disturbed sleep in only one subject. The apparent lack of effect is in agreement with the study of Baekeland & Lasky (1968), although it has been reported that a higher dose (100 mg) counteracts sleep deprivation and fatigue (Herbert, Gelfand, Clarke & Gelfand, 1968; Gelfand, Clarke, Herbert, Gelfand & Holmes, 1968). Prolintane (10–20 mg) also had minimal effects on sleep, though, like amphetamine, it possesses sympathomimetic activity (Bachmann & Baer, 1957; Hollister & Gillespie, 1970; Kadatz & Poetzsch, 1957). However, it is considered that, in appropriate doses, the effect of all heterocyclic compounds on sleep may be similar to that of amphetamine. Baekeland (1966) observed an increase in the latency to the first REM period with only 5 mg methylphenidate, and this observation together with our data suggest dose related effects with respect to both latency and duration of REM sleep.

The conclusion that differences in activity between these drugs may simply be dose related may also be drawn from the studies of Oswald (1970) and Lewis (1970) with the anorexigenic derivatives of amphetamine. Amphetamine (7.5 mg) and the anorexigenic compounds, chlorphentermine (50 mg), diethylpropion (25 and 50 mg) and fenfluramine (40 mg), increased the latency to the first REM period, and amphetamine and chlorphentermine also reduced the duration of REM sleep over the whole night. Nevertheless, it would appear that drugs with similar stimulant or anorexigenic activity may have different effects on sleep.

Studies on the central effects of caffeine have been carried out by several workers. Goldstein, Murphree & Pfeiffer (1963), using electroencephalography, observed effects with 250 mg caffeine for only 3 h after ingestion, and a relatively short duration of action was suggested by Gresham, Webb & Williams (1963) who failed to detect an effect of 5 mg $kg^{-1}$ on REM sleep. However, the effect of caffeine, at least in doses around 300 mg, may well persist beyond a few hours. We have observed reduced slow wave sleep during the early part, and in one study reduced REM sleep during the latter part of the night. In this study

**Table 13** Effect of drugs on subjective assessments (100 mm analogue scale)

| *Assessment* | *Placebo* | *Caffeine (mg)* | *Methylphenidate (mg)* | | *Pemoline (mg)* | | *Fencamfamine (mg)* | |
|---|---|---|---|---|---|---|---|---|
| | | *300* | *10* | *20* | *20* | *40* | *10* | *20* |
| A | 67.1 | 39.3* | 63.3 | 31.0** | 61.0 | 40.6* | 63.8 | 39.8 |
| B | 72.7 | 63.6 | 68.5 | 47.8 | 70.3 | 68.6 | 66.0 | 65.0 |
| C | 64.3 | 57.3 | 71.1 | 56.3 | 69.1 | 52.3 | 75.0 | 52.0 |
| D | 73.8 | 69.5 | 64.3 | 34.1*** | 60.0 | 43.1** | 66.5 | 46.8* |

Significance levels: $*P<0.05$; $**P<0.01$; $***P<0.001$.
Assessments:—I slept, *Very poorly—Very well;* B: Now I feel, *Very sleepy—Wide awake;* C: I fell asleep, *Never—Immediately;* D: After I fell asleep I slept, *Very badly—Very well.*

**Table 14** Effect of fencamfamine and methylphenidate on REM sleep (means for six subjects)

| | *Placebo* | *Caffeine (mg)* | *Fencamfamine (mg)* | | *Methylphenidate (mg)* | |
|---|---|---|---|---|---|---|
| | | *300* | *10* | *20* | *10* | *20* |
| *First period* | | | | | | |
| Onset | 92.7 | 103.4 | 103.3 | 159.1* | 102.8 | 191.1** |
| Duration | 15.2 | 21.6 | 25.1 | 15.9 | 15.7 | 18.6 |
| *Second period* | | | | | | |
| Onset | 172.8 | 197.6 | 229.0 | 279.6** | 229.4 | 303.3*** |
| Duration | 26.6 | 20.1 | 24.2 | 23.8 | 34.1 | 26.0 |
| *Third period* | | | | | | |
| Onset | 292.2 | 300.7 | 333.6 | 366.5 | 337.3 | 407.9*** |
| Duration | 41.1 | 19.8 | 31.1 | 33.2 | 30.4 | 26.1 |

Analysis of intervals between REM periods was not significant.

the reduced REM sleep was due to increased wakefulness with the second and third REM periods delayed.

The question also arises whether caffeine may change the sleep of young adults in a different way from that of the middle aged. Gresham *et al.* (1963) did not observe an effect on REM sleep in young adults, but Brezinová (1974) found reduced REM sleep in the middle aged. The results of Karacan, Thornby, Anch, Booth, Williams & Sallis (1977) in young adults are similar to those of Brezinová (1974), and so, together with the present studies, suggest that sensitivity to caffeine, in particular modification of REM sleep, may not vary over a wide age range. Though the effect of caffeine on individual subjects may be well established with a dose around 300 mg, Goldstein, Warren & Kaizer (1965) have emphasized the differences between subjects in their sensitivity to caffeine, and individual response may explain the differences observed between laboratories. In our studies there were clear differences between subjects and within the same subject in separate experiments, and similar effects were observed with higher doses of methylphenidate and fencamfamine.

It would appear that wakefulness with marked disturbances of REM sleep is associated with both the stimulant and anorexigenic derivatives of amphetamine, whereas wakefulness with reduced slow wave sleep is likely to relate to the xanthines. In the dose ranges studied, methylphenidate and fencamfamine fundamentally modify the basic rest and activity cycle by their effects on REM activity, whereas caffeine leads to increased wakefulness without serious modification of the sleep cycle.

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