Caffeine Effects on Sleep Taken 0, 3, or 6 Hours before Going to Bed

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SCIENTIFIC INVESTIGATIONS

Study Objective: Sleep hygiene recommendations are widely disseminated despite the fact that few systematic studies have investigated the empirical bases of sleep hygiene in the home environment. For example, studies have yet to investigate the relative effects of a given dose of caffeine administered at different times of day on subsequent sleep.

Methods: This study compared the potential sleep disruptive effects of a fixed dose of caffeine (400 mg) administered at 0, 3, and 6 hours prior to habitual bedtime relative to a placebo on self-reported sleep in the home. Sleep disturbance was also monitored objectively using a validated portable sleep monitor.

Results: Results demonstrated a moderate dose of caffeine at bedtime, 3 hours prior to bedtime, or 6 hours prior to bedtime each have significant effects on sleep disturbance relative to placebo (p < 0.05 for all).

Conclusion: The magnitude of reduction in total sleep time suggests that caffeine taken 6 hours before bedtime has important disruptive effects on sleep and provides empirical support for sleep hygiene recommendations to refrain from substantial caffeine use for a minimum of 6 hours prior to bedtime.

Keywords: Caffeine, sleep hygiene, insomnia, sleep habits, stimulant

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Caffeine in doses ranging from 200-400 mg have been shown to be effective and are often utilized to sustain performance in the context of sleep deprivation, sedation, and sleep restriction.[1-7] Up to 500 mg of caffeine can be found in commercially available 16-oz servings of brewed coffee.[8] The use of similarly high doses of caffeine-containing beverages, including energy drinks has led to a doubling of caffeine-related emergency department visits from 2007-2011.[9] The increase in ED visits in association with cardiovascular and other adverse events has been labeled a "rising public health problem in the US" and has led the Food and Drug Administration to investigate the cardiovascular safety of high caffeine content beverages.[10] Importantly, the adverse effects of caffeine intake are not limited to the cardiovascular system but also produce significant sleep disruptive effects, particularly when taken later in the day or when multiple doses are utilized.[11] One recent population-based study of 18- to 58-year-olds (mean age = 28.5 years of age) estimated that 90% of individuals consume caffeine in the afternoon (12:00-18:00) and 68.5% of people consume caffeine in the evening (18:00-00:00).[12]

Caffeine content in beverages and foods is increasing in terms of dose and availability, with recent estimates of total daily caffeine consumption suggesting that the average person consumes 319.32 ± 180.94 mg of caffeine per day.[12] Information on the sleep-disrupting effects of high doses of caffeine taken in the afternoon and early evening is important, given the increasingly popular use of caffeinated energy drinks and the high caffeine content of premium coffee.[13] Such investigations are also critical due to increased caffeine use in younger age groups, where chronic sleep restriction is also increasingly

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BRIEF SUMMARY

Current Knowledge/Study Rationale: Despite widespread but often disparate recommendations to refrain from caffeine intake close to bedtime, no studies have investigated the effects of a given dose of caffeine taken at different times before sleep. Understanding the temporal effects of caffeine on sleep are important given the increased utilization of caffeine, and need for empirical data to support specific sleep hygiene recommendations regarding caffeine.

Study Impact: This study demonstrates caffeine consumption even 6 hours before bedtime can have important disruptive effects on both objective and subjective measure of sleep. These findings provide empirical support for sleep hygiene recommendations to refrain from substantial caffeine use for a minimum of 6 hours prior to bedtime.

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common.[8,14,15] Indeed, recent data show that in younger samples, 37% report first use of caffeine during the day at 17:00 or later.[16]

The sleep disruptive effects of caffeine administration at bedtime are well documented.[17] Indeed, caffeine administration has been used as a model of insomnia.[18] Dose-response studies demonstrate that increasing doses of caffeine administered at or near bedtime are associated with significant sleep disturbance.[19-21] One of the most common recommendations for appropriate sleep hygiene practices is to avoid caffeine close to bedtime. However, evidence is less clear regarding the consumption of caffeine at earlier time points in the day. Due to the high variability in the elimination half-life of caffeine administered to healthy adults,[22,23] specific recommendations on what time of day to discontinue caffeine use vary widely from 4 to 11 hours prior to bedtime.[24-26] One limiting factor for such recommendations is that few studies have compared the sleep disruptive effects of

caffeine given at different times before bed. Thus, it remains unclear to what degree caffeine taken in the afternoon disrupts nocturnal sleep relative to doses consumed closer to bedtime.

One study examining the sleep effects of 400 mg caffeine administered 30 minutes before bedtime demonstrated both severe sleep disruption as well as important cardiovascular effects during sleep likely related to increased sympathetic activity.[27] In one of the few studies that evaluated caffeine administered in the evening, a 200 mg dose was used with 100 mg 3 h before bed and an additional 100 mg 1 h before bed. The caffeine condition reduced sleep efficiency by 5%, prolonged sleep latency by 12-16 min, and reduced total sleep time by 25-30 min relative to placebo.[28] However, as this study investigated the combined effects of the 2 doses, the comparative effects of time of administration could not be determined. A study that administered caffeine (200 mg) 16 h prior to bedtime produced minimal effects on standard sleep parameters compared to a dose near bedtime, likely due to low blood levels of caffeine at bedtime[29] and the relatively low dose utilized. Nonetheless, even at such small doses with a large intervening time before bed, the effects of caffeine were detectable on sleep parameters.

To our knowledge, no studies have systematically determined the disruptive effects of a fixed dose of caffeine administered at different times prior to sleep. The present study aimed to determine the magnitude of caffeine effects on sleep when administered in the home environment at 0, 3, and 6 hours prior to habitual bedtime.

METHODS

Subjects

Participants were recruited from the Detroit tri-county area through local advertisements. The study group comprised 12 healthy normal sleepers, as determined by a physical examination and clinical interview. The exclusion of insomnia was based on systematic clinical evaluations by a sleep specialist that included no history of difficulty falling asleep, staying asleep or non-restorative sleep for a month or more. Subjects were confirmed to be free of insomnia and sleepiness based on the Insomnia Severity Index (2.3 ± 1.5) (mean ± standard deviation)[30] and the Epworth Sleepiness Scale (3.9 ± 1.5).[31] As polysomnography was not performed, sleep apnea was screened out during the clinical evaluation using the Berlin Questionnaire.[32] Habitual sleep data were determined by self-report with a 1-week sleep diary the week prior to participation. Only individuals with habitual total sleep times between 6.5 and 9 h, with a sleep onset < 30 min were included. All subjects reported good health based on both medical history and physical examination. Any individuals with reported current or previous history of any psychiatric illness or current medical disorder were excluded from participation. Individuals currently using oral contraceptives, hypnotics, or any central nervous system acting medications were also excluded. Habitual caffeine consumption was based on self-report. Habitual caffeine consumption was calculated from the question "How much caffeine do you consume in an average day, including coffee, pop, tea, chocolate, or energy drinks? Please specify type and amount." Daily

and weekly servings (100 mg) of caffeine were then estimated based on type and amount indicated. The amount of caffeine in specific beverages/sources was determined based on information provided at the brand website and published literature.[33] If home-brewed coffee was indicated, an 8-oz cup was calculated to be equal to 100 mg of caffeine (1 serving). Subjects were selected if they met either of the following criteria: (1) ≥ 3 servings of caffeine in any single day or (2) ≥ 5 caffeinated servings per week. Subjects who consumed > 5 caffeinated beverages per day were excluded from participation. There were no inclusion or exclusion criteria as to time of caffeine consumption. All subjects were screened for current depression using the Hamilton Depression Rating Scale (HDRS), and only individuals with < 10 on the HDRS participated.[34] The mean body mass index (BMI) of the sample was 25.1 ± 4.9.

A total of 16 healthy day workers met initial screening criteria; data were not used from 4 subjects due to violation of the study protocol before the study blind was broken. This included 2 subjects who took caffeine on 4 consecutive nights without the required 1 night washout, one subject who did not go to bed at the scheduled times 3 of 4 nights, and one subject who did not comply with 8-h time in bed on study nights. Thus, 12 subjects completed the full protocol (6F, 6M; aged 19-48; mean age 29.3 ± 7.6). The mean baseline caffeine intake for the sample was 115 ± 169 mg/day of caffeine. All study procedures were approved by the institutional review board and informed consent was obtained from all participants. Individuals were compensated for their participation.

Procedures

The protocol was a randomized, double-blind, double dummy, placebo-controlled, balanced Latin Square treatment sequence design. For the experimental period, participants were instructed to maintain their normal sleep schedules, including a bedtime between 21:00 and 01:00, wake times between 06:00 and 09:00, time in bed of 6.5-9 h, and no habitual napping. Study protocol began following one week of baseline sleep diaries. Each subject completed 4 conditions/nights which consisted of 400 mg of caffeine taken in pill form at either 6, 3, or 0 hours prior to scheduled bedtime, with identical placebo given at each of the other times. Thus, subjects were instructed to take 3 pills each study day with one of the pills being caffeine and the other 2 placebo. On one of the days, all 3 pills were placebo. Conditions were presented in a Latin Square Design. Each caffeine condition was preceded by 1 washout night where subjects did not wear any sensors and did not take study drug. Thus, experimental nights occurred every other night during the protocol. However, sleep diary data were collected in the morning for all nights (experimental and washout). Subjects were given caffeine pills in an alarm activated pill case. Participants were required to maintain a fixed bedtime and wake time schedule based on sleep diaries throughout the protocol. Subjects were also given a sleep diary to complete each morning throughout the study. The pill case alarms were set according to the subjects' habitual bedtime, and the alarm was designed to sound until the subject manually turned it off. In order to avoid any potential caffeine withdrawal effects subjects were allowed to use caffeine during the study. However, subjects

were instructed to refrain from consuming any alcohol or caffeine after 16:00 on study days.

The aim of the present study was to determine if caffeine administered at different times before bed in the home environment impacts measures of sleep disturbance compared to placebo. It was important to measure reported sleep disturbance in response to home caffeine administration because disturbed sleep (e.g., sleep quality, difficulty falling asleep) is, at least in part, determined by self-report, insomnia is a symptom-based diagnosis, and because adherence to sleep hygiene rules is likely to be dependent upon perceived sleep quality effects. Thus, the impact of different caffeine administration times on sleep was measured using a standard sleep diary with items similar to those used for the consensus sleep diary.[35]

Sleep disturbance was also measured objectively using a widely available and previously validated in-home sleep monitor.[36] The monitor was comprised of a headband unit containing dry fabric sensors that wirelessly transmitted a single-channel EEG signal obtained from the forehead to a bedside device for processing. Sleep parameters were computed in real-time by the device shown to have concordance with the current gold standard, polysomnography (PSG), as well as with actigraphy.[36] The intraclass correlation coefficients between the monitor and PSG were > 0.90 for total sleep time (TST) and sleep efficiency (SE), and > 0.81 for latency to persistent sleep (LPS) and wake time during sleep (WTDS), the duration and continuity measures that are of primary interest regarding the sleep disrupting effects of caffeine. The device also showed high concordance with actigraphy measures of sleep in the validation study.[36] While a more recent validation study showed moderate overall agreement between the headband device and PSG scoring, the portable device may significantly underestimate the number of wake epochs.[37] A separate study also found similarly moderate to high agreement between the device and PSG, but with underestimation of wake epochs.[38] Finally, the sensitivity of the ambulatory monitoring device to sleep extension in the home environment has also been documented.[39] Sleep variables measured included TST, LPS (first epoch of 10 min of consecutive sleep), WTDS, and SE. Although these were the primary measures of interest, we also examined exploratory measures of combined stage 1 and 2 sleep, slow wave sleep, and REM sleep. As previously reported, an important limitation regarding sleep architecture is that the device does not provide separate measures for stage 1 and stage 2 sleep; therefore, only a combined measure of these 2 sleep stages was available.

Subjects were instructed to put on the wireless system headband immediately upon going to bed with the intent to go to sleep, and to keep the headband on all night long and place it back on its bedside device upon rising from bed in the morning. Adherence with the timing of the 3 daily pill administrations was done through the use of 3 timed pill alarm cases, which contained study drug for each night. Study drug intake was monitored by having subjects call in to a time stamped answering machine to verify that the study drug was taken at each predetermined time period (6 h prior, 3 h prior, and at bedtime).

Data were analyzed using repeated-measures ANOVA with planned comparisons testing for differences between each caffeine administration time and placebo night. Data transformations were performed where appropriate when deviations

Table 1—Baseline demographics and sleep diary measures

Baseline Demographics	N	Mean ± SD
Sex	12	6 females
Age	12	29.33 ± 7.62
Insomnia severity index	12	2.25 ± 1.54
Body mass index	12	25.08 ± 4.85
Epworth sleepiness scale	12	3.92 ± 1.50
Pittsburgh Sleep Quality Index	12	4.50 ± 3.32
Global Sleep Assessment Questionnaire	12	2.17 ± 1.75
Baseline Sleep Diary	**N**	**Mean ± SD**
Total sleep time (h)	12	7.63 ± 0.55
Sleep latency (min)	12	22.26 ± 26.46
Wake time during sleep (min)	12	7.28 ± 7.84
Sleep efficiency (%)	12	94.5 ± 3.25
Time in bed (h)	12	8.10 ± 0.53
Sleep quality	12	6.61 ± 1.62

from normality occurred. Significant omnibus results were followed by post hoc analyses to identify pairwise differences. A two-tailed α level of 0.05 was used for all statistical tests. A nonparametric Friedman two-way analysis of variance by ranks was used for variables which deviated from normality.

RESULTS

Both subject report and objective measures of time in bed, bedtime, and wake time indicated the subjects maintained their normal sleep schedule throughout the study period as instructed. Data for the 7-day sleep diary taken during baseline as well as other self-report sleep-wake related measures are shown in **Table 1**. There were no differences in these parameters across the study conditions (p > 0.05). There were no differences in non-study related caffeine intake between any of the 4 conditions: 0 h = 126.1 ± 164.9 mg, 3h = 139.1 ± 199.2 mg, 6h = 154.1 ± 199.2 mg, placebo = 139.4 mg ± 189.6 (p > 0.05 for all pairwise comparisons). During the study protocol, time-stamped telephone verification indicated that all subjects took the required doses on each night at the instructed times.

Means and standard deviations of diary measures of sleep including latency to sleep, total sleep time, and WTDS during each condition are shown in **Table 2**. Caffeine had the most consistent effects on reducing total sleep time relative to placebo, with both administration at bedtime and 3 h prior to bedtime reaching statistical significance. Caffeine administered 6 h prior to bedtime reduced total sleep time by 41 min, which approached significance (p = 0.08). Significant effects were observed for sleep latency with caffeine taken 3 h before bed having the greatest effect relative to placebo. Although caffeine taken 6 h before bedtime more than doubled the reported time take to fall asleep, this effect did not reach statistical significance (p = 0.06). No significant effects were observed for WTDS, SE, or sleep quality. There were no significant differences between caffeine conditions for any of the sleep diary measures (**Table 2**).

Means and standard deviations of objective measures of sleep (i.e., latency to sleep, total sleep time, and WTDS)

Table 2—Means ± SD of sleep diary-based measures for each condition

Sleep Measure	Placebo	Caffeine at bedtime	Caffeine 3 hours before bed	Caffeine 6 hours before bed	F (3,33)	p
Latency to sleep (min)	21.00 ± 8.99	56.67 ± 74.23	62.50 ± 66.18*	44.17 ± 44.56^	3.06	0.04
Total sleep time (h)	7.82 ± 0.54	6.92 ± 1.10*	6.77 ± 0.95*	7.13 ± 0.93^	4.14	0.01
Wake time during sleep (min)	11.00 ± 11.24	9.18 ± 9.41	17.67 ± 33.99	9.27 ± 14.01	0.71	0.55
Sleep efficiency %	93.60 ± 3.47	86.43 ± 13.87	83.98 ± 12.68	89.05 ± 9.22	2.65	0.07
Sleep quality	6.20 ± 2.04	5.83 ± 2.33	5.17 ± 1.53	5.67 ± 2.19	0.63	0.60

Follow-up pairwise compairsons, where omnibus F-values are significant : *$p < 0.05$ vs. placebo, ^$p < 0.10$.

Table 3—Objective sleep measures for each condition (mean ± SD)

Sleep Measure	Placebo	Caffeine at bedtime	Caffeine 3 hours before bed	Caffeine 6 hours before bed	F (3,33)	P
Latency to persistent sleep (min)	20.59 ± 9.79	43.0 ± 38.93	37.82 ± 29.91	44.68 ± 54.60	2.05	0.13
Total sleep time (h)	7.68 ± 0.85	6.60 ± 1.10*	6.54 ± 1.36*	6.50 ± 1.32*	3.43	0.03
Wake time during sleep (min)	9.55 ± 14.73	27.04 ± 40.06	37.18 ± 43.0*	17.59 ± 22.28*	3.29	0.03
Sleep efficiency %	91 ± 5.71	83.1 ± 12.11*	82.51 ± 12.73*	82.33 ± 12.15*	7.50	0.058#
Stage 1 & 2 (min)	266.77 ± 40.15	226.17 ± 57.75*	222.68 ± 62.24*	222.82 ± 48.83*	3.66	0.02
Stage 1 & 2 (%)	58.02 ± 7.37	56.47 ± 7.77	56.77 ± 10.48	57.28 ± 6.26	0.22	0.88
Slow wave sleep (min)	71.45 ± 26.48	56.67 ± 21.48*	57.0 ± 16.78	48.91 ± 15.81*	4.26	0.01
Slow wave sleep (%)	15.47 ± 5.28	14.47 ± 4.85	14.84 ± 3.87	12.71 ± 3.88	1.22	0.32
REM (min)	123.27 ± 33.89	114.36 28.53	112.5 ± 46.57	118.73 ± 39.75	0.30	0.83
REM (%)	26.62 ± 6.35	29.21 ± 7.19	28.39 ± 11.25	29.99 ± 6.54	0.88	0.46

*$p < 0.05$ pairwise comparisons vs. placebo; #Nonparametric related samples test of Friedman two-way analysis of variance by ranks was performed as data was not normally disturbed following transformation.

are shown in **Table 3**. Evidence for the disruptive effects of caffeine was demonstrated for each of the sleep duration and continuity parameters. The different caffeine administration times (0, 3, or 6 h before bed) did not produce differential sleep disruption among the 3 active caffeine conditions. For TST, reductions in duration relative to placebo were significant at each of the caffeine administration time points, reducing TST between 1.1 to 1.2 hours. The 3-h condition significantly prolonged latency to persistent sleep (+17.2 min) relative to placebo. Latency to persistent sleep was similarly prolonged in the 0 and 6 h condition (+22.4 and +24.1 min, respectively), but neither reached statistical significance compared to placebo. The amount of wake time during sleep was also increased with all 3 caffeine administration times, reaching statistical significance for the 6 h (+8 min) and 3 h (+27.6 min) conditions. Sleep efficiency was reduced for each condition relative to placebo.

Sleep Architecture

Although the study aim was to detect the effects of caffeine on measures of sleep disturbance, the effects of caffeine on sleep stages was also explored. Caffeine administration at each of the 3 time points significantly reduced minutes of stage 1 and 2 sleep combined relative to placebo (**Table 3**). In each case, reduction in stage 1 and 2 sleep (combined measure) from placebo were similar, ranging from -40.6 min for caffeine administered at bedtime to -44.1 min for caffeine administered 6 h before bedtime, with no differences between the time of administration of caffeine. Reductions in the duration of slow wave sleep were observed for all 3 caffeine conditions, but reached significance only for

administration at bedtime and 6 h before bedtime. As expected, caffeine had no effect on REM sleep for any time of administration. There were no significant differences in percentage of sleep stage distributions between caffeine conditions.

DISCUSSION

The results of this study suggest that 400 mg of caffeine taken 0, 3, or even 6 hours prior to bedtime significantly disrupts sleep. Even at 6 hours, caffeine reduced sleep by more than 1 hour. This degree of sleep loss, if experienced over multiple nights, may have detrimental effects on daytime function.[40-42] Thus, the present results suggest the common practice of afternoon consumption of caffeine should at a minimum be restricted to before 17:00, particularly with regard to the moderate-large doses of caffeine commonly found in increasingly popular premium coffees and energy drinks. Future research is needed to determine the sleep disruptive effects of afternoon caffeine in insomniacs relative to normal sleepers.

Caffeine-induced sleep disturbance was detected by both the self-report diary and objective sleep measures when taken at bedtime and 3 hours prior to bedtime, whereas only the objective measure detected differences when caffeine was taken 6 hours prior to bedtime. The discrepancy in subjective-objective measures is particularly evident in cases where awakenings may be relatively short lived as in the case of sleep fragmentation.[43] Sleep fragmentation is a characteristic of nocturnal caffeine administration,[17] and therefore may explain some of the subjective-objective discrepancy observed in the present study.

We believe this discrepancy (i.e., lack of subjective awareness of caffeine-induced sleep disturbance) is an important finding of the present study and suggests one potential reason for non-adherence to sleep hygiene recommendations regarding caffeine intake close to bedtime. The lack of perceived sleep disruption during early evening administration combined with the objective findings of the present study argue for continued education regarding the sleep disruptive effects of caffeine.

Disturbed sleep due to caffeine administered in divided doses within 3 hours of bedtime, including reduced total sleep time and stage 1-2 sleep, have previously been reported.[28] The finding that sleep was disrupted even 6 hours prior to bedtime adds to our current knowledge of caffeine effects on sleep and suggests that larger doses will have an important impact even during daytime hours. Importantly, future studies should monitor blood levels of caffeine to determine if individual differences in absorption and or elimination during afternoon administration are directly related to the degree of nocturnal sleep disruption.

The study has several limitations. As plasma concentrations were not obtained, we were unable to determine the extent to which such variations influenced the disruptive sleep effects observed. However, this possibility was offset by the repeated measures design limiting the effects of intersubject variability related to caffeine sensitivity, absorption, and bioavailability and individual differences in habitual sleep patterns.[44] Another limitation was the small number of subjects assessed in the present study, which may have contributed to reduced power to detect caffeine effects on sleep disturbance using self-report. Intermittent exposure to caffeine used in the present design precludes us from making any conclusions regarding possible tolerance to the effects observed. Habitual caffeine use by participants may have added to total caffeine exposure and increased the effects on sleep disturbance, although the crossover design minimizes the possibility of the influence of individual differences in habitual caffeine consumption. As the device used to assess sleep stages has only recently been validated against polysomnographic measures of sleep the effects of caffeine on sleep architecture found in the present study should be considered preliminary, particularly the effects on stage 2. Finally, the use of young/middle-age participants with moderate habitual caffeine use limits the generalizability of the findings. Future studies are required to determine if the effects would be elevated in samples of older subjects where nocturnal sleep disruption is more common or in naïve caffeine users.

Tolerance to the alertness enhancing effects of caffeine develops quickly,[45] and the practice of using high doses of caffeine to improve alertness is becoming increasingly common among both adults and adolescents.[46,47] However, the risks of caffeine use in terms of sleep disturbance are underestimated by both the general population and physicians.[17] The present results show that high doses of caffeine will have an important negative impact upon sleep duration in the home environment even when used in the early evening hours.

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DISCLOSURE STATEMENT