

Caffeine Effects on Sleep Taken 0, 3, or 6 hours Before Going to Bed

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Christopher L. Drake has received funding from Merck, Teva, and Zeo. He has consulted for Teva. He has been a speaker for Teva, Purdue, and Jazz.

Timothy Roehrs has been a speaker for Pfizer. He has been a consultant for Sanofi Aventis.

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Thomas Roth has served as a consultant for Abbott, Accadia, AstraZenca, Aventis, AVER, Bayer, BMS, Cypress, Ferrer, Glaxo Smith Kline, Impax, Intec, Jazz, Johnson and Johnson, Merck, Neurocrine. He has received research support from Cephalon, Merck, Transcept. He has been a speaker bureau for Purdue..

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Abstract

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, no studies have investigated the effects of a given dose of caffeine administered at different times of day on 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 showed that 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 ($p < .05$ 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

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 (Substance Abuse and Mental Health Services Administration, Center for Behavioral Health Statistics and Quality. (January 10, 2013). *The DAWN Report: Update on Emergency Department Visits Involving Energy Drinks: A Continuing Public Health Concern*. Rockville, MD.) The increase in ED visits in association with cardiovascular and other adverse events has been labeled a “rising public health problem in the US” (<http://rt.com/usa/news/energy-drink-emergencies-126/>) and has led the Food and Drug Administration to investigate the cardiovascular safety of high caffeine content beverages. 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.⁹ One recent population-based study of 18-58 year olds (mean age = 28.5 years of age) estimated that 90% of individuals consume caffeine in the afternoon (12 noon – 6 pm) and 68.5% of people consume caffeine in the evening (6 pm – 12 midnight).¹⁰

Caffeine content in beverages and foods is increasing in terms of dose and availability thus recent estimates of total daily caffeine consumption suggest that the average person consumes 319.32 ± 180.94 mg of caffeine per day.¹⁰ 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 high caffeine content of premium

coffee.¹¹ Such investigations are also critical due to increased caffeine use in younger age groups where chronic sleep restriction is also increasingly common.^{8, 12, 13} Indeed, recent data shows that in younger samples 37% report first use of caffeine during the day at 5 pm or later.¹⁴

The sleep disruptive effects of caffeine administration at bedtime are well documented.¹⁵ Indeed, caffeine administration has been used as a model of insomnia.¹⁶ Dose-response studies demonstrate that increasing doses of caffeine administered at or near bedtime are associated with significant sleep disturbance.¹⁷⁻¹⁹ Indeed, one of the most common recommendations for good 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. Because the elimination half-life of caffeine administered to healthy adults is quite variable ranging between 2.7-9.9 hours^{20, 21}, specific recommendations on what time of day to discontinue caffeine use vary widely from four^{22, 23} to eleven²⁴ hours prior to bedtime. 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.²⁵ In one of the few studies that evaluated caffeine administered in the evening, a 200 mg dose was used with 100 mg 3 hours before bed and an additional 100 mg 1 hour before bed. The caffeine condition reduced sleep efficiency by 5%, prolonged sleep latency by 12-16 minutes and reduced total sleep time

by 25-30 minutes relative to placebo.²⁶ However, this study investigated the combined effects of the two doses, and therefore information on the comparative effects of time of administration could not be determined. A study that administered caffeine (200 mg) 16 hours 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 bedtime²⁷ 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. In the present study our aim was 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.

Method

Subjects:

Participants were recruited from the Detroit tri-county area through advertisements. The study group was comprised of 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 \pm standard deviation)²⁸ and the Epworth Sleepiness Scale (3.9 ± 1.5).²⁹ As polysomnography was not performed, sleep apnea was screened out during the clinical evaluation using the Berlin Questionnaire.³⁰ Habitual sleep data was determined by self-report with a one week sleep

diary the week prior to participation. Only individuals with a habitual total sleep times between 6.5 and 9 hours, with a sleep onset of less than 30 minutes 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.³¹ If home brewed coffee was indicated an 8oz cup was calculated to be equal to 100mg of caffeine (1 serving). ; Subjects were selected if they met either of the following criteria 1) at least 3 servings of caffeine in any single day or 2) ≥ 5 caffeinated servings per week. Subjects who consumed more than 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.³² The mean body mass index 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 did not go to bed at the scheduled times 3 out of 4 nights, and one subject did not comply with 8 hours time in bed on all four study nights. Thus, 12 subjects completed the full protocol (6F, 6M; aged 19-48; mean age 29.3 ± 7.6). Mean baseline total sleep time based on the one week sleep diary was $7.8 \pm .5$ hours per night. 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 2100 and 0100, wake times between 0600 and 0900, time in bed of 6.5-9 hours and no habitual napping. Study protocol began following one week of baseline sleep diaries. Each subject completed four conditions/nights which consisted of 400mg of caffeine taken in pill form at either 6, 3, or 0 hours prior to scheduled bedtime with identical appearing placebo given at each of the other times. Thus, subjects were instructed to take three pills each study day with one of the pills being caffeine and the other two 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 was collected in the morning for all nights (experimental and washout). Subjects were given caffeine pills in an alarm activated pill case, and a scheduled regular bedtime and

wake time based on their sleep diary to be maintained 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 subject's habitual bedtime and the alarm was designed to sound until the subject manually turned it off. In order to avoid any potential caffeine withdraw effects subjects were allowed to use caffeine during the study, however, subjects were instructed to refrain from consuming any alcohol or caffeine after 1600 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.³³

Sleep disturbance was also measured objectively using a widely available and previously validated in-home sleep monitor.³⁴ 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 as well as actigraphy, with respect to sleep disturbance measures.³⁴ The intraclass correlation coefficients between the monitor and PSG were above 0.90 for TST and SE, and above 0.81 for LPS and 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.³⁴ 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.³⁵ A separate study also found similarly moderate to high agreement between the device and PSG but with underestimation of wake epochs.³⁶ Finally, the sensitivity of the ambulatory monitoring device to sleep extension in the home environment has also been documented.³⁷ Sleep variables measured included; total sleep time (TST), latency to persistent sleep (first epoch of 10 minutes of consecutive sleep; LPS), wake time during sleep (WTDS), and sleep efficiency (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 has been reported previously, an important limitation regarding sleep architecture is that the device does not provide separate measures for stage 1 and stage 2 sleep and 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 three 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 calling in to a time stamped answering machine to verify that study drug was taken at each pre determined time period (6 hours prior, 3 hours 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 from normality occurred. Significant omnibus results were followed by post-hoc analyses to identify pairwise differences. A two-tailed alpha level of .05 was used for all statistical tests. A non-parametric Friedman's 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 seven-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 ($p > .05$). There were no differences in non-study related caffeine intake between any of the 4 conditions: 0hr = 126.1 ± 164.9 mg, 3hr = 139.1 ± 199.2 mg, 6hr = 154.1 ± 199.2 mg, placebo = 139.4 ± 189.6 ($p > .05$ 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 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 hours prior to bedtime reaching statistical significance. Caffeine administered 6 hours prior to bedtime reduced total sleep time by 41 minutes which approached significance ($p = .08$). Significant effects were observed for sleep latency with caffeine taken 3 hours before bed

having the greatest effect relative to placebo. Although caffeine taken 6 hours before bedtime more than doubled the reported time take to fall asleep this effect did not reach statistical significance ($p = .06$). No significant effects were observed for WTDS, sleep efficiency, 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) are shown in Table 3. Evidence for the disruptive effects of caffeine was demonstrated for each of the sleep duration/continuity parameters. The different caffeine administration times (0, 3 or 6 hrs before bed) did not produce differential sleep disruption between the three active caffeine conditions. For total sleep time, reductions in duration relative to placebo were significant at each of the caffeine administration time points, reducing total sleep time between 1.1 to 1.2 hours. The -3 hour 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 hours 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 three caffeine administration times, reaching statistical significance for the 6 hour (+ 8 min) and 3 hour (+ 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 hours before bedtime, with no differences between the time of administration of caffeine. Reductions in the duration of slow wave sleep were observed for all three caffeine conditions, but reached significance only for administration at bedtime and 6 hours 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 or 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.³⁸⁻⁴⁰ Thus, the present results suggest the common practice of afternoon consumption of caffeine should at a minimum be restricted to before 5 PM, 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.⁴¹ Sleep fragmentation is a characteristic of nocturnal caffeine administration,¹⁵ and therefore may explain some of the subjective-objective discrepancy observed in the present study. Indeed, 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 Stage1- 2 sleep, have previously been reported.²⁶ 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. Because plasma or salivary concentrations of caffeine were not obtained, we were not able 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.⁴² 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 cross over 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 quickly⁴³ and the practice of using high doses of caffeine to improve alertness is becoming increasingly common among both adults and adolescents.^{44, 45} However the risks of caffeine use in terms of sleep disturbance are underestimated by both the general population and physicians.¹⁵ 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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Table 1: Baseline Demographics and Sleep Diary Measures

<u>Baseline Demographics</u>	N	Mean ± SD
Gender	12	6F
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
<u>Baseline Sleep Diary</u>		Mean ± SD
Total Sleep Time (hrs)	12	7.63 ± .55
Sleep latency (mins)	12	22.26 ± 26.46
Wake Time During Sleep (mins)	12	7.28 ± 7.84
Sleep Efficiency (%)	12	94.5 ± 3.25
Time In Bed (hrs)	12	8.10 ± .53
Sleep Quality	12	6.61 ± 1.62

ISI, Insomnia Severity Index; BMI, Body Mass Index; ESS, Epworth Sleepiness Scale; PSQI, Pittsburgh Sleep Quality Index; GSAW, Global Sleep Assessment Questionnaire; TST, Total Sleep Time; SE, Sleep Efficiency; TIB, Time in Bed; SQ, Sleep Quality

Table 2. Means \pm 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 (mins)	21.00 \pm 8.99	56.67 \pm 74.23	62.50 \pm 66.18*	44.17 \pm 44.56^	3.06	.04
Total Sleep Time (hrs)	7.82 \pm .54	6.92 \pm 1.10*	6.77 \pm .95*	7.13 \pm .93^	4.14	.01
Wake Time During Sleep (Mins)	11.00 \pm 11.24	9.18 \pm 9.41	17.67 \pm 33.99	9.27 \pm 14.01	.71	.55
Sleep Efficiency %	93.60 \pm 3.47	86.43 \pm 13.87	83.98 \pm 12.68	89.05 \pm 9.22	2.65	.07
Sleep Quality	6.20 \pm 2.04	5.83 \pm 2.33	5.17 \pm 1.53	5.67 \pm 2.19	.63	.60

Follow up pairwise comparisons where omnibus F-values are significant : *p <.05 vs. placebo, ^p <.10

Table 3. Objective Sleep Measures for Each Condition (Mean \pm 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 (mins)	20.59 \pm 9.79	43.0 \pm 38.93	37.82 \pm 29.91	44.68 \pm 54.60	2.05	.13
Total Sleep Time (hrs)	7.68 \pm 0.85	6.60 \pm 1.10*	6.54 \pm 1.36*	6.50 \pm 1.32*	3.43	.03
Wake Time During Sleep (mins)	9.55 \pm 14.73	27.04 \pm 40.06	37.18 \pm 43.0*	17.59 \pm 22.28*	3.29	.03
Sleep Efficiency %	91 \pm 5.71	83.1 \pm 12.11*	82.51 \pm 12.73*	82.33 \pm 12.15*	7.50	.058 [#]
Stage 1 & 2 (mins)	266.77 \pm 40.15	226.17 \pm 57.75*	222.68 \pm 62.24*	222.82 \pm 48.83*	3.66	.02
Stage 1 & 2 (%)	58.02 \pm 7.37	56.47 \pm 7.77	56.77 \pm 10.48	57.28 \pm 6.26	.22	.88
Slow Wave Sleep (mins)	71.45 \pm 26.48	56.67 \pm 21.48*	57.0 \pm 16.78	48.91 \pm 15.81*	4.26	.01
Slow Wave Sleep (%)	15.47 \pm 5.28	14.47 \pm 4.85	14.84 \pm 3.87	12.71 \pm 3.88	1.22	.32
REM (mins)	123.27 \pm 33.89	114.36 \pm 28.53	112.5 \pm 46.57	118.73 \pm 39.75	.30	.83
REM (%)	26.62 \pm 6.35	29.21 \pm 7.19	28.39 \pm 11.25	29.99 \pm 6.54	.88	.46

*p< .05 pairwise comparisons vs. placebo; [#] Nonparametric related samples test of Friedman's two-way analysis of variance by ranks was performed as data was not normally disturbed following transformation.

References

1. Kamimori GH, Johnson D, Thorne D, Belenky G Multiple caffeine doses maintain vigilance during early morning operations. *Aviation, space, and environmental medicine* 2005;76:1046-50.
2. Bonnet MH, Gomez S, Wirth O, Arand DL The use of caffeine versus prophylactic naps in sustained performance. *Sleep: Journal of Sleep Research & Sleep Medicine* 1995.
3. Kohler M, Pavy A, VAN DEN HEUVEL C The effects of chewing versus caffeine on alertness, cognitive performance and cardiac autonomic activity during sleep deprivation. *Journal of sleep research* 2006;15:358-68.
4. Walsh JK, Muehlbach MJ, Humm TM, Dickins QS, Sugerman JL, Schweitzer PK Effect of caffeine on physiological sleep tendency and ability to sustain wakefulness at night. *Psychopharmacology* 1990;101:271-73.
5. Reyner LA, Horne JA Early morning driver sleepiness: effectiveness of 200 mg caffeine. *Psychophysiology* 2000;37:251-56.
6. Wyatt JK, Cajochen C, Cecco A, Czeisler CA, Dijk D-J Low-dose repeated caffeine administration for circadian-phase-dependent performance degradation during extended wakefulness. *SLEEP-NEW YORK THEN WESTCHESTER-* 2004;27:374-82.
7. Drake CL, Roehrs T, Turner L, Scofield HM, Roth T Caffeine reversal of ethanol effects on the multiple sleep latency test, memory, and psychomotor performance. *Neuropsychopharmacology* 2003;28:371-78.
8. McCusker RR, Goldberger BA, Cone EJ Caffeine content of specialty coffees. *J Anal Toxicol* 2003;27:520-2.
9. Nordt SP, Vilke GM, Clark RF et al. Energy drink use and adverse effects among emergency department patients. *J Community Health* 2012;37:976-81.
10. Penolazzi B, Natale V, Leone L, Russo PM Individual differences affecting caffeine intake. Analysis of consumption behaviours for different times of day and caffeine sources. *Appetite* 2012;58:971-7.
11. Reissig CJ, Strain EC, Griffiths RR Caffeinated energy drinks--a growing problem. *Drug Alcohol Depend* 2009;99:1-10.
12. Roberts RE, Roberts CR, Xing Y Restricted Sleep Among Adolescents: Prevalence, Incidence, Persistence, and Associated Factors. *Behavioral Sleep Medicine* 2010;9:18-30.
13. Carskadon MA Sleep in adolescents: the perfect storm. *Pediatr Clin North Am* 2011;58:637-47.
14. Bryant Ludden A, Wolfson AR Understanding adolescent caffeine use: connecting use patterns with expectancies, reasons, and sleep. *Health Educ Behav* 2010;37:330-42.
15. Roehrs T, Roth T Caffeine: sleep and daytime sleepiness. *Sleep Med Rev* 2008;12:153-62.
16. Bonnet MH, Arand DL Caffeine use as a model of acute and chronic insomnia. *Sleep* 1992;15:526-36.
17. Karacan I, Thornby JI, Anch M, Booth GH, Williams RL, Salis PJ Dose-related sleep disturbances induced by coffee and caffeine. *Clin Pharmacol Ther* 1976;20:682-9.
18. Lasagna L Dose-related sleep disturbances induced by coffee and caffeine. *Clin Pharmacol Ther* 1977;21:244.

19. Yanik G, Glaum S, Radulovacki M The dose-response effects of caffeine on sleep in rats. *Brain Res* 1987;403:177-80.
20. Blanchard J, Sawers SJ Comparative pharmacokinetics of caffeine in young and elderly men. *J Pharmacokinet Biopharm* 1983;11:109-26.
21. Blanchard J, Sawers SJ The absolute bioavailability of caffeine in man. *Eur J Clin Pharmacol* 1983;24:93-8.
22. Dement WC. How to Sleep Well. In: <http://www.stanford.edu/~dement/howto.html>. Stanford, 11/12, 2011
23. National Sleep Foundation. Sleep Hygiene. In: <http://www.sleepfoundation.org/article/ask-the-expert/sleep-hygiene>. Alexandria, 2012
24. American Academy of Sleep Medicine. SleepEducation.com. In: <http://www.sleepeducation.com/Hygiene.aspx>. Chicago, 2012
25. Bonnet M, Tancer M, Uhde T, Yeragani VK Effects of caffeine on heart rate and QT variability during sleep. *Depress Anxiety* 2005;22:150-5.
26. Drapeau C, Hamel-Hebert I, Robillard R, Selmaoui B, Filipini D, Carrier J Challenging sleep in aging: the effects of 200 mg of caffeine during the evening in young and middle-aged moderate caffeine consumers. *J Sleep Res* 2006;15:133-41.
27. Landolt HP, Werth E, Borbely AA, Dijk DJ Caffeine intake (200 mg) in the morning affects human sleep and EEG power spectra at night. *Brain Res* 1995;675:67-74.
28. Bastien CH, Vallieres A, Morin CM Validation of the Insomnia Severity Index as an outcome measure for insomnia research. *Sleep Med* 2001;2:297-307.
29. Johns MW A new method for measuring daytime sleepiness: the Epworth sleepiness scale. *Sleep* 1991;14:540-5.
30. Netzer NC, Stoohs RA, Netzer CM, Clark K, Strohl KP Using the Berlin Questionnaire to identify patients at risk for the sleep apnea syndrome. *Ann Intern Med* 1999;131:485-91.
31. McCusker RR, Goldberger BA, Cone EJ Caffeine content of energy drinks, carbonated sodas, and other beverages. *J Anal Toxicol* 2006;30:112-4.
32. Knesevich JW, Biggs JT, Clayton PJ, Ziegler VE Validity of the Hamilton Rating Scale for depression. *Br J Psychiatry* 1977;131:49-52.
33. Carney CE, Buysse DJ, Ancoli-Israel S et al. The consensus sleep diary: standardizing prospective sleep self-monitoring. *Sleep* 2012;35:287-302.
34. Shambroom JR, Fabregas SE, Johnstone J Validation of an automated wireless system to monitor sleep in healthy adults. *J Sleep Res* 2012;21:221-30.
35. Griessenberger H, Heib D, Kunz A, Hoedlmoser K, Schabus M Assessment of a wireless headband for automatic sleep scoring. *Sleep and Breathing* 2012;1-6.
36. Tonetti L, Cellini N, de Zambotti M et al. Polysomnographic validation of a wireless dry headband technology for sleep monitoring in healthy young adults. *Physiology & Behavior* 2013;118:185-88.
37. Gumenyuk V, Roth T, Korzyukov O, Jefferson C, Bowyer S, Drake CL Habitual short sleep impacts frontal switch mechanism in attention to novelty. *Sleep* 2011;34:1659-70.
38. Belenky G, Wesensten NJ, Thorne DR et al. Patterns of performance degradation and restoration during sleep restriction and subsequent recovery: a sleep dose-response study. *J Sleep Res* 2003;12:1-12.
39. Drake CL, Roehrs TA, Burduvali E, Bonahoom A, Rosekind M, Roth T Effects of rapid versus slow accumulation of eight hours of sleep loss. *Psychophysiology* 2001;38:979-87.

40. Van Dongen HP, Maislin G, Mullington JM, Dinges DF The cumulative cost of additional wakefulness: dose-response effects on neurobehavioral functions and sleep physiology from chronic sleep restriction and total sleep deprivation. *Sleep* 2003;26:117-26.
41. Levine B, Roehrs T, Stepanski E, Zorick F, Roth T Fragmenting sleep diminishes its recuperative value. *Sleep* 1987;10:590.
42. Bchir F, Dogui M, Ben Fradj R, Arnaud MJ, Saguem S Differences in pharmacokinetic and electroencephalographic responses to caffeine in sleep-sensitive and non-sensitive subjects. *C R Biol* 2006;329:512-9.
43. Zwyghuizen-Doorenbos A, Roehrs TA, Lipschutz L, Timms V, Roth T Effects of caffeine on alertness. *Psychopharmacology (Berl)* 1990;100:36-9.
44. Howland J, Rohsenow DJ Risks of energy drinks mixed with alcohol. *JAMA* 2013;309:245-6.
45. Sepkowitz KA Energy drinks and caffeine-related adverse effects. *JAMA* 2013;309:243-4.