Alterations in Cyclic Alternating Pattern Associated with Phase Advanced Sleep are Differentially Modulated by Gaboxadol and Zolpidem

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Objective: To evaluate cyclic alternating pattern (CAP) in a phase advance model of transient insomnia and the effects of gaboxadol and zolpidem.
Design: A randomized, double-blind, cross-over study in which habitual sleep time was advanced by 4 h.
Setting: 6 sleep research laboratories in US
Participants: 55 healthy subjects (18-57 y)
Interventions: Gaboxadol 15 mg (GBX), zolpidem 10 mg (ZOL), and placebo (PBO).
Measurements: Routine polysomnographic (PSG) measures, CAP, spectral power density, and self-reported sleep measures
Results: The phase advance model of transient insomnia produced significant changes in CAP parameters. Both GBX and ZOL significantly and differentially modified CAP parameters in the direction of more stable sleep. GBX brought the CAP rate in stage 1 sleep and slow wave sleep (SWS) closer to baseline levels but did not significantly change the CAP rate in stage 2. ZOL reduced the CAP rate in stage 2 to near baseline levels, whereas the CAP rate in stage 1 and SWS was reduced substantially below baseline levels. The CAP parameter A1 index (associated with SWS and sleep continuity) showed the highest correlation with self-reported sleep quality, higher than any traditional PSG, spectral, or other self-reported measures.
Conclusion: Disruptions in CAP produced by phase advanced sleep were significantly and differentially modulated by gaboxadol and zolpidem. The relative independence of CAP parameters from other electrophysiological measures of sleep, their high sensitivity to sleep disruption, and their strong association with subjective sleep quality suggest that CAP variables may serve as valuable endpoints in future insomnia research.
Keywords: Gaboxadol, zolpidem, phase advance, transient insomnia, CAP, extrasynaptic GABA agonist, spectral analysis
Citation: Svetnik V; Ferri R; Ray S; Ma J; Walsh JK; Snyder E; Ebert B; Deacon S. Alterations in cyclic alternating pattern associated with phase advanced sleep are differentially modulated by gaboxadol and zolpidem. *SLEEP* 2010;33(11):1562-1570.

CYCLIC ALTERNATING PATTERN (CAP) IS A SPONTANEOUS RHYTHM DETECTABLE DURING NREM SLEEP CHARACTERIZED BY EEG OSCILLATIONS BELIEVED to correspond to periods of cyclic activation and unstable sleep depth. Each oscillation is composed of an EEG transient (phase A of the cycle) separated by intervals of background activity (phase B of the cycle). Three main CAP phase A EEG patterns have been described: Subtype A1 is based on the type and frequency of EEG synchronized slow waves; subtype A3 on the EEG fast rhythms; and subtype A2 on a combination of both.[1] The hierarchical activation from slower EEG patterns (moderate autonomic activation without sleep disruption)[2-4] to faster EEG patterns (robust activation associated with visible sleep fragmentation) can have different meanings. A1 subtypes are associated with SWS and sleep continuity; A2 and A3 are associated with initiation of REM and relative arousability.[5]

Sequences of CAP are present in NREM sleep, and the ratio of CAP time to NREM sleep time, i.e., CAP rate, has been described as a physiological marker of sleep instability.[5-7] It has been reported that CAP rate increases[8] in patients with insomnia while the amount of standard EEG arousals does not necessarily increase[9,10] indicating that CAP is a sensitive marker of unstable sleep.[11,12] It has also been found[13-17] that CAP was significantly correlated with self-reported measures of sleep quality, and more strongly than traditional PSG measures. Such findings suggest that CAP can be used not only as a marker of sleep disruption but also for evaluating insomnia treatments with regards to their effects on sleep stability and to predict self-reported sleep quality.

The present work applies CAP analysis to PSG data from a large clinical study evaluating sleep restoring effects of GBX in a human model of transient insomnia.[18] This current analysis is a post hoc evaluation of this study data with the focus on CAP. Since ZOL was used as an active reference drug, the study provides a unique opportunity to evaluate effects on CAP of two sleep agents with different mechanisms of actions. Although GBX is no longer in clinical development for insomnia, it represents a useful pharmacological probe to evaluate the effects of enhancing SWS/SWA through direct $GABA_A$ receptor mechanisms. GBX has functional selectivity for the d-containing receptor $GABA_A$ subtype that is insensitive to benzodiazepines. By comparison, ZOL allosterically modulates $GABA_A$ receptors. Therefore, a comparison of the 2 drugs with respect to CAP may help to further understand the differences in sleep state stability between these 2 mechanisms of action.

The phase advance sleep model of transient insomnia used in the study by Walsh et al.[18] involves moving bedtime earlier by 2-5 h and produces reliable sleep disruption in otherwise

Submitted for publication December, 2009
Submitted in final revised form April, 2010
Accepted for publication April, 2010
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good sleepers. The first hours of the advanced sleep period occur during the "forbidden zone" for sleep, when the circadian arousal system promotes alertness, reducing the likelihood of sleep.[19] A key advantage of the acute phase advance model is to produce the transient insomnia known to result from time zone shifts, which typically prevents people from obtaining adequate sleep after travelling to a new time zone. Drug treatment effects have been demonstrated in prior studies using a phase advance procedure.[20,21] Walsh et al.[18] presented results on the effects of GBX on conventional polysomnographic (PSG) and spectral measures of NREM sleep in this model.

This paper extends the prior findings of Walsh et al.[18] using post hoc analysis of the same data to test for CAP effects. Firstly, it evaluates the effects of transient insomnia on CAP parameters. Secondly, it compares effects of transient insomnia on CAP parameters and its effects on spectral and traditional PSG measures. Thirdly, it compares the differential effects of the 2 drugs, ZOL and GBX, on CAP parameters and assesses if the changes are in the direction of a more stable, "normal" sleep when subjects in this study are allowed to sleep during their habitual bedtime. Finally, taking advantage of having a multitude of objective and subjective sleep measures, this paper compares them with respect to their correlations with self-reported sleep quality.

Presented results may also serve to define new valuable endpoints in future insomnia research and potentially other diseases where an altered sleep pattern is considered a core component of the disease.

METHODS

Subjects and Screening Procedures

Data analyzed here was collected from a randomized, double-blind, placebo-controlled, cross-over study. Subjects were excluded if they had any chronic sleep disturbance based upon the DSM-IV sleep criteria and a Pittsburgh Sleep Quality Index (PSQI)[22] score > 5. Subjects were required to report normal sleep patterns during the past 3 months, with normal defined as a standard bedtime between 21:00 and 24:00 on ≥ 5 of 7 nights per week and reported average sleep duration between 6.5 and 8.5 h. Shift workers or subjects who maintained/ initiated irregular sleep/wake schedules during the preceding month or during the study were excluded. Additional exclusion criteria can be found in Walsh et al.[18]

Procedures

This study, described in detail in Walsh et al.,[18] was conducted at 6 sleep laboratories in the United States under a common protocol which was approved by an institutional review board for each site. Prior to initiating study procedures, subjects gave written informed consent. The study consisted of a screening session, 5 treatment sessions, and a follow-up visit. In the original study, there were 82 healthy subjects (45 females, 37 males) with a mean age 31.8 years (SD 10.0, range 18.7-57.5 years) in the per protocol set. The treatments consisted of GBX (5 mg, 10 mg, and 15 mg), ZOL (10 mg), and placebo (PBO); however, in this paper we only focus on the results obtained at baseline (see below), and after PBO, GBX, and ZOL in 55 subjects randomly selected from the per protocol set. The 2 highest doses of gaboxadol were chosen as the most likely to show an effect in this exploratory post hoc analysis.

On Day 1 of the first treatment session, the subjects were randomly allocated to one of 10 treatment sequences in a cross-over design. Each treatment session consisted of 2 consecutive nights at the sleep laboratory for PSG evaluation. On the first night (Night 1) of each treatment session, subjects received PBO in a single-blind fashion 30 min before their habitual bedtime. On the second night (Night 2) of the session, subjects received PBO, ZOL, or one of the GBX doses in a double-blind fashion. Bedtime and rise time on Night 2 was 4 h earlier than on Night 1. Data from Night 1 preceding Night 2 of the PBO condition were chosen as the reference.[18] These data represent a sample of the "normal" condition without 4-h sleep advancement. Throughout this paper the term "baseline" is used to refer to this condition.

The size of the random sample, 55 patients, was chosen as a compromise between having a representative sample, 67% of all patients, and our capacity for visual scoring of CAP parameters. There were 30 females and 25 males with a mean age of 31.3 years (SD 9.7, range 18.7-57.0 years) in this random sample, thus matching the distribution in the per protocol set of the original paper. The proportions of patients allocated to the treatment sequences were also similar; for 9 of 10 sequences in the random sample of 55 patients the proportions were within 0.7% of those in per protocol set. In the remaining sequence, the difference was 1.3%. Visual PSG scoring was performed by Clinilabs (New York, US) with scorers blinded to the treatment codes and study conditions.

PSG and Self-Reported Variables

The PSG variables based on the visual scoring according to Rechtschaffen and Kales rules[23] included total sleep time (TST; time spent in NREM and REM sleep plus the duration of body movement, MVT), latency to persistent sleep (LPS; lights out to the beginning of 10 consecutive minutes of uninterrupted sleep), wake after sleep onset (WASO; the total amount of time spent awake after onset of persistent sleep until lights on), number of awakenings (NAW; the number of wake epochs after sleep onset separated by any of the sleep intervals of at least one epoch duration), time spent in REM sleep (REM), REM sleep latency (RSL; time from sleep onset to the first epoch of REM), and time spent in sleep stages 1 and 2 and in slow wave sleep (SWS, as time in sleep stages 3 and 4 combined).

Self-reported efficacy measures of sleep were collected on a morning questionnaire and included time to sleep onset (sTSO), total sleep time (sTST), number of awakenings (sNAW), and total duration of night awakenings (sWASO).

The Leeds Sleep Evaluation Questionnaire (LSEQ)[24] was performed on Day 1 and Day 2 of each treatment period approximately 30 min following lights on. The LSEQ is a self-rating questionnaire pertaining to different aspects of sleep, of which quality of sleep (QOS) is relevant to the present paper.

EEG Spectral Analysis

An internally developed and validated system was used to remove EEG segments containing artifacts and then calculate EEG power spectra for NREM sleep segments for each sub-

ject-treatment combination. The spectral resolution was equal to 0.25 Hz within the frequency range from 0.25 to 32.0 Hz. Values of the power spectra were averaged in order to calculate the average power within the following 8 frequency bands: slow delta (sDelta, 0.25-0.5 Hz), slow wave activity (SWA, 0.75-4.5 Hz), theta (4.75-7.75 Hz), alpha (8.0-12.0 Hz), sigma (12.25-15.0 Hz), beta1 (15.25-20.0 Hz), beta2 (20.25-25 Hz), and beta3 (25.25-32 Hz). Due to the somewhat poor quality of some of the recordings, the corresponding band powers were abnormally large or small in some or all frequency bands. To reduce the influence of these values on the statistical estimates and inferences, band power values for all 275 recordings (5 conditions × 55 patients) were pooled together separately for each band, and then the highest and lowest 2.5% of values in each band pool of data were excluded.

Cyclic Alternating Pattern

All PSG signals, converted to European Data Format (EDF), as well as the corresponding and synchronized time series of sleep stages, were transferred in a blinded fashion to the CAP scorer. The EDF files were imported into the Hypnolab 1.2 sleep software (SWS Soft, Italy). All the recordings were visually scored by one expert CAP scorer who was blind to the study condition and night; the parameters derived were tabulated for statistical analysis. CAP was scored following the criteria of Terzano et al.[1] CAP is a periodic EEG activity occuring during NREM sleep and characterized by repeated spontaneous sequences of transient events (phase A), recurring at intervals up to 2 min. The return to background activity identifies the interval that separates the repetitive elements (phase B). In particular, phase-A candidates are scored within a CAP sequence only if they precede and/or are followed by another phase A in the temporal range of 2-60 s. For example, if there are 3 consecutive A-phases followed by a NCAP condition, the CAP sequence is stopped at the end of the second B-phase and the last (third) A-phase is quantified as non-CAP. This is because the CAP procedure is based on the succession of complete CAP cycles (phase A + phase B).

CAP A phases have been subdivided into a 3-stage hierarchy of arousal strength:

A1: A phase with synchronized EEG patterns (intermittent alpha rhythm in stage 1; sequences of K-complexes or delta bursts in the other NREM stages) associated with mild or trivial polygraphic variations;

A2: A phase with desynchronized EEG patterns preceded by or mixed with slow high-voltage waves. These waves include K-complexes with alpha and beta activities, k-alpha, and arousals with slow wave synchronization associated with a moderate increase of muscle tone and/or cardiorespiratory rate;

A3: A phase with desynchronized EEG patterns alone (transient activation phases or arousals) or exceeding 2/3 of the phase A length, and coupled with a remarkable enhancement of muscle tone and/or cardiorespiratory rate.[1]

The following CAP parameters were measured:

a. CAP rate (percentage of total NREM sleep time occupied by CAP sequences);
b. duration of CAP cycles; number and duration of CAP sequences;
c. duration and percentage of A phase subtypes;
d. A1 index, A2 index, A3 index (number of A1, A2, or A3 subtypes per hour of NREM sleep);
e. duration of B phases.

Statistical Analysis

The main focus of this paper is the analysis of the transient insomnia model and treatment effects of GBX and ZOL on CAP variables, but we also included results showing the effects on PSG, spectral, and self-reported variables, some of which were presented in Walsh et al.[18] using a larger sample. The rationale was (a) to analyze these variables with respect to both baseline and placebo conditions; (b) to provide a basis for analysis of the transient insomnia effects on all variables so CAP parameters could be compared with traditional PSG endpoints, spectral measures, and subjective endpoints, as well as their associations with self-reported sleep quality; and (c) to show consistency of our results obtained with a smaller sample size with the results obtained in Walsh et al.[18]

To make variable distributions closer to normal, values of LPS, WASO, NAW, RSL, ST1, sTSO, sTST, sWASO, sNAW, and all frequency band powers were increased by 1.0 and then log transformed.

To estimate the treatment and phase advanced sleep effects, mixed effect models (SAS Proc Mixed[25]) were used separately for each variable of interest as the response. Models included terms for treatment, study site, period, and sequence as fixed effects and a term for subjects as a random effect. The LSMEANS option of SAS Proc Mixed[25] was used for estimation of means and standard errors as well as significance testing, and confidence intervals. Means and confidence intervals corresponding to the log-transformed variables were exponentiated, yielding estimates of the geometric means (or geometric mean ratios) and their confidence intervals.

To assess associations with the self-reported QOS, Spearman (rank) correlations[26] were calculated between the difference in baseline and PBO values in QOS and corresponding differences in the values of each of CAP, PSG, spectral, and self-reported variables. Spearman correlation was chosen instead of the more commonly used Pearson correlation, since the latter is more sensitive to outlying or high-leverage values of correlates.

RESULTS

Presenting Results for GBX 15 mg Dose

All statistical analyses were done for the data with both doses of GBX included. However, for compactness of the presentation and because effects of GBX 10 mg are generally similar or smaller that those of GBX 15, only results for GBX 15 mg are presented and discussed.

Standard PSG Measures

Table 1 shows least squares means (geometric means for log-transformed variables) for PSG variables on baseline and treatment nights, as well as magnitudes of the effects for treatment nights as compared to baseline and PBO. From baseline to PBO nights, LPS and WASO increased while TST, stage 2, and REM decreased.

Relative to placebo treatment during the phase shift night GBX and ZOL treatments significantly increased TST and SWS and reduced WASO. LPS and NAW were also reduced with

Table 1—Effects of the phase advance model (PBO and treatments vs. baseline) and treatment effects (treatments vs. PBO) on PSG measures. Least squares means or geometric means and (SE) or 95% (lower confidence limit, upper confidence limit)

PSG variables	Baseline	PBO	GBX	ZOL	Magnitude of Effect (mean difference or geometric mean ratio) vs. Baseline PBO	vs. Baseline GBX	vs. Baseline ZOL	vs. PBO GBX	vs. PBO ZOL
LPS (min)	12.45 (9.50,16.31)	21.22 (16.20,27.79)	15.67 (11.96,20.53)	12.79 (9.77,16.76)	1.70** (1.24,2.34)	1.26 (0.92,1.73)	1.03 (0.75,1.41)	0.74 (0.54,1.01)	0.60** (0.44,0.83)
TST (min)	425.62 (7.93)	371.04 (7.94)	402.51 (7.94)	418.83 (7.94)	−54.57*** (8.82)	−23.11** (8.82)	−6.79 (8.82)	31.46*** (8.83)	47.78*** (8.82)
WASO (min)	32.36 (25.83,40.55)	55.64 (44.41,69.72)	39.42 (31.46,49.40)	30.94 (24.69,38.76)	1.72*** (1.36,2.17)	1.22 (0.96,1.54)	0.96 (0.76,1.21)	0.71** (0.56,0.89)	0.56*** (0.44,0.70)
NAW	30.24 (26.91,33.99)	30.24 (26.91,33.98)	29.13 (25.92,32.74)	26.97 (24.00,30.31)	1.00 (0.89,1.12)	0.96 (0.86,1.08)	0.89* (0.80,1.00)	0.96 (0.86,1.08)	0.89* (0.80,1.00)
Stage 1 (min)	35.13 (30.26,40.79)	32.23 (27.76,37.43)	27.63 (23.80,32.09)	29.24 (25.18,33.95)	0.92 (0.80,1.05)	0.79*** (0.68,0.90)	0.83** (0.72,0.96)	0.86* (0.75,0.99)	0.91 (0.79,1.04)
Stage 2 (min)	253.03 (6.79)	228.28 (6.79)	236.44 (6.80)	266.20 (6.79)	−24.75*** (6.98)	−16.60* (6.98)	13.17 (6.98)	8.15 (6.99)	37.92*** (6.98)
SWS (min)	49.20 (4.99)	48.21 (4.99)	69.04 (4.99)	62.29 (4.99)	−0.98 (3.40)	19.84*** (3.40)	13.09*** (3.40)	20.83*** (3.40)	14.08*** (3.40)
REM (min)	84.81 (3.11)	60.08 (3.11)	65.84 (3.11)	58.03 (3.11)	−24.73*** (3.22)	−18.96*** (3.22)	−26.78*** (3.22)	5.76 (3.22)	-2.05 (3.22)
RSL (min)	86.23 (76.01,97.83)	98.59 (86.81,111.96)	85.84 (75.65,97.40)	92.83 (81.82,105.33)	1.14 (0.97,1.34)	1.00 (0.85,1.17)	1.08 (0.92,1.26)	0.87 (0.74,1.02)	0.94 (0.80,1.11)

*P ≤ 0.05, **P < 0.01, ***P < 0.001

both treatments but statistical significance was reached only under ZOL. Stage 1 was significantly reduced by GBX; stage 2 increased significantly under ZOL.

As a result of both treatments, LPS and WASO returned to values not statistically different from baseline. Although increased, TST and stage 2 did not return to baseline values under GBX. Duration of stage 1 was shorter under both GBX and ZOL than baseline, while SWS duration was increased compared to baseline. GBX increased the duration of REM sleep compared to placebo but was still significantly different from baseline values. REM duration under ZOL treatment was significantly lower than baseline.

Self-Reported Sleep Measures

Table 2 shows least squares means (geometric means for log-transformed variables) for self-reported variables as well as magnitudes of the effects. All variables showed a significant degradation in self-reported sleep properties under PBO in comparison to baseline, thus confirming the transient insomnia effect induced by phase advanced sleep.[18] Comparison with PBO showed a significant decrease in sWASO and sNAW, with both GBX and ZOL (and of comparable magnitude). A significant reduction in sTSO was observed under ZOL.

sTSO and sWASO were significantly longer and QOS significantly shorter than baseline under GBX but not under ZOL. The transient insomnia model did not induce a substantial increase in the number of sNAW, but both treatments showed a better return to baseline conditions than placebo.

Spectral Analysis

Table 3 shows least squares geometric means and magnitudes of the effects in band power spectra. With respect to baseline, phase advanced sleep did not produce a significant difference in power spectra in any of the considered frequency bands. On the other hand, GBX significantly increased power in SWA, sDelta and theta bands. ZOL significantly decreased power in the theta and alpha bands while significantly increasing activity in the sigma band. With respect to PBO, a significant reduction of the sigma power by GBX was observed in addition to the other effects, which were similar to the effects reported with respect to baseline.

CAP Analysis

Effect of sleep phase advance

Table 4 shows least squares means for CAP variables on baseline and treatment nights, as well as magnitudes of the effects for treatment nights as compared to baseline and PBO. Most of the variables showed significant differences caused by the phase advanced sleep. First, global CAP rate increased due to an increase in all NREM sleep stages; all 3 CAP A phase subtypes showed a significant increase in their number per hour of sleep (index). In addition to an increase in the number of CAP A phases, the phase-advance model induced a significant increase in duration of all CAP A phase subtypes, with a significant shortening of B phase. The CAP cycle (phases A + B) was significantly shortened. The duration of CAP sequences and percentage of A2 subtypes were significantly increased.

Effect of GBX

NREM and Stage 2 CAP rates remained higher than that of baseline. However, GBX induced a significant decline in CAP rate with respect to PBO during SWS and in stage 1, bringing them closer to the baseline.

Table 2—Effects of the phase advance model (PBO and treatments vs. baseline) and treatment effects (treatments vs. PBO) on self-reported variables. Least squares means or geometric means and (SE) or 95% (lower confidence limit, upper confidence limit)

Self-reported variables	Baseline	PBO	GBX	ZOL	Magnitude of Effect (mean difference or geometric mean ratio) vs. Baseline PBO	GBX	ZOL	vs. PBO GBX	ZOL
sTSO (min)	13.05 (10.55,16.15)	26.07 (21.07,32.26)	22.09 (17.82,27.38)	15.35 (12.40,19.00)	2.00*** (1.55,2.58)	1.69*** (1.31,2.19)	1.18 (0.91,1.52)	0.85 (0.66,1.10)	0.59*** (0.46,0.76)
sTST (min)	460.53 (429.02,494.37)	395.81 (368.72,424.89)	415.88 (387.13,446.77)	425.05 (395.70,456.58)	0.86** (0.78,0.94)	0.90* (0.82,0.99)	0.92 (0.84,1.01)	1.05 (0.96,1.16)	1.07 (0.98,1.18)
sWASO (min)	5.22 (3.46,7.86)	16.38 (10.87,24.69)	8.09 (5.35,12.23)	7.53 (4.98,11.37)	3.14*** (2.05,4.80)	1.55* (1.01,2.38)	1.44 (0.94,2.21)	0.49** (0.32,0.76)	0.46*** (0.30,0.70)
sNAW	2.29 (1.95,2.70)	3.03 (2.57,3.56)	2.40 (2.04,2.83)	2.24 (1.90,2.63)	1.32** (1.11,1.58)	1.05 (0.88,1.25)	0.97 (0.82,1.16)	0.79* (0.66,0.95)	0.74*** (0.62,0.88)
QOS	53.04 (1.88)	43.68 (1.88)	47.80 (1.87)	52.19 (1.86)	−9.36*** (2.27)	−5.23* (2.26)	−0.85 (2.26)	4.13 (2.26)	8.51*** (2.26)

*P ≤ 0.05, **P < 0.01, ***P < 0.001

Table 3—Effects of the phase advance model (PBO and treatments vs. baseline), treatment effects (treatments vs. PBO) on power spectral variables. Least squares geometric mean ratios and 95% (lower confidence limit, upper confidence limit).

Frequency band	Magnitude of Effect (geometric mean ratio) vs. Baseline PBO	GBX	ZOL	vs. PBO GBX	ZOL
0.25-0.5 Hz	0.96 (0.82,1.14)	1.24* (1.05,1.46)	1.12 (0.95,1.32)	1.29** (1.09,1.51)	1.16 (0.99,1.36)
SWA (0.75-4.5 Hz)	1.07 (0.97,1.17)	1.33*** (1.21,1.47)	1.02 (0.93,1.13)	1.25*** (1.13,1.37)	0.96 (0.87,1.06)
Theta (4.75-7.75 Hz)	1.00 (0.91,1.09)	1.25*** (1.14,1.37)	0.75*** (0.68,0.82)	1.25*** (1.14,1.38)	0.75*** (0.68,0.82)
Alpha (8.0-12.0 Hz)	1.02 (0.94,1.11)	1.01 (0.94,1.10)	0.81*** (0.75,0.88)	0.99 (0.92,1.07)	0.80*** (0.74,0.86)
Sigma (12.25-15.0 Hz)	1.07 (0.98,1.16)	0.95 (0.88,1.03)	1.24*** (1.14,1.35)	0.89** (0.82,0.97)	1.16*** (1.07,1.26)
Beta-1 (15.25-20.0 Hz)	1.05 (0.95,1.16)	1.01 (0.91,1.12)	1.00 (0.90,1.10)	0.96 (0.87,1.07)	0.95 (0.86,1.05)
Beta-2 (20.25-25.0 Hz)	1.00 (0.91,1.11)	0.96 (0.87,1.06)	0.95 (0.86,1.04)	0.96 (0.87,1.06)	0.94 (0.85,1.04)
Beta-3 (25.25-32.0 Hz)	1.05 (0.94,1.17)	0.99 (0.89,1.11)	0.99 (0.89,1.11)	0.95 (0.85,1.05)	0.95 (0.85,1.05)

*P ≤ 0.05, **P < 0.01, ***P < 0.001

All 3 A-phase subtype indices were not statistically different from those observed with PBO, and hence remained higher than those at baseline. The relative percentages of subtypes were not significantly affected by GBX with respect to PBO, except for A3. The relative percentage of A2 and A1 remained significantly different from their baseline levels.

Durations of A2 and A3 increased with respect to placebo. Durations of all subtypes remained higher than those at baseline. Conversely, GBX did not change the duration of B phase with respect to PBO remaining shorter compared to baseline.

CAP cycle duration was different from PBO and remained shorter than baseline. The number of CAP sequences was significantly increased with respect to PBO and remained significantly higher compared to baseline. The duration of CAP sequences was not statistically different from PBO but was significantly higher than baseline.

Effect of ZOL

ZOL treatment was followed by a global NREM CAP reduction as well as stage-specific rate reduction with respect to placebo, resulting in values similar to those of baseline or significantly below them as seen in stage 1 and SWS.

All 3 A-phase subtype indices decreased with respect to PBO, bringing them to levels not significantly different from baseline. The relative percentages of some CAP A-phase subtypes remained different from baseline, with a lower percentage of A1 and higher percentage of A2.

Durations of CAP subtypes were not significantly reduced by ZOL, except for the A2 type, and remained higher than baseline in the case of A1 and A3. In contrast, B phase duration increased, approaching baseline levels.

The CAP cycle duration was significantly longer than baseline and PBO. CAP sequence number was not significantly different from PBO or from baseline. The duration of CAP sequences was significantly reduced with respect to placebo and approached baseline levels.

GBX vs. ZOL

ZOL produced significantly lower global and stage-specific CAP rates compared to GBX treatment, as well as lower subtype

Table 4—Effects of the phase advance model (PBO and treatments vs. baseline), treatment effects (treatments vs. PBO) on CAP variables. Least squares means and (SE).

					Magnitude of Effect (mean difference)					
					vs. Baseline			vs. Placebo		vs. GBX
Cap Variables	**Baseline**	**PBO**	**GBX**	**ZOL**	**PBO**	**GBX**	**ZOL**	**GBX**	**ZOL**	**ZOL**
CAP Rate, NREM (%)	31.17 (2.00)	50.06 (2.00)	48.48 (2.00)	30.53 (2.00)	18.89*** (1.74)	17.31*** (1.74)	−0.64 (1.74)	−1.58 (1.74)	−19.53*** (1.74)	−17.95*** (1.74)
CAP Rate, S1 (%)	45.07 (3.58)	63.38 (3.58)	48.93 (3.59)	31.79 (3.58)	18.31*** (4.60)	3.86 (4.60)	−13.28** (4.60)	−14.45** (4.60)	−31.59*** (4.60)	−17.14*** (4.60)
CAP Rate, S2 (%)	30.41 (2.25)	49.65 (2.25)	49.36 (2.26)	30.29 (2.26)	19.23*** (1.98)	18.95*** (1.98)	−0.12 (1.98)	−0.29 (1.98)	−19.36*** (1.98)	-19.07*** (1.98)
CAP Rate, SWS (%)	51.92 (2.86)	69.95 (2.84)	56.85 (2.82)	37.72 (2.82)	18.02*** (3.39)	4.92 (3.38)	−14.21*** (3.38)	−13.10*** (3.36)	−32.23*** (3.36)	−19.13*** (3.34)
A1 (%)	71.97 (2.08)	71.19 (2.08)	68.76 (2.08)	68.25 (2.08)	−0.78 (1.68)	−3.21 (1.68)	−3.72* (1.68)	−2.43 (1.68)	−2.94 (1.68)	−0.51 (1.68)
A2 (%)	14.08 (1.34)	16.69 (1.34)	19.79 (1.34)	18.22 (1.34)	2.61* (1.19)	5.70*** (1.19)	4.13*** (1.19)	3.09* (1.19)	1.52 (1.19)	−1.57 (1.19)
A3 (%)	13.93 (1.15)	12.12 (1.15)	11.46 (1.15)	13.53 (1.15)	−1.82 (1.02)	−2.47* (1.02)	−0.40 (1.02)	−0.66 (1.02)	1.41 (1.02)	2.07* (1.02)
A1 index (no./hour)	32.13 (2.44)	50.51 (2.44)	47.79 (2.44)	28.92 (2.44)	18.37*** (2.05)	15.66*** (2.05)	−3.22 (2.05)	−2.71 (2.05)	−21.59*** (2.05)	−18.88*** (2.05)
A2 index (no./hour)	6.02 (1.27)	12.28 (1.27)	14.06 (1.27)	7.07 (1.27)	6.26*** (1.10)	8.04*** (1.10)	1.05 (1.10)	1.78 (1.10)	−5.21*** (1.10)	−6.99*** (1.10)
A3 index (no./hour)	3.33 (0.85)	7.05 (0.85)	5.81 (0.85)	3.57 (0.85)	3.73*** (0.82)	2.49** (0.82)	0.24 (0.82)	−1.24 (0.82)	−3.49*** (0.82)	−2.25** (0.82)
A1 duration, s	6.29 (0.11)	7.03 (0.11)	7.09 (0.11)	6.85 (0.11)	0.74*** (0.13)	0.80*** (0.13)	0.56*** (0.13)	0.06 (0.13)	−0.19 (0.13)	−0.24 (0.13)
A2 duration, s	8.49 (0.32)	10.02 (0.32)	11.16 (0.32)	9.00 (0.32)	1.53*** (0.29)	2.67*** (0.29)	0.51 (0.29)	1.14*** (0.29)	−1.02*** (0.29)	−2.16*** (0.29)
A3 duration, s	10.92 (0.45)	12.14 (0.45)	13.34 (0.45)	11.99 (0.45)	1.22* (0.48)	2.41*** (0.48)	1.07* (0.48)	1.19* (0.48)	−0.15 (0.48)	-1.34** (0.48)
B duration, s	25.89 (0.36)	22.07 (0.36)	21.68 (0.36)	26.51 (0.36)	−3.82*** (0.38)	−4.20*** (0.38)	0.62 (0.38)	−0.39 (0.38)	4.44*** (0.38)	4.82*** (0.38)
CAP cycle duration, s	32.90 (0.35)	29.98 (0.35)	30.00 (0.35)	34.31 (0.35)	−2.92*** (0.36)	-2.90*** (0.36)	1.41*** (0.36)	0.02 (0.36)	4.32*** (0.36)	4.31*** (0.36)
CAP sequence number	32.20 (1.23)	34.43 (1.23)	38.42 (1.23)	34.07 (1.23)	2.23 (1.53)	6.22*** (1.54)	1.87 (1.54)	3.99* (1.54)	−0.36 (1.54)	−4.35** (1.54)
CAP sequence duration, s	206.08 (12.39)	289.90 (12.39)	266.28 (12.40)	195.48 (12.39)	83.81*** (13.85)	60.19*** (13.86)	−10.61 (13.85)	−23.62 (13.87)	−94.42*** (13.86)	−70.80*** (13.85)

*P ≤ 0.05, **P < 0.01, ***P < 0.001

indices. Relative percentages of A1 and A2 subtypes were similar, while the percentage of A3 subtype under ZOL was significantly higher. The duration of A1 was not significantly different between GBX and ZOL. The durations of A2 and A3 were significantly shorter under ZOL, while the duration of B phase was significantly longer. The CAP cycle durations were significantly longer under ZOL, while the number of CAP sequences was significantly smaller and CAP sequence duration was significantly shorter.

Associations with self-reported sleep quality

Figure 1 shows Spearman correlations between differences in baseline and PBO values in QOS, and corresponding differences in the values of each of CAP, PSG, spectral, and self-reported variables. The list of CAP variables with the strongest statistically significant (negative or positive) correlations with QOS consisted of A1 index and CAP cycle duration, NREM CAP rate, stage 2 CAP rate, A3%, and B duration. Among PSG variables, log(WASO) and log (NAW), and among self-reported variables, log(sNAW), log(sTSO), and log(sTSO), have the largest correlation with QOS. Correlations between QOS with the other self-reported variables while being relatively high when compared to the other variables, are still low enough to suggest that perception of QOS is completely based on one particular perceived sleep characteristic such as, for example, sNAW, or sTSO. Correlations between QOS with any of the spectral variables did not reach statistical significance at P = 0.05. Overall, change in A1 index (Spearman = -0.46) has the strongest association with reduction in QOS in the transient insomnia model in this study.

DISCUSSION

There are some limitations to the analysis which should be addressed before the results are discussed. Only analyzing a

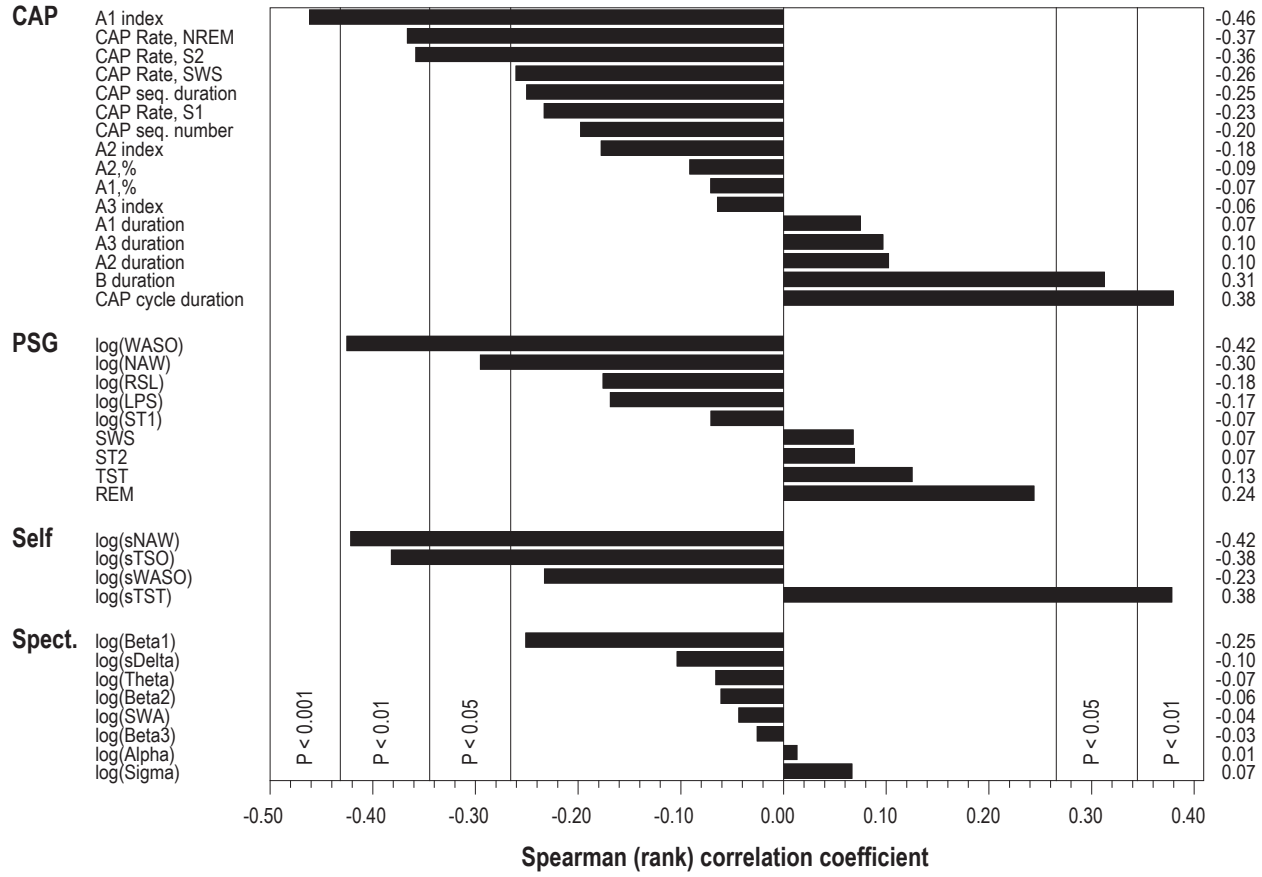

Figure 1—Spearman (rank) correlation between difference in baseline and PBO values of QOS and corresponding differences in the values of each of CAP, PSG, spectral variables, as well as self-reported measures. Variables are presented in 4 groups, CAP, PSG, Self. (Self-reported), and Spectral. Values of correlations are shown in the horizontal axis and repeated to the right of the bars. P-values show the corresponding regions to the left (for negative correlations) and to the right (for positive correlations) of the vertical bars where the correlations are significantly different from zero.

subset of subjects (67%) and treatments (4 out of 5) presents some limitations. However, we believe that 55 subjects (67%) constituted a representative sample of the original dataset. The 55 subjects were randomly chosen, and their demographic characteristics, self-reported sleep measures, and traditional PSG sleep measures reflected the data from the original full (82 subject) dataset well.[18] The treatment sequence was well-balanced with the 5-way crossover study design. However, since one treatment was removed in the current analysis this may have had an impact on the measures of interest. GBX 5 mg was excluded from the analysis, since it was the dose most unlikely to show an effect in this exploratory post hoc analysis. Nine of ten treatment sequences were within 0.7% of the original, and 1.3% for the remaining sequence. The study was originally designed with sufficient washout periods to avoid carryover effects, and period (as well as treatment sequence) was used as a factor in the statistical model. Thus the results presented here have already "estimated out" these effects.

Data from Night 1 preceding the phase advanced night of the PBO condition were chosen as the reference or baseline. Such a choice for the baseline may increase variability of comparisons between treatment and baseline nights due to the fact that (a) Night 1, although not disturbed by the sleep phase advancement, is a habituation night under PBO; and (b) for different subjects this night occurs at different times during the study, and hence the "normal" sleep in the beginning of the study may be different from that at the end. However, as expected, and as our results indicate, sleep phase advancement causes powerful sleep disturbance much greater than "normal" sleep variability during the study.

Finally, it is important to take into account that CAP analysis is limited to NREM sleep; the impact of drugs on REM sleep should be investigated further.

Substances that enhance synaptic γ-aminobutyric acid (GABA) neurotransmission, such as benzodiazepines and ZOL, are the most commonly used sedative-hypnotic drugs. The primary locus of action of these drugs is the postsynaptic junction. In contrast, GBX is a selective extrasynaptic GABA receptor agonist acting on a unique δ-containing GABA-A receptor subtype found exclusively outside of the synapse and highly expressed in the thalamus, where it might behave as a "gain control" in the corticothalamic pathways that govern sleep-relevant neuronal oscillations.[27] GBX has been investigated as a potential hypnotic agent, and its efficacy has been demonstrated by effects on traditional sleep parameters reported in normal controls and patients with different types of insomnia.[18,28-30]

As expected, given our random selection of subjects from the same study, results reported in this paper for traditional PSG, self-reported, and spectral measures are consistent with those published by Walsh et al.[18] and extend them with respect to

CAP in a number of directions. Firstly, CAP analysis appears to reveal important sleep disruptions induced by transient insomnia. Secondly, CAP parameters seem to be more sensitive to these disruptions than spectral parameters. Thirdly, different drug treatments, GBX and ZOL, result in partial, total, or overcompensation of these disruptions evident from the analysis of global and stage-specific CAP rates. Fourthly, not only CAP rates but also CAP structure parameters, such as indices and durations, are modified significantly and differentially by the different treatments. Finally, consistent with the previous results on CAP in insomnia, CAP parameters in transient insomnia have higher correlation with self-reported sleep quality than PSG and spectral measures.

Specifically, transient insomnia, in which strong circadian influences affect sleep initiation via increase in LPS and maintenance via increase in WASO, also increases the number and duration of all CAP subtypes. This increase is accompanied by time structure modifications, with a significant shortening of the B phase of CAP and, consequently, of the CAP cycle (phases A+B of CAP) and significant lengthening of the CAP sequence duration. Spectral properties, on the other hand, are affected in a relatively small way. If CAP parameters are markers of the sleep stability as has been suggested in previous studies then transient insomnia did indeed increase NREM sleep instability. In this respect, our CAP results are consistent with those obtained in a different model of transient situational insomnia, obtained by means of increasing intensities of acoustic perturbation during sleep.[31] Also in that study, a remarkable enhancement of CAP was found, and this was significantly correlated with the personal evaluation of sleep quality. On the other hand, if transient insomnia causes instability of NREM sleep, then spectral parameters, which, like CAP parameters are calculated within NREM sleep intervals, seem to be insensitive to sleep instability. This is consistent with an interpretation of the EEG power spectrum as a global measure, i.e., a measure which combines power of EEG patterns of all frequencies, amplitudes, and durations. Even a large change in CAP may make a small contribution to the change in total power. Another factor to take into account, regarding this point, is the different time-base of CAP and spectral EEG analysis. CAP analysis takes into account very slow EEG amplitude changes (from 4 to 120 s) while EEG power spectra are usually obtained from epochs with a duration of very few seconds (4 s in our case) and then averaged. Probably, the changes induced by the experimental procedure of this study require a long time-based analysis to be picked up with high sensitivity and CAP analysis was able to do so.

Our results and those of Walsh[18] show the efficacy of GBX and ZOL with respect to sleep initiation and maintenance. One of the questions we address via CAP analysis is whether these drugs are also efficacious in reducing CAP rates, thus compensating sleep instability induced by the transient insomnia. We found that both drugs do this but in a very different way. GBX has a relatively small effect on CAP rates in NREM and stage 2 sleep, while CAP rates during stage 1 and SWS are reduced significantly and brought closer to the baseline levels.

This reduction in CAP rates during SWS complements previous findings on the effects of GBX on traditional PSG and spectral measures.[18,29,30] It appears that GBX not only enhances SWS/SWA but that this enhancement is accompanied by the compensatory reduction of SWS instability in transient insomnia.

In contrast, ZOL induced a much stronger reduction in the CAP rate in stage 2, and hence NREM sleep, bringing it close to baseline levels. The effects of ZOL on CAP rates in stage 1 and SWS were very strong as their values were reduced to substantially below baseline. Direct comparison of GBX and ZOL shows that CAP rates in all sleep stages are much lower under ZOL than those under GBX. The other CAP structure parameters are significantly different between the two drugs. Note that interpretation of differences between ZOL and GBX on CAP is limited, since equipotency was not established.

The fact that ZOL reduces CAP rate has been reported in the literature before.[11,32,33] The detailed analysis of CAP parameters presented here provides an important insight on how CAP sequences are changing under sleep disruption and treatments. In particular, comparison of baseline and PBO shows that phase-advanced sleep lengthens phase A of CAP and shortens phase B, resulting in the shortening of the CAP cycle (A+B). These effects are likely the results of the interaction between sleep and the circadian timing system especially during the so-called forbidden zone. It is interesting to review these results in light of results presented in Smerieri et al.[34] indicating that the CAP sequence length in normal controls is determined by a different number of CAP cycles while the CAP cycle length remains approximately the same. The authors hypothesize that CAP cycles are "time-constant" structures of NREM sleep. Our results show that phase- advanced sleep alters these time-constant features of sleep, while the treatments bring some of them closer to their baseline levels, as ZOL does in stage 2 or GBX does in SWS.

Of particular interest is the finding that one of the CAP parameters, A1 index, has the highest correlation with self-reported sleep quality. This is in general agreement with the results reported by Terzano et al.[13] where NREM CAP rate also had the highest correlation, 0.50 (Pearson), with self-reported sleep quality as measured by visual analog scale. Note, however, that interpretation of correlations between subjective and objective sleep parameters in this paper and in the literature, in general, has to be approached with a caution because the correlations are quite small and their statistical significance means only that they are not different from zero. In our analysis we found that it is not the CAP rate by itself, but rather the A1 index that has the highest correlation with sleep quality. To investigate this further, we calculated two partial (Spearman) correlations: (1) QOS with A1-index after controlling for the correlation of QOS with CAP rate; and (2) QOS with CAP rate after controlling for the correlation of QOS with A1-index. The partial correlation with A1 index was (-0.31, $P = 0.02$) while the partial correlation with CAP rate was (-0.08, $P = 0.55$). This may suggest that CAP A1 phases have a higher association with sleep quality.

The relative independence of CAP parameters from other electrophysiological measures of sleep, their high sensitivity to sleep disruption, and their strong association with subjective sleep quality further strengthen the fact that CAP variables can serve as valuable endpoints in future insomnia research.

DISCLOSURE STATEMENT

This post hoc analysis of a study[18] sponsored by H. Lundbeck A/S was sponsored by Merck. Gaboxadol is an experimental drug developed by Lundbeck and Merck for use in insomnia. In March of 2007 Lundbeck and Merck cancelled work on the drug. Zolpidem was developed by Sanofi-Aventis for treatment of insomnia. Drs. Svetnik, Ray, Ma, and Snyder are employees of Merck. Dr. Ferri indicated that research support has been provided to his institution by Sanofi-Aventis, Boehringer Ingelheim, and GlaxoSmithKline, and that he has consulted for Merck and Sapio Life. Dr. Walsh indicated that research support has been provided to his institution by Pfizer, Lundbeck, Merck, Somaxon, Evotec, Actelion, Vanda, Neurogen, Sanofi-Aventis, Ventus, and Jazz Pharmaceuticals, and that he has consulted for Pfizer, Lundbeck, Sanofi-Aventis, Cephalon, Organon, Neurocrine, Takeda America, Actelion, Sepracor, Jazz, Respironics, Transcept, Neurogen, GlaxoSmithKline, Somaxon, Eli Lilly, Evotec, Merck, Kingsdown, Vanda, and Somnus. Dr. Ebert is an employee of Lundbeck. Dr. Deacon was an employee of Lundbeck at the time this research was carried out. Dr. Deacon is a current employee of Ono Pharma, London, UK.

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