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Original Article

Hyperarousal in insomnia: pre-sleep and diurnal cortisol levels in response to chronic zolpidem treatment

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ABSTRACT

Objectives: To determine whether cortisol levels, both diurnal and pre-sleep, would vary as a function of MSLT and would be reduced by nightly placebo versus zolpidem 10 mg.
Methods: DSM-IVR diagnosed subjects with insomnia (N = 95), aged 32–70 yrs, having no other sleep disorder, unstable medical or psychiatric diseases or drug dependency served. On a screening MSLT 27 had MSLTs <10 min (Lo) and 42 > 15 min (Hi). Participants took 10 mg zolpidem or placebo, double-blind, nightly for 12 months. In months one and 12 urine was collected over 24 h in 8 hr-aliquots and assayed for cortisol (Ward Laboratories, Ann Arbor, MI). Saliva samples were collected 35 min before bedtime and the 30 min drug administration in month one and eight, and analyzed for cortisol levels (Salimetrics, State College, PA).
Results: Pre-sleep salivary cortisol was higher in insomniacs than controls, but did not differ as a function of MSLT. Nightly zolpidem reduced pre-sleep cortisol relative to placebo on month one and eight, with no month effects or interaction. Diurnal (0700–1500 h) urinary cortisol was higher overall in the Hi vs Lo MSLT subjects with insomnia, was stable across months, and was not reduced with zolpidem.
Conclusions: Hyperarousal among subjects with insomnia as operationalized by MSLT is associated with higher diurnal urinary cortisol than those without hyperarousal, but not differential pre-sleep salivary cortisol. Zolpidem relative to placebo reduced pre-sleep salivary cortisol in all subjects, but not diurnal urinary cortisol.
Clinical trial: Safety and Efficacy of Chronic Hypnotic Use: http://www.clinicaltrials.gov NCT01006525.

1. Introduction

Insomnia disorder (and likely co-morbid insomnia as well) is hypothesized to reflect a 24-hr state of hyperarousal [1]. This hyperarousal is evident in prolonged sleep latencies (ie, about one standard deviation above normal levels) on the Multiple Sleep Latency Tests (MSLT) during the day, despite disrupted and shortened nocturnal sleep the previous night [2–4]. Evidence also suggests that this physiologic hyperarousal is associated with activation of the sympathetic nervous system (SNS) and hypothalamic-pituitary-adrenal (HPA) axis. People with Insomnia disorder show elevated levels of circulating catecholamines [5], increased metabolic rates [4], increased body temperature [6], altered heart rate variability [7], and pupillometry patterns [8]. HPA augmentation in insomnia is indicated by elevated levels of nighttime urinary free cortisol proportional to the amount of wakefulness during the night [5]. An activated SNS and HPA axis suggests a central mechanism, although the nature of the central pathophysiology has not been determined.

Neuroimaging findings in people with insomnia support a hyperarousal hypothesis. People with insomnia, relative to healthy controls, showed greater cerebral glucose metabolism during sleep, when awakening, at the transition from wake to sleep, and particularly in brain arousal centers [9]. Notably, these studies all compared people with insomnia to people without insomnia rather than assessing individual differences among people with insomnia in level of hyperarousal.

We confirmed the presence of hyperarousal in some people with insomnia (about half) as defined by the MSLT [10]. Further, given that no previous study had assessed the stability of MSLT elevation within an individual across time, we found that MSLT

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Abbreviations

CRF	Corticotropin releasing factor
DSM-IVR	Diagnostic Statistical Manual of Mental Disorders, Fourth Edition, Revised
FDA	Food & Drug Administration
EEG	Electroencephalogram
C3-A2, Oz-A2	central (C3), occipital (Oz) EEG placements referenced to ear (A2)
HPA	Hypothalamic-pituitary-adrenal axis
IRB	Institutional Review Board
MANOVA	Multivariate analysis of variance
MSLT	Multiple Sleep Latency Test
NIDA	National Institute of Drug Abuse
NPSG	Nocturnal Polysomnogram
Pbo	Placebo
SCID	Structured Clinical Interview for DSM-IVR
SEM	Standard error of the mean
SNS	Sympathetic Nervous System
TOD	Time of day
Ug/L	Micrograms per liter
Zol	Zolpidem

elevation in insomnia is a stable "trait-like" finding across eight months [10]. Finally, we found that elevated MSLTs were associated with elevated levels of daytime urinary norepinephrine relative to people with insomnia and without elevated MSLTs [11]. These observations validated the construct of hyperarousal among some people with insomnia using two concurrent "independent" measures.

While Insomnia disorder is considered a disorder of hyperarousal, the principle symptoms of Insomnia disorder are difficulty initiating and maintaining sleep. HPA augmentation in insomnia has been shown to be associated with patient complaints of difficulty maintaining sleep and increased wakefulness during sleep. Vgontzas et al., reported significantly elevated plasma concentrations of cortisol on repeated 20-min plasma samples taken across 24-hrs in people with insomnia compared to healthy controls [12]. Of note, the Vgontzas data showed a specific elevation in cortisol levels relative to the healthy controls on the 20-min samples taken just prior to and following bedtime.

However, other studies are equivocal regarding cortisol elevations related to sleep disturbance in insomnia. Cortisol levels did not differ among people with insomnia and disturbed sleep, people with insomnia and normal sleep, and controls, although across those with insomnia higher arousal during sleep was predictive of higher cortisol levels [13]. On the other hand, several studies have failed to find any relation of cortisol levels to sleep disturbance [14,15]. These studies failing to find HPA augmentation have not recognized that not all people with insomnia are hyperaroused, which may explain the equivocal results in this literature. As noted above, only about half of people with insomnia show elevated MSLTs and elevated levels of daytime urinary norepinephrine.

The question then arises as to whether diurnal and pre-sleep cortisol levels vary as a function of MSLT, as previously reported for norepinephrine [11], and whether or not cortisol levels would be reduced by 12 months of nightly zolpidem 10 mg versus placebo. We assessed cortisol levels in saliva before sleep and in urine throughout the day and specifically concurrent with the timing of MSLT as part of a large clinical trial assessing the efficacy and abuse liability of 12 months of nightly use of 10 mg zolpidem vs placebo.

This study sought to determine how diurnal and pre-sleep cortisol varies as a function of MSLT defined hyperarousal and whether or not diurnal and pre-sleep cortisol levels change as a function of long-term nightly use of zolpidem versus placebo. We hypothesized zolpidem may reduce pre-sleep cortisol given zolpidem has been shown to reduce sleep latency, but may not affect diurnal cortisol given it has been found to be a stable characteristic of hyperarousal in insomnia [10].

2. Methods

2.1. Participants

Healthy, volunteers (N = 95: 53 women, 42 men) aged 23–70 years old with chronic insomnia according to DSM-IVR criteria and a standard sleep laboratory screening to confirm disturbed sleep, which was defined as a sleep efficiency of less than 85% on the 8-hr NPSG and the absence of sleep disordered breathing and periodic leg movement disorders (apnea/hypopnea or periodic leg movement indices < 10) participated [16]. They were in otherwise good physical and psychological health as determined by medical, psychiatric, clinical laboratory, and drug/alcohol abuse screening. Participants were recruited using metropolitan newspaper advertisements, on-line advertisements, university-medical school and community flyers, job fairs, and word of mouth.

The protocol was approved by the Institutional Review Board (IRB) and each participant signed an informed consent and was paid for participation. The conduct of the study was monitored by a Data Safety Monitoring Board which reviewed study progress quarterly. The trial was registered at ClinicalTrials.gov #NCT01116525.

2.2. Insomnia, medical and psychological screening

Each volunteer completed a telephone interview, sleep diaries and a sleep disorders questionnaire prior to their clinic visit. The insomnia diagnosis was established through a clinical interview with a certified sleep disorders specialist. Each participant also received a physical examination, the Cornell Medical Index, as well as clinical laboratory analyses of blood and urine samples for hematologic, hepatic, renal and other major system functions. Volunteers with BMIs >30 were excluded. Any volunteer with positive laboratory findings was excluded from the study with special attention paid to liver function results to exclude persons with liver disease. Participants underwent the Structured Clinical Interview (SCID) for DSM-IVR to rule out major psychiatric disease.

2.3. Study design

Participants were randomized to receive zolpidem 10 mg or placebo nightly taken 30 min before bedtime for 12 months. During the 12 months they returned to the sleep laboratory for NPSGs and MSLT the following day in months 1, 4, 8 and 12. Between in-laboratory nights participants slept at home with the instruction to take their medication 30 min before sleep and to remain in bed for 8 h. Morning self-reports and monthly pill counts documented a greater than 80% nightly treatment compliance [13].

2.4. NPSGs

The NPSGs consisted of central (C3-A2) and occipital (Oz-A2) electroencephalograms, bilateral horizontal electro-occulograms, a submental electromyogram, and electrocardiogram recorded with a V5 lead [8]. In addition on the screening night, leg movements and airflow was monitored [16]. The sleep recordings were scored

in 30-second epochs according to the standards of Rechtschaffen and Kales by scorers who maintained a 90% scoring reliability [17]. Nasal-oral recordings were scored for apneas, defined as 10-sec or longer cessations of airflow, and hypopneas, defined as 10-sec or longer reductions (50% or greater) of airflow [16]. Tibialis muscle recordings were scored for leg movements associated with arousal, defined as 0.5 s or greater tibialis flexions coincident with brief EEG speeding [16]. Respiratory events (ie, apnea and hypopnea) and leg movement events were tabulated and expressed as indices per hour of total sleep time. On all nights time-in-bed was fixed to 8 h adjusted to the participant's diary reported sleep habits.

2.5. Multiple Sleep Latency Tests (MSLT)

On the day after the screening NPSG nights a standard research MSLT (1000, 1200, 1400, 1600 h) was conducted [18]. Among the 95 participants entered into the clinical trial, n = 42 had average latencies of ≥15 min and n = 27 had ≤10 min average latencies on the screening MSLT which defined the Hi and Lo MSLT groups for the comparisons in this study.

2.6. Cortisol measurement

In month one (wk 1 and 4) and month 12 (wk 1), urine was collected over 32 h in 8-hr aliquots and assayed for cortisol (Ward Laboratories, Ann Arbor, MI). The T1 aliquot was collected from 2300–0700, T2 from 0700–1500, T3 1500–2300, and T4 from 2300–0700 h. Participants were instructed to collect and pool all voids within a given 8-hr aliquot. The month one (wk 1) 8-hr aliquots were tested for time-of-day (TOD) and Hi-Lo MSLT group differences. The daytime 8-hr urinary aliquots (0700–1500) of month one (wk 4) and month 12 (wk 1) were compared between the Lo and Hi MSLT groups and between the placebo versus zolpidem groups. Saliva samples were collected 35 min before bedtime and before the 30 min drug administration in month one and eight and analyzed for cortisol levels (Salimetrics, State College, PA) and compared between the Lo and Hi MSLT groups and placebo versus zolpidem groups. Given the 35 min pre-sleep sampling and the 30 min drug administration, the salivary cortisol levels did not reflect the immediate, direct effects of zolpidem or placebo.

2.7. Pre-sleep salivary controls

Pre-sleep (30 min) salivary cortisol was collected on a baseline PSG night (before subsequent drug administration nights) in a study of caffeine's effects on sleep (N = 45: 24 women, 21 men) in volunteers, aged 19–62 yrs, which served as the control cortisol levels for this study. These volunteers were screened by questionnaire and telephone interview. None reported insomnia symptoms qualifying for a DSM-IVR insomnia diagnosis, loud snoring ≥3 times per week and BMI >30, restless legs, shiftwork, history of psychiatric disorders, current medical disease or medication use, current marijuana, cocaine, or opiate use, and >7 alcohol drinks per week.

2.8. Analyses

The basal pre-sleep salivary cortisol measures for the whole insomnia group and the Hi MSLT group were compared to the controls using between group t-tests. The month one urinary cortisol levels for each of the four 8-hr aliquots were tested for TOD and MSLT group effects by a two factor mixed design MANOVA with TOD levels a repeated factor and MSLT group a between group factor. The month one and month eight or 12 cortisol measures, pre-sleep and diurnal (0700–1500 h), were submitted to two factor mixed design MANOVAs with the between subject variable MSLT group in one analysis, and placebo vs zolpidem groups in the other, and months as the within repeated variable in both analyses. Sample sizes became too small to conduct a three factor analysis (ie placebo vs zolpidem within the Hi MSLT group vs a placebo vs zolpidem comparison in the Lo MSLT group).

3. Results

3.1. Salivary cortisol

At baseline, pre-sleep salivary cortisol was higher in participants (N = 95) with insomnia compared to controls (N = 45) 2.23 ± 2.12 vs 1.23 ± 1.41 ug/L ($t = 2.87$, $p < 0.005$) and as might be expected higher than controls in the Hi MSLT (N = 27) insomnia group 2.36 ± 1.41 ug/L ($t = 3.07$, $p < 0.003$) than the controls. Pre-sleep salivary cortisol levels for months one and eight as a function of MSLT group are presented in Fig. 1. While the Lo MSLT group had numerically higher pre-sleep salivary cortisol in both months one and eight, that difference did not reach statistical significance ($p = 0.11$). There also was no significant month effect or an interaction. Fig. 2 presents the pre-sleep salivary cortisol levels for months one and eight as a function of zolpidem versus placebo. Zolpidem reduced pre-sleep salivary cortisol in both months one and eight ($F = 5.12$, $p < 0.03$). There was no month effect or an interaction with MSLT group.

3.2. Urinary cortisol

The urinary cortisol levels for month one in the two MSLT groups as a function of TOD is presented in Table 1. Urinary cortisol was significantly elevated in the Hi MSLT group relative to the Lo group ($F = 4.09$, $p < 0.05$) and significantly elevated as a function of TOD ($F = 3.28$, $p < 0.02$) with levels from 0700–1500 h elevated relative to the remaining 8-hr aliquots ($p < 0.05$). Finally, in the MSLT group by TOD interaction ($F = 2.68$, $p < 0.05$), the only aliquot in which the MSLT groups differed was on the 0700–1500 h aliquot, with the Hi MSLT group having higher urinary cortisol than the Lo group.

Months one and 12 urinary cortisol levels for the two MSLT groups are presented in Fig. 3. Urinary cortisol levels were higher in both months one and 12 in the Hi MSLT group relative to the Lo group ($F = 4.69$, $p < 0.03$). There was no month effect or an interaction of group by time. Finally, Fig. 4 presents urinary cortisol in month one and 12 for the zolpidem vs placebo treatment

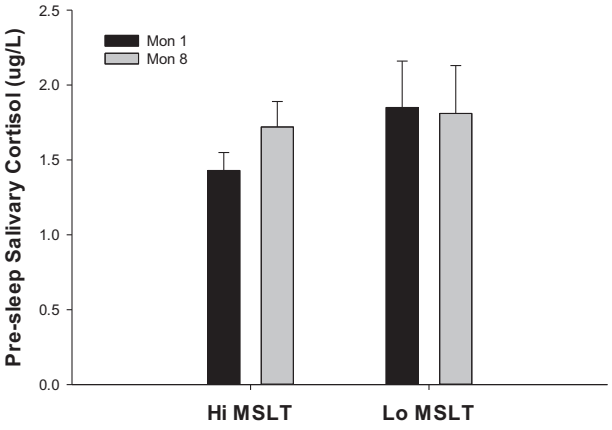

Fig. 1. Pre-sleep salivary cortisol in months one and eight as a function of MSLT groups. Means and SEM; No significant effects of MSLT group, months or interaction.

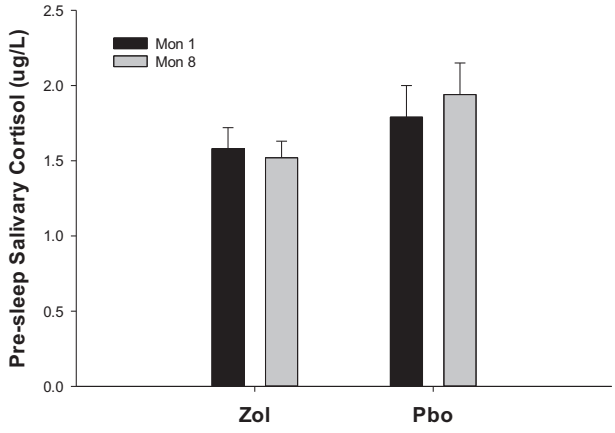

Fig. 2. Pre-sleep salivary cortisol in months one and eight as a function of Drug groups. Means and SEM; Zol vs Pbo, $p < 0.02$.

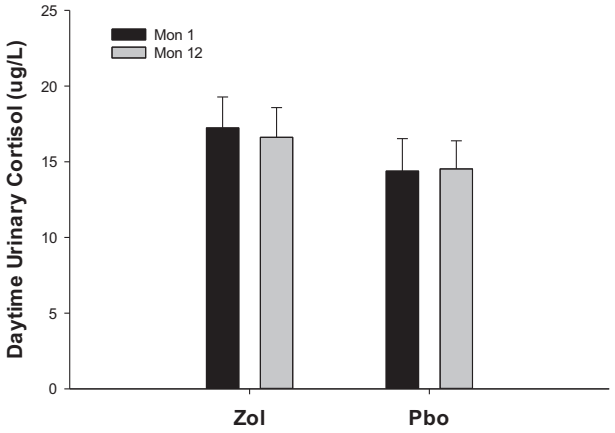

Fig. 4. Daytime (0700–1500 h) urinary cortisol in months one and 12 as a function of Drug. Means and SEM; No significant drug, month, or interaction effects.

comparison. One month and 12 months of nightly zolpidem vs placebo did not significantly reduce 0700–1500 h cortisol. Furthermore, there also was no month effect or interaction.

4. Discussion

These are the first data to show that chronic use of a short-acting hypnotic does not reduce the characteristic hyperarousal of insomnia as reflected in diurnal urinary cortisol and Hi MSLTs. It should be noted in a previous paper we showed in this sample of people with insomnia that chronic zolpidem 10 mg nightly increased total sleep time and reduced sleep latency and wake after sleep onset relative to placebo [13]. Hypnotic treatment did not improve daytime hyperarousal, suggesting this is a "trait-like" characteristic of insomnia.

Conversely, the pre-sleep elevation in salivary cortisol showed a response to hypnotic treatment; relative to placebo; cortisol levels before sleep were reduced in the zolpidem group. Again we note in our previously published paper latency to persistent sleep was reduced by zolpidem relative to placebo [13]. This suggests the difficulty initiating sleep onset with its elevated pre-sleep cortisol is a "state-like" phenomenon characteristic of all insomnia (see Fig. 1). Consistent with such an interpretation is the fact that both MSLT groups showed the pre-sleep elevation and in both groups hypnotic treatment reduced the elevation. In other words, the pre-sleep cortisol elevation in insomnia is not a differential expression of the hyperarousal of some people with insomnia.

All those with insomnia, regardless of diurnal hyperarousal (ie, MSLT group), showed the pre-sleep elevation and they all differed from controls in that regard. But, unlike daytime urinary cortisol, as Fig. 1 suggests, pre-sleep cortisol in the Lo MSLT group on both month one and eight appears numerically higher than the Hi MSLT group. But, due to large variability this comparison did not achieve statistical significance. This raises a number of interesting questions, the first being given a sufficient "n" is this a repeatable and statistically significant observation?

Also, does this identify an insomnia sub-group in whom risk for hypnotic abuse is lessoned relative to the Hi MSLT group in whom both pre-sleep and diurnal cortisol is elevated? In our recent published paper we found diurnal elevation of norepinephrine was associated with the likelihood of escalating the "dose" of self-administered hypnotic over the 12 months of nightly zolpidem [11]. Two of the characteristics identified in case reports of hypnotic abuse is rapid dose escalation and daytime use of the hypnotic [19,20]. An earlier study of daytime versus nighttime self-administration of triazolam 0.25 mg found a subset of the participants with insomnia, self-administered triazolam during the day and those who did so were those with elevated MSLTs [21].

The question then arises as to whether there are clinical characteristics that may help differentiate those with heightened versus lessoned risk for hypnotic abuse. Clinically, some people with insomnia complain, regardless of how poor their previous night's sleep has been and how fatigued they feel, that they are not able to initiate daytime naps and do not un-intentionally fall asleep during the day. Unfortunately, we did not specifically ask the Hi versus Lo MSLT groups of this study regarding their ability versus inability to daytime nap. Based on the lower MSLT latencies of this group, it is likely they would not report difficulty napping during the day.

Table 1
Urinary cortisol (ug/L) over 8-hr aliquots as a function of MSLT group.

MSLT Group	2300–0700 h	0700–1500 h	1500–2300 h	2300–0700 h
Hi (≥15 min)				
Mean	12.42	18.58	6.44	8.68
SD	9.51	10.97	6.79	6.98
Lo (≤10 min)				
Mean	9.57	12.94	4.51.	7.32
SD	4.50	7.08	1.56	4.39

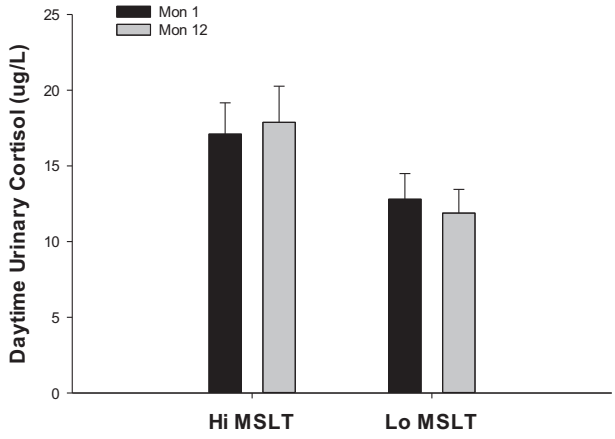

Fig. 3. Daytime (0700–1500 h) urinary cortisol in months one and 12 as a function of MSLT. Means and SEM; Hi vs Lo, $p < 0.03$.

An important limitation of this paper is the small "n" in the Hi-Lo MSLT by zolpidem versus placebo sub-groups, which did not allow for three factor analyses that could compare zolpidem versus placebo within each of the Hi-Lo MSLT groups. This study was designed and initiated before it was appreciated that not all people with insomnia are hyper-aroused as reflected by MSLT and markers of HPA augmentation and that these differential characteristics are stable phenomena. This also limits our ability to correlate NPSG sleep findings to these differential cortisol characteristics.

Additionally, the control data used to compare pre-sleep salivary cortisol levels in people without sleep complaints to the subjects with insomnia in this study were collected for a different study and not concurrent to this study. Moreover, these normal volunteers were screened by phone and self-report and not in-person interviews as the subject with insomnia in this study. However, these study differences would more likely introduce greater variability and diminish our ability to find the differences we report.

Another limitation of our salivary cortisol assessment was that only a single sample was collected before sleep and minute-to-minute changes during the 30-min pre-sleep period were not captured. In this regard, the sample was collected immediately before capsule (zolpidem or placebo) administration. As such, we were not able to assess any pre to post administration changes that might reflect a cortisol response to the capsule administration per se (ie, placebo effect). Of note, while sleep latency in months one and eight averaged 13 min for the zolpidem group compared to 30 min in the placebo group [13], at baseline sleep latency was about 44 min for both groups, suggesting a possible placebo effect.

The differential response to zolpidem versus placebo in pre-sleep salivary cortisol versus diurnal urinary cortisol may reflect methodological differences in the measurement of cortisol that diminishes sensitivity (ie, that is a single time-point measure versus accumulated levels over an 8-hr period) or concentration in saliva versus urine. However, it should be pointed out that urinary cortisol differed as a function of MSLT levels and salivary cortisol was elevated relative to the controls.

In conclusion, these data show: 1) hyperarousal among people with insomnia as operationalized by MSLT is associated with higher diurnal urinary cortisol, but with similar pre-sleep salivary cortisol to those without hyperarousal, 2) zolpidem relative to placebo reduced pre-sleep salivary cortisol, but not diurnal urinary cortisol, and 3) these differential hypnotic effects on cortisol suggest the pre-sleep cortisol elevation is a state expression of arousal, while the diurnal cortisol is a trait expression of arousal.

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Conflict of interest

T Roehrs - Research funding: NIDA, Merck; Consultancies: Purdue. T Roth - Consultancies: Flamel, Novion, Merck, Jazz, Eisai, SEQ, Idorsia, Purdue.

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: https://doi.org/10.1016/j.sleep.2019.04.010.

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