

SCIENTIFIC INVESTIGATIONS

## The Acute and Post-Discontinuation Effects of a Glucocorticoid Receptor (GR) Antagonist Probe on Sleep and the HPA Axis in Chronic Insomnia: A Pilot Study

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**Study Objective:** Hypothalamic-pituitary-adrenal axis (HPA) hyperactivity has been reported in patients with chronic insomnia without depression. A glucocorticoid receptor (GR) antagonist may re-regulate HPA axis activity even after discontinuation and may have clinical benefit.

**Methods:** Ten subjects with chronic insomnia participated in a placebo controlled double-blinded prospective 30-day pilot study of the acute and post-discontinuation effects of a 5-day course of 600 mg of the glucocorticoid antagonist, mifepristone. Sleep outcome measures were polysomnogram and Insomnia Severity Index. Hormonal outcome measures were mean overnight cortisol and ACTH (23:00-07:00). We predicted sleep would improve and that overnight cortisol and ACTH would decrease at 2 weeks post-treatment discontinuation.

**Results:** At 2 weeks post-discontinuation, Insomnia Severity Index (ISI) decreased by 4.0 points (effect size = 0.97). Polysomnogram findings were limited. Mean cortisol (0.84 µg/dL, effect size = 0.91)

and ACTH (5.50 pg/mL, effect size = 0.96) were still mildly increased (23:00 to 07:00). Post hoc analysis revealed that, the ratio of cortisol/ACTH decreased (-0.21, effect size = 1.15) as did mean cortisol from 18:00 to 23:00 (-0.47 µg/dL, effect size = 0.56).

**Conclusions:** This is the first study of a GR antagonist in chronic insomnia. Sleep improvement manifests in terms of decreased ISI post-treatment discontinuation. The decrease in cortisol in the early evening (18:00 to 23:00) in combination with the decrease in cortisol/ACTH ratio may be an indicator of the longer term biological mode of action of the drug.

**Keywords:** Insomnia, cortisol, HPA axis, glucocorticoid receptor, CRH

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HPA axis hyperactivity may contribute to the biology of chronic insomnia,<sup>1-4</sup> though not all studies agree. The mechanism for sleep disruption likely derives from increased corticotropin releasing hormone (CRH). Early studies report that exogenous CRH increases EEG frequency in rats.<sup>5</sup> Similarly, exogenous CRH decreases slow wave sleep (SWS) and increases light sleep and awakenings in healthy males.<sup>6</sup> The awakening effect may reflect CRH stimulating pathways on locus ceruleus (LC) mediated norepinephrine release.<sup>7</sup>

Assuming HPA axis hyperactivity is indeed present in chronic insomnia, interventions to alter nocturnal HPA axis and/or brain CRH activity (i.e., CRH or GR antagonists) may provide either adjunctive or alternate pharmacologic intervention for

treating the physiologic component of chronic insomnia. The use of a GR antagonist in patients with chronic insomnia to accomplish this has not been studied.

GR antagonists may act at the level of the hypothalamus as well as at the amygdala-locus ceruleus circuit. In the brain, cortisol binds glucocorticoid receptors (GRs, type II) in the hypothalamus, pituitary and elsewhere to exert feedback inhibition on the HPA axis. Contrary to its inhibitory influence at the pituitary and hypothalamus, GR activation may exert positive feedback on the HPA axis (i.e., via activation of amygdala GRs).<sup>8</sup>

Limited data exist for effects of GR antagonists on sleep. Afternoon administration of 400 mg mifepristone, a glucocorticoid and progesterone receptor antagonist, disrupts sleep during acute administration in a healthy male.<sup>4</sup> Morning cortisol and ACTH increase, but early evening cortisol and ACTH remained unchanged. It is unknown if mifepristone similarly disrupts sleep in chronic insomnia with presumed baseline HPA axis hyperactivity.

Regardless of whether mifepristone may disrupt sleep during acute treatment in healthy controls, we propose that a brief course of a GR antagonist in insomnia may be useful even post-discontinuation, to potentially down-regulate the HPA axis and decrease nocturnal CRH. Acutely, the drug raises cortisol by blocking feedback but then may theoretically result in lower HPA axis activity by increasing inhibitory cortisol feedback on hypothalamic CRH and downregulating the axis. We propose this downregulation occurs after the previously blocked GRs

### Disclosure Statement

This was not an industry supported study. Dr. Schatzberg is cofounder of Concept Therapeutics Incorporated, a pharmaceutical company engaged in the development of medications for the treatment of severe psychiatric and metabolic diseases. The other authors have indicated no financial conflicts of interest.

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are released from the blocking effects of the antagonist then flooded with the inhibitory influences of cortisol or MR flooding. A subsequent and prolonged decrease in CRH is expected to improve sleep in insomnia.

Alternatively, we consider that a GR antagonist may also improve insomnia during acute treatment by blocking positive feedback of endogenous cortisol at the level of the amygdala and outgoing LC circuits. In this manner, stress related activation of norepinephrine, a wake promoting neurotransmitter, is mitigated.

The aim of this study was to explore both the acute and post-discontinuation effects of a brief course of a GR antagonist as compared with placebo on sleep and the HPA axis in subjects with chronic insomnia. We predicted that polysomnogram measured sleep would improve, insomnia severity index (ISI) would decrease, and nocturnal cortisol and ACTH (23:00 to 07:00) would be decreased at 2 weeks post-discontinuation. We also measured these parameters during active treatment. This was a pilot study, and the focus was hypothesis generating descriptive statistics.

## METHODS

### Participants

Healthy subjects with chronic insomnia were recruited from the community. Phone interviews were conducted first, and subjects who met initial criteria were asked to keep a sleep diary for one week.

*Inclusion criteria* were: (1) by diary, have sleep latency > 30 min, wake after sleep onset > 30 min, or total sleep time < 6.5 h  $\geq$  3 times per week; (2) insomnia symptoms at least 3 nights/week over 6 months; (3) ability to tolerate multiple nights in the Human Sleep Research Center and Stanford General Clinical Research Center (GCRC); (4) age 20 to 65 years; (5) good physical health; (6) if female and sexually active, using birth control and willing to use the double barrier method during the study; (7) meet clinical criteria for an International Classification of Sleep Disorders (ICSD) diagnosis of either idiopathic insomnia or psychophysiological insomnia.

*Exclusion criteria* were the following: (1) presence of another primary sleep disorder as the primary cause of insomnia (e.g., restless legs, sleep apnea, periodic leg movement disorder, delayed sleep phase syndrome); (2) by in-house overnight polysomnogram, a respiratory index (RDI) > 10; (3) periodic leg movement index > 10; (4) currently pregnant or breast feeding; (5) currently on psychotropics, hypnotics, benzodiazepines, or use for 2 weeks prior to screening with sleep diary; (6) shift workers; (7) current or recent history (last 6 months) of substance abuse; (8) females with an IUD; (9) subjects with chronic adrenal failure; (10) subjects with history of allergy to mifepristone, misoprostol, or prostaglandin; (11) subjects with hemorrhagic disorders, on concurrent anticoagulant therapy, or with inherited prophyrias; (12) subjects with concurrent Diagnostic and Statistical Manual (DSMIV-TR) Axis I disorder; (13) diabetes; (14) subjects who drank grapefruit juice.

To eliminate extraneous increases in cortisol, all subjects had restrictions on their physical activity (no vigorous exercise for 3 days prior to the first overnight and throughout the study) and diet (no caffeine) prior to and during the study. All subjects

were asked to abstain from alcohol for 2 weeks before and during the study. Subjects abstained from hypnotics throughout the course of the study.

Thirteen subjects met all inclusion/exclusion criteria. Twelve subjects completed the protocol. One subject withdrew due to difficulty with IV access during the first overnight blood draw, prior to receiving medication versus placebo. One subject was excluded from the analysis who had much higher baseline cortisol levels compared to the rest of the insomnia subjects (>2 standard deviations above the mean). This subject received placebo. Another subject was excluded for non-compliance with the protocol. Thus, a total of 10 subjects were included in the analysis (5 active treatment and 5 placebo; 5 males and 5 females). The mean age and standard deviation was similar in the 2 groups: 52.2 (5.8) in the mifepristone group and 52.6 (7.1) in the placebo group. The gender distribution was similar as well: 2F/3M for mifepristone and 3F/2M for placebo. One female on placebo was premenopausal, the other 4 females had all undergone natural or surgical menopause.

### Study Design

#### Overall

This 30-day placebo controlled double-blind prospective pilot study assessed the effects of a 5-day course of 600 mg of the glucocorticoid antagonist mifepristone on sleep, cortisol, and ACTH in subjects with chronic insomnia. Subjects were assessed at 3 time points: baseline, day 5, and day 19. Both objective and subjective sleep measures as well as cortisol and ACTH hormonal measures were made.

Two consecutive nights of polysomnogram were performed followed by one night of hormonal measures to determine baseline values for each group (Time 1). Subjects then received a 5-day course of medication versus placebo, administered at 09:30 each morning. This 3-night sequence was repeated on days 3 through 5 during acute administration (Time 2). Because mifepristone may produce delayed effects, repeated sleep studies and hormonal measures were administered 2 weeks after medication discontinuation (Time 3).

During an open-label test trial of the protocol (n = 2), subjects reported greater sleep duration after treatment discontinuation. In order to capture this potentially clinically useful effect, the design permitted subjects to control their amount of time spent in bed (TIB). To allow for this degree of freedom in the design, the study did not control for lights out time or sleep efficiency; there was not a strict limit 8 h time in bed, as is typical in other clinical trials in insomnia.

### Sleep EEG Measures

Polysomnograms were conducted in the Stanford Human Sleep Research Laboratory using the Alice 4.0 polysomnogram device and acquisition software. Two consecutive nights were performed at each study time point and results averaged. The screening polysomnogram served as the initial adaptation night. During the study, polysomnogram included electro-oculograms (EOG), submental electromyogram (EMG), and 4 EEG leads (C3-A4, C4-A1, O1-A2, O2-A1).

The sleep recording protocol simulated the subjects natural sleep pattern. Polysomnogram was placed at 20:45. Subjects were given a sleep opportunity window between 21:45 and 07:45. After placement of polysomnograms, subjects were allowed to leisure in a living room or bedroom and do their usual bedtime routine until desired bedtime and lights out time. Subjects were permitted to sleep until desired wake time or until 07:45, if earlier. Lights out and lights on occurred at the subject's desired preference each night, within the above window.

### Sleep EEG Analysis

Sleep studies were manually scored according to the Rechtschaffen and Kales 1968 standard scoring criteria. A single scorer scored all studies and was blinded to the condition of each subject. Scoring was conducted using Alice 4.0 and Alice 5.0 software, reported to be compatible by the manufacturer. Parameters collected include total sleep time (TST); min of wake after sleep onset (WASO); stage 1 (S1), stage 2 (S2), stage 3 (S3), stage 4 (S4), and REM sleep; percentages of S1, S2, S3, S4, and REM; REM latency (from sleep onset); number of awakenings and arousal index (number of EEG microarousals/h).

### Subjective Sleep Measures

Subjects completed the Insomnia Severity Index (ISI) before and after treatment. The ISI measures severity of insomnia and its validity in assessing response to treatments has been demonstrated.<sup>9</sup> Scores range from 0 to 28, with highest scores indicating greatest severity.

### Hormonal Assays

At 16:00 on Day 1, an indwelling catheter was inserted. Blood samples were collected for cortisol and ACTH starting at 18:00. The 2-h delay before the first blood draw was permitted to minimize the effects of venipuncture on the HPA axis. The catheter remained in place overnight and subjects were allowed to sleep during the night, while samples were collected.

Samples were kept frozen at  $-70^{\circ}\text{C}$ . Hormonal assays were conducted by the Stanford General Clinical Research Laboratory. For cortisol, the analytic sensitivity was 0.3  $\mu\text{g}/\text{dL}$  with a coefficient of variation less than 8%. For ACTH, the analytic sensitivity was 0.46  $\text{pg}/\text{mL}$  with a coefficient of variation of less than 6.2%.

### Statistics

This was a pilot study; thus only exploratory statistics are reported in terms of group averages, standard deviations, and effect sizes. As a pilot study with a small sample size, hypothesis testing with inferential statistics is not applicable.

Objective sleep measures are reported as change scores from baseline for polysomnogram. Subjective sleep measures are reported as change scores for ISI for each group.

The primary hormonal measures were mean cortisol and ACTH during the typical nocturnal sleep period, from 23:00 to 07:00, at 2 weeks post-discontinuation. Other measures in-

cluded mean cortisol and ACTH for the following time periods: early evening (18:00 to 23:00) and morning (07:00 to 11:00) at 2 weeks post-discontinuation as well as the same measures on the fifth day of treatment. Post hoc analysis was performed on the ratio of cortisol/ACTH as an approximate measure of adrenal sensitivity.

To determine longitudinal effects of time for each subject and measure, a difference score from baseline to T2 (day 5 of 5 days consecutive acute treatment versus placebo) and from baseline to T3 (2 weeks post-discontinuation of treatment versus placebo) was computed.

To determine differences in treatment versus placebo, Cohen's  $d$  effect size was computed on difference scores in each group. Standard deviations were first computed for the difference scores. Next, a pooled standard deviation was computed based upon the standard deviations of difference scores for each group.

## RESULTS

### Polysomnogram Data

Polysomnogram results are given in Table 1. Results demonstrate mean values (SD) for each group at each time point, change scores from baseline for each group at each time point and effect sizes computed on change scores at each time point.

Table 1 suggests no clinically significant polysomnogram effect of 5 days of mifepristone at 600 mg on sleep efficiency and SWS at 2 weeks post-discontinuation of treatment. In contrast, changes in REM were observed. Minutes of REM (10.45 min, effect size = 0.49), percentage REM (1.31%, effect size = 0.28) and REM density (2.73, effect size = 1.10) increased at 2 weeks post-treatment. At days 3 and 4 of treatment, relative to baseline min of REM (36.7 min, effect size = 1.51) and percentage REM (9.7%, effect size = 1.8) had decreased.

### Subjective Sleep Data

Table 2 includes subjective measures of ISI with time. Post hoc analysis indicated an average 4-point (effect size = 0.97) decrease from baseline in ISI in the treatment group relative to the placebo group at two weeks post-discontinuation. Earlier post-discontinuation measures also showed a decrease in ISI.

### Hormonal Data

#### CORTISOL AND ACTH

From baseline to 2 weeks post-treatment (23:00 to 07:00), mean cortisol increased by 0.84  $\mu\text{g}/\text{dL}$  (effect size = 0.91) in the mifepristone group compared to the placebo group. During the same time period, mean ACTH increased by 5.50  $\text{pg}/\text{mL}$  (effect size = 0.96) in the mifepristone group compared to the placebo group. Results are given in Figures 1 and 2. From baseline to 2 weeks post-treatment (18:00 to 23:00), mean cortisol *decreased* in the mifepristone group compared to the placebo group. In contrast, at all other time points and time intervals, both cortisol and ACTH increased as indicated in Table 3.

**Table 1**—Polysomnogram Results

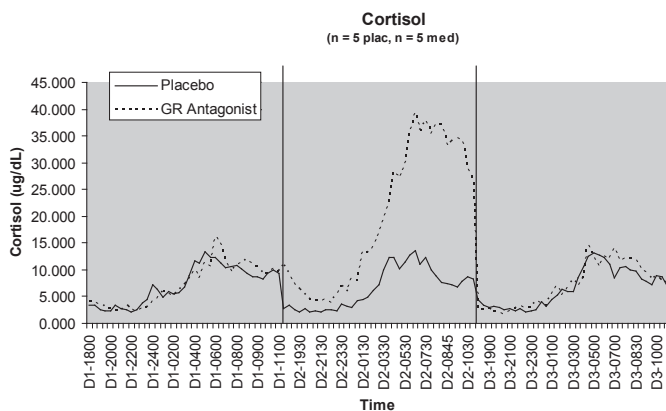
Measure	Mifepristone (SD) (n = 5)	Placebo (SD) (n = 5)	Mifepristone Change from Baseline (SD)	Placebo Change from Baseline (SD)	Mifepristone Net Change	Cohen d Effect Size
Total Sleep Time (min)						
Baseline	373.60 (74.21)	364.20 (64.4)				
Days 3, 4 Tx	390.65 (61.95)	385.00 (21.34)	17.05 (26.63)	20.3 (47.62)	-3.75	-0.10
2 Wk Post-Tx	412.10 (58.34)	381.05 (26.64)	38.5 (33.72)	16.85 (57.02)	21.65	0.46
WASO (min)						
Baseline	66.95 (24.22)	83.35 (69.71)				
Days 3, 4 Tx	83.35 (42.34)	61.90 (37.43)	-6.4 (31.14)	-21.45 (40.1)	37.85	1.05
2 Wk Post-Tx	56.55 (19.73)	65.10 (44.75)	-10.4 (8.01)	-18.25 (43.27)	7.85	0.25
SWS (%)						
Baseline	11.24 (11.40)	17.14 (8.56)				
Days 3, 4 Tx	11.99 (12.37)	16.76 (8.45)	0.75 (1.36)	-0.38 (3.011)	1.13	0.48
2 Wk Post-Tx	10.85 (8.04)	15.98 (7.05)	-0.39 (3.87)	-1.16 (3.30)	0.77	0.21
REM (%)						
Baseline	20.95 (2.97)	21.33 (5.41)				
Days 3, 4 Tx	11.62 (5.86)	21.69 (3.72)	-9.33 (6.9)	0.36 (3.04)	-9.69	-1.82
2 Wk Post-Tx	22.58 (3.98)	21.65 (4.08)	1.63 (6.16)	0.32 (2.60)	1.31	0.28
# Awakenings						
Baseline	24.30 (10.47)	25.30 (10.90)				
Days 3, 4 Tx	27.60 (10.39)	23.60 (18.46)	3.3 (4.78)	-1.7 (14.5)	5.00	0.46
2 Wk Post-Tx	24.30 (15.53)	23.80 (16.37)	0	-1.5 (14.3)	1.50	0.13
SWS (min)						
Baseline	40.80 (37.08)	57.60 (25.93)				
Days 3, 4 Tx	47.90 (47.22)	63.45 (30.65)	7.1 (10.65)	5.85 (15.66)	1.25	0.09
2 Wk Post-Tx	43.75 (30.55)	60.05 (26.28)	2.95 (10.39)	2.45 (10.9)	0.50	0.05
REM Sleep (min)						
Baseline	79.00 (22.97)	80.05 (30.72)				
Days 3, 4 Tx	47.00 (26.00)	84.75 (18.43)	-32 (31.35)	4.7 (14.08)	-36.70	-1.51
2 Wk Post-Tx	92.15 (13.54)	82.75 (18.10)	13.15 (22.88)	2.7 (19.49)	10.45	0.49
REM Density						
Baseline	7.99 (3.16)	9.68 (5.14)				
Days 3, 4 Tx	7.16 (3.73)	8.20 (4.54)	-0.83 (2.873)	-1.48 (1.8)	0.65	0.27
2 Wk Post-Tx	9.95 (2.99)	8.92 (4.60)	1.97 (3.27)	-0.76 (1.26)	2.73	1.10
Arousal Index (#/hr)						
Baseline	16.60 (5.31)	17.28 (5.98)				
Days 3, 4 Tx	16.25 (3.51)	16.64 (7.68)	-0.35 (2.25)	-0.64 (6.07)	0.29	0.06
2 Wk Post-Tx	15.75 (3.51)	17.52 (7.04)	-0.85 (3.35)	0.24 (3.44)	-1.09	-0.32
Total Sleep Period (min)						
Baseline	440.55 (75.72)	447.60 (58.59)				
Days 3, 4 Tx	469.24 (66.18)	446.90 (34.85)	28.69 (12.16)	-0.7 (41.95)	29.39	0.95
2 Wk Post-Tx	468.65 (65.41)	446.15 (40.17)	38.5 (33.7)	16.85 (57.02)	29.55	0.57
Time in Bed (min)						
Baseline	477.20 (61.6)	492.20 (50.38)				
Days 3, 4 Tx	486.70 (74.21)	477.90 (39.07)	9.5 (34.55)	-14.3 (31.33)	23.8	0.72
2 Wk Post-Tx	481.40 (61.12)	479.30 (56.05)	4.2 (45.2)	-12.9 (17.8)	17.1	0.50
SE (TST/TIB)						
Baseline	78.08 (9.42)	74.77 (14.28)				
Days 3, 4	80.39 (8.03)	81.03 (7.82)	2.31 (8.65)	6.26 (6.6)	-3.95	-0.51
2 Wk Post-Tx	85.58 (3.57)	80.10 (7.41)	7.5 (6.86)	5.33 (9.91)	2.17	0.25

**Table 2**—Insomnia Severity Index (ISI)

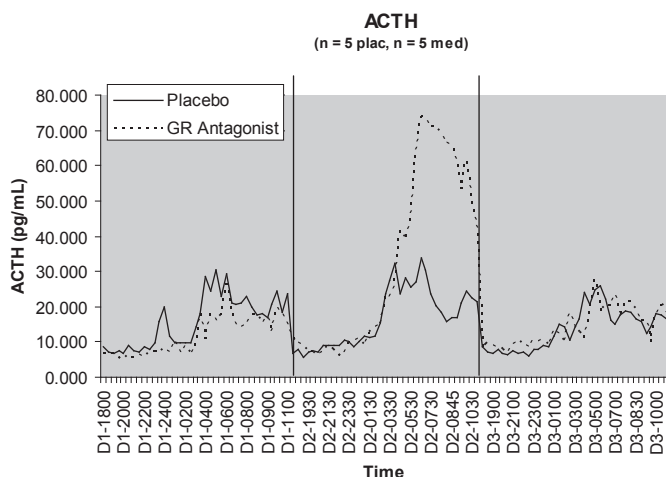
Measure	Mifepristone (SD) (n = 5)	Placebo (SD) (n = 5)	Mifepristone Change from Baseline (SD)	Placebo Change from Baseline (SD)	MifepristoneNet Change	Cohen's d Effect Size
Baseline ISI	13.6 (2.30)	13.8 (6.14)				
Day 2 Post Tx	12.0 (3.16)	14.0 (6.16)	-1.6 (4.83)	0.2 (5.17)	-1.8	-0.36
Day 6 Post Tx	9.0 (1.41)	14.8 (6.26)	-4.6 (1.82)	1.0 (4.82)	-5.6	-1.74
Day 12 Post Tx	9.2 (4.49)	13.4 (7.37)	-4.4 (3.51)	-0.4 (4.67)	-4.0	-0.97

At baseline to day 5 of acute treatment and during all time intervals considered, mean cortisol and ACTH increased as indicated in Table 4. We observed an increase in cortisol in the

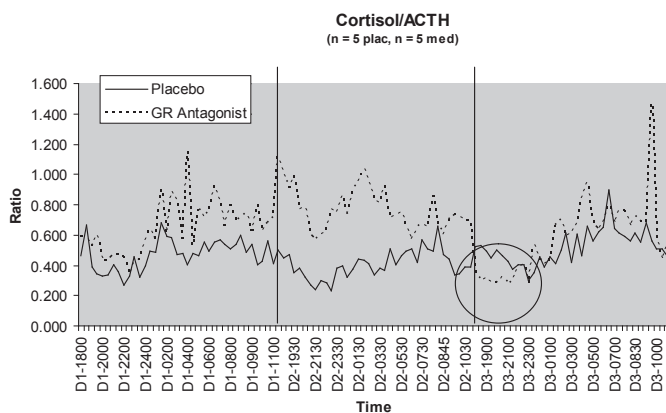
early evening and overnight, as well as in the morning, in contrast with healthy controls who had an increase in cortisol, but not ACTH, limited to the morning only.<sup>10</sup>



**Figure 1**—Absolute Cortisol Values with Time (D1 = baseline, D2 = day 5 Tx, D3 = 2 weeks post Tx)



**Figure 2**—Absolute ACTH Values with Time (D1 = baseline, D2 = day 5 Tx, D3 = 2 weeks post Tx)



**Figure 3**—Absolute Ratio Cortisol/ACTH with Time (D1 = baseline, D2 = day 5 Tx, D3 = 2 weeks post Tx)

#### CORTISOL/ACTH RATIO

On day 5 of treatment, compared to placebo, mifepristone increased the mean cortisol/ACTH ratio for all overnight periods considered (18:00 to 23:00, 23:00 to 07:00, and 07:00 to 11:00). See Figure 3. In contrast, this ratio decreased 2 weeks post-discontinuation (18:00 to 23:00 and 23:00 to 07:00). This

decreased ratio is largely attributed to an increase of ACTH. One exception occurred during the period from 18:00 to 23:00 at 2 weeks post-discontinuation when cortisol decreased in the setting of an increased ACTH. Thus, this time period coincided with the largest effect size for a net decrease in the ratio of mean cortisol/ACTH.

#### Adverse Events

No serious adverse events occurred. Mifepristone was well tolerated. Non-serious adverse events included rash in 1 subject who received active drug. Additional non-serious adverse events included one episode of vaginal spotting, headache, and brief abdominal discomfort.

#### DISCUSSION

Although we did not detect a clinically meaningful improvement in either sleep efficiency or slow wave sleep at 2 weeks post-discontinuation, we did observe changes in REM sleep. The polysomnogram portion of this study was limited by the latitude of time subjects were allowed to spend in bed. Thus, compared to other insomnia studies, polysomnogram measures were inconclusive, limited by study design and do not indicate that objective improvement does not occur.

Regarding subjective sleep measures, we did detect clinically meaningful changes. Most importantly, we observe a decrease in ISI at 2 weeks post-discontinuation as well as at day 6.

Our findings do not preclude potential benefit to sleep architecture with a pure glucocorticoid antagonist without anti-progesterone effects. Progesterone enhances sleep, likely via GABA A activity, and the antiprogestosterone effect of mifepristone may mask any potential antiglucocorticoid benefit. For example, it is conceivable that acute treatment with a GR antagonist may still have clinically useful benefit due to anticipated blockade of the amygdala-LC circuit and reduced activation of the wake promoting neurotransmitter, norepinephrine.

Contrary to our prediction that both cortisol and ACTH might decrease during the nocturnal period (23:00 to 07:00) at 2 weeks post-discontinuation, these hormones remained increased with one exception. In the early evening, from 18:00 to 23:00, cortisol levels were decreased. Since the first part of the night (21:00 to 00:30) is the time period when greatest HPA axis activation has been reported in chronic insomnia,<sup>3</sup> a decrease in the early part of the night (instead of from 23:00 to 07:00) may be what is most important to achieve benefit in insomnia.

Finally, post hoc analysis revealed a decrease in cortisol/ACTH ratio at 2 weeks post-discontinuation which was most prominent in the early evening (18:00 to 23:00). This finding may suggest an ongoing re-regulation of the axis in the following context. In chronic depression with possible elevated brain CRH levels, HPA axis dysregulation has been characterized by a decrease in ACTH response to CRH combined with an increase in adrenal sensitivity.<sup>11</sup> These HPA axis changes normalize with successful treatment of the depression<sup>11</sup> such that ACTH increases and adrenal sensitivity (approximated by cortisol/ACTH ratio herein) decreases.

If we apply this same model for the changes seen in our patients with insomnia, the decrease in cortisol/ACTH ratio at 2

**Table 3**—Neuroendocrine Results

Measure	Mifepristone (SD) (n=5)	Placebo (SD) (n=5)	Mifepristone Change from Baseline (SD)	Placebo Change from Baseline (SD)	Mif Net Change	Cohen's d Effect Size
Mean Cortisol, µg/dL (23:00-07:00)						
Baseline	8.32 (2.64)	8.62 (2.07)				
Days 3, 4 Tx	20.33 (7.28)	8.13 (1.87)	12.02 (7.06)	-0.49 (1.97)	12.51	2.41
2 Wk Post-Tx	8.49 (2.47)	7.96 (2.05)	0.17 (0.73)	-0.66 (1.07)	0.84	0.91
Mean ACTH, pg/mL (23:00-07:00)						
Baseline	12.71 (3.02)	18.45 (3.42)				
Days 3, 4 Tx	30.56 (6.82)	20.68 (3.57)	17.85 (7.15)	2.23 (4.089)	15.62	2.68
2 Wk Post-Tx	15.76 (6.55)	16.00 (3.36)	3.05 (4.91)	-2.45 (6.49)	5.50	0.96
Mean Cortisol, µg/dL (18:00-23:00)						
Baseline	2.98 (0.71)	2.84 (0.81)				
Days 3, 4 Tx	5.95 (2.59)	2.53 (0.81)	2.96 (2.17)	-0.31 (0.42)	3.27	2.10
2 Wk Post-Tx	2.59(0.82)	2.91 (0.80)	-0.4 (0.799)	0.071 (0.873)	-0.47	-0.56
Mean ACTH, pg/mL (18:00-23:00)						
Baseline	6.26 (1.61)	7.89 (2.22)				
Days 3, 4 Tx	7.88 (2.96)	7.99 (2.35)	1.618 (2.66)	0.10 (0.65)	1.52	0.79
2 Wk Post-Tx	9.01 (3.56)	7.13 (1.69)	2.75 (3.24)	-0.76 (2.96)	3.51	1.13
Mean Cortisol, µg/dL (07:00-11:00)						
Baseline	10.37 (2.83)	9.55 (1.35)				
Days 3, 4 Tx	33.95 (7.68)	8.50 (1.16)	23.59 (8.78)	-1.05 (1.46)	24.64	3.91
2 Wks Post-Tx	10.01 (1.95)	8.86 (1.85)	-0.36 (1.36)	-0.69 (1.29)	0.33	0.25
Mean ACTH, pg/dL (07:00-11:00)						
Baseline	16.26 (5.77)	20.34 (3.88)				
Days 3, 4 Tx	60.87 (31.79)	20.19 (3.65)	44.61 (28.11)	-0.16 (4.24)	44.17	2.23
2 Wk Post-Tx	17.78 (7.54)	16.59 (3.55)	1.52 (4.73)	-3.76 (3.93)	5.27	1.21
Mean Cort/ACTH (18:00-23:00)						
Baseline	0.49 (0.11)	0.39 (0.10)				
Days 3, 4 Tx	0.80 (0.34)	0.34 (0.09)	0.31 (0.249)	-0.05 (0.049)	0.36	2.01
2 Wk Post-Tx	0.32 (0.14)	0.44 (0.17)	-0.16 (0.074)	0.047 (0.248)	-0.21	-1.15
Mean Cort/ACTH (23:00-07:00)						
Baseline	0.73 (0.27)	0.50 (0.15)				
Days 3,4 Tx	0.80 (0.28)	0.41 (0.11)	0.073 (0.034)	-0.09 (0.135)	0.16	1.63
2 Wk Post-Tx	0.65 (0.37)	0.54 (0.23)	-0.08 (0.25)	0.043 (0.145)	-0.12	-0.6
Mean Cort/ACTH (07:00-11:00)						
Baseline	0.71 (0.22)	0.50 (0.08)				
Days 3, 4 Tx	0.70 (0.37)	0.46 (0.16)	-0.01 (0.243)	-0.04 (0.127)	0.03	0.16
2 Wk Post-Tx	0.73 (0.35)	0.56 (0.16)	0.026 (0.209)	0.064 (0.136)	-0.04	-0.21

\* = primary hypothesis

weeks post-discontinuation may represent an ongoing re-regulation in the same direction expected with the resolution of depression. Such re-regulation may include increased mineralocorticoid receptor activity. Supporting this concept, we observe a similar evening decrease in both evening cortisol and the cortisol/ACTH ratio in healthy controls during treatment with an MR agonist.<sup>12</sup> This may be beneficial in insomnia, since MR activity inhibits CRH via hippocampal inputs. Finally, mifepristone has been shown to alter 11 β-dehydrogenase activity, suggesting an additional potential mechanism of action.

Limitations of the polysomnogram design of this pilot include the latitude for time in bed (TIB) given subjects with insomnia during the in-patient PSG portions at all time periods tested. Though this flexibility was intentional to allow for adequate opportunities for clinically useful differences in TST to occur between groups (if driven by the subject), we realize that this is a nonconventional approach and makes polysomnogram comparison to other clinical trials in insomnia difficult.

Another limitation was that subjects were not selected for HPA axis hyperactivity. Rather, they were presumed to be hy-

percortisolemic based upon prior reports of HPA axis hyperactivity in insomnia without depression.<sup>1-3</sup> Moreover, not all studies agree that there is HPA axis hyperactivity in insomnia. However, the acute rise in early evening cortisol in our subjects given mifepristone, in contrast to a lack of rise in healthy controls<sup>4,10</sup> suggests that HPA axis regulation may differ between healthy controls and those with insomnia.

We employed a limited number of time points and intervals post-discontinuation. Although we expected decreases in cortisol and ACTH to be apparent at 2 weeks, it is possible that these changes may not occur until much later. Also, we did not directly measure CRH activity or adrenal sensitivity which would elucidate mechanisms of re-regulation in the axis. Because this was a pilot study, sample size was too small for hypothesis-driven inferential statistical evaluation.

A limitation of mifepristone is its antiprogesterone effects. However, no pure GR antagonist is currently available for testing. Once available, use of a pure GR antagonist would delineate and eliminate the potential confounding masking effects of progesterone antagonism on our results. Rash of unknown

etiology has been observed in some patients. We only studied one dose of the drug and cannot infer much about effects of higher doses. Thus, further study to optimize dosage and safety is needed.

In summary, this is the first pilot study of a GR antagonist in chronic insomnia. We predicted that benefits to sleep would occur post-discontinuation. Polysomnogram data was limited by the nature of the design. However, favorable decreases in ISI suggest a promising effect of the drug. Further study is required.

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