LBA 1

AN ENDOGENOUS CONSTITUENT OF CSF ENHANCES GABAA RECEPTOR FUNCTION IN THE PRIMARY HYPERSOMNIAS.

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Introduction: The primary hypersomnias are a poorly understood construct lacking an etiology or rational treatments. We probed for biomarkers in 31 such cases and 16 controls.

Methods: We assessed sleepiness with standard metrics, and plasma and cerebrospinal fluid (CSF) for sedative-hypnotic use, GABA excess, and hypocretin-1 deficiency. We tested for GABA-ergic activity employing ligand binding assays and voltage-clamp electrophysiological recordings of cells expressing recombinant human GABAA receptors.

Results: Three primary hypersomnia subgroups (viz., narcolepsy without cataplexy (N—C), and idiopathic hypersomnia with and without long sleep time), habitually long sleepers, and controls exhibited no differences in CSF hypocretin-1 (F=0.51, df 4,45, p =0.73) or GABA (F=0.93, df 4,26, p = 0.46) concentrations, and no benzodiazepines (BZDs), BZD metabolites, nor newer α1 GABA receptor preferring sedative/hypnotics were detected by gas and liquid chromatography/tandem mass spectrometry, and
conventional ligand binding assays. Co-application of GABA and pooled CSF from 4 hypersonsomolent patients produced a large (186±34%) enhancement of inward chloride currents (t= 7.71, p <0.001) that was blocked with 5 µM flumanzenil. Enhancement in BZD insensitive α 1(H102R) β 2 γ 2s GABAA receptors was smaller (72±12%, t=6.89, p<0.001), yet significant. Pooled CSF from two vigilant controls only modestly enhanced α1 β 2 γ 2s (31±3%, t= 2.58, p = 0.037) and α 1(H102R) β 2 γ 2s GABAA receptors (23±4%, t=3.45, p=0.014), and both were only weakly blocked by flumazenil. The magnitudes of enhancement determined for individual CSFs at α1β2γ2s receptors differed amongst the four hypersonsomolent groups and controls (F=4.95, df 4,46, p=0.0023), and were significantly greater in N-C (p=0.0066) and long sleepers (p=0.01) versus controls.

Conclusions: Inhibitory GABAA receptor enhancement occurs by way of a positive allosteric modulator unique to patients with primary hypersomnia. This altered biology is antagonized in vitro by flumazenil and suggests a novel pathophysiology to disorders of primary hypersonmolence.

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LBA 2

SLEEP DEPRIVATION IMPAIRS THE RECOGNITION OF COMPLEX SOCIAL EMOTIONS

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Introduction: Facial expressions provide the most salient emotional cues impacting human behavior, markedly altering aversive and affiliative feelings and actions. Despite the striking overlap between the known limbic and prefrontal brain networks that interpret facial emotions, and those impacted by sleep deprivation, the influence of sleep deprivation on evaluation of social emotions remains unknown. Using fMRI and high-density EEG (hdEEG), here we examine the detriment of sleep deprivation, and sleep recovery, on the ability of the human brain to recognize complex social cues.

Methods: 12 healthy adults (7-female,18-25yrs) participated in a repeated-measures, within-subject fMRI experiment involved the judging and discrimination of two separate complex social emotions – Trust (affiliative) and Threat (aversive) – once after a normal night of sleep and once after 24 hours of deprivation. After deprivation, subjects were given an hdEEG monitored recovery sleep period.

Results: Sleep deprivation imposed a dramatic impairment in the discrimination of threatening (aversive) facial cues, but resulted in no impairment for the discrimination of
trustworthy (affiliative) facial cues. For threatening cues, deprivation did not produce a global perceptual impairment related to primary visual regions, but a selective impairment only for the most threatening facial expressions (p<0.001), related to prefrontal cortex and limbic networks. Most striking, the degree of this discrimination impairment was strongly predicted by the extent of NREM SWS activity obtain during recovery, both in the amount of slow-wave activity, the steepness of the slow-wave slope and its amplitude (R<-0.64, p<0.045).

**Conclusion:** Together, these findings demonstrate a marked and selective impairment by sleep deprivation on the ability of the human brain to recognize complex social emotions, specifically aversive-relevant facial cues. Furthermore, these deficits were inversely predicted by the intensity of subsequent NREM recover sleep physiology. Considering the relevance of emotional face-cues to human behavior, these data have marked professional and societal ramifications.

**LBA 3**

**DISTINCT PHASE RELATIONSHIPS BETWEEN SUPRACHIASMATIC MOLECULAR RHYTHMS AND BEHAVIORAL RHYTHMS IN EARLY RUNNER (CAST/Ei) AND NOCTURNAL (C57BL/6) MICE**

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**Introduction:** Mice of the CAST/EiJ (CAST) and C57Bl/6J (B6) strains exhibit differences in phase angle of entrainment, as measured by the timing of wheel-running onset relative to a light/dark 12:12 cycle. These populations provide an animal model for studies on the neurobiological basis for circadian phase misalignment in humans. Neither differences in endogenous circadian period nor the shape of the photic phase response curve can explain the difference in the phase angle of entrainment between CAST and B6 mice. Therefore, we hypothesized that alterations in the output or downstream mechanisms of the circadian system, rather than the timing of the master circadian pacemaker in the suprachiasmatic nucleus (SCN) might mediate the circadian phenotypic difference between CAST and B6.

**Methods:** Sleep/wake cycles in both strains were recorded using a high-throughput piezoelectric system. Clock-gene mPer1 and mPer2 transcript levels across the circadian cycle were measured in the SCN, subparaventricular zone (sPVZ), cerebral cortex, and paraventricular hypothalamic nucleus (PVH) using in situ hybridization.

**Results:** Entrained sleep/wake cycles were advanced by ~3-6 hrs in CAST mice relative to B6, consistent with previous wheel-running data. This was paralleled by
advanced rhythms of cortical mPer1 and mPer2 expression in CAST relative to B6. Expression of mPer1 in the PVH also oscillated with an advanced phase in CAST mice compared to B6. In contrast, the timing of daily cycles of mPer1 and mPer2 expression in the SCN, mPer1 expression in the sPVZ, and the circadian gating of light-induced mPer1 and mPer2 expression in the SCN were unaffected by strain.

**Conclusion:** The advanced circadian phase in CAST mice relative to B6 is associated with differences in mPer1 and mPer2 gene expression in extra-SCN regions, but not in the SCN or its nearest efferent target, the sPVZ. These data indicate an altered mechanism downstream of the SCN in CAST mice.

**LBA 4**

**SKP-1041, A NOVEL MODIFIED-RELEASE FORMULATION OF ZALEPLON, SIGNIFICANTLY IMPROVES SLEEP IN PATIENTS WITH MIDDLE-OF-THE-NIGHT AWAKENING: RESULTS OF A PHASE II, DOUBLE-BLIND, CROSSOVER, PLACEBO-CONTROLLED, DOSE-RANGING TRIAL**

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**Introduction:** Most chronic insomnia patients report middle-of-the-night (MOTN) sleep difficulty, with or without sleep onset complaints. Bedtime ingestion of current hypnotics provide a sleep initiation effect whether or not it is needed. SKP-1041 is a novel formulation of zaleplon designed to release active drug over a 2-hour period beginning 2 hours after ingestion. This release profile provides zaleplon during the hours needed to reduce MOTN wake time, while allowing physiologic sleep initiation.

**Methods:** This phase II, double-blind, crossover study enrolled adult, non-elderly patients with primary insomnia characterized by MOTN awakening. Participants received placebo and SKP-1041 10 mg, 15 mg, and 20 mg before bedtime for 2 consecutive nights with 4-7 days of washout between treatments. Previous reports have confirmed an identical zaleplon release profile with all 3 doses, and dose-proportional Cmax and AUC. Sleep/wake episodes were recorded by polysomnography for 8 hours after lights-out. The primary endpoint was Wake After Sleep Onset during hours 3-7 (WASO 3-7); secondary endpoints included Total Sleep Time 3-7 (TST 3-7) and Number of Awakenings After Sleep Onset 3-7 (NAASO 3-7). Residual effects were
evaluated within 1 hour of awakening using the Digit Symbol Substitution Test (DSST) and Digit Span Test (DST).

**Results:** 62 patients were evaluated for efficacy. WASO 3-7 was significantly \((p \leq 0.01)\) decreased and TST 3-7 was significantly \((p \leq 0.009)\) increased with all SKP-1041 doses compared to placebo; TST analyzed by hour was significantly \((p < 0.0001 \text{ to } p = 0.0259)\) greater at hours 3, 4, and 5 compared to placebo. NAASO 3-7 was significantly \((p \leq 0.02)\) decreased with SKP-1041 15 mg and 20 mg compared to placebo. Residual drug effects were not detected on the DSST and DST. All doses were well-tolerated.

**Conclusion:** All doses of SKP-1041 significantly reduced MOTN wakefulness, relative to placebo, without evidence of residual effects.

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**LBA 5**

**THE EFFECT OF ARMODAFINIL ON CLINICAL CONDITION AND EXCESSIVE SLEEPINESS LATE IN THE NIGHT SHIFT AND OVERALL FUNCTIONING IN PATIENTS WITH SHIFT WORK DISORDER**

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**Introduction:** Patients with shift work disorder (SWD) may be more vulnerable to the consequences of excessive sleepiness at the end of the night shift and morning commute home. The current study, the largest ever conducted in patients with SWD, examined whether armodafinil improved clinical condition and sleepiness late in the night shift. Overall patient functioning was also examined.

**Methods:** In this randomized, double-blind, placebo-controlled multi-center study, patients were administered 150 mg armodafinil or placebo for 6 weeks. Patients with diagnosed SWD (DSM-IV and ICSD-2 criteria), worked at least five 6-12 hour night shifts a month, had late shift sleepiness (mean Karolinska Sleepiness Scale [KSS] >6) and functional impairment (Global Assessment of Functioning [GAF] <70). The primary efficacy endpoint was improvement in Clinical Global Impressions-Change (CGI-C) with regard to excessive sleepiness late in the shift (0400 to 0800) at Week 6. Secondary efficacy measures included mean change in GAF and late shift KSS from baseline to final visit. Tolerability was also assessed.

**Results:** A total of 383 patients were enrolled and a similar proportion of patients in both groups completed the study (82% armodafinil; 88% placebo). At the final visit, more patients treated with armodafinil demonstrated improved late-in-shift CGI-C scores versus placebo (77% vs. 57%; \(p < 0.0001\)). Armodafinil-treated patients also had a greater mean change in GAF (+9.5 vs. +5.2; \(p < 0.0001\)) and KSS (-2.8 vs. -1.8;
p<0.0001) from baseline to final visit. The most common adverse events (AEs) were headache and nausea with no serious events observed with armodafinil treatment.

**Conclusion:** Armodafinil significantly improved clinical condition late in shift, including the commute home, during the critical circadian nadir period of 0400 to 0800 in patients with SWD. Armodafinil improved patient functioning and reduced late shift sleepiness. Adverse events with armodafinil were similar to those observed in a previous SWD study with armodafinil.

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