Introduction: Sleep-promoting drugs should facilitate sleep without hindering the ability to awaken to salient stimuli. Here we present baseline results of an ongoing study of the dual orexin receptor antagonist lemborexant on the auditory awakening threshold (AAT) - a measure of environmental responsiveness during sleep.
Methods: Double-blind, single-dose, 4-way crossover in healthy females (≥55y) and males (≥65y). Eligible subjects underwent 8hr baseline PSG. After several subjects unexpectedly met the exclusion criterion of latency to persistent sleep (LPS) >30 min, a protocol amendment permitted repeat baseline PSG. Subjects slept with insert earphones. The auditory stimulus apparatus produced 1000Hz tones for 3secs at 15-sec intervals. Starting dB level was 15, increasing 5dB to a maximum 105dB, until the subject stated, "I'm awake." Awakening threshold was the dB level one level below the response. The AAT was initiated 4h after bedtime if subjects were in non-REM stage 2 (N2). If >5 consecutive min of N2 sleep did not occur between 4-4.5h post-bedtime, the AAT was initiated at 4.5h post-bedtime regardless of stage.
Results: Of 120 subjects screened, 48 were randomized. Major reasons for failing screening: apnea-hypopnea index >15 (16 subjects) and LPS >30min (19). 9 repeated baseline; 8 subsequently passed the LPS criterion. Of the 48, 5 were awake from the 4-4.5h. Of the 43, 38 (88%) were in N2. The mean intensity required to awaken subjects at baseline was 45dB (range: 15dB - 95dB). 3 (7%) subjects did not awaken to the maximum tone of 105dB; all were in stage N2 at the AAT start.
Conclusion: Although healthy, many subjects had prolonged baseline LPS, anecdotally due to anticipatory anxiety associated with the AAT. Allowing for a second baseline appears to mitigate this issue. Due to interindividual variability in baseline AAT, analyses from studies that do not include a time-matched baseline would be potentially problematic. Relatively low dB awakened subjects at baseline, indicating that AAT as implemented may be sensitive to changes in threshold resulting from administration of sleep-promoting drugs.
Support (If Any): Eisai, Inc. and Purdue Pharma L.P.

0413

EFFECTS OF TRAZODONE ON BLOOD PRESSURE: A LONGITUDINAL, OBSERVATIONAL STUDY OF PATIENTS PRESENTING TO A SLEEP DISORDER CLINIC

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Introduction: Insomnia is associated with an increased risk for hypertension, especially in those sleeping objectively less than 6 hours. We sought to observe the effects of trazodone, a sedative antidepressant that is commonly prescribed off-label for treatment of insomnia, on blood pressure (BP) in a clinical sample.
Methods: The electronic medical record at Penn State Hershey Sleep Research & Treatment Center was searched using Informatics for Integrating Biology & the Bedside (i2b2), which extracted 42 patients with a diagnosis of insomnia disorder who were also prescribed trazodone (47.6 ± 12.8y, 57.1% female, BMI=30.0 ± 5.7 kg/m^2). Exclusion criteria included a diagnosis of sleep apnea, CPAP use, and prescription of anti-hypertensive medications after being prescribed trazodone. Change in mean arterial blood pressure (ΔMAP) was calculated from systolic and diastolic BP at pre-treatment and at six months of follow-up. Data were analyzed using repeated-measures t-test and ANCOVA, with sex, age, BMI, and time-to-follow-up as covariates.
Results: There were no significant changes in MAP (ΔMAP) in the full sample. While MAP did not significantly change across 6 months (ΔMAP=3.0 ± 1.7 mmHg, p=0.113, unadjusted analyses) in patients with normal BP (<120/80 mmHg, n=13) at pre-treatment, MAP significantly decreased in those who had elevated BP (≥120/80 mmHg, n=23) at pre-treatment (ΔMAP=-5.8 ± 1.9 mmHg, p=0.006). Compared to those with normal BP, patients who had elevated BP at pre-treatment had a significant decrease in multivariable-adjusted MAP after 6 months of follow-up (ΔMAP=Δ3.8 ± 1.9 vs. -6.4 ± 1.6 mmHg, p<0.001).
Conclusion: Trazodone has the potential to lower BP in patients with chronic insomnia independent of anti-hypertensive medication. Future randomized controlled trials should examine this important question, particularly among patients with insomnia with objective short sleep duration, as they are more likely to present with comorbid hypertension, and/or develop hypertension in the future.
Support (If Any): none.

0414

RESULTS FROM AN ON-ROAD DRIVING PERFORMANCE STUDY IN NON-ELDERLY AND ELDERLY HEALTHY SUBJECTS WITH DUAL OREXIN RECEPTOR ANTAGONIST LEMBOREXANT

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Introduction: Sedating CNS-active drugs are typically studied for the potential to impair next-morning driving. Data from an on-road driving performance study are presented for lemborexant (LEM), a dual orexin receptor antagonist under development for insomnia disorder.
Methods: Randomized, double-blind, 4-period, incomplete crossover design. Healthy subjects (n=24 non-elderly, n=24 elderly; 26M, 22F) received placebo (P), zopiclone 7.5mg (Z; positive control), and 2 of 3 LEM doses (2.5/5/10mg). P and LEM were taken for 8 consecutive nights; Z was dosed on Night 1 and Night 8 with P on Nights 2–7. The standardized 1-hr on-road driving tests on Day 2 (D2) and Day 9 (D9) started ~9h post dose. Standard deviation of lateral position (SDLP in cm) was the primary endpoint.
Results: All 48 subjects completed the study. Assay sensitivity was demonstrated, as for Z vs P, the 95% CI upper bound was >2.4cm (standard threshold for impairment) at both D2 and D9. Additionally, mean SDLP for Z vs P and symmetry analyses of subjects with SDLP difference in Z vs P >2.4cm vs <2.4cm were statistically significant at D2 and D9 (P<0.01). For each LEM dose vs P, the 95% CI upper bound was <2.4cm. No mean SDLP for LEM vs P was significant for any dose on D2 (P>0.05) or D9 (P>0.05). Symmetry analyses were not statistically significant for any LEM dose on D2 or D9 (P>0.05). Results were similar in age and sex subgroups. No serious or severe adverse events (AEs) were reported. AEs of somnolence were reported more frequently after LEM 10mg than LEM 2.5 and 5mg administration.
Conclusion: As measured by SDLP and at the doses tested, lemborexant did not impair driving performance after either single (Day 2) or multiple (Day 9) dose administration. These results warrant continued testing of the efficacy and safety of LEM for the treatment of insomnia disorder.
Support (If Any): Eisai, Inc and Purdue Pharma L.P.

0415

DOES TIME IN BED VARY WITH THE USE OF HYPNOTICS?

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