**Safety and efficacy of suvorexant during 1-year treatment of insomnia with subsequent abrupt treatment discontinuation: a phase 3 randomised, double-blind, placebo-controlled trial.**

Citation: Michelson D, Snyder E, Paradis E, et al. Safety and efficacy of suvorexant during 1-year treatment of insomnia with subsequent abrupt treatment discontinuation: a phase 3 randomised, double-blind, placebo-controlled trial. Lancet Neurol. 2014; 13(5):461-71.

Background:

- Insomnia affects up to 30% of the American adult population
- Current drugs includes benzodiazepine hypnotics (e.g. temazepam) and non-benzodiazepine hypnotics (e.g. eszopliclone, zolpidem, zaleplon)
- Current options are efficacious, but not without side effects and dependency issues.
- The study aimed to assess the safety and tolerability of suvorexant as compared to placebo during a long-term trial.
- Exploratory objectives were to assess the effects of abruptly stopping treatment after 1 year.

Objective:

- Assess safety and tolerability through the 1 year treatment phase measured by adverse event rates.
- Efficacy of suvorexant at 1 month compared to placebo
- Exploratory endpoints of suvorexant vs placebo at 1 month and 12 months
- Assessment of rebound insomnia and withdrawal effects as well as efficacy and safety following abrupt discontinuation following 12 months of treatment.

Methods:

- Randomized, double-blind, placebo controlled trial.
- The study was a 14 months study.
- Inclusion Criteria:
  - 18 years old
  - Met criteria for primary insomnia based on DSM-IV criteria.
  - Authors aimed to have equal proportions of patients <65 years old with patiens >65 years old (% enrolled could not be greater than 60% of planned total subjects)
- Major Exclusion Criteria:
  - Potentially confounding neurological disorders
  - Major affective or psychotic illness
  - Substance abuse
  - Unstable medical disorders
  - Subject's insomnia was due to tobacco, caffeine or alcohol use.
  - BMI > 40 kg/m2
  - Investigator felt the enrollee was unlikely to adhere to the study procedures.
- 1 week placebo run-in screening phase

- Randomization in a 2:1 ratio determined treatment (suvorexant) and placebo groups.
- At the end of 1 year, half of the suvorexant group will be randomly selected to either continue therapy or begin taking placebo for two months. This will give 3 treatment groups to analyze:
  - Suvorexant-suvorexant
  - Suvorexant-placebo
  - Placebo-placebo
- 781 patients were enrolled
  - 522 to the treatment group (suvorexant
  - 259 to placebo group
- Patients in the treatment group received 30mg of suvorexant nightly if they were older than 65 and 40mg nightly is they were younger than 65. The placebo group received an identical placebo pill.
- Subjects kept a daily electronic sleep diary to log their data.
- Subjects returned the investigation center for assessment and for questionnaires at 2 weeks, and months 1,2,6,9,12,13,14.
- Adverse events were noted at follow up or through electronic diary.
- The primary efficacy outcome data was based on subjective total sleep time (sTST) and subjective time to sleep onset (sTSO). Other parameters included amount of time spent awake after sleep onset (sWASO) and number of awakenings (sNAW).
- Other rating scale were used to determine the level of severity of the patient's insomnia. These were statistically analyzed as well
- Given that the primary outcome measures were based on adverse events, power was not needed for this data. However, the authors noted a 99% power to detect a difference between treatments of 20 min for change from baseline in sTST, and greater than 97% to detect a difference between treatments of 10 min for change from baseline in sTSO.
- Authors used intent to treat method of analyzing data of adverse events. Per protocol method was used to evaluate efficacy data.

Results:

- Somnolence was the most commonly reported AE in the treatment group and occurred in 13.2% of patients, compared to 2.7% in the placebo group. This gave a difference of 10.5% with a confidence interval of 6.8-14.1.
- Other statistically significant differences in adverse event (along with associated rates in the treatment group) included Fatigue (6.5%), Dry mouth (5.0%), Dyspepsia (1.9%) and Peripheral edema (1.7%).
- 34.9% of patients in the treatment group reported at least one drug-related adverse event as compared to 20.5% in the placebo group.
- Other pre-specified adverse events that were looked at, but not found to be statistically significant from the placebo group include suicidal ideation, events suggesting drug-abuse potential, complex sleep-related begaviors, hypnagogic hallucinations, hypnopompic hallucinations, excessive daytime sleepiness, sleep paralysis, sleep onset paralysis, cataplexy, and falls

- After 1 month and after 12 months, suvorexant was found to be more efficacious than placebo in terms of sTST, sTSO, and sWASO.
    - sTST- Difference of 23.3 minutes after 1 month and 27.5 minutes after 12 months.
    - sTSO- Difference of 10.3 minutes after 1 month and 17.0 minutes after 12 months
    - sWASO- Difference of 9.0 minutes after 1 month and 9.7 minutes after 12 months.
- After discontinuation of the drug, there were no statistically significant differences in worsening of sTST or sTSO for the first 3 nights of discontinuation.
- The proportions of patients with rebound insomnia were higher in the patients taking suvorexant for 12 months followed by placebo as compared to continuing treatment of placebo patients that continued placebo.

Authors conclusions:

- Suvorexant is generally safe and well tolerated
- Most common AE was somnolence
- Abrupt discontinuation was not associated with an increase in AE's or significant withdrawal or rebound insomnia
- Hallucinations not due to orexin receptor antagonism but a class effect
- Other drugs indicated for insomnia saw similar rates
- No marked likelihood for worsening mood or SI but cannot rule out a small risk.
- Despite 4 occasions of suicidal ideation, authors claim new onset stressors are the culprit for two patients and the others occurred in patients with a history of depression and SI.
- Patients reported greater improvements in sleep onset and sleep maintenance with suvorexant as compared to placebo.
- Improvements were evident early and throughout the year
- Maintaining treatment after 1 year was associated with better retention of treatment gains.
- Cannot distinguish the cause of the return of insomnia
- No meaningful effects on body weight (orexin 1 receptor seems to modulate feeding drive in rats)

Strengths:

- Randomized, double-blind, placebo controlled clinical trial (Gold Standard)
- Innovation (first of a study this long looking at tolerability upon discontinuation)
- Large population
- Power was sufficient to reach secondary outcome assessments (sTST & sTSO)
- Subjects came from North America (approx. 60%), Europe (30%), South Africa, and Australia.

Limitations:

- The dosages used in the study were higher than the recently approved FDA doses (maximum of 20mg).

- All of the study data was subjective data reported by the subjects.
- No objective tests were done involving daytime function, work performance, quality of life, etc.
- Although this is the longest trial completed for insomnia medication, it is still relatively short considering the chronic nature in which insomnia drugs are prescribed.
- The trial did not compare suvorexant with another currently available insomnia agent, and thus we cannot make inference about its efficacy related to other drugs indicated for insomnia
- The sponsor of the study (Merck) was involved in the design and conduct of the study, the collection, management, analysis, and interpretation of the data, and the preparation, review, and approval of the report

Conclusions:

I agree with the authors conclusions about tolerability during therapy. There are certainly areas of concern (e.g. suicidal ideation) but these concerns exist with the current therapy options for insomnia as well. Also, this drug might find its niche as being a drug that doesn't possess the physical dependence and withdrawal issues that other drugs have, making it much easier to discontinue therapy when appropriate.

Based on the information of this study, I believe this drug has a place in the treatment of insomnia. All of the efficacy data reported was subjective so these are outcomes that the patient felt they had (regardless of what actually happened). If a patient reports better outcomes, it certainly has a place in therapy.

At this point, it is unclear where this drug should land in the scope of insomnia treatment. No studies have been done comparing Belsomra to any current drugs indicated for insomnia. Based on studies available it appears it may be safer than some other options in regards to dependence and rebound insomnia following discontinuation. However, generic availability of current agents makes them advantageous to patients who need more cost-effective options.

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