Solriamfetol for the Treatment of Excessive Sleepiness in OSA

BACKGROUND

- Obstructive sleep apnea's (OSA) primary therapy includes using a CPAP machine, oral appliance, or oral surgical interventions. However, even with primary therapy, excessive sleep (ES) can persist. Current medications that help with ES, but don't treat OSA, are amphetamines, modafinil, and armodafinil. Solriamfetol (Sunosi) has a novel mechanism of action compared to current treatment. It is a selective dopamine and norepinephrine reuptake inhibitor with robust wake promoting effects.

OBJECTIVE

- The purpose of this trial was to test solriamfertol's effectiveness and safety of ES in OSA
- The study is a phase III, double-blind, placebo-controlled, withdrawal trial
    - There was a 2 week titration phase, 2 week stable dose phase, and 2 week double blind randomization withdrawal phase, giving a total of 6 weeks all together
- Inclusion criteria is as follows:
    - Adults (age range, 18-75 years)
    - OSA diagnosed according to International Classification of Sleep Disorders-3 criteria
    - Current or prior primary OSA therapy including CPAP, oral appliance, or surgical intervention
    - BMI 18 to < 45 kg/m2
    - baseline ESS score $\geq$ 10 and mean sleep latency < 30 minutes on the first four trials of a five-trial, 40-minute MWT; and usual nightly sleep time $\geq$6 hours
- Exclusion criteria is as follows:
    - any disorder other than OSA associated with ES
    - an occupation requiring nighttime shift work or variable shift work
    - excessive caffeine use 1 week prior to the study or nicotine dependence with a reported effect on sleep
    - presence of any acutely unstable medical condition
    - behavioral or psychiatric disorder,
    - surgical history that could affect participant safety or interfere with study assessments
    - use of any over-the-counter or prescription medications that could affect ES evaluation within a period corresponding to at least 5 half-lives of the drug
    - Pregnant, breastfeeding, or lactating women
- 402 patients were screened, 174 went into the titration phase, where 17 patients discontinued for various reasons (6 were due to ADEs.) 157 patients entered the stable dose phase, at which point 9 more patients dropped out. 24 patients didn't enter the randomized portion of the trial mostly because they did not meet the criteria. In order for patients to meet critera, they had to have positive effects from the first two phases. Finally 124 patients entered the randomization phase. 2 patients were lost due to failure to meet criteria and consent withdrawal, both in the solriamfetol group. In total 122 patient reached the end of the trial, 62 in placebo and 60 in solriamfetol.
- Patients could be on 75mg, 150mg, or 300 mg /day of solriamfertol by mouth or taking a placebo by mouth
- Coprimary end points were change from weeks 4 to 6 in Mean Wake time (MWT) and Epworth sleepiness scale (ESS)
- The key secondary end point was the percentage of participants who reported worsening of their condition on the PGI-C from week 4 to week 6
    - Another secondary endpoint is change in FOSQ-10 total score and were evaluated from the beginning of the titration phase to end of the stable dose phase (week 4) and from end of the stable dose phase to end of the double-blind randomized withdrawal phase (week 6)
- Calculated power of 90% to detect differences of 6 minutes in the MWT mean sleep latency time (mean of the first four trials) and 3.5 points in ESS changes from the beginning to the end of the randomized withdrawal phase. This calculation assumed SDs of 9.5 minutes and 5 points for changes in the MWT and ESS, respectively, during the randomized withdrawal phase with a minimum of 122 patients.
    - Data handling:
        - Patients were treated as a modified intention-to-treat (mITT) population, defined as participants who were randomly assigned who received at least one dose of study medication and who had an MWT or ESS assessment at week 4 and at least one assessment after week 4
        - A last-observation-carried-forward approach was used for early withdrawals

RESULTS

- 122 patients completed the study, 62 in the placebo and 60 in the solriamfertol group
- Mean sleep latency on the MWT in the mITT population increased after 4 weeks of treatment, from approximately 12 to 13 minutes to approximately 30 minutes, and participant-reported ES decreased from approximately 15 or 16 to approximately 6, which is within the normal range.
- During the subsequent randomized withdrawal phase (from week 4 to week 6), participants who continued solriamfetol maintained result, whereas participants who were switched to placebo had worsened MWT and ESS scores. The

difference between treatments for these observed changes was statistically significant for both measures.
    - The least squares (LS) mean (SE) change in MWT mean sleep latency was -12.1 (1.3) minutes with placebo compared with -1.0(1.4) minute with solriamfetol; LS mean difference between solriamfetol and placebo was 11.2 minutes (95% CI, 7.8-14.6; P < .0001).
    - The LS mean changes in ESS score were 4.5 (0.7) and -0.1 (0.7) for placebo and solriamfetol, respectively, resulting in an LS mean difference of -4. (95% CI, -6.4 to -2.8; P < .0001).
- Functional outcomes (ie, FOSQ-10 total score) improved from mean baseline scores of 13.5 to 13.7 to mean scores of 17.6 to 17.8 after 4 weeks of treatment. At the end of the randomized withdrawal phase (week 6), mean +/-SD FOSQ-10 scores were 16.4 +/- 2.9 in the placebo group and 17.4 +/-3.0 with solriamfetol.
- Adverse effects summary are outlined on table 3 and 4, at different points in the trial. There were no deaths and no findings of suicidality. Most experienced ADEs during the titration (48.9%) and stable dose phases (10.2%), suggesting a dose response
    - Most frequent side effect that lead to withdrawal were headache and palpitations
    - The most common adverse events in the titration phase were: (5%) during the titration phase included: headache (9.8%), dry mouth (6.9%), nausea (6.9%), dizziness (5.7%), insomnia (5.7%)
    - During the randomized withdrawal phase, 29.0% of participants who continued using solriamfetol experienced any adverse event relative to 9.7% of those switched to placebo. Nasopharyngitis was the most frequent adverse event (4.8%), and there was no evidence of rebound hypersomnia or withdrawal effects after abrupt discontinuation of solriamfetol in the placebo group.
- Authors final conclusion: "This study demonstrated that solriamfetol substantially increased objective wakefulness and decreased subjective ES, with effects that were maintained in participants who continued using treatment relative to a loss of efficacy among those randomly assigned to placebo. The safety profile was consistent with those of other solriamfetol studies, and abrupt discontinuation was not associated with rebound hypersomnia or withdrawal effects."

STRENGTHS

- This was a randomized, double- blind, placebo controlled trial in the withdrawal phase
- The trial used appropriate outcome measures to evaluate subjects response

LIMITATIONS

- Short term, enriched withdrawal trial design may have predisposed the outcomes to be more favorable
- Included patients who may not currently be on primary OSA therapy. Patients who were on OSA therapy could have been on several primary treatments, and it is unknown if some benefitted more this. The grouping of patients to primary OSA therapy and their adherence to primary therapy was unclear and could have an effect on results.
    - Authors down played the difference in adherent and non-adherent primary OSA therapy
- Subjective information, limited data on patient and physician interactions, enrollment is not clear, specific study population, measures of variance were potentially misleading (LE +/-SEM used to downplay the spread of variation in results), effect size used a large SD to yield high power), adherence not tested
- Authors compared solriamfertol's efficacy to current treatment standards in the discussion with no data from this trial to base this on

CONCLUSIONS

- The findings of this study are hard to interpret, the authors themselves realize how subjective the information is, however relief in this disease state is subjective in the clinical world as well. There are not many options for medications for excessive sleepiness is OSA in clinical practice, only 3, and 1 of them is a controlled substance. This medication is a novel approach with a favorable side effect profile. The data shows statistical significance but the clinical significance is unclear. The chance for bias is high when taking into consideration the long list of conflicts of interest, statistical analysis used, and bold conclusions alluded to by authors. A different trial design with more participants with more a better defined inclusion criteria could help better show the medications clinical significance. Also, further studies on this medication compared to current treatment could be valuable.

Citation: Schweitzer PK, Rosenberg R, Zammit GK, Gotfried M, Chen D, Carter LP, Wang H, Lu Y, Black J, Malhotra A, Strohl KP. Solriamfetol for Excessive Sleepiness in Obstructive Sleep Apnea (TONES 3): A Randomized Controlled Trial. Am J Respir Crit Care Med. 2018 Jun 1 2019; 199(11):1421-1431.

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