The decrease in ODI with MAD + placebo relative to baseline was not statistically significant. However, the decrease in ODI - MAD + pharmacotherapy relative to ODI - MAD + placebo was statistically significant, p-value= 0.022. (Table III).

The mean Respiratory Effort-Related Arousals (RERA) from baseline (7.87±5.91) was higher than mean RERA Index of MAD + placebo (3.45 ± 4.00) and MAD + pharmacotherapy (2.63 ± 2.26). The mean RERA index decreased from baseline to both treatments (Table II). However, the decrease in RERA index –MAD + pharmacotherapy relative to RERA- MAD + placebo was not statistically significant. (Table III).

The mean Sleep Efficiency (%) at baseline was lower than Sleep Efficiency (%) at MAD + placebo. This indicated that sleep efficiency improved with MAD + placebo (78.33 ± 10.04) relative to baseline (65.24 ± 17.12). The increase in Sleep Efficiency (%)-MAD + placebo relative to baseline was statistically significant, p-value=0.012, although a decrease in sleep efficiency in MAD + pharmacotherapy (76.99 ± 11.35) relative to placebo did not indicate statistical significance mean difference. (Table III).

The mean Epworth Sleepiness Scale (ESS) score at baseline was higher than mean ESS at MAD + placebo and the MAD + pharmacotherapy (Table II). The decrease in ESS score at MAD + placebo relative to baseline indicated a statistically significant mean difference, p-value= 0.047.

Psychomotor Vigilance Test (PVT) Mean Response Time (RT), Functional Outcomes of Sleep Questionnaire (FOSQ) and Visual Analog Scale of sleepiness (VAS) tests did not show statistical significance comparing baseline with MAD + placebo and MAD + placebo with MAD + pharmacotherapy.

Patient compliance with both MAD and medications were recorded via self-report and showed a mean MAD compliance rate of 6.45 ± 1.49 hours of wear per night for at least 6 nights per week. The medication compliance with placebo was 100 ± 0.01% whereas the compliance with pharmacotherapy was 99 ± .03%.

Discussion

The goal of this pilot study was to determine if combination treatment of oral appliance therapy with pharmacological intervention was a viable treatment option in moderate to severe obstructive sleep apnea patients. Oral appliance therapy has not been shown to be fully effective in moderate to severe OSA. In an investigation of objective success of MAD treatment, Vanderveken and colleagues described that in a population with mild-moderate OSA, OAT successfully treats the disease in 1/3 of patients, lowers the AHI by half in another third of the patients, and does not produce any significant change in the remaining third.[22] This study was unique as it explored the feasibility of treating a more severe OSA patient population (moderate to severe) with an oral appliance augmented with previously investigated drugs to provide a viable alternative to continuous positive airway pressure.

This study was quite labor intensive as we designed a robust clinical study following a very stringent inclusion-exclusion criteria as outlined previously. It took almost three years to complete this study due to difficulty finding specific subjects that met the moderate to severe AHI range of 25-50 and ensuring that those subjects were good candidates for oral appliance therapy. A number of patients were not eligible due to their oral health status. Once a prospective patient was consented, it was very challenging to match schedules as we strictly had to schedule the 2 week and 4 week overnight polysomnogram studies. For some subjects, sudden changes their personal schedules made these study visits inconvenient, but these were immutable time points as we needed to capture effects after placebo and after combination therapy respectively. To our knowledge, this is the first study to investigate the combination of oral appliance therapy for obstructive sleep apnea, particularly a mandibular advancement device, with pharmacotherapy, specifically a fluoxetine – ondansetron regimen.

The results of this study are quite promising as in this small sample size, MAD + placebo showed no statistically significant difference from baseline upon examination of objective outcome variables AHI, ODI, and RERAs, but once the medication combination were added to the treatment regimen, significant differences in AHI and ODI appeared.

Night-to-night variability in polysomnogram studies is a well-established phenomenon.[23] Stöberl and colleagues followed 77 patients with OSA for two weeks with pulse-oximetry and found significant variability in severity as measured by AHI from night-to-night.[24] This could explain the increase in AHI for 5 of our 10 subjects from baseline to MAD + placebo. But more importantly, when comparing the AHI scores at MAD + placebo to those at MAD + pharmacotherapy, 8 of 10 subjects showed a decrease in AHI. This suggests that our combination intervention had a positive effect on reducing the number of apneas and hypopneas experienced during sleep, assuming a stationary effect of MAD by the time of introducing the pharmacotherapy.

Eight subjects had a decrease in AHI of 40% or greater from baseline to the end of the study. They were defined as positive responders. No report of adverse drug side effects was recorded from patient study logs, and both oral appliances and medications were well tolerated, and with high compliance rates. Some subjects reported mild jaw soreness the morning after wearing the oral appliance, but this subsided after 1-2 weeks of wear. Recent literature suggests that side effects of oral appliances, though fairly common, are mostly manageable by a qualified dentist.[13]

We found that response to treatment varied significantly with all subjects. For oral appliances, the best responders tend to have mild to moderate OSA, have a greater amount of advancement in their appliance, have a lower BMI, and have a greater difference in respiratory events between supine and lateral sleep positions.[11] In this pilot study, some of these abovementioned factors were not met by our chosen study population, i.e. our patients had moderate to severe OSA, and had higher BMI. It is possible that the therapeutic actions of the medications helped balance the inadequate effects of oral appliance therapy in this patient cohort.

The initial trial for fluoxetine-ondansetron combination followed a 28-day study protocol.[16] The onset of action of ondansetron is almost immediate, peaking at around 2 hours post ingestion, whereas it takes much longer for fluoxetine. It is widely accepted that the full therapeutic benefit of fluoxetine is not reached until approximately 4-6 weeks. For this reason, we chose to have the subjects remain on the

combination drug treatment for 28 days, similar to Prasad et al.'s medication combination trial before undergoing the last polysomnogram of the study.[16]

It is important to note that AHI is not the only important variable recorded during sleep. There are also inherent problems with the Apnea-Hypopnea Index. It is an imperfect outcome measure. There is no quantification of work of breathing. There is also no differentiation between short and long events. AHI may or may not be the optimal metric to evaluate sleep-disordered breathing. Additionally, some patients may experience a greater proportion of apneas and hypopneas during specific stages (REM-related OSA) or positions of sleep such as during supine sleep.[25] The majority of our subjects showed improvement in AHI from MAD + placebo to MAD + pharmacotherapy, and from baseline to MAD + pharmacotherapy. Severity was reduced from severe to moderate in 6 subjects and mild in 1 subject. Because treatment was not fully effective, subjects were referred to their sleep physician for follow-up evaluation and treatment.

Respiratory effort-related arousals (RERA) can be thought of as a milder form of an apnea or hypopnea. It defined as a subtle fluctuation in airway of 1-2%, lasting 10 seconds or longer, and leads to an arousal or decrease in oxygen saturation.[26] The significance of this is that these are not captured in the AHI score. They are an important outcome measure that can affect overall sleep quality and restfulness. Our data showed a statistically significant decrease in RERA index from baseline, despite not showing the same with AHI. This highlights the fact that AHI may not be the only important outcome measure to assess when evaluating treatment efficacy of an intervention.

Sleep efficiency is a measure of time spent sleeping compared to the time spent in bed.[27] There was a statistically significant increase in sleep efficiency with the MAD + placebo compared to baseline, however no further difference was found upon introduction of pharmacotherapy. This finding is similar to what Pitarch and colleagues found in their clinical trial with the use of MAD compared to baseline. [28]

Oxygen desaturation index (ODI) is another important sleep variable, which measures the number of drops in blood oxygen levels throughout the night.[29] This may or may not be correlated with the number of sleep arousals and can be predictive of long-term cardiovascular risks such as hypertension,

stroke, and heart attack.[29] We found a statistically significant decrease in ODI between MAD + placebo and MAD + meds.

Our subject pool had a very high initial average body mass index (38.54±3.4) which is reflective of the OSA population at our center. Mandibular advancement devices have been shown to decrease in effectiveness as BMI and neck circumference increases.[30] One subject with a BMI of 61 showed a poor response to treatment and was discontinued in our study.

Subjective outcome measures included the Epworth Sleepiness Scale, Functional Outcomes of Sleep Questionnaire, Visual Analog Scale, and Treatment Satisfaction Questionnaire for Medication. All outcome measures showed some improvement from baseline to the end of our study, although we only found statistical significance with the Epworth Sleepiness Scale, which is a well-validated outcome measure. The study patients exhibited a mean ESS score under 11 at baseline, however, an important point to note is the clinical significance of the decrease in ESS scores at subsequent time points. Any decrease greater than 2-3 in the ESS scores lead to clinically significant changes in daytime sleepiness.[31] Thus there was a clinical significant change in daytime sleepiness with MAD + placebo compared to baseline. It remains to be elucidated if prolonged use of the medications would have allowed such a significant change with MAD + medications.

Interestingly, all our subjects reported feeling improvements in daytime sleepiness and increased energy level with our combination intervention of MAD + pharmacotherapy. This is contradictory to some of our observed sleep data. This sleep data was recorded at two time points during our study four weeks apart, and only provides short-term picture of the response to treatment. A much longer follow up period would be ideal to determine how patients adapt to the treatment modality. How much of this effect is due to pharmacotherapy alone also remains to be expounded.

We collected data on robust variables and successfully established the feasibility of our intervention. However, the scope and funding of our pilot study was limited. We found it difficult to find suitable subjects that fit all our inclusion and exclusion criteria and were willing to complete the entire

study. We recruited subjects from a single sleep center, which may have reduced the diversity of our subject pool.

Our results highlight the complexity of obstructive sleep apnea and illustrate the importance of identifying traits that may predict treatment response to MAD therapy. Future studies need to be adequately powered to draw conclusions about the effectiveness of combination MAD and pharmacotherapy in order to serve the unmet need of finding a practical treatment alternative for the moderate to severe OSA patient population.

Conclusions

This study determined that augmentation of oral appliances by pharmacotherapy (ondansetron + fluoxetine) may increase oral appliance therapeutic efficacy. Combination of pharmacotherapy and oral appliance may be a viable option in treating patients with moderate to severe obstructive sleep apnea. Subjects generally reported sleeping better with the oral appliance and having increased alertness during the day on their follow-up appointment. Further larger scale studies based on effect sizes gathered from these data will help to provide more understandable relationships among the outcome measures of interest in this type of therapy for sleep apnea.

Abbreviations

AHI	Apnea-Hypopnea Index
CPAP	Continuous positive airway pressure

ESS	Epworth sleepiness scale
FOSQ	Functional outcomes of sleep questionnaire
MAD	Mandibular advancement device
MAS	Mandibular advancement splint
OA	Oral appliance
ODI	Oxygen Desaturation Index
OSA	Obstructive sleep apnea
PSG	Polysomnography
PVT	Psychomotor vigilance test
RERA	Respiratory Effort Related Arousal
SaO_2	Blood-Oxygen Saturation
SBD	Sleep Disordered Breathing
VAS	Visual analog scale

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Figure Legends

Figure 1. Flowchart of study procedures

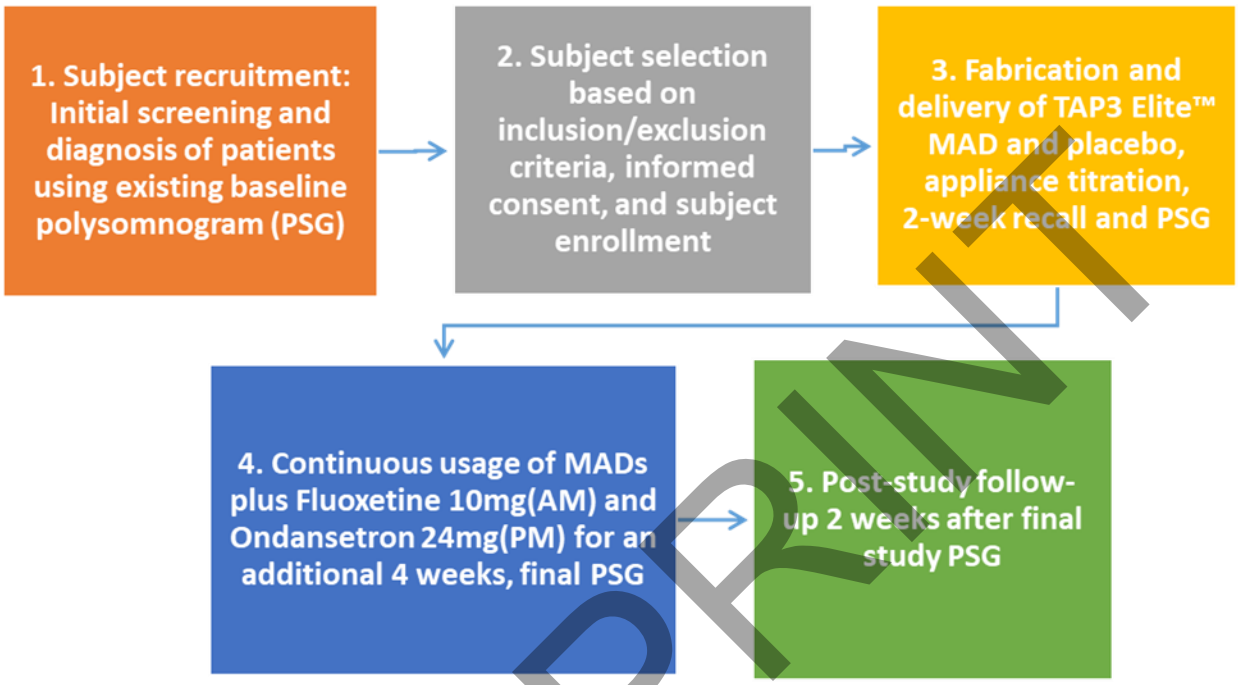

Table I. Descriptive Statistics

	Gender	N	Mean	Std. Error Mean
BMI (kg/m^2)	Male	7	34.21	3.02
	Female	3	48.63	5.75
AGE (years)	Male	7	49.29	3.86
	Female	3	47.67	7.36
		N	Mean BMI	Std. Error Mean
Positive Responder to Treatment V1-7	Yes	8	36.18	3.77
	No	2	48.00	0.00

Table II- Descriptive Statistics of the outcome variables - Mean and Standard deviation

Variables	Mean	Standard Deviation
AHI-baseline	32.96	10.09
AHI-MAD + placebo	28.38	17.83
AHI-MAD + drugs	18.02	13.53
ODI-baseline	34.38	12.62
ODI-MAD + placebo	26.42	18.56
ODI-MAD + drugs	18.46	15.17
RERA-baseline	7.87	5.91
RERA-MAD + placebo	3.45	4.00
RERA-MAD + drugs	2.63	2.26
Sleep Efficiency-baseline	65.24	17.12
Sleep Efficiency-MADD + placebo	78.33	10.04
Sleep Efficiency- MAD+ drugs	76.99	11.35
ESS-baseline	10.30	4.60
ESS-MAD + placebo	7.20	4.94
ESS-MAD + drugs	6.30	5.06

Table III. Paired Mean Differences -

Variables	Mean	Std. Deviation	Mean Difference	95% Confidence Interval	p-value
AHI-baseline	32.96	10.09			
AHI-MAD + placebo	28.38	17.83	4.58	(-10.30, 19.45)	0.504
AHI-MAD + placebo	28.38	17.83			
AHI-MAD + drugs	18.02	13.53	10.36	(3.01, 17.71)	0.011*
ODI-baseline	34.38	12.62			
ODI-MAD + placebo	26.42	18.56	7.96	(-9.55, 25.47)	0.331
ODI-MAD + placebo	26.42	18.56			
ODI-MAD + drugs	18.46	15.17	7.96	(1.48, 14.44)	0.022*
RERA-baseline	7.87	5.91			
RERA-MAD + placebo	3.45	4.00	4.42	(-1.19, 10.03)	0.109
RERA-MAD + placebo	3.45	4.00			
RERA-MAD + drugs	2.63	2.26	0.82	(-2.22, 3.86)	0.557
Sleep Efficiency-baseline	65.24	17.12			
Sleep Efficiency-MAD + placebo	78.33	10.04	-13.09	(-22.49, -3.69)	0.012*
Sleep Efficiency-MAD + placebo	78.33	10.04			
Sleep Efficiency-MAD + drugs	76.99	1.35	1.34	(-7.96, 10.64)	0.752
ESS-baseline	10.30	4.60			
ESS-MAD + placebo	7.20	4.94	3.10	(0.57, 6.14)	0.047*
ESS-MAD + placebo	7.20	4.94			
ESS-MAD + drugs	6.30	5.06	0.90	(-0.77, 2.57)	0.253

* Statistically significant at 5%.