Effects of the combination of atomoxetine and oxybutynin in Japanese patients with obstructive sleep apnoea

（日本人閉塞性睡眠時無呼吸に対するアトモキセチンとオキシブチニンの併用療法に関する検討）

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INTRODUCTION

Obstructive sleep apnoea (OSA) is a common disorder that involves repeated hypopnoeas and apnoeas caused by the narrowing or obstruction of the upper airway during sleep.[1,2] Recent findings have revealed multifactorial pathophysiology, including a collapsible pharyngeal airway (anatomical factors), elevated loop gain (unstable respiratory control), the dilator muscles in the upper airway with poor response during sleep and a lower respiratory arousal threshold (waking up with slight airway narrowing).[3–5] Since various OSA-associated mechanisms induce progressive atherosclerosis formation and exacerbate the risk of cerebrovascular and ischemic heart diseases,[3,6] the incidence of fatal and nonfatal cardiovascular events is considerably increased in individuals with severe untreated OSA compared with those without OSA.[5,7] However, despite the multifactorial mechanisms and clinical importance of OSA, few treatment options are available.

Continuous positive airway pressure (CPAP) is the primary treatment option for severe OSA. It improves prognosis; however, in current clinical settings, poor adherence and low treatment retention rates are major problems associated with CPAP.[8] Oral appliance therapy would be a better- tolerated treatment option than CPAP but may not be effective for severe OSA.[8] Therefore, despite the long anticipation for effective drug therapy with suitable adherence for OSA, there remains an unavailability of efficacious drugs for OSA.[9] A recent study reported that a one-night combination treatment of atomoxetine (ATO), a selective noradrenaline uptake inhibitor and oxybutynin (OXY), an antimuscarinic antagonist, reduced OSA severity by 63%.[3] This finding uncovers potential avenues for a novel treatment strategy or an alternative OSA treatment option. However, the efficacy of this treatment is yet to be investigated in Japanese patients with OSA.

To address this research gap, we performed a randomized, crossover trial to assess the effect of ATO–OXY therapy on OSA severity and its safety in Japanese patients with OSA.

METHODS

Subjects and study design

This randomized, crossover, phase II, single-centre prospective trial included 18 patients (aged 20–70 years) diagnosed with OSA based on their sleep study data (Table 1). The general exclusion criteria included acute organ disease and hypersensitivity to ATO and OXY (the more specific exclusion criteria are detailed in Appendix S1 in the Supporting Information).

Protocols

The procedures involving in-laboratory polysomnography (PSG) were performed at Chiba University Hospital from May 2020 to August 2022. The patients were divided into ATO–OXY first group and non-medication (no-Med) first group. ATO–OXY first group received 80 mg ATO plus 5 mg OXY before the first PSG and did not receive any medication before the second PSG. No-Med first group did not receive any medication before the first PSG and received ATO and OXY before the second PSG. ATO–OXY was administered 30 min before switching off the lights in the room. In principle, the lights were switched off at 9 p.m. and all the patients were prepared to sleep at that time. PSGs were performed on two separate nights and the wash- out period was 1–4 weeks (Figure 1).

The patients who originally used CPAP or oral appliances were indicated to discontinue treatment 3 days before PSG to minimize any residual treatment effects. Following the first or second PSG, the treatments were resumed.

Randomization and masking

The eligible participants were randomly assigned in a 1:1 ratio to either the ATO–OXY first group or no-Med first group. The factors considered for randomization included age (≥60 years, <60 years) and body mass index (BMI ≥30, BMI < 30). After obtaining the participants' consent, the principal investigators contacted the research secretariat and confirmed the allocated treatment groups. Since this trial was a randomized, open-label, crossover study, no blinding or masking was performed.

Measurements and outcomes

PSG scores were recorded according to the American Academy of Sleep Medicine

Manual for Scoring of Sleep and Associated Events version 2.3 (more details regarding the PSG recording and scoring are presented in Appendix S1).

PSG recording and scoring are presented in Appendix S1. The predefined primary outcome endpoint was the apnoea hypopnoea index (AHI; events/h). The secondary outcomes included 3% ODI, 4% ODI, nadir SpO2, SpO2 drop time (<90%), arousal index, total sleep time (TST) and sleep architecture (stage N3 time, rapid eye movement [REM)], sleep time and sleep efficiency). The safety endpoints were drug side effects and incidence of adverse events, including abnormal changes in laboratory values. These major out- comes were based on a previous study regarding the effects of ATO–OXY on patients with OSA in the United States.[3]

Sample size setting and statistical analyses

The primary objective of the present study was to compare the AHI of the no-Med and ATO–OXY treatments. The null hypothesis was that between-group differences in AHI would not be significant. A previous study has shown that the median AHI in placebo and ATO–OXY to be 28.5 (10.9, 51.6) events/h and 7.5 (2.4, 18.6) events/h, respectively.[3] Therefore, the sample size was determined according to the expected mean difference (SD) of 21 (26) events/h. Based on these assumptions, the required total sample size for a 2 × 2 crossover design was determined to be 16 patients (two-tailed, $\alpha = 0.05$, $\beta = 0.2$). Considering a 10% dropout rate, at least 18 patients were included.

Data are presented as mean with SD or median with interquartile range for continuous variables and frequencies with percentages for categorical variables. The primary out- come was analysed using Wilcoxon signed-rank test. Sec- ondary outcome analysis did not involve multiple comparison adjustment. We analysed the secondary out- comes using a similar approach as the primary analysis. The safety analysis computed the frequencies and percentages of adverse events. General characteristics and PSG data between the nonresponders and responders were compared using chi-squared test or Fisher's exact test for categorical variables and Student's t-test or Wilcoxon rank-sum test for continuous variables. All the tests were two-tailed. p-values of <0.05 were considered statistically significant. Statistical analyses were performed using the SAS statistical software package ver. 9.4 (SAS Institute, Cary, NC).

RESULTS

Study participants

Overall, 18 patients were enrolled in the study after eligibility assessment (Figure 1). One patient (ATO–OXY first group) withdrew after randomization because she started a prohibited drug before study initiation. Thus, 17/18 patients completed the entire study. The clinical characteristics of these 17 patients are shown in Table 1. Regarding OSA treatments before the study, 13/17 patients (76%) used CPAP and 1/17 (5%) used oral appliances. Most participants were nonobese (5 patients [29%], BMI <25 kg/m2; 9 patients [52%], 25 ≤ BMI < 30 kg/m2).

Effect of ATO–OXY on the AHI (primary outcome)

Regarding the total AHI and nadir SpO2, no significant difference was observed between the ATO–OXY and no-Med, indicating that ATO–OXY did not obviously improve AHI or OSA severity (Figure 2). Furthermore, although no over- all difference was detected, several patients (n = 5) showed a decrease in total AHI; however, this effect was not observed in the remaining patients (n = 12; Figure 2).

Effect of ATO–OXY on oxygen saturation and sleep architecture (secondary outcomes)

The PSG parameters are shown in Table 2. The values of 3% ODI, 4% ODI and SpO2 drop time (SpO2 < 90%) did not differ between the ATO–OXY and no-Med. However, arousal index, TST and sleep architecture demonstrated sig- nificant changes. The ATO–OXY medication increased arousal index and sleep stage N1 and decreased TST, sleep stage N2, REM sleep and sleep efficiency (Figure 3). REM sleep was robustly decreased in most patients, and 15/17 patients experienced no REM sleep post ATO–OXY administration. This effect can be potentially associated with the disappearance of REM–AHI (Figure 4).

Subanalysis of responders to ATO–OXY

Responders were defined as patients whose AHI improved by ≥10 events/h or 20% after receiving ATO–OXY (n = 5) and the other patients were defined as nonresponders (n = 12). To examine the clinical characteristics of responders to ATO–OXY, clinical

and PSG data on the no-Med night were compared between the responders and nonresponders (Figure S1 and Table S1 in the Sup- porting Information). No significant differences in age, neck circumference, waist circumference, BMI, Mallampati score, tonsil score, AHI supine, nadir SpO2, arousal index, sleep stages N1, N2, N3, REM or 3% ODI were observed. TST was significantly lower ($p = 0.03$) and sleep efficiency tended to be lower ($p = 0.065$) in responders than in nonresponders, suggesting that the sleep architecture or sleep–wake state might be affected by ATO–OXY.

Adverse events of ATO–OXY

No patients experienced severe adverse events or side effects on either the ATO–OXY or the no-Med night. Mild nausea was reported by one patient during the ATO–OXY night. No adverse events were observed on the no-Med night.

DISCUSSION

The present study is the first clinical trial to evaluate the efficacy of oral ATO–OXY administration in Japanese patients with OSA. Contrary to our expectation, an overall significant improvement in OSA severity, such as in the total AHI, 3% ODI, or nadir SpO2, was not observed. This result is inconsistent with that of a previous report using almost the same study design to investigate the efficacy of ATO–OXY in patients with OSA in the United States.[3] However, in the present study, sleep architecture was significantly altered by ATO–OXY administration. We observed increased sleep stage N1, decreased sleep stage N2 and a nearly complete absence of REM (and an almost complete absence of REM– AHI). However, some patients (5/17) exhibited preferable effects (improved AHI, lower SpO2), similar to the findings of the previous report.[3]

In the current study, ATO–OXY did not significantly improve the total AHI of Japanese patients with OSA. ATO potentially alleviates the narrowing of the upper airway by stimulating the upper airway motoneurons in the brainstem and worsening the arousal threshold.[10,11] OXY is an anti- muscarinic agent with a high affinity for all muscarinic receptors, originally used to treat overactive bladders. OXY has been reported to potentially prevent the muscle contrac- tion effect of acetylcholine on upper airway muscle tone.[3] According to a recent report regarding ATO–OXY therapy, improvements of AHI were probably driven by an increase in the responsiveness of the upper airway dilator mus- cles.[10,11] The conceivable reasons for the inconsistency of our

results with that of the previous study performed in the United States are (1) ethnic or phenotypic trait differences in OSA pathogenesis and (2) differences in ATO–OXY reactivity in Japanese patients. The most recent report regarding ATO–OXY therapy for patients with OSA revealed that the concomitant use of zolpidem, which improves the arousal threshold, enhanced sleep efficiency.[12] Additionally, Perger et al. reported that reboxetine–OXY and not ATO showed potential for the pharmacologic treatment of OSA.[13] There- fore, the treatment of Japanese patients with OSA with oral medication needs to include additional drug usage, a different type of medication or appropriate patient selection to achieve better outcomes.

Previous reports suggest that craniofacial factors and dif- ferential obesity contribute to OSA in Caucasian and east Asian patients.[14,15] For the same degree of OSA severity, Caucasians were more overweight, whereas east Asians exhibited more craniofacial bony restriction.[14] Therefore, discrepancies in the effects of ATO–OXY in American and Japanese patients might be attributed to such racial differences in the OSA phenotype.

The present study showed a significant change (or worsening) in sleep architecture, with a decrease in sleep stages N2 and REM sleep and sleep efficiency after ATO– OXY administration. These sleep architecture changes were also observed in previous studies using ATO only[16] or reboxetine, another type of noradrenaline reuptake inhibitor.[13,17–19] Reboxetine, a noradrenaline reuptake inhibitor similar to ATO, is considered to worsen arousal thresholds, causing shallower sleep architecture.[13,17–19] However, ATO– OXY administration did not significantly alter sleep archi- tecture in the Wellman et al. study,[3] suggesting that ATO 80 mg may be an appropriate dose for American patients but is potentially an overdose for Japanese patients. In the present study, REM sleep disappeared in 16/18 patients, with the concomitant absence of REM–AHI (Figure 4). This may be an ethnic characteristic of Japanese people, although existing studies have not reported such extreme changes.[13,16] CYP2D6*10 is an allele of CYP2D6, a metabolizing gene for ATO, which is known to be highly prevalent in Asians and may have increased the ATO blood concentration.[20] Since OXY is reported to improve OSA mainly in the REM phase,[3] it is possible that the effect of OXY was not obvious in this study, thereby causing the total AHI improvement to be much poorer than expected.

Nevertheless, the subanalysis showed ATO–OXY to be effective in 5 of 17 patients. The responders exhibited pre- dominantly lower TST than nonresponders. Sleep efficiency also tended to be lower. Patients with low TST are consid- ered to belong to the population having low sleep efficiency, which is associated with a lower arousal threshold. Accord- ing to previous reports,[10,11] ATO reduces the arousal threshold, thereby causing the patients to require a lower ventilatory drive to trigger arousal from

sleep and reducing the oversensitive ventilatory control system (loop gain). Noradrenergic agents, such as ATO, promote the central augmentation of motoneurons controlling the upper airway dilator muscles. Therefore, ATO improves the collapsibility of the upper airway during sleep. Since using ATO–OXY to reduce the arousal threshold is considered to lead to sleep and respiratory instability, the reasons behind why the ATO–OXY responders exhibited poor sleep efficiency and a lower arousal threshold in the original state could not be explained. In a recent report of zolpidem + ATO–OXY administration in patients with OSA,[12] the addition of zolpidem increased the arousal threshold and improved sleep efficiency in a state of potential wake-promoting properties of ATO.

In terms of adverse events, no severe symptoms were observed. Specifically, there was no incidence of dysuria, oral blackmail or early morning headaches, which have been reported in previous studies.[3,9,21] From this point of view, one benefit of ATO–OXY therapy per se is that it is well tolerated by Japanese patients with OSA.

This study has several limitations. First, although the number of participants was determined according to a previous study,[3] larger studies are warranted to confirm the results since patients with OSA generally show diversity and the OSA phenotypic trait and/or reaction to drug treatment appears to differ in the Japanese population from that in the US population. Second, possibility of gender difference to drug responsiveness was not evaluated, since most patients in this study were male. Third, unlike previous studies,[3,9,21] this study did not employ a placebo. However, as PSG was performed during sleep (i.e., a subjective outcome with less bias), any placebo effect is considered to be small. Finally, unlike the previous study based in the United States,[3] we did not measure electromyographic activity due to certain limitations at our institution. Nevertheless, the primary aim of testing the effect of ATO– OXY therapy on AHI severity in Japanese patients with OSA was achieved.

In conclusion, the effects of ATO–OXY therapy on AHI severity in the present study were not clearly observed and ATO–OXY therapy appeared to not be as effective in Japanese patients with OSA compared with that in Ameri- can patients with OSA. The drug effects were inconsistent in Japanese patients with OSA, with several participants responding to the treatment, whereas the others were not responding. Future studies investigating the characteristics of treatment responders are warranted.

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TABLES

Table 1. Patients' characteristics

Characteristics	Values
Age, year	55.1 (44–65)
Male, number (%)	15 (88)
Height, cm	170.1 (163–179)
Weight, kg	79.5 (61.6–120.4)
Body mass index (kg/m^2)	27.3 (21.5–39.3)
Waist circumference, cm	96.1 (77.5–127)
Neck circumference, cm	39.9 (32–46.4)
Mallampati score (1/2/3/4)	1.94
Tonsils score (0/1/2/3)	1
AHI	36.1 (14–115.1)
CPAP user, N (%)	13 (76)
Comorbidities, N (%)	
Hypertension	6 (35)
Diabetes	3 (17)
Dyslipidemia	4 (23)

Notes: Data are presented as the mean for numerical data and N (%) for categorical data.

Abbreviations: AHI, apnea–hypopnea index; CPAP, continuous positive airway pressure.

Table 2. OSA severity and sleep architecture on and off the drugs for all the participants (N = 17)

	no-Med Median (IQR)	ATO-OXY Median (IQR)	P value
AHI total, events/h	25.3 (12.9, 32.3)	20.6 (15.0, 43.4)	0.854
AHI NREM, events/h	22.3 (11.9, 31.9)	20.6 (15.0, 43.4)	0.890
AHI REM, events/h	28.2 (14.4, 48.5)	0.0 (0.0, 0.0)	0.001
AHI supine, events/h	34.5 (28.3, 61.4)	35 (19.9, 59.5)	0.597
HI, events/h	10.8 (7.2, 14.3)	16.4 (8.8, 22.0)	0.011
3%ODI, events/h	26.2 (11.5, 42.4)	23.1 (8.8, 50.9)	0.636
4%ODI, events/h	16.8 (6.5, 31.0)	14.6 (4.0, 37.7)	0.899
SpO_2<90%, min	8.9 (2.5, 24.0)	2.1 (0.0, 19.0)	0.081
Nadir SpO_2, %	83.0 (75.0, 86.0)	83.0 (78.0, 88.0)	0.104
Arousal index, events/h	37.8 (22.6, 42.4)	48.2 (38.9, 53.8)	0.015
TST, min	372 (343, 456)	308 (272, 406)	0.0337
N1, %TST	37.6 (29.7, 47.8)	64.4 (54.0, 73.9)	<0.0001
N2, %TST	46.6 (35.7, 54.3)	35.6 (26.1, 44.9)	0.0315
N3, %TST	0.0 (0.0, 0.4)	0.0 (0.0, 0.8)	0.922
REM, %TST	16.6 (13.0, 19.4)	0.0 (0.0, 0.0)	<0.0001
Sleep efficiency, %TIB	62.2 (54.7, 71.2)	53.2 (46.0, 66.9)	0.022

Abbreviations: No-Med: no medication, ATO-OXY: atomoxetine and oxybutynin, IQR: interquartile range, AHI: apnea hypopnea index, NREM: non-rapid eye movement, REM: rapid eye movement, AI: apnea index, HI: hypopnea index, ODI: oxygen desaturation index, TST: total sleep time, TIB: time in bed

Fig. 1

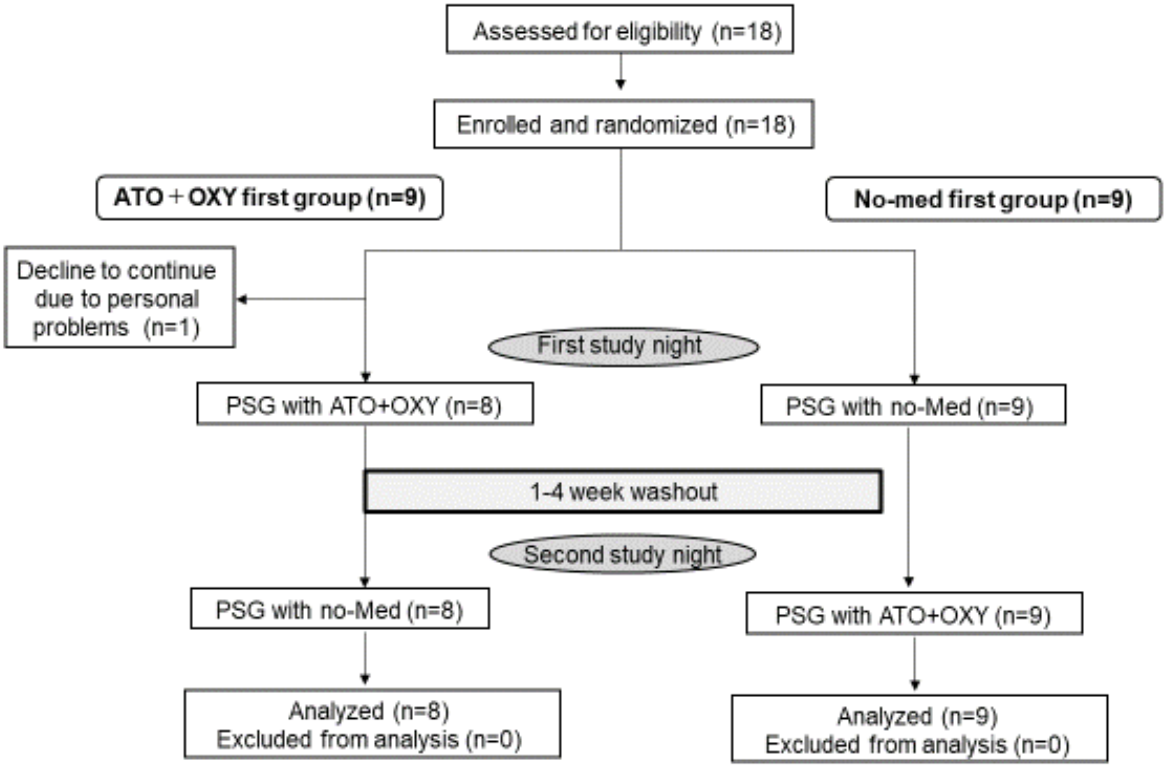

Assessed for eligibility (n=18)
Enrolled and randomized (n=18)
ATO＋OXY first group (n=9)
No-med first group (n=9)
Decline to continue due to personal problems (n=1)
First study night
PSG with ATO+OXY (n=8)
PSG with no-Med (n=9)
1-4 week washout
Second study night
PSG with no-Med (n=8)
PSG with ATO+OXY (n=9)
Analyzed (n=8)
Excluded from analysis (n=0)
Analyzed (n=9)
Excluded from analysis (n=0)

Fig. 2

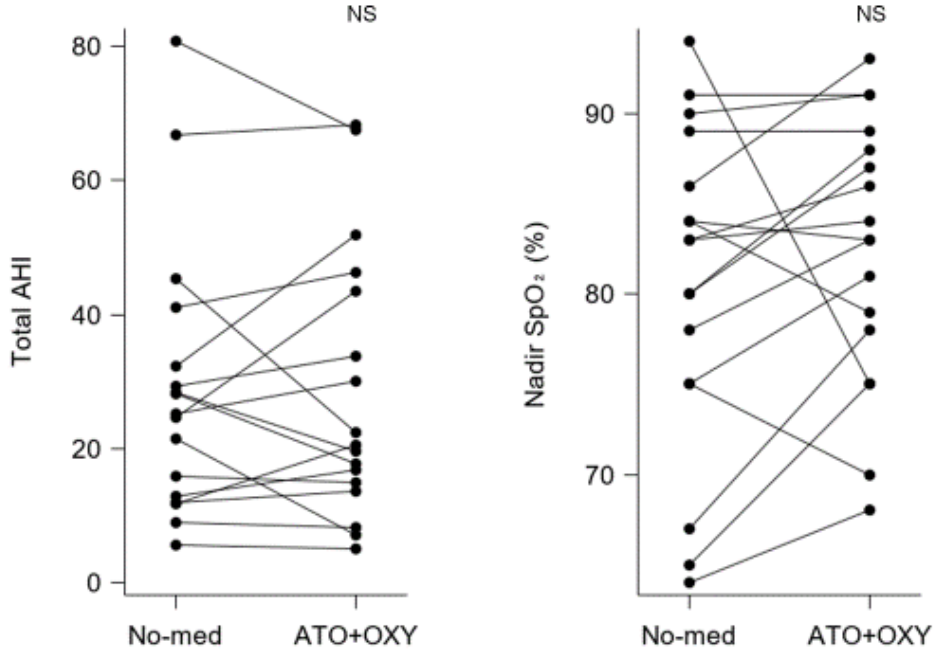

NS
Total AHI
80
60
40
20
0
No-med
ATO+OXY
NS
Nadir SpO₂ (%)
90
80
70
No-med
ATO+OXY

Fig. 3

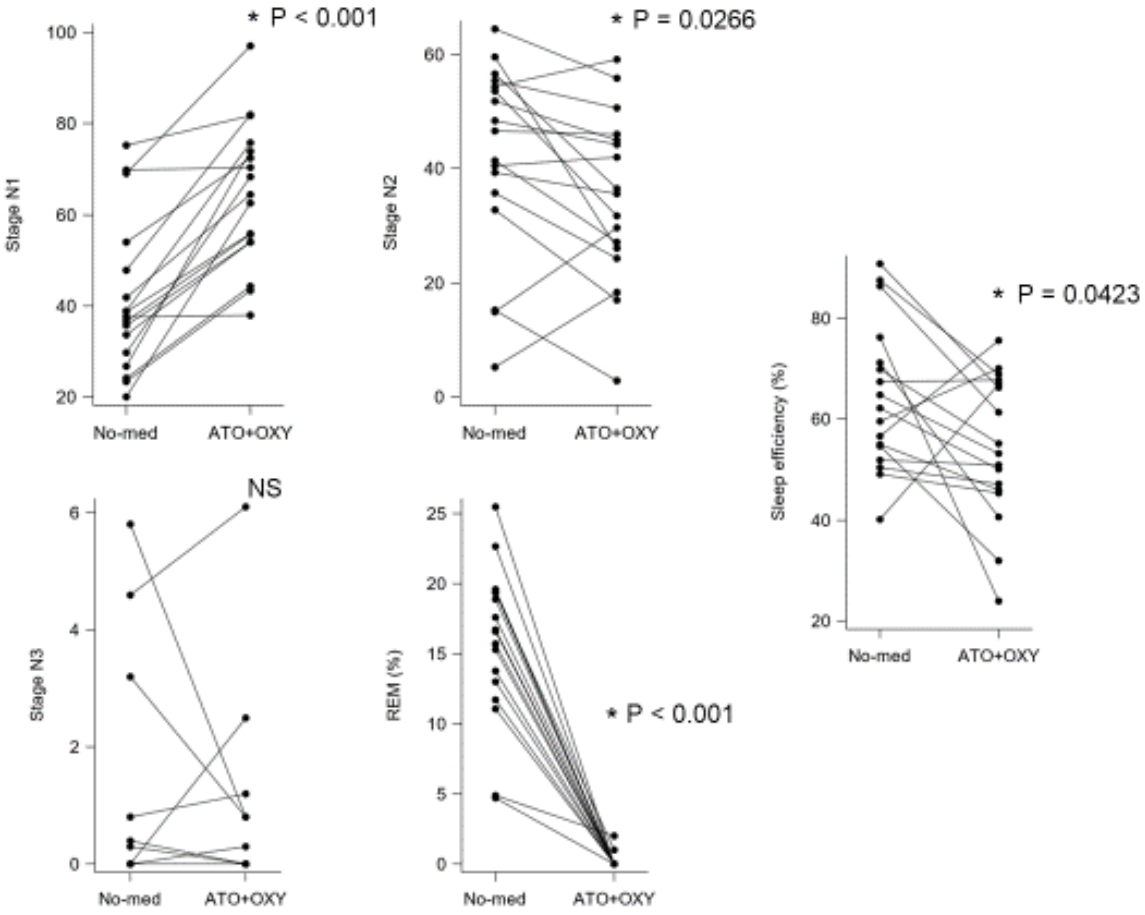

* P < 0.001
Stage N1
100
80
60
40
20
No-med
ATO+OXY
* P = 0.0266
Stage N2
60
40
20
0
No-med
ATO+OXY
* P = 0.0423
Sleep efficiency (%)
80
60
40
20
No-med
ATO+OXY
NS
Stage N3
6
4
2
0
No-med
ATO+OXY
REM (%)
25
20
15
10
5
0
* P < 0.001
No-med
ATO+OXY

Fig. 4

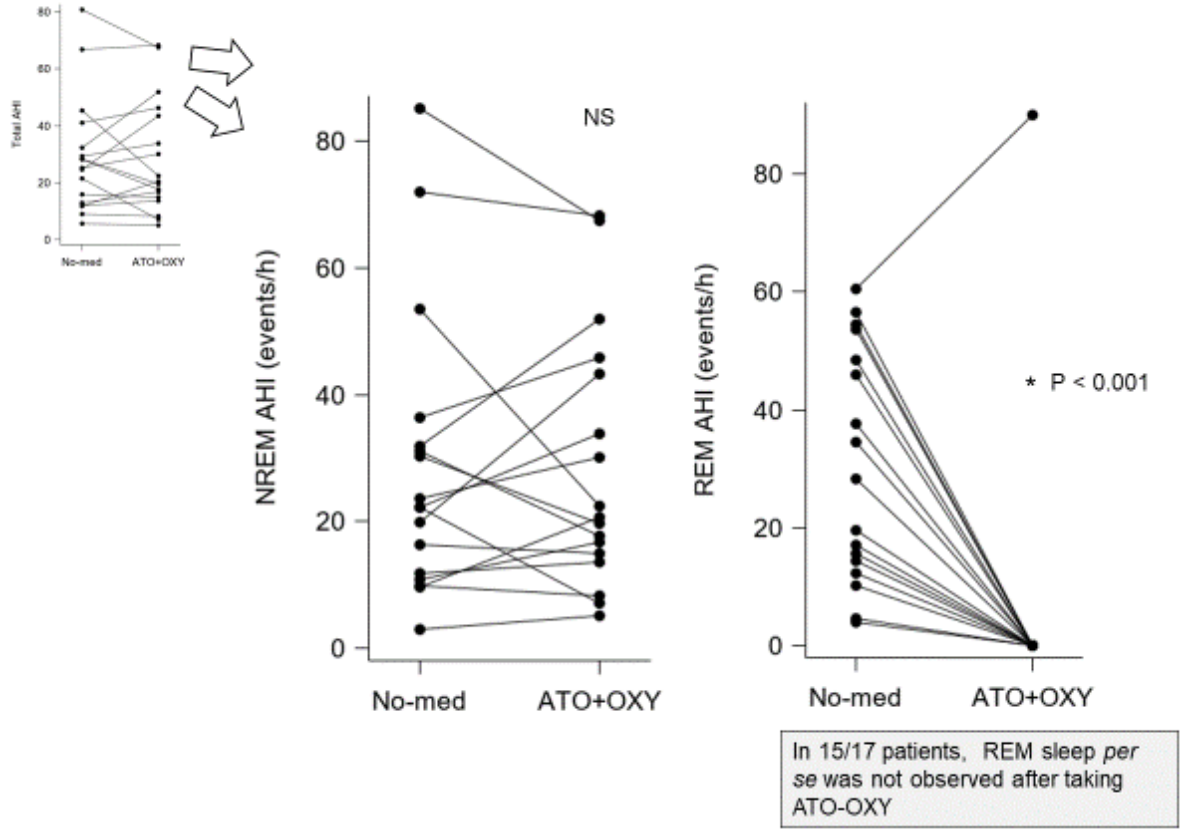

Total AHI
No-med
ATO+OXY
NREM AHI (events/h)
NS
REM AHI (events/h)
* P < 0.001
In 15/17 patients, REM sleep *per se* was not observed after taking ATO-OXY

FIGURE LEGENDS

Figure 1. Clinical study flow chart: CONSORT diagram showing recruitment, randomization, and analysis procedures for the clinical trial.

ATO, atomoxetine; OXY, oxybutynin; no-Med, no medication.

Figure 2. The effect of ATO + OXY on (A) AHI and (B) nadir SpO_2 during sleep, compared to those with no-Med.

A total of 5/17 subjects had a reduction in obstructive sleep apnea severity.
ATO, atomoxetine; OXY, oxybutynin; no-Med, no medication; AHI, apnea–hypopnea index; NS, not statistically significant.

Figure 3. The effect of ATO + OXY on stages (A) N1, (B) N2, (C) REM sleep and (D) sleep efficiency, compared to those with no-Med.

*$p < 0.05$, ATO, atomoxetine; OXY, oxybutynin; no-Med, no medication; NS, not statistically significant; REM, rapid eye movement.

Figure 4. The effect of ATO + OXY on (A) AHI during NREM and (B) AHI during REM sleep, compared to those with no-Med.

REM-AHI disappeared in 16/17 patients after taking ATO-OXY (mainly because REM sleep *per se* was not observed after taking ATO-OXY).
*$p < 0.05$, ATO, atomoxetine; OXY, oxybutynin; no-Med, no medication; NS, not statistically significant; REM, rapid eye movement; NREM, nonrapid eye movement.

Appendix S1

Specific exclusion criteria

Patients who were <20 years and >70 old, and patients with a predominant central apnea, drug allergies to atomoxetine and oxybutynin, severe liver function, cardiac function, renal function, pulmonary dysfunction, severe central nervous system disease, severe hyperthyroidism, ulcerative colitis, tachyarrhythmia, long QT syndrome, seizures, cerebrovascular accident, history of angle-closure glaucoma, paralytic ileus, pheochromocytoma, benign prostatic hyperplasia, urinary retention, myasthenia gravis, and pregnant woman.

Polysomnography recording and scoring

PSG scores were recorded according to the American Academy of Sleep Medicine Manual for the Scoring of Sleep and Associated Events, version 2.3. Apnea was defined as a reduction in nasal airflow to <10% of baseline for 10 s or longer, while hypopnea was defined as a reduction in nasal airflow signal amplitude of ≥30% for ≥10 s in association with either a ≥3% oxygen desaturation or electroencephalographic arousal. OSA was defined as an apnea–hypopnea index (AHI) of ≥5 events per hour combined with predominantly obstructive respiratory events. OSA severity was classified according to AHI values as mild, 5–15; moderate, >15–30, or severe, >30.

Table S1.

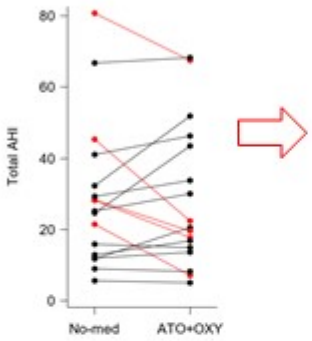
General characteristics and polysomnography data of effective (n = 5) and noneffective groups (n = 12)

	Responders	Non-responders	p-value
Age, year	56.2 (7.60)	54.9 (8.04)	0.711
Neck circumference, cm	40.3 (3.55)	39.7 (3.43)	1.00
Waist circumference, cm	99.8 (15.34)	94.6 (11.32)	1.00
Body mass index, kg/m^2	28.4 (6.06)	26.8 (3.30)	0.915
Mallampati score (1/2/3/4)	1.2	2.25	0.180
Tonsils score (0/1/2/3)	1.6	0.75	0.190
AHI supine, events/h	59.5 (28.67)	37.2 (22.44)	0.105
Nadir SpO_2 (nondrug PSG), %	77.2 (7.69)	81.8 (9.40)	0.245
Arousal index (nondrug PSG), events/h	48.7 (18.88)	33.3 (14.77)	0.0896
TST (nondrug PSG), min	324.4 (36.45)	422.5 (87.41)	0.0305
N1 (nondrug PSG), %TST	50.4 (17.6)	37.6 (15.5)	0.187
N2 (nondrug PSG), %TST	34.0 (18.14)	45.4 (15.96)	0.255
N3 (nondrug PSG), %TST	0.7 (1.40)	1.0 (2.01)	0.950
REM (nondrug PSG), %TST	14.8 (5.85)	16.0 (5.62)	0.832
3% ODI (nondrug PSG), events/h	37.8 (28.32)	24.2 (19.11)	0.268
Sleep efficiency (nondrug PSG), %TIB	53.7 (10.02)	68.8 (14.07)	0.065

Notes: Data are presented as the mean (SD). Significant p-values <0.05.

Abbreviations: PSG, polysomnography; TST, total sleep time; REM, rapid eye movement; ODI, oxygen desaturation index.

Figure S1: General characteristics and PSG data of responders and non-responders



	Responders (n=5)	Non-responders (n=12)	P value
Age, year	56.2 (7.60)	54.9 (8.04)	0.711
Neck circumference, cm	40.3 (3.55)	39.7(3.43)	1.00
Waist circumference, cm	99.8 (15.34)	94.6 (11.32)	1.00
Body mass index, kg/m^2	28.4 (6.06)	26.8 (3.30)	0.915
Mallampati score (1 / 2 / 3 / 4)	1.2	2.25	0.180
Tonsil's score (0/1/2/3)	1.6	0.75	0.190
Nadir SpO_2 (non-drug PSG), %	77.2 (7.69)	81.8 (9.40)	0.245
N1 (non-drug PSG), %TST	50.4 (17.6)	37.6 (15.5)	0.187
N2 (non-drug PSG), %TST	34.0 (18.14)	45.4 (15.96)	0.255
N3 (non-drug PSG), %TST	0.7 (1.40)	1.0 (2.01)	0.950
REM (non-drug PSG), %TST	14.8 (5.85)	16.0 (5.62)	0.832
3%ODI (non-drug PSG), events/h	37.8 (28.32)	24.2 (19.11)	0.268
Sleep efficiency (Non-med PSG), %TIB	53.7 (10.02)	68.8 (14.07)	0.065

Data are Mean (SD). REM: rapid eye movement, NREM: non-rapid eye movement, ODI: oxygen, desaturation index, PSG: polysomnography, TST: total sleep time, TIB: time in bed

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