

ONLINE DATA SUPPLEMENT

The combination of atomoxetine and oxybutynin greatly reduces obstructive sleep apnea severity.

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SUPPLEMENTAL RESULTS

Table E1. Genioglossus muscle responsiveness on and off the drugs.

Muscle responsiveness	Placebo	Ato-oxy	Median change	P value
%baseline/cmH ₂ O	2.2 [1.0 to 4.9]	6.3 [3.0 to 20.8]	2.8 [1.0 to 10.5]	0.0006
%change			102 [50 to 183]	
%wakefulness/cmH ₂ O	3.5 [2.0 to 9.3]	7.5 [3.0 to 25.8]	4 [0.8 to 17.8]	0.065
%change			71 [-13 to 207]	
% maximum/cmH ₂ O	0.2 [0.1 to 0.4]	0.3 [0.1 to 0.6]	0.1 [0.1 to 0.3]	0.43
%change			141 [-26 to 536]	

Data are presented as median [interquartile range].

Baseline was calculated as the median Peak EMG_{GG} during non-REM sleep with non flow-limited breaths and relatively small esophageal pressure swings (-11.0 [-17.6 to -6.8] cmH₂O). Wakefulness value was calculated as the median EMG_{GG} peak value during quiet breathing (absence of movement artifacts such as swallowing, speech, yawns) in supine position from at least 5 minutes of wakefulness recording.

Maximum EMG_{GG} activity was measured during wakefulness on each night by triplicate measures of swallowing and tongue protrusion against the upper or lower incisors. The single maximum value obtained was used for normalization.

Table E2. OSA severity and sleep architecture on and off the drugs in patients with AHI>15 on the placebo night (N=13).

	Placebo	Ato-oxy	Median change	P value
Total AHI, events/h	36.8 [31.2 to 54.1]	11.8 [5.0 to 21.2]	-31.7 [-38.5 to -16.1]	<0.001
%change			-70.6 [-89.8 to -61.6]	
AHI supine, events/h	37.2 [31.2 to 54.7]	11.8 [4.5 to 22.2]	-35.4 [-42.5 to -28.0]	<0.001
%change			-73 [-90 to -62]	
NREM*, events/h	37.0 [32.5 to 54.9]	11.1 [2.3 to 4.5]	-35.5 [-43.2 to -22.1]	<0.001
%change			-72 [-90 to -61]	
REM*†, events/h	41.0 [24.6 to 63.2]	2.2 [0 to 14.3]	-34.0 [-61.0 to -13.2]	0.004
%change			-88 [-96 to -61]	
Apnea Index, events/h	8.1 [5.3 to 20.1]	0.3 [0 to 0.4]	-5.8 [-18.8 to -1.3]	<0.001
ODI 3%, events/h	22.7 [6.4 to 39.3]	3.7 [0.3 to 26.2]	-9.2 [-17.7 to -2.4]	<0.001
Nadir SaO ₂ , %	82 [76.5 to 92.5]	92 [87.5 to 95.9]	7 [3.4 to 17.5]	0.001
Arousal index, events/h	55.8 [46.4 to 63.2]	47.3 [39.9 to 49.4]	-11.3 [-21 to 7.8]	0.040
Total sleep time, mins	196 [155 to 237]	278 [221 to 305]	55 [-6 to 139]	0.071
Sleep efficiency, %TIB	49 [38 to 61]	67 [63 to 77]	16 [1 to 38]	0.046
N1, %TST	46 [19 to 56]	33 [29 to 42]	-18 [-25 to 14]	0.210
N2, %TST	19 [15 to 24]	28 [24 to 39]	11 [4 to 17]	0.049
N3, %TST	0 [0 to 6]	0 [0 to 0]	0 [-4 to 0]	0.5
REM, %TST	4 [0 to 10]	7 [1 to 13]	0 [-2 to 12]	0.399
Subjective sleep quality, VAS score	5 [2 to 8]	5 [4 to 8]	1 [0 to 2]	0.076
Heart rate, bpm	73 [63 to 78]	74 [70 to 81]	6 [1 to 7]	0.009

Systolic blood pressure, mmHg	142 [136 to 151]	144 [138 to 150]	0 [-7 to 5]	0.78
Diastolic blood pressure, mmHg	84 [75 to 91]	89 [85 to 92]	2 [-9 to 7.5]	0.89

Data are presented as median [interquartile range]. AHI: apnea-hypopnea index; NREM: non-rapid eye movement sleep; ODI 3%, Oxygen desaturation index, 3% desaturation; SaO₂: arterial oxygen saturation; ODI: oxygen desaturation index; TIB: time in bed; TST, total sleep time; N1-2-3: non-REM stage 1-2-3; VAS, visual analog scale.

*AHI is calculated in supine position.

†REM AHI was calculated only in 6 patients in which at least 10 minutes of REM sleep were available in both nights.

Table E3. OSA severity and sleep architecture at baseline and after 1 week of atomoxetine 80 mg + oxybutynin 5 mg (N=6). Pilot data from a prospective study.

	Baseline	Ato-oxy	Median change	P value
Total AHI, events/h	32.8 [20.5 to 51.9]	11.4 [9.1 to 19.3]	-23.0 [-33.2 to -10.4]	0.031
%change			-63 [-86 to -34]	
AHI supine, events/h	52.8 [28.4 to 78.6]	18.1 [12.6 to 22.0]	-39.3 [-51.5 to -11.8]	0.031
%change			-65 [-76 to -50]	
NREM*, events/h	59.4 [27.1 to 78.6]	18.8 [12.6 to 21.9]	-41.0 [-57.7 to -10.0]	0.031
%change			-63 [-75 to -48]	
REM†, events/h	52.0 [18.2 to 80.5]	13.5 [4.8 to 23.0]	-33.2 [-72.3 to -4.0]	0.25
%change			-65 [-79 to -29]	
ODI 3%, events/h	25.4 [16.9 to 46.7]	13.1 [9.8 to 34.0]	-10.5 [-17.2 to -5.4]	0.063
Mean SaO ₂ , %	95.1 [92.8 to 98.0]	95.8 [94.4 to 97.8]	0.4 [-0.7 to 2.4]	0.625
Nadir SaO ₂	82.0 [69.5 to 89.8]	88.0 [76.8 to 92.3]	4.5 [1.0 to 11.0]	0.031
Arousal index, events/h	37.1 [21.6 to 66.0]	30.6 [27.6 to 36.2]	-11.1 [-30.8 to 11.6]	0.438
Total sleep time, mins	309 [237 to 371]	314 [259 to 352]	-8 [-39 to 74]	>0.99
Sleep efficiency, %TIB	78 [56 to 87]	77 [65 to 85]	1 [-6 to 13]	0.688
N1, %TST	28 [15 to 44]	33 [23 to 42]	4 [-13 to 17]	0.688
N2, %TST	47 [26 to 64]	49 [44 to 56]	-1 [-10.5 to 21.5]	0.844
N3, %TST	7 [1 to 13.5]	11 [3 to 25]	4 [-7 to 21]	0.469
REM, %TST	14 [11 to 27]	5 [0 to 8]	-11 [-16 to -9]	0.031
ESS score	8 [6 to 11]	4.5 [2 to 6]	-4.5 [-8.5 to 0.3]	0.125
Heart rate, bpm	68.5 [59.0 to 79.5]	74.0 [59.3 to 88.8]	3.5 [-11 to 15.5]	0.687

Systolic blood pressure, mmHg	132.0 [131.0 to 152.3]	139.0 [127.3 to 142.0]	-1 [-18.3 to 9.3]	0.625
Diastolic blood pressure, mmHg	77 [75.3 to 86.8]	73 [67.3 to 87.8]	-3.5 [-14 to 7.8]	0.563

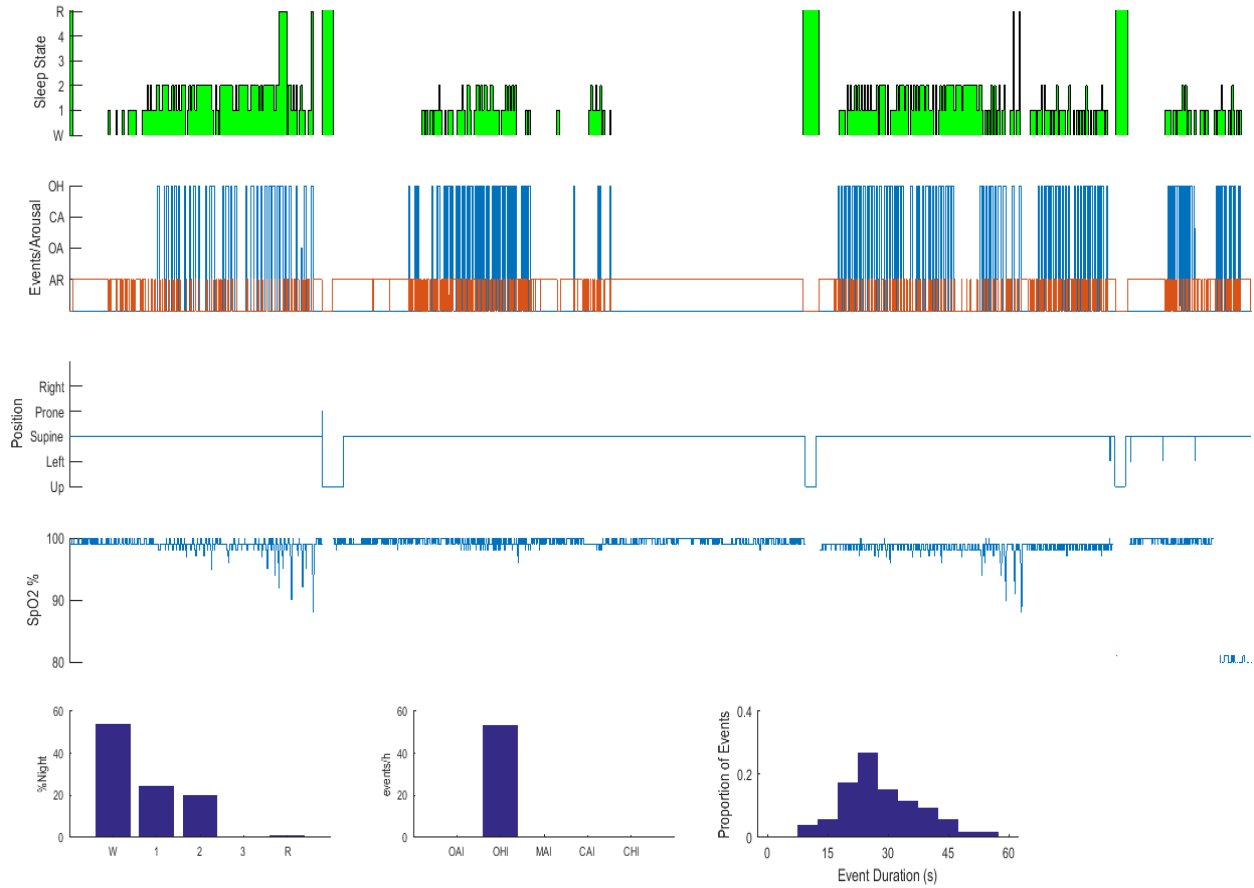
Data are presented as median [interquartile range]. AHI: apnea-hypopnea index; NREM: non-rapid eye movement sleep; ODI 3%, Oxygen desaturation index, 3% desaturation; SaO₂: arterial oxygen saturation; ODI: oxygen desaturation index; TIB: time in bed; TST, total sleep time; N1-2-3: non-REM stage 1-2-3; ESS, Epworth sleepiness scale; bpm, beats per minutes.

*AHI is calculated in supine position.

†REM AHI was calculated only in 4 patients in which at least 10 minutes of REM sleep were available in both nights.

SUPPLEMENTAL FIGURES

A. Placebo.



B. Atomoxetine and oxybutynin.

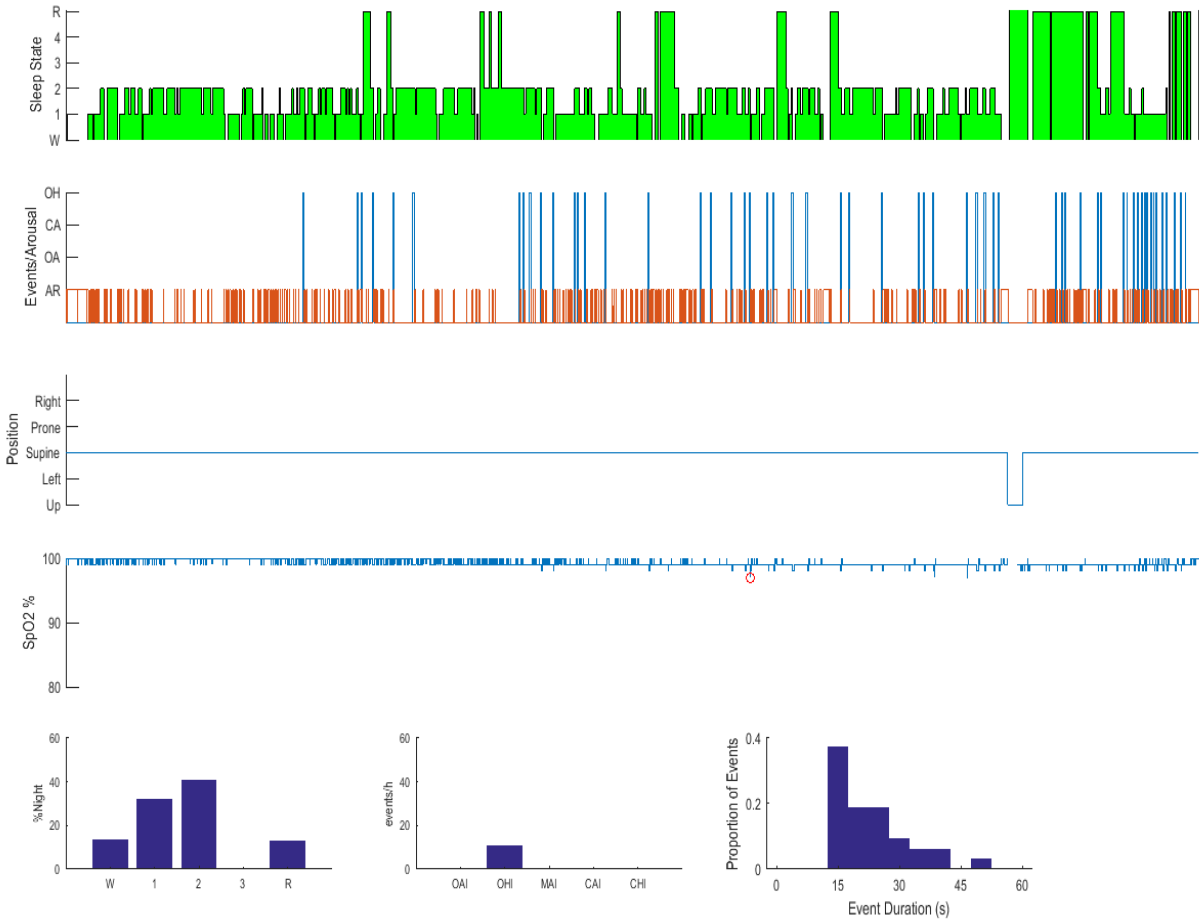


Figure E1.

Example of hypnograms of a representative patient. Figure A and B show from top to bottom: Sleep stages, respiratory events/arousals, body position, oxygen saturation (SpO₂) and plots with summaries of sleep stages (left), respiratory events index (center) and the proportion of events for any given length (right). Figure A shows hypnogram on placebo night. This subject's sleep was highly fragmented with several hypopneas (AHI 54/h), arousals and periods of wakefulness placebo night (A). On ato-oxy night (B) sleep was more consolidated with less wakefulness and more non-REM sleep stage 1 (N1), N2 and REM while N3 was absent on both nights. There were no oxygen saturation drops and hypopneas were reduced in number (AHI 7/h) and duration. R: rapid eye movement (REM) sleep; W, wakefulness; OH, obstructive hypopneas; CA, central apneas; OA, obstructive apneas; AR, arousals.

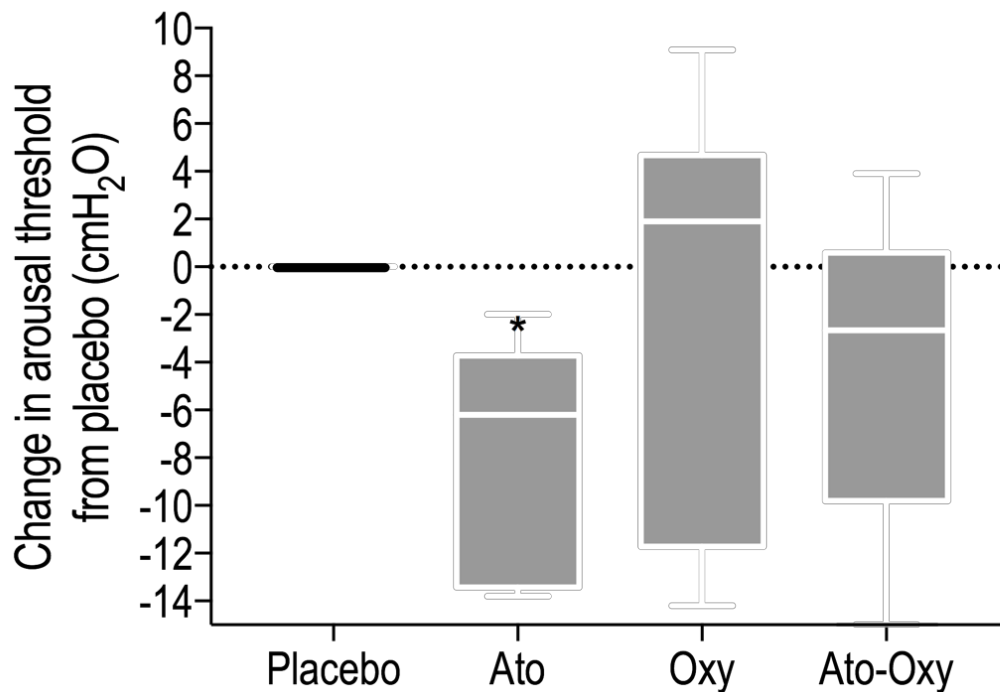


Figure E2. Esophageal pressure (Pes) swings were quantified based on the nadir pressure minus the level at the start of inspiration. Similar to previous physiological studies (1), Pes swings immediately prior to arousal onset were identified and included in the analysis if they were preceded by at least 3 progressively greater esophageal pressure swings in presence of flow-limited breaths or apneas in the flow signal. Arousals were otherwise considered spontaneous (non-respiratory) and excluded from the analysis. A low respiratory arousal threshold can limit the neuromuscular compensation of the upper airway and it is considered deleterious for the pathogenesis of obstructive sleep apnea (2, 3).

Atomoxetine caused a reduction in the arousal threshold by 6.2 cmH₂O (*p=0.03 vs placebo) likely because of its adrenergic properties, but the reduction in arousal threshold on atomoxetine-plus-oxybutynin (ato-oxy) was a non-significant 2.6 cmH₂O (p=0.79). These data suggest that the administration of oxybutynin could attenuate the alerting effect of atomoxetine. Accordingly, previous data suggest that antimuscarinics can antagonize the central activating properties of noradrenergic drugs in animal models (4). These data refer to 6 patients who performed Pes measurements in all 4 conditions. White lines indicate medians, boxes indicate 25th (bottom) and 75th (top) percentiles.

SUPPLEMENTAL REFERENCES

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