

Combination Pharmacological Therapy Targeting Multiple Mechanisms of Sleep Apnea

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Rationale: Currently there are two leading experimental pharmacological interventions under investigation for obstructive sleep apnea (OSA): Acetazolamide, an agent that acts to stabilize ventilatory control, lowers the apnea-hypopnea index (AHI) by ~38%. More recently, atomoxetine-plus-oxybutynin (“AtoOxy”), acting via improvements to dilator muscle responsiveness and baseline tone was found to lower AHI by >50%. Given the different pathophysiology targeted by each potential therapy, we tested whether AtoOxy-plus-acetazolamide would be more efficacious than AtoOxy alone.

Methods: In an multicenter randomized crossover trial, 19 patients with moderate-to-severe OSA received AtoOxy (80/5 mg respectively), acetazolamide (500 mg), combined AtoOxy-plus-acetazolamide, or placebo at bedtime for 3 nights (half doses on first night); outcomes were assessed at baseline and night 3 of each treatment period. Mixed model analysis compared the reduction in AHI (3% desaturation or arousal criterion) from baseline between AtoOxy-plus-acetazolamide and AtoOxy (primary outcome). Secondary outcomes included hypoxic burden, arousal index, and visual analog scale for sleep quality.

Results: Compared with placebo, AHI was lowered with AtoOxy by +49 [33, 62] %_{baseline} (estimate [95%CI]), AtoOxy-plus-acetazolamide by +47 [31, 61] %_{baseline}, and acetazolamide by +34 [14, 50] %_{baseline}. However, there was no effect of AtoOxy-plus-acetazolamide vs. AtoOxy alone (-3 [-33, 20] %_{baseline}, P=0.8). Likewise, hypoxic burden was lowered vs. placebo with AtoOxy by +60 [38, 74] %_{baseline}, with AtoOxy-plus-acetazolamide by +47 [19, 65] %_{baseline}, and with acetazolamide by +38 [5, 59] %_{baseline}; again, there was no effect of AtoOxy-plus-acetazolamide vs. AtoOxy alone. Likewise, AtoOxy and acetazolamide both lowered arousal index but no differential effect of combination therapy was observed. There was no impact on the visual analog scale for sleep quality.

Conclusions: While AtoOxy halved AHI, and acetazolamide lowered AHI by a third, the combination of these leading experimental interventions provided no greater efficacy (per AHI, hypoxic burden, or arousal frequency) than AtoOxy alone.