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SCIENTIFIC INVESTIGATIONS

The combination of atomoxetine and oxybutynin for the treatment of obstructive sleep apnea in children with Down syndrome

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Study Objectives: Children with Down syndrome (DS) are at very high risk for obstructive sleep apnea (OSA). Current OSA treatments have limited effectiveness in this population. We evaluated the effectiveness of atomoxetine and oxybutynin (ato-oxy) to treat OSA in children with Down syndrome.

Methods: Children ages 6–7 years old with Down syndrome and OSA participated in a double-blind crossover clinical trial evaluating two dose regimens of ato-oxy. Participants received low-dose ato-oxy (0.5 mg/kg atomoxetine and 5 mg oxybutynin) and high-dose ato-oxy (1.2 mg/kg atomoxetine and 5 mg oxybutynin) for 1 month in random order. The primary study outcome was change in obstructive apnea-hypopnea index. Health-related quality of life as measured by the OSA-18 as well as changes in sleep architecture were secondary outcomes.

Results: Fifteen participants qualified for randomization and 11 participants had complete data at all points. Baseline obstructive apnea-hypopnea index was 7.4 ± 3.7 (mean ± standard deviation), obstructive apnea-hypopnea index with low-dose ato-oxy was 3.6 ± 3.3 (P = .001 vs baseline), and obstructive apnea-hypopnea index with high-dose ato-oxy was 3.9 ± 2.8 (P = .003 vs baseline). No significant sleep architecture differences were present with ato-oxy. No significant difference in OSA-18 score was present. OSA-18 total score was 51 ± 19 at baseline, 45 ± 17 (P = .09) at the end of 4 weeks of low-dose ato-oxy, and 45 ± 16 (P = .37) at the end of high-dose ato-oxy therapy. The most common adverse effects were irritability and fatigue, and these were generally mild.

Conclusions: Ato-oxy is a promising treatment for OSA in children with Down syndrome.

Clinical Trial Registration: Registry: Clinicaltrials.gov; Name: Medications for Obstructive Sleep Apnea In Children With Down Syndrome (MOSAIC); URL: https://clinicaltrials.gov/ct2/show/NCT04115878; Identifier: NCT04115878.

Keywords: obstructive sleep apnea, Down syndrome

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BRIEF SUMMARY

Current Knowledge/Study Rationale: Obstructive sleep apnea is common in children with Down syndrome, and current treatments have limited efficacy. The combination of atomoxetine and oxybutynin is a promising treatment for obstructive sleep apnea in adults with Down syndrome and may be particularly effective in children with Down syndrome, as it targets airway hypotonia, an important cause of obstructive sleep apnea in this population.

Study Impact: In this crossover study of 11 children with Down syndrome, there was an observed 47%–53% statistically significant reduction in obstructive sleep apnea severity with the combination of atomoxetine and oxybutynin. The combination of atomoxetine and oxybutynin is a promising therapy for obstructive sleep apnea in children with Down syndrome.

INTRODUCTION

Down syndrome (DS) is the most common genetic cause of intellectual disability, with a prevalence of 1 in 700 births.[1] Obstructive sleep apnea (OSA) is one of the most common comorbidities present in children with DS. In children without DS, OSA has a prevalence of 2%–5%[2] while the prevalence of OSA in children with DS has been estimated at 50%–79% in prior studies.[3–6] Current treatments for OSA have limited effectiveness in children with DS. Adenotonsillectomy has been shown to have limited efficacy, as 65%–73% of children with DS have residual OSA after adenotonsillectomy.[7,8] Similarly, positive airway pressure (PAP) effectiveness is limited by poor adherence.[9,10] Airway hypotonia has been linked to OSA treatment failure in children with DS.[11] OSA treatment aimed at improving airway tone is likely particularly well suited to children with DS. Consistent with this, hypoglossal nerve stimulation has been shown to be effective in adolescents with DS, reducing the apnea-hypopnea index (AHI) by 51%.[12] However, use of hypoglossal nerve stimulation may be limited in younger children who are expected to grow a significant amount. Additionally, surgical complications were more common in adolescents with DS compared to adults without DS.[12] Given these findings, a nonsurgical treatment of OSA for children with DS would be advantageous.

The combination of nightly atomoxetine and oxybutynin (ato-oxy) has shown promise for the treatment of OSA in adults

without DS. Studies in adults without DS have shown that ato-oxy can improve airway muscle tone during sleep and treat OSA.[13,14] Sleep-related airway hypotonia in OSA is mediated by two causes. Sleep-related withdrawal of endogenous noradrenergic drive results in genioglossus hypotonia,[15] while active muscarinic inhibition mediates pharyngeal hypotonia.[16] Atomoxetine is a selective norepinephrine reuptake inhibitor while oxybutynin is an antimuscarinic agent. Both medications are separately Food and Drug Administration-approved in children (atomoxetine for treatment of attention deficit hyperactivity disorder [ADHD] and oxybutynin for treatment of overactive bladder), although the combination has not been studied in children. Given airway hypotonia is an important cause of OSA in children with DS[11] and ato-oxy targets airway hypotonia, we hypothesized that ato-oxy would be an effective treatment for OSA in children with DS.

METHODS

Study design

We performed a double-blind crossover clinical trial to evaluate two dose regimens of ato-oxy for treatment of OSA in children ages 6–17 years old with DS. At baseline, participants completed polysomnography and completed health-related quality of life (HR-QOL) and demographic surveys. Participants with a total AHI > 5 were then randomized to receive 1 month of low-dose ato-oxy (5 mg oxybutynin and 0.5 mg/kg/d [max 40 mg] atomoxetine) and 1 month of high-dose ato-oxy (5 mg oxybutynin and 0.5 mg/kg/d [max 40 mg] atomoxetine for 1 week, then 5 mg oxybutynin and 1.2 mg/kg/d [max 80 mg] atomoxetine for remainder) in random order, separated by a 2-week washout period. Polysomnography and evaluation of HR-QOL was repeated on the last night of each dosing regimen (**Figure 1**). This study was registered on clinicaltrials.gov prior to patient enrollment (NCT04115878).

Eligibility criteria

Children ages 6–17 years old with trisomy 21 (no translocation or mosaic DS) were eligible to participate. Exclusion criteria included currently adherent to PAP therapy, monoamine oxidase inhibitor use, urinary retention, prematurity < 37 weeks estimated gestational age, seizure disorder, inadequately treated hypothyroidism, history of significant traumatic brain injury, current untreated depression, history of liver disease, 3+ or greater tonsillar hypertrophy, or a positive urine pregnancy test. Children with congenital heart disease were allowed to participate if given clearance by their cardiologist. Participants were excluded from randomization if baseline polysomnography showed hypoxemia independent of respiratory events (≥ 5 minutes with oxygen saturation < 90%), central sleep apnea (central AHI ≥ 5), or total AHI < 5.

Participant recruitment and data safety monitoring

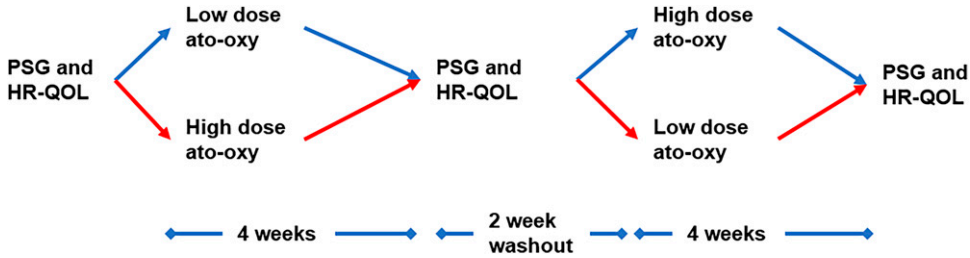
Participants were recruited from a community DS clinic and a university-affiliated pediatric sleep medicine clinic. Advertisements were distributed through a local DS research registry and DS advocacy groups. Written informed consent was obtained from a parent, and assent was obtained from all participants ages 7 years and older. The study was approved by the University of Arizona Institutional Review Board (#1908864846). A National Institutes of Health-appointed data safety monitoring board met biannually to review the study. Participants were monitored weekly for possible adverse events while taking ato-oxy.

Outcomes and assessments

The prespecified primary outcome was change in obstructive AHI from baseline. Prespecified secondary outcomes were change in OSA-18 score and arousal index. Prespecified exploratory outcomes included change in Pediatric Quality of Life inventory (PedsQL) total score, Caregiver Global Impression of Change and changes in N1, N3, and rapid eye movement sleep percentage. An optional self-reported neurocognitive assessment was performed, with prespecified exploratory outcome of the Conners Attention Deficit Hyperactivity Disorder Index score.

Polysomnography was performed at baseline and at the end of each dose period of ato-oxy. In-lab polysomnography was

Figure 1—Study design.



Participants were randomized to either high- (5 mg oxybutynin and 1.2 mg/kg/d [max 80 mg]) or low-dose ato-oxy (5 mg oxybutynin and 0.5 mg/kg/d [max 40 mg] at baseline. For high-dose ato-oxy, participants took low-dose ato-oxy for the first week prior to increasing to the high ato-oxy dose for the remaining 3 weeks. Polysomnography and a health-related quality of life assessment were performed after 2 weeks of ato-oxy. Participants then took no drug for 2 weeks, then took the alternate ato-oxy dose for 4 weeks with repeat polysomnography and health-related quality of life assessment at the end of therapy. Participants who agreed to participate in the neurocognitive assessment completed the Conners at the same timepoints as polysomnography and the health-related quality of life assessment. ato-oxy = atomoxetine and oxybutynin.

done using an Alice (Philips-Respironics, Murraysville, PA) system. Polysomnography was performed and scored following the current American Academy of Sleep Medicine pediatric standards. Hypopneas were scored if a 30%–90% reduction in air flow was accompanied by a 3% relative oxygen desaturation or an arousal.

HR-QOL evaluation was performed using two validated pediatric HR-QOL assessments, the OSA-18 and PedsQL. The OSA-18 is a pediatric OSA-specific HR-QOL scale[17] that includes questions in five domains: sleep disturbance, physical suffering, emotional distress, daytime problems, and caregiver concerns. The PedsQL is a general pediatric HR-QOL questionnaire with subscales for physical, emotional, social, and school function.[18] A change of 4.4 in PedsQL total scale score has been shown to represent the minimal clinically important significant difference.[19] The OSA-18 and PedsQL have been previously used in children with DS.[12,20]

The Caregiver Global Impression of Change scale is a single question designed to assess satisfaction with ato-oxy, considering both safety and efficacy. Parents of participants were asked, "Since the start of this therapy, my child's overall status is (please only consider the current medication compared to before starting the study)." Responses on a 7-point Likert scale included "very much improved," "much improved," "minimally improved," "no change," "minimally worse," "much worse," or "very much worse."

Participants' parents were invited to complete an optional neurocognitive assessment using the Conners, third edition (Pearson, San Antonio, TX). The Conners has been used in prior studies of children with DS and is validated in individuals with intellectual and developmental disabilities.[21]

Parent-reported demographic and socioeconomic data were collected at baseline. Socioeconomic status was determined using the Hollingshead socioeconomic status index (calculated from parent education level and occupation). Parents completed a brief medical history form at baseline. Body mass index (BMI) was obtained from baseline visit height and weight and converted to age and sex-adjusted percentiles based on the Centers for Disease Control and Prevention data.[22] BMI percentiles were calculated using standard data rather than Down syndrome-specific growth curves as current research recommends use of the standard data as it is more reflective of body composition and identifying obesity and obesity-related complications.[23,24] Heart rate was measured at each visit. Blood pressure was measured three times with at least 2 minutes between readings, and the average reading was calculated at each visit.

Statistical analysis

The initial study of ato-oxy in adults showed an effect size (Cohen's d) of 1.4 for reducing AHI.[13] *A priori*, we planned to randomize 24 participants, which would have 80% power (alpha of 0.05) to detect an effect size of 1.20 standard deviations. Due to COVID-19 pandemic-related recruitment delays, we ended enrollment at 15 randomized participants.

Participants were randomized to one of the two dose sequences via stratified block randomization (stratified by age 6–12 years old and 13–17 years old). Study personnel were blinded to participant treatment arm except for a statistician responsible for providing data for safety monitoring. Statistical analysis was done using SPSS 27 (IBM, Armonk, NY). Continuous outcome variable normality was assessed using the Shapiro-Wilk test. Paired *t* tests were used for unadjusted analysis. For adjusted comparison of low-dose vs high-dose ato-oxy, to account for the features of a crossover design, a linear mixed effects model with a participant random effect and a dose sequence indicator, a period indicator, and a high-dose ato-oxy dose indicator as the covariates were fitted to the changes in outcomes. Sensitivity analysis to account for variation in supine sleep percentage was performed via the same linear mixed effects model with the addition of supine sleep percentage as a time-dependent covariate included in the model. Fisher's exact test was used to compare differences in adverse events between high- and low-dose ato-oxy. All statistical tests were two-sided and a P value $< .05$ was considered significant. For outcomes data, only the 11 participants with complete data were included. For safety data, all randomized participants (n = 15) were included. Continuous data is presented as mean ± standard deviation.

RESULTS

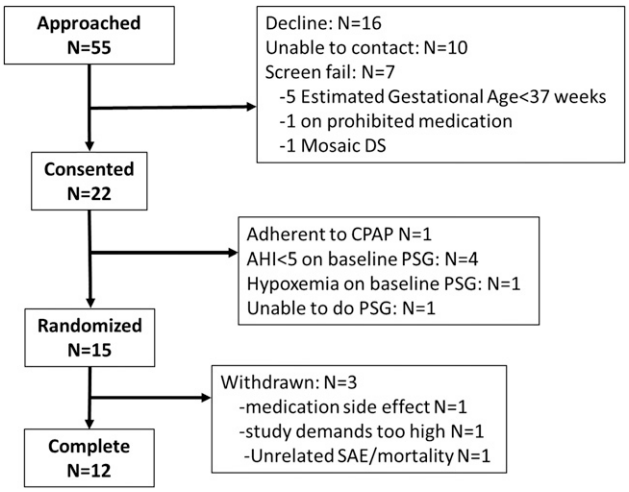
Study enrollment and safety

Twenty-two of 55 potential participants approached agreed to participate in the study. Of these 22, 7 did not progress to randomization, most commonly due to AHI below the study threshold of 5 events/h. Fifteen participants were randomized to study medications. One participant withdrew due to medication side effects (mood changes), one participant withdrew due to study burden being too high, and one participant developed sepsis and respiratory failure and subsequently died. Data safety monitoring board review of this event determined it was unrelated to the study. Twelve participants completed the study. However, as one participant had insufficient data on their last polysomnogram, data from the 11 participants with complete polysomnography data are presented. Details of study enrollment are presented in **Figure 2**.

Participants were 82% White and 18% Black. Fifty-eight percent of White participants were of Latino or Hispanic ethnicity. Participants were predominantly male (73%). Participants ranged in age from 6 to 16 years old (mean 10.4 ± 4.1 years). Mean BMI percentile was 79 ± 23, and 55% of participants had obesity, defined as BMI ≥ 95th percentile. Seventy-three percent of participants had congenital heart disease. All participants had a reported prior adenotonsillectomy. Details of participant demographics are reported in **Table 1**. Medication adherence was 92 ± 10% for low-dose ato-oxy and 93 ± 7% for high-dose ato-oxy ($P = .73$). The median time interval between baseline polysomnography and initiation of treatment was 7 days (range 2–35 days), and the time interval between baseline polysomnography and first sleep study on study medications was 35 days (range 30–63 days).

The most commonly reported adverse events included fatigue and mood changes. Fatigue and mood changes (typically irritability) were more common in participants taking the high dose of

Figure 2—Clinical trial enrollment.



One participant did not have sufficient data recorded on their third polysomnogram; therefore complete data were available from 11 participants. Among individuals who declined participation, 2 reported this was due to study burden being too high, 2 reported this was due to concern about taking medication, and the remaining individuals did not provide a specific reason for declining. Individuals were considered unable to be contacted if they were unreachable after at least two attempts to contact following the initial contact where they initially expressed interest in the study. AHI = apnea-hypopnea index, CPAP = continuous positive airway pressure, SAE = severe adverse event.

ato-oxy, although this did not reach statistical significance. Full details of adverse events are provided in **Table 2**.

Given the high rate of congenital heart disease in people with DS, we examined cardiovascular effects of ato-oxy. No significant difference was seen in resting heart rate with ato-oxy: mean baseline heart rate was 90 ± 20, and heart rate on low-dose ato-oxy was 88 ± 12 and 88 ± 9 on high-dose ato-oxy (P = .59 low dose vs baseline, P = .75, high dose vs baseline, P = .95 low dose vs high dose). Systolic blood pressure was slightly lower with ato-oxy, baseline 110 ± 11, 103 ± 9 with low-dose ato-oxy, and 107 ± 13 with high-dose ato-oxy, but this did not reach statistical significance (P = .09 low dose vs baseline, P = .27, high dose vs baseline, P = .19 low dose vs high dose). No significant difference was seen in diastolic blood pressure, baseline 72 ± 9, 70 ± 7 with low-dose ato-oxy, and 74 ± 7 with high dose ato-oxy (P = .46 low dose vs baseline, P = .70, high dose vs baseline, P = .26 low dose vs high dose).

Table 1—Participant demographics.

Age (Years)	10.4 ± 4.1
Sex (%)	
Female	3 (27)
Male	8 (73)
Race (%)	
Black	2 (18)
White	9 (82)
Hispanic or Latino ethnicity	5 (46)
Socioeconomic status	40 ± 18
BMI percentile	79 ± 23
Congenital heart disease (%)	8 (73)
Depression (%)	1 (9)
Autism spectrum disorder (%)	2 (18)
ADHD (%)	2 (18)

Data are presented as mean ± standard deviation for continuous variables. Hollingshead socioeconomic status index was used to calculate socioeconomic status. Higher scores indicate higher status; scores can range from 8 to 66. ADHD = attention deficit hyperactivity disorder, BMI = body mass index.

Table 2—Ato-oxy adverse events reported in children with Down syndrome.

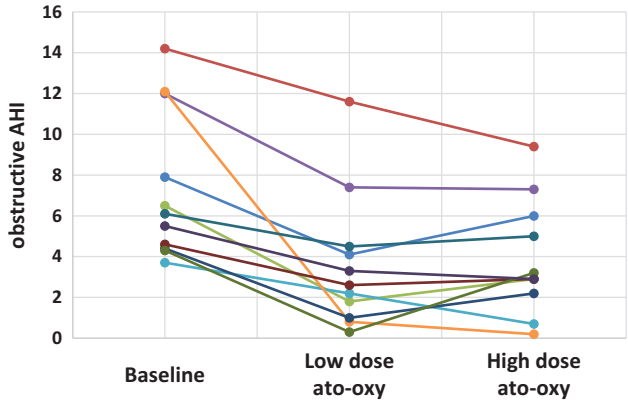
Adverse Event	High Dose (%)	Low Dose (%)	*P*
Fatigue	27	13	.65
Mood changes	27	20	1.00
Diarrhea	7	7	1.00
Headaches	7	0	1.00
Abdominal pain	0	7	1.00
Decreased urinary frequency	7	0	1.00
Dry mouth	0	7	1.00

ato-oxy = atomoxetine and oxybutynin.

Polysomnographic outcomes

Mean obstructive AHI decreased from 7.4 ± 3.7 events/h to 3.6 ± 3.3 events/h for low-dose ato-oxy and 3.9 ± 2.8 events/h for high-dose ato-oxy (P = .001 low dose vs baseline, P = .003 high dose vs baseline, P = .54 low dose vs high dose). Individual participant responses to ato-oxy are shown in **Figure 3**.

Figure 3—Participant-level changes in obstructive AHI (events/h) with low-dose and high-dose ato-oxy.



AHI = apnea-hypopnea index, ato-oxy = atomoxetine and oxybutynin.

There was no significant difference in arousal index or sleep architecture seen with ato-oxy. Full details of polysomnographic results are presented in **Table 3**. Adjusted results were not meaningfully different from unadjusted results and are presented in **Table 4**. Sensitivity analysis including supine sleep percentage as a covariate at each point (baseline, low-dose, and high-dose ato-oxy) did not change the findings of the adjusted analysis. There remained a significant difference ($P < .001$ for baseline vs both low- and high-dose ato-oxy), while the difference between high- and low-dose ato-oxy was not significant ($P = .12$). Eighty-two percent of participants had a residual obstructive AHI less than 5 events/h with low-dose ato-oxy, and 64% of participants had a residual obstructive AHI less than 5 with high dose ato-oxy. Eighteen percent of participants had a residual obstructive AHI less than 1 with both high- and low-dose-ato-oxy.

Quality of life and neurocognitive outcomes

There was no statistically significant improvement in HR-QOL on the OSA-18 or PedsQL. OSA-18 total scores were lower (lower scores indicate improved HR-QOL on the OSA-18) with both high- and low-dose ato-oxy compared to placebo, but this did not reach statistical significance. PedsQL total scores were slightly higher (higher scores indicate improved HR-QOL on the PedsQL) with both high- and low-dose ato-oxy compared to placebo, but this again was not statistically significant. Full details of HR-QOL outcomes are provided in **Table 5**. No significant difference was seen in HR-QOL on either OSA-18 or PedsQL for low-dose compared to high-dose ato-oxy. Caregiver Global Impression of Change scores favored low-dose ato-oxy over high-dose ato-oxy, but this did not reach statistical significance (3.2 ± 0.6 vs 3.7 ± 0.9, $P = .24$, lower score indicates higher treatment satisfaction). For context, a score of 3 reflects "minimally improved" while a score of 4 corresponds to "no change."

Eight participants had complete Conners data at all time points. The Conners ADHD index score was 9.1 ± 6.3 at baseline, 7.9 ± 6.5 with low-dose ato-oxy, and 5.6 ± 4.9 with high-dose ato-oxy ($P = .47$ low dose vs baseline, $P = .047$, high dose vs baseline, $P = .37$ low dose vs high dose).

DISCUSSION

Ato-oxy is a promising treatment for OSA in children with DS. There was an observed 47%–51% reduction in OAHI compared to baseline following treatment with ato-oxy, with obstructive AHI reduced to < 5 in 64%–82% of participants, and 18% of

Table 3—Polysomnographic outcomes of ato-oxy for OSA treatment in children with Down syndrome.

				P		
	Baseline	Low Dose	High Dose	Low vs Baseline	High vs Baseline	Low vs High
Obstructive AHI	7.4 ± 3.7	3.6 ± 3.3	3.9 ± 2.8	**.001**	**.003**	.54
Total AHI	9.1 ± 4.5	6.3 ± 5.0	6.1 ± 3.5	.08	.06	.83
REM obstructive AHI	17.6 ± 11	7.2 ± 5.3	8.0 ± 9.8	**.02**	**.004**	.79
REM total AHI	19.5 ± 10.6	11.9 ± 10.3	12.0 ± 15.2	.12	.09	.98
Non-REM obstructive AHI	5.9 ± 3.1	3.1 ± 3.3	2.9 ± 2.8	**.002**	**.008**	.89
Non-REM total AHI	4.5 ± 3.7	5.2 ± 4.6	5.0 ± 3.7	.2	.06	.79
Supine AHI	10.5 ± 7.2	7.2 ± 6.3	5.9 ± 3.8	.11	**.03**	.34
Nonsupine AHI	8.3 ± 9.7	2.4 ± 2.8	4.0 ± 4.9	.14	.26	.08
Mean oxygen saturation	94.5 ± 3.8	95.1 ± 0.8	95.0 ± 1.3	.54	.54	.83
Oxygen saturation < 90% (minutes)	4.6 ± 10.6	1.1 ± 1.8	1.3 ± 1.3	.32	.33	.75
Sleep onset (minutes)	19 ± 22	11 ± 13	9 ± 13	.27	.21	.7
Total sleep time (minutes)	420 ± 61	416 ± 51	416 ± 88	.85	.84	.98
Sleep efficiency (%)	87 ± 10	92 ± 4.5	86 ± 13	.07	.95	.19
Arousal index	15 ± 6	17 ± 8	15 ± 10	.23	.79	.51
N1 sleep (%)	3 ± 4	4 ± 3	4 ± 3	.68	.68	.97
N2 sleep (%)	50 ± 15	55 ± 9	52 ± 8	.35	.68	.53
N3 sleep (%)	33 ± 14	29 ± 9	33 ± 10	.3	.87	.36
REM sleep (%)	13 ± 5	12 ± 9	11 ± 8	.61	.05	.82
Supine sleep (minutes)	257 ± 187	303 ± 135	265 ± 157	.32	.83	.12
Supine sleep (%)	63 ± 37	80 ± 19	63 ± 13	.11	.49	.09

Data is presented as mean ± standard deviation. Bold indicates $P < .05$. AHI = apnea-hypopnea index, ato-oxy = atomoxetine and oxybutynin, REM = rapid eye movement.

Table 4—Multivariate analysis results of outcomes of ato-oxy for OSA treatment in children with Down syndrome.

	Baseline	Low Dose	High Dose	*P*		
				Low vs Baseline	High vs Baseline	Low vs High
Obstructive AHI	7.4 ± 3.7	3.6 ± 3.3	3.9 ± 2.8	<.001	<.001	.31
Arousal index	15 ± 6	17 ± 8	15 ± 10	.99	.80	.54
N1 sleep (%)	3 ± 4	4 ± 3	4 ± 3	.16	.16	.93
N3 sleep (%)	33 ± 14	29 ± 9	33 ± 10	.21	.49	.23
REM sleep (%)	14 ± 5	12 ± 8	13 ± 10	.67	.62	.94
OSA-18 total score	52 ± 18	44 ± 17	47 ± 16	.76	.96	.53
PedsQL total score	64 ± 16	68 ± 15	67 ± 14	.83	.92	.76

Data is presented as mean ± standard deviation. OSA-18: OSA-specific health-related quality of life, lower scores indicate better quality of life. PedsQL: General pediatric health-related quality of life, higher scores indicate better quality of life. *P* values derived from linear mixed effects model after adjusting for period and dose sequence effects. AHI = apnea-hypopnea index, ato-oxy = atomoxetine and oxybutynin, OSA = obstructive sleep apnea, PedsQL = Pediatric Quality of Life inventory, REM = rapid eye movement.

participants had resolution of resolution of OSA (oAHI<1). Medication adherence was high, with greater than 90% of planned doses taken by participants. To put these results in perspective, hypoglossal nerve stimulation for OSA in adolescents with DS showed a 54% reduction in mean obstructive AHI, and 34% of participants had an AHI reduced to < 5.[12] Participants in our study had milder OSA (mean baseline obstructive AHI of 7.4) compared to the study of hypoglossal nerve stimulation (mean baseline obstructive AHI of 22). Unlike the prior study of hypoglossal nerve stimulation,[12] we included individuals with obesity (BMI > 95th percentile), who made up 55% of participants. Our results suggest that ato-oxy may be a therapy even for obese individuals who may be excluded from treatment using hypoglossal nerve stimulation.

Studies of ato-oxy in adults with OSA have generally shown a similar reduction in AHI as the reduction seen in our study. The initial study of ato-oxy in 20 adults showed a 63% reduction in median AHI in a one-night study,[13] and a subsequent one-night study of 60 adults with OSA showed a 57% decrease in AHI.[25] A small single-night study of ato-oxy of 17 Japanese adults showed a 19% reduction in median AHI.[26] A recent 1-month study of ato-oxy in 39 adults with OSA showed an approximately 50% reduction in mean AHI compared to baseline.[27] Finally, a one-night study of atomoxetine and

Table 5—Health-related quality of life and neurocognitive outcomes of ato-oxy for OSA treatment in children with Down syndrome.

	Baseline	Low Dose	High Dose	*P*		
				Low vs Baseline	High vs Baseline	Low vs High
Health-related quality of life						
OSA-18 total score	51 ± 19	45 ± 17	45 ± 16	.09	.37	.85
PedsQL total score	64 ± 16	67 ± 15	66 ± 15	.48	.69	.73
Conners (n = 8)						
ADHD index score	9.1 ± 6.3	7.9 ± 6.5	5.6 ± 4.9	.47	**.047**	.37
Inattention	70 ± 14	67 ± 14	64 ± 11	.45	.15	.23
Hyperactivity/impulsivity	70 ± 14	67 ± 13	65 ± 11	.49	.29	.59
Learning problems	78 ± 9	77 ± 9	75 ± 13	.73	.13	.61
Executive function	61 ± 14	65 ± 11	61 ± 8	.47	.89	.32
Defiance/aggression	64 ± 10	53 ± 10	58 ± 11	**.02**	.06	.33
Peer relations	68 ± 21	69 ± 17	62 ± 19	.8	.31	**.01**
Global index	66 ± 16	65 ± 13	61 ± 13	.5	.17	.37

Data is presented as mean ± standard deviation. OSA-18: OSA-specific health-related quality of life, lower scores indicate better quality of life. PedsQL: General pediatric health-related quality of life, higher scores indicate better quality of life. For Conners, higher scores indicate worse function. Bold indicates *P* < .05. ADHD = attention deficit hyperactivity disorder, ato-oxy = atomoxetine and oxybutynin, OSA = obstructive sleep apnea, PedsQL = Pediatric Quality of Life inventory.

aroxybutynin (an enantiomerically pure form of oxybutynin) showed a 40%–58% reduction in median AHI in a study of 27 adults with OSA.[28]

We found that ato-oxy was well tolerated in children with DS. Side effects reported were all known side effects of atomoxetine and oxybutynin. We found a lower rate of side effects compared to prior studies of atomoxetine in individuals with developmental disabilities.[29] Rapid dose titration of atomoxetine is associated with increased fatigue compared to a slower titration.[29] In our study, patients were titrated over the course of 1 week to high-dose ato-oxy; a longer titration may decrease adverse events.

Our study found a different side-effect profile for ato-oxy in children with DS compared to prior studies of ato-oxy in adults. Fatigue and mood changes were most common adverse events in our study, consistent with prior pediatric experience.[29,30] Adult studies have identified dry mouth and insomnia as the most common side effects reported[25,27,28] Furthermore, we found that there was no increase in heart rate or blood pressure with ato-oxy.

Efficacy of ato-oxy was similar between the low- and high-dose regimens, but more side effects were reported with high-dose ato-oxy. Prior research has suggested that drug levels for the same dose of a medication may be higher in children with DS compared to children without DS.[31] This may explain both the increased side effects of high-dose ato-oxy as well as why low- and high-dose ato-oxy showed similar efficacy in children with DS, when prior study of ato-oxy in adults has shown increased efficacy of high-dose ato-oxy compared to low-dose ato-oxy.[28] Based on individual level results shown in **Figure 1**, high-dose ato-oxy may be more effective than low-dose ato-oxy for individuals with more severe OSA but had similar efficacy in individuals with moderate OSA. As ato-oxy studies in adults have generally included participants with a higher AHI, this may also explain why a dose effect was present in adult studies of ato-oxy but not in the present study.

While PedsQL and OSA-18 scores were improved on ato-oxy therapy compared to baseline, there was no statistically significant improvement in HR-QOL in our study. In this 1-month study, OSA-18 scores improved by 12%, less than the 53% improvement seen after 1 year of hypoglossal nerve stimulation in adolescents with DS.[12] Differences in study design may explain this difference. This study evaluated changes after only 1 month of therapy, not an entire year of therapy. Additionally, it is possible that medication side effects may have offset the benefits of OSA treatment on HR-QOL. These side effects, particularly irritability and aggression, may resolve after the first few months on atomoxetine.[32]

ADHD symptoms improved with ato-oxy therapy. This is consistent with the known efficacy of atomoxetine as a treatment for ADHD, although these are the first data on atomoxetine and ADHD in individuals with DS. High-dose ato-oxy was associated with larger improvements on the Conners compared to low-dose ato-oxy, suggesting that while a low-dose of ato-oxy was effective for OSA treatment, higher levels of atomoxetine may be needed to treat ADHD symptoms. While mood changes including irritability were one of the more common adverse effects reported, ato-oxy at both doses was associated with a reduced defiance/aggression scale score (**Table 3**). This suggests that while participants may experience irritability as a side effect, ato-oxy therapy at the population level was associated with improvement of aggressive behaviors.

Our results suggest ato-oxy is a promising therapy for OSA in children with DS. Further research is needed to expand these findings to adults with DS, as well as to children without DS. Ato-oxy is a readily available combination of two Food and Drug Administration-approved medications. Given this, it has several advantages that make it particularly useful for treatment of OSA in children. First, current standard therapies for OSA in children include adenotonsillectomy and PAP therapy.[2] There is typically a delay of several months from OSA diagnosis to treatment via either of these options. Ato-oxy could conceivably be started the same night as a clinic visit following a diagnostic sleep study, greatly reducing time to therapy initiation. Therefore, ato-oxy could be used as an interim therapy in children pending definitive treatment with adenotonsillectomy. Additionally, given the high reported rate of spontaneous resolution of OSA[33,34] in children, ato-oxy may be a useful temporary option compared to the permanent effects of adenotonsillectomy. Additionally, adherence to ato-oxy was high in this study. Given PAP therapy adherence is limited for many individuals in both real-world[35,36] and clinical trial settings,[37] ato-oxy may be a therapeutic option for children unable to tolerate PAP therapy.

Our study has several limitations. Due to COVID-19, we ended enrollment below our initial recruitment target. As a result, while we found statistically significant differences in oAHI, our primary endpoint, our secondary endpoints were under-powered and improvements in HR-QOL were not statistically significant. Similarly, while we showed no significant changes in blood pressure or heart rate, given the small sample size, type II error cannot be excluded, and a larger sample size would be useful to confirm these findings. Additionally, given the exploratory nature of the endpoints beyond obstructive AHI and total scores on the OSA-18, we chose to not adjust for multiple comparisons. Therefore, these exploratory results should be considered as hypothesis-generating data rather than definitive results. Additionally, this study only evaluated the effects of 1 month of ato-oxy treatment. Future studies are needed to confirm the long-term efficacy of ato-oxy. A longer-term study would also be useful to evaluate potential cognitive benefits of OSA treatment with ato-oxy, as limited cognitive benefits may occur over a short treatment duration. Finally, while our study included some individuals with severe OSA, the mean OSA severity was consistent with moderate OSA. Future study of individuals with more severe OSA are needed to confirm the efficacy of ato-oxy in individuals with severe OSA.

We chose not to include a placebo arm in this study. We decided against including placebo as stakeholder opinion was against inclusion of a placebo condition and there was concern that we would be unable to enroll sufficient participants if the study design included placebo. Additionally, we felt the dose-finding aspect of the study was important as lower drug levels may be sufficient in children with DS.[31] Inclusion of both doses of ato-oxy and placebo along with a baseline polysomnogram would have required four sleep studies over approximately

4 months, which would be a significant burden on participants and limited study accrual. Given this we cannot exclude a placebo effect in our study. While spontaneous improvement of OSA is known to occur in typically developing children,[33] there is no evidence for this in children with DS. Cross-sectional studies have generally demonstrated OSA is persistent at all ages in people with DS, suggesting spontaneous resolution is unlikely. A study of 2- to 4-year-old children with DS found that 57% of participants had OSA.[3] A study of children with DS (mean age 9 years) found OSA present in 79% of participants.[6] A study of adolescents with DS (mean age 12.5 years) found OSA present in 66% of participants.[38] Finally, studies of OSA prevalence in adults with DS have shown a prevalence of 82%–100%.[39,40] Additionally, control groups from prior studies have shown that OSA severity appears to be the same or worse over time in children with DS. The control group from a study of montelukast and/or nasal steroids showed a slight worsening of AHI over the course of 10.5 months, AHI 3.5 at baseline to 4.3 at follow-up.[41] A similar study of anti-inflammatory medications for OSA in children with DS had essentially the same findings, with a baseline AHI of 2.9 and an AHI of 3.6 15.4 months later. Given this, spontaneous resolution of OSA is unlikely to explain our findings. Similarly, prior research on OSA in children with DS has suggested there is minimal night-to-night variation in AHI; therefore night-to-night variability is unlikely to explain our findings. A study of myofunctional therapy showed a baseline AHI of 6.4 ± 8.6 with a treatment AHI of 6.4 ± 10.8 1 week later.[42]

Our project has several strengths. First, the treatment adherence was high—over 90% for both dose regimens. Second, participants in our study were diverse and highly representative of the local community, with 64% of participants from race/ethnicity groups underrepresented in research. Third, study participants had comorbidities such as congenital heart disease that are common in individuals with DS. Thus, our study results are highly generalizable to the larger population of individuals with DS.

Our study is unique in the extension of a promising therapy to children with DS while the therapy is still in clinical development. Typical drug development follows a serial progression of clinical trial in healthy adults, then studies in healthy children (often done after initial Food and Drug Administration approval for the medication in adults). Individuals with DS are often excluded from clinical trials.[43] This often leads to individuals with DS being given therapies in clinical practice in the absence of any data in DS. This study demonstrates safety and efficacy of ato-oxy for OSA treatment in children with DS, a population with an urgent need for novel OSA treatments.

Ato-oxy was well tolerated in our study and significantly reduced OSA severity. Larger studies over a longer time are needed to confirm the utility of ato-oxy as a novel therapy for OSA in children with DS.

ABBREVIATIONS

ADHD, attention deficit hyperactivity disorder
AHI, apnea-hypopnea index
ato-oxy, atomoxetine and oxybutynin
BMI, body mass index
DS, Down syndrome
HR-QOL, health-related quality of life
OSA, obstructive sleep apnea
PAP, positive airway pressure
PedsQL, Pediatric Quality of Life inventory

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