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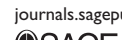

Efficacy and Safety of Dasotraline in Children With ADHD: A Laboratory Classroom Study

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Abstract

Objective: To evaluate the efficacy and safety of dasotraline for treatment of ADHD in children. **Method:** Children (ages 6-12 years; $N = 112$) with ADHD were randomized, double-blind, to 14 days of once-daily evening doses of dasotraline 4 mg or placebo. ADHD symptom severity was measured at baseline and Day 15 in seven, 30-min classroom sessions using the Swanson, Kotkin, Agler, M-Flynn, and Pelham (SKAMP) and the Permanent Product Measure of Performance (PERMP) math test. **Results:** Significant improvement was observed for dasotraline versus placebo in the SKAMP-combined score (−3.2 vs. +2.0; $p < .001$; effect size = 0.85) and SKAMP and PERMP subscale scores. The three most common adverse events for dasotraline (vs. placebo) were insomnia (19.6% vs. 3.6%), headache (10.7% vs. 8.9%), and decreased appetite (10.7% vs. 3.6%). **Conclusion:** In this laboratory classroom study, dasotraline 4 mg was found to be an efficacious and generally well-tolerated treatment for ADHD in children aged 6 to 12 years. *(J. of Att. Dis. 2020; 24(2) 192-204)*

Keywords

ADHD, dasotraline, randomized controlled trial, children

Introduction

ADHD (American Psychiatric Association, 2013) is one of the most common neurodevelopmental disorders in children and adolescents, with an estimated prevalence of 7.2% (Thomas, Sanders, Doust, Beller, & Glasziou, 2015). The pervasive inattention and/or hyperactivity-impulsivity characteristic of childhood ADHD is associated with significant impairment in social and academic functioning (American Psychiatric Association, 2013; Erskine et al., 2016).

Monoaminergic receptor systems have been implicated in the pathophysiology of ADHD (Bralten et al., 2013; Faraone & Mick, 2010; Gizer, Ficks, & Waldman, 2009; Sharma & Couture, 2014), and drugs that enhance dopamine and norepinephrine neurotransmission have demonstrated efficacy in the treatment of ADHD symptoms (Chan, Fogler, & Hammerness, 2016; May & Kratochvil, 2010). Based on results from randomized clinical trials, practice guidelines for the treatment of ADHD in children and adolescents recommend two main classes of medications: central nervous system (CNS) stimulants and nonstimulant medication, most notably norepinephrine reuptake inhibitors (e.g., atomoxetine), and selective alpha-2 adrenergic agonists (e.g., extended-release formulations of guanfacine and clonidine; Arnsten, 2010; Subcommittee on ADHD, 2011). Currently, CNS stimulant medication is prescribed for at least two thirds of children with ADHD who are treated with medication (Albert, Rui, & Ashman, 2017). Limitations of currently available stimulant medicines include insufficient duration of treatment effect throughout the dosing interval, risk of symptom rebound, poor tolerability of stimulant effects in selected patients, the potential for tachyphylaxis, which may, at times, benefit from dose escalation, and a significant risk of abuse and/or diversion. Hence, there remains a need for additional treatment options for ADHD, including nonstimulant alternatives (Childress & Sallee, 2014).

Dasotraline, a novel oral medication for the treatment of ADHD in children and adults, is a potent inhibitor of presynaptic dopamine (IC_{50} 3 nM) and norepinephrine (IC_{50} 4 nM) transporters (Koblan et al., 2015). Unlike amphetamine compounds, dasotraline does not stimulate dopamine release from presynaptic vesicles. The pharmacokinetic (PK) profile

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of dasotraline in adults is characterized by slow absorption (t_{max}, 10-12 h), and a long elimination half-life ($t_{½}$, 47-77 h), resulting in stable plasma concentrations over 24 h permitting once-daily dosing (Chen et al., 2016; Hopkins et al., 2016). The PK profile of dasotraline in children and adolescents is similar to the adult profile, with a t_{max} of 9.6 to 12 h, and an elimination half-life of 56 to 84 h (data-on-file, Sunovion Pharmaceuticals, Inc).

The pharmacodynamic profile (absence of direct stimulation of dopamine release) and PK profile (delayed t_{max} and long elimination half-life) suggest that dasotraline will be associated with a reduced risk of abuse. A placebo-controlled, active-comparator (methylphenidate) study was conducted in recreational stimulant users to evaluate abuse liability (Koblan et al., 2015). The study found that dasotraline, in single doses up to 16 mg, was indistinguishable from placebo in subjective and behavioral effects associated with abuse liability, while single doses of dasotraline 36 mg was associated with modest stimulant-like effects that were significantly less than the 40 mg dose of methylphenidate.

Efficacy for once-daily dosing with dasotraline in ADHD has been demonstrated in short-term, randomized, double-blind studies in adults (Adler et al., 2018; Koblan et al., 2015), and in children aged 6 to 12 years (Goldman et al., 2017). The aim of this study was to evaluate the efficacy and safety of dasotraline in children with ADHD assessed in a laboratory classroom setting, a widely used paradigm (Swanson et al., 2000; Swanson et al., 2002; Wigal & Wigal, 2006) that permits precise and objective assessment of ADHD symptoms and behaviors over the course of an extended classroom day.

Method

Study Patients

This study (clinicaltrials.gov identifier: NCT02734693) enrolled children 6 to 12 years of age who met *Diagnostic and Statistical Manual of Mental Disorders* (5th ed.; *DSM-5*; American Psychiatric Association, 2013) criteria for a primary diagnosis of ADHD (inattentive, hyperactive-impulsive, or combined subtypes). Diagnosis was confirmed at screening using the Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children Present and Lifetime Version (K-SADS-PL; Kaufman et al., 2019). Recruitment was limited to patients who were currently receiving treatment with methylphenidate (any formulation) for at least 6 weeks prior to Study Day -7, and who had demonstrated an adequate clinical response based on clinical assessment and informant interview, as well as review of available medical records. Furthermore, during a 3- to 5-day methylphenidate washout, patients were required to show ≥30% worsening in ADHD Rating Scale IV–Home Version (ADHD-RS-IV HV) total score compared with their last assessment on methylphenidate, with an ADHD-RS-IV HV total score ≥26.

Exclusion criteria included a diagnosis of bipolar or major depressive disorders, conduct disorder, obsessive-compulsive disorder, disruptive mood dysregulation disorder, intellectual disability, any history of psychosis, autism spectrum disorder, Tourette's Syndrome; any CNS disorder; suicidal ideation; and any acute or unstable medical condition and/or clinically significant laboratory abnormalities. Cognitive behavioral therapy or school-based interventions for the treatment of ADHD were permitted only if these therapies were stable and had been ongoing for more than 1 month prior to study participation. Prohibited medications included lithium, alpha-2 adrenergic receptor agonists, sedating antihistamine medications, antidepressant or anticonvulsant medication, or medication for the treatment of ADHD.

Study Design

This double-blind, parallel-group study randomized children with ADHD to fixed, once-daily evening doses of dasotraline, 4 mg and 6 mg, or placebo in a laboratory classroom setting. Randomization, initially in a 1:1:1 ratio, was performed utilizing a computerized random number generator. However, after blinded safety review that identified a higher than expected rate of discontinuation due to nonserious, neuropsychiatric adverse events, and following a protocol amendment, the 6 mg/day dose of dasotraline was discontinued. The study remained fully blinded, and no further changes were made to any other aspect of study design.

To ensure allocation concealment, an Interactive Response System was used to manage randomization at baseline, and study drug capsules were identical in appearance and packaging. Patients, relatives, research staff, and sponsor personnel were blinded to treatment allocation during the time of study initiation until the completion of data analysis.

The study was conducted at five sites in the United States between April 2016 and February 2017. The study was approved by the institutional review board at each investigational site and was conducted in accordance with the International Conference on Harmonization Good Clinical Practice guidelines and with the ethical principles of the Declaration of Helsinki. An independent Data and Safety Monitoring Board reviewed safety data at regular intervals.

The study consisted of three periods as outlined below and displayed in Figure 1.

Screening period. At Visit 1 (Day -35 to Day -8, prior to the first laboratory classroom day), the investigator confirmed that patients were currently being treated with methylphenidate (any formulation) for at least 6 weeks prior to Day -7 and had demonstrated adequate clinical response (based on

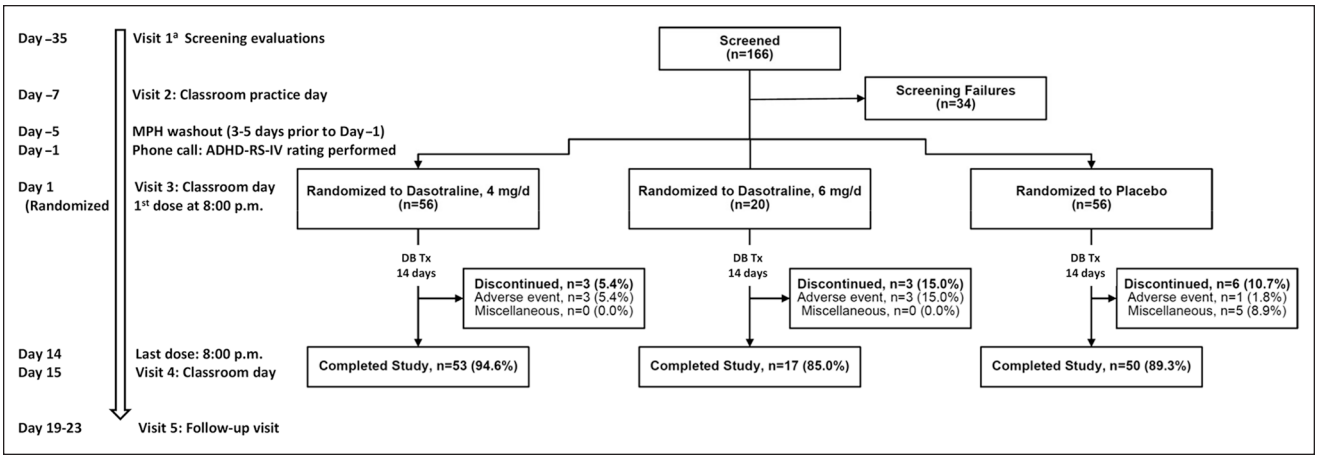

Figure 1. Study design and disposition.
Note. MPH = methylphenidate; DB = double-blind; Tx = treatment; ADHR-RS-IV = ADHD Rating Scale IV–Home Version (modified for investigator administration).
[a]Visit 1 could occur on Day –35 to Day –8 prior to the first classroom day; patient were required to be currently treated with MPH for more than 6 weeks prior to Day –7 with adequate clinical response.

clinical assessment, informant interview, review of medical records). At Visit 1, informed assent was obtained from the child, and informed consent was obtained from at least one of the child's parents or legal guardians. On Day -7 (Visit 2), the ADHD-RS-IV HV (modified for investigator administration; DuPaul, Power, Anastopoulos, & Reid, 1998) was completed, and patients attended a half-day practice laboratory classroom session intended to orient them to testing procedures (Visit 2). Medical screening procedures, including laboratory tests, were completed by this visit. All patients discontinued methylphenidate for 3 to 5 days prior to Day 1 to ensure a minimum 72-h washout prior to baseline assessment of ADHD symptoms on the first laboratory classroom day on Visit 4 (Day -1). The day before baseline randomization (Visit 3, telephone contact), the patient's parent/legal guardian was contacted to confirm clinical worsening of the patient's ADHD symptoms during washout (ADHD-RS-IV HV total score ≥26 with ≥30% increase compared with the on-treatment score).

Double-blind treatment period. On Day 1, patients who met all study entry criteria were randomized to receive a 14-day course of treatment with dasotraline 4 mg or placebo, to be dosed once-daily in the evening at approximately 8:00 p.m.

On the day of randomization, and prior to the first dose of study medication in the evening, study patients (in groups of at least seven) attended a baseline classroom day in which they were evaluated for ADHD symptoms and behaviors during 30-min sessions conducted at 8:00 a.m., 10:00 a.m., 12:00 p.m., 2:00 p.m., 4:00 p.m., 6:00 p.m., and 8:00 p.m. The first dose of study medication was administered by the parents, under supervision of the study staff, after completion of the 8:00 p.m. classroom session. Subsequent doses of study medication were administered by the parents, at home, at approximately 8:00 p.m. On the night (Day 14) before the second long classroom day (Visit 5), study treatment supervised by the parent was taken, as usual, at approximately 8:00 p.m. On Day 15 (Visit 5), patients returned to the clinic in the morning and were evaluated for ADHD symptoms at regular intervals utilizing the same study day schedule of seven assessment periods as at baseline (Visit 4).

Posttreatment period. Seven (±2) days after the last dose of study treatment, all patients returned to the clinic and completed final efficacy and safety assessments. Study completers were then referred for further evaluation and treatment in the community; the sponsor provided support, as needed, for up to 3 months poststudy treatment.

Efficacy and Safety Measures

Efficacy. The primary efficacy outcome was the Combined Score on the Swanson, Kotkin, Agler, M-Flynn, and Pelham (SKAMP-CS) rating scale. In seven, 30-min simulated classroom sessions (at regular intervals from 8:00 a.m. to 8:00 p.m.), trained observers used the SKAMP to assess the presence and severity of behavioral and attentional manifestations of ADHD. The SKAMP is a validated 13-item measure, with each item rated on a 7-point scale (0 = *normal* to 6 = *maximal impairment*; Murray et al., 2009; Wigal, Gupta, Guinta, & Swanson, 1998; Wigal & Wigal, 2006). In addition to the primary analysis of the SKAMP-CS, secondary analyses were performed on the two subscale scores, SKAMP-attention (getting started, sticking with tasks, attending to an activity,

making activity transitions, completing assigned tasks, performing work accurately, and being neat and careful while writing or drawing), and SKAMP-deportment (interacting with other children, interacting with adults, remaining quiet, staying seated, complying with the teacher's directions, and following the classroom rules). At each of the seven assessment time-points during the simulated classroom sessions, efficacy was also measured using the skill-level adjusted Permanent Product Measure of Performance (PERMP), which consists of performing a series of math problems (Wigal & Wigal, 2006). The appropriate math level for each patient was determined based on results of a math pretest administered at the screening visit. The PERMP quantifies the number of math problems attempted, and the number completed correctly (PERMP-problems attempted; PERMP-problems correct) in a 10-min period.

Safety. Safety and tolerability were monitored throughout the study by physical and neurological examinations, 12-lead electrocardiograms (ECGs), vital signs, adverse event recordings, clinical laboratories (hematology, chemistry, and urinalysis), and the children's version of the Columbia Suicide Severity Rating Scale (C-SSRS; Posner et al., 2011). A Data and Safety Monitoring Board reviewed safety and clinical outcome data, including data on adverse events, and serious adverse events, at regular intervals. During the posttreatment period (7 ± 2 days after the last dose of study treatment), patients returned to the clinic and completed safety assessments.

Statistical Analyses

The intent-to-treat population (ITT) population comprised all patients who were randomized. The safety population comprised all randomized patients who received at least one dose of study medication.

The primary efficacy endpoint was mean change from pre-treatment baseline (Day 1; Visit 4) to Day 15 (Visit 5) in manifestations of ADHD in a classroom setting (attention and deportment) as measured by the SKAMP-Combined score averaged across the seven assessments obtained during the 12-h laboratory classroom day (12-24 h postdose). For the ITT population, an analysis of covariance (ANCOVA) model was applied to evaluate the effect of study treatment on the primary efficacy endpoint between dasotraline 4 mg/day and placebo. The model included treatment, mean SKAMP-Combined score at baseline, and site as fixed effects. For the dasotraline 6 mg/day dose group, efficacy analyses were exploratory because randomization to this group was discontinued, as described earlier in this article, after the first 20 patients were enrolled.

A similar ANCOVA model was used to analyze the secondary efficacy endpoints (SKAMP-attention, SKAMP-deportment, PERMP-problems attempted; PERMP-problems correct), which were also based on mean change scores averaged over the seven assessment time-points. In addition, the SKAMP (combined, attention, deportment) and PERMP (problems attempted and correct) were also analyzed Day 15 (Visit 5) using an ANCOVA model for each assessment time-point (12, 14, 16, 18, 20, 22, and 24 h postdose). No adjustments for multiplicity were made for secondary efficacy analyses; therefore, all secondary efficacy analyses should be viewed as exploratory, with nominal p values.

The sample size for this study was determined by a two-sample t test using nQuery Advisor (Version 7.0) software. Based on results of a previous 12-h laboratory classroom study (Wigal, Childress, Belden, & Berry, 2013), a sample size of 50 patients per treatment arm was estimated to provide at least 95% power to detect a mean 4-point difference ($SD = 5$) in baseline-to-Day-15 SKAMP-Combined change scores as statistically significant for dasotraline versus placebo at a 5% significance level (two-sided). To account for an expected attrition rate of 10%, the sample size per treatment arm was adjusted to 55 patients.

Descriptive statistics were used for safety variables, including adverse events, vital signs, and laboratory test results. Number needed to harm (NNH) for selected adverse events was calculated by assessing the reciprocal of the difference in adverse effect rates for the dasotraline and placebo groups. Cohen's d effect sizes were calculated for efficacy measures as the difference in drug versus placebo change scores divided by the pooled standard deviation (Cohen, 1992).

Results

Patients and Disposition

A total of 166 patients were screened, of whom 112 were randomized to double-blind treatment (dasotraline 4 mg/day, $n = 56$; placebo, $n = 56$) and comprised both the ITT and safety populations. In addition, a total of 20 patients had been randomized to the 6 mg/day dose of dasotraline at the time of protocol amendment and subsequent discontinuation of this treatment arm. Baseline demographic and clinical characteristics were comparable for the two treatment groups (Table 1). Study completion rates for the dasotraline 4 mg/day and placebo groups were 94.6% and 89.3%, respectively (Figure 1).

Efficacy

Treatment with dasotraline 4 mg/day (vs. placebo) was associated with significantly greater least squares (LS) mean improvement from baseline (Visit 4) to Day 15 (Visit 5) in the SKAMP-combined score (primary endpoint; −3.2 vs. +2.0; $p < .001$; effect size = 0.85; Table 2). Treatment with dasotraline 4 mg/day was associated with significantly greater LS mean improvement from baseline (Visit 4) to

Table 1. Baseline Patient Characteristics (ITT Population).

	Dasotraline 4 mg/day ($N = 56$)		Placebo ($N = 56$)	
Characteristic	*n*	%	*n*	%
Male	39	69.6	38	67.9
Race				
White	26	46.4	31	55.4
Black/African American	25	44.6	23	41.1
Other	5	8.9	2	3.6
Ethnicity: Hispanic/Latino	19	33.9	11	19.6
Age category				
6-9 years	30	53.6	24	42.9
10-12 years	26	46.4	32	57.1
	Mean	*SD*	*Mean*	*SD*
Age (years)	9.3	1.8	9.7	1.9
Weight (kg)	35.1	9.8	37.7	9.7
Body mass index (kg/m^2)	17.8	2.6	18.2	2.4
Baseline scores				
ADHD-RS-IV Inattentive subscale score	20.8	2.5	21.4	3.4
ADHD-RS-IV Hyperactivity/ Impulsivity score	18.1	4.7	17.9	5.3
SKAMP-combined score	21.8	10.2	21.0	9.5

Note. ITT = intent-to-treat; ADHD-RS-IV = ADHD Rating Scale Version IV–Home Version; SKAMP = Swanson, Kotkin, Agler, M-Flynn, and Pelham.

Day 15 (Visit 5) in the SKAMP-attention subscale score (−0.7 vs. +0.8; $p<.001$; effect size = 0.81) and the SKAMP-deportment subscale scores (−1.4 vs. +0.2; $p < .001$; effect size = 0.70; Table 2).

Onset of significant improvement in the SKAMP-combined score for dasotraline 4 mg/day was observed at the second assessment time-point (10:00 a.m.; 14 h postdose) and was maintained through the seventh and final time-point (8:00 p.m.; 24 h postdose; Figure 2). Significant improvement was observed starting at 8:00 a.m. on the SKAMP-attention subscale and starting at 10:00 a.m. on the SKAMP-deportment subscale and was maintained on both subscales through the final time-point (8:00 p.m.; 24 h postdose; Figure 3a and b).

Treatment with dasotraline 4 mg/day (vs. placebo) was associated with significantly greater LS mean improvement from baseline (Visit 4) to Day 15 (Visit 5) in the PERMP-problems attempted score (+22.6 vs. −1.1; $p = .002$; effect size = 0.63), and in the PERMP-problems correct scores (+22.1 vs. −2.0; $p = .002$; effect size = 0.64; Table 2).

Onset of significant improvement in the PERMP-problems attempted and PERMP-problems correct scores for dasotraline 4 mg/day was observed at the second assessment time-point (10:00 a.m.; 14 h postdose) and was maintained through the seventh and final time-point (8:00 p.m.; 24 h postdose; Figure 4).

Efficacy in Clinical Subgroups

Differences were noted in the SKAMP-combined score at baseline, with higher mean scores in younger (6-9 years) versus older (10-12 years) children (26.1 vs. 16.9), and in males versus females (23.2 vs. 17.3). Treatment with dasotraline 4 mg/day (vs. placebo) was associated with significantly greater LS mean change from baseline (Visit 4) to Day 15 (Visit 5) in the SKAMP-combined scores for younger (−6.1 vs. +1.1; $p = .002$; effect size = 0.95) and older (−0.9 vs. +2.8; $p = .015$; effect size = 0.70) age groups, and for males (−3.9 vs. +2.9; $p < .001$; effect sizes = 0.97) and females (−3.6 vs. +1.1; $p = .008$; effect size = 0.98).

Exploratory Efficacy Analysis: Dasotraline 6 mg/day Group

Treatment with dasotraline 6 mg/day ($N = 20$; vs. placebo) was associated with significantly greater LS mean improvement from baseline (Visit 4) to Day 15 (Visit 5) in the SKAMP-combined score (−3.5 vs. +2.9; $p < .001$; effect size = 1.10), as well as scores on the SKAMP-attention (−0.4 vs. +1.0; $p = .007$; effect size = 0.78) and the SKAMP-deportment (−1.8 vs. +0.4; p=.002; effect size, 0.93) subscales. Treatment with dasotraline 6 mg/day was not associated with significantly greater LS mean improvement from baseline (Visit 4) to Day 15 (Visit 5) in the PERMP-problems attempted score (+6.3 vs. −2.4; *ns*; effect size = 0.34) and the PERMP-problems completed score (+6.9 vs. −3.2; *ns*; effect size = 0.40).

Safety. At least one treatment-emergent adverse event was reported by 51.8% of patients in the dasotraline 4 mg/day group and 33.9% in the placebo group. The three most frequent adverse events in the dasotraline 4 mg/day group (vs. placebo) were insomnia (19.6% vs. 3.6%), headache (10.7% vs. 8.9%), and decreased appetite (10.7% vs. 3.6%; Table 3). The number of patients who discontinued due to an adverse event was 3/56 (5.4%) in the dasotraline 4 mg/day group (one each: insomnia, hallucination, rash), and 1/56 (1.8%) in the placebo group (fatigue). No serious adverse events occurred in the dasotraline 4 mg/day group, and one serious adverse event (hand fracture) occurred in the placebo group outside the laboratory classroom school day. Adverse events were rated as "severe" for two patients in the dasotraline 4 mg/day group (insomnia, reduced appetite), and one patient in the placebo group (hand fracture) reported an adverse event as "severe" (also noted above as serious). Three patients in the dasotraline 4 mg/day group reported hallucinations (one each: tactile, auditory, visual); none were rated as "severe." In two patients,

Table 2. Primary and Secondary Efficacy Measures: Mean Baseline to Endpoint Change (ITT Population; ANCOVA).

	Dasotraline 4 mg/day ($N = 56$)	Placebo ($N = 56$)	LS mean treatment difference (95% CI)	p value (effect size)
SKAMP-combined score				
Baseline mean (*SD*)	22.1 (10.0)	20.8 (9.5)		
LS mean change at Endpoint (*SE*)	−3.2 (0.9)	+2.0 (0.9)	−5.2 [−7.6, −2.8]	<.001 (0.85)
SKAMP-attention score				
Baseline mean (*SD*)	4.7 (2.9)	4.3 (2.8)		
LS mean change at Endpoint (*SE*)	−0.7 (0.3)	+0.8 (0.3)	−1.5 [−2.2, −0.8]	<.001 (0.81)
SKAMP-deportment score				
Baseline mean (*SD*)	5.0 (3.6)	4.9 (3.6)		
LS mean change at Endpoint (*SE*)	−1.4 (0.4)	+0.2 (0.4)	−1.6 [−2.5, −0.7]	<.001 (0.70)
PERMP-problems attempted				
Baseline mean (*SD*)	58.7 (36.4)	58.5 (43.2)		
LS mean change at Endpoint (*SE*)	+22.6 (5.8)	−1.1 (5.9)	23.7 [9.0, 38.3]	.002 (0.63)
PERMP-problems correct				
Baseline mean (*SD*)	54.6 (37.1)	53.4 (40.8)		
LS mean change at Endpoint (*SE*)	+22.1 (5.8)	−2.0 (5.9)	24.1 [9.4, 38.7]	.002 (0.64)

Note. Mean baseline scores, and endpoint (Day 15) change scores, represent the average of the seven assessments performed during the 12-h classroom day (12-24 h postdose). The LS mean baseline to endpoint change scores for dasotraline and placebo were evaluated using an ANCOVA model with study treatment, mean SKAMP or PERMP score at baseline, and site as fixed effects. ITT = intent-to-treat; ANCOVA = analysis of covariance; LS = least squares; CI = confidence interval; SKAMP = Swanson, Kotkin, Agler, M-Flynn, and Pelham scale; PERMP = Permanent Product Measure of Performance.

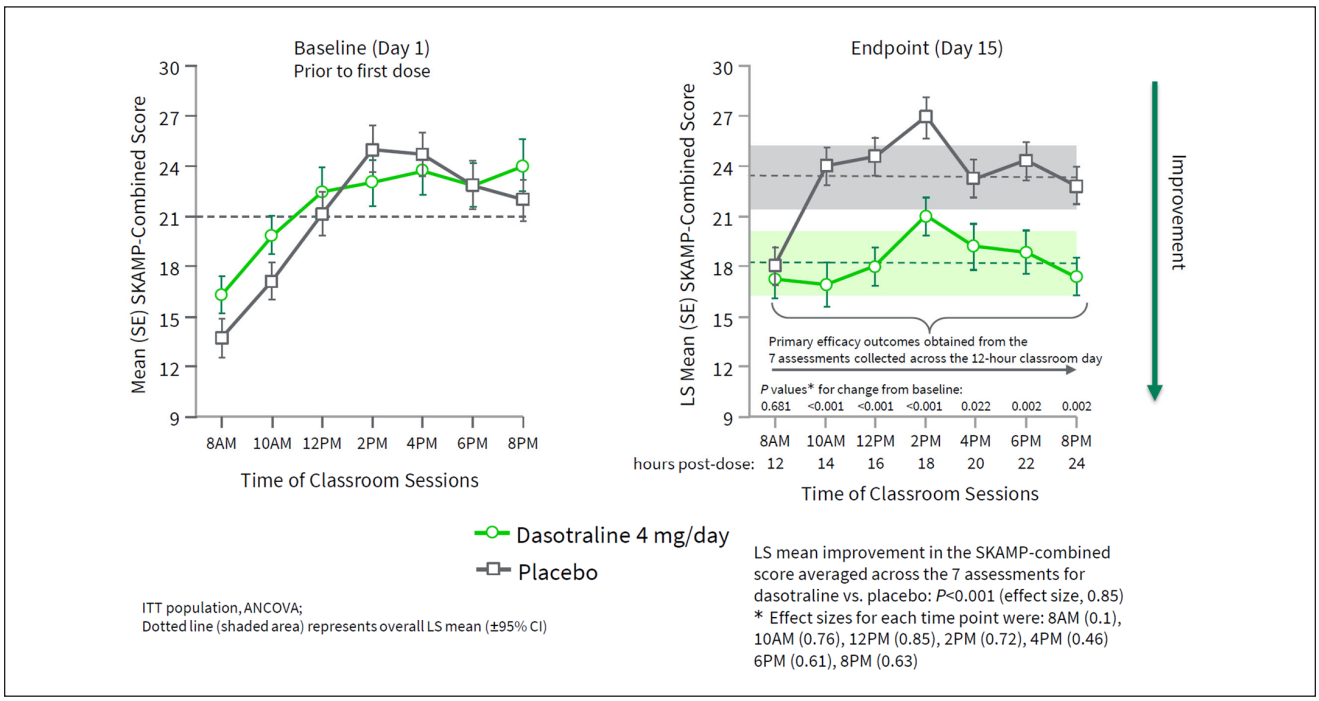

Figure 2. Mean SKAMP-combined scores during seven assessments performed on pre-treatment Day 1, and at double-blind endpoint on Day 15 for patients assigned to dasotraline 4 mg/day and placebo.
Note. SKAMP = Swanson, Kotkin, Agler, M-Flynn, and Pelham.

the hallucinations were transient and resolved with continued treatment, while in the third patient (a 10-year-old male), the hallucinations resolved within 48 h after discontinuation of study medication. The three patients who reported hallucinations were the 10-year-old male weighing 25.9 kg (weight-adjusted dose equal to 0.154 mg/kg), an 8-year-old male

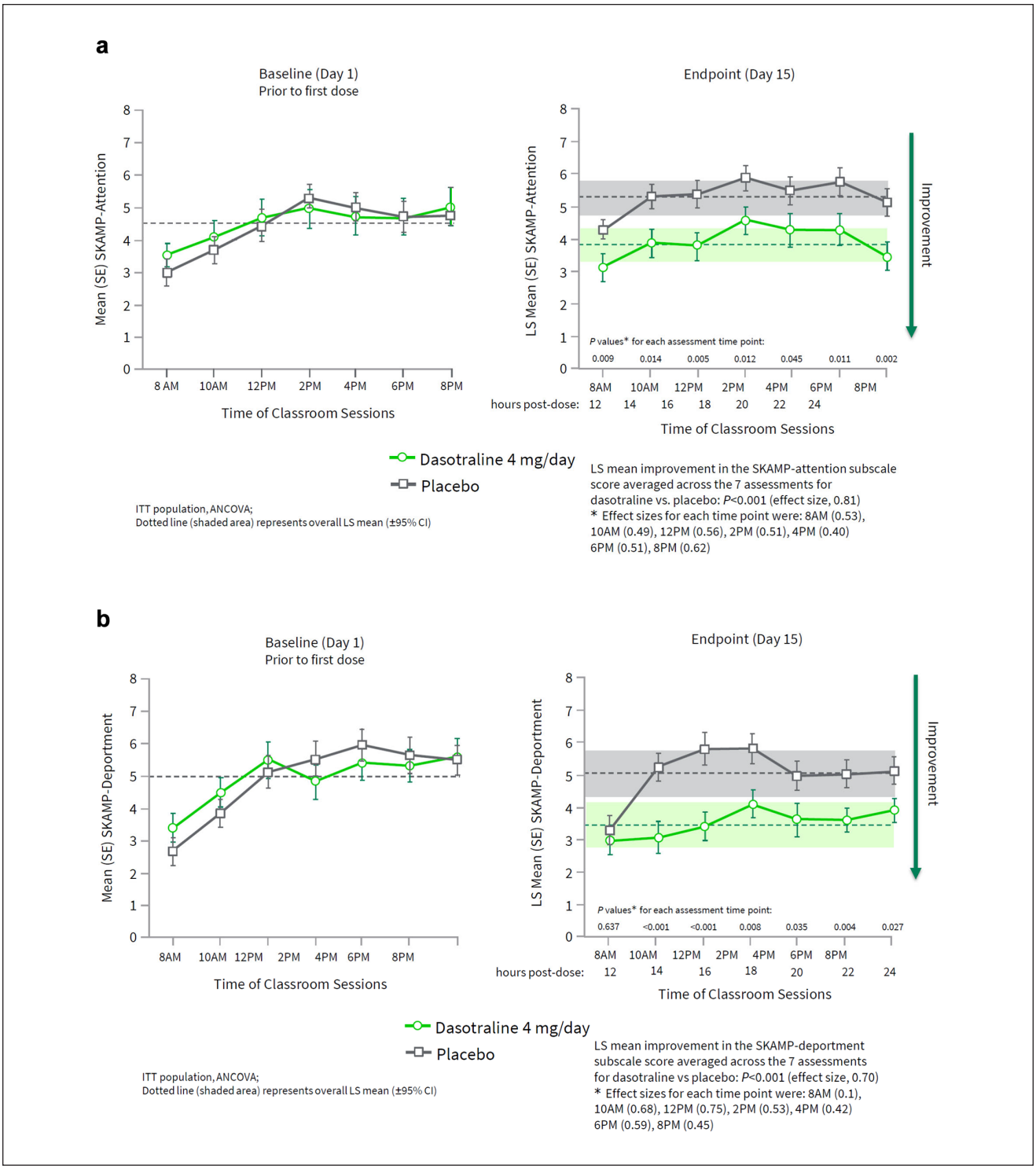

Figure 3. Mean SKAMP subscale scores during seven assessments performed on pre-treatment Day 1 (left panels) and at double-blind endpoint on Day 15 (right panels): (a) SKAMP-attention subscale score and (b) SKAMP-deportment subscale score.
Note. SKAMP = Swanson, Kotkin, Agler, M-Flynn, and Pelham.

weighing 27.5 kg (0.145 mg/kg), and an 8-year-old female weighing 23.4 kg (0.171 mg/kg). No patient reported hallucinations in the placebo group.

For dasotraline 4 mg/day versus placebo, mean change in weight from baseline (Visit 4) to Day 15 (Visit 5) was −0.54 versus +0.31 kg, and mean change in body mass

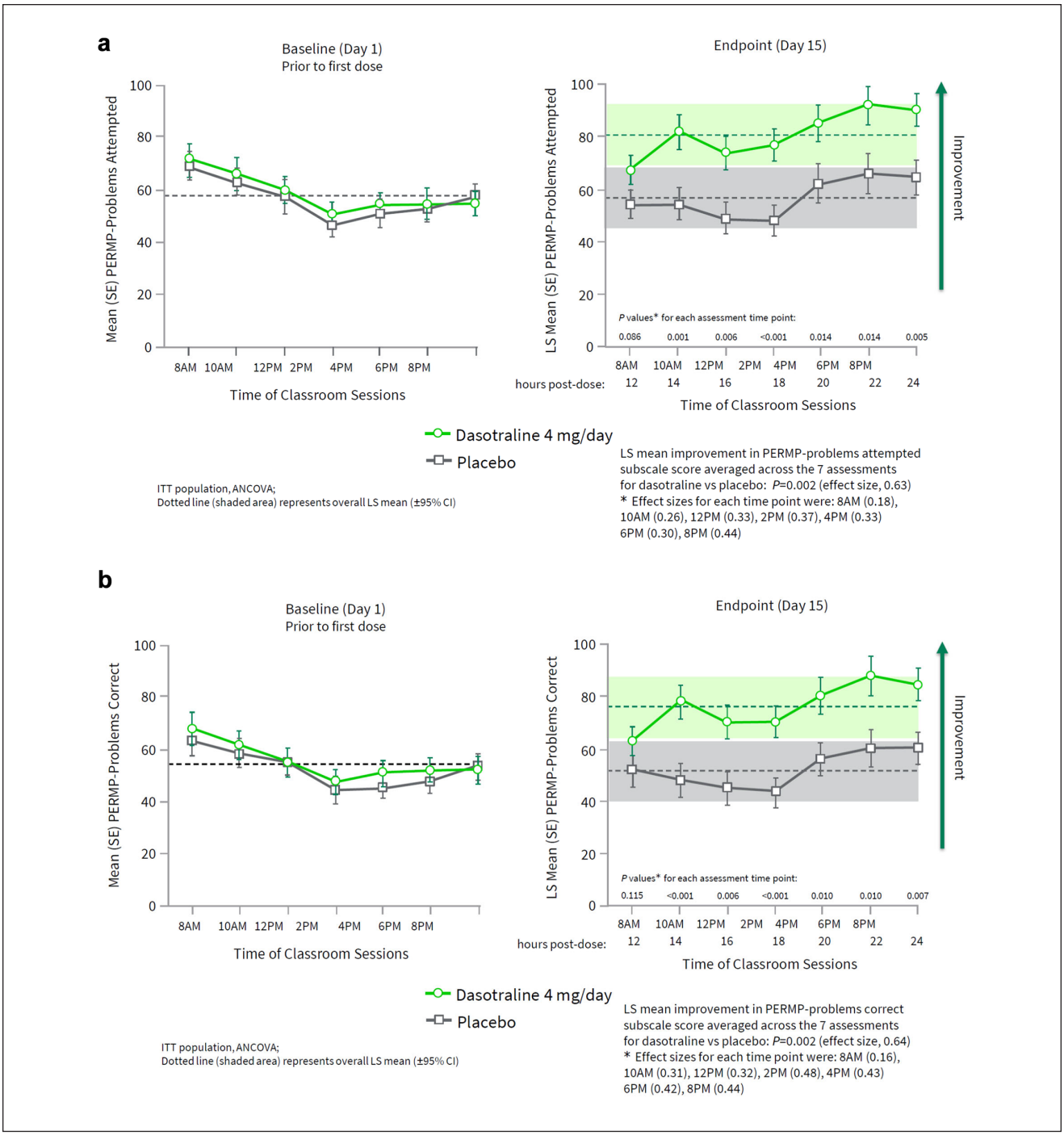

Figure 4. Mean PERMP subscale scores during seven assessments performed on pre-treatment Day 1 (left panels) and at double-blind endpoint on Day 15 (right panels): (a) PERMP-problems attempted score and (b) PERMP-problems correct score.
Note. PERMP = Permanent Product Measure of Performance.

index (BMI) was −0.30 versus +0.14 kg/m^2. Mean change from baseline (Visit 4) to Day 15 (Visit 5) was comparable for dasotraline 4 mg/day versus placebo in supine (+1.4 vs. −2.2 bpm) and standing (−0.3 vs. 0.0 bpm) heart rate, supine (+0.3 vs. −0.6 mmHg), and standing (+1.8 vs. −0.9 mmHg) systolic blood pressure, and supine (+0.8 vs. −0.7 mmHg) and standing (+3.0 vs. −1.3 mmHg) diastolic blood pressure. Small increases were observed in systolic and diastolic blood pressure and heart rate. No clinically meaningful changes in ECG or laboratory parameters were noted.

Table 3. Adverse Events (Incidence ≥2% on Dasotraline and >Placebo).

	Dasotraline 4 mg/day ($N = 56$)		Placebo ($N = 56$)
	n (%)	NNH	*n* (%)
Insomnia	11 (19.6)	7	2 (3.6)
Headache	6 (10.7)	56	5 (8.9)
Decreased appetite	6 (10.7)	15	2 (3.6)
Affect lability	5 (8.9)	56	4 (7.1)
Irritability	3 (5.4)	56	2 (3.6)
Perceptual disturbances[a]	3 (5.4)	19	0
Orthostatic tachycardia	3 (5.4)	19	0
Increased appetite	2 (3.6)	28	0
Rash	2 (3.6)	28	0
Diarrhea	2 (3.6)	28	0

Note. NNH = number needed to harm.
[a]Hallucinations (tactile, auditory, visual).

A total of 20 patients ($N = 17$ completers) received the 6 mg/day dose of dasotraline (mean age, 9.9 years; male, 70%; mean weight, 34.3 kg). The following adverse events occurred in more than one patient in the dasotraline 6 mg/day dose group: insomnia ($n = 6/20$), affect lability and decreased appetite (n=4/20), hallucinations ($n = 2/20$ [one each: tactile, auditory, visual]; weights, 21.1 and 33.1 kg [equivalent to a weight-adjusted dose range of 0.18 mg/kg to 0.28 mg/kg]), and decreased weight, upper abdominal pain, and vomiting ($n = 2$). Two patients discontinued due to adverse events: one patient (21.1 kg; weight-adjusted dose of 0.28 mg/kg) reported hallucinations and delusions (both rated as "moderate" in severity), and one (33.0 kg; weight-adjusted dose of 0.18 mg/kg) reported hallucinations (visual and tactile; both "moderate" in severity). For dasotraline 6 mg/day versus placebo, mean weight change from baseline (Visit 4) to Day 15 (Visit 5) was −1.1 versus +0.31 kg, and mean change in BMI was −0.51 versus +0.14 kg/m^2. During study treatment, one patient in the dasotraline 6 mg/day group had a ≥20 mmHg orthostatic drop in systolic blood pressure that was not accompanied by other symptoms (e.g., dizziness or lightheadedness). Overall, there were small increases in systolic and diastolic blood pressure and heart rate. No clinically meaningful changes in ECG or laboratory parameters were noted.

Discussion

Dasotraline was found to be an efficacious treatment for ADHD in children aged 6 to 12 years in this double-blind, placebo-controlled, simulated classroom study. Two weeks of treatment with fixed-dose dasotraline 4 mg/day was associated with significant improvement in the SKAMP-combined score, the primary efficacy endpoint (effect size = 0.85; averaged over the seven assessment time-points), and across all secondary efficacy endpoints, comprising SKAMP-attention (effect size = 0.81) and SKAMP-deportment (effect size = 0.70) subscale scores, and PERMP scores for problems attempted (effect size = 0.63) as well as problems correct (effect size = 0.64).

An exploratory analysis of patients ($N = 20$) randomized to the discontinued 6 mg/day fixed-dose of dasotraline found that treatment with this dose was associated with significant efficacy compared with placebo on the SKAMP-combined score (effect size = 1.1). The decision to discontinue this treatment arm was made following a blinded safety review that noted the potential for increased adverse events on this dose.

Based on this study design that provided serial efficacy assessments for the 12- to 24-h (daytime) interval after dosing, dasotraline is the first agent for the treatment of ADHD to demonstrate significant efficacy for the time-period extending up to 24 h postdose. On the final study treatment day, significant improvement was observed at 10:00 a.m. in the SKAMP-combined score (primary outcome measure), and on all secondary efficacy measures, and significance was maintained through the seventh and final classroom assessment time-point at 8:00 p.m., 24 h after the parent-reported administration of once-daily dasotraline the previous evening.

At the first assessment time-point (8:00 a.m.), significant separation on SKAMP-CS was not observed for dasotraline versus placebo. This was largely due to lack of significance on the SKAMP-deportment subscale at this early morning time-point. Unlike SKAMP-attention scores, SKAMP-deportment scores were low at the 8:00 a.m. time-point in both the dasotraline and placebo groups (see Figures 3a and 3b), and no significant separation was observed.

In studies utilizing the laboratory classroom design, extended-release formulations of stimulants have demonstrated significant efficacy for up to 12 h, though typically there is a reduction in the magnitude of improvement versus placebo beginning at about 6 to 7 h after the morning dose (Brams et al., 2012; Childress et al., 2015; Childress, Kollins, Cutler, Marraffino, & Sikes, 2017; Childress et al., 2018; Swanson et al., 2004; Wigal et al., 2017; Wigal et al., 2013; Wigal, Kollins, Childress, Squires, & 311 Study Group, 2009; Wigal et al., 2005).

A laboratory classroom study of atomoxetine has also reported results similar to findings for stimulants, with diminishing effects noted 7-h after morning dosing on the SKAMP-attention scale and after 9-h postdose on the SKAMP-deportment scale (Wigal et al., 2005). In a subsequent clinic-based, nonlaboratory classroom study comparing evening versus morning dosing with atomoxetine (Whalen et al., 2006), use of evening dosing demonstrated reduced next-day efficacy when compared with morning dosing. The pharmacodynamic findings of these studies are

consistent with the short half-life of atomoxetine (approximately 5 h).

Waning of stimulant treatment effect in the evening, and the occurrence of early morning return of ADHD symptoms and behaviors, may lead to significant disruption in function in both the child and the family (Coghill et al., 2008; Shaw et al., 2012). In a large survey of the impact of ADHD on everyday activities, behavior, and family relationships (Shaw et al., 2012), children treated with extended-release stimulants had significantly greater daytime improvement compared with children with ADHD not receiving treatment but exhibited significant worsening (vs. the unmedicated group) in disruptive behaviors in the evening, at bedtime, and in the morning routine. The results of this study suggest that dasotraline, with its long elimination half-life (44-77 h), may provide sustained early evening symptom control in this ADHD population; however, this will need to be confirmed by additional randomized, controlled trials in naturalistic settings, preferably studies that include evening assessments.

The effect sizes on the primary (0.85) and secondary endpoints (0.63-0.81) observed in the current lab class study are notably larger than the effect sizes observed in the previously published 6-week clinical trial in children with ADHD (primary = 0.48; secondary = 0.25-0.46). This finding is consistent with results from previous classroom studies which have also reported larger effect sizes for both stimulants and atomoxetine (Childress et al., 2015; Childress et al., 2018; Swanson et al., 2004; Wigal et al., 2017; Wigal et al., 2013; Wigal et al., 2005). We suspect that this may be due to a measurement effect rather than a drug effect. In contrast to treatment studies in the community, laboratory classroom studies are conducted in controlled settings, with assessments based on either objective performance measures (PERMP-problems attempted and correct), and direct observation by trained raters. We speculate that the resulting measurement precision and reduced assessment "noise" contribute to the larger effect size.

Three adverse events in the dasotraline 4 mg group occurred with an incidence >10%: insomnia (19.6%; NNH, 7), headache (10.7%; NNH, 56), and decreased appetite (10.7%; NNH, 15). No patients discontinued due to insomnia, and the event was rated as severe by only 1/56 patients on the 4 mg/day dose of dasotraline (and in two patients on the 6 mg/day dose). Common adverse events reported for stimulants in previous classroom studies consisted of decreased appetite (range = 26%-56%), affect lability/mood swings (6%-27%), irritability (13%-16%), insomnia (7%-27%), upper abdominal pain (15%-42%), and headache (6%-18%) (Brams et al., 2012; Childress et al., 2015; Childress et al., 2017; Childress et al., 2018; Swanson et al., 2004; Wigal et al., 2017; Wigal et al., 2013). The treatment period in this study was short, and therefore, safety and tolerability findings should be interpreted with caution as longer term studies are needed to specifically address such issues.

Three patients in the 4 mg/day dose group reported perceptual disturbances (one each: tactile, auditory, visual hallucinations), rated as mild-to-moderate in severity, which led to study discontinuation in one patient. We note that body weight at baseline in the three patients ranged from 23.4 to 27.5 kg, resulting in a weight-adjusted dasotraline dose in the range of 0.145 to 0.171 mg/kg. Among patients ($N = 20$) randomized to the dasotraline 6 mg/day group, two patients reported perceptual disturbances (one with auditory hallucinations and delusions, and one with tactile and visual hallucinations), which led to study discontinuation. Body weight in these patients ranged from 21.1 to 33.0 kg, resulting in a weight-adjusted dasotraline dose in the range of 0.182 to 0.284 mg/kg. An increased risk of perceptual disturbance has previously been reported in a 6-week clinical trial (Goldman et al., 2019), notably transient hallucinations in children weighing less than 30 kg treated with dasotraline 4 mg/day, yielding a weight-adjusted dose of ≤0.15 mg/kg. Therefore, the current results indicate that the weight-adjusted dose of dasotraline should generally not exceed 0.15 mg/kg. Given that a robust treatment effect was demonstrated for dasotraline in this study at 4 mg/day (effect size = 0.85), it is possible that lower doses may also be effective for some children with ADHD, particularly with lower body weights. Additional results from fixed-dose studies are needed to better characterize dose-response effects for dasotraline.

Limitations of this study include exclusion of children with clinically significant psychiatric comorbidity and limiting enrollment to children whose ADHD symptoms were shown to be methylphenidate-responsive. Establishing initial treatment response is a study design feature common to most lab classroom protocols (Brams et al., 2012; Childress et al., 2015; Childress et al., 2018; Swanson et al., 2004; Wigal et al., 2017; Wigal et al., 2013). However, it should be noted that requiring patients to be responsive to a stimulant medication yields a biased sample, and the magnitude of the effect size of 0.85 may not generalize to other patient subgroups (treatment-resistant, etc.).

Another study limitation was that the efficacy of dasotraline in doses lower than 4 mg/day was not assessed, nor was efficacy assessed for treatment durations longer than 14 days. Finally, other than Day 1 (Visit 4) dosing at each laboratory school site, parents administered study medication at home at approximately 8:00 p.m. with daily reminders from study staff; however, adherence was not further verified.

In conclusion, in this placebo-controlled, laboratory classroom study, dasotraline 4 mg, given once-daily in the evening, was found to be an efficacious and generally well-tolerated treatment for ADHD in children aged 6 to 12 years that may provide sustained 24-h control of a broad range of attentional and behavioral symptoms of ADHD.

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