Research Article

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A matching-adjusted indirect comparison of centanafadine versus lisdexamfetamine, methylphenidate and atomoxetine in adults with attention-deficit/hyperactivity disorder: long-term safety and efficacy

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Aim: To compare long-term safety and efficacy outcomes of centanafadine versus lisdexamfetamine dimesylate (lisdexamfetamine), methylphenidate hydrochloride (methylphenidate) and atomoxetine hydrochloride (atomoxetine), respectively, in adults with attention-deficit/hyperactivity disorder (ADHD) using matching-adjusted indirect comparisons (MAICs). **Patients & methods:** Patient-level data from a centanafadine trial (NCT03605849) and published aggregate data from a lisdexamfetamine trial (NCT00337285), a methylphenidate trial (NCT00326300) and an atomoxetine trial (NCT00190736) were used. Patient characteristics were matched in each comparison using propensity score weighting. Study outcomes were assessed up to 52 weeks and included safety (rates of adverse events [AEs]) and efficacy (mean change from baseline in the Adult ADHD Investigator Symptom Rating Scale [AISRS] or ADHD Rating Scale [ADHD-RS] score). **Results:** In all comparisons of matched populations, risks of AEs were statistically significantly lower with centanafadine or non-different between centanafadine and comparator; the largest differences in AE rates included upper respiratory tract infection (risk difference in percentage points: 18.75), insomnia (12.47) and dry mouth (12.33) versus lisdexamfetamine; decreased appetite (20.25), headache (18.53) and insomnia (12.65) versus methylphenidate; and nausea (26.18), dry mouth (25.07) and fatigue (13.95) versus atomoxetine (all $p < 0.05$). Centanafadine had a smaller reduction in the AISRS/ADHD-RS score versus lisdexamfetamine (6.15-point difference; $p < 0.05$) and no statistically significant difference in the change in AISRS score versus methylphenidate (1.75-point difference; $p = 0.13$) and versus atomoxetine (1.60-point difference; $p = 0.21$). **Conclusion:** At up to 52 weeks, centanafadine showed significantly lower incidence of several AEs than lisdexamfetamine, methylphenidate and atomoxetine; efficacy was lower than lisdexamfetamine and non-different from methylphenidate and atomoxetine.

Plain language summary: What is this article about?: Attention-deficit/hyperactivity disorder (ADHD) is a long-term condition that disrupts a person's ability to stay focused, sit still and control their behavior. Adults with ADHD may be treated with traditional stimulants or non-stimulants. Stimulants are typically more efficacious but are associated with side effects that are not tolerated by all patients. Centanafadine sustained-release is an investigational medication for adults with ADHD that has a different mechanism of action than stimulants. No clinical trials have been conducted to compare the long-term safety and efficacy of centanafadine versus other common ADHD medications. In this study, we used clinical trial data to indirectly compare the long-term safety and efficacy of centanafadine versus lisdexamfetamine dimesylate (lisdexamfetamine; Vyvanse®), methylphenidate hydrochloride (methylphenidate; Concerta®) and atomoxetine hydrochloride (atomoxetine; Strattera®), respectively, across balanced patient populations.

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What were the results?: At up to a year of treatment, centanafadine was associated with fewer cases of upper respiratory tract infection, dry mouth, headache, decreased appetite and irritability than all of its comparators. Efficacy of centanafadine, as measured by reduction in ADHD symptoms, was statistically lower than lisdexamfetamine and non-different from methylphenidate and atomoxetine.
What do the results of the study mean?: Our indirect comparisons show that centanafadine has fewer cases of some side effects and lower or non-different efficacy than common ADHD treatments over time. These findings can help doctors and patients understand the long-term safety and efficacy profiles of different ADHD medications and select a suitable option based on their need.

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Keywords: adverse events • attention-deficit/hyperactivity disorder • centanafadine • clinical trials • comparative effectiveness research • efficacy • indirect comparison • propensity score • treatment outcome

Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disorder affecting approximately 4.4% of adults in the US [1,2]. The disorder interferes with patient functioning and multiple aspects of daily living [3]. While often diagnosed in childhood, ADHD can persist to adulthood and impose considerable burden throughout a patient's life [4–6]. For instance, adults with ADHD are more likely to be unemployed and have higher rates of mental health impairments than those without the disorder [7,8].

For adults with ADHD, medication options typically include traditional stimulants and selective norepinephrine reuptake inhibitors (SNRIs) [1]. Among the common stimulants are lisdexamfetamine dimesylate (lisdexamfetamine; Vyvanse®) and methylphenidate hydrochloride (methylphenidate; Concerta®) [9–11]. For SNRIs, atomoxetine hydrochloride (atomoxetine; Strattera®) is the first medication specifically approved for adults with ADHD [9,12,13], whereas viloxazine extended release (viloxazine ER; Qelbree®) is the latest approved ADHD medication in the US market [14,15]. While stimulants are typically more efficacious in reducing ADHD core symptoms, they are associated with adverse events (AEs) that are not tolerated by all patients; thus, the need for new effective ADHD medications with better tolerability remains [16,17].

Safety and efficacy data supporting the use of various ADHD medications were originally derived from randomized clinical trials (RCTs) that typically lasted 4–12 weeks [18–22]. Although these trials generated important evidence on treatment outcomes in the short term, they could not provide information on potential changes in therapeutic effects over time; furthermore, certain AEs may not have sufficient time to develop within the relatively short timeframes. Given the often chronic course of ADHD [4], treatments generally last for more than a few weeks in real-world patients; thus, data comparing longer-term outcomes of different ADHD treatments will provide a fuller picture of their potential safety and efficacy in the long run, which may facilitate better treatment decision-making. Furthermore, with the changing treatment landscape in ADHD [23], physicians and patients would need to be informed about the relative safety and efficacy of newer treatment options relative to existing ones to aid their treatment decisions.

In view of potential changes in treatment attributes over time and the need for long-term treatment in ADHD, there had been initiatives to conduct longer-term clinical trials among adults with ADHD [19,24,25]; however, direct comparisons of ADHD treatments from head-to-head trials, particularly for long-term outcomes, are often lacking. Although several prior studies have indirectly compared ADHD treatments in adults, most of them used data from trials with short treatment duration ($\leq$12 weeks) and did not include novel agents [17,26–28]. Recently, matching-adjusted indirect comparisons (MAICs) have demonstrated favorable short-term safety and tolerability of centanafadine sustained-release, a norepinephrine/dopamine/serotonin triple reuptake inhibitor currently investigated for adult ADHD, compared with some existing ADHD medications [29]. In two phase III RCTs, centanafadine significantly reduced the core symptoms of ADHD by week 6 and appeared to be well tolerated [30]. However, centanafadine has not been compared head-to-head with other ADHD treatments. MAIC is a well-validated method to generate comparative evidence when individual patient data (IPD) are available for at least one trial in the comparison [31–33]. To understand long-term outcomes of centanafadine sustained-release relative to common ADHD treatments, this study sought to leverage available IPD from a long-term centanafadine trial and compare the safety and efficacy of centanafadine versus lisdexamfetamine, methylphenidate and atomoxetine, respectively, up to 52 weeks in adults with ADHD using MAICs.

Methods

Data source & trial selection

IPD from the phase III, single-arm, open-label centanafadine trial NCT03605849 [34] were provided by the trial sponsor (Otsuka Pharmaceutical Development & Commercialization, Inc). The trial was conducted at 40 sites across the US and included 662 adult patients treated with centanafadine for up to 52 weeks. Potential comparator trials were identified through a search of the ClinicalTrials.gov database based on pre-specified criteria – condition or disease: ADHD; interventions: lisdexamfetamine, methylphenidate, atomoxetine; recruitment status: completed; eligibility criteria: adult (18–64); trial type: interventional (clinical trial); trial phase: phase III or IV. Supplemental search was conducted on the PubMed database using the above criteria as keywords and applying the filter "Article Type: Clinical Trial". The US prescribing information of the comparators was also manually reviewed to ensure key trials were covered. The search identified 17 potential long-term (i.e., ≥6 months) comparator trials (3 lisdexamfetamine trials, 7 methylphenidate trials and 7 atomoxetine trials) for further assessment for eligibility to be included in this study. Specifically, trials were excluded if they used a design noncomparable with the centanafadine trial (e.g., crossover), focused on a subpopulation (e.g., children and adolescents), or did not report the main outcomes of interest (i.e., Adult ADHD Investigator Symptom Rating Scale [AISRS]/ADHD Rating Scale [ADHD-RS] scores and AEs). Details of assessment outcomes including number of excluded trials and reasons for exclusions are described in Supplementary Tables 1 & 2.

Finally, published aggregate data from the phase III lisdexamfetamine trial NCT00337285 [25], the phase III methylphenidate trial NCT00326300 [24] and the phase IV atomoxetine trial NCT00190736 [19] were used in the respective MAIC with centanafadine. The characteristics of the included trials are provided in Supplementary Table 3.

Patient population

Based on a critical review of the eligibility criteria of the centanafadine and comparator trials, patients included in the MAICs met the following criteria: aged 18–55 years (centanafadine vs lisdexamfetamine), 18–65 years (centanafadine vs methylphenidate), or 18–54 years (centanafadine vs atomoxetine); had confirmed diagnosis of ADHD per the Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV, DSM-IV-text revision, or DSM-5 criteria; had moderate to severe ADHD at baseline; met the minimum weight requirement of ≥100 pounds (centanafadine vs methylphenidate only); had no moderate or severe comorbid psychiatric diagnoses; and were not currently taking prohibited medications (e.g., mood stabilizers, antipsychotics, investigational medications).

Each of the trials in this study included a safety population and an efficacy population. For each comparison, baseline characteristics and outcomes were reported separately in the safety population (for safety analyses) and in the efficacy population (for efficacy analyses) based on IPD for centanafadine and the data available for the respective comparator trial.

Outcome measures

Safety outcomes were defined as the rates of AEs for which the incidence was at least 5% among patients in either of the trials in a given comparison (except for the methylphenidate trial, in which the AE incidence–reporting threshold was at least 10%).

The efficacy outcome was defined as the mean change in the AISRS/ADHD-RS score from baseline. Efficacy was assessed using AISRS in the centanafadine, methylphenidate and atomoxetine trials. The lisdexamfetamine trial assessed efficacy using ADHD-RS, which contains the same components and scoring as AISRS [35,36]; thus, the two measures were considered interchangeable.

Safety and efficacy outcomes were compared between centanafadine and each comparator, separately, considering the timepoint at which the respective outcomes were reported in each comparator trial. For centanafadine versus lisdexamfetamine, both safety and efficacy outcomes were compared at week 52. For centanafadine versus methylphenidate, since the methylphenidate trial only reported pooled AE rates and efficacy outcome at final observation, which could be at week 26 or week 52, conservative comparisons assessing safety outcomes at week 52 in the centanafadine trial versus pooled week 26/week 52 AE rates in the methylphenidate trial, and efficacy outcomes at week 26 in the centanafadine trial versus pooled week 26/week 52 efficacy results in the methylphenidate trial, were conducted. Specifically, using a later timepoint for safety outcomes and an earlier timepoint for efficacy outcomes in the centanafadine trial for the comparisons was a conservative approach favoring the comparator, as

more AEs would be expected to happen over time whereas efficacy could increase with longer treatment duration. For centanafadine versus atomoxetine, both safety and efficacy outcomes were compared at week 26.

Statistical analyses

Baseline characteristics of the safety and efficacy populations of the centanafadine and each of the comparator trials were described, separately, using frequencies and proportions for categorical variables, and means and standard deviations (SDs) for continuous variables. Differences in baseline characteristics across trial populations were compared using Wald tests (i.e., chi square tests for categorical variables and z tests for continuous variables).

For MAIC analyses, a model using the propensity score approach was employed to estimate the likelihood (propensity) of enrollment in the comparator trials for each patient in the centanafadine trial. To develop weights, logistic regression models were created in which all available baseline prognostic factors and/or effect modifiers reported across comparator trials (i.e., age, sex, race [for lisdexamfetamine and atomoxetine], ethnicity [for lisdexamfetamine], baseline AISRS [or ADHD-RS for lisdexamfetamine], baseline AISRS subscales [for atomoxetine], baseline Clinical Global Impression-Severity of Illness [CGI-S], height [for lisdexamfetamine] and weight [for lisdexamfetamine]) were considered for adjustment. Weights were generated separately for the safety and efficacy populations. IPD from the centanafadine trial were reweighted to match the means, SDs and proportions of the baseline characteristics reported for the respective comparator trials. To demonstrate quantitatively the impact of population adjustment, baseline characteristics were summarized before and after matching.

Safety and efficacy outcomes were compared between the centanafadine and each of the comparator trials before and after weighting using unanchored comparisons. For safety analyses, the risk difference (RD) between centanafadine and the respective comparators, along with the corresponding 95% confidence intervals (CIs), was reported for each AE. For efficacy analyses, the difference in change from baseline in AISRS (or ADHD-RS for lisdexamfetamine) score between centanafadine and the respective comparators were reported. Weighted Wald tests were used for comparisons.

Results

Centanafadine versus lisdexamfetamine

Baseline characteristics

For the centanafadine versus lisdexamfetamine analyses, the safety analysis population included 492 patients from the centanafadine trial and 349 patients from the lisdexamfetamine trial; and the efficacy analysis population included 490 patients from the centanafadine trial and 349 patients from the lisdexamfetamine trial (Table 1).

Before matching, there were no significant differences in age and sex across trials. The centanafadine trial had a lower proportion of White patients and a higher proportion of Hispanic or Latino patients than the lisdexamfetamine trial. Compared with those in the lisdexamfetamine trial, patients in the centanafadine trial had lower height and higher weight, and on average experienced less severe ADHD symptoms with lower mean AISRS/ADHD-RS and CGI-S scores at baseline. After matching, there were no differences in aggregate baseline characteristics across trials (Table 1).

Safety & efficacy

Overall, centanafadine had a better safety profile and lower efficacy compared with lisdexamfetamine (Figure 1). In the matched populations, compared with lisdexamfetamine at week 52, centanafadine was associated with a lower risk of upper respiratory tract infection (RD in percentage points: 18.75), insomnia (12.47), dry mouth (12.33), headache (11.34), irritability (8.55), decreased appetite (7.61) and decreased weight (4.97) (all $p < 0.05$); there were no significant differences in the risk of nasopharyngitis ($p = 0.13$) and the risk of anxiety ($p = 0.16$). The difference in change in AISRS/ADHD-RS score from baseline to week 52 for patients treated with centanafadine versus lisdexamfetamine was 6.15 points (95% CI = 4.31, 7.99; $p < 0.05$), indicating a greater reduction in symptom severity among patients treated with lisdexamfetamine. The arm-by-arm safety and efficacy outcomes before and after matching are presented in Supplementary Figure 1.

Table 1. Baseline characteristics of patients in the centanafadine versus lisdexamfetamine analyses.

Baseline characteristics	Comparator trial	Before matching		After matching[§]	
Safety analysis population[‡]	**Lisdexamfetamine (A) n = 349**	**Centanafadine (B) n = 492**	**p-value[¶] (A) vs (B)**	**Centanafadine (C) n = 492**	**p-value[¶] (A) vs [C)**
Age (years), mean ± SD	35.8 ± 10.1	36.3 ± 10.0	0.448	35.8 ± 10.1	–
Sex, n (%)					
Male	190 (54.4%)	236 (48.0%)	0.075	54.4%	–
Female	159 (45.6%)	256 (52.0%)	0.075	45.6%	–
Race, n (%)					
White	310 (88.8%)	410 (83.3%)	0.033[†]	88.8%	–
Ethnicity, n (%)					
Hispanic/Latino	36 (10.3%)	124 (25.2%)	<0.001[†]	10.3%	–
Height (cm), mean ± SD	171.7 ± 9.1	169.9 ± 10.6	0.008[†]	171.7 ± 9.1	–
Weight (kg), mean ± SD	79.3 ± 17.3	82.2 ± 17.7	0.018[†]	79.3 ± 17.3	–
AISRS/ADHS-RS at baseline, mean ± SD	40.6 ± 6.6	38.8 ± 6.6	<0.001[†]	40.6 ± 6.6	–
CGI-S at baseline, mean ± SD	4.8 ± 0.7	4.5 ± 0.7	<0.001[†]	4.8 ± 0.7	–
Efficacy analysis population[#]	**Lisdexamfetamine (A) n = 349**	**Centanafadine (B) n = 490**	**p-value[¶] (A) vs (B)**	**Centanafadine (C) n = 490**	**p-value[¶] (A) vs (C)**
Age (years), mean ± SD	35.8 ± 10.1	36.3 ± 10.0	0.482	35.8 ± 10.1	–
Sex, n (%)					
Male	190 (54.4%)	236 (48.2%)	0.085	54.4%	–
Female	159 (45.6%)	254 (51.8%)	0.085	45.6%	–
Race, n (%)					
White	310 (88.8%)	409 (83.5%)	0.037[†]	88.8%	–
Ethnicity, n (%)					
Hispanic/Latino	36 (10.3%)	124 (25.2%)	<0.001[†]	10.3%	–
Height (cm), mean ± SD	171.7 ± 9.1	169.9 ± 10.6	0.009[†]	171.7 ± 9.1	–
Weight (kg), mean ± SD	79.3 ± 17.3	82.2 ± 17.7	0.018[†]	79.3 ± 17.3	–
AISRS/ADHS-RS at baseline, mean ± SD	40.6 ± 6.6	38.8 ± 6.6	<0.001[†]	40.6 ± 6.6	–
CGI-S at baseline, mean ± SD	4.8 ± 0.7	4.5 ± 0.7	<0.001[†]	4.8 ± 0.7	–

[†] Significant at the 5% level.
[‡] The safety analysis population for centanafadine included all patients who received ≥1 dose of centanafadine and had a baseline AISRS score of ≥28 (150 patients in the centanafadine trial who had a baseline AISRS score of <28 were excluded); for lisdexamfetamine, all randomized patients who received ≥1 dose of lisdexamfetamine were included.
[§] Analyses were matched on age, sex, race, ethnicity, height, weight, AISRS at baseline and CGI-S at baseline.
[¶] Based on the Wald test; p-values could not be calculated when characteristics were exactly balanced between the centanafadine and the comparator trial.
[#] The efficacy analysis population for centanafadine included all randomized patients who received ≥1 dose of centanafadine, had a baseline and ≥1 post-baseline AISRS total score and had a baseline AISRS score of ≥28 (150 patients in the centanafadine trial who had a baseline AISRS score of <28 were excluded); for lisdexamfetamine, all patients in the intention-to-treat population of the lisdexamfetamine trial, i.e., those who were treated and had both baseline and ≥1 post-baseline ADHD-RS total score were included.
ADHD-RS: Attention-deficit/hyperactivity disorder rating scale; AISRS: Adult ADHD investigator symptom rating scale; CGI-S: Clinical Global Impression-Severity of Illness Scale; SD: Standard deviation.

Centanafadine versus methylphenidate

Baseline characteristics

For the centanafadine versus methylphenidate analyses, the safety analysis population included 552 and 550 patients from the centanafadine and methylphenidate trials, respectively; and the efficacy analysis population included 550 patients each from the respective trials (Table 2).

Before matching, there were no significant differences in sex and baseline AISRS across trials. Patients in the centanafadine trial had a lower mean CGI-S score at baseline compared with patients in the methylphenidate trial. Statistical significance of differences in age between the trials could not be determined because the methylphenidate trial did not report SD for age. After matching, there were no differences in aggregate baseline characteristics across trials.

Safety & efficacy

Overall, centanafadine had a better safety profile and no significant difference in efficacy compared with methylphenidate (Figure 2). After matching, compared with methylphenidate at final observation (week 26 or

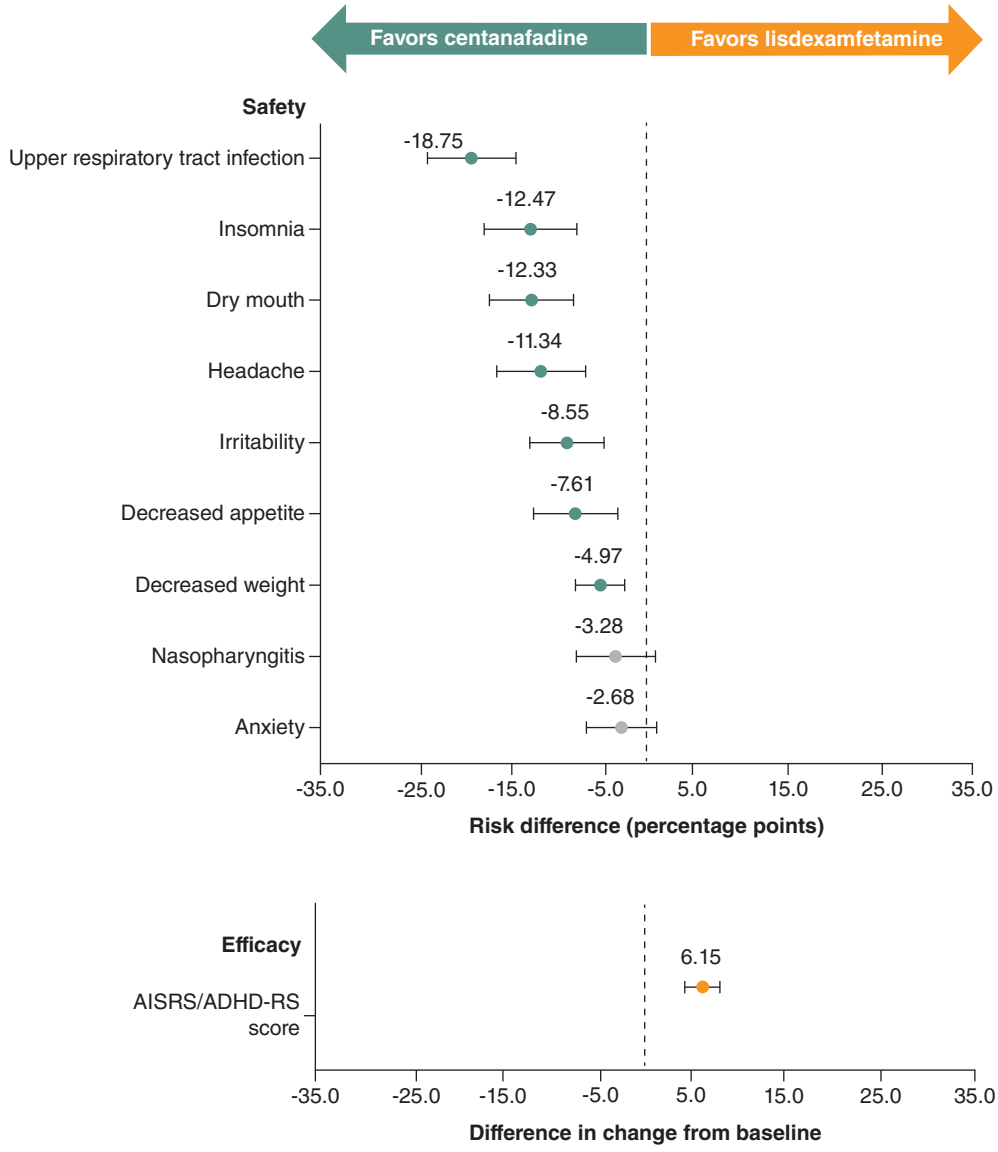

Figure 1. Comparisons of safety and efficacy between centanafadine and lisdexamfetamine. Statistical significance was set at the 5% level. Green dots denote significantly in favor of centanafadine. Orange dots denote significantly in favor of lisdexamfetamine. Gray dots denote non-significance. Safety and efficacy outcomes were compared at week 52 (as available in the lisdexamfetamine trial). Analyses were matched on age, sex, race, ethnicity, height, weight, AISRS at baseline and CGI-S at baseline.
ADHD-RS: Attention-Deficit/Hyperactivity Disorder Rating Scale; AISRS: Adult ADHD Investigator Symptom Rating Scale; CGI-S: Clinical Global Impression-Severity of Illness Scale.

week 52), centanafadine at week 52 was associated with a lower risk of decreased appetite (RD in percentage points: 20.25), headache (18.53), insomnia (12.65), dry mouth (10.76), upper respiratory tract infection (8.72), anxiety (8.26) and irritability (7.95) (all $p < 0.05$); there was no significant difference in the risk of nausea ($p = 0.91$). The change in AISRS score from baseline was not significantly different between centanafadine at week 26 versus methylphenidate at final observation (week 26 or week 52) (1.75 points; 95% CI = -0.51, 4.01; $p = 0.13$). The arm-by-arm safety and efficacy outcomes before and after matching are presented in Supplementary Figure 2.

Table 2. Baseline characteristics of patients in the centanafadine versus methylphenidate analyses.

Baseline characteristics	Comparator trial	Before matching		After matching[§]	
Safety analysis population[‡]	**Methylphenidate (A) n = 550**	**Centanafadine (B) n = 552**	**p-value[¶] (A) vs (B)**	**Centanafadine (C) n = 552**	**p-value[¶] (A) vs (C)**
Age (years), mean ± SD	39.1 ± –	36.4 ± 10.0	–	39.1 ± 9.7	–
Sex, n (%)					
Male	286 (52.0%)	265 (48.0%)	0.206	52.0%	–
Female	264 (48.0%)	287 (52.0%)	0.206	48.0%	–
AISRS at baseline, mean ± SD	38.2 ± 10.1	37.3 ± 7.5	0.102	38.2 ± 10.1	–
CGI-S at baseline, mean ± SD	4.6 ± 0.7	4.4 ± 0.7	<0.001[†]	4.6 ± 0.7	–
Efficacy analysis population[#]	**Methylphenidate (A) n = 550**	**Centanafadine (B) n = 550**	**p-value[¶] (A) vs (B)**	**Centanafadine (C) n = 550**	**p-value[¶] (A) vs (C)**
Age (years), mean ± SD	39.1 ± –	36.4 ± 10.0	–	39.1 ± 9.7	–
Sex, n (%)					
Male	286 (52.0%)	265 (48.2%)	0.228	52.0%	–
Female	264 (48.0%)	285 (51.8%)	0.228	48.0%	–
AISRS at baseline, mean ± SD	38.2 ± 10.1	37.3 ± 7.5	0.105	38.2 ± 10.1	–
CGI-S at baseline, mean ± SD	4.6 ± 0.7	4.4 ± 0.7	<0.001[†]	4.6 ± 0.7	–

[†]Significant at the 5% level.
[‡]The safety analysis population for centanafadine included all patients who received ≥1 dose of centanafadine, had a weight >100 pounds and had a baseline AISRS score of ≥24 (4 patients in the centanafadine trial who had weight ≤100 pounds and 86 patients who had a baseline AISRS score of <24 were excluded); for methylphenidate, all randomized patients who received ≥1 dose of methylphenidate were included.
[§]Analyses were matched on age, sex, AISRS at baseline and CGI-S at baseline.
[¶]Based on the Wald test; p-values could not be calculated when characteristics were exactly balanced between the centanafadine and the comparator trial.
[#]The efficacy analysis population for centanafadine included all randomized patients who received ≥1 dose of centanafadine, had a baseline and ≥1 post-baseline AISRS total score, had a weight >100 pounds and had a baseline AISRS score of ≥24 (4 patients in the centanafadine trial who had weight ≤100 pounds and 86 patients who had a baseline AISRS score of <24 were excluded); for methylphenidate, the efficacy population was not clearly defined in the trial publication, but it was assumed that all patients who received ≥1 dose of methylphenidate and had a baseline and ≥1 post-baseline AISRS total score were included in the efficacy analysis.
AISRS: Adult ADHD Investigator Symptom Rating Scale; CGI-S: Clinical Global Impression-Severity of Illness Scale; SD: Standard deviation.

Centanafadine versus atomoxetine

Baseline characteristics

For the centanafadine versus atomoxetine analyses, the safety and efficacy analysis populations included 314 patients from the centanafadine trial and 250 patients from the atomoxetine trial, respectively (Table 3).

Before matching, there were no significant differences in sex, race, baseline AISRS total score and baseline AISRS inattentive subscale score across trials. Patients in the centanafadine trial had a higher mean AISRS hyperactive-impulsive subscale score and a lower mean CGI-S score at baseline compared with patients in the atomoxetine trial. Statistical significance of differences in age across trials could not be determined because the atomoxetine trial did not report SD for age. After matching, there were no differences in aggregate baseline characteristics across trials.

Safety & efficacy

Overall, centanafadine had a better safety profile and no significant difference in efficacy compared with atomoxetine (Figure 3). After matching, compared with atomoxetine at week 26, centanafadine was associated with a lower risk of nausea (RD in percentage points: 26.18), dry mouth (25.07), fatigue (13.95), headache (11.04), dizziness (9.17), decreased appetite (6.02), constipation (5.69), upper respiratory tract infection (5.06), irritability (4.59) and somnolence (4.15) (all $p < 0.05$); there were no significant differences in the risk of insomnia ($p = 0.13$) and the risk of diarrhea ($p = 0.07$). The change in AISRS score from baseline to week 26 for patients treated with centanafadine versus atomoxetine was not significantly different (-1.60; 95% CI = -4.07, 0.87; $p = 0.21$). The arm-by-arm safety and efficacy outcomes before and after matching are presented in Supplementary Figure 3.

Discussion

In this MAIC study of ADHD treatments comparing data from clinical trials lasting for up to 52 weeks, centanafadine showed a better long-term safety profile than all comparators, including lisdexamfetamine, methylphenidate and atomoxetine. Compared with these common ADHD treatments, centanafadine was associated with significantly lower incidence of upper respiratory tract infection, dry mouth, headache, decreased appetite and irritability; and depending on the comparator, the incidence of insomnia, decreased weight, anxiety, nausea, fatigue, dizziness,

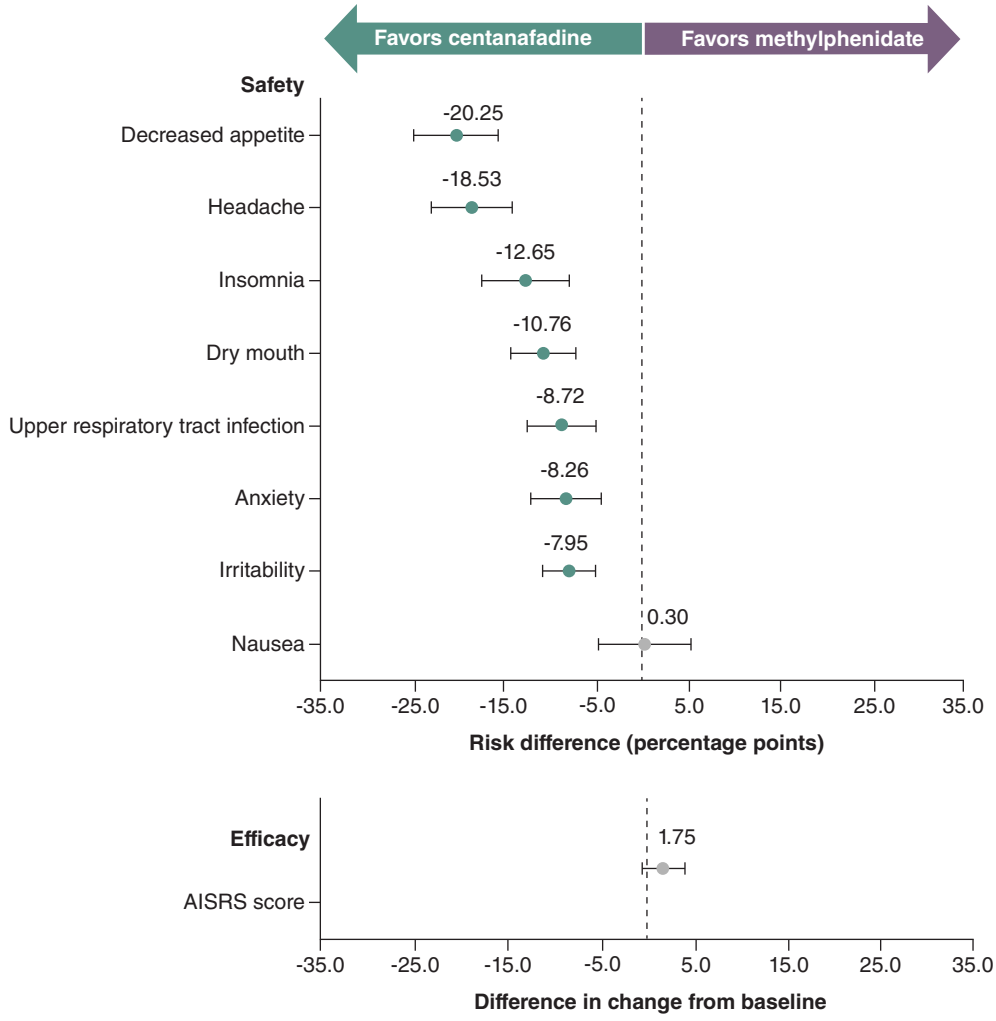

Figure 2. Comparisons of safety and efficacy between centanafadine and methylphenidate. Statistical significance was set at the 5% level. Green dots denote significantly in favor of centanafadine. Gray dots denote non-significance. Safety outcomes were compared for centanafadine at week 52 vs methylphenidate at final observation (week 26 or week 52). Efficacy outcomes were compared between centanafadine at week 26 and methylphenidate at final observation (week 26 or week 52). Analyses were matched on age, sex, AISRS at baseline and CGI-S at baseline. AISRS: Adult ADHD Investigator Symptom Rating Scale; CGI-S: Clinical Global Impression-Severity of Illness Scale.

constipation and somnolence was also significantly lower with centanafadine. Translating the differences in the risks of AEs using an example, an RD of 12 percentage points for the risk of insomnia between centanafadine and lisdexamfetamine at week 52 means that for every 100 adults with ADHD receiving treatment, 7 would experience insomnia after a year of treatment with centanafadine, whereas 19 would experience insomnia with lisdexamfetamine at the same timepoint (Figure 4). Although the AEs assessed in the MAICs were limited to those reported in both trials in a given comparison, the risks of all AEs included in this study were lower or non-different in patients treated with centanafadine than with comparators, suggesting that centanafadine may be a more tolerable ADHD treatment in the long term relative to commonly available options.

With respect to efficacy, although some differences in baseline AISRS/ADHD-RS and CGI-S scores were observed between patients in the centanafadine trial and those in the respective comparator trials, the differences were small. After matching all patient characteristics, the efficacy of centanafadine was found to be statistically lower than lisdexamfetamine and non-different from methylphenidate and atomoxetine. To interpret the statistically significant difference between centanafadine and lisdexamfetamine found in this study, it is important to note that a result can be statistically significant without being clinically meaningful. Prior research may help interpret the clinical meaningfulness of the difference between centanafadine and lisdexamfetamine. Specifically, studies have

Table 3. Baseline characteristics of patients in the centanafadine versus atomoxetine analyses.

Baseline characteristics	Comparator trial	Before matching		After matching[§]	
Safety analysis population[‡]	**Atomoxetine (A) n = 250**	**Centanafadine (B) n = 314**	**p-value[¶] (A) vs (B)**	**Centanafadine (C) n = 314**	**p-value[¶] (A) vs (C)**
Age (years), mean ± SD	36.7 ± –	36.5 ± 9.9	–	36.7 ± 9.7	–
Sex, n (%)					
Male	125 (50.0%)	150 (47.8%)	0.659	50.0%	–
Female	125 (50.0%)	164 (52.2%)	0.659	50.0%	–
Race, n (%)					
White	220 (87.9%)	260 (82.8%)	0.117	87.9%	–
AISRS at baseline, mean ± SD	38.5 ± 7.4	37.7 ± 7.9	0.202	38.5 ± 7.4	–
AISRS inattentive subscale score at baseline, mean ± SD	22.4 ± 3.4	21.1 ± 4.1	0.376	16.2 ± 5.8	0.733
AISRS hyperactive/impulsive score at baseline, mean ± SD	16.2 ± 5.8	16.6 ± 5.5	<0.001[†]	22.3 ± 3.5	–
CGI-S at baseline, mean ± SD	4.7 ± 0.7	4.5 ± 0.6	<0.001[†]	4.7 ± 0.7	–
Efficacy analysis population[#]	**Atomoxetine (A) n = 250**	**Centanafadine (B) n = 314**	**p-value[¶] (A) vs (B)**	**Centanafadine (C) n = 314**	**p-value[¶] (A) vs (C)**
Age (years), mean ± SD	36.7 ± –	36.5 ± 9.9	–	36.7 ± 9.7	–
Sex, n (%)					
Male	125 (50.0%)	150 (47.8%)	0.659	50.0%	–
Female	125 (50.0%)	164 (52.2%)	0.659	50.0%	–
Race, n (%)					
White	220 (87.9%)	260 (82.8%)	0.117	87.9%	–
AISRS at baseline, mean ± SD	38.5 ± 7.4	37.7 ± 7.9	0.202	38.5 ± 7.4	–
AISRS inattentive subscale score at baseline, mean ± SD	22.4 ± 3.4	21.1 ± 4.1	0.376	22.3 ± 3.5	0.733
AISRS hyperactive/impulsive score at baseline, mean ± SD	16.2 ± 5.8	16.6 ± 5.5	<0.001[†]	16.2 ± 5.8	–
CGI-S at baseline, mean ± SD	4.7 ± 0.7	4.5 ± 0.6	<0.001[†]	4.7 ± 0.7	–

[†]Significant at the 5% level.
[‡]The safety analysis population for centanafadine included all patients who received ≥1 dose of centanafadine, aged <55, had a baseline CGI-S score ≥4 and had a non-missing AISRS score change of <25% from the first to second visit (14 patients in the centanafadine trial who were aged ≥55, 102 patients with a baseline CGI-S score <4, 5 patients with missing AISRS change from visit 1 to visit 2, and 207 patients with AISRS score change of ≥25% from visit 1 to visit 2 were excluded); for atomoxetine, all randomized patients who received ≥1 dose of atomoxetine were included.
[§]Analyses were matched on age, sex, race, AISRS total score at baseline, AISRS inattentive and hyperactive/impulsive subscale score at baseline and CGI-S at baseline.
[¶]Based on the Wald test; p-values could not be calculated when characteristics were exactly balanced between the centanafadine and the comparator trial.
[#]The efficacy analysis population for centanafadine included all randomized patients who received ≥1 dose of centanafadine, had a baseline and ≥1 post-baseline AISRS total score, aged <55, had a baseline CGI-S score ≥4 and had a non-missing AISRS score change of <25% from the first to second visit (14 patients in the centanafadine trial who were aged ≥55, 101 patients with a baseline CGI-S score <4, 4 patients with missing AISRS change from visit 1 to visit 2 and 207 patients with AISRS score change of ≥25% from visit 1 to visit 2 were excluded); for atomoxetine, the efficacy population was not clearly defined in the trial publication, but it was assumed that all patients who received ≥1 dose of atomoxetine during the treatment period were included in the efficacy analysis.
AISRS: Adult ADHD Investigator Symptom Rating Scale; CGI-S: Clinical Global Impression-Severity of Illness Scale; SD: Standard deviation.

reported that clinically meaningful improvement in ADHD symptoms in adults may be achieved with a change in AISRS/ADHD-RS score of 8 to 10 points [37,38], a threshold that was not reached by the efficacy difference between centanafadine and lisdexamfetamine found in this study (i.e., 6.15 points). Therefore, the impact of the difference between centanafadine and lisdexamfetamine in terms of real-world benefit is unclear. Considering the long-term safety and efficacy profiles from the current indirect comparisons of trial data, centanafadine may be a promising treatment option for adults with ADHD. Future real-world data would be needed to determine the relative effectiveness of these treatments in clinical practice.

There have been limited studies directly or indirectly comparing treatments for ADHD in adults, especially ones that included longer treatment durations and newer treatments [17,26–28]. Recently, MAICs comparing centanafadine with common treatments for adults with ADHD using data from RCTs with treatment duration of up to 10 weeks have been published [29], and results of the current study are largely consistent with those reported in that shorter-term MAICs. In both studies, centanafadine relative to lisdexamfetamine was associated with a lower risk of dry mouth and insomnia, whereas differences in rates of some AEs such as upper respiratory tract infection, headache

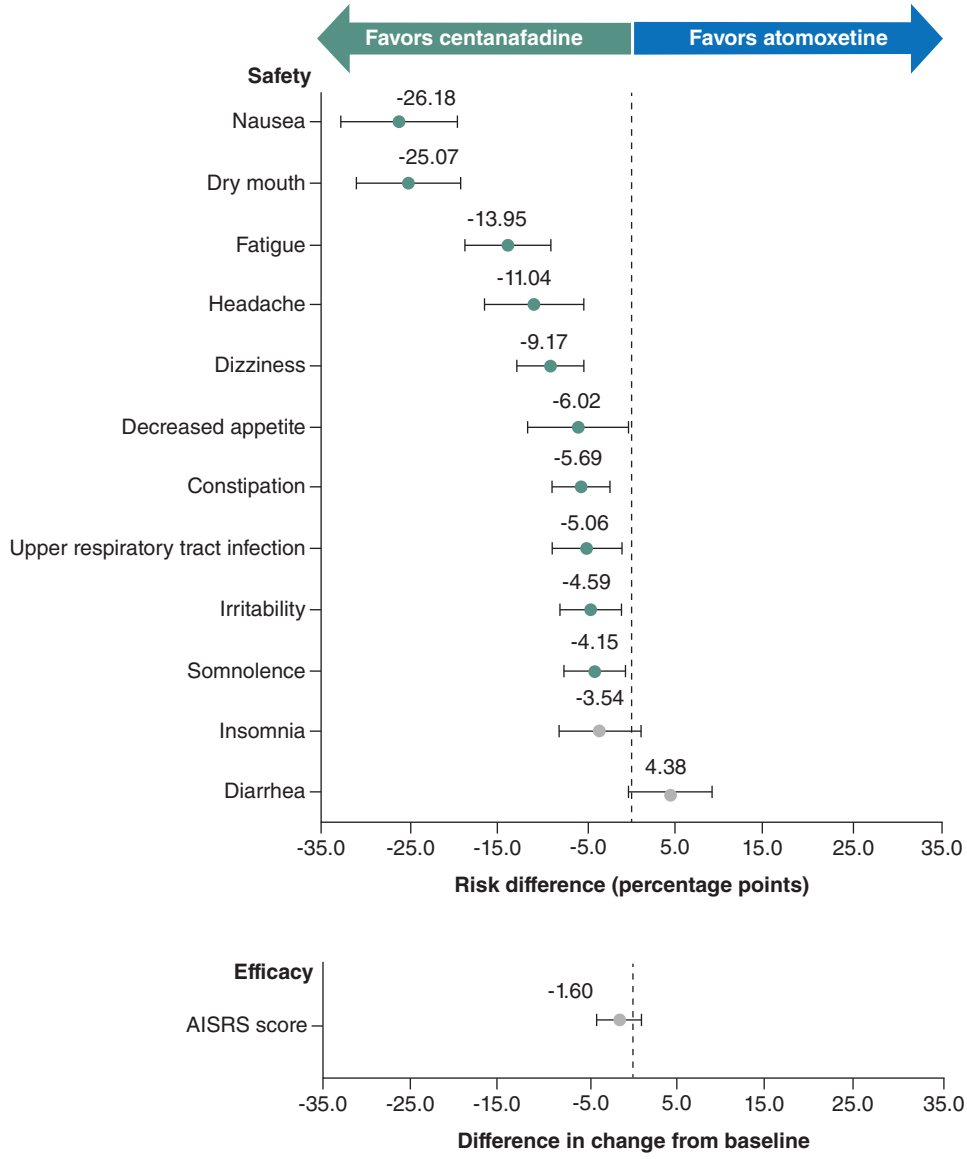

Figure 3. Comparisons of safety and efficacy between centanafadine and atomoxetine. Statistical significance was set at the 5% level. Green dots denote significantly in favor of centanafadine. Gray dots denote non-significance. Safety and efficacy outcomes were compared at week 26 (as available in the atomoxetine trial). Analyses were matched on age, sex, race, AISRS total score at baseline, AISRS inattentive and hyperactive/impulsive subscale score at baseline and CGI-S at baseline.
AISRS: Adult ADHD Investigator Symptom Rating Scale; CGI-S: Clinical Global Impression-Severity of Illness Scale.

and irritability emerged with longer treatment favoring centanafadine. The risks of these latter AEs were also found to be lower with centanafadine than with atomoxetine and were only captured using the longer-term data in this study. Similar to the current study, the previous MAICs found that the efficacy of centanafadine was statistically lower than that of lisdexamfetamine (6.58-point difference in AISRS/ADHD-RS score from baseline to week 4; $p < 0.05$) and non-different from atomoxetine (2.02-point difference in AISRS score from baseline to week 6; $p = 0.38$) [29]. Notably, the previous MAIC study also included comparisons with viloxazine ER, the long-term data for which were not available at the time this study was conducted. Future analyses comparing long-term safety and efficacy outcomes of centanafadine versus viloxazine ER are warranted to assess potential differences in their attributes with longer treatment durations. It is also worth mentioning that short-term clinical trials may favor medications with a faster mechanism of action, such as stimulants. Meanwhile, although long-term trials are subject to caveats such as lack of placebo arms, they may provide better insight to the real-world impact of

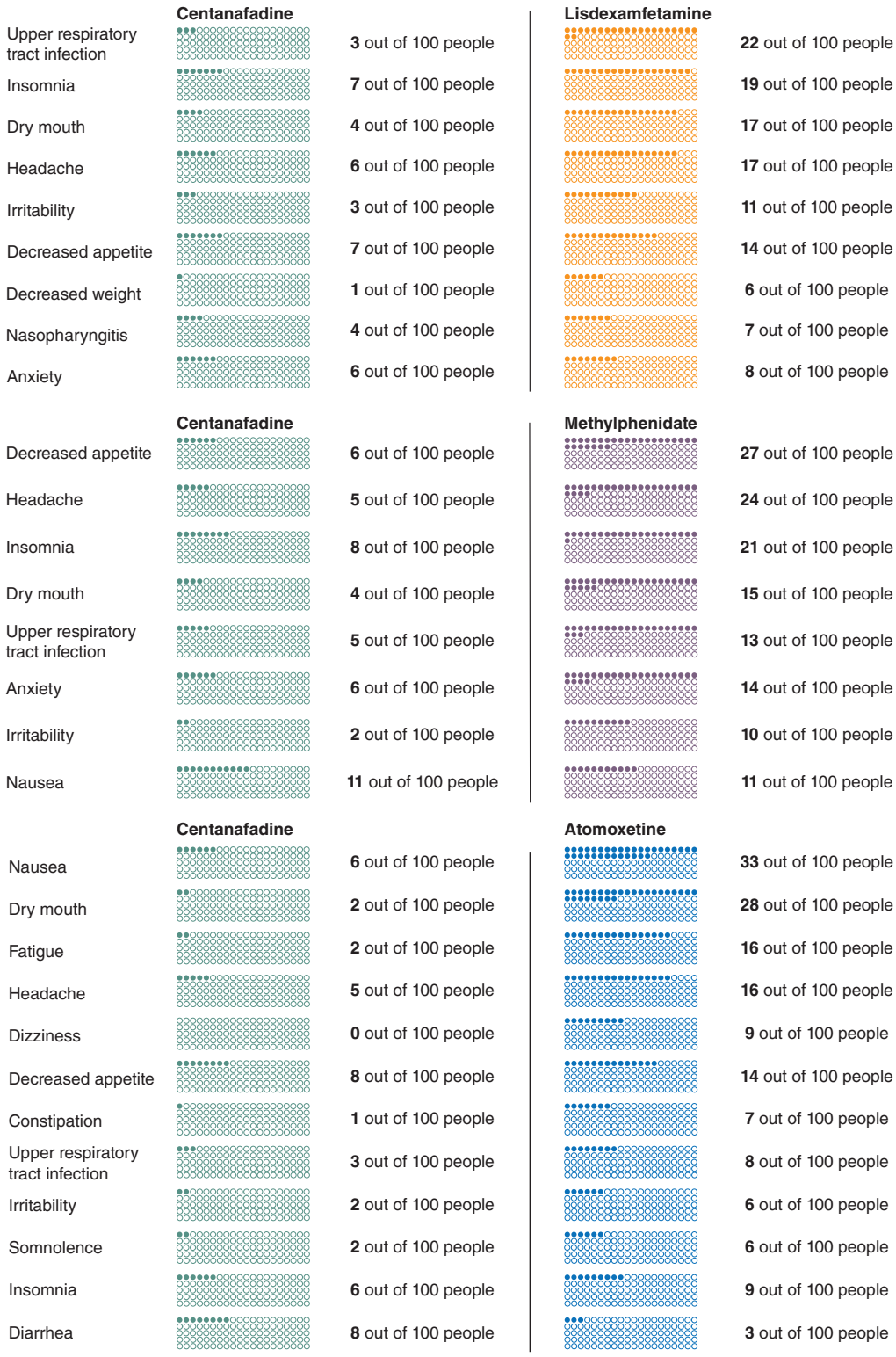

Figure 4. Risk of adverse events with centanafadine vs respective comparators. Adverse events (AEs) for which information was available in both trials in a given comparison. The timepoint for assessment was at week 52 for comparison with lisdexamfetamine, week 26/52 for comparison with methylphenidate, and week 26 for comparison with atomoxetine, as available in the respective comparator trials. The filled circles represent the proportions of people receiving centanafadine or comparator who experienced AEs after matching to adjust for differences in baseline characteristics across trials. The proportions may not match the forest plots due to rounding.

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ADHD treatments. Interestingly, the efficacy difference found in a short-term MAIC between centanafadine and methylphenidate is no longer significant in this study using longer-term data [39].

Understanding potential long-term outcomes associated with ADHD treatments is important because ADHD may exhibit a chronic course with fluctuating symptoms throughout a patient's life [4], mandating treatments over a lifetime. Unfortunately, common ADHD treatments are associated with many AEs that negatively affect different aspects of a patient's daily living, such as sleeping (e.g., with insomnia, headache), eating (e.g., with decreased appetite, dry mouth) and social relationships (e.g., with anxiety) [19,24,25]. It has also been suggested that symptoms associated with ADHD/treatment-related AEs could impair patient's work performance and health-related quality of life [40]. Over time, many patients with ADHD may discontinue or become non-adherent to their prescribed treatment for different reasons, with safety issues and suboptimal efficacy being reported as key factors underlying treatment changes and poor adherence [41,42]. Thus, knowledge on comparative long-term outcomes of ADHD treatments during initial treatment selection may help physicians and patients optimize treatment choice by considering individual patient circumstances and preferences, potentially leading to fewer treatment changes and better adherence. Furthermore, with the evolving ADHD treatment landscape, physicians and patients should also be informed about the long-term safety and efficacy profiles of newer treatments as compared with existing options to facilitate treatment decisions.

The current MAICs provide timely comparative evidence on long-term outcomes of the novel agent, centanafadine, versus common ADHD treatments and shed some light on the impact different ADHD treatments may have over time, which has important implications for patients requiring chronic treatment. For example, centanafadine may be considered as an alternative to methylphenidate and atomoxetine for long-term treatment of ADHD in adults in view of its non-different efficacy and better safety profile, and to lisdexamfetamine when patients are intolerant to stimulant-related AEs. Future studies should aim to better understand the ADHD treatment landscape by comparing long-term safety and efficacy outcomes of new versus existing treatments, their impact on different patient populations (e.g., pediatric patients), as well as how trade-off between safety and efficacy may affect clinical practice and patient preferences for treatment.

Limitations

The current study is subject to some limitations. First, matching of baseline patient characteristics was only possible on variables collected across trials in a given comparison; thus, other unobserved differences in baseline characteristics (e.g., comorbidities, concomitant medications) could exist. Second, differences in trial design and specific definitions used across trials could not be accounted for despite the overall consistent inclusion and exclusion criteria across trials; these included the long-term centanafadine trial recruiting patients not following the short-term trials, differences in the specific definition of ADHD across trials, and different outcome assessment timepoints in the centanafadine versus atomoxetine trials (in this study, conservative comparisons using timepoints favoring atomoxetine were conducted). Third, although the efficacy instruments ADHD-RS (used in the lisdexamfetamine trial) and AISRS (used in the centanafadine trial) are similar, variations in wording and interpretation could have resulted in differences in measurements. Finally, while anchored MAICs further adjusting for cross-trial heterogeneity such as placebo effect could be more robust, anchored comparisons were not possible for this study because the long-term centanafadine and some comparator trials were single-arm, and there was no common comparator arm (i.e., placebo) across trials; therefore, unanchored MAICs were conducted.

Conclusion

Using unanchored indirect comparisons and propensity score weighting, centanafadine showed a better safety profile than lisdexamfetamine, methylphenidate and atomoxetine, as evidenced by a significantly lower incidence of several AEs at up to 52 weeks. Efficacy of centanafadine, as measured by validated instruments, was statistically lower than lisdexamfetamine and non-different from methylphenidate and atomoxetine. Considering its long-term safety and efficacy profile, centanafadine may be a promising treatment option for adults with ADHD. Future studies should aim to better understand how the trade-off between safety and efficacy may affect clinical practice and patient preferences for treatment.

Summary points

- Patients with attention-deficit/hyperactivity disorder (ADHD) may experience persistent disease course and require long-term treatment; however, randomized clinical trials of ADHD medications typically lasted a few weeks.
- Direct comparisons of ADHD treatments from clinical trials, particularly those including long-term outcomes and newer treatments, are often lacking.
- Matching-adjusted indirect comparison (MAIC) is a well-validated method to generate comparative evidence when individual patient data (IPD) are available for at least one trial in the comparison.
- This study leveraged IPD from a trial of centanafadine, an investigational treatment for ADHD in adults, and published aggregate data from trials of common ADHD treatments to compare the safety and efficacy of centanafadine versus the respective comparators at up to 52 weeks in adults with ADHD using MAICs.
- Across matched populations, the risks of several adverse events were significantly lower with centanafadine than with the respective comparators, including upper respiratory tract infection (risk difference in percentage points: 18.75), insomnia (12.47) and dry mouth (12.33) versus lisdexamfetamine; decreased appetite (20.25), headache (18.53) and insomnia (12.65) versus methylphenidate; and nausea (26.18), dry mouth (25.07) and fatigue (13.95) versus atomoxetine.
- Efficacy of centanafadine, as measured by changes from baseline in Adult ADHD Investigator Symptom Rating Scale/ADHD Rating Scale score, was statistically lower than lisdexamfetamine and non-different from methylphenidate and atomoxetine.
- Knowledge on treatment attributes over the long term may help optimize treatment decisions in consideration of individual patient circumstances and preferences.
- Future studies should aim to better understand how the trade-off between safety and efficacy may affect clinical practice and patient preferences for treatment.

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at:
https://bpl-prod.literatumonline.com/doi/10.57264/cer-2024-0089

Author contributions

J Schein and A Childress contributed to study conception and design, data analysis and interpretation. M Cloutier, M Gauthier-Loiselle, M Catillon, C Xu, A Qu and F Lee contributed to study conception and design, collection and assembly of data, and data analysis and interpretation. All authors reviewed and approved the final content of this manuscript.

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Competing interests disclosure

The authors have no competing interests or relevant affiliations with any organization or entity with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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Ethical conduct of research
This was a post-hoc analysis of previously collected, anonymized trial data; thus, no ethical review was required.

Data sharing statement
The authors certify that this manuscript reports the secondary analysis of clinical trial data that have been shared with them, and that the use of this shared data is in accordance with the terms agreed upon their receipt. Data for the centanafadine trial were provided by the trial sponsor, Otsuka Pharmaceutical Development & Commercialization, Inc. Data for the comparator trials were publicly available on the ClinicalTrials.gov website and the respective trial publications cited in this manuscript.

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