Assessment of centanafadine in adults with attention-deficit/hyperactivity disorder: A matching-adjusted indirect comparison vs lisdexamfetamine dimesylate, atomoxetine hydrochloride, and viloxazine extended-release

Jeff Schein, DrPH, MPH; Martin Cloutier, MSc; Marjolaine Gauthier-Loiselle, PhD; Maryaline Catillon, PhD, MPH; Chunyi Xu, MS; Deborah Chan, RNBN, MscPH; Ann Childress, MD

Plain language summary

Centanafadine is an investigational therapy for adults with attention-deficit/hyperactivity disorder (ADHD). No clinical trials have directly compared centanafadine with other treatments. We performed indirect comparisons and found that centanafadine had fewer side effects than all 3 comparators. ADHD symptom improvement with centanafadine was smaller than with lisdexamfetamine dimesylate and nondifferent than with atomoxetine hydrochloride and viloxazine extended-release (ER). Future studies should aim to understand how patients are willing to trade off between treatment safety and efficacy.

Implications for managed care pharmacy

Knowledge on the relative safety and efficacy of ADHD treatment options may help inform treatment decisions. This matching-adjusted indirect comparison found that centanafadine had lower incidence of several adverse events (AEs) than comparators. Efficacy was lower than with lisdexamfetamine and nondifferent than with atomoxetine and viloxazine ER. Given the paucity of novel ADHD therapies and the association of AEs with costly treatment changes, centanafadine may be an option to effectively manage ADHD symptoms while minimizing AE-related costs.

Author affiliations

Otsuka Pharmaceutical Development & Commercialization, Inc., Princeton, NJ (Schein); Analysis Group, Inc., Montréal, QC, Canada (Cloutier, Gauthier-Loiselle, Xu, Chan); Analysis Group, Inc., New York, NY (Catillon); Center for Psychiatry and Behavioral Medicine, Las Vegas, NV (Childress).

AUTHOR CORRESPONDENCE:
Maryaline Catillon, 1.857.222.6863;
Maryaline.Catillon@analysisgroup.com

J Manag Care Spec Pharm.
2024;30(6):528-40

Copyright©2024, Academy of Managed Care Pharmacy. All rights reserved.

ABSTRACT

BACKGROUND: Head-to-head trials comparing centanafadine, an investigational therapy for adults with attention-deficit/hyperactivity disorder (ADHD), with other treatment options are lacking.

OBJECTIVE: To compare safety and efficacy outcomes of centanafadine sustained-release vs lisdexamfetamine dimesylate (lisdexamfetamine), atomoxetine hydrochloride (atomoxetine), and viloxazine extended-release (viloxazine ER), respectively, using matching-adjusted indirect comparison (MAIC).

METHODS: This MAIC included patient-level data pooled from 2 centanafadine trials (NCT03605680 and NCT03605836) and published aggregate data from comparable trials of 3 comparators—lisdexamfetamine (NCT00334880), atomoxetine (NCT00190736), and viloxazine ER (NCT04016779)—in adult patients with ADHD. Propensity score weighting was used to match characteristics of individual patients from the centanafadine trials to aggregate baseline characteristics from the respective comparator trials. Safety outcomes were rates of adverse events for which information was available in the centanafadine and respective comparator trials. Efficacy outcome was mean change from baseline in the Adult ADHD Investigator Symptom Rating Scale (AISRS) score (ADHD Rating Scale [ADHD-RS] was used as proxy in the comparison with lisdexamfetamine). Anchored indirect comparisons were conducted across matched populations of the centanafadine and respective comparator trials.

RESULTS: After matching, baseline characteristics in the centanafadine trials were the same as those in the respective comparator trials. Compared with lisdexamfetamine, centanafadine was associated with a significantly lower risk of lack of appetite (risk difference [RD]

ABSTRACT *continued*

in percentage points: 23.42), dry mouth (19.27), insomnia (15.35), anxiety (5.21), nausea (4.90), feeling jittery (3.70), and diarrhea (3.47) (all $P<0.05$) but a smaller reduction in the AISRS/ADHD-RS score (6.58-point difference; $P<0.05$). Compared with atomoxetine, centanafadine was associated with a significantly lower risk of nausea (RD in percentage points: 18.64), dry mouth (17.44), fatigue (9.21), erectile dysfunction (6.76), lack of appetite (6.71), and urinary hesitation (5.84) (all $P<0.05$) and no statistically significant difference in the change in AISRS score. Compared with viloxazine ER, centanafadine was associated with a significantly lower risk of fatigue (RD in percentage points: 11.07), insomnia (10.67), nausea (7.57), and constipation (4.63) (all $P<0.05$) and no statistically significant difference in the change in AISRS score.

CONCLUSIONS: In an anchored MAIC, centanafadine showed a significantly better short-term safety profile than lisdexamfetamine, atomoxetine, and viloxazine ER; efficacy was lower than with lisdexamfetamine and comparable (ie, nondifferent) with atomoxetine and viloxazine ER. This MAIC provides important insights on the relative safety and efficacy of common treatment options to help inform treatment decisions in adults with ADHD. Safety assessment was limited to rates of adverse events reported in both trials of a given comparison.

Study registration numbers: NCT03605680, NCT03605836, NCT00334880, NCT00190736, and NCT04016779.

Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disorder with an overall prevalence of 4.4% and a lifetime prevalence of 8.1% among adults in the United States.[1-3] ADHD is characterized by persistent symptoms of inattention and/or hyperactivity-impulsivity that interfere with academic, occupational, and social functioning.[4,5] Compared with adults without ADHD, those with the condition have poorer educational attainment, higher rates of unemployment, reduced work productivity, increased high-risk behaviors such as substance abuse and criminal activity, and an overall lower quality of life.[6-10]

Pharmacological treatment options for ADHD primarily include 2 main drug classes: stimulants and nonstimulants.[1] Although both drug classes and individual treatments within each class have different attributes, stimulants are generally considered more efficacious, whereas nonstimulants may be used when stimulants are not tolerated, when patients present with certain comorbidity profiles, or when potential for diversion is a particular concern.[11,12] Among the most commonly used stimulants is lisdexamfetamine dimesylate (lisdexamfetamine; Vyvanse), which is well established and considered a standard of care for adults with ADHD.[11,13] Among nonstimulants, atomoxetine hydrochloride (atomoxetine; Strattera) is a leading option as it is the first medication specifically approved for the treatment of ADHD in adults[14,15]; and viloxazine extended-release (viloxazine ER; Qelbree) is the most recent treatment for adults with ADHD on the US market.[16,17] Meanwhile, centanafadine is a novel serotonin-norepinephrine-dopamine triple-reuptake inhibitor that is currently being investigated for adult patients with ADHD. In 2 similarly designed phase 3 clinical trials, centanafadine resulted in significant reductions in ADHD symptoms after 6 weeks compared with placebo and appeared to be well tolerated.[18]

In the absence of head-to-head trials comparing centanafadine with other common treatment options for adults with ADHD, it can be challenging for stakeholders to make informed treatment decisions based on timely and reliable comparative evidence. It is notable that study outcomes across clinical trials cannot be compared directly, as the results may be confounded by, for example, differences in patient characteristics (eg, age, sex, race, and disease severity) or other trial characteristics.[19] In addition, adjustments for confounding using most standard methods such as regression analysis typically require individual patient data (IPD) for all trials in the comparison, but IPD is generally only available for one trial (eg, data provided by a trial sponsor).[19]

Matching-adjusted indirect comparison (MAIC) is a well-validated method to provide evidence for the comparative safety and efficacy of treatments when head-to-head trials are not available.[19-21] MAIC leverages IPD from one trial and published aggregate data from comparator trials to adjust for cross-trial differences so that the trials are comparable in inclusion and exclusion criteria, population characteristics, and outcome definitions.[19] Analyses using MAIC have been published in top journals[22-24] and accepted by health technology assessment and payer organizations globally (eg, the National Institute for Health and Care Excellence of the United Kingdom,[25] the Haute Autorité De Santé of France,[26] the Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen of Germany,[27] and the Canadian Agency for Drugs and Technologies in Health of Canada[28]).

In this context, this MAIC compared the safety and efficacy outcomes of centanafadine sustained-release vs 3 common treatments for adults with ADHD, including lisdexamfetamine, atomoxetine, and viloxazine ER, respectively, in balanced populations by leveraging IPD from the centanafadine trials and published aggregate data from the comparator trials. Given a common comparator arm (ie, placebo) is available for all trials, anchored MAICs were conducted to account for the difference between placebo arms across trials to further reduce cross-trial heterogeneity.[25]

Methods

DATA SOURCES

Data sources for this anchored MAIC of ADHD treatments in adults included IPD from 2 phase 3 centanafadine trials (NCT03605680 and NCT03605836[18]) and published aggregate data from 3 comparator trials, including a phase 3 lisdexamfetamine trial (NCT00334880[29]), a phase 4 atomoxetine trial (NCT00190736[30]), and a phase 3 viloxazine ER trial (NCT04016779[31]). IPD from the centanafadine trials were provided by the trial sponsor (Otsuka Pharmaceutical Development & Commercialization, Inc). Given the 2 centanafadine trials had identical designs and were reported in the same publication,[18] IPD from these 2 trials were pooled. Published aggregate data from comparator trials were obtained from public databases, as described in the next section.

TRIAL AND SAMPLE SELECTION

Potential comparator trials with published results were identified through a search of the ClinicalTrials.gov registry on January 24, 2022, using the following prespecified criteria: (1) condition or disease: ADHD; (2) intervention: lisdexamfetamine, atomoxetine, or viloxazine ER; (3) recruitment status: completed; (4) eligibility criteria: adult (aged 18-64 years); and (5) study phase: phase 3 or 4. To supplement the search, the PubMed database was also queried using the above criteria as keywords with the filter "clinical trials" for article type. A manual search of the US prescribing information of the respective comparators was also conducted to ensure key trials were covered.

The search identified 22 potential comparator trials (4 lisdexamfetamine trials, 15 atomoxetine trials, and 3 viloxazine ER trials) for further assessment for eligibility. Cross-study similarities and differences in trial design, study populations, interventions, comparators, and outcomes were assessed. Specifically, trials were excluded if they used a different design than the centanafadine trials (eg, open label), focused on a specific subpopulation (eg, only males), included other interventions than the comparator drugs (eg, atomoxetine + amphetamine/dextroamphetamine), compared the drug with any intervention other than placebo (eg, behavioral intervention), or did not include comparable safety and efficacy outcomes as the centanafadine trials. The assessment yielded 1 trial for each comparator (ie, the number of excluded trials was 3 for lisdexamfetamine, 14 for atomoxetine, and 2 for viloxazine ER; Supplementary Table 1, available in online article); details on reasons for exclusion are summarized in Supplementary Table 2.

The characteristics of all trials included in this MAIC are presented in Supplementary Table 3. Based on the inclusion and exclusion criteria of the centanafadine and comparator trials, patients included in this MAIC met the following criteria: (1) aged 18-65 years; (2) had confirmed diagnosis of ADHD (per the *Diagnostic and Statistical Manual of Mental Disorders, Fourth/Fifth Edition* criteria); (3) had moderate to severe ADHD at baseline; (4) had no comorbid psychiatric diagnoses; and (5) were not currently taking prohibited medication (eg, psychotropic medications and medications that affect the central nervous system or blood pressure).

Each of the trials included in this MAIC had 2 analytical populations: (1) a safety population that comprised all randomized patients who received at least 1 dose of trial medication or placebo and (2) an efficacy population that comprised all patients who had a baseline and at least 1 postrandomization efficacy outcome assessment. All safety analyses were conducted in the safety population, and all efficacy analyses were conducted in the efficacy population.

OUTCOME MEASURES

The safety outcomes were rates of adverse events (AEs) for which information was available in both trials of a given comparison and reported by at least 5% of patients in any treatment group with an incidence twice that of placebo. Following this rule, the comparison of centanafadine vs lisdexamfetamine assessed anxiety, lack of appetite, diarrhea, dry mouth, feeling jittery, insomnia, and nausea. The comparison vs atomoxetine assessed constipation, lack of appetite, dizziness, dry mouth, erectile dysfunction, fatigue, irritability, nausea, and urinary hesitation. The comparison vs viloxazine ER assessed constipation, lack of appetite, dry mouth, fatigue, insomnia, nausea, and headache.

The time points for safety outcome assessments were based on the availability of safety data from the respective comparator trials (ie, Week 4 for centanafadine vs lisdexamfetamine; Week 10 for centanafadine vs atomoxetine, and Week 6 for centanafadine vs viloxazine ER). For the comparison of centanafadine vs atomoxetine, outcomes for centanafadine were forecasted at Week 10 based on the polynomial extrapolation of the data observed from Week 1 to Week 6 (ie, the last time point assessed). A sensitivity analysis comparing safety outcomes at Week 6 for centanafadine vs at Week 10 for atomoxetine was also conducted.

The efficacy outcome was mean change from baseline in the Adult ADHD Investigator Symptom Rating Scale (AISRS) score. For the comparison with lisdexamfetamine, the ADHD Rating Scale (ADHD-RS) was used as a proxy as the AISRS was not reported. Both instruments contain the same number of questions (18 items), review the same symptoms, and are scored in the same way.[18,32] A clinical expert confirmed that the 2 instruments are comparable.

The time points for efficacy outcome assessments were based on the availability of efficacy data from the respective comparator trials (ie, from baseline to Week 4 for centanafadine vs lisdexamfetamine and from baseline to Week 6 for centanafadine vs atomoxetine and for centanafadine vs viloxazine ER).

STATISTICAL ANALYSES

Baseline characteristics were described and compared between the centanafadine and comparator trials to identify differences between trial populations. Based on information published in the comparator trials and available as IPD in the centanafadine trials, the following patient demographic and clinical characteristics were included: age, sex, race, baseline AISRS (or ADHD-RS for lisdexamfetamine), baseline Clinical Global Impression-Severity of Illness Scale (CGI-S), and body mass index (BMI; for viloxazine ER only). For each comparison, baseline characteristics were reported for both active treatment and placebo arms, separately for the safety and efficacy populations. Descriptive statistics included frequencies and proportions for categorical variables and means and SDs for continuous variables. Wald tests (ie, chi-square tests for categorical variables and z-tests for continuous variables) were used for arm-by-arm comparisons (ie, active treatment vs active treatment and placebo vs placebo).

For the MAIC analyses, a model using the propensity score approach was used to estimate the likelihood (propensity) of enrollment in the comparator trials for each patient in the centanafadine trials. To develop weights, logistic regression models were created in which all available baseline prognostic factors and/or effect modifiers reported across comparator trials (ie, age, sex, race, baseline AISRS/ADHD-RS, baseline CGI-S, and BMI [for viloxazine ER only]) were considered for adjustment. Weights were generated separately for treatment arms and placebo arms and for the safety and efficacy populations. IPD from the centanafadine trials 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 centanafadine and each of the comparators before and after matching using anchored comparisons. Compared with unanchored MAICs in which active treatment arms are compared across trials, anchored MAICs compare the differences between the active treatments and a common comparator (ie, placebo in this study), thereby further adjusting for cross-trial heterogeneity.[25]

For the safety analyses, the risk difference (RD) between centanafadine and the respective comparators, along with the corresponding 95% CIs, was reported for each AE. For the efficacy analyses, the difference in change from baseline in AISRS (or ADHD-RS for lisdexamfetamine) score between centanafadine and the respective comparators was reported. Weighted Wald tests (ie, weighted chi-square tests for categorical outcomes and weighted z-tests for continuous outcomes) were used for comparisons.

Results

CENTANAFADINE VS LISDEXAMFETAMINE

Baseline Characteristics. The safety analyses of centanafadine vs lisdexamfetamine included 876 patients from the centanafadine trials (centanafadine: n=586; placebo: n=290) and 420 patients from the lisdexamfetamine trial (lisdexamfetamine: n=358; placebo: n=62). The efficacy analyses included 859 patients from the centanafadine trials (centanafadine: n=574; placebo: n=285) and 420 patients from the lisdexamfetamine trial (lisdexamfetamine: n=358; placebo: n=62) (Table 1).

Before matching, there were no significant differences in age, sex, and race across trials. Patients included in the centanafadine trials generally experienced less severe ADHD symptoms than those included in the lisdexamfetamine trial, with a lower mean AISRS/ADHD-RS score and a lower proportion of patients in the severe category of the CGI-S. After matching, baseline characteristics of patients were the same in both trials.

Safety and Efficacy. Overall, centanafadine had a better safety profile and lower efficacy compared with lisdexamfetamine (Figure 1). After matching and anchoring, compared with lisdexamfetamine at Week 4, centanafadine was associated with a lower risk of lack of appetite (RD in percentage points: 23.42), dry mouth (19.27), insomnia (15.35), anxiety (5.21), nausea (4.90), feeling jittery (3.70), and diarrhea (3.47) (all $P<0.05$). The difference in change in AISRS/ADHD-RS score from baseline to Week 4 for patients treated with centanafadine vs lisdexamfetamine was 6.58 points (95% CI=2.72-10.43; $P<0.05$), indicating a greater reduction in symptoms severity among patients treated with lisdexamfetamine. The arm-by-arm safety and efficacy outcomes before and after matching are presented in Supplementary Figure 1.

CENTANAFADINE VS ATOMOXETINE

Baseline Characteristics. The safety analyses of centanafadine vs atomoxetine included 876 patients from the centanafadine trials (centanafadine: n=586; placebo: n=290) and 501 patients from the atomoxetine trial (atomoxetine:

TABLE 1 Baseline Characteristics of Patients in the Centanafadine vs Lisdexamfetamine Analyses

Baseline characteristics	Comparator trial		Before matching				After matching[a]			
			Centanafadine trials		*P*[b]		Centanafadine trials		*P*[b,c]	
Safety analysis population										
	Lisdexamfetamine [A]	Placebo [B]	Centanafadine [C]	Placebo [D]	[C] vs [A]	[D] vs [B]	Centanafadine [E]	Placebo [F]	[E] vs [A]	[F] vs [B]
	(n = 358)	(n = 62)	(n = 586)	(n = 290)			(n = 586)	(n = 290)		
Age, mean ± SD, years	35.1 ± 10.2	35.2 ± 10.9	35.5 ± 10.0	35.3 ± 9.6	0.519	0.971	35.1 ± 10.2	35.2 ± 10.9	—	—
Sex, %										
Male	54.7	51.6	51.4	52.8	0.346	0.981	54.7	51.6	—	—
Female	45.3	48.4	48.6	47.2	0.346	0.981	45.3	48.4	—	—
Race, %										
White	84.1	77.4	79.2	81.4	0.076	0.589	84.1	77.4	—	—
AISRS/ADHD-RS at baseline, mean ± SD	40.9 ± 6.5	39.4 ± 6.4	38.9 ± 6.8	38.6 ± 6.9	<0.001[d]	0.378	40.9 ± 6.5	39.4 ± 6.4	—	—
CGI-S at baseline, %										
Moderate	32.1	43.5	49.0	51.0	<0.001[d]	0.352	32.1	43.5	—	—
Marked	54.5	40.3	46.4	46.2	0.020[d]	0.481	54.5	40.3	—	—
Severe	13.1	16.1	4.4	2.8	<0.001[d]	<0.001[d]	13.1	16.1	—	—
Extreme	0.3	0.0	0.0	0.0	0.379	1.000	0.0	0.0	—	—
Efficacy analysis population										
	Lisdexamfetamine [A]	Placebo [B]	Centanafadine [C]	Placebo [D]	[C] vs [A]	[D] vs [B]	Centanafadine [E]	Placebo [F]	[E] vs [A]	[F] vs [B]
	(n = 358)	(n = 62)	(n = 574)	(n = 285)			(n = 574)	(n = 285)		
Age, mean ± SD, years	35.1 ± 10.2	35.2 ± 10.9	35.6 ± 10.0	35.2 ± 9.7	0.500	1.000	35.1 ± 10.2	35.2 ± 10.9	—	—
Sex, %										
Male	54.7	51.6	51.4	51.9	0.352	1.000	54.7	51.6	—	—
Female	45.3	48.4	48.6	48.1	0.352	1.000	45.3	48.4	—	—
Race, %										
White	84.1	77.4	79.6	81.8	0.107	0.542	84.1	77.4	—	—
AISRS/ADHD-RS at baseline, mean ± SD	40.9 ± 6.5	39.4 ± 6.4	38.9 ± 6.8	38.6 ± 6.8	<0.001[d]	0.383	40.9 ± 6.5	39.4 ± 6.4	—	—
CGI-S at baseline, %										
Moderate	32.1	43.5	49.0	50.9	<0.001[d]	0.365	32.1	43.5	—	—
Marked	54.5	40.3	46.3	46.3	0.019[d]	0.472	54.5	40.3	—	—
Severe	13.1	16.1	4.5	2.8	<0.001[d]	<0.001[d]	13.1	16.1	—	—
Extreme	0.3	0.0	0.0	0.0	0.384	1.000	0.0	0.0	—	—

[a]*Analyses were matched on sex, race, age, AISRS/ADHD-RS at baseline, and CGI-S at baseline.*

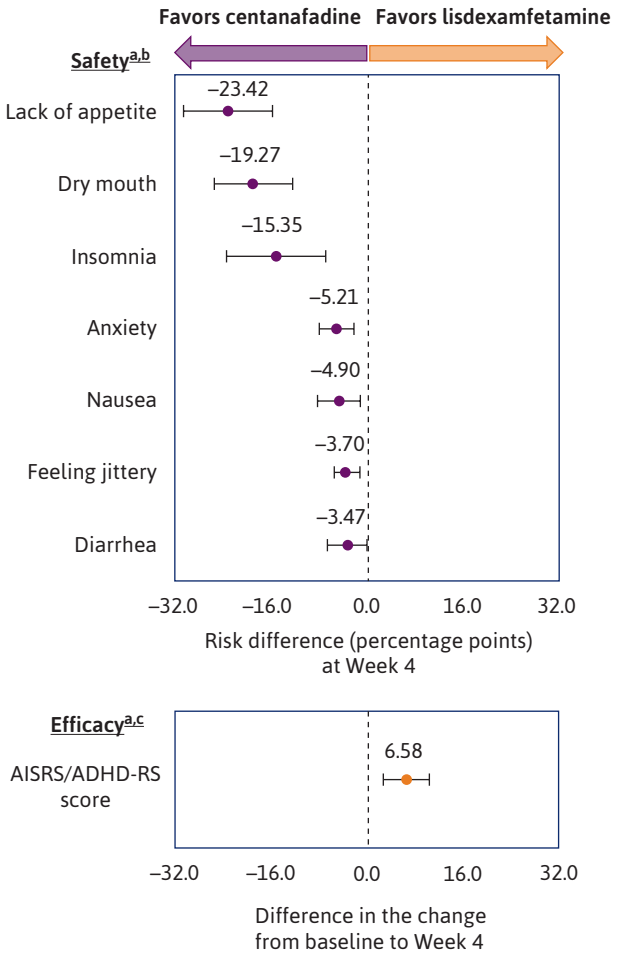
[b]*P values were calculated using the Wald test (ie, chi-square tests for categorical variables and z-tests for continuous variables).*

[c]*Dashes (—) indicate that P values could not be calculated because characteristics were exactly balanced between the centanafadine trials and the comparator trial.*

[d]*Significant at the 5% level.*

ADHD-RS = Attention-Deficit/Hyperactivity Disorder Rating Scale; AISRS = Adult ADHD Investigator Symptom Rating Scale; CGI-S = Clinical Global Impression-Severity of Illness Scale.

FIGURE 1 Comparisons of Safety and Efficacy Between Centanafadine and Lisdexamfetamine



Purple dots indicate that the comparison is significantly in favor of centanafadine at the 5% level. Orange dots indicate that the comparison is significantly in favor of lisdexamfetamine at the 5% level.

[a]*Analyses were matched on sex, race, age, AISRS/ADHD-RS at baseline, and CGI-S at baseline.*

[b]*Safety outcomes were rates of AEs for which information was available in both trials and for which the incidence was greater than or equal to 5% and twice that of placebo.*

[c]*The primary efficacy outcome instrument used in the lisdexamfetamine trial was the ADHD-RS, which contains the same number of questions (18 items), reviews the same symptoms, and is scored in the same way as the AISRS.*

ADHD-RS = Attention-Deficit/Hyperactivity Disorder Rating Scale; AE = adverse event; AISRS = Adult ADHD Investigator Symptom Rating Scale; CGI-S = Clinical Global Impression-Severity of Illness Scale.

n = 250; placebo: n = 251). The efficacy analyses included 859 patients from the centanafadine trials (centanafadine: n = 574; placebo: n = 285) and 501 patients from the atomoxetine trial (atomoxetine: n = 250; placebo: n = 251) (Table 2).

Before matching, sex and AISRS scores at baseline were not significantly different across trials. Patients included in the centanafadine trials had significantly lower mean CGI-S scores than those included in the atomoxetine trial. In addition, the proportion of White patients was significantly lower in the centanafadine trial. Age could not be compared because SD was not reported in the atomoxetine trial. After matching, baseline characteristics of patients were the same in both trials.

Safety and Efficacy. Centanafadine had an overall better safety profile than atomoxetine with no statistical difference in efficacy (Figure 2). After matching and anchoring, compared with atomoxetine at Week 10, centanafadine was associated with a lower risk of nausea (RD in percentage points: 18.64), dry mouth (17.44), fatigue (9.21), erectile dysfunction (6.76), lack of appetite (6.71), and urinary hesitation (5.84) (all $P < 0.05$); there was no statistically significant difference for dizziness, constipation, and irritability. Similar results were obtained in the sensitivity analysis comparing RD between centanafadine at Week 6 and atomoxetine at Week 10 (Supplementary Figure 2). The difference in change in AISRS score from baseline to Week 6 for centanafadine vs atomoxetine was not significant (2.02 points, 95% CI = –2.46 to 6.50; $P = 0.38$). The arm-by-arm safety and efficacy outcomes before and after matching are presented in Supplementary Figure 3.

CENTANAFADINE VS VILOXAZINE ER

Baseline Characteristics. The safety analyses of centanafadine vs viloxazine ER included 876 patients from the centanafadine trials (centanafadine: n = 586; placebo: n = 290) and 354 patients from the viloxazine ER trial (viloxazine ER: n = 175; placebo: n = 179). The efficacy analyses included 859 patients from the centanafadine trials (centanafadine: n = 574; placebo: n = 285) and 354 patients from the viloxazine ER trial (viloxazine ER: n = 175; placebo: n = 179) (Table 3).

Before matching, age, sex, race, AISRS score, CGI-S score, and BMI were not significantly different across trials; baseline characteristics of patients were the same in both trials after matching.

Safety and Efficacy. Centanafadine had an overall better safety profile than viloxazine ER with no statistical difference in efficacy (Figure 3). After matching and anchoring, compared with viloxazine ER at Week 6, centanafadine was associated with a lower risk of fatigue (RD in percentage points: 11.07), insomnia (10.67), nausea (7.57), and constipation (4.63) (all $P < 0.05$); no statistically significant differences were found for headache, dry mouth, and

TABLE 2 Baseline Characteristics of Patients in the Centanafadine vs Atomoxetine Analyses

Baseline characteristics	Comparator trial[a]		Before matching				After matching[b]			
			Centanafadine trials		*P*[c,d]		Centanafadine trials		*P*[c,e]	
Safety analysis population										
	Atomoxetine [A]	Placebo [B]	Centanafadine [C]	Placebo [D]	[C] vs [A]	[D] vs [B]	Centanafadine [E]	Placebo [F]	[E] vs [A]	[F] vs [B]
	(n = 250)	(n = 251)	(n = 586)	(n = 290)			(n = 586)	(n = 290)		
Age, mean ± SD, years	37.6 ± —	37.6 ± —	35.5 ± 10.0	35.3 ± 9.6	—	—	37.6 ± 10.2	37.6 ± 9.4	—	—
Sex, %										
Male	50.0	50.0	51.4	52.8	0.775	0.580	50.0	50.0	—	—
Female	50.0	50.0	48.6	47.2	0.775	0.580	50.0	50.0	—	—
Race, %										
White	87.9	87.9	79.2	81.4	0.004[f]	0.049[f]	87.9	87.9	—	—
AISRS at baseline, mean ± SD	38.5 ± 7.4	39.2 ± 7.5	38.9 ± 6.8	38.6 ± 6.9	0.477	0.335	38.5 ± 7.4	39.2 ± 7.5	—	—
CGI-S at baseline, mean ± SD	4.7 ± 0.7	4.7 ± 0.6	4.5 ± 0.6	4.5 ± 0.6	0.003[f]	<0.001[f]	4.7 ± 0.7	4.7 ± 0.6	—	—
Efficacy analysis population										
	Atomoxetine [A]	Placebo [B]	Centanafadine [C]	Placebo [D]	[C] vs [A]	[D] vs [B]	Centanafadine [E]	Placebo [F]	[E] vs [A]	[F] vs [B]
	(n = 250)	(n = 251)	(n = 574)	(n = 285)			(n = 574)	(n = 285)		
Age, mean ± SD, years	37.6 ± —	37.6 ± —	35.6 ± 10.0	35.2 ± 9.6	—	—	37.6 ± 10.2	37.6 ± 9.4	—	—
Sex, %										
Male	50.0	50.0	51.4	51.9	0.770	0.719	50.0	50.0	—	—
Female	50.0	50.0	48.6	48.1	0.770	0.719	50.0	50.0	—	—
Race, %										
White	87.9	87.9	79.6	81.8	0.006[f]	0.065	87.9	87.9	—	—
AISRS at baseline, mean ± SD	38.5 ± 7.4	39.2 ± 7.5	38.9 ± 6.8	38.6 ± 6.8	0.433	0.341	38.5 ± 7.4	39.2 ± 7.5	—	—
CGI-S at baseline, mean ± SD	4.7 ± 0.7	4.7 ± 0.6	4.5 ± 0.6	4.5 ± 0.6	0.003[f]	<0.001[f]	4.7 ± 0.7	4.7 ± 0.6	—	—

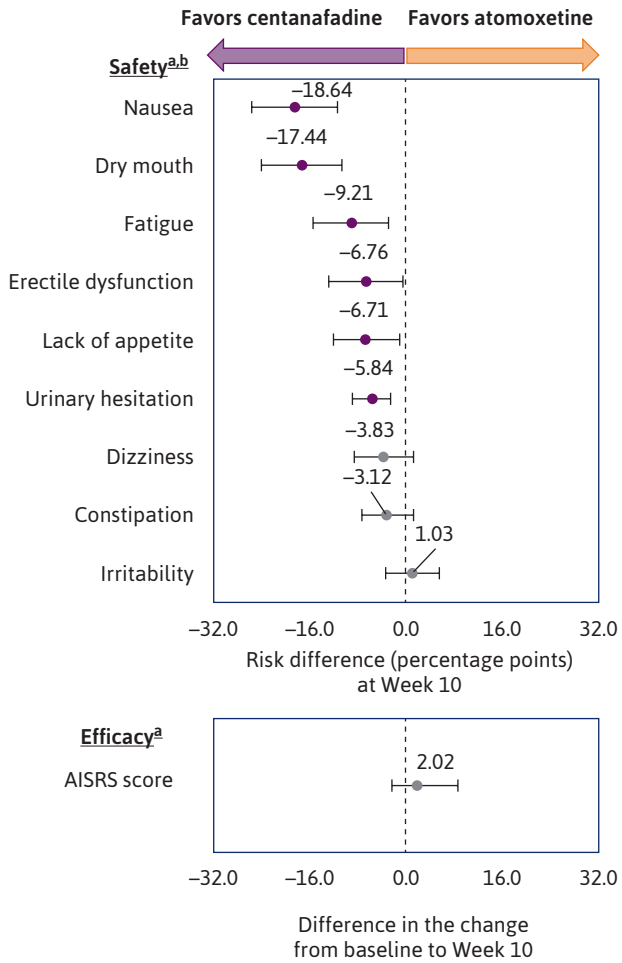
[a]*Dashes (—) indicate that SDs were not reported.*
[b]*Analyses were matched on sex, race, age, AISRS at baseline, and CGI-S at baseline.*
[c]*P values were calculated using the Wald test (ie, chi-square tests for categorical variables and z-tests for continuous variables).*
[d]*Dashes (—) indicate that P values could not be calculated because SDs were not reported for the comparator trial.*
[e]*Dashes (—) indicate that P values could not be calculated because characteristics were exactly balanced between the centanafadine trials and the comparator trial.*
[f]*Significant at the 5% level.*
AISRS = Adult ADHD Investigator Symptom Rating Scale; CGI-S = Clinical Global Impression-Severity of Illness Scale.

lack of appetite. The difference in change in AISRS score from baseline to Week 6 for centanafadine vs viloxazine ER was not significant (0.90 points, 95% CI = −2.17 to 3.97; P = 0.57). The arm-by-arm safety and efficacy outcomes before and after matching are presented in Supplementary Figure 4.

Discussion

In the absence of head-to-head trials, an MAIC provides useful insights on the comparative safety and efficacy of different treatments across balanced patient populations.[19] In the current anchored MAIC using IPD from trials

FIGURE 2 Comparisons of Safety and Efficacy Between Centanafadine and Atomoxetine



Purple dots indicate that the comparison is significantly in favor of centanafadine at the 5% level. Gray dots indicate nonsignificance.

[a]*Analyses were matched on sex, race, age, AISRS at baseline, and CGI-S at baseline.*

[b]*Safety outcomes were rates of AEs for which information was available in both trials and for which the incidence was greater than or equal to 5% and twice that of placebo. Outcomes for centanafadine were forecasted at Week 10 based on the polynomial extrapolation of the data observed from Week 1 to Week 6.*

AE = adverse event; AISRS = Adult ADHD Investigator Symptom Rating Scale; CGI-S = Clinical Global Impression-Severity of Illness Scale.

of centanafadine, an investigational drug for adults with ADHD, centanafadine showed a significantly better short-term safety profile with significantly lower incidence of several AEs than all 3 comparators, including the stimulant lisdexamfetamine and the nonstimulants atomoxetine and viloxazine ER. Efficacy of centanafadine was statistically lower than that of lisdexamfetamine and not statistically different compared with atomoxetine and viloxazine ER.

Understanding the trade-off between safety and efficacy requires interpreting the magnitude of the safety and efficacy differences. The meaningfulness of safety differences depends on the magnitude of the differences between AE rates and the burden associated with each AE. The clinical meaningfulness of the efficacy differences may be more challenging to interpret, especially when the instruments for measuring efficacy are not widely used in clinical practice. Based on existing evidence, the clinical implications of the statistically significant difference in efficacy between centanafadine and lisdexamfetamine in adults with ADHD appear unclear. Spencer et al validated the AISRS using data from an atomoxetine trial in adults with ADHD (NCT00190736; a comparator in the current study) and found that the between-treatment minimal clinically important difference (MCID) for the AISRS score was 10.1 points.[33] Zhang et al reported that the between-treatment MCID for the ADHD-RS-IV score was 6.6 points[34]; however, the study by Zhang et al was performed in children and adolescents with ADHD, and the finding may not be generalizable to adults. Goodman et al compared the scores of ADHD-RS and CGI-S from an adult lisdexamfetamine trial (NCT00334880; a comparator in the current study) using equipercentile linking (ie, a method that identifies scores on 2 measures that have the same percentile rank, irrespective of which patients had particular scores on either measure).[35] They found that a change in baseline ADHD-RS score of 8-10 points in adults with ADHD corresponded to a change of one CGI-S level, which is the smallest unit for a clinically detectable response to treatment. Based on the above studies, it appears that a 6.58-point difference in AISRS/ADHD-RS scores between centanafadine and lisdexamfetamine may not reach the MCID threshold in adults with ADHD; nonetheless, the potential difference in the clinical efficacy of the 2 treatments should be further explored.

Regarding safety, this MAIC found that the incremental risk of acute or subacute AEs relative to placebo was generally smaller for centanafadine than for the respective comparators. To put the differences of safety outcomes into perspective, for instance, for every 100 adults treated for ADHD, 15 fewer patients treated with centanafadine vs lisdexamfetamine would experience insomnia after 4 weeks, 19 fewer patients treated with centanafadine vs atomoxetine would experience nausea after 10 weeks, and 11 fewer patients treated with centanafadine vs viloxazine ER would experience fatigue after 6 weeks. As an example, to help interpret the magnitude

TABLE 3 Baseline Characteristics of Patients in the Centanafadine vs Viloxazine ER Analyses

Baseline characteristics	Comparator trial	Before matching				After matching[a]			
		Centanafadine trials		*P*[b]		Centanafadine trials		*P*[b,c]	
Safety analysis population									
	Viloxazine ER [A]	Placebo [B]	Centanafadine [C]	Placebo [D]	[C] vs [A]	[D] vs [B]	Centanafadine [E]	Placebo [F]	[E] vs [A]	[F] vs [B]
	(n = 175)	(n = 179)	(n = 586)	(n = 290)			(n = 586)	(n = 290)		
Age, mean ± SD, years	34.1 ± 10.2	35.4 ± 10.0	35.5 ± 10.0	35.3 ± 9.6	0.100	0.877	34.1 ± 10.2	35.4 ± 10.0	—	—
Sex, %										
Male	56.0	53.6	51.4	52.8	0.322	0.929	56.0	53.6	—	—
Female	44.0	46.4	48.6	47.2	0.322	0.929	44.0	46.4	—	—
Race, %										
White	81.1	76.0	79.2	81.4	0.647	0.199	81.1	76.0	—	—
AISRS at baseline, mean ± SD	38.5 ± 6.6	37.6 ± 6.6	38.9 ± 6.8	38.6 ± 6.9	0.495	0.118	38.5 ± 6.6	37.6 ± 6.6	—	—
CGI-S at baseline, mean ± SD	4.6 ± 0.7	4.6 ± 0.6	4.5 ± 0.6	4.5 ± 0.6	0.329	0.135	4.6 ± 0.7	4.6 ± 0.6	—	—
BMI, mean ± SD, kg/m^2	27.3 ± 4.6	26.9 ± 4.6	28.1 ± 5.3	27.5 ± 5.3	0.061	0.211	27.3 ± 4.6	26.9 ± 4.6		
Efficacy analysis population										
	Viloxazine ER [A]	Placebo [B]	Centanafadine [C]	Placebo [D]	[C] vs [A]	[D] vs [B]	Centanafadine [E]	Placebo [F]	[E] vs [A]	[F] vs [B]
	(n = 175)	(n = 179)	(n = 574)	(n = 285)			(n = 574)	(n = 285)		
Age, mean ± SD, years	34.1 ± 10.2	35.4 ±10.0	35.6 ± 10.0	35.2 ± 9.6	0.096	0.832	34.1 ± 10.2	35.4 ± 10.0	—	—
Sex, %										
Male	56.0	53.6	51.4	51.9	0.326	0.793	56.0	53.6	—	—
Female	44.0	46.4	48.6	48.1	0.326	0.793	44.0	46.4	—	—
Race, %										
White	81.1	76.0	79.6	81.8	0.739	0.167	81.1	76.0	—	—
AISRS at baseline, mean ± SD	38.5 ± 6.6	37.6 ± 6.6	38.9 ± 6.8	38.6 ± 6.9	0.452	0.115	38.5 ± 6.6	37.6 ± 6.6	—	—
CGI-S at baseline, mean ± SD	4.6 ± 0.7	4.6 ± 0.6	4.5 ± 0.6	4.5 ± 0.6	0.339	0.146	4.6 ± 0.7	4.6 ± 0.6	—	—
BMI, mean ± SD, kg/m^2	27.3 ± 4.6	26.9 ± 4.6	28.1 ± 5.3	27.5 ± 5.2	0.050	0.188	27.3 ± 4.6	26.9 ± 4.6		

[a] *Analyses were matched on sex, race, age, AISRS at baseline, CGI-S at baseline, and BMI.*

[b] *P values were calculated using the Wald test (ie, chi-square tests for categorical variables and z-tests for continuous variables).*

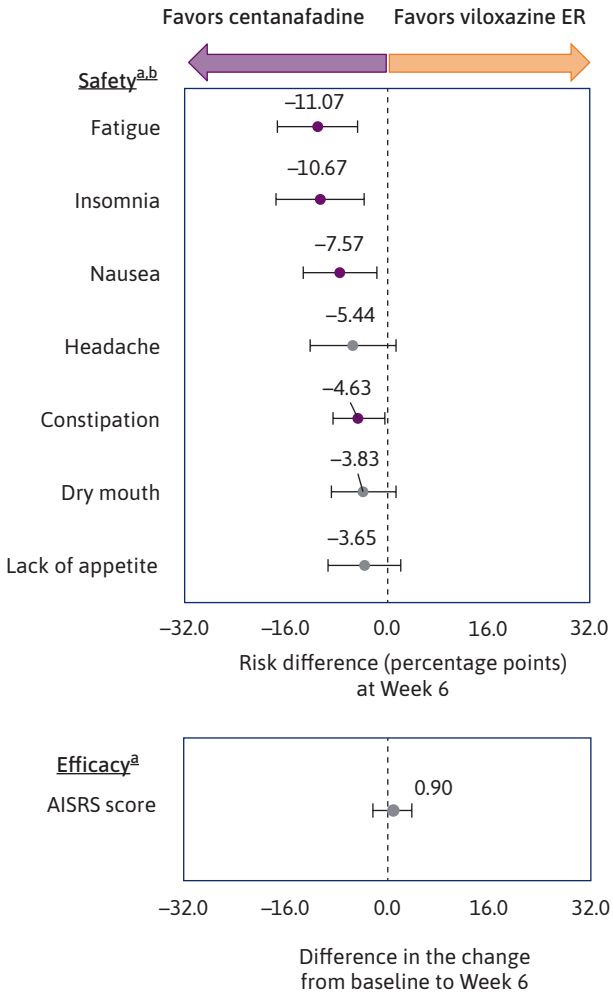
[c] *Dashes (—) indicate that P values could not be calculated because characteristics were exactly balanced between the centanafadine trials and the comparator trial.*

AISRS = Adult ADHD Investigator Symptom Rating Scale; BMI = body mass index; CGI-S = Clinical Global Impression-Severity of Illness Scale; ER = extended-release.

of the risk differences reported in Figure 1, Supplementary Figure 5 illustrates the incremental risk of AEs compared with placebo for centanafadine and lisdexamfetamine. Prior systematic reviews and pooled analyses of lisdexamfetamine and atomoxetine have found sustained efficacy and similar safety profiles in long-term vs short-term studies.[36-38] As data become available, future MAICs comparing longer-term outcomes of centanafadine vs these medications are warranted.

It is notable that in addition to considering improvements in core symptoms and risk of AEs, treatment selection for

FIGURE 3 Comparisons of Safety and Efficacy Between Centanafadine and Viloxazine ER



Purple dots indicate that the comparison is significantly in favor of centanafadine at the 5% level. Gray dots indicate nonsignificance.

[a]*Analyses were matched on sex, race, age, AISRS at baseline, CGI-S at baseline, and BMI.*

[b]*Safety outcomes were rates of AEs for which information was available in both trials and for which the incidence was greater than or equal to 5% and twice that of placebo.*

AE = adverse event; AISRS = Adult ADHD Investigator Symptom Rating Scale; BMI = body mass index; CGI-S = Clinical Global Impression-Severity of Illness Scale; ER = extended-release.

patients with ADHD should also account for factors such as duration of treatment effect, abuse potential, convenience, cost, impact on quality of life, and comorbidities.[39] Nevertheless, the overall better short-term safety profile of centanafadine found in this study based on the rates of acute or subacute AEs reported in clinical trials could have important implications on adults with ADHD, as prior research has suggested that the number of symptoms associated with ADHD/treatment-related AEs is significantly correlated with increased activity impairment, reduced employment and work productivity, and decreased health-related quality of life.[40] Furthermore, AEs can be expensive to treat and may also trigger treatment changes such as discontinuation,[41] which may further add to the ADHD management costs.[42]

With the exception of viloxazine ER,[17] there have been no new treatment options for adults with ADHD in the United States for more than a decade[43,44] and ADHD often remains untreated among adult patients.[1,45] In addition, of those receiving medications, a large proportion cycle through multiple regimens within a short time.[42] Poor treatment adherence and low persistence remain ongoing challenges in ADHD management, with suboptimal efficacy and AEs often underlying these issues.[41,42,46] In this context, understanding patient and physician preferences regarding treatment attributes (eg, trade-off between safety and efficacy of medications) is warranted to better inform treatment decisions. Furthermore, the provision of safe and effective treatment to patients with ADHD can also have an important impact at the societal level considering the substantial economic burden associated with ADHD in the United States.[47] Although future studies are needed to assess real-world outcomes associated with these treatment options as data become available, based on clinical trial data, centanafadine shows a better short-term safety profile than 3 of the 3 comparators and comparable efficacy with 2 of the 3 comparators. These treatment attributes suggest that centanafadine may have the potential to alleviate some of the unmet needs associated with existing treatment options for adults with ADHD.

LIMITATIONS

This analysis is associated with some limitations. First, matching on baseline characteristics was only possible when variables were collected across trials; however, there might be other differences in characteristics that were unobserved, such as comorbidities and concomitant medications. Second, although the inclusion and exclusion criteria were overall consistent across trials, there were minor differences in the specific definitions of the criteria used across trials (eg, specific definition of ADHD, cardiac health criteria, and prohibited medications) that could not be accounted for. Third, the centanafadine trial measured efficacy using the AISRS, whereas the lisdexamfetamine trial measured efficacy using the ADHD-RS. Although these instruments are highly similar, differences in measurements may have occurred because of variations in wording and interpretation. Consequently,

the estimated difference in efficacy between centanafadine and lisdexamfetamine should be interpreted with caution. Differences in other trial design components (eg, placebo lead-in in the centanafadine trials, study duration, and treatment allocation ratios) could also have an impact on the study outcomes; for instance, the placebo lead-in design in the centanafadine trials excluded placebo responders from the double-blind phase, which may have affected the comparisons of efficacy outcomes in this study. Fourth, the assessment of safety outcomes was limited to rates of AEs that were reported in both trials of a given comparison and reported by at least 5% of patients in any treatment group with an incidence twice that of placebo. As such, information not reported in both trials (eg, rates of rare AEs, severity of AEs, AEs that were reported in only one of the trials in comparison, and long-term AEs and safety) could not be considered. Finally, given the reweighting was conducted to match the populations in the centanafadine trials to those in the respective comparator trials, the target population of this MAIC would more closely represent the populations included in the comparator trials than those in the centanafadine trials; therefore, generalizability to a broader or different population may be limited. Of note, all studied trials excluded patients who had psychiatric comorbidities; thus, the current analyses could not compare the efficacy and safety outcomes among adult patients with ADHD and concurrent psychiatric disorders. Meanwhile, the vast majority of patients included in the ADHD clinical trials were of White race; hence, the results may not be generalizable to other racial and ethical populations. As racial disparities in ADHD diagnosis, treatment, and access to care have been recognized in the United States,[48,49] future clinical trials and research should address this issue by including more diverse populations.

Conclusions

In an anchored indirect comparison using propensity score weighting, centanafadine showed a better short-term safety profile than lisdexamfetamine, atomoxetine, and viloxazine ER, as evidenced by a significantly lower incidence of several AEs. Efficacy of centanafadine, as measured by validated instruments, was statistically lower than lisdexamfetamine and nondifferent from atomoxetine and viloxazine ER. Considering its safety and efficacy profile, centanafadine may be a promising treatment option for adults with ADHD, with the potential to alleviate some of the current unmet needs in ADHD management. Future studies are warranted to better understand how the trade-off between safety and efficacy affects management in clinical practice and patient preferences for treatment.

DISCLOSURES

This study was funded by Otsuka Pharmaceutical Development & Commercialization, Inc. The study sponsor was involved in several aspects of the research, including the study design, interpretation of data, writing of the manuscript, and decision to submit the manuscript for publication.

Dr Schein is an employee of Otsuka Pharmaceutical Development & Commercialization, Inc. Mr Cloutier, Dr Gauthier-Loiselle, Dr Catillon, Ms Xu, and Ms Chan are employees of Analysis Group, Inc., a consulting company that has provided paid consulting services to Otsuka Pharmaceutical Development & Commercialization, Inc. Dr Childress received research support from Allergan, Emalex, Akili, Cingulate, Corium, Lumos, Neurocentria, Otsuka, Purdue, Adlon, Sunovion, Tris, KemPharm, and Supernus; was on the advisory board of Corium, Otsuka, Tris, and Supernus; received consulting fees from Aytu, Cingulate, Corium, Lumos, Neurocentria, Noven, Otsuka, Tris, KemPharm, Supernus, and Tulex; received speaker fees from Takeda, Corium, Ironshore, Tris, and Supernus; and received writing support from Takeda, Corium, Ironshore, Purdue, and Tris.

ACKNOWLEDGMENTS

Medical writing assistance was provided by professional medical writer, Flora Chik, PhD, MWC, an employee of Analysis Group, Inc., and was funded by Otsuka Pharmaceutical Development & Commercialization, Inc.

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

REFERENCES

1. Faraone SV, Asherson P, Banaschewski T, et al. Attention-deficit/hyperactivity disorder. *Nat Rev Dis Primers*. 2015;1(1):15020. doi:10.1038/nrdp.2015.20

2. Kessler RC, Adler L, Barkley R, et al. The prevalence and correlates of adult ADHD in the United States: Results from the National Comorbidity Survey Replication. *Am J Psychiatry*. 2006;163(4):716-23. doi:10.1176/ajp.2006.163.4.716

3. Kessler RC, Berglund P, Demler O, Jin R, Merikangas KR, Walters EE. Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. *Arch Gen Psychiatry*. 2005;62(6):593-602. doi:10.1001/archpsyc.62.6.593

4. National Institute of Mental Health (NIMH). Attention-Deficit/Hyperactivity Disorder. Accessed March 23, 2023. https://www.nimh.nih.gov/health/topics/attention-deficit-hyperactivity-disorder-adhd

5. Posner J, Polanczyk GV, Sonuga-Barke E. Attention-deficit hyperactivity disorder. *Lancet*. 2020;395(10222):450-62. doi:10.1016/S0140-6736(19)33004-1

6. Biederman J, Monuteaux MC, Mick E, et al. Young adult outcome of attention deficit hyperactivity disorder: A controlled 10-year follow-up study. *Psychol Med*. 2006;36(2):167-79. doi:10.1017/S0033291705006410

7. Biederman J, Faraone SV. The effects of attention-deficit/hyperactivity disorder on employment and household income. *MedGenMed*. 2006;8(3):12.

REFERENCES *continued*

8. Charach A, Yeung E, Climans T, Lillie E. Childhood attention-deficit/hyperactivity disorder and future substance use disorders: Comparative meta-analyses. *J Am Acad Child Adolesc Psychiatry*. 2011;50(1):9-21. doi:10.1016/j.jaac.2010.09.019

9. Mohr-Jensen C, Steinhausen HC. A meta-analysis and systematic review of the risks associated with childhood attention-deficit hyperactivity disorder on long-term outcome of arrests, convictions, and incarcerations. *Clin Psychol Rev*. 2016;48:32-42. doi:10.1016/j.cpr.2016.05.002

10. Agarwal R, Goldenberg M, Perry R, IsHak WW. The quality of life of adults with attention deficit hyperactivity disorder: A systematic review. *Innov Clin Neurosci*. 2012;9(5-6):10-21.

11. Cortese S, Adamo N, Del Giovane C, et al. Comparative efficacy and tolerability of medications for attention-deficit hyperactivity disorder in children, adolescents, and adults: A systematic review and network meta-analysis. *Lancet Psychiatry*. 2018;5(9):727-38. doi:10.1016/S2215-0366(18)30269-4

12. Geffen J, Forster K. Treatment of adult ADHD: A clinical perspective. *Ther Adv Psychopharmacol*. 2018;8(1):25-32. doi:10.1177/2045125317734977

13. Vyvanse (lisdexamfetamine dimesylate). Prescribing information. Takeda Pharmaceuticals America, Inc.; January 2022.

14. Strattera (atomoxetine). Prescribing information. Lilly USA, LLC; February 2020.

15. Children and Adults with Attention-Deficit/Hyperactivity Disorder (CHADD). Medication Management. Accessed March 23, 2023. https://chadd.org/for-parents/managing-medication/

16. Qelbree (viloxazine extended-release capsules). Prescribing information. Supernus Pharmaceuticals, Inc.; April 2022.

17. Supernus Announces FDA Approval of Qelbree for the Treatment of ADHD in Adults. April 29, 2022, https://ir.supernus.com/node/12951/pdf

18. Adler LA, Adams J, Madera-McDonough J, et al. Efficacy, safety, and tolerability of centanafadine sustained-release tablets in adults with attention-deficit/hyperactivity disorder: Results of 2 phase 3, randomized, double-blind, multicenter, placebo-controlled trials. *J Clin Psychopharmacol*. 2022;42(5):429-39. doi:10.1097/jcp.0000000000001575

19. Signorovitch JE, Sikirica V, Erder MH, et al. Matching-adjusted indirect comparisons: A new tool for timely comparative effectiveness research. *Value Health*. 2012;15(6):940-7. doi:10.1016/j.jval.2012.05.004

20. Cheng D, Ayyagari R, Signorovitch J. The statistical performance of matching-adjusted indirect comparisons: Estimating treatment effects with aggregate external control data. *Ann Appl Stat*. 2020;14(4):1806-33, 28.

21. Signorovitch J, Diels J, Van Sanden S, et al. Matching-adjusted indirect comparison (MAIC) results confirmed by head-to-head trials: A case study in psoriasis. *J Dermatolog Treat*. 2023;34(1):2169574. doi:10.1080/09546634.2023.2169574

22. Douglas RS, Dailey R, Subramanian PS, et al. Proptosis and diplopia response with teprotumumab and placebo vs the recommended treatment regimen with intravenous methylprednisolone in moderate to severe thyroid eye disease: A meta-analysis and matching-adjusted indirect comparison. *JAMA Ophthalmol*. 2022;140(4):328-35. doi:10.1001/jamaophthalmol.2021.6284

23. Halmos B, Burke T, Kalyvas C, Vandormael K, Frederickson A, Piperdi B. Pembrolizumab+chemotherapy versus atezolizumab+chemotherapy+/-bevacizumab for the first-line treatment of non-squamous NSCLC: A matching-adjusted indirect comparison. *Lung Cancer*. 2021;155:175-82. doi:10.1016/j.lungcan.2021.03.020

24. Sikirica V, Findling RL, Signorovitch J, et al. Comparative efficacy of guanfacine extended release versus atomoxetine for the treatment of attention-deficit/hyperactivity disorder in children and adolescents: Applying matching-adjusted indirect comparison methodology. *CNS Drugs*. 2013;27(11):943-53. doi:10.1007/s40263-013-0102-x

25. Phillippo DM, Ades AE, Dias S, Palmer S, Abrams KR, Welton NJ. *NICE DSU Technical Support Document 18: Methods for population-adjusted indirect comparisons in submission to NICE*. 2016. http://www.nicedsu.org.uk

26. Haute Autorité de Santé (HAS). *Indirect comparisons Methods and validity*. 2009. https://www.has-sante.fr/upload/docs/application/pdf/2011-02/summary_report__indirect_comparisons_methods_and_validity_january_2011_2.pdf

27. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWiG). *General Methods Version 6.1*. 2022. https://www.iqwig.de/en/methods/methods-paper.3020.html

28. Canadian Agency for Drugs and Technologies in Health (CADTH). *Indirect Evidence: Indirect Treatment Comparisons in Meta-Analysis*. 2009. https://www.cadth.ca/sites/default/files/pdf/H0462_itc_tr_e.pdf

29. Adler LA, Goodman DW, Kollins SH, et al; 303 Study Group. Double-blind, placebo-controlled study of the efficacy and safety of lisdexamfetamine dimesylate in adults with attention-deficit/hyperactivity disorder. *J Clin Psychiatry*. 2008;69(9):1364-73. doi:10.4088/JCP.v69n0903

30. Adler LA, Spencer T, Brown TE, et al. Once-daily atomoxetine for adult attention-deficit/hyperactivity disorder: A 6-month, double-blind trial. *J Clin Psychopharmacol*. 2009;29(1):44-50. doi:10.1097/JCP.0b013e318192e4a0

31. Nasser A, Hull JT, Chaturvedi SA, et al. A phase III, randomized, double-blind, placebo-controlled trial assessing the efficacy and safety of viloxazine extended-release capsules in adults with attention-deficit/hyperactivity disorder. *CNS Drugs*. 2022;36(8):897-915. doi:10.1007/s40263-022-00938-w

REFERENCES *continued*

32. DuPaul GJ, Power TJ, Anastopoulos AD, Reid R. *ADHD Rating Scale-IV: Checklists, Norms, and Clinical Interpretation*. 1998. doi:10.1177/0734282905285792

33. Spencer TJ, Adler LA, Meihua Qiao, et al. Validation of the adult ADHD investigator symptom rating scale (AISRS). *J Atten Disord*. 2010;14(1):57-68. doi:10.1177/1087054709347435

34. Zhang S, Faries DE, Vowles M, Michelson D. ADHD Rating Scale IV: Psychometric properties from a multinational study as a clinician-administered instrument. *Int J Methods Psychiatr Res*. 2005;14(4):186-201. doi:10.1002/mpr.7

35. Goodman D, Faraone SV, Adler LA, et al. Interpreting ADHD rating scale scores: Linking ADHD rating scale scores and CGI levels in two randomized controlled trials of lisdexamfetamine dimesylate in ADHD. *Primary Psychiatry*. 2010;17(3):44-52.

36. Asherson P, Bushe C, Saylor K, Tanaka Y, Deberdt W, Upadhyaya H. Efficacy of atomoxetine in adults with attention deficit hyperactivity disorder: An integrated analysis of the complete database of multicenter placebo-controlled trials. *J Psychopharmacol*. 2014;28(9):837-46. doi:10.1177/0269881114542453

37. Fredriksen M, Halmøy A, Faraone SV, Haavik J. Long-term efficacy and safety of treatment with stimulants and atomoxetine in adult ADHD: A review of controlled and naturalistic studies. *Eur Neuropsychopharmacol*. 2013;23(6):508-27. doi:10.1016/j.euroneuro.2012.07.016

38. Coghill DR, Caballero B, Sorooshian S, Civil R. A systematic review of the safety of lisdexamfetamine dimesylate. *CNS Drugs*. 2014;28(6):497-511. doi:10.1007/s40263-014-0166-2

39. Caye A, Swanson JM, Coghill D, Rohde LA. Treatment strategies for ADHD: An evidence-based guide to select optimal treatment. *Mol Psychiatry*. 2019;24(3): 390-408. doi:10.1038/s41380-018-0116-3

40. Schein J, Cloutier M, Gauthier-Loiselle M, Bungay R, Guerin A, Childress A. Symptoms associated with ADHD/treatment-related adverse side effects and their impact on quality of life and work productivity in adults with ADHD. *Curr Med Res Opin*. 2023;39(1):149-59. doi:10.1080/03007995.2022.2122228

41. Gajria K, Lu M, Sikirica V, et al. Adherence, persistence, and medication discontinuation in patients with attention-deficit/hyperactivity disorder - A systematic literature review. *Neuropsychiatr Dis Treat*. 2014;10:1543-69. doi:10.2147/NDT.S65721

42. Schein J, Childress A, Adams J, et al. Treatment patterns among adults with attention-deficit/hyperactivity disorder in the United States: A retrospective claims study. *Curr Med Res Opin*. 2021;37(11): 2007-14. doi:10.1080/03007995.2021.1968814

43. Centers for Disease Control and Prevention (CDC). ADHD Throughout the Years. National Center on Birth Defects and Developmental Disabilities. Updated August 9, 2022. Accessed March 28, 2023. https://www.cdc.gov/ncbddd/adhd/timeline.html

44. US Food and Drug Administration (FDA). Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations. Accessed March 28, 2023. https://www.accessdata.fda.gov/scripts/cder/ob/index.cfm

45. Ginsberg Y, Quintero J, Anand E, Casillas M, Upadhyaya HP. Underdiagnosis of attention-deficit/hyperactivity disorder in adult patients: A review of the literature. *Prim Care Companion CNS Disord*. 2014;16(3):PCC.13r01600. doi:10.4088/PCC.13r01600

46. Mattingly GW, Wilson J, Rostain AL. A clinician's guide to ADHD treatment options. *Postgrad Med*. 2017;129(7):657-66. doi:10.1080/00325481.2017.1354648

47. Schein J, Adler LA, Childress A, et al. Economic burden of attention-deficit/hyperactivity disorder among adults in the United States: A societal perspective. *J Manag Care Spec Pharm*. 2022;28(2): 168-79. doi:10.18553/jmcp.2021.21290

48. Shi Y, Hunter Guevara LR, Dykhoff HJ, et al. Racial disparities in diagnosis of attention-deficit/hyperactivity disorder in a US national birth cohort. *JAMA Netw Open*. 2021;4(3):e210321. doi:10.1001/jamanetworkopen.2021.0321

49. Yang KG, Flores MW, Carson NJ, Cook BL. Racial and ethnic disparities in childhood ADHD treatment access and utilization: Results from a national study. *Psychiatr Serv*. 2022;73(12):1338-45. doi:10.1176/appi.ps.202100578