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Effectiveness and safety of dexamphetamine sulfate (Attentin®) in the routine treatment of children and adolescents with ADHD: results from a 12-month non-interventional study

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Abstract

Background: Randomized controlled trials have shown that dexamphetamine sulfate (DEX) is efficacious in the treatment of attention-deficit/hyperactivity disorder (ADHD) in children and adolescents; however, data on the effectiveness and safety of DEX in routine practice are scarce.
Objective: This study investigated the long-term effectiveness and safety of Attentin® (immediate-release DEX) in children and adolescents with ADHD in routine practice.
Methods: ATTENTION was a multicenter, prospective, observational, non-interventional study that enrolled pediatric patients with ADHD (aged 6-17 years) with a clinically inadequate response to previous methylphenidate (MPH) treatment. Patients were assessed at baseline and two follow-up visits after approx. 6 and 12 months of DEX treatment. The primary endpoint was the investigator-rated ADHD rating scale IV (ADHD-RS-IV) total score change from baseline to the first follow-up visit.
Results: The study enrolled 140 patients (mean age: 11.2 years). Significant reductions in ADHD-RS-IV total scores were observed in the titration phase and were maintained up to the second follow-up visit. The mean ADHD-RS-IV total score change from baseline to the first follow-up visit was -11.9 (27.1 vs. 13.4, $p < .001$). Beneficial effects of DEX were observed on both ADHD-RS-IV subscales ('hyperactivity/impulsivity' and 'inattention') and in both children and adolescents. Clinical response, defined as a reduction in the ADHD-RS-IV total score of at least 30% at the first follow-up visit, was observed in 78.1% of patients. Patients reported an average onset of action of 36.2 minutes and an average duration of action of 6.5 hours after intake of the first dose of DEX in the morning. DEX was well tolerated. Small significant increases in mean systolic and diastolic blood pressure compared to baseline were observed.
Conclusions: Attentin® is an effective and well-tolerated long-term treatment for pediatric ADHD patients with a clinically inadequate response to previous MPH treatment.

Keywords: ADHD, dexamphetamine, children, adolescents

Introduction

Attention-deficit/hyperactivity disorder (ADHD) is one of the most common neurodevelopmental disorders of childhood, with an estimated worldwide prevalence of 7.2% in children ≤18 years (1). According to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), ADHD is characterized by the core symptoms of inattention, hyperactivity and impulsivity that negatively impact social and academic/occupational functioning (2). The International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10) refers to ADHD as Hyperkinetic Disorder and provides generally similar but stricter criteria for the diagnosis of the disorder (3).

Current practice guidelines recommend a comprehensive multimodal treatment approach for the management of ADHD (4-7). Stimulants, including methylphenidate (MPH) and amphetamines (AMP), are the most commonly used

pharmacological treatment. Numerous randomized controlled trials (RCTs) and meta-analyses have demonstrated the efficacy and safety of stimulants for the treatment of ADHD in children and adolescents (8-12).

The exact mechanism of action of stimulants in humans with ADHD is not fully known, however, it is thought that both MPH and AMP increase levels of extracellular dopamine (DA) and norepinephrine (NE) in the synaptic cleft and thereby enhance noradrenergic and dopaminergic neurotransmission in the central nervous system (13). Both MPH and AMP inhibit the dopamine transporter (DAT) and norepinephrine transporter (NET) (14), resulting in increased extracellular DA and NE levels (13). In contrast to MPH, AMP also promotes the release of DA from the presynaptic neuron into the synaptic cleft (Supplementary Figure S1) (13, 15-17).

Various amphetamine products are currently marketed for the treatment of ADHD, including oral immediate-release and extended-release formulations containing different AMP salts and stereoisomers (18). Attentin/Amfexa/Tentin® is an immediate-release tablet formulation of dexamphetamine sulfate that is available at doses of 5 mg, 10 mg and 20 mg (19). The product was first authorized in Germany in 2011 and has subsequently been approved in several further countries (Supplementary Table S1). For simplicity, the following sections refer to the product as Attentin®.

Attentin® is indicated as part of a comprehensive treatment program for ADHD in children and adolescents aged 6 to 17 years when response to previous methylphenidate treatment is considered clinically inadequate. A comprehensive treatment program typically includes psychological, educational and social measures. Diagnosis should be made according to DSM-5 criteria or the guidelines in ICD-10 and should be based on a comprehensive multidisciplinary evaluation of the patient. DEX is not indicated in all children with ADHD and the decision to use DEX must be based on a very thorough assessment of the severity and chronicity of the child's symptoms in relation to the child's age and potential for abuse, misuse or diversion. Treatment should be under the supervision of a specialist in childhood and/or adolescent behavioral disorders (19).

Careful dose titration is necessary at the start of treatment with DEX. Dose titration should be started at the lowest possible dose. The recommended starting daily dose is 5 mg once or twice daily (e.g. at breakfast and lunch), increasing if necessary by weekly increments of 5 mg in the daily dose according to tolerability and degree of efficacy observed. The regimen that achieves satisfactory symptom control with the lowest total daily dose should be employed. The maximum daily dose in children and adolescents usually is 20 mg, although doses of 40 mg may in rare cases be necessary for optimum titration (an overview of the dosing recommendations is given in Supplementary Figure S2) (19).

The pharmacokinetic properties of Attentin® tablets were assessed in 18 healthy adults. Following the administration of one 5 mg tablet, average maximal plasma concentrations (C_{max}) of 11.5 ng/mL were achieved at a mean ± SD t_{max} of 1.5 ± 0.4 hours (Supplementary Figure S3) (19).

Several studies have demonstrated the superiority of DEX over placebo in improving core symptoms and functional outcomes in pediatric patients *with* ADHD. DEX was also shown to have equivalent efficacy compared to other stimulants (20-26). A network meta-analysis that assessed the comparative efficacy and tolerability of oral ADHD medications supports MPH in children and adolescents, and amphetamines in adults, as first-choice medications for short-term ADHD treatment (27). A review of response data from studies directly comparing MPH- and AMP-based stimulants found that 71% of patients responded to MPH, 68% responded to AMP, and 91% responded to either type of stimulant (28). These data indicate that, although the response rates to MPH and AMP are similar in the overall population, individual response to either class of stimulant may vary, i.e. some individuals respond better to MPH and some respond better to AMP. Thus, if an ADHD patient does not respond to or does not tolerate one type of stimulant, the other type of stimulant should be tried.

The safety profiles of different stimulant classes and formulations are generally comparable (18). A recent Cochrane review found that the most common adverse events (AEs) reported in RCTs of pediatric ADHD patients treated with AMP products included decreased appetite, insomnia/trouble sleeping, abdominal pain, nausea/vomiting, headaches, and anxiety (9). Most AEs are mild and/or temporary and can be managed by the clinician through dose and timing adjustments (29). In most cases, medication discontinuation is not necessary (30). Serious side effects are rare and disappear when the dose is reduced or treatment is discontinued (29).

RCTs are considered the gold standard of evidence-based medicine, providing the highest level of evidence on clinical efficacy and safety of therapeutic interventions. However, most RCTs have strict inclusion criteria, meaning that the trial populations are highly homogeneous and often not representative of the prevailing patient population in a real-world *community*-based setting. Real-world studies can complement the results from RCTs by

providing data on the treatment effectiveness in heterogeneous patient populations encountered in routine clinical practice (31).

The non-interventional study (NIS) ATTENTION (**Attent**in® in children and adolescents with ADHD – a non-interven**tion**al study) investigated the real-world effectiveness and safety of Attentin® in children and adolescents with ADHD.

Methods

Objective

The objective of the study was to investigate the long-term effectiveness and safety of DEX treatment in children and adolescents with ADHD under daily routine conditions.

Participants

The study included children/adolescents between 6 and 17 years with a confirmed ADHD diagnosis (according to DSM-IV/5 or ICD-10) who had a clinically inadequate response to previous MPH treatment. The indication for DEX treatment was at the discretion of the treating physician. Patients with contraindications to Attentin® were excluded. All patients/caregivers provided written informed consent to participate.

Study design

This was a multicenter, prospective, observational, non-interventional study (ClinicalTrials.gov Identifier: NCT02801604). The necessary ethics approvals were obtained before study start. The study was conducted between June 2016 and April 2019. Overall, 40 study centers (37 in Germany and one each in Denmark, Norway and Sweden) participated in the study; all participating sites were specialized in childhood and/or adolescent behavioral disorders. The study consisted of a baseline visit (baseline examinations and retrospective assessment of efficacy and safety of previous ADHD medications; V1), a titration phase to determine the optimal dose of DEX, and a maintenance phase that included two follow-up visits after approx. 6 months (V2) and 12 months (V3) of DEX treatment. All decisions regarding treatment of patients (e.g. initial dose, titration scheme, follow-up) were at the sole discretion of the treating physician. The study protocol recommended that Attentin® be given according to the approved label in each country.

Outcome measures

The primary efficacy variable was the ADHD rating scale IV (ADHD-RS-IV), a validated instrument for assessing the severity of ADHD symptoms in children and adolescents. The ADHD-RS-IV is an 18-item scale based on the ADHD symptoms described in the DSM-IV. Each item is rated on a 4-point Likert scale ranging from 0 (none) to 3 (severe) (32). The primary endpoint was defined as the investigator-rated ADHD-RS-IV total score change from V1 to V2.

Secondary endpoints included ADHD-RS-IV total score changes from V1 to titration and from V1 to V3, as well as changes from V1 in ADHD-RS-IV subscales. Further secondary endpoints included subgroup analyses of the primary endpoint stratified by gender, total daily DEX dose and baseline ADHD-RS-IV total score. Additionally, the primary and all secondary endpoints were stratified by age group (children and adolescents). The DEX dose as well as the onset of action and duration of action of DEX were also assessed. The overall burden of impairments in daily functioning on the parents or family was assessed using a 4-point Likert question ranging from 0 (not at all) to 3 (a great deal). Compliance to treatment was estimated using a 5-point Likert question (1 = 100% compliance, 2 = ≥90%, 3 = ≥75% and <90%, 4 = ≥50% and <75%, 5 = <50%).

Safety

Adverse drug reactions (ADRs) were recorded by the physician at each study visit. The safety of the last ADHD medication was retrospectively assessed at the baseline visit (ADRs in the previous 6 months before initiation of DEX). Weight, height, blood pressure and heart rate were assessed at each study visit. Any signs of drug abuse, drug dependency, misuse, incorrect use or off-label use were to be documented.

Statistical analysis

All clinical data were captured in electronic case report forms (Clincase, Quadratek Data Solutions Ltd, Berlin, Germany). The software complied with Good Clinical Practice (GCP) and international standards for capturing study data.

All enrolled patients were included in the statistical analysis. For the calculation of ADHD-RS-IV total/subscale scores and the response rate, only complete cases were used (no imputation of missing values). Responders were defined as patients with a relative reduction in the ADHD-RS-IV total score from V1 to V2 of at least 0.3 (i.e. 30%).

Differences in ADHD-RS-IV total scores were assessed using a two-sided paired t-test. The correlation between total daily dose and age or weight was analyzed using Pearson's correlation coefficient (r). All analyses were performed using SAS 9.4 (SAS Institute Inc., Cary, NC, USA) and R 4.0.2 (R Foundation for Statistical Computing, Vienna, Austria) with the R-package haven (33, 34).

Body mass index (BMI) z-scores were calculated based on the WHO growth reference data for 5 to 19 years of age (2007) using AnthroPlus software (www.who.int/growthref/en).

Results

Participants

A total of 140 patients were enrolled in the study and included in the statistical analyses. Most of the patients were included in Germany (N=133, 95.0%); four (2.9%) patients were included in Denmark, two (1.4%) in Norway and one (0.7%) in Sweden.

Demographic and other baseline characteristics

All enrolled patients attended V1, 138 (98.6%) patients attended the titration visits, 98 (70%) patients attended V2 and 89 (63.6%) patients attended V3. The most common reasons for discontinuing DEX treatment included noncompliance of the patients (n=12, 8.6%), insufficient efficacy, and ADRs (n=10; 7.1% each). Demographic and other baseline characteristics of the study population are described in Table 1.

TABLE 1. Baseline demographics and disease characteristics

Characteristic	
Age (years)	
Mean ± SD	11.2 ± 3.1
Median (minimum, maximum)	11.0 (6, 17)
Age group, n (%)	
Children (<12 years)	82 (58.6)
Adolescents (≥12 years)	58 (41.4)
Race, n (%)	
White	140 (100.0)
Sex, n (%)	
Male	100 (71.4)
Female	40 (28.6)
Time since ADHD diagnosis (months), median (IQR) (N=138)	22.0 (44.5)
ADHD diagnosis according to	
ICD-10	138 (98.6)
DSM-5	1 (0.7)
DSM-IV	1 (0.7)
ADHD diagnosis according to ICD-10, n (%)	
F90.0: disturbance of activity and attention	97 (69.3)
F90.1: hyperkinetic conduct disorder	38 (27.1)
F90.9: hyperkinetic disorder, unspecified	3 (2.1)
ADHD diagnosis according to DSM-5, n (%)	
314.01: combined presentation	1 (0.7)
ADHD diagnosis according to DSM-IV, n (%)	
314.01: predominantly hyperactive/impulsive type	1 (0.7)
Additional conduct disorder, n (%)	61 (43.6)
Concomitant diseases, n (%) (n≥3)	
All	53 (37.9)
Autism spectrum disorder	9 (6.4)
Disturbance in social behavior	7 (5.0)
Depression	5 (3.6)
Enuresis	4 (2.9)
Sleep disorder	4 (2.9)
Tic	3 (2.1)

Notes. ADHD: Attention-deficit/hyperactivity disorder; DSM-IV/5: Diagnostic and Statistical Manual of Mental Disorders IV/5; ICD-10: International Statistical Classification of Diseases and Related Health Problems, Tenth Revision; IQR: Interquartile range; n: Number of patients; SD: Standard deviation

TABLE 2. Characteristics of treatment with previous MPH medications and DEX

Previous MPH treatment	
Number of MPH therapies, n (%) (N=137)	
1	118 (86.1)
2	15 (11.0)
3	3 (2.2)
5	1 (0.7)
Number of single doses per day, mean ± SD (N=137)	1.4 ± 0.5
Immediate-release (N=33)	1.5 ± 0.6
Extended-release (N=114)	1.4 ± 0.5
Total daily MPH dose (mg), mean ± SD (N=137)	27.5 ± 14.1
Immediate-release (N=33)	20.7 ± 12.2
Extended-release (N=114)	28.9 ± 14.0
DEX treatment	
Total daily dose at the respective visit (mg), median (IQR)	
First titration visit (initial dose) (N=138)	5.0 (5.0)
Children (<12 years) (N=80)	5.0 (5.0)
Adolescents (≥12 years) (N=58)	5.0 (5.0)
Titration (last recorded dose) (N=138)	11.3 (10.0)
Children (<12 years) (N=80)	10.0 (10.6)
Adolescents (≥12 years) (N=58)	15.0 (10.0)
V2 (N=95)	12.5 (10.0)
Children (<12 years) (N=57)	10.0 (10.0)
Adolescents (≥12 years) (N=38)	15.0 (10.0)
V3 (N=82)	15.0 (10.0)
Children (<12 years) (N=53)	12.5 (10.0)
Adolescents (≥12 years) (N=29)	20.0 (10.0)
Optimal total daily dose (mg), median (IQR) (N=120)	10.0 (10.0)
Children (<12 years) (N=69)	10.0 (10.0)
Adolescents (≥12 years) (N=51)	15.0 (10.0)
Optimal total daily dose per body weight (mg/kg), median (IQR) (N=120)	0.3 (0.3)
Children (<12 years) (N=69)	0.4 (0.3)
Adolescents (≥12 years) (N=51)	0.3 (0.2)
Number of titration steps to optimal total daily dose, n (%) (N=140)	
1	16 (11.4)
2	46 (32.9)
3	24 (17.1)
4	22 (15.7)
5	4 (2.9)
6	7 (5.0)
10	1 (0.7)
Optimal total daily dose not achieved	18 (12.9)
No titration performed	2 (1.4)
Dose regimen, n (%) (N=129)	
Once daily	76 (58.9)
Twice daily	50 (38.8)
Three times daily	2 (1.6)
Four times daily	1 (0.8)

Notes. DEX: Dexamphetamine; IQR: Interquartile range; MPH: Methylphenidate; SD: Standard deviation

The mean age was 11.2 years (range, 6-17 years); 82 (58.6%) patients were classified as children (<12 years) and 58 (41.4%) patients were classified as adolescents (≥12 years). Most patients (n=100, 71.4%) were male.

All but two patients (98.6%) were diagnosed based on ICD-10 criteria, with 69.3% of patients having a disturbance of activity and attention (ICD-10 code F90.0), which corresponds to the predominantly inattentive presentation of ADHD according to DSM-5, and 27.1% of patients having a hyperkinetic conduct disorder (ICD-10 code F90.1), which corresponds to the predominantly hyperactive/impulsive presentation (2).

The median (interquartile range [IQR]) time since ADHD diagnosis was 22.0 (44.5) months. Overall, 53 (37.9%) patients had concomitant psychiatric or physical diseases. The most frequent psychiatric disorders included autism spectrum disorder (n=9, 6.4%), disturbance in social behavior (n=7, 5.0%) and depression (n=5, 3.6%). Concomitant therapies were used by 21 (15.0%) patients. Medications used by more than two patients included antidepressants (n=6, 4.3%), antipsychotics (n=4, 2.9%) and hypnotics and sedatives (n=2, 1.4%). Seven patients received non-drug therapies, most commonly behavior therapy and occupational therapy (n=2, 1.4% each). Previous or current ADHD medications were documented for 139 (99.3%) patients. All patients had used MPH products as per the inclusion criteria. Further commonly used ADHD medications included lisdexamfetamine (n=36; 25.7%), atomoxetine (n=22, 15.7%) and guanfacine (n=6, 4.3%).

Treatment with MPH and DEX

Main treatment characteristics are summarized in Table 2. Data on the previous/current MPH medications were collected at V1. Most patients (n=118, 86.1%) had one recorded MPH therapy, 15 (11.0%) patients had two MPH therapies, three (2.2%) patients had three MPH therapies, and one (0.7%) patient had five MPH therapies. The mean total daily MPH dose was 27.5 ± 14.1 mg/d (ranging from 5.0 to 80.0 mg/d). The mean doses for extended-release preparations were higher than those for immediate-release preparations (Table 2).

Overall, the reasons (multiple answers possible) for switching from the previous ADHD medication to DEX were insufficient efficacy in 110 (79.1%) patients, short duration of action of current drug in 47 (33.8%) patients, insufficient tolerability in 25 (18.0%) patients and other reasons in 16 (11.5%) patients.

The median (IQR) initial total daily DEX dose was 5.0 (5.0) mg/d. At the end of the titration phase, the last recorded total daily dose was 11.3 (10.0) mg/d. The total daily dose was 12.5 (10.0) mg/d at V2 and 15.0 (10.0) mg/d at V3.

At the first titration visit, most patients used an initial total daily dose of 5 mg/d (n=62, 45.0%) or 10 mg/d (n=46, 33.3%). Four (2.9%) patients used 20 mg/d and one (0.7%) patient used 60 mg/d. At V2, the most commonly used doses were 10 mg/d (n=26, 27.4%) or 15 mg/d (n=21, 22.1%), and at V3 the most commonly used doses were 10.0 mg/d (n=21, 25.6%) or 20 mg/d (n=17, 20.7%).

At the initial titration visit, the median (IQR) total daily dose was 5.0 (5.0) mg/d for both children and adolescents, however, adolescents received a higher median total daily dose compared to children at end of titration, V2 and V3 (Table 2).

At V1, the total daily dose correlated with age ($r = 0.17$, $p = .04$) and with weight ($r = 0.23$, $p = .01$). At V2, positive correlation coefficients of the same magnitude were observed (total daily dose and age: $r = 0.16$, $p = .12$; total daily dose and weight: $r = 0.17$, $p = .09$). However, they are not significant at the 5% level due to the sample size, likewise at V3 (total daily dose and age: $r = 0.09$, $p = .43$; total daily dose and weight: $r = 0.16$, $p = .15$).

Two titration steps were performed in 46 (32.9%) patients, three titration steps were performed in 24 (17.1%) patients, and four titration steps were performed in 22 (15.7%) patients. The optimal daily dose was not achieved in 18 patients and no titration was performed in two patients. DEX was most commonly administered once daily (n=76, 58.9%) or twice daily (n=50, 38.8%). The dose regimen was not documented for 11 patients.

DEX was used in combination with other ADHD medications in 29 (20.7%) patients. Combination therapy was used in 15 (10.7%) patients at V1, 22 (15.7%) patients at V2 and four (2.9%) patients at V3. Most patients used risperidone (n=12, 8.6%), lisdexamfetamine (n=10, 7.1%) or guanfacine (n=3, 2.1%).

Efficacy

The mean ADHD-RS-IV total score decreased from 27.1 ± 11.7 at V1 to 13.4 ± 9.1 at V2. The mean change in the ADHD-RS-IV total score from V1 to V2 was -11.9 (95% confidence interval [CI]: -14.0 to -9.7; $p < .001$) (Figure 1).

Decreases in ADHD-RS-IV total scores compared to baseline were also observed at the last titration visit (14.9 ± 10.1) and at V3 (12.3 ± 8.5). The mean change from V1 to the last titration visit was -11.8 (95% CI: -13.4 to -10.1; $p < .001$) and the mean change to V3 was -12.7 (95% CI: -15.1 to -10.4; $p < .001$).

Statistically significant improvements ($p < .001$) were observed for both ADHD-RS-IV subscale

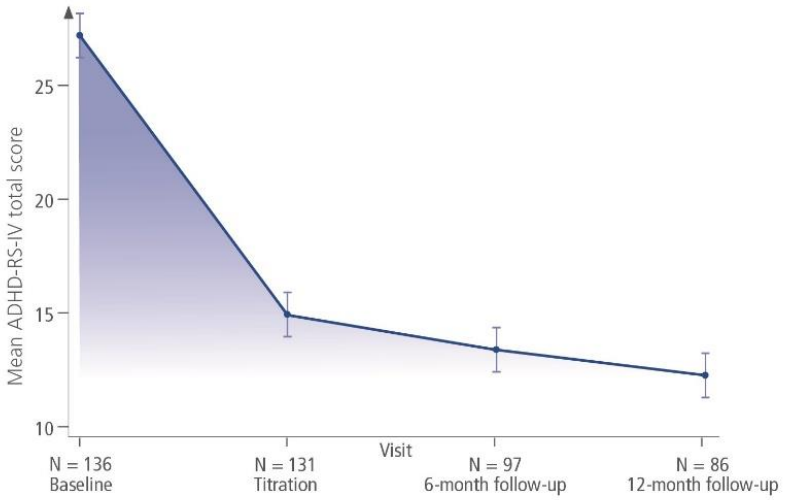

FIGURE 1. Mean ADHD-RS-IV total scores from baseline to study end. Data are shown as mean ± SEM.

TABLE 3. ADHD-RS-IV total and subscale score changes during the study and subgroup analyses stratified by age group (children and adolescents)

Subgroup	V1 (previous MPH treatment)		Δ V2 – V1			Δ V3 – V1		
	N	Mean ± SD	N	Mean ± SD	*p*	N	Mean ± SD	*p*
Total population								
ADHD-RS-IV total score	136	27.1 ± 11.7	96	-11.9 ± 10.8	< .001	85	-12.7 ± 10.9	< .001
ADHD-RS-IV subscale hyperactivity/impulsivity	136	11.1 ± 7.3	96	-5.0 ± 6.1	< .001	85	-5.7 ± 5.8	< .001
ADHD-RS-IV subscale inattention	136	16.0 ± 5.4	97	-6.8 ± 5.6	< .001	85	-7.1 ± 5.9	< .001
Subgroup analysis according to age group								
ADHD-RS-IV total score								
Children	80	27.7 ± 12.9	58	-11.7 ± 11.7	< .001	54	-12.8 ± 11.3	< .001
Adolescents	56	26.2 ± 9.8	38	-12.1 ± 9.3	< .001	31	-12.5 ± 10.3	< .001
ADHD-RS-IV subscale hyperactivity/impulsivity								
Children	80	11.8 ± 8.2	58	-5.0 ± 6.8	< .001	54	-6.0 ± 6.0	< .001
Adolescents	56	10.0 ± 5.6	38	-5.1 ± 4.9	< .001	31	-5.1 ± 5.4	< .001
ADHD-RS-IV subscale inattention								
Children	80	15.9 ± 5.7	59	-6.7 ± 5.6	< .001	54	-6.9 ± 6.0	< .001
Adolescents	56	16.1 ± 5.1	38	-7.0 ± 5.6	< .001	31	-7.4 ± 5.9	< .001

Notes. MPH: Methylphenidate; N: Number of patients; SD: Standard deviation
Only complete ADHD total scores were used; p-value based on t-test for paired samples

TABLE 4. Subgroup analyses of ADHD-RS-IV total score changes during the study

Subgroup	V1 (previous MPH treatment)		Δ V2 – V1			Δ V3 – V1		
	N	ADHD-RS-IV total score (mean ± SD)	N	ADHD-RS-IV total score (mean ± SD)	*p*	N	ADHD-RS-IV total score (mean ± SD)	*p*
Gender								
Male	98	27.6 ± 12.1	69	-12.8 ± 11.2	< .001	64	-13.3 ± 10.9	< .001
Female	38	25.8 ± 10.8	27	-9.4 ± 9.3	< .001	21	-11.1 ± 10.8	< .001
Maximum total daily DEX dose (mg/d)								
≤10	62	28.4 ± 10.8	46	-13.0 ± 11.0	< .001	40	-14.7 ± 11.2	< .001
>10 to ≤20	51	28.2 ± 12.9	34	-10.4 ± 12.3	< .001	28	-11.3 ± 11.5	< .001
>20	22	20.4 ± 9.8	16	-11.7 ± 4.7	< .001	17	-10.5 ± 8.5	< .001
Baseline ADHD-RS-IV total score								
≤20	45	13.4 ± 3.0	40	-4.5 ± 8.7	.002	36	-5.1 ± 7.0	< .001
>20 to ≤40	71	30.5 ± 5.1	41	-15.0 ± 7.9	< .001	37	-16.6 ± 9.3	< .001
>40	20	45.7 ± 3.9	15	-22.8 ± 9.1	< .001	12	-23.8 ± 9.4	< .001

Notes. ADHD-RS-IV: ADHD rating scale IV; DEX: Dexamphetamine; MPH: Methylphenidate; N: Number of patients; SD: Standard deviation
Only complete ADHD total scores were used; *p*-value based on t-test for paired samples

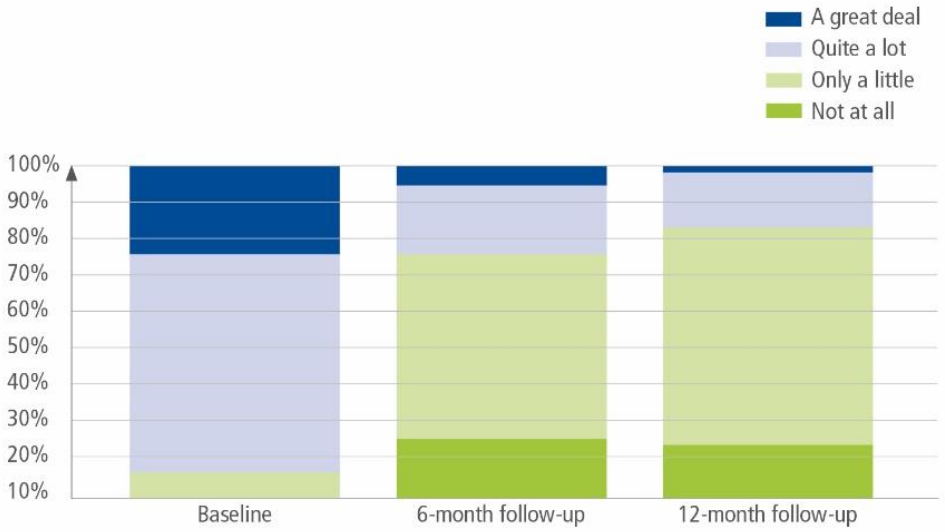

FIGURE 2. Overall burden of impairments in daily functioning during the study period.
The proportions of patients at the respective visit are shown.

scores at all assessed time-points. The mean change from V1 in hyperactivity/impulsivity scores was -5.1 (95% CI: -6.0 to -4.2) at titration, -5.0 (95% CI: -6.3 to -3.8) at V2 and -5.7 (95% CI: -6.9 to -4.4) at V3. The mean change from V1 in inattention scores was -6.7 (95% CI: -7.6 to -5.8) at titration, -6.8 (95% CI: -7.9 to -5.7) at V2 and -7.1 (95% CI: -8.3 to -5.8) at V3 (Table 3).

Subgroup analyses of the ADHD-RS-IV total score and subscale scores stratified by age group found significant beneficial effects of DEX in both children and adolescents (Table 3).

Treatment response was defined as a reduction in the ADHD-RS-IV total score of at least 30% from V1 to V2. According to this definition, the response rate was 78.1% (75/96). The mean reduction in the ADHD-RS-IV total score from V1 to V2 was 43%. A dose-response relationship was not observed. The response rates were similar for patients treated with ≤10 mg (72.0%, 36/50) or >10 to ≤20 mg (78.1%, 25/32). For patients treated with >20 mg, the response rate was 100% (14/14). Subgroup analyses indicated that the response rates were comparable between children and adolescents (79.3% [46/58] vs. 76.3% [29/38]). For doses ≤10 mg, the response rate was 72.7% (24/33) in children and 70.6% (12/17) in adolescents, for doses >10 mg to ≤20 mg, the response rate was 81.3% (13/16) in children and 75.0% (12/16) in adolescents. For doses >20 mg, the response rate was 100% in both children (9/9) and adolescents (5/5).

The results of subgroup analyses of the primary endpoint were consistent when stratified by gender, maximum total daily DEX dose and baseline ADHD-RS-IV total score. Significant reductions in ADHD-RS-IV total scores from V1 to V2 were observed in all analyzed subgroups. No differences in ADHD-RS-IV total scores at V2 were observed in subgroups stratified by gender or maximum total daily DEX dose. However, the baseline ADHD-RS-IV total score appears to influence the degree of symptom improvement at V2. The mean change in ADHD-RS-IV total scores was higher for patients with a baseline ADHD-RS-IV score of >40 (-22.8 [95% CI: -27.8 to -17.8]; $p < .001$) compared to patients with a baseline ADHD-RS-IV score of >20 to ≤40 (-15.0 [95% CI: -17.5 to -12.5]; $p < .001$) or ≤20 (-4.5 [95% CI: -7.3 to -1.7]; $p = .002$) (Table 4).

Significant reductions in ADHD-RS-IV total scores from V1 were also observed at titration and V3 (Table 4) in all subgroups.

Patients estimated the onset of action and duration of action of DEX after intake of the study drug in the morning. The mean onset of action was 36.2 minutes and the mean duration of action was 6.5 hours.

DEX treatment reduced the overall burden of functional impairment due to ADHD in most patients. At V1, 70.3% (97/138) of patients reported "quite a lot" and 23.9% (33/138) of patients reported "a great deal" of burden of impairment, whereas at V3, this was the case for 15.1% (13/86) and 1.2% (1/86) of patients, respectively, with most patients reporting "only a little" (70.9% [61/86]) or "no" (12.8% [11/86]) burden of impairment (Figure 2). Overall, the burden of impairment was improved for 74 patients, unchanged for 11 patients and worse for one patient at V3 compared to V1.

At baseline, a treatment compliance of ≥90% was documented for 74.6% (103/138) of patients treated with MPH and 79.6% (43/54) of patients treated with non-MPH ADHD medications. Comparable compliance rates were observed for DEX over the whole study period, with 77.6% (76/98) of patients at V2 and 80.5% (70/87) of patients at V3 having a treatment compliance of ≥90%.

Safety

Overall, 114 ADRs to ADHD medications (including previous medications) were documented for 39 patients during the course of the study.

Forty-six ADRs to DEX were reported in 19 patients. The most common ADRs were decreased appetite (n=7) and depressed mood (n=3) (Table S2). Most ADRs were of mild or moderate intensity; eight severe ADRs occurred in three patients (hyperacusis, crying, rebound effect, decreased appetite, abnormal behavior, apathy, depressed mood, and restlessness).

From V1 to V3, a mean increase in height (5.7 ± 2.9 cm, $p < .001$) and weight (3.6 ± 3.7 kg, $p < .001$) was observed. Compared to V1, the mean BMI z-score was significantly decreased at V2 (-0.18 ± 0.49, $p < .001$) and V3 (-0.16 ± 0.63, $p = .018$) (Table 5). Small, statistically significant increases in mean systolic and diastolic blood pressure compared to baseline were observed throughout the study. At V3, mean systolic blood pressure was increased by 3.8 ± 9.1 mmHg ($p < .001$) and mean diastolic blood pressure was increased by 3.8 ± 9.0 mmHg ($p < .001$) (Table 5). Seventeen patients who were classified as having "normal blood pressure" (<120/<80 mmHg) at V1 shifted to the "prehypertension" (120-139/80-89 mmHg) category at V3. One patient who was prehypertensive at V1 shifted to the "stage 1 hypertension" (140-159/90-99 mmHg) category at V3. No significant changes in heart rate were observed (Table 5).

DEX was generally well tolerated during the course of the study. At V3, all patients (N=87, 100%) reported "no interference" of DEX with daily functioning. Compared to that, 91 (67.4%) patients

TABLE 5. Changes in height, weight, BMI z-scores and vital signs during the study

	V1		V2		V3		Δ V2 – V1			Δ V3 – V1		
	N	Mean ± SD	N	Mean ± SD	N	Mean ± SD	N	Mean ± SD	*p*	N	Mean ± SD	*p*
Height [cm]	140	147.7 ± 18.9	96	149.3 ± 17.1	86	151.8 ± 16.6	96	2.1 ± 2.1	< .001	86	5.7 ± 2.9	< .001
Weight [kg]	140	42.7 ± 17.7	97	41.6 ± 15.6	87	43.4 ± 15.7	97	1.2 ± 2.7	< .001	87	3.6 ± 3.7	< .001
BMI z-score	140	0.20 ± 1.20	96	-0.12 ± 1.08	86	-0.10 ± 1.11	96	-0.18 ± 0.49	< .001	86	-0.16 ± 0.63	0.018
Systolic blood pressure [mmHg]	140	112.1 ± 12.0	98	113.5 ± 11.9	87	114.3 ± 12.4	98	2.4 ± 9.6	0.017	87	3.8 ± 9.1	< .001
Diastolic blood pressure [mmHg]	140	71.5 ± 8.6	98	73.3 ± 8.4	87	74.7 ± 8.5	98	2.2 ± 8.8	0.016	87	3.8 ± 9.0	< .001
Heart rate [beats/min]	140	79.9 ± 13.7	98	78.4 ± 12.0	87	80.1 ± 13.1	98	0.01 ± 9.5	ns	87	0.64 ± 13.0	ns

Notes. BMI: Body mass index; N: Number of patients; ns: Not significant; SD: Standard deviation
p-value based on t-test for paired samples

taking MPH and 27 (50.0%) patients taking medications other than MPH reported "no interference" under the respective medications.

Furthermore, no indication for drug abuse, dependency, misuse, incorrect use or diversion was reported.

Discussion

RCTs are considered the gold standard of evidence-based medicine; however, RCTs usually have strict enrolment criteria and treatment protocols, meaning that the patient samples and treatment conditions are often not representative of real-world clinical practice. In contrast, observational, non-interventional studies provide data on the effectiveness and tolerability of medications in routine clinical practice. The ATTENTION study was a prospective, observational, non-interventional study that investigated the effectiveness and safety of DEX treatment under routine conditions in pediatric ADHD patients with a clinically inadequate response to previous MPH treatment. DEX treatment significantly improved ADHD symptoms over the whole study period. The mean ADHD-RS-IV total score change from baseline to the first follow-up visit after approx. 6 months (primary endpoint) was -11.9 (27.1 vs. 13.4, $p < .001$). Significant reductions in ADHD-RS-IV total scores were observed in the titration phase and were maintained up to the second follow-up visit after approx. 12 months of DEX treatment, indicating that the therapeutic effectiveness of DEX is maintained during long-term treatment in routine clinical practice. These findings are in line with results from a long-term, placebo-controlled study conducted by Gillberg and colleagues that showed sustained efficacy of amphetamines in children with ADHD over a treatment period of 15 months (25). Furthermore, beneficial effects of DEX were observed on both ADHD-RS-IV subscales ('hyperactivity/impulsivity' and 'inattention') and in both children and adolescents. Patients with more severe ADHD symptoms at baseline appear to benefit the most from DEX treatment.

The study population consisted of patients with a clinically inadequate response to MPH. A high response rate was observed in the study, with 78.1% of patients responding to DEX. These data confirm findings from other studies that have shown that some individuals respond preferentially to MPH whereas others respond preferentially to DEX (20, 21, 26, 28), indicating that a trial of both MPH and DEX may increase the probability for a favorable response and optimal response strength for an individual patient. Therefore, in children with an unsatisfactory response to MPH, a trial of DEX should be considered. The response to DEX was not dose-dependent, which confirms findings from clinical trials and clinical experience that indicate that the dose needs to be individually titrated for each patient.

Patients in this study reported an average onset of action of 36.2 minutes and an average duration of action of 6.5 hours after intake of the first dose of DEX in the morning. These findings are in line with results from earlier studies that reported a rapid onset of action of DEX in the 30 to 60 min range (35) and a duration of action in the 4 to 6 hour range (35-38).

DEX was administered as a single dose in the morning by 58.9% of patients, suggesting that the reported duration of the therapeutic effect is sufficient for most patients, while 38.8% of patients administered two doses per day, presumably to extend the duration of action to the late afternoon and evening. Administering DEX twice or more daily is in line with the Attentin® label, which recommends that the times at which the doses are administered should be selected to provide the best effect when it is most needed to combat school and social behavioral difficulties (19). Current practice guidelines also note that immediate-release formulations of stimulants may be more suitable than extended-release formulations if flexible dosing regimens are needed (7).

Overall, "insufficient efficacy" was reported as a reason for switching to DEX for 79.1% of patients, while "insufficient tolerability" was reported for 18.0% of patients. The mean total daily MPH dose was 27.5 mg (ranging from 5.0 to 80.0 mg). One possible explanation for these findings is that the recommended up-titration to the maximum tolerable dose of MPH, as recommended by current practice guidelines (4), was not performed in all patients. Current ADHD treatment guidelines recommend optimizing MPH dosage to the patients' individual needs (39). Clinicians should initiate treatment at a low dose and slowly increase the dose until maximum benefit with minimum adverse effects is achieved. These recommendations are based on studies that have shown a substantial interindividual variability in clinical response to MPH. It is also possible that patients who reported "insufficient tolerability" as reason for switching to DEX experienced intolerable ADRs, such as insomnia or weight loss, that precluded any further up-titration of MPH.

DEX was generally well tolerated during the course of the study, and no new safety findings were identified. The most commonly reported ADRs to DEX were decreased appetite and depressed mood. Mean BMI z-scores significantly decreased during the study, however, the changes in BMI z-scores were not large enough to be clinically meaningful. A review of longitudinal studies investigating growth effects of stimulant treatment in children with

ADHD found that stimulants led to modest reductions in expected height and weight, although these effects attenuated over time (40). More clinical studies are needed to elucidate the impact of stimulant treatment on final height and weight. Current practice guidelines recommend regular monitoring of weight and height in children and adolescents receiving stimulant treatment (4, 6-7).

A statistically significant increase in mean systolic and diastolic blood pressure was observed during the study, whereas no significant changes in heart rate were observed. Small but significant increases in blood pressure and heart rate are well documented adverse effects of stimulant treatment in children and adults (27, 41-43). In a meta-analysis of cardiovascular effects of stimulants in adults, the mean increase in heart rate was 5.7 beats/min and the mean increase in systolic blood pressure was 2.0 mmHg (43). Generally small increases in blood pressure (≤ 5 mmHg) and heart rate (≤ 10 beats/min) have also been observed in children and adolescents treated with stimulants (44). However, a recent meta-analysis found no association between ADHD medications and risk of sudden death/arrhythmia, stroke, myocardial infarction and all-cause death, although some of the confidence intervals for the pooled risk ratios did not exclude modest elevated risks (45). Cardiovascular status, including blood pressure and heart rate, should be carefully and regularly monitored during stimulant treatment (4-6).

The findings of this study should be interpreted in light of several limitations. The main limitation is the uncontrolled, open-label design, which may have introduced bias in the estimation of treatment effects. Furthermore, the small sample size may limit the validity and generalizability of study results. Another limitation is the potential for recall bias, as the data regarding previous ADHD/MPH treatment (including data on effectiveness and safety) were reported retrospectively by the patient at the baseline visit. Since the study only included patients with a clinically inadequate response to previous MPH treatment, the study results may not be generalized to a broader population of ADHD patients that includes e.g. treatment-naïve patients. Conversely, the patient population in this study is consistent with the population for which Attentin® is indicated according to the approved label, thus, the study population is likely similar to the patient population that is prescribed Attentin® in routine clinical practice. ADRs were not assessed in a structured fashion in this study, for example by using an adverse event checklist or questionnaire. This was an observational study that aimed to gain insights into the use of DEX in routine clinical practice; thus, additional diagnosis or monitoring procedures for the patient beyond the usual medical practice were not included in the observational study plan. Therefore, a specific adverse event questionnaire, that may not be a part of routine practice, was not employed in this study. Unsystematic documentation of ADRs through general inquiry prompts has several drawbacks, including reliance on patient/parent recall and potential misclassification of adverse events by the investigator, especially behavioral changes. Since no structured method was used for the collection of ADRs in this study, the incidence of ADRs may have been underestimated. Nevertheless, the ADRs observed in this study are in line with the known safety profile of stimulant medications.

Future research on the treatment of ADHD should focus on providing insights into the long-term effects of stimulants, using randomized withdrawal trials, population-based studies with self-controlled methodologies and longitudinal follow-up studies (46).

Clinical significance

The study shows that Attentin® is an effective and well-tolerated long-term treatment option for pediatric ADHD patients with a clinically inadequate response to MPH treatment. The results of this real-world study conducted in a heterogeneous patient population under naturalistic treatment conditions complement the findings from randomized controlled trials of DEX in children and adolescents with ADHD. Furthermore, the high response rate achieved in this study confirms the findings from other studies that have shown that some individuals respond preferentially to MPH whereas others respond preferentially to DEX. Thus, in ADHD patients who do not respond to or do not tolerate MPH, treatment with DEX should be tried.

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Supplementary files

Figure S1: Mechanisms of action of methylphenidate and amphetamine at the dopaminergic synapse

Table S1: Marketing authorization status of Attentin/Amfexa/Tentin® (dexamphetamine sulfate) in Europe

Figure S2: Dosing recommendations for Attentin/Amfexa/Tentin® (dexamphetamine sulfate)

Figure S3: Pharmacokinetics of Attentin®(5 mg tablet) in healthy adults

Table 2S: Summary of adverse drug reactions to DEX