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RESEARCH

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Functional outcomes of extended-release methylphenidate and atomoxetine in children: retrospective chart analysis

Armagan Aral*, Merve Onat and Hilal Aydemir

Abstract

Background: Recent guidelines emphasize the importance of functional outcomes in children with attention-deficit/hyperactivity disorder (ADHD). Here, we assess the functional outcomes of the oral delivery system of osmotic-release methylphenidate (OROS-MPH) and atomoxetine (ATX) from the retrospective review of the chart for the last 2 years in the clinic.

Results: Linear mixed-effects models were performed with outcome measures of difference in ADHD symptoms and functional impairment. After 9–12 weeks, OROS-MPH and ATX were statistically equivalent for total Weiss Functional Impairment Rating Scale-Parent Report (WFIRS-P) scores (difference in slope is $\beta = 0.004$, $p = 1.000$). However, OROS-MPH was superior to ATX in terms of school domain (difference in slope is $\beta = 0.139$, $p < 0.001$); ATX was superior in the family domain (slope difference in slope is $\beta = 0.103$, $p < 0.001$). The other domains of functioning both were not responsive to pharmacotherapy and were similar between the two medications.

Conclusions: Optimal management should monitor functional progress in ADHD beyond the core symptoms. As expected, ADHD medications provide a distinct pattern of functional improvement. Pharmacotherapy alone offers promising and reliable outcomes to improve school and family functions in ADHD. Some functional improvements did not respond to the medication; therefore, many of the techniques derived from behavioral interventions should be considered.

Keyword: Atomoxetine, Attention-deficit/hyperactivity disorder, Family function, Methylphenidate, School function

Background

Attention-deficit/hyperactivity disorder (ADHD) is a neuropsychiatric disorder with a prevalence of 13% in the Turkish school population [1]. Diagnostic criteria for ADHD include symptoms of inattention/hyperactivity and functional impairment in social, academic, and occupational areas [2]. As stated in the diagnostic criteria, functional impairment is typically the leading cause of admission [3], but it typically fades and becomes less germane during routine in clinical practice. Recent evidence suggests that ADHD-related emotional dysregulation symptoms (poor management of anger and irritability), fear learning [4] and difficulties in motor inhibition [5] which are thought to be related to some neuroanatomical [6] and neurochemical [7] developmental processes, could impact functioning [8]. Besides, functional impairment in ADHD has attracted considerable interest in literature, which suggests that its trends are not always in parallel to symptoms [9, 10]. A significant number of those who may be considered asymptomatic might suffer from unmet functional impairment with ADHD [9]. Moreover, the guidelines of the last decade underline the use of functional outcomes in children with ADHD; nonetheless, it still has not become a standard approach in clinical settings [11, 12]. Despite the accumulated data

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in the literature, few studies have considered comparing ATX and other medications, including stimulants. Generally speaking, the evidence shows the superiority of the stimulants [13]. As such, randomized controlled studies indicated that ATX was weaker on the Weiss Functional Impairment Rating Scale—Parent Report (WFIRS-P) total score and school subscale than other lisdexamfetamine and guanfacine in children and adolescents [14, 15]. This has been challenged by research in the adult population reported that ATX was as efficient as immediate release methylphenidate (IR-MPH) in functional outcomes [16]. However, systematic data comparing the osmotic-release oral delivery system (OROS)-MPH form and ATX in a naturalistic setting were sparse. An exceptional study suggested that there was no significant difference between ATX and OROS-MPH [17]. The study mentioned is an open-label randomized controlled study using stringent inclusion and exclusion criteria; hence, it may not be generalized to the clinical sample. To address the question outlined above, our primary outcome measure was comparing the functional outcomes of OROS-MPH and ATX at 9–12 weeks, in a naturalistic retrospective review of the charts for last 2 years.

Methods

456 children and adolescents with ADHD aged 6–14 years with Turgay DSM-IV-based ADHD and Disruptive Behavior Disorders Screening Scale (T-DSM-IV-S) total scores of > 32, stating symptoms were moderate or severe, were screened for study eligibility from the child and adolescent psychiatry clinic between May 2019 and May 2021. The diagnosis and selection of treatment was decided by the physician who was treating the patient after comprehensive clinical examination and T-DSM-IV-S parent ratings. 81 subjects who were diagnosed with any psychiatric comorbidity except oppositional defiant disorder (ODD) and conduct disorder (CD); and chronic medical illnesses were excluded [obtained the online data protection system of the Turkish Ministry of Health (E-nabız)] (details could be seen in Fig. 1). The remaining 375 children and adolescents who enrolled in the study (T0) consisted of 238 treated with OROS-MPH and 137 treated with ATX. 54 participants have missing values, 8 participants dropped out, 9 were excluded from T1 (second visit at 4th–7th weeks) due to non-adherence or not obeying the titration schedule and, 4 were excluded due to adverse effects. 300 participants were analyzed in T1, consisting of 198 treated with OROS-MPH and 102 treated with ATX. 21 participants had missing values, 10 participants dropped out and 5 participants who did not adhere to medication were excluded in T2. 3 participants were excluded due to adverse effects. 19 participants in the OROS-MPH group switched to other medications and were not included in the T2 analysis. Finally, 242 participants, consisting of 150 treated with OROS-MPH and 92 treated with ATX, were analyzed in T2 (Fig. 1 for details).

A retrospective naturalistic observational study was conducted to explore the functional outcomes of OROS-MPH and ATX in the clinical setting without a G power analysis. We applied the scales used in the study as a part of routine clinical care for 2 years in our clinic, recorded scores and information about titration, adherence, descriptive variables to the abstraction form. Abstraction forms were included in Additional file 2. The measures were unfamiliar to data collectors before 2 years. Hence, for training, the data abstractors classified several patient records that did not participate in the study. The scheduled meetings were aimed at discussing issues encountered in the encoding process. All data collectors were physicians in Child and Adolescent Psychiatry. The same clinician collected the data and conducted treatment on the children over 9–12 weeks. Data collectors were blind to changes in WFIRS-P scores, but not to T-DSM-IV-S and the objectives of the study. First author collected 56%, second author 30% and third author 14% of the cases. Later, we chose the appropriate data based on predefined criteria on the adherence, titration, and missing data. We would like to stress that this is not a prospective research.

The study protocol was conducted accordance with the Helsinki Declaration and the International Council for Harmonisation Note for Guidance on Good Clinical Practice. The study was reviewed and approved by the Local Ethics Committee on 15 May 2019 (No: OMÜKAEK 2019/298) (B.30.2.ODM.0.20.08/304-431). Informed consent and assent forms were signed applicable by Local Ethical Committee, as well. Due to the retrospective design, not all participants gave their informed assent included in the study. After obtaining informed assent for eligible patients, the researchers first reported a sociodemographic-clinical data form. Parents completed the Turgay Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) Disruptive Behavior Disorders Rating Scale (T-DSM-IV-S), and Weiss Functıonal Impairment Rating Scale—Parent Report (WFIRS-P) at three visits (baseline, 4–7 weeks, and 9–12 weeks). The interview, data collection, and medication administration were carried out three times at baseline (T0), weeks 4–7 (T1) and weeks 9–12 (T2). No multiple raters were used for the scales. If the children has more than T-DSM-IV-S > 32, the data collector recorded the information of the participant in the chart. The exclusion criteria were: (1) switching the ADHD medication during the last 2 years; (2) non-adherence: defined as taking the ADHD medication lower than 80% of the time during the study period;

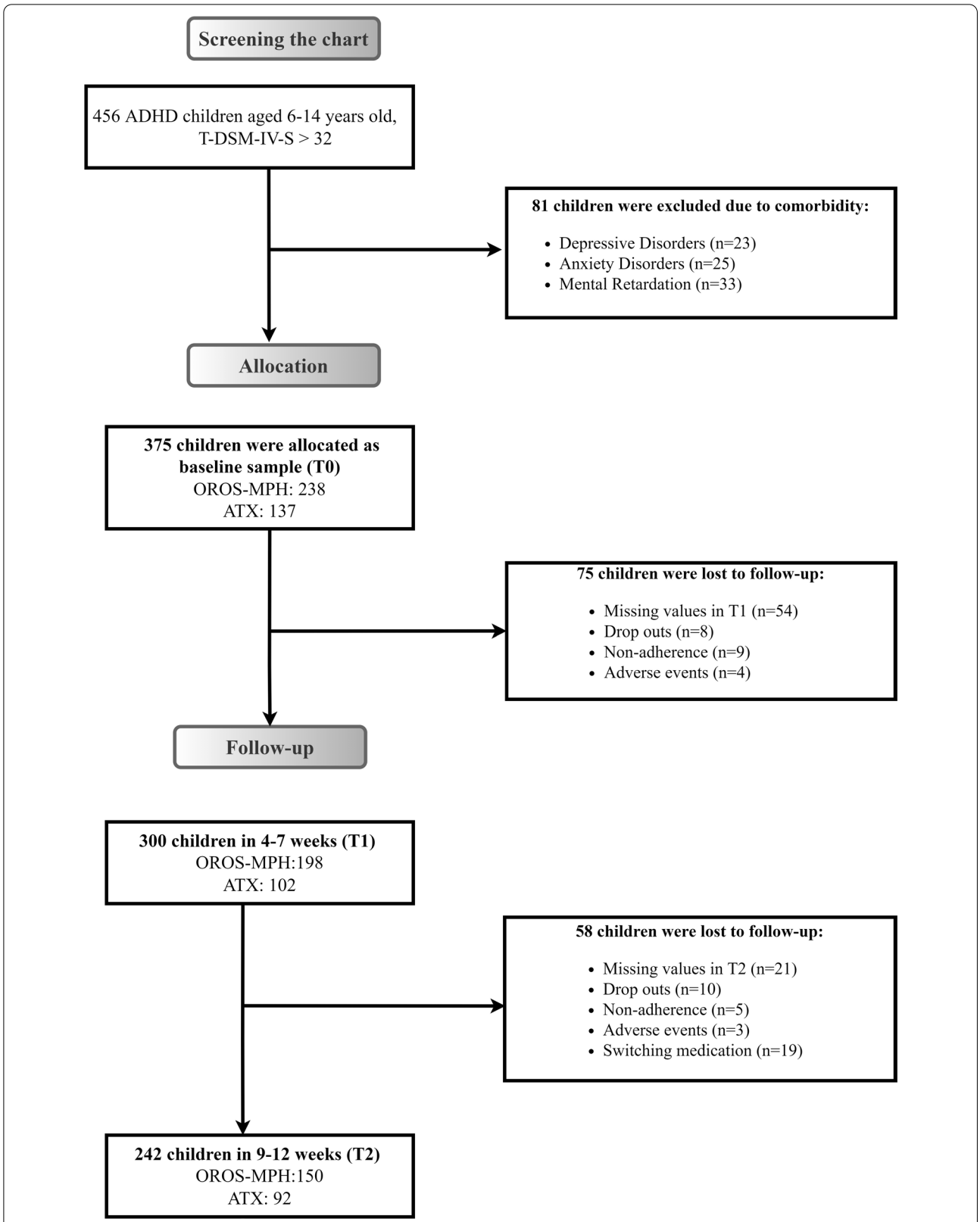

Fig. 1 Flow diagram of the sample selection in the retrospective chart review. †*ADHD* attention-deficit/hyperactivity disorder, *ATX* atomoxetine, *OROS-MPH* osmotic-release oral delivery system methylphenidate, *T-DSM-IV-S* the Turgay DSM-IV disruptive behavior disorders rating scale

(3) encountering any adverse events require to stop the medication; (4) missing data on any items in T-DSM-IV-S scale; (5) missing data in more than 1 item on a domain in WFIRS-P and more than 10% on the whole scale.

The indication for each drug was determined by the regular pediatric physicians. The dose of OROS-MPH and ATX was established based on clinical guidelines, as a part of routine clinical care for the study period [18]. The dose of OROS-MPH was titrated at T1 based on at least 40% improvement in T-DSM-IV-S, changed to the other medications with less improvement, and continued with the same dose if the children did not meet the DSM-5 ADHD criteria. The dose of ATX was not titrated until T2 (those weighing 70 kg or more initially received 40 mg/day, after 2 weeks, the dose was titrated to 100 mg/day; less than 70 kg initially received approximately 0.5 mg/kg/day, after 2 weeks, the dose was titrated to a final target dose of approximately 1.2 mg/kg/day); no other medications were used due to the absence of comorbidity except antipsychotics for disruptive behavior disorders. Children were excluded from the study if their medication changed, non-adherence or adverse events occurred during the 9–12 weeks.

An accurate measurement of the number of missing doses was based on pill counts. We considered the patient as adherent if he had taken medication at least 80% of the time. If the patient did not adhere, was excluded.

Sociodemographic-clinical data form

This form, which was prepared and completed by the researchers, included data on sex, age, education and job of parents, subtype of ADHD, medication choice, weight, dose/weight calculation of the ADHD medication.

Socioeconomic status evaluation (SES)

The SES is evaluated by using the Hollingshead index, based on the work and education of parents, as shown in Additional file 1: Table S1 [19].

Turgay DSM-IV-based ADHD and disruptive behavior disorders screening scale (T-DSM-IV-S)

The T-DSM-IV-S scale has been used as an outcome measure in clinical trials to diagnose children with probable ADHD, ODD, and CD [1]. The T-DSM-IV-S was developed by Turgay [20] and was translated and adapted into Turkish by Ercan and colleagues [21] The T-DSM-IV-S is a 41-item scale completed by parents or teachers. Each item is scored 0–3 (0 not at all; 1 just a little, 2 quite a bit, and 3 very much). It has been founded as acceptable for internal consistency with Cronbach α; 0.88 for the inattention score, 0.90 for hyperactivity/impulsivity score; 0.91 for the ODD score and 0.76 for the CD score [21]. Missing data on any items were not allowed. In this study, we used the scale to check ADHD diagnoses and measure the severity of ADHD symptoms.

Weiss functional impairment rating scale-parent report (WFIRS-P)

It was developed by Dr. Margaret Weiss [22]. The scale provides a metric for ADHD-specific functional impairments without taking into account ADHD DSM-5 criteria. Scores from 0 to 3 on the 50 item questionnaire are listed as mean scores in total and in each WFIRS-P domain: family, school (with learning and behavior subscale), life skills, self-concept, social activities, and risky activities. The parent form adapted to the Turkish population by Tarakçıoğlu and colleagues and Cronbach alfa was 0.93 [23]. Maximum 1 item on a domain and 10% on the whole scale were allowed to missing data and calculation of ındex score were made as the sum-score divided by the items completed as previously ascertained in studies with the same issue [24].

Statistical analysis

SPSS 25.0 (Statistical Package for Social Sciences Software, 2019, IBM, New York, USA) was used to analyze the data. Baseline similarities in descriptive statistics were tested in two groups using a t-test and Mann–Whitney U test for continuous variables and Chi-square tests for categorical variables. Linear mixed-effects models were performed to address the lack of statistical independence of repeated measurements of the same participants at three time points. The outcome variables were the T-DSM-IV-S and WFIRS-P scores. The time was measured as ordinal variable coded T0–T1–T2. Both intercepts and slope (time) effects in the linear mixed model with time-dependent variables (T-DSM-IV-S and WFIRS-P) were treated as random effects to account for variations among subjects in baseline values and slopes for individual trajectories of changes, in addition to the main treatment and fixed time effects of the two treatment groups. To test the difference in the slope of change between the two medications, the interaction terms between drug x time were analyzed. Unstructured covariance type for repeated measures within the medication groups and AR [1]: heterogeneous between the medication groups fitted best to the data as judged by the Akaike Information Criterion (AIC). Cohen's *d* was used to calculate the effect size for comparisons between baseline (T1) and weeks 4–7 (T2) to 9–12 (T3). Cohen's *d* calculation was based on the formula: mean difference/standard deviation of mean difference for repeated measure within subjects (OROS-MPH or ATX) [25]. Holm–Bonferroni adjustment was used on the *p*-values for multiplicity on the WFRIS-P subscales in Table 3. As a result, certain *p* values that appear statistically significant (e.g., 0.05) are

not considered significant after multiplicity adjustment. The alpha value was determined as $p<0.05$ for other comparisons. Missing data on items of T-DSM-IV-S were not allowed. 10% missing data were allowed for WFIRS-P subscales.

Results

The initial sample consisted of 375 participants, 238 treated with OROS-MPH, and 137 with ATX. Descriptive statistics for the initial sample are shown in Table 1. The mean doses were determined as 0.88 ± 0.17 mg/kg/day for the OROS-MPH group and 1.19 ± 0.10 mg/kg/day for the ATX group (the dose represented the participants who remained through three phases of 9–12 weeks).

Changes in ADHD symptoms from baseline to weeks 4–7 to 9–12 are detailed in Table 2. Change in scores of total, inattention, and hyperactivity/impulsivity subscales from baseline to 9–12 weeks revealed significant reductions with effect size ranges 0.59–2.94. However, only OROS-MPH has significant reductions in the first 4–7 weeks with effect size ranges 1.33–2.64 (Table 2). Figure 2a–c represents the decrease in total, inattention, and hyperactivity/impulsivity scores for T-DSM-IV-S, indicating that OROS-MPH was superior to ATX (the difference in slope difference is $\beta=6.125$, $\beta=3.917$ and $\beta=2.085$ in between 9–12 weeks (T2) and baseline (T0), $p<0.001$). The difference in slope in the first 4–7 weeks was even greater; $\beta=20.199$, $\beta=12.321$ and $\beta=7.877$ ($p<0.001$), respectively, for total, inattention

Table 1 Descriptive statistics for two groups in the baseline

	OROS-MPH ($n=238$)	ATX ($n=137$)	Statistics	p
Demographics				
Age	9.29 ± 2.30	9.51 ± 2.33	t = − 0.908	0.919
Sex			$\chi^2=0.243$	0.622
Female	100 (42%)	54 (39.4%)		
Male	138 (58%)	83 (60.4%)		
Hollingshead Index (mean of both parents total score)	3.88 ± 2.37	3.97 ± 2.31	t = − 0.354	0.723
ADHD subtype			$\chi^2=0.587$	0.746
Inattentive	113 (47.5%)	69 (50.4%)		
Hyperactive/impulsive	20 (8.4%)	13 (9.5%)		
Combined	105 (44.1%)	55 (40.1%)		
ODD	53 (22.3%)	26 (19%)	$\chi^2=0.566$	0.452
CD	92 (%38.7)	58 (%42.3)	$\chi^2=0.491$	0.484
AP usage	39 (%16.4)	21 (%15.3)	$\chi^2=0.072$	0.788
AD usage	14 (%5.9)	7 (%5.1)	$\chi^2=0.098$	0.754
T-DSM-IV-S				
Total	35.80 ± 2.60	35.72 ± 2.71	t = 0.267	0.790
Inattention	21.53 ± 4.21	21.20 ± 4.69	t = 0.690	0.491
H/I	14.27 ± 4.38	14.22 ± 4.50	t = -0.526	0.600
Opposition-defiance	7.72 ± 5.82	7.02 ± 5.19	t = 1.158	0.247
Conduct disorder	4.22 ± 2.90	4.56 ± 2.99	t = -1.091	0.276
WFIRS-P				
Total	1.29 ± 0.32	1.32 ± 0.35	t = -0.966	0.335
Family	1.40 ± 0.84	1.32 ± 0.79	t = 0.915	0.361
School	1.51 ± 0.86	1.59 ± 0.86	t = -0.881	0.379
Learning***	1.85 ± 0.94	1.47 ± 0.97	t = 3.668	< 0.001
Behavior***	1.27 ± 0.89	1.65 ± 0.87	t = -3.973	< 0.001
Life skills	1.47 ± 0.85	1.57 ± 0.84	t = -1.052	0.294
Self-concept	0.51 ± 0.42	0.53 ± 0.37	t = -0.453	0.651
Social activities	1.44 ± 0.85	1.43 ± 0.83	t = 0.057	0.954
Risky activities	0.90 ± 0.85	0.98 ± 0.59	t = -1.216	0.225

ADHD attention-deficit/hyperactivity disorder, *AP* antipsychotics, *AD* antidepressants, *ATX* atomoxetine, *CD* conduct disorder, *H/I* hyperactivity–impulsivity, *ODD* oppositional defiant disorder, *OROS-MPH* osmotic-release oral delivery system methylphenidate, *T-DSM-IV-S* the Turgay DSM-IV Disruptive Behavior Disorders Rating Scale, *WFIRS-P* Weiss Functional Impairment Rating Scale-Parent Report

Table 2 Changes in ADHD symptoms from baseline to weeks 4–7 to 9–12

	OROS-MPH					ATX					Slope difference between OROS-MPH and ATX					
	Estimate	SE	95%CI		Cohen's *d*[a]	Estimate	SE	95%CI		Cohen's *d*[a]	Estimate	SE	95% CI		t value	Cohen's *d*[a]
			LL	UL				LL	UL				LL	UL		
Week 4–7 to baseline																
T-DSM-IV-S scores																
Total	22.333***	0.404	21.360	23.307	2.647	2.082	0.939	− 0.201	4.365	0.143	− 20.199***	0.857	− 21.882	− 18.515	23.557	1.012
İnattention	13.203***	0.392	12.260	14.146	1.613	0.911	0.494	− 0.283	2.105	0.119	− 12.321***	0.790	− 13.873	− 10.769	15.585	0.669
Hyperactivity/impulsivity	8.936***	0.320	8.166	9.707	1.337	1.027	0.871	− 1.085	3.139	0.076	− 7.877***	0.753	− 9.357	− 6.398	10.454	0.449
Oppositional defiance	0.079	0.471	− 1.506	1.214	0.008	− 0.240	0.570	− 1.618	1.139	0.028	0.304	0.764	− 1.807	1.199	0.398	0.017
Conduct disorder	0.427	0.249	− 0.173	1.027	0.082	0.250	0.364	− 0.631	1.131	0.044	0.184	0.425	− 1.021	1.199	0.435	0.018
Week 9–12 to 4–7																
T-DSM-IV-S scores																
Total	4.473***	0.509	3.244	5.701	0.471	12.893***	1.215	9.947	15.840	0.762	8.498***	0.947	6.632	10.364	8.969	0.345
İnattention	2.968***	0.423	1.948	3.988	0.376	7.617***	0.645	6.049	9.184	0.848	4.782***	0.532	3.734	5.831	8.987	0.345
Hyperactivity/impulsivity	1.632	0.277	− 0.962	2.301	0.315	5.369***	0.989	2.970	7.769	0.390	3.717***	0.803	2.135	5.299	4.625	0.178
Oppositional defiance	0.793	0.560	− 0.557	2.143	0.075	3.666***	0.542	2.351	4.980	0.485	2.703**	0.849	1.030	4.376	3.183	0.122
Conduct disorder	1.463***	0.242	0.881	2.045	0.324	2.856***	0.286	2.161	3.551	0.717	1.368***	0.341	0.697	2.039	4.009	0.154
Week 9–12 to baseline																
T-DSM-IV-S scores																
Total	26.806***	0.462	25.691	27.921	2.941	14.975***	0.892	12.805	17.146	1.109	− 6.125***	0.490	− 7.088	− 5.161	12.492	0.503
İnattention	16.171***	0.428	15.142	17.200	1.918	8.527***	0.723	6.777	10.277	0.779	− 3.917***	0.410	− 4.725	− 3.110	9.545	0.384
Hyperactivity/impulsivity	10.568***	0.368	9.684	11.452	1.458	6.396***	0.710	4.678	8.114	0.595	− 2.085***	0.367	− 2.807	− 1.362	5.678	0.228
Oppositional defiance	0.872	0.603	− 0.580	2.323	0.073	3.426***	0.512	2.191	4.662	0.442	1.196**	0.374	0.460	1.933	3.199	0.128
Conduct disorder	1.890***	0.258	1.270	2.510	0.372	3.107***	0.285	2.419	3.794	0.712	0.617**	0.208	0.206	1.028	2.957	0.119

SE standard errors, *d* Cohen's *d* for effect size, *β* parameter estimates of the slope of changes over time, *ADHD* attention-deficit/hyperactivity disorder, *ATX* atomoxetine, *OROS-MPH* osmotic-release oral delivery system methylphenidate, *T-DSM-IV-S* the Turgay DSM-IV Disruptive Behavior Disorders Rating Scale

[a] Cohen's *d* calculation was based on; *M* or *β* divided by standard deviation of *M* or *β* *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$

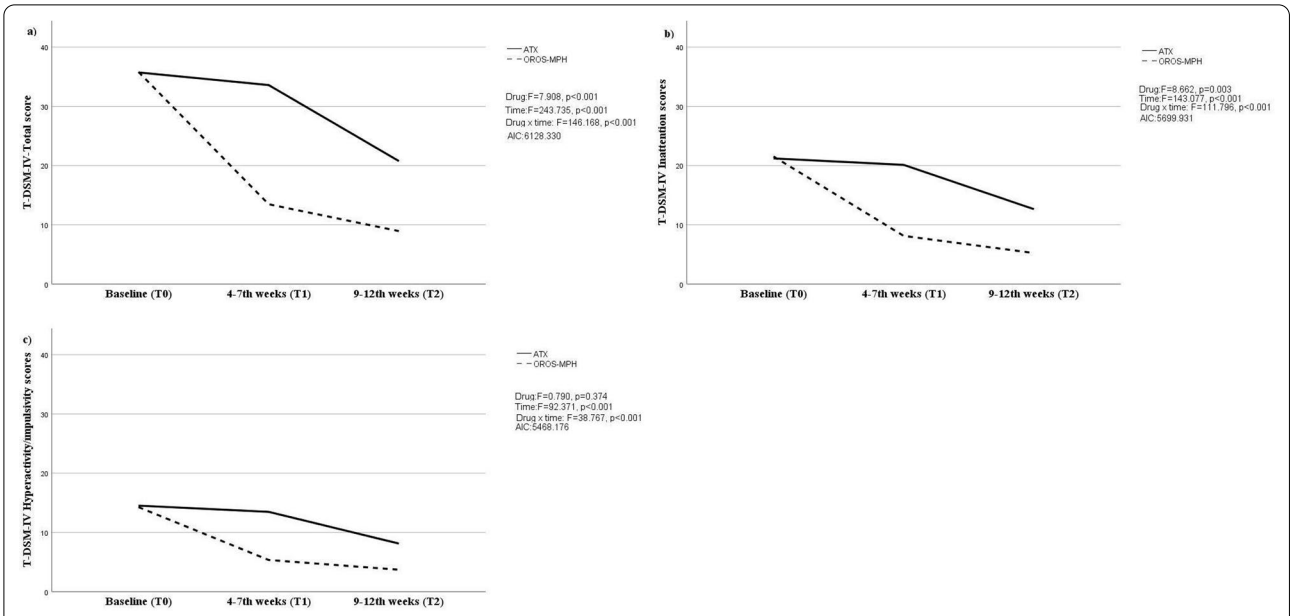

Fig. 2 Line chart depicts the result of mixed-model repeated-measures analysis of ADHD symptom severity. †*ATX* atomoxetine, *OROS-MPH* osmotic-release oral delivery system methylphenidate, *T-DSM-IV-S* the Turgay DSM-IV disruptive behavior disorders rating scale, *AIC* Akaike information criterion. **a** Is total score, **b** is inattention score, and **c** is hyperactivity/impulsivity score

and hyperactivity/impulsivity scores. A reversal was presented skid into ATX $\beta = 8.498$ (total score), $\beta = 4.782$ (inattention score) and $\beta = 3.717$ (hyperactivity/impulsivity score) ($p < 0.001$) over the course of 9–12 weeks. However, ATX was superior in the oppositional defiance (ODD) ($\beta = 1.96$, $p = 0.002$) and conduct disorder (CD) ($\beta = 0.617$, $p = 0.003$) scores. The T-DSM-IV-S scores at the end of the study (T2) are displayed in the Additional file 1: Table S3.

The baseline index scores of WFIRS-P for all domains and the total score were higher than the optimal thresholds [24], as seen from Table 1. Change in scores of total, school, and family domains from baseline to 9–12 weeks revealed significant reductions with effect size ranges 0.19–0.91 (Table 3). However, only OROS-MPH has significant reductions in the first 4–7 weeks with effect size ranges of 0.33–1.03. The highest mean reductions were in the school domain (highest for OROS-MPH with 0.398) and family domain (highest for ATX with 0.361) for both medications. All reductions in WFIRS-P except for total, school and family domains were insignificant (Table 3). Figure 3a shows a clear trend of decreasing WFIRS-P scores in two groups at different visit periods; dramatic decrease at first 4–7 weeks of OROS-MPH treatment then plateau through 9–12 weeks; a rush of decreasing is seen after 4–7 weeks of ATX treatment, on top of that, mixed-model repeated-measures analysis (MMRM) did not show any significant differences between two drugs at the end of the study. From Fig. 3b it can be noted that ATX is superior in family domain, accelerating after 4–7 weeks. Figure 3c represents the decrease in school domain scores, indicating that OROS-MPH was superior to ATX ($\beta = 0.139$, $p < 0.001$). When the school domain was divided into learning and behavior (Fig. 3d–e), the results converted; OROS-MPH superiority in learning ($\beta = 0.704$, $p < 0.001$), ATX superiority in behavior ($\beta = 0.244$, $p < 0.001$) subscales. The other WFIRS-P domains did not indicate any difference between the within-subjects level (detailed analysis in Table 3). WFIRS-P scores at the end of the study (T2) are displayed in Additional file 1: Table S3.

Discussion

This study is a naturalistic retrospective chart review aimed at investigating the progression of the functional outcome of OROS-MPH and ATX in a routine clinical setting. After carefully analyzing the two alternatives, it was found that OROS-MPH was better in school; nonetheless, ATX was better in the family domains. MMRM analysis with two independent variables as OROS-MPH and ATX, did not display any significant differences between WFIRS-P total scores. Overall, both ADHD medications provide an improvement in functionality on total, school, and family domains. Expectedly, changes were established in T1; preserved toward T2 and the slope of improvement decreased for OROS-MPH, while ATX did not have a significant positive impact on functioning at the first 4–7 weeks; the notable improvement

Table 3 Changes in WFIRS-P scores from baseline to weeks 4–7 to 9–12

	OROS-MPH						ATX						Slope difference between OROS-MPH and ATX						
	Estimate	SE	95%CI		Cohen's *d*[a]	Adjusted P values[b]	Estimate	SE	95%CI		Cohen's *d*[a]	Adjusted P values[b]	Estimate	SE	95%CI		t value	Cohen's *d*[a]	Adjusted P values[b]
			LL	UL					LL	UL					LL	UL			
Week 4-7 to baseline																			
WIFRS scores																			
Total	0.105***	0.015	0.068	0.142	0.335	< 0.001	− 0.018	0.021	− 0.068	0.032	0.055	1.000	− 0.092	0.053	− 0.197	0.012	− 1.725	0.074	0.510
Family	0.070***	0.009	0.047	0.092	0.374	< 0.001	0.032	0.018	− 0.012	0.077	0.115	1.000	− 0.015	0.132	− 0.275	0.244	− 0.120	0.004	1.000
School	0.387***	0.018	0.343	0.431	1.034	< 0.001	− 0.027	0.012	− 0.056	0.002	0.145	0.560	− 0.364**	0.135	0.630	− 0.098	− 2.690	0.115	0.049
Learning	1.107***	0.046	0.997	1.216	1.153	< 0.001	− 0.254***	0.053	− 0.382	− 0.126	0.310	< 0.001	1.352***	0.074	− 1.500	− 1.205	18.047	0.785	< 0.001
Behavior	− 0.100**	0.031	− 0.175	− 0.026	0.154	0.002	0.126**	0.038	0.036	0.217	0.214	0.024	0.230***	0.050	0.130	0.330	4.544	0.197	< 0.001
Life skills	0.050	0.043	− 0.053	0.154	0.055	0.727	− 0.035	0.036	− 0.122	0.052	0.062	1.000	− 0.046	0.143	− 0.327	0.234	− 0.325	0.013	1.000
Self-concept	0.050*	0.019	0.003	0.096	0.126	0.132	0.043	0.031	− 0.032	0.118	0.089	1.000	− 0.021	0.063	− 0.146	0.102	− 0.346	0.014	1.000
Social activity	0.010	0.078	− 0.177	0.197	0.006	1.000	− 0.036	0.111	− 0.305	0.234	0.021	1.000	− 0.044	0.136	− 0.313	0.223	− 0.329	0.013	1.000
Risky activity	0.009	0.015	− 0.028	0.045	0.028	1.000	− 0.026	0.028	− 0.093	0.041	0.060	1.000	0.002	0.096	− 0.187	0.192	0.028	0.000	1.000
Week 9–12 to 4–7																			
WIFRS scores																			
Total	− 0.017	0.018	− 0.062	0.027	0.050	1.000	0.127***	0.021	0.076	0.177	0.434	< 0.001	0.137***	0.029	0.078	0.195	4.632	0.181	< 0.001
Family	0.079***	0.011	0.052	0.105	0.385	< 0.001	0.328***	0.018	0.284	0.373	1.312	< 0.001	0.250***	0.022	0.206	0.293	11.235	0.437	< 0.001
School	0.011	0.019	− 0.035	0.057	0.031	1.000	0.150***	0.013	0.120	0.180	0.833	< 0.001	0.139***	0.030	0.079	0.199	4.615	0.178	< 0.001
Learning	− 0.021	0.044	− 0.126	0.084	0.025	1.000	− 0.034	0.055	− 0.168	0.100	0.044	1.000	− 0.002	0.068	− 0.136	0.131	− 0.037	0.001	0.970
Behavior	0.045	0.034	− 0.038	0.128	0.070	1.000	0.287	0.038	0.194	0.379	0.543	< 0.001	0.234***	0.055	0.124	0.344	4.206	0.163	< 0.001
Life skills	− 0.005	0.048	− 0.120	0.110	0.005	1.000	0.077	0.039	− 0.170	0.016	0.142	0.705	0.077	0.076	− 0.073	0.227	1.012	0.039	0.771

Table 3 (continued)

	OROS-MPH						ATX						Slope difference between OROS-MPH and ATX						
	Estimate	SE	95%CI		Cohen's *d*[a]	Adjusted P values[b]	Estimate	SE	95%CI		Cohen's *d*[a]	Adjusted P values[b]	Estimate	SE	95%CI		t value	Cohen's *d*[a]	Adjusted P values[b]
			LL	UL					LL	UL					LL	UL			
Self-concept	− 0.028	0.023	− 0.085	0.028	0.065	1.000	0.016	0.035	− 0.070	0.102	0.032	1.000	0.047	0.042	− 0.034	0.130	1.137	0.043	0.771
Social activity	− 0.204	0.086	− 0.411	0.004	0.127	0.456	0.004	0.120	− 0.288	0.296	0.002	1.000	0.206	0.142	− 0.075	0.487	1.441	0.055	0.635
Risky activity	− 0.006	0.018	− 0.039	0.050	0.017	1.000	0.050	0.029	− 0.120	0.020	0.012	1.000	0.056	0.036	− 0.016	0.128	1.531	0.059	0.635
Week 9–12 to baseline																			
WIFRS scores																			
Total	0.088**	0.023	0.032	0.143	0.194	0.006	0.109***	0.027	0.043	0.175	0.267	< 0.001	0.004	0.011	− 0.017	0.026	0.427	0.014	1.000
Family	0.149***	0.015	0.113	0.184	0.505	< 0.001	0.361***	0.026	0.298	0.424	0.918	< 0.001	0.103***	0.012	0.079	0.127	8.320	0.346	< 0.001
School	0.398***	0.026	0.334	0.462	0.778	< 0.001	0.123***	0.017	0.082	0.165	0.478	< 0.001	− 0.139***	0.013	− 0.166	− 0.112	− 10.131	0.431	< 0.001
Learning	1.086***	0.061	0.938	1.233	0.904	< 0.001	− 0.287**	0.076	− 0.470	− 0.105	0.249	0.005	− 0.704***	0.034	− 0.772	− 0.637	− 20.469	0.834	< 0.001
Behavior	− 0.056	0.043	− 0.160	0.049	0.066	1.000	0.413***	0.048	0.297	0.530	0.568	< 0.001	0.244***	0.024	0.195	0.293	9.892	0.410	< 0.001
Life skills	0.046	0.056	− 0.090	0.182	0.041	1.000	0.042	0.052	− 0.083	0.167	0.053	1.000	0.010	0.013	− 0.015	0.036	0.799	0.031	1.000
Self-concept	0.021	0.030	− 0.051	0.093	0.035	1.000	0.059	0.043	− 0.046	0.163	0.090	1.000	0.006	0.015	− 0.024	0.036	0.392	0.016	1.000
Social activity	− 0.194	0.087	− 0.403	0.015	0.113	0.395	− 0.032	0.111	− 0.299	0.235	0.019	1.000	0.076	0.067	− 0.057	0.210	1.127	0.045	1.000
Risky activity	0.003	0.024	− 0.054	0.060	0.006	1.000	0.024	0.038	− 0.067	0.115	0.041	1.000	0.012	0.013	− 0.013	0.039	0.953	0.037	1.000

SE standard errors, *d* Cohen's *d* for effect size, *β* parameter estimates of the slope of changes over time, *ATX* atomoxetine, *OROS-MPH* osmotic-release oral delivery system methylphenidate, *WFIRS-P* Weiss Functional Impairment Rating Scale-Parent Report

[a] Cohen's *d* calculation was based on; M or *β* divided by standard deviation of M or *β*

[b] *p* values considering Holm–Bonferroni adjustments for multiplicity

*$p < 0.05$. **$p < 0.01$. ***$p < 0.001$(significant values before Holm–Bonferroni adjustments)

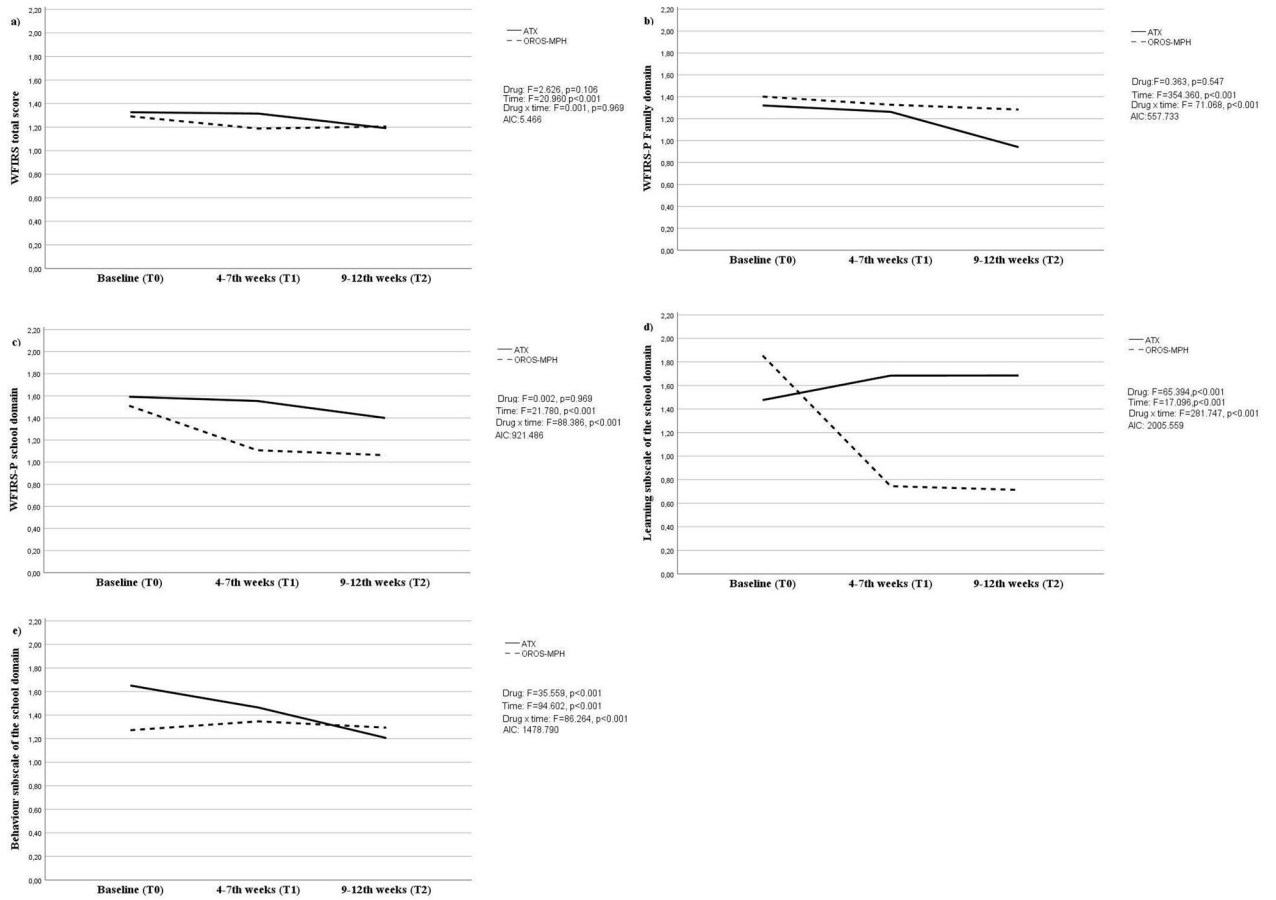

Fig. 3 Line chart depicts the result of mixed-model repeated-measures analysis of functional impairment. †*ATX* atomoxetine, *OROS-MPH* osmotic-release oral delivery system methylphenidate, *WFIRS-P* Weiss Functional Impairment Rating Scale-Parent Report, *AIC* Akaike information criterion. **a** Is total score, **b** is family domain, **c** is school domain, **d** is learning subscale of the school domain, and **e** is behavior subscale of the school domain

was observed between 4–7th weeks and 9–12th weeks. The improvement pattern signifies greater progress over time in more extended designs. Similar conclusions were drawn by Fuentes et.al, in the comparison of ATX and other medications, suggesting more excessive reductions in the total WFIRS-P mean scores at 6 months of follow-up [26]. The results corroborate the suggestion that the appreciation of ADHD should include the evaluation of functional impairment using a reliable rating scale. To our knowledge, this work makes an original contribution as the first naturalistic observational retrospective research comparing functional improvement in extended-release MPH and ATX.

As seen from the effect sizes, the WFIRS-P school and family domains were the most prominent and sensitive to the two medications, which corresponds well to previous evidence [26–28]. Contrary to expectations, one interesting aspect that emerged from the correlation analysis is, for both total and two separate medication groups; reductions of the family domain did not correlate neither inattention, hyperactivity/impulsivity, ODD and CD symptom decrease; the school domain correlates with both inattention and hyperactivity/impulsivity coefficient of lower than 0.3, did not correlate with a reduction in ODD and CD symptoms (Additional file 1: Tables S4–S6). In contrast to earlier findings of Coghill [13] (2017) and (2021) [29], even though the relatively higher initial scores of WFIRS-P and T-DSM-IV-S than previous reports [30, 31], these results suggest that symptom-based outcomes are not intersecting with functional outcomes. Also, the T-DSM-IV-S total score had a greater effect size at the endpoint than any other domain of the WFIRS-P, indicating that symptoms and functioning are different but related phenomena. It seems possible that both drugs have the ability to strengthen appropriate behavior in these functional domains not just improving ADHD symptoms [32, 33], might be precipitated by other factors such as emotion regulation [34, 35], self-control

[32], and theory of mind [36, 37]. OROS-MPH had the most substantial impact on the school domain (especially learning subscale), ATX have in the family domain. Moreover, these two domains showed the largest observed divergences between the two drugs. In both cases, the effect size varies 0.34–0.83, hence possess valuable clinical significance. This might reflect the reality of the pharmacokinetics of two drugs. The effect of MPH, even in extended release, is most significant during school hours, and a possible rebound effect might arise after late hours while the action of ATX is prolonged over 24 h. Thus, the improvement of the school domain was presented predominantly in OROS-MPH. Some quantitative analysis implied the advantage of MPH (any form) in school subscale scores [26, 38]; was matched by present results. However, our results reveal that ATX has a larger impact on the behavior subscale of the school domain. As noted previously, ATX has been shown to have a considerable impact on school interactions [39], some trials demonstrated a limited impact on academic performance [40]. It is plausible that strong dopamine-enhancing property of methylphenidate may have a role in academic achievement through memory and learning [38]. Nevertheless, our results may differ because parents have less direct access to information about school-based achievement and peer interaction. School observations and classroom studies would also be valuable in examining school functioning. OROS-MPH had a substantial impact on the school domain (effect size = 0.778). The learning subscale of the school domain had a larger effect size, even higher equal 0.904. ATX also have a significant improvement in school domain with smaller effect size (0.478). The effect size of OROS-MPH and ATX was smaller than more heterogeneously aged studies [17, 28]. Even for these otherwise successful ADHD probands, the adolescent and college years pose a serious challenge, with a mix of higher level academic tasks, sudden personal autonomy, and considerably broader responsibilities [41]. This may lead to a large window of impairment to treatment, resulting in a larger effect size [28], otherwise in our study the sample age was much more smaller (mean was between 9 and 11). OROS-MPH has a greater improvement in the learning subscale, ATX had superiority in behavior subscale and did not significantly improve learning, validates the previous works [40]. The learning subscale maps closely onto executive function, attention [42], and academic achievement [40, 43]. The extensive data about MPH on neuropsychologic [44], memory [38] and learning [45]; behavioral benefits [40, 46] of ATX that support the psychometric soundness of our results, are therefore not shocking therein. However, WFIRS-P does not tap all areas related school such as homework [47], and academic productivity that could be fully measured with classroom studies [45]. Future research should be done to learn more about the ways in which ATX affects school functions. Much like that tryptophan–kynurenine pathway, which have shown positive effects on various neurodegenerative and neurodevelopmental diseases [48], is thought to be potential target for future pharmacotherapy studies by suppression of this pathway allow memory enhancement [49, 50].Unlike the results of the school functioning subscale, family functions improved better in the ATX group. Insufficient control of ADHD symptoms during the waking day has negative consequences not only for the child, but also for their caregivers. For working parents, mornings and evenings are the times have the greatest contact with their children. Inadequate management of symptoms and concomitant impairment during these bookends of the day is a source of stress for families and caregivers [51, 52]. Instead, the decline in systemic concentrations of OROS-MPH during rebound or off periods may lead to a loss in potential benefits on family functioning [29]. Additional stimulant dose in the afternoon has considerable benefit for parents' pleasantness [53]. Similarly, in a randomized placebo-controlled study that evaluated the ADHD-specific family stress index, ATX had a significant positive effect on family perception of the burden associated with ADHD symptoms after 10 weeks [54]. In general, these findings indicate that improvements in family functioning related to ATX treatment occur rather quickly over a short period of time. On the contrary, a 24-week open-label trial with smaller sample size and a different measure of family functioning by Shang (2020) and colleagues suggested no considerable improvement for OROS-MPH and ATX as home behaviors [17]. The disparity with our study can be attributed to the use of a family functioning scale not specific to ADHD in the Shang study [17], and a high percentage of AP medication and CD comorbidity in our study (%15.3 and %39.7 in the endpoint). Therefore, ODD and CD are defined by a pattern of inappropriate negative, hostile, and defiant behaviors that impede social, family, or academic performance and are likely to worsen family functions. Therefore, a great variance in improving family functioning could also be attributed to reduction of symptoms of CD or ODD rather than duration of ATX action, but correlation analyses were not significant between family functioning and ODD/CD symptoms; whereas, the placebo-controlled effect of OROS-MPH was found to be higher than ATX in post hoc analyses, suggesting that our results might be contaminated by AP medication [29]. The same research also found that the standardized mean differences were highest with ODD and without ODD in family among all areas of functioning. Further, multiple ADHD-related impairments in family functions may result from

combinations of multiple factors that are only partially compensated by MPH or ATX, such as parent–child interactions. Similarly, behavioral and parental interventions were associated with improvements in parent–child interactions in individuals with ADHD in several researches [55]. Further, recent guidelines gave weight to the benefits of behavioral treatments in family context in ADHD [56], still, WFIRS-P family domain did not precisely construe elements of family–child interaction. This restricts the overall assessment of what types of family difficulties are triggered by ADHD symptoms and even the depth to which of these may be utilized in the treatment protocol. More studies are needed to determine whether medication paired with behavioral and parental interventions is the right way to approach parent–child relationships in ADHD families. Still, our results support the efficacy of ATX in familyfunctioning given its larger effect size (Cohen's *d*: 0.918). OROS-MPH also had an acceptable effect size on family functioning (Cohen's *d*: 0.505). In sum, the evidence herein suggests that both family and school domains of WFIRS-P, help detect to extent of the treatment benefit.

Generally speaking, extended-release formulations of MPH have moderate-to-large improvements in sum and across most WFIRS-P domains with the most substantial improvement in school/learning [9, 28]. Our results do not agree with previous researches, suggesting that OROS-MPH have significant improvements only in the total, school and family domain. Some comment on the trend in the WFIRS-P score have been made by Canu (2020) [42]; on the surface, several aspects appear to excel in detecting short-term improvements with pharmacologic treatment. The school items seem to be notoriously well formulated for this purpose, while other scales can reasonably be supposed to change only with longer-term follow-up therein. To build on this, a placebo-controlled study with 56 children and adolescents suggested that both extended-release MPH and extended-release mixed amphetamine salts have a positive impact on most WFIRS-P domains except life-skills and self-esteem [57]. Also, the ATX group in our study has the same pattern of WFIRS-P improvement; only significant changes were in the total, family and school domains. A pilot study on ATX in children supports our results in the first 2 months, but life skills and self-concept improved at 6 months, suggesting that these two domains may lag after the improvement of ADHD core symptoms [58]. In a similar vein, placebo-controlled study more similar to our sample, confirmed our results, speaks clearly that only the total and school domains change with ATX [15]. Furthermore, a systematic review of randomized placebo-controlled studies indicated that life skills and self-concept were less responsive to ADHD medication [13]. By the nature of the real-life setting study design, not all samples have impairment in all WFIRS-P domains. The reality of functional impairment varies interpersonally, which likely causes the observed effect sizes to be lower for some WFIRS-P domains. In the present study, a possible explanation for lack of significance in self-concept and risky activity is low initial scores in these domains, whereas this is not valid for life skills and social activity. The WFIRS-P self-concept domain has just three items; scales with more items are typically more reliable, and hence better at discriminating across groups than scales with fewer items, so WFIRS-P self-concept domain might not reflect self-esteem properly [59]. The majority of studies that said ADHD symptoms were highly related to functional impairment in self-esteem were conducted with the adolescent sample [46, 60]. Since ADHD-related risky activities are expected to be more common in mid- and late-adolescent period [61, 62], possibly our younger ADHD sample did not encounter adolescence challenges that drive to risky behavior herein [63]. So age group might have been responsible for self-esteem and risky behavior domains in our results. In fact, some life skills tap into different aspects that are not detected by WFIRS-P, in which four items are sleep and appetite (interrelated with various factors including medication and comorbidity) and two were about medical help. However, WFIRS-P is a well-known scale for ADHD, it was not intended to cover all aspects of social functioning such as conflict resolution [64], social competence [64], leisure time and social satisfaction [65]. Some evidence indicated that MPH has a positive impact on social cognition by interacting with the oxytocin system [66, 67]. While not strictly focus of the current research, internalizing symptoms might contaminate domain scores, therefore, WFIRS-P might not be independently linked with ADHD [42]. This may not be expected given the general nature of life impairment associated with psychopathology and in itself will not pose critical drawbacks in clinical assessment where comorbidity is the rule rather than the exemption. Further research is indicated to determine whether specific treatments are somewhat effective for different functional impairments beyond what has been indicated herein. Thus, interventions that specifically target these residual domains of dysfunction over and beyond the medication may be more useful. To give a notable example, transcranial magnetic stimulation (TMS) could be a promising alternative for improving pharmacotherapy-resistant clinical and cognitive symptoms of ADHD [68].

The main strength of the study was the inclusion of a representative sample of children in a real-life setting with a retrospective chart design. Furthermore, eligible participants were included from a well-defined dataset.

However, the present study has several additional notable strengths. The sample size was much larger than previous studies to allow the detection of differences in functional domains. The large sample size and linear mixed-effects models (preventing false-positive associations) increase the power of the study. As was the case in our sample here, data on individual improvement are important, together with group responses to treatment. Linear-mixed model indicates individual significance of change rather than distributional methods that are based exclusively on variation around the group mean, so it might be valuable for the prevention of false-positive associations [69].

Conclusions

In summary, we believe that the research points in this document toward ADHD medications provide a clinically relevant benchmark for reading progression in functioning. This research is the first naturalistic observational retrospective study to compare the functional improvement in extended-release MPH and ATX, approaching the issue with a novel perspective. The results propose a distinct pattern of improvement in functional outcomes. To our knowledge, our findings are unique in that OROS-MPH is superior to ATX in the school domain of functioning, while OROS-MPH is inferior in the family domain after linear mixed-model analysis. Conversely, there were no significant differences in the WFIRS-P total scores between the two medications. The short-term outcome of these medications can be translated into clinically relevant improvements in global, family, and school functioning. Therefore, this pattern should be taken into account in management of ADHD. To place a clinical context, it might be worth looking at functionality once choosing a particular ADHD medication. Improved functioning would be a conceivable target for ADHD pharmacotherapy. The data presented here underlie that clinicians should receive baseline information on functioning and monitor in follow-up with standardized measurements. These results can help clinicians understand the potential effect of ADHD drugs and help researchers conduct clinical research.

The data in this document have potential for clinical management, but the study contains some limitations that must be recognized before considering further conclusions. Retrospective design for ethical reasons limits us from having randomization with a placebo. Hence, this precludes the elimination of spontaneous improvement with time, and further testing is necessary before one could state that the effect sizes are reliable. Improvement in the other areas, except school and family, might be incremental, and longer periods of time could be required to capture functional improvement therein [58]. Furthermore, the retrospective design did not allow us to make comparisons of the same age and sex. There are no neuropsychological test data to objectively assess symptoms, other than rating scales, which are subjected to reporting bias. The scales were scored based on parent reports; no teacher evaluations were included. Since the WFIRS-P is principally used to assess global functioning, little particular information concerning problems in each area could inevitably be gleaned. Finally, considerable number of children with ODD and CD were part of the sample. This may have impacted WFIRS-P scores, as discussed above.

Our results speaks directly that OROS-MPH and ATX give a unique pattern of functional recovery and provide adequate depth and breadth to clinical practice. However, pharmacotherapy might be a powerful treatment for improving school and family functions in ADHD, whether improvement is the result of comorbid pharmacotherapy remains to be tested. Furthermore, it would be striking to investigate the long-term trends of two medications' effectiveness beyond what has been shown here. Future research should consider the potential effects of different formulations of methylphenidate. Some functional impairments were less responsive to medication; therefore, multimodal approaches derived from behavioral interventions should be considered [70]. Larger samples might be helpful to detect improvements in these separate areas of functioning. For such studies, it is necessary to use effective recruitment and retention strategies to maximize the effectiveness of research in difficult target groups. By exploring these therapeutic possibilities, the effect of ADHD symptoms may be minimized.

Abbreviations

ADHD: Attention-deficit/hyperactivity disorder; AD: Antidepressants; AIC: Akaike information criterion; AP: Antipsychotics; ATX: Atomoxetine; CD: Conduct disorder; IR-MPH: Immediate release methylphenidate; MMRM: Mixed-model repeated-measures analysis; ODD: Oppositional defiant disorder; OROS-MPH: Oral delivery system of osmotic-release methylphenidate; T-DSM-IV-S: Turgay DSM-IV-based ADHD and Disruptive Behavior Disorders Screening Scale; T0: Baseline visit; T1: Second visit between 4 and 7 weeks; T2: Third visit between 9 and 12 weeks; WFIRS-P: Weiss Functional Impairment Rating Scale-Parent Report.

Supplementary Information

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Additional file 1. Table S1. Socioeconomic status of both parents according to the Hollingshead index. **Table S2**. Baseline descriptives of the sample at the end of the study (9-12th weeks). **Table S3**. T-DSM-IV-S and WFIRS scores at the end of the study (9-12th weeks). **Table S4**. Correlations between the reductions of the T-DSM-IV-S and WFIRS-P scores in the whole sample. **Table S5**. Correlations between the reductions of

the T-DSM-IV-S and WFIRS-P scores in OROS-MPH. **Table S6**. Correlations between the reductions of the T-DSM-IV-S and WFIRS-P scores in ATX.

Additional file 2. Data Abstraction Form.

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Author contributions
AA proposed research study, produced a manuscript blueprint, performed a literature search, conducted the statistical analysis, read and edited the final draft of the manuscript. MO and HA read and edited the final draft of the manuscript. AA collected 56%, M.O 30% and HA 14% of the cases. All authors are committed to and have accepted the final manuscript. All authors read and approved the final manuscript.

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Availability of data and materials
The data that support the findings of this study are openly available in Mendeley Data at http://doi.org/10.17632/836kn5j47p.2, reference number V2.

Declarations

Ethics approval and consent to participate
The study protocol was conducted in accordance with the Helsinki Declaration and the International Council for Harmonisation Note for Guidance on Good Clinical Practice. The study was reviewed and approved by the Local Ethics Committee on 15 May 2019 (No: OMÜKAEK 2019/298) (B.30.2.ODM.0.20.08/304-431). Informed written consent to participate in the study was obtained from the parents, informed written assent were obtained from children him/herself. Informed consent and assent forms were signed applicable by Local Ethical Committee, as well.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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