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Sleep habits of children diagnosed with attention/ deficit/ hyperactivity disorder and effects of treatment on sleep related parameters

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ABSTRACT

This study aimed to evaluate the baseline sleep habits of children with ADHD and the effects of treatment with methylphenidate (MPH) and atomoxetine (ATX) on sleep parameters. Treatment naive children with clinically normal intelligence diagnosed with ADHD were enrolled in the study. Children were treated naturalistically with MPH and ATX. Treatments were started at 0.5 mg/ kg/ day and titrated weekly to a maximum of 1.2 mg/ kg/ day. The daily equivalent dose was calculated according to clinician toolkits of Utah Academy of Child and Adolescent Psychiatry. DSM-IV Based Screening and Assessment Scale for Disruptive Behavior Disorders- Parent form (DBSASDBD) and Clinical Global Impression Scale were used to assess ADHD symptoms and Children's Sleep Habits Questionnaire (CSHQ)- Short Form was used to assess the sleep habits and problems before and after the treatment. Both MPH and ATX reduced symptom severity of ADHD in all domains and also reduced total CSHQ scores with similar effect sizes. (0.7 for MPH vs. 0.8 for ATX). The rate of clinically significant sleep problems at baseline was 93.5 %. At the end-point, 83.9 % of the sample still displayed clinically significant sleep problems while none of the children were judged to have moderate-severe sleep problems. Our results suggest that both ATX and MPH may selectively improve different sleep domains in children with ADHD. Studies using standardized dosing schemes for longer durations and evaluating sleep with objective measurements may clarify the differential effects of treatments on sleep among children with ADHD.

1. Introduction

Attention deficit/ Hyperactivity Disorder (ADHD) is one of the most common neurodevelopmental disorders of childhood with a global prevalence of 5.0–12.0 % (Polanczyk et al., 2007). Sleep problems are known to be more prevalent among children diagnosed with ADHD compared to controls (Kirov and Brand, 2014; Owens, 2008). Those problems include higher levels of resistance at bedtimes, delayed settling to sleep, frequent awakenings during the night, higher apnea/ hypopnea indices and day time sleepiness according to self- and parent-reports as well as objective (i.e. Actigraphy/ polysomnography) measurements (Choi et al., 2010; Cortese et al., 2006, 2009). Studies on relationships between pharmacological treatment for ADHD and changes in sleep parameters have produced conflicting results probably due to sampling bias and methodological variations (Cortese et al., 2009; Sadeh et al., 2006).

Psychostimulants have been reported in some studies to delay sleep onset, reduce total sleep duration and suppress non-REM cycles although other studies reported no significant effects (Herman, 2015). As for atomoxetine (ATX), which is a non-stimulant widely used in the treatment of ADHD, some of the studies report somnolence as an adverse effect while others report no significant disruption in sleep parameters in children using this agent (Herman, 2015; Cheng et al., 2007; Yildiz et al., 2011).

Previous studies of sleep problems in Turkish children with ADHD were conducted cross-sectionally and did not evaluate the effects of pharmacological treatment (Ekinci et al., 2017a, b; Rodopman-Arman et al., 2011; Tarakcioglu et al., 2018; Yürümez and Kılıç, 2016). Therefore, the primary aims of this study were;

a) to evaluate the baseline sleep habits of treatment-naive children with ADHD applying to the outpatient clinics of the child psychiatry department of a tertiary treatment center

b) to evaluate the effects of treatment with methylphenidate (MPH) and ATX on sleep parameters.

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2. Materials and methods

2.1. Study center, time-frame, sampling and ethics

This study was conducted at the outpatient clinics of the Child Psychiatry Department of Duzce University Medical Faculty in between January and September 2018. IRB approval for the study was procured from the Ethics Committee of Duzce University [2018/207]. All of the study procedures were in accordance with the WHO Declaration of Helsinki and local laws and regulations.

Treatment naive children with clinically normal intelligence diagnosed with ADHD according to DSM-5 criteria [APA 2013] and semi-structured interviews (via K-SADS-PL- Turkish) who gave verbal assent and whose parents provided informed consent were enrolled in the study. Treatment compliance (according to pill counts), receiving treatment for at least three months, lack of general medical disorders requiring treatment (according to pediatric consultations), lack of primary sleep disorders (according to clinical interview and pediatric neurology consultation) were criteria for inclusion. Children were treated naturalistically with MPH or ATX formulations (ATC: N06BA04, N06BA09).

Most of the children using MPH received long-acting forms (Osmotic Release, OsR or Retard, Rt). Only one patient received immediate-release (IR) form. Regardless of formulations, treatment was started at 0.5 mg/ kg/ day and titrated weekly to a maximum of 1.2 mg/ kg/ day. The daily equivalent dose was calculated according to clinician toolkits of Utah Academy of Child and Adolescent Psychiatry (http://www.uacap.org/clinicianstoolkit.html#adhd) as well as product sheets to standardize dosages. Mean dose of MPH regardless of formulations was also computed.

3. Measures

1 **Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children- Present and Lifetime Version (K-SADS-PL)- Turkish**: This semi-structured interview was developed by Kaufman et al. (1997) to evaluate present and lifetime psychopathology in children and adolescents according to DSM-III-R and DSM-IV criteria. Reliability and validity study of the Turkish translation was conducted by Gokler et al. (2004).

2 **Children's Sleep Habits Questionnaire (CSHQ)- Short Form**: This form was used to evaluate sleep habits and problems in children and a total CSHQ score of 41 has been reported to be a sensitive cutoff for clinically significant sleep problems (Owens et al., 2000). Parents completed the Turkish version of CSHQ at baseline and the end of treatment in this study (Fis et al., 2010).

3 **DSM-IV Based Screening and Assesment Scale for Disruptive Behavior Disorders- Parent form (DBSAS-DBD)**: This form was developed to evaluate symptoms of inattention, hyperactivity/ impulsivity, oppositionality and, conduct disorders as per DSM-IV criteria.

Parents completed the Turkish version of the form at baseline and end of treatment (Ercan et al., 2001).

4 **Clinical Global Impressions Scale (CGI)**: CGI scale includes three sub-scales evaluating disorder severity, improvement and severity of adverse effects (Guy, 1976). Clinicians blinded to treatment status scored the CGI-Severity and CGI-Improvement scales in this study.

5 **Children's Depression Inventory (CDI)**: This self-report Likert-type scale was developed to evaluate symptoms of depression in children aged 6–17 years (Kovacs, 1985). Children completed the Turkish version of CDI in this study at baseline and end of treatment (Öy, 1991).

6 **Screen for Child Anxiety Related Disorders (SCARED)**: This self-report scale was developed to evaluate anxiety and associated somatic symptoms in children (Birmaher et al., 1997). Children completed Turkish version of SCARED in this study at baseline and end of treatment (Çakmakci, 2004).

4. Statistical analyses

4.1. Sample size

According to previous studies, an alpha level of 0.05 (two-tailed) for detecting an effect size of d = 0.4 (small to moderate) for t-tests independent groups will reach 80.0 % power for a sample size of 52 (Ekinci et al., 2017b; Giblin and Strobel, 2011). Within the specified time frame we could enroll 62 patients to yield 87.0 % power.

5. Analyses

Data were entered into a database prepared with Statistical Program for Social Sciences (SPSS™, IBM Inc., Armonk, NY) Version 22.0. Nominal data were summarized as counts and frequencies while non-normally distributed quantitative data were summarized as medians and inter-quartile ranges (IQR). Quantitative data which are normally distributed are summarized as means and standard deviations. Comparisons of nominal variables between groups were conducted with a chi-square test and Fisher or Yates' corrections were applied as needed. Quantitative variables which are non-normally distributed were compared across groups with Mann-Whitney U tests. P was set at 0.05 (two-tailed). Effect sizes (ES) for significant findings are also reported.

6. Results

Sixty-two children with ADHD (61.3 % male, n = 38) were enrolled in the study. Subtypes in order of frequency were Inattentive (45.2 %, n = 28), Combined (41.9 %, n = 26) and Hyperactive/ Impulsive (12.9 %, n = 8). The groups were matched in terms of age, ADHD symptom scores and subjective depression/ anxiety levels (Table 1). Most common comorbidities were Specific Learning Disorders (17.7 %, n = 11), Generalized Anxiety Disorder (12.9 %, n = 8), Oppositional Defiant Disorder (6.5 %, n = 4), Enuresis Nocturna (6.5 %, n = 4) and Provisional Tic Disorder (1.6 %, n = 1).

MPH was prescribed to 50 children (OsR = 29, Ret = 22, IR = 1) with a mean daily equivalent dose of 10.7 mg (S.D. = 5.3). Mean dose of MPH regardless of formulations was 22.2 (S.D. = 5.9) mg/ day. The median duration of treatment was 5.0 months (IQR = 2.0). Mean dose of ATX was 39.0 mg/ day (S.D. = 14.0). Treatment lasted for a median of 5.0 months (IQR = 1.8). Most of the children with inattentive (75.0 %, n = 21) and combined (88.5 %, n = 23) subtypes received MPH with no significant difference across subtypes ($\chi 2$ = 1.8, p = 0.40). Median baseline CGI-S scores for children receiving MPH and ATX were

Table 1
Clinical and sociodemographic features of children diagnosed with Attention Deficit Hyperactivity Disorder according to choice of treatment.

Median, IQR	MPH (n = 50)	ATX (n = 12)	P*
Age	8.1 (2.9)	8.1 (3.7)	0.99
DBSAS- DBD-Inattentive score	18.0 (8.5)	15.5 (8.0)	0.82
DBSAS- DBD- Hyperactive/ Impulsive score	11.5 (10.3)	8.5 (16.5)	0.48
DBSAS- DBD- Total score	28.0 (10.3)	28.5 (16.8)	0.96
CDI	6.5 (7.3)	9.0 (6.8)	0.58
SCARED	26.0 (16.3)	26.0 (18.8)	0.72

* Mann-Whitney U test, IQR: Inter-quartile Range, MPH: methylphenidate, ATX: atomoxetine, DBSAS- DBD: DSM-IV Based Screening and Assessment Scale for Disruptive Behavior Disorders- Parent form, CDI: Children's Depression Inventory, SCARED: Screen for Child Anxiety Related Disorders.

Table 2
Changes in symptoms of children diagnosed with Attention Deficit/ Hyperactivity Disorder according to choice of treatment.

Median, IQR	MPH (n = 50)		P*	E.S.	ATX (n = 12)		P*	E.S.
	Baseline	End-point			Baseline	End-point		
DBSAS- DBD-Inattentive score	18.0 (8.5)	11.0 (6.3)	0.00	0.86	15.5 (8.0)	12.0 (5.5)	0.00	0.89
DBSAS- DBD- Hyperactive/ Impulsive score	11.5 (10.2)	6.5 (7.0)	0.00	0.82	8.5 (16.0)	5.0 (12.0)	0.01	0.80
DBSAS- DBD- Total score	28.0 (10.3)	18.0 (10.0)	0.00	0.87	28.5 (16.8)	18.0 (14.0)	0.00	0.89

* Wilcoxon signed-ranks test, IQR: Inter-quartile range, ATX: atomoxetine, MPH: methylphenidate, DBSAS-DBD: DBSAS- DBD: DSM-IV Based Screening and Assessment Scale for Disruptive Behavior Disorders- Parent form.

5.0 (IQR = 1.3) and 4.5 (IQR = 3.0) respectively. MPH and ATX groups were similar in terms of gender, baseline disorder severity and treatment duration (all $p > 0.05$). Children with comorbid diagnoses received ATX significantly more frequently ($\chi 2 = 8.8$, $p = 0.004$, Fisher) with a small effect size (Phi = 0.38).

Clinical and sociodemographic features of children according to treatment are listed in Table 1. Baseline and end-point symptom scores according to treatment choices are illustrated in Table 2.

Both MPH and ATX reduced symptom severity of ADHD, in all domains with similar effect sizes (Pallant, 2007). Treatment-related improvement and adverse effects according to clinician evaluations did not show any significant difference across the groups ($p > 0.05$). 93.5 % of children with ADHD (n = 58) had clinically significant sleep problems at baseline and 12 were treated with ATX while the rest received MPH ($p > 0.05$). With a cut-off score of 56 at CSHQ, this reduced to 33.9 % (n = 21). Of those four were prescribed ATX while the rest received MPH with no significant difference. Baseline CSHQ scores of children receiving ATX and MPH were similar except daytime sleepiness (Mann-Whitney U test, Z= - 2.3, $p = 0.03$, ES, r = 0.29). After treatment, 83.9 % of children (n = 52) were reported to have clinically significant sleep problems while none scored 56 or above in the CSHQ. Children reported to have sleep problems at the endpoint did not differ in treatments (Chi-square test). Treatment-related changes in sleep dimensions according to CSHQ are listed in Table 3.

Both methylphenidate (Z= - 4.8, $p = 0.000$) and atomoxetine (Z= - 2.8, $p = 0.005$) significantly reduced total CSHQ scores (Wilcoxon signed ranks test) with similarly large effect (0.7 for MPH vs. 0.8 for ATX).

ATX treatment reduced parasomnias and daytime sleepiness. NNTs for parasomnias and daytime sleepiness for ATX receiving children were 1.2 and 1.1; respectively. MPH treatment improved all domains of sleep except delayed sleep onset and sleep-disordered breathing with moderate effect sizes. NNTs for sleep problems for MPH receiving children varied between 3.1 and 1.7.

Comorbidity did not affect CSHQ scores at baseline (Mann-Whitney U test). However, day time sleepiness scores of those with comorbidity were significantly higher at the endpoint (Mann-Whitney U test, Z= -3.1, $p = 0.002$, ES, r = 0.39).

Rescue/ adjunctive treatments were used in eleven children (17.7 %). Those mostly involved SSRIs (fluoxetine, 11.3 %, n = 7; sertraline, 3.2 %, n = 2). Four patients were started on risperidone. Patients receiving additional treatments did not differ significantly in terms of baseline CSHQ scores (Mann-Whitney U test).

7. Discussion

In this single-center, naturalistic follow-up study, ATX treatment significantly improved parasomnias and daytime sleepiness in our sample while MPH improved all sleep domains except delayed sleep onset and sleep-disordered breathing. Both significantly reduced total CSHQ scores, so none of the children were judged to have 'moderate-severe' sleep problems anymore at the endpoint.

Although, sleep problems are the most significant reported adverse effects in children with ADHD receiving MPH; study results were found to be contradictory. Some of the studies reported that MPH delayed sleep onset, reduced total sleep duration and disrupted REM sleep cycles (Kidwell et al., 2015; Simonoff et al., 2013; Stein et al., 2011) while others reported MPH did not disrupt sleep and even decreased existing sleep problems and improved sleep architecture (Giblin and Strobel, 2011; Owens et al., 2016; Hyo-Won et al., 2010). The conflicting results may be explained by study design (follow-up vs. retrospective), measurement methods (parent reports vs. polysomnography), sampling characteristics (age, weight, ADHD subtypes, comorbidity, severity of baseline sleep problems, daily dose regimes), different forms of MPH (long-acting vs. IR) and duration of treatment (Corkum, 2007; Becker and Froehlich, 2016; Stein et al., 2003; Cortese et al., 2013). In our sample, MPH treatment reduced clinically significant sleep problems and none of our patients developed ***de novo*** sleep problems in accordance with follow up studies (Becker and Froehlich, 2016; Faraone et al., 2009). This may suggest that MPH treatment, at least in the short term, improves sleep problems in various domains in children with ADHD. However, the effects of chronic treatment, as well as objective

Table 3
Treatment related changes in sleep problems according to Children's Sleep Habits Questionnaire (CSHQ) in children diagnosed with Attention deficit/ Hyperactivity Disorder.

Median, IQR	ATX (n = 12)				MPH (n = 50)			
	Baseline	Endpoint	P*	E.S. (r)	Baseline	Endpoint	P*	E.S. (r)
Bedtime resistance	10.0 (4.7)	8.5 (3.0)	0.06	0.54	10.0 (5.0)	8.5 (5.3)	0.01	0.37
Delayed sleep onset	1.0 (1.0)	1.0 (1.0)	0.41	–	1.0 (1.0)	1.0 (1.0)	0.27	–
Sleep duration	4.0 (2.0)	4.0 (2.0)	0.79	–	4.0 (3.0)	3.0 (2.0)	0.03	0.31
Sleep anxiety	6.0 (4.3)	6.5 (2.8)	0.08	0.49	7.0 (3.3)	6.0 (3.3)	0.02	0.32
Night awakenings	3.5 (2.0)	4.0 (1.8)	0.76	–	4.0 (2.0)	4.0 (2.0)	0.04	0.28
Parasomnias	10.5 (4.3)	8.0 (2.5)	0.01	0.71	9.0 (3.0)	8.0 (3.3)	0.03	0.31
Daytime sleepiness	14.0 (5.0)	12.0 (2.8)	0.01	0.74	11.0 (6.3)	9.0 (3.5)	0.00	0.51
Sleep-disordered breathing	3.0 (0.0)	3.0 (0.0)	0.66	–	3.0 (0.0)	3.0 (0.0)	0.05	0.28

IQR: Inter-quartile range, ATX: atomoxetine, MPH: methlyphenidate.
* Wilcoxon signed ranks test, E.S.: effect size.

changes in sleep indices should be evaluated in further studies.

The mean daily equivalent dose of MPH (i.e. 10.7 mg/ day) as well as the mean daily dose of MPH regardless of formulations (i.e. 22.2 mg/ day) were lower than those reported in previous studies. Chen and colleagues in their recent book reported that most of the studies assessing effects of MPH treatment on sleep variables among children with ADHD used 10 − 72 mg/ day in various formulations (Chen et al., 2019). In the studies reported by Owens and colleagues (Owens et al., 2016) mean doses of MPH across two studies were 25.7 ± 6.2 and 36.6 ± 12.8 mg/ day; respectively. As such, our doses were lower than those reported previously and this may prevent adverse effects of treatment on sleep. Alternatively, our patients may have less severe forms of ADHD which may be associated with milder sleep problems. The differences may also be due to our patient sample being younger and weighting less. Further studies on samples from diverse age ranges and using different dosing schedules may clarify those observations.

Previous studies reported that ATX caused significantly lower problems in sleep structure and sleep-wake cycles, probably due to lack of dopaminergic effects and seemed to be superior to stimulant medications (Padilha et al., 2018; Garnock-Jones and Keating, 2009; Block et al., 2010). In a previous randomized controlled study comparing twice-daily MPH with atomoxetine, ATX was found to reduce nightly awakenings and also improved bedtime resistance, settling down to sleep, sleep quality and morning wakefulness (Sangal et al., 2006). In our study, ATX improved parasomnias and daytime sleepiness and none of our patients developed ***de novo*** sleep problems during ATX treatment. However, parents of children receiving ATX reported clinically significant problems at baseline and all of those parents continued to report significant problems at the endpoint. Our results partially conflict with those reported previously (Garnock-Jones and Keating, 2009; Block et al., 2010; Sangal et al., 2006; Hollway et al., 2018). This may be due to reporting and/ or recall bias, comorbid diagnoses or shorter duration of treatment. Further studies are needed to evaluate effects of ATX on sleep parameters in ADHD.

ADHD is a long life disorder and usually associated with sleep problems that effect daily function and quality of life. Pharmacological treatment choices for insomina in children with ADHD inculdes sedative-hypnotic agents, benzodiazepines and melatonine (Cortese et al., 2013). Zolpidem which is a sedative hypnotic agent is is associated with minimal rebound insomnia and may be a treatment choice for the pharmacological treatment of insomnia in adult ADHD patients (Furuhashi, 2019). Zolpidem and eszopiclone can also be a treatment choice in pediatric sleep-onset Sleep Problems in Children with ADHD but their effectiveness based on actigraphy and polismonigraphy were not found to be adequate on sleep onset latency altough an improvement was shown in Clinical Global Impression Improvement/Severity scores in controlled trials and, dizziness, headaches, enuresis and hallucinations are reported as most common side effects in children (Blumer et al., 2009; Sangal et al., 2014). So further studies should be designed to understand the effectiveness and side effects of sedative hypnotic agents in sleep problems of pediatric ADHD patients.

Our results should be evaluated within their limitations. Firstly, those results are valid for treatment naïve children with ADHD applying for treatment at the study center within the specified time-frame and may not be valid for clinical samples at other centers or those from the community. Secondly, this is a naturalistic follow-up study and apart from dosing schedules in accordance with established practices, selection of MPH formulations as well as additional treatments were left to the discretion of the primary clinicians. Those variables may have affected our results. Thirdly, dependence on parental reports for sleep problems may increase reporting and recall bias as well as regression to the mean. Fourth, we used pill counts and parent/ child reports as a proxy for compliance. Measuring plasma levels of MPH and ATX may lead to more objective measurements of compliance. Fifth, it is known that CYP2D6 polymorphisms may affect the metabolism and efficacy of atomoxetine and we did not evaluate our patients for those polymorphisms. Sixth, children with comorbid diagnoses received ATX significantly more frequently and those may affect the results of treatment. Seventh, due to the naturalistic design we allowed rescue and adjunctive medications during the study period and those may affect our findings. Eight, we did not evaluate for parenting dimensions which may affect sleep variables. Last, but not least, we used lower doses of MPH in treating patients with ADHD and this may have affected our results.

8. Conclusions

Our results suggest that both ATX and MPH may selectively improve sleep domains in children with ADHD. Studies using standardized dosing and treatment schemes with longer treatment durations and using both objective and subjective (i.e. sleep diaries, CSHQ, etc.) measurements may clarify differential effects of treatments on sleep among children with ADHD.

Financial disclosure

There is no financial disclosure in this study.

Declaration of Competing Interest

None.

Acknowledgement

None.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.ajp.2020.102045.

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