Alpha Psychiatry

ORIGINAL ARTICLE
Alpha Psychiatry 2023;24(5):174-179
DOI: 10.5152/alphapsychiatry.2023.231185

The Effects of Methylphenidate on Ventricular Repolarization Parameters in Children with Attention-Deficit Hyperactivity Disorder

ABSTRACT

Background: Long-acting methylphenidate (MPH), a psychostimulant agent, is widely used in the treatment of attention-deficit hyperactivity disorder (ADHD). Methylphenidate might cause an increment in the risk of lethal arrhythmias by deteriorating ventricular repolarization. QT intervals, the corrected QT (QTc), QT dispersion, T-peak to T-end (TpTe), and the TpTe/QTc ratio are the most utilized indicators of ventricular repolarization in electrocardiogram (ECG). The present study was conducted to examine the effects of long-term MPH use on the ECG in pediatric patients.

Methods: A total of 52 children with ADHD and 51 age- and gender-matched controls were enrolled in the study. The children had been using MPH regularly for at least 6 months. Comparisons were made regarding ECG parameters, including the mean intervals of QT, QTc, QTc dispersion interval duration, TpTe intervals, TpTe/QT, and TpTe/QTc ratio.

Results: The median duration of treatment with MPH was 30 months (minimum–maximum: 6-120), and the median MPH dose was 30 mg/day (minimum–maximum: 18-54). The main findings showed significantly prolonged P-wave dispersion, TpTe interval, TpTe dispersion, and TpTe/QT and TpTe/QTc ratios in the ADHD group compared to the healthy controls ($P < .001$). These parameters were not associated with MPH dose or treatment duration. Additionally, nearly half of the patients had QTc values of 460 ms or higher, but there were no significant differences in treatment duration and dose compared to the remaining group ($P = .792$ and $P = .126$).

Conclusion: Methylphenidate may have proarrhythmogenic effects in children with ADHD, which may not be adversely affected by long-term use and treatment dose. Considering the extensive use of MPH, cardiac monitoring of these children is important.

Keywords: Attention-deficit hyperactivity disorder, cardiovascular effects, electrocardiography, methylphenidate, children

Introduction

Attention-deficit hyperactivity disorder (ADHD) is one of the most common psychiatric disorders of childhood. Children with ADHD have decreased functioning in several areas of their lives.[1] Attention-deficit hyperactivity disorder, affecting approximately 3%-5% of children, stands as one of the most prevalent neurodevelopmental disorders.[2] Attention-deficit hyperactivity disorder is strongly related to inadequate self-esteem and social functioning outcomes in the long term if left untreated.[3,4] The treatment of ADHD focuses on improving behavioral, social, and cognitive functioning of the patients.[4]

Successful management of patients with ADHD may include parental education, behavioral interventions, and pharmacological treatment. Methylphenidate (MPH), a psychostimulant drug, is the most commonly used psychotropic drug for ADHD.[5,6] Methylphenidate inhibits dopamine and norepinephrine reuptake by presynaptic neurons.[7] Methylphenidate has been shown to decrease symptoms of ADHD in children and improve functioning in several

Yaşar Tanır[1]
Muhammed Furkan Erbay[1]
Selçuk Özkan[2]
Rahmi Özdemir[3]
Abdurrahman Cahid Örengül[1]

[1]*Department of Child and Adolescent Psychiatry, Istanbul Medical Faculty, Istanbul University, Istanbul, Turkey*
[2]*Department of Child and Adolescent Psychiatry, Evliya Celebi Training and Research Hospital, Kütahya Health Sciences University, Kütahya, Turkey*
[3]*Department of Pediatric Cardiology, Evliya Celebi Training and Research Hospital, Kütahya Health Sciences University, Kütahya, Turkey*

Corresponding author:
Yaşar Tanır
yasar.tanir@istanbul.edu.tr

Received: April 07, 2023
Accepted: August 11, 2023
Publication Date: September 27, 2023

Cite this article as: Tanır Y, Erbay MF, Özkan S, Özdemir R, Örengül AC. The effects of methylphenidate on ventricular repolarization parameters in children with attention-deficit hyperactivity disorder. *Alpha Psychiatry*. 2023;24(5):174-179.

randomized controlled trials.[8,9] Guidelines recommend the use of long-acting MPH to improve the functioning of children with ADHD.[10]

The prevalence of ADHD and the positive effects of MPH on the functioning of children with ADHD make it one of the most prescribed medications in children. However, serious side effects of MPH have been reported.[11] One of the most important side effects of MPH is increased heart rate and blood pressure.[12] Guidelines recommend close monitoring of blood pressure and heart rate in children using MPH regularly. Psychostimulant agents may have proarrythmogenic effects because of their sympathomimetic properties.[13] Methylphenidate has been accused to prolong corrected QT (QTc) intervals, which might result in sudden cardiac death through torsades de pointes, a potentially lethal polymorphic ventricular arrhythmia.[14] In addition, the use of MPH is associated with disturbances in cardiac repolarization, as indicated by a significantly increased T-peak to T-end (TpTe) interval, TpTe dispersion, and TpTe/QT ratio in patients with ADHD.[14] In contrast, these effects were not observed on the ECG 2 hours after the administration of MPH (10 mg per os).[13] There are a limited number of studies in the literature examining the effects of MPH on cardiac repolarization, and the results are conflicting. Further research is necessary to investigate the cardiac side effects of this widely used psychotropic drug in children with ADHD.

Recently, it has been reported that prolonged QTc (≥500 ms), which is suggested to be a risk factor for lethal arrhythmias, solely is not sufficient on its own to ascertain ventricular repolarization.[15] In order to better predict potential risks, additional parameters such as QT dispersion (QTd) and TpTe have been suggested. QT dispersion, which measures the variability between QT intervals in an electrocardiogram (ECG), is determined by calculating the difference between the highest and lowest values observed across all QT intervals.[16] The QTd prolongation is considered a more reliable predictor, with a value exceeding 100 ms being considered a potential risk factor for life-threatening arrhythmias.[13] T-peak to T-end, which has emerged as a promising marker for ventricular arrhythmias, is defined as the duration between the peak and the end of the T-wave.[13] Studies have demonstrated an independent association between the prolongation of TpTe in lead V5 and sudden cardiac death. This finding suggests that TpTe may serve as a reliable predictor of adverse cardiac events, even when the QTc interval falls within the normal range.[17,18] Moreover, it has been reported that the TpTe/QTc ratio may be able to show early findings in asymptomatic patients.[18,19]

To the best of the authors' knowledge, there is a scarcity of studies in the existing literature that specifically examine the impact of MPH usage on QTd, TpTe values, and the TpTe/QTc ratio among pediatric patients diagnosed with ADHD.[13,14,15] The first purpose of this study is to evaluate the impact of MPH on QTd, TpTe values, and the TpTe/QTc ratio by comparing these parameters with those of age- and gender-matched healthy children. The second objective of the study is to compare the electrocardiographic features of patients using MPH for more and less than 2 years.

MAIN POINTS

- *Methylphenidate (MPH) may have proarrhythmogenic effects in children with attention-deficit hyperactivity disorder (ADHD).*
- *T-peak toT-end may be a useful parameter for cardiac follow-up in children with ADHD using MTH.*
- *Cardiac monitoring may be recommended in children using MPH.*

Material and Methods

Study Population

A total of 52 children diagnosed with ADHD and 51 age- and gender-matched controls were enrolled in the study. All children diagnosed with ADHD were using MPH regularly for at least 6 months. A child and adolescent psychiatrist examined all children with ADHD to confirm the diagnosis based on the Diagnostic and Statistical Manual of Mental Disorders (DSM)-5 criteria. The control group consisted of children who were receiving care at the pediatric clinics of Kütahya University of Health Sciences Hospital. Children with a history of cardiac disease, current use of medications known to prolong QT intervals (such as antihistamines and betamimetics), electrolyte disorders, hypothyroidism, and other psychotropic medications were excluded from the study. Additionally, children with chronic cardiac disease, the use of other medications, and the presence of other major psychiatric disorders such as schizophrenia and intellectual disability were also excluded. In all enrolled patients, treatment with immediate-release MPH was started at an initial dosage of 5 mg/day. The dosage was gradually adjusted over a period of 4 weeks until reaching the therapeutic dose. After this period, all patients were switched to long-acting MPH. Based on the weight of each subject, the low and medium doses of MPH were determined as 18 mg and 36 mg, respectively. Among the participants, only 3 adolescents reached the highest dose of 54 mg. All patients included in the study had body weights exceeding 18 kg. Consequently, the administered dosage range varied between 0.75 mg/kg and 0.97 mg/kg based on the individual's weight. Each dose of drug was administered once a day for 7 days at breakfast, approximately 08:00 AM.

A sociodemographic form was used to collect information on parameters such as age, gender, MPH use, and dose. The form was completed by the parents of the children after the psychiatric examination. Written consent and verbal assent were obtained from all subjects and their families prior to their participation in the study. The study received approval from the Clinical Research Ethics Committee of Kütahya University of Health Sciences (Date: February 18, 2021, Approval No: 2021/03-08).

Electrocardiogram

Prior to conducting the electrocardiography (ECG), all children were provided with a detailed explanation of the procedure and the purpose of the ECG. To ensure accurate readings, a standard ECG machine with a 12-channel ECG recorder was used. The ECG signals were recorded at a standard speed of 25 mm/s and amplitude. The ECG findings were manually measured by 2 different physicians. using a ruler. Inclusion in the study was based on the condition that the difference between the measurements conducted by the 2 physicians was less than 5%. Subsequently, all of the ECG findings were evaluated by an experienced pediatric cardiologist (R.O.).

The heart rate was initially determined by analyzing the ECG recordings. Subsequently, the P-wave dispersion, defined as the difference between the widest and narrowest P-wave durations, was measured. The duration or interval of the QRS complex was determined as the mean time from the onset of the Q wave to the end of the S wave across all leads. The QT interval was calculated as the average time

from the onset of the QRS complex to the point where the T wave returns to the isoelectric line. This measurement was performed on leads DII, V5, and V6. To determine the QTc interval, Bazett's correction formula was employed: (QTc = QT/√RR in seconds).[19,20] QT dispersion was defined as the difference between the lowest and highest QT intervals observed across the 12 leads of the ECG.[20] In order to determine the TpTe interval, the length was measured from the highest point of the T wave, where it was most appropriate in the precordial leads. This measurement was taken to the intersection point of the isoelectric baseline and the downward slope of the T wave. The TpTe dispersion was defined as the discrepancy between the highest and lowest TpTe values observed in the precordial leads. T-peak to T-end/corrected QT ratios were recorded, finally.[18] The systolic and diastolic blood pressures, as well as the median heart rate, were documented for all groups.

Statistical Analyses

All analyses were conducted with Statistical Package for the Social Sciences (SPSS) version 21.0 (IBM SPSS Corp.; Armonk, NY, USA). Categorical descriptive variables were presented as frequencies and percentages. Continuous variables were reported as either mean ± SD or median (minimum–maximum) based on the distribution of the variable (normal or non-normal, respectively). The normality of continuous variables was assessed using the Shapiro–Wilk test. The chi-square test was employed to examine the differences between categorical variables in the sample. For normally distributed variables, the Student's *t*-test was used to compare the differences between the 2 groups. Non-normally distributed continuous data were analyzed using the Mann–Whitney *U*-test. The associations between variables were evaluated using the Pearson correlation coefficient. A *P* value of less than .05 was considered statistically significant for indicating a difference or relationship.

Results

The 2 groups did not exhibit a statistically significant difference in terms of age (ADHD group: 11.0 ± 2.5 years, control group: 11.0 ± 2.3 years), and gender [male/female (%): 39/13 (75/25) in the ADHD group and 35/16 (68/32) in the control group]. The demographic characteristics of the patients are shown in Table 1. The mean heart rate was found to be significantly higher in the ADHD group compared to the control group (*P* = .019). Table 2 illustrates the significant differences in ECG parameters between the 2 groups.

Characteristics of Patients with QTc > 460

The subjects were further examined based on their QTc values, with a cutoff of 460 ms. The analysis investigated the potential differences in age, gender, treatment dosage, and treatment duration between children with QTc values below 460 ms and those with values equal to or above 460 ms. The results indicated no significant differences in terms of age, gender, and treatment dosage between these 2 groups (*P* = .122, *P* = .873, and *P* = .792, respectively). Additionally, there were no significant differences in TpTe interval, TpTe dispersion, and TpTe/QT ratio between the groups, as shown in Table 3 (*P* = .728, *P* = .689, and *P* = .557, respectively).

Table 1. Demographic Data of the 2 Groups

Variables	ADHD (n = 52)	Control (n = 51)	*P*
Age (years, mean ± SD)	11.0 ± 2.5	11.0 ± 2.3	.987
Gender [male, n (%)]	39 (75.0)	35 (68.6)	.472
Weight (kg, mean ± SD)	40 ± 12.9	40.4 ± 12	.861
Height (cm, mean ± SD)	143.6 ± 14.1	144.2 ± 13.6	.832
Duration of therapy, months (median, minimum–-maximum)	18, 6-120		
Methylphenidate dosage, mg/day (median, minimum–max)	30, 18-54		

ADHD: Attention Deficit Hyperactivity Disorder.

Table 2. Electrocardiographic Characteristics of Groups

Variables	Patient (n = 52)	Control (n = 51)	*P*
Heart rate, bpm	91.6 ± 18	83.3 ± 14	**.019**
Systolic BP (mmHg)	102.6 ± 11.2	95 ±8.4	**<.001**
Diastolic BP (mmHg)	64.1 ± 8.4	58 ± 6	**<.001**
P-wave maximum, ms	110 ± 21	89 ± 14	**<.001**
P-wave minimum, ms	49 ± 19	43 ± 8	.064
P-wave dispersion, ms	61 ± 18	46 ± 14	**<.001**
QT interval maximum, ms	383 ± 47	352 ± 36	**<.001**
QT interval minimum, ms	319 ± 44	304 ± 34	.054
QT interval dispersion, ms	63 ± 20	48 ± 16	**<.001**
QTc interval maximum, ms	470 ± 72	427 ± 24	**<.001**
QTc interval minimum, ms	391 ± 65	373 ± 28	**.070**
QTc interval dispersion, ms	78 ± 27	54 ± 23	**<.001**
TpTe interval maximum, ms	145 ± 63	90 ± 15	**<.001**
TpTe interval minimum, ms	36 ± 15	46 ± 11	**<.001**
TpTe interval dispersion, ms	109 ± 58	43 ± 15	**<.001**
TpTe/QT	0.21 ± 0.06	0.12 ± 0.05	**<.001**
TpTe/QTc	1.51 ± 0.9	0.9 ± 0.7	**<.001**

BP, blood pressure; bpm, beats per minute; QTc, corrected QT; TpTe, T-peak to T-end. Statistically significant results are indicated in bold.

Electrocardiographic Characteristics of Patients Using Methylphenidate for More Than 2 Years

There was a positive association between MPH treatment duration and dosage, with patients using MPH for longer durations receiving higher treatment doses (*P* < .001 and *P* = .048, respectively). There was no significant difference among the patients using MPH for less and more than 2 years in terms of electrocardiographic characteristics (Table 4).

Discussion

The present study showed significantly more cardiac repolarization problems in children using long-acting MPH for at least 6 months than control subjects. The main findings were significantly prolonged P-wave dispersion, TpTe interval, TpTe dispersion, and TpTe/QT and TpTe/QTc ratios in the ADHD group compared to healthy controls. These parameters were not related to MPH dose and treatment

Table 3. Stratification of Dose and Treatment Duration by QTc Interval in Patient Group

Variables	QTc < 460 ms (n = 27)	QTc ≥ 460 ms (n = 25)	*P*
Gender (male/female)	20/7	19/6	.873
Age (years, mean ± SD)	11.5 ± 2.5	10.4 ± 2.5	.122
Dose (mg)	30.7 ± 9.2	30.0 ± 9.9	.792
Treatment duration (months)	25.3 ± 16.3	19.2 ± 10.9	.126

Table 4. Electrocardiographic Characteristics of Patients Using MPH for a Longer Duration

Variables	< 2 Years (n = 30)	≥ 2 Years (n = 22)	*P*
Duration (months)	13.8 ± 4.8	36.3 ± 22.2	<.001
Dose (mg/kg)	0.75 ± 0.3	0.87 ± 0.3	.048
Heart rate, bpm	92.2 ± 16	90.9 ± 21	.636
Systolic BP (mmHg)	102.6 ± 11.8	102.7 ± 10.8	.985
Diastolic BP (mmHg)	65.3 ± 8.6	62.5 ± 8.1	.202
P-wave maximum, ms	114 ± 24	106 ± 19	.208
P-wave minimum, ms	52 ± 22	45 ± 16	.247
P-wave dispersion, ms	62 ± 16	61 ± 22	.702
QT interval maximum, ms	394 ± 56	369 ± 29	.060
QT interval minimum, ms	326 ± 54	310 ± 26	.145
QT interval dispersion, ms	67 ± 22	59 ± 18	.142
QTc interval maximum, ms	486 ± 89	449 ± 34	.154
QTc interval minimum, ms	402 ± 79	378 ± 37	.211
QTc interval dispersion, ms	84 ± 31	71 ± 21	.101
TpTe interval maximum, ms	153 ± 73	136 ± 46	.728
TpTe interval minimum, ms	38 ± 17	34 ± 13	.223
TpTe interval dispersion, ms	115 ± 65	101 ± 48	.689
TpTe/QT	0.12 ± 0.06	0.11 ± 0.05	.557
TpTe/QTc	1.5 ± 0.9	1.5 ± 0.8	.547

BP, Blood pressure; bpm, beats per minute; QTc, corrected QT; TpTe, T-peak to T-end.

duration. Additionally, almost half of the patients had QTc values of 460 ms or higher, but these patients did not differ from the remaining group in terms of treatment duration and dose. There was an association between the treatment with long-acting MPH and a modest increase in systolic and diastolic BP. However, BP values over the normal range were not encountered in any of the patients.

In the present study, the majority of parameters indicating cardiac repolarization problems were significantly higher in children using long-acting MPH. There are few studies in the literature on the cardiac effects of MPH monotherapy in the pediatric population with ADHD.[13,14,15] Lamberti et al[13] conducted a study examining the electrocardiographic outcomes of children with ADHD. The study assessed the ECG parameters both before and 2 hours after the administration of orally delivered MPH at a dose of 10 mg. The results of the study revealed no significant differences in TpTe, QTc, and QTd values between the pre- and post-MPH administration. However, a statistically significant increase was observed in TpTe/QTc values following the administration of MPH. It has been shown that the TpTe interval, TpTe dispersion, and TpTe/QT ratio were significantly higher in the patients on medication (MPH, risperidone, and combination) than in the untreated ADHD and control groups.[14] In the present study, the patients on MPH medication exhibited significantly higher values of P-wave dispersion, TpTe interval, TpTe dispersion, and TpTe/QT ratio compared to the control group. Studies investigating P-wave dispersion in children using MPH are currently limited. Further research is necessary to explore the potential association between MPH use and P-wave dispersion, which could indicate atrial conduction abnormalities. In summary, MPH treatment may have detrimental effects on the aforementioned parameters. However, longitudinal follow-up studies are required to determine the clinical significance of these findings, particularly in terms of the potential risk for arrhythmias and other cardiac complications.

Another noteworthy finding of this study is that approximately half of the patients using MPH had QTc values of 460 ms and above. There was no statistically significant difference between those with and without QTc values above 460 ms in terms of age, gender, drug dose, and duration of treatment. While the duration of the QT interval has been implicated in the heterogeneity of myocardial repolarization, it is not consistently recognized as a reliable predictor of polymorphic ventricular tachycardia (torsades de pointes) and sudden cardiac death.[21] Given that T-wave morphology plays a predictive role in drug-induced polymorphic ventricular tachycardia, it is crucial to thoroughly examine and understand it.[22,23,24] Several studies have proposed that the TpTe interval, TpTe dispersion, and TpTe/QT ratio may serve as more accurate markers than the QT interval and QTd in predicting ventricular arrhythmias. Therefore, these parameters were investigated due to their potential for improved predictive value.[25,26] Interestingly, these parameters were not different in patients with a QTc of 460 ms or greater and in those with lower values. In conclusion, it may be important to follow up with children with ADHD regarding the potential proarrhythmogenic effects associated with long-term use of MPH.

One of the main objectives of our study was to compare the electrocardiographic characteristics of patients using long-acting MPH for a duration of 2 years or more with those using it for 6 months to 2 years. The results revealed that the electrocardiographic characteristics of patients using it for longer durations were not different from those using it for shorter durations. To the best of our knowledge, there is no study that has specifically investigated the effects of medium- and long-term treatment with MPH on the ECG. Considering the other findings of our study, it suggests that long-term use of MPH may not have a negative impact on ECG parameters related to cardiac repolarization when compared to short-term use. However, it is important to investigate the risk of arrhythmias in children who are planning to use MPH by assessing the family history of sudden cardiac death and monitoring blood pressure and heart rate.[27] Electrocardiogram examination may also offer additional benefits, particularly in cases where there may be an increased risk.

Numerous studies have been conducted to explore the potential cardiovascular effects and safety profile of MPH in adult populations. However, there are a limited number of studies that have specifically investigated the safety of MPH in the pediatric population over the past decades. Recent studies that have aimed to assess the long-term safety of MPH use in children have produced inconsistent results regarding the potential association between stimulant use and adverse cardiovascular outcomes.[28,29,30] In an open-label extension trial of long-acting MPH, statistically significant but slight increases were observed in heart rate (+3.9 bpm), systolic blood pressure (+3.3 mmHg), and diastolic blood pressure (+1.5 mmHg). These changes, although small, were found to be statistically significant.[12] Similarly,the present study also observed higher mean heart rate, systolic blood pressure, and diastolic blood pressure compared to the control group.

The present study is a cross-sectional case–control study that aimed to investigate differences in cardiac repolarization between children

using long-acting MPH for more than 6 months (with nearly 40% of the cases having been using MPH for 2 years or more) and healthy controls. This study is the first in the literature to demonstrate an increase in ECG parameters related to ventricular repolarization in cases using long-acting MPH for more than 6 months. However, the study has several limitations. The cross-sectional design limits the ability to establish a cause-and-effect relationship. Longitudinal studies are needed to provide further insight into the effects of MPH on cardiac repolarization. Additionally, including drug-naive children with ADHD as a control group would have been beneficial in terms of isolating the cardiac effects of ADHD. Furthermore, being a single-center study may restrict the generalizability of the findings. It should be noted that other methods, such as echocardiography, could be employed to assess cardiac function and structure. Lastly, the study lacked baseline ECG parameters, which could have provided valuable comparative information.

Methylphenidate may have proarrhythmogenic effects in children with ADHD, but these effects may not be worsened by long-term use or treatment dose. It is important to monitor the cardiac function of these children due to the widespread use of MPH. Further longitudinal studies are necessary to investigate the cardiac effects of MPH in children with ADHD.

Ethics Committee Approval: *The study received approval from the Clinical Research Ethics Committee of Kütahya University of Health Sciences (Approval no: 2021/03-08, Date: February 18, 2021).*

Informed Consent: *Written consent and verbal assent were obtained from all subjects and their families prior to their participation in the study.*

Peer-review: *Externally peer-reviewed.*

Author Contributions: *Concept – Y.T., S.Ö.; Design – Y.T., S.Ö.; Supervision – Y.T., R.Ö.; Resources – Y.T., R.Ö.; Materials – Y.T., S.Ö.; Data Collection and/or Processing – Y.T., S.Ö.; Analysis and/or Interpretation – Y.T., M.F.E.; Literature Search – Y.T., A.C.Ö.; Writing – Y.T., A.C.Ö.; Critical Review – Y.T., A.C.Ö.*

Declaration of Interests: *The authors have no conflict of interest to declare.*

Funding: *The authors declared that this study has received no financial support.*

References

1. Klassen AF, Miller A, Fine S. Health-related quality of life in children and adolescents who have a diagnosis of attention-deficit/hyperactivity disorder. *Pediatrics*. 2004;114(5):e541-e547. [CrossRef]
2. Sayal K, Prasad V, Daley D, Ford T, Coghill D. ADHD in children and young people: prevalence, care pathways, and service provision. *Lancet Psychiatry*. 2018;5(2):175-186. [CrossRef]
3. Harpin V, Mazzone L, Raynaud JP, Kahle J, Hodgkins P. Long-term outcomes of ADHD: a systematic review of self-esteem and social function. *J Atten Disord*. 2016;20(4):295-305. [CrossRef]
4. Shaw M, Hodgkins P, Caci H, et al. A systematic review and analysis of long-term outcomes in attention deficit hyperactivity disorder: effects of treatment and non-treatment. *BMC Med*. 2012;10:99. [CrossRef]
5. Faraone SV, Asherson P, Banaschewski T, et al. Attention-deficit/hyperactivity disorder. *Nat Rev Dis Primers*. 2015;1:15020. [CrossRef]
6. Subcommittee on Attention-Deficit/Hyperactivity Disorder, Steering Committee on Quality Improvement and Management, Wolraich M, et al. ADHD: clinical practice guideline for the diagnosis, evaluation, and treatment of attention-deficit/hyperactivity disorder in children and adolescents. *Pediatrics*. 2011;128(5):1007-1022. [CrossRef]
7. Reddy DS. Current pharmacotherapy of attention deficit hyperactivity disorder. *Drugs Today (Barc)*. 2013;49(10):647-665. [CrossRef]
8. Conners CK. Forty years of methylphenidate treatment in Attention-Deficit/Hyperactivity Disorder. *J Atten Disord*. 2002;6(suppl 1):S17-S30. [CrossRef]
9. Marcus SC, Wan GJ, Kemner JE, Olfson M. Continuity of methylphenidate treatment for attention-deficit/hyperactivity disorder. *Arch Pediatr Adolesc Med*. 2005;159(6):572-578. [CrossRef] [published correction appears in *Arch Pediatr Adolesc Med*. 2005;159(9):875]
10. Greenhill L, Beyer DH, Finkleson J, et al. Guidelines and algorithms for the use of methylphenidate in children with Attention-Deficit/Hyperac tivity Disorder. *J Atten Disord*. 2002;6(suppl 1):S89-S100. [CrossRef]
11. Krinzinger H, Hall CL, Groom MJ, et al. Neurological and psychiatric adverse effects of long-term methylphenidate treatment in ADHD: a map of the current evidence. *Neurosci Biobehav Rev*. 2019;107:945-968. [CrossRef]
12. Wilens TE, Biederman J, Lerner M, Concerta Study Group. Effects of once-daily osmotic-release methylphenidate on blood pressure and heart rate in children with attention-deficit/hyperactivity disorder: results from a one-year follow-up study. *J Clin Psychopharmacol*. 2004;24(1):36-41. [CrossRef]
13. Lamberti M, Italiano D, Guerriero L, et al. Evaluation of acute cardiovascular effects of immediate-release methylphenidate in children and adolescents with attention-deficit hyperactivity disorder. *Neuropsychiatr Dis Treat*. 2015;11:1169-1174. [CrossRef]
14. Karpuz D, Hallioglu O, Toros F, Tasdelen B. The effect of metilpheniydate, risperidone and combination therapy on ECG in children with attention-deficit hyperactivity disorder. *J Electrocardiol*. 2017;50(4):410-415. [CrossRef]
15. Türkmenoğlu YE, Esedova C, Akpinar M, Uysal T, İrdem A. Effects of medications on ventricular repolarization in children with attention deficit hyperactivity disorder. *Int Clin Psychopharmacol*. 2020;35(2):109-112. [CrossRef]
16. Dabrowski A, Kramarz E, Piotrowicz R, Kubik L. Predictive power of increased QT dispersion in ventricular extrasystoles and in sinus beats for risk stratification after myocardial infarction. *Circulation*. 2000;101(14):1693-1697. [CrossRef]
17. Bieganowska K, Sawicka-Parobczyk M, Bieganowski M, Piskorski J. Tpeak -tend interval in 12-lead electrocardiogram of healthy children and adolescents tpeak -tend interval in childhood. *Ann Noninvasive Electrocardiol*. 2013;18(4):344-351. [CrossRef]
18. Panikkath R, Reinier K, Uy-Evanado A, et al. Prolonged Tpeak-to-tend interval on the resting ECG is associated with increased risk of sudden cardiac death. *Circ Arrhythm Electrophysiol*. 2011;4(4):441-447. [CrossRef]
19. Barbhaiya C, Po JR, Hanon S, Schweitzer P. Tpeak - Tend and Tpeak - Tend/QT ratio as markers of ventricular arrhythmia risk in cardiac resynchronization therapy patients. *Pacing Clin Electrophysiol*. 2013;36(1):103-108. [CrossRef]
20. Bazett HC. An analysis of the time-relations of electrocardiograms. *Heart*. 1920;7:353-370.
21. Gopal S, Hough D, Karcher K, et al. Risk of cardiovascular morbidity with risperidone or paliperidone treatment: analysis of 64 randomized, double-blind trials. *J Clin Psychopharmacol*. 2013;33(2):157-161. [CrossRef]
22. Vieweg WV, Hasnain M, Hancox JC, et al. Risperidone, QTc interval prolongation, and torsade de pointes: a systematic review of case reports. *Psychopharmacol (Berl)*. 2013;228(4):515-524. [CrossRef]
23. Castro Hevia J, Antzelevitch C, Tornés Bárzaga F, et al. Tpeak-Tend and Tpeak-Tend dispersion as risk factors for ventricular tachycardia/ventricu lar fibrillation in patients with the Brugada syndrome. *J Am Coll Cardiol*. 2006;47(9):1828-1834. [CrossRef]

24. Gupta P, Patel C, Patel H, et al. T(p−e)/QT ratio as an index of arrhythmogenesis. *J Electrocardiol*. 2008;41(6):567-574. [CrossRef]
25. Mozos I, Serban C. The relation between QT interval and T-wave variables in hypertensive patients. *J Pharm Bioallied Sci*. 2011;3(3):339-344. [CrossRef]
26. Rosenthal TM, Stahls PF 3rd, Abi Samra FM, et al. T-peak to T-end interval for prediction of ventricular tachyarrhythmia and mortality in a primary prevention population with systolic cardiomyopathy. *Heart Rhythm*. 2015;12(8):1789-1797. [CrossRef]
27. Wren C. Screening children with a family history of sudden cardiac death. *Heart*. 2006;92(7):1001-1006. [CrossRef]
28. Vitiello B, Elliott GR, Swanson JM, et al. Blood pressure and heart rate over 10 years in the multimodal treatment study of children with ADHD. *Am J Psychiatry*. 2012;169(2):167-177. [CrossRef]
29. Dalsgaard S, Kvist AP, Leckman JF, Nielsen HS, Simonsen M. Cardiovascular safety of stimulants in children with attention-deficit/hyperactivit y disorder: a nationwide prospective cohort study. *J Child Adolesc Psychopharmacol*. 2014;24(6):302-310. [CrossRef]
30. Clavenna A, Bonati M. Safety of medicines used for ADHD in children: a review of published prospective clinical trials. *Arch Dis Child*. 2014;99(9):866-872. [CrossRef]