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**electrocardiograms changes in children with functional gastrointestinal disorders** **on low dose amitriptyline**

Chogle A *et al*. EKG for amitriptyline in children

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**Abstract**

**Aim:** To study the effects of low dose amitriptyline on cardiac conduction in children.

**Methods:** Secondary analysis of data obtained from a double-blind, randomized placebo-controlled trial, evaluating low dose amitriptyline in children with a diagnosis of functional abdominal pain, functional dyspepsia, and irritable bowel syndrome according to the Rome II criteria. Children 8–17 years of age were recruited from the pediatric gastroenterology clinics of 6 tertiary care centers in the United States. The electrocardiograms (EKGs) done prior to initiation of tricyclic antidepressants and 1 mo after initiation of amitriptyline were examined. The changes in cardiac conduction were evaluated in patients and controls.

**Results:** Thirty children were included in the study. There were 12 patients, ages 9-17 years of both genders, in the amitriptyline treatment group and 18 patients, ages 9-17 years of both genders, in the placebo treatment group. None of the patients had any baseline EKG abnormality. amitriptyline use was associated with an increase in heart rate (*p =* 0.024) and QTc interval (*p =* 0.0107) as compared to pre-EKGs. Children in the placebo group were also noted to present a statistically significant increase in QTc interval (*p =* 0.0498). None of the patients developed borderline QTc prolongation or long-QT syndrome after they were started on amitriptyline.

**Conclusion:** The study findings suggest that once patients with functional gastrointestinal disorders have been screened for prolonged QTc interval on baseline EKG, they probably do not need a second EKG for reevaluation of cardiac conduction after starting low dose amitriptyline.

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**Key words:** Amitriptyline; Electrocardiogram; Children; Abdominal pain related Functional gastrointestinal disorders

**Core tip:** Information on electrocardiogram changes in children who are on low dose amitriptyline for treatment of abdominal pain associated-functional gastrointestinal disorders (AP-FGIDs) is sparse. To better understand the effects of low dose amitriptyline on cardiac conduction in children, we reviewed the electrocardiogram findings before and after initiation of amitriptyline. We found that use of low dose amitriptyline in children with AP-FGIDs was not associated with clinically significant changes in cardiac conduction.

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**Introduction**

Abdominal pain associated-functional gastrointestinal disorders (AP-FGIDs) are among the most common medical afflictions in childhood and adolescence[[1](#_ENREF_1),[2](#_ENREF_2)]. The AP-FGIDs have been categorized by the Rome III criteria into irritable bowel syndrome (IBS), functional abdominal pain (FAP), functional dyspepsia (FD) and abdominal migraine (AM). These disorders have been shown to significantly affect the children’s quality of life[[1](#_ENREF_1),[2](#_ENREF_2)]. Tricyclic antidepressants (TCAs) like amitriptyline have played an important role in the treatment of pediatric psychiatric disorders. However, the increased risk of adverse cardiac events, sudden deaths in children and a black box warning by the FDA on the risk of suicidality have led to a decline in their use[[3](#_ENREF_3),[4](#_ENREF_4)] TCAs have now been relegated to second line status for treatment of depression. Studies in adults have shown benefit in using TCAs for treatment of AP-FGIDs[[5-11](#_ENREF_5)]. amitriptyline has not been found to be better than placebo for treatment of AP-FGIDs in children and is not approved for the treatment of FGIDs in children or adolescents, but its off label use is prevalent[[12-15](#_ENREF_12)]. The dose of amitriptyline commonly used in the treatment of FGIDs in children is much lower than that used for depression. A dose-response association of TCAs has been demonstrated with QTc prolongation[[16](#_ENREF_16)]. TCA overdose has been shown to cause conduction delays and prolonged corrected QT (QTc) in children[[17](#_ENREF_17)]. There is limited data in the literature regarding the cardiac toxicity in therapeutic antidepressant doses of amitriptyline in children. Information on electrocardiogram (EKG) changes in children who are on low dose amitriptyline for treatment of FGIDs is sparse. To better understand the effects of low dose amitriptyline on cardiac conduction in children, we reviewed the EKG findings before and after initiation of amitriptyline in a multicenter study conducted by our group assessing the efficacy of amitriptyline in children with AP-FGIDs[[14](#_ENREF_14)].

**MATERIALS AND METHODS**

This study was a secondary analysis of data obtained from a double-blind, randomized placebo-controlled trial, evaluating amitriptyline in children with a diagnosis of functional abdominal pain, functional dyspepsia, and IBS according to the Rome II criteria[[14](#_ENREF_14)]. In the original study children 8–17 years of age were recruited from the pediatric gastroenterology clinics of 6 tertiary care centers geographically dispersed in the United States: Children’s Hospital of Pittsburgh (Pittsburgh, PA), Goryeb Children’s Hospital at Atlantic Health System (Morristown, NJ), Kansas University Medical Center (Kansas City, KS), Children’s Hospital of Boston (Boston, MA), Children’s Hospital of Wisconsin (Milwaukee, WI), and Children’s Memorial Hospital (Chicago, IL). In the current study only those patients in both groups (amitriptyline treatment and placebo groups) who had a standard 12-lead EKG before starting the study medication (pre-EKGs) and a second EKG 1 mo after initiation of the medication (post-EKGs) were included. Only the centers located at Chicago, Pittsburgh and Boston required EKGs to be done prior to and after starting amitriptyline. amitriptyline was dosed based on their weight: (1) < 35 kg–10 mg capsule by mouth daily; and (2) ≥ 35 kg–20 mg capsule by mouth daily. All EKGs were read by pediatric cardiologists at the respective study locations. We examined the effect of amitriptyline and placebo on heart rate (HR), PR, QRS, and QTc interval with the 2 tailed *t*-test using GraphPad statistical software.

A QTc interval at or above 480 ms in females or 470 ms in males was considered diagnostic of long-QT syndrome (LQTS)[[14](#_ENREF_14)]. The diagnosis of borderline QT prolongation was given when a patient had a QTc value between 440 and 470 ms.

**Results**

Thirty children were included in the study. There were 12 patients (10 females), ages 9-17 years (10 patients were 10 years or older), in the amitriptyline treatment group and 18 patients (15 females), ages 9-17 years (16 patients were 10 years or older), in the placebo treatment group. Using the D'Agostino-Pearson test for normality, the data was found to have normal distribution. None of the patients had any baseline EKG abnormality. amitriptyline use was associated with an increase in heart rate (*p =* 0.024) and QTc interval (*p =* 0.0107) as compared to pre-EKGs (Table 1). Children in the placebo group were also noted to present a statistically significant increase in QTc interval (*p =* 0.0498) (Table 1). None of the patients developed borderline QTc prolongation or LQTS after they were started on amitriptyline

**Discussion**

Amitriptyline at low doses is thought to work primarily by inducing pain tolerance through peripheral or central anti-nociceptive properties as well through its anticholinergic effects, and secondarily through its anxiolytic effects[[8](#_ENREF_8),[14](#_ENREF_14),[18](#_ENREF_18)].

A meta-analysis of adult studies showed that amitriptyline is beneficial in treatment of FGIDs in adults[[5](#_ENREF_5),[7](#_ENREF_7),[8](#_ENREF_8),[19](#_ENREF_19)]. There have been 2 randomized controlled pediatric trials that have examined the efficacy and safety profile of low dose amitriptyline in treatment of FGIDs[[13](#_ENREF_13),1[4](#_ENREF_14)]. Both studies found no statistically significant differences between amitriptyline and placebo for most efficacy outcomes including improvement of abdominal pain (Bahar study found improvement exclusively in RLQ pain and a beneficial effect in quality of life). A review by the Cochrane’s Group concluded that there was no evidence to support the use of amitriptyline for the treatment of abdominal pain-related FGIDs in children and adolescents[[12](#_ENREF_12)]. Despite the lack of evidence of its efficacy, clinicians commonly prescribe amitriptyline to children with AP-FGIDs. Typically a 0.5-1 mg/kg per day dose of amitriptyline to a maximum of 50 mg daily is used as opposed to 1-3 mg/kg per day used for depression in children[[14](#_ENREF_14)].

Amitriptyline activates cardiac ryanodine channels causing efflux of calcium from the sarcoplasmic reticulum[[20](#_ENREF_20)]. As a result, amitriptyline is pro-arrhythmogenic and increases the risk of sudden cardiac death in patients with underlying heart disease and at doses above 100 mg daily[[3](#_ENREF_3)]. amitriptyline has been classified as a “conditional risk” drug for development of torsade de pointes[[21](#_ENREF_21)]. Drugs with “conditional risk” have significant evidence of prolonging QT and causing torsade de pointes but only under certain conditions, such as excessive dose or drug interaction[[22](#_ENREF_22)]. Some studies have documented changes in EKG tracings in children on the higher doses of amitriptyline used for depression[[23](#_ENREF_23),[24](#_ENREF_24)]. These have included findings ranging of no changes in any of the tracings to increases in the heart rate, PR, QRS and QTc intervals. In a recent risk prevention study, the incidence of prolonged QTc interval in a subpopulation of children with IBS before the initiation of amitriptyline was found to be 0.4%, which is similar to the incidence of prolonged QTc in adult and adolescent athletes[[25](#_ENREF_25),[26](#_ENREF_26)]. This study concluded that a screening EKG should always be performed on children with FGIDs, before initiating amitriptyline therapy[[25](#_ENREF_25)].

We found practice variation in conducting EKGs after starting patients on amitriptyline, with only 3 of the 6 tertiary centers doing the pre and post amitriptyline initiation EKGs. This practice variation likely exists due to paucity of data on the effect of low dose amitriptyline on cardiac conductance. Our study shows that post amitriptyline EKGs might not be necessary. The cost of performing an EKG as per CMS reimbursement schedule ranges from $39-47. For every additional EKG there are additional intangible costs such as lost wages for parents, childcare costs for siblings, cost of transportation, etc. Performing unnecessary EKGs after initiating amitriptyline can add to the existing lofty healthcare expenditure in managing children with FGIDs, especially considering the high prevalence of chronic abdominal pain in school age children[[1](#_ENREF_1),[27](#_ENREF_27)].

The chronic use of TCAs in adult patients with chronic pain was not shown to result in clinically significant changes in cardiac conduction[[28](#_ENREF_28)]. In our study amitriptyline use was associated with an increase in the heart rate and the QTc interval but none of these changes were significant enough to warrant discontinuation of amitriptyline. These findings suggest that once patients with FGIDs have been screened for prolonged QTc interval on baseline EKG, they probably do not need a second EKG for reevaluation of cardiac conduction after starting low dose amitriptyline. Limitations of our study include the small sample size. Studies with larger sample size and longer duration are needed to confirm our findings and possibly influence future monitoring recommendations post initiation of TCA for FGID treatment. The findings might not be generalizable to other TCAs. The frequent use of TCAs other than amitriptyline for the treatment of FGIDs in children stress the importance of conducting similar studies with other TCAs[[15](#_ENREF_15)].

Our preliminary study suggests that amitriptyline used in low doses can be considered a relatively safe drug in the arsenal of pediatric gastroenterologists.

Our retrospective placebo controlled study suggests that the use of low dose amitriptyline in children with AP-FGIDs is probably not associated with clinically significant changes in cardiac conduction. A larger prospective study should be designed to confirm these findings.

**comments**

***Background***
Abdominal pain associated-functional gastrointestinal disorders (AP-FGIDs) commonly occur in childhood and adolescence. Low dose Amitriptyline is commonly used for off label treatment of AP-FGIDs in children although it has not been found to be better than placebo nor is it not approved for the treatment of FGIDs in children or adolescents. A dose-response association of tricyclic antidepressants has been demonstrated with QTc prolongation. There is limited data in the literature regarding the cardiac toxicity of low dose Amitriptyline in children.

***Research frontiers***

Information on electrocardiogram (EKG) changes in children who are on low dose Amitriptyline for treatment of FGIDs is sparse. We present data for the first time, which examines the effect of low dose Amitriptyline on cardiac conduction.

***Innovations and breakthroughs***

Our study shows that the use of low dose amitriptyline in children with AP-FGIDs is not associated with clinically significant changes in cardiac
conduction.

***Applications***

Performing unnecessary EKGs after initiating amitriptyline can add to the existing lofty healthcare expenditure in managing children with FGIDs, especially considering the high prevalence of chronic abdominal pain in school age children. There is a lot of practice variation amongst physicians in ordering a post Amitriptyline initiation EKG. Our data has the potential to decrease healthcare expenditure and to reduce practice variation.

***Terminology***

Abdominal pain associated-functional gastrointestinal disorders (AP-FGIDs) are among the most common medical afflictions in childhood and adolescence The AP-FGIDs have been categorized by the Rome III criteria into irritable bowel syndrome (IBS), functional abdominal pain (FAP), functional dyspepsia (FD) and abdominal migraine (AM).

***Peer review***

The study was a secondary analysis of data obtained from a double-blind, randomized placebo-controlled trial, evaluating Amitriptyline in children with a diagnosis of functional abdominal pain, functional dyspepsia, and IBS according to the Rome II criteria. They aimed to better understand the effects of low dose Amitriptyline on cardiac conduction in children. They reviewed the EKG findings before and after initiation of Amitriptyline in a large multicenter study conducted by their group assessing the efficacy of Amitriptyline in children with AP-FGIDs. They found that none of the patients had any baseline EKG abnormality. None of the patients developed borderline QTc prolongation or LQTS after they were started on Amitriptyline. They conclude that the study findings suggest that once patients with FGIDs have been screened for prolonged QTc interval on baseline EKG, they probably do not need a second EKG for reevaluation of cardiac conduction after starting low dose amitriptyline. What the authors found may induce cost saving in the management of pediatric patients with FGIDS treated with amitriptyline.

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**Table 1 Effect of amitriptyline and placebo on cardiac conduction in children**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **HR (**beats/min) | **PR**(ms) | **QRS**(ms) | **QTc**(ms) |
| **Parameters** | **Pre EKG** | **Post EKG** | **Pre EKG** | **Post EKG** | **Pre EKG** | **Post EKG** | **Pre EKG** | **Post EKG** |
| **Drug** |
| Mean ± SD | 75.92 ± 9.44 | 85.2 ± 17.4 | 135 ± 12.97 | 134.5 ± 11.25 | 83.67 ± 6.81 | 85.33 ± 7.15 | 406.91 ± 12.6 | 418 ± 13.8 |
|  |
| 2 tailed *t* test *p* value | 0.024a  | 0.8429  | 0.2098  | 0.0107a  |
| Correlation coefficient - *r* | 0.7367  | 0.7608  | 0.8084  | 0.4923  |
| **Placebo** |  |
| Mean ± SD | 69.22 ± 12.26 | 74.05 ± 10.06 | 132.6 ± 16.35 | 137.5 ± 21.53 | 86.7 ± 8.95 | 83.8 ± 8.98 | 415.5 ± 16.82 | 422.6 ± 18.53 |
|  |
| *n* | 18 | 18 | 18 | 18 | 18 | 18 | 18 | 18 |
| 2 tailed *t* test *p* value | 0.0783 | 0.1394 | 0.0937 | 0.0498a |
| Correlation coefficient - *r* | 0.5343 | 0.7841 | 0.7037 | 0.6773 |

a*p* < 0.05, placebo group *vs* control group.