

March 27, 2014

Dear Editor,



Please find enclosed the edited manuscript in Word format (file name: Elavil EKG Manuscript - 031814.doc).

Title: EKG changes in children on low dose Amitriptyline

Authors: Ashish Chogle, MD, MPH; Miguel Saps, MD

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 8232

The manuscript has been improved according to the suggestions of reviewers:
We appreciate the reviewers' comments that we found thoughtful and helpful. We have adopted all the changes that were suggested and those have been integrated to the manuscript. To follow is a point-by-point response to each of the reviewers' comments. We sincerely hope that we have satisfactorily addressed the concerns of the reviewers.

Reviewer #1:

This is a "brief article" about the effects of Amitriptyline on ECG in kids with AP-FGIDs. The following changes should be performed: 2- 3- 4- 5- 6- 7- Thank you for this suggestion.

- 1) Omit tables from abstract :
We have deleted the tables from the abstract as per your recommendation.
- 2) Abbreviations should come with the complete word in the abstract (i.e. LQTS):
We apologize for this oversight. We have added the complete word with the abbreviations in the abstract.
- 3) Introduction: please change "a large multicenter study conducted" to " a multicenter study conducted". The study is not large enough:
As per your recommendation, the suggested correction from "a large multicenter study" to a "multicenter study as been made. Thank you.
- 4) Conclusion: PP-FGIDs should be AP-FGIDs:
To maintain consistency in the terminologies used in the manuscript, the word PP-FGID has been changed to AP-FGID in the conclusion section. Thank you.
- 5) Table 1 is not necessary. Bring the data in the text:
As per your recommendation, the data from table 1 has been added to the main text.

- 6) What normality test was performed. If the data was normal just mention it in the text. Tables 2 and 3 should be combined. If data was normal, Mean +/- SD (p-value), and if it was not median (range; p value) would be enough. Don't forget the units (Second, mm, etc.):

We have made the following changes as per your suggestion: We have added that the D'Agostino-Pearson test for normality was used and that the data had normal distribution. The Mean and SD was retained in the table and rest of the results were deleted. Units for the results were added to the table.

- 7) in the limitation and future direction, please mention studies with larger sample size and with longer duration are necessary. Also, please mention this study cannot be generalized to all TCAs:

In the limitations we have now mentioned that studies with larger sample size with longer duration are needed and that the study cannot be generalized to other TCAs. Thank you for this addition.

Reviewer #2:

What the Authors found may induce cost saving in the management of pediatric patients with FGIDS treated with Amitriptyline, but the question is: why pediatric patients with FGIDs should be treated with Amitriptyline if the largest non-industry sponsored pharmacological clinical trial in abdominal pain associated FGIDs and the first multicenter clinical trial investigating the effect of pharmacological therapy in children and adolescents with chronic abdominal pain (Saps M et al Gastroenterology 2009), of which the same Author was the first Author and the present study is a secondary analysis did not demonstrate efficacy of this drug?

Answer: We agree that there is no convincing evidence to support the usage of Amitriptyline for AP-FGIDs in children. Despite this fact, there is rampant off label use of this drug to treat chronic abdominal pain.¹ Considering this fact, our data may enable clinicians to make an informed decision about performing EKGs after starting Amitriptyline, when they use the drug for treatment of AP-FGIDs.

Moreover, as the same Authors state in the Discussion, this study has the sample size limitation that is more important for assessing safety than efficacy of a drug that has not been approved for the treatment of FGIDs in children or adolescents even though its off label use is prevalent. Therefore the sentence in the Discussion "There are very few medications that have been shown to be effective in improving symptoms of IBS in children, amitriptyline being one of them" is not supported by the results of the previously published study (Saps M et al Gastroenterology 2009) of which the present study is a secondary analysis.

Answer: We agree with your observation and have removed the sentence “There are very few medications that have been shown to be effective in improving symptoms of IBS in children, amitriptyline being one of them” from the discussion.

It seems wiser to adopt the conclusions of that study for the rare patients in whom the inability to manage patients with a holistic care in practice may justify amitriptyline treatment. The conclusions of the present study may encourage physicians to further use of a off label drug. Finally but not less important, the high placebo effect found in the previous study(Saps M et al Gastroenterology 2009), according to what the Authors state, underscores the importance of a positive and caring therapeutic alliance between physicians, patients and families that is time consuming but drug saving and effective in the management of FGIDs also in primary care.

Answer: We agree that holistic care is extremely important in treatment of functional pain conditions and has a clear advantage over using drugs. On a personal note, we try to use holistic methods prior to starting patients on medications but if we do reach a point where we start them on Amitriptyline, our data helps us to avoid the post drug initiation EKG. We have made changes in the manuscript to clearly mention the absence of efficacy of Amitriptyline in treatment of pediatric AP-FGIDs. We did not intend to present data in a way that will encourage off label use of this medication. We are only providing additional information to make an informed decision.

Thank you again for publishing our manuscript in the *World Journal of Gastroenterology*.

Sincerely yours,

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1. Teitelbaum JE, Arora R. Long-term efficacy of low-dose tricyclic antidepressants for children with functional gastrointestinal disorders. *Journal of pediatric gastroenterology and nutrition*. Sep 2011;53(3):260-264.