Dear Editor,

Please find enclosed a manuscript entitled: “Efficacy of vitamin C as an adjunct to fluoxetine therapy in pediatric major depressive disorder: a randomized, double-blind, placebo-controlled pilot study” which is being re-submitted for exclusive consideration of publication as an article in Nutrition Journal.

In regards to the requested formatting changes, the Methods section already includes that the study was performed with IRB approval from Mansoura University Hospital. It also lists that the trial was conducted in accordance with the Declaration of Helsinki and subsequent revisions.

We thank the reviewers for their invaluable feedback. We have meticulously reviewed their comments and have revised our paper accordingly. Please find our point-by-point responses to the reviewers' comments below:

Reviewer 1:

1. Added to the Discussion: Measuring plasma vitamin C levels pre- and post-treatment may also be of interest, but although these levels were not measured, previous studies have demonstrated the association between hypovitaminosis C (vitamin C deficiency) and psychological abnormalities and this deficiency is highly prevalent in acutely hospitalized patients (30, 34). Furthermore, the increase in plasma and mononuclear leukocyte vitamin C from subnormal to normal concentrations after the administration of vitamin C administration implicate that the metabolic properties of hypovitaminosis C are consistent with deficiency as opposed to different mechanisms such as tissue redistribution (34). These findings also indicate that patients with depression, such as those who participated in this study, may experience vitamin C deficiency and that the decrease in depressive symptoms that was observed may be directly attributed to the synergistic antidepressant effect of vitamin C and fluoxetine. Future studies that involve measuring plasma vitamin C levels may
further support these findings.


2. Added to the Introduction: In one particular study that investigated mood, patients who were acutely hospitalized were either treated with vitamin C or vitamin D as a deficiency in both of these vitamins has been associated with psychological abnormalities. The results showed that only vitamin C led to an improved mood. More specifically, treating the vitamin C deficiency led to a decrease in mood disturbance while vitamin D supplementation had no effect on mood (30). Similar findings were observed in non-critically ill hospitalized patients who were treated with vitamin C for hypovitaminosis C (34).


3. Added to Methods: It has been shown that patients who are young in age at the onset of bipolar disorder demonstrate an illness progression that is characterized by high rates of switching into mania or hypomania in response to antidepressant treatment (36).


4. Added to the Results: Three subjects were removed (withdrew) from the trial due to noncompliance.

5. Added to Methods: The scores for the CDRS were based on parent ratings, CDI on children ratings, and CGI on clinician ratings.

Added to Discussion: The differences between the scores may have also been related to the individuals who supplied the ratings for each instrument. More specifically, the scores for the CDRS were based on parent ratings, the scores for the CDI were based on children ratings, and the scores for the CGI were based on clinician ratings. The scores from the CGI were computed based on clinical criteria such as that which is listed in the DSM-IV-TR as well as semi-structured interview. Therefore, the clinician's rating and score interpretations adhered to strict guidelines and training, whereas the ratings from parents and children may have been more subjective leading to significantly different scores. Nonetheless, these preliminary findings, including the results of ANOVA suggest that vitamin C may be an effective adjuvant agent for the treatment of depression in pediatric patients.
Reviewer 2

1. Added to the Methods: Patients less than eight years of age received fluoxetine (10 mg/day), whereas patients eight years of age or older were given 10 mg/day of fluoxetine for one week and 20 mg/day all subsequent weeks as per the prescribing information [38]. There are several published studies which support the administration of 20 mg/day of fluoxetine for children at least eight years of age [39-42], and it is within FDA indication. The use of fluoxetine for children under the age of eight is off-label.


2. Addressed in first response to reviewer 1 (above).

3. Although this is a preliminary study, the findings are promising and provide implications regarding the direction of future studies involving the administration of vitamin C in conjunction with SSRIs to treat MDD, which would include long-term studies and plasma vitamin C measurements.

Thank you for your consideration of this manuscript.

Sincerely,
Shaheen E Lakhan