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FROM : Korotzer, Andrew </O=FOREST LABORATORIES/OU=FRX/CN=RECIPIENTS/CN=ANDREW.KOROTZER>
TO : Korotzer, Andrew </O=FOREST LABORATORIES/OU=FRX/CN=RECIPIENTS/CN=Andrew.Korotzer>
DATE = 12/22/2008
TIME : 4:21 PM
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SOURCE : Andrew Korotzer
ATTACHMENT : .\Attachment\MDL-FOREM0021245\001.Escitalopram_Revised_v2.doc
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BODY : From: Korotzer, Andrew
Sent: Monday, December 22, 2008 4:21:31 PM
To: Korotzer, Andrew
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Attachments: Escitalopram_Revised_v2.doc; Escitalopram_Response to Editor v2.doc

Taryn Mayes [Taryn.Mayes@UTSouthwestern.edu]

214-456-4242

November 18, 2008

John T. Walkup, MD
Deputy Editor

RE: Ms. #JAACAP-D-08-00476, "Escitalopram in the Treatment of Adolescents Depression"

Thank you for your comments on our manuscript, and we have attempted to address the concerns raised by the reviewers.

Below we outline our responses to each of the comments/concerns raised.

Editor Comments:
*1. Financial disclosure statement for publication with the manuscript.*
The financial disclosure statement has been inserted before the Acknowledgment section.

*2. We also ask that you make clear in the Methods section of your manuscript who designed the study, who gathered the data, who analyzed the data, who vouches for the data and the analysis, who wrote the paper, and who decided to publish the paper. Please state as well if there were any agreements concerning confidentiality of the data between the sponsor and the authors or the institutions named in the credit lines. (see NEJM September 13, 2001.)*
The sponsor ran all statistical analyses and drafted the results and methodology section, and then provided the data to the primary author. The primary author then wrote the remainder of the manuscript draft, includong the introduction and discussion sections, with several meetings with the sponsor to request additional data analyses; the primary author also made substantial revisions to the Results section. All authors, including those employed by the sponsor, made critical revisions to the manuscript, and the final version was agreed upon prior to submission. An additional paragraph about the analyses and drafting of the manuscript have been included in the manuscript.

*3. In addition, please indicate who wrote the first draft of your manuscript. If it was not one of the authors, please name the person or persons and indicate who paid them. If any writing assistance other than copyediting was provided, please name the person or persons and indicate who paid them.*
See response to item #2. (With the exception of the method and results section draft, the primary author wrote the first draft.)

*4. We expect your revised manuscript to include detailed reporting of adverse events. In general, this should be in the form of a table containing descriptions of all serious adverse events and all other common or important adverse events. The abstract should contain a statement regarding adverse events, including suicidality.*
The abstract has been revised to include a summary of common adverse events and suicidality.

**Comment [MSOffice1]:** Graham would like to move the current AE table to the online Article Plus format, and replace it with Table 12.2.4 from the data report.

*5. As noted by the final reviewer, please indicate what may be clinically vs. statistically significant, how your findings 'stack up' in terms of effect sizes, NNT, comparison to fluoxetine, etc.*
We recognize that there are differences in statistical and clinical meaningfulness of outcomes, and appreciate the editor's, as well as the reviewers' comments. We have added a section to the discussion about clinical relevance and interpretation of clinical trials.

*Reviewer #1:*
*1. I would characterize the effect size on the primary outcome (0.27) as "small to medium" using standard ES classifications…. Would it not be more appropriate to write that the data here suggest that escitalopram is a "mildly", "modestly" or at best "moderately" effective treatment?*
We have added a sentence to the second paragraph of the Discussion section clearly stating that the effect size we observed for escitalopram in this trial is modest, and we speculate that this might have been due to the high placebo response. However, we also point out in the first paragraph of the Discussion section that the effect size in this study (0.27) is similar to that observed for escitalopram in adults (0.31), which allows the reader to have a reference point for "effect size". Despite the modest effect size, we do not want to diminish the fact that escitalopram is an effective antidepressant, with similar effect sizes in adolescents as seen in adults). We have removed the reference to the effect size for fluoxetine, as this effect size was for both children and adolescents, which may have contributed to the difference.

*2. The comparison to the data with the fluoxetine RCT's is very superficially presented in the discussion. For example, it would seem worthwhile to include in the discussion more details of the comparisons between the escitalopram studies and the fluoxetine studies in terms of trial design characteristics, sample differences, quantitative presentation of effect sizes and NNT, as well as safety comparisons.*
Additional discussion of the outcomes noted in the original fluoxetine trial has been added, with a caution that is difficult to make such comparison across studies.

*3. Introduction, paragraph 1- last sentence: wouldn't one include patient and parent / legal guardian preference as one factor influencing treatment choice?*
We have added this to the text, noting that there are multiple factors that influence treatment.

*2. Introduction, paragraph 3- 2nd sentence: the "risks" in the Bridge et al. meta-analysis are confined only to treatment emergent suicidality- this should be clarified- also note here that the authors suggest the effect size here for the efficacy data is described as "modest" although it is nearly exactly the effect size found in the trial (0.27).*
We have revised the section in the Introduction about safety substantially, as we note above, we refer in the Discussion section to the effect size we observe as a modest one.

*3. Same paragraph: why not briefly summarize the other antidepressants that have been evaluated: tricyclics, nefazodone, Effexor XR?*
We include that other classes of antidepressants have been evaluated, and have modified this paragraph to emphasize that limited evidence of efficacy for antidepressants in this patient population. However, currently there is a distinction between SSRIs and non-SSRIs with regard to staging of treatment, with SSRIs considered the first and second line medication treatments for pediatric depression. Therefore, ~~because escitalopram is the only SSRI without a second clinical trial in pediatric depression (sans fluvoxamine, that is),~~ we focus here on the results of the SSRI trials.

*4. Introduction, 4th paragraph, 4th sentence- not accurate, the re-analysis was done by the FDA, the Columbia group only provided the classification system- see Hammad et al.*
As noted, this section has been revised, and the information is clearer now.

*5. Introduction, 4th paragraph, 5th sentence- needs a reference- see Hammad et al.*
We now cite Hammad's paper here.

*6. Introduction, 5th paragraph, last sentence- not accurate- all RCTs of pediatric depression had prospective, systematic collection of suicidality data. Most of these studies prospectively and systemically assessed suicidality using items on clinician-rated or self-rated depression scales, but TADS also used multiple prospective systematic assessments..... From what I can tell the only new methodology in this trial is the SSRS.*
With the exception of the TADS study, no other trial included specific suicidality measures as an independent pre-defined study outcome measure. While it is true that some of the depression severity outcome measures also included a single item on suicidality in earlier trials, there were no measures specific to suicide. Therefore, this study is among the first to include a prospective measure of suicidality. In addition, this is the first study to systematically assess (by the investigators) each adverse event as to whether or not it is considered self-harm at the time of the event.

*7. Methods, paragraph 3, last sentence- the language here is confusing regarding exclusion for suicidality. Can the authors clarify what is meant by "active suicidal ideation"?.... Could the authors clarify this?*
We have amended the description of the suicide-related exclusion criteria to make it clear that the consideration of a patient being a suicide risk is judged by the investigator. The exclusion criteria captured by the clauses, "had made a suicide attempt" and "had ever been hospitalized because of a suicide attempt" are not contradictions, nor mutually exclusive criteria.

*8. Methods, paragraph 9- The reference to the C-SSRS (13) is a reference for the Posner et al C-CASA classification system and data from the FDA analysis. Are there other references to items on this scale and psychometric / reliability / validity work done with this instrument? Is this a clinician administered instrument, a self-report instrument? Who administered the C-SSRS? Are data systematically collected from both the adolescent and parent / legal guardian? What time-frame of reference was used in the administrations at screening, baseline and throughout the study? Since some of the assessments were done at weekly intervals and others with longer intervals, did the SSRS cover all time since the previous assessment? Additionally, this scale seems to be referred to as the "MC-SSRS" in other places in the manuscript.*
With the FDA re-analyses of the suicidal events in pediatric antidepressant trials, it became clear that there was no sufficient rating scale to rate suicidality. As such, a group from Columbia, led by Kelly Posner, developed the Columbia Suicide Severity Rating Scale, which has been increasingly used in clinical trials of depression. The scale has undergone modifications, and the Modified Columbia Suicide Severity Rating Scale (MC-SSRS) was used for this study. The scale is not yet validated, and the Methods section has been amended to state this explicitly. We have also corrected the manuscript to only use "MC-SSRS". As noted in the Methods, the MC-SSRS is a clinician-rated instrument. Data is collected from multiple sources at screening the entire history is used; we have added to the description that scoring is based on symptoms since the last visit.

**Comment [T&TM2]:** Can we just say, "More information is needed on the MC-SSRS to shorten?

*9. Statistical methods, paragraph 6, last sentence- what is the authors' definition of "observed cases"?*

We employed a conventional Observed Cases approach, meaning data from assessments that were performed, without imputation for missing data. ~~We have also amended the phrase within the "Statistical Methods" section.~~

*10. Results, paragraph 1- could the authors present data on how many subjects were excluded due to improving during the evaluation period and the single-blind placebo lead-in? This would be valuable to other researchers considering using these procedures.*
The depression severity criteria for randomization was a CDRS-R total score ≥45 at baseline, and improvement from the initial screening visit to baseline was not a cause for exclusion. That said, there were two patients who had a CDRS-R score of at least 45 at the screening visit, and less than 45 at baseline. Unfortunately, these were both randomized (1 per group) and were therefore protocol violations; since both baseline scores were 44, it is unlikely that these protocol violations significantly affected the outcome. ~~We do not have specific data on how many subjects were excluded at baseline due to improvement in depressive symptoms.~~

*11. Efficacy, paragraph 4- could the authors include a number needed to treat (NNT) statistic here?*
This has been incorporated.

*12. Tolerability, paragraph 5- it is a bit confusing how the Adverse Events data that were "suggestive of self-harm" can be integrated with the C-SSRS data... Why is there such a discrepancy between the different methods of tracking patients with worsening suicidality?... Perhaps the methodological issues could be discussed a bit more in the methods section and in the discussion.*
Suicidal ideation and behavior scores on the MC-SSRS and adverse events related to "self-harm" were reported independent of each other. In other words, an adverse event report of suicidal ideation did not require that there a corresponding shift in MC-SSRS ideation score, and that a shift in MC-SSRS ideation or behavior did not "trigger" an adverse event report, although the investigator could report an adverse event upon reviewing any and all available data on the patient at that time. These were simply two means of reporting data concerning suicidality. We have added text to the Discussion section to clarify this. Although an interesting idea, it would be beyond the scope of this paper to requite the findings observed using these different methods.

*13. Discussion, second paragraph- There were some procedures used in this study to ostensibly reduce the placebo response rate which were apparently unsuccessful (setting a rather high CDRS score at baseline, using multiple assessments to assess stability of depressive illness, single blind placebo lead-in). Perhaps these should be highlighted in this paragraph as well for balance.*
We have amended this paragraph accordingly.

*Reviewer #2:*
*1. Typo on Page 3 (Line 24 - should say North America instead of American)*
The typo has been corrected.

*2. In the Introduction the authors refer to a trial by Wagner et al - it might be helpful to draw the differences between this study and the Wagner study....*
The Discussion section has been amended as suggested.

*3. On page 4 the authors refer to a recent study of depressed children (sounds like the Wagner and Jonas study) and refer to a sub-set of subjects who responded favorably to escitalopram - It would be helpful to give some more details about the sub-set: what were the characteristics of this group?*
The age range is now provided; also, as noted above, the Discussion section now mentions that the Wagner and Jonas study, and our study, were similarly designed.

*4. Given the 40 sites that the study was conducted at - how was quality control maintained and since the diagnosis was based on the subjects receiving the KSADS how was inter-rater reliability established between the various interviewers across the country?*
The K-SADS was performed by two independent experienced clinicians at each site. When they disagreed on a diagnosis, they either had to come to an agreement or not enter the patient into the study. The text has been amended to clarify that the two clinicians had to agree with regard to the diagnosis.

*5. The authors excluded any subject who met a DSM IV Axis 1 diagnosis at baseline - however in the results section they refer to the comorbidity with ADHD, enuresis and GAD.... Did these subjects meet criteria for these comorbid conditions at baseline or at the completion of the study? If the former they could not have been excluded!*
The text has been amended in the Methodology section to explain that other comorbid Axis I disorders were allowed if they were not a primary diagnosis. Please note that, as we state within the results section describing comorbid conditions, there were no patients with ongoing ADHD enrolled in this trial.

*6. It also appears that the subjects were not severely depressed since if they had had any suicidal sxs or previous hospitalization - they were also excluded. This may have an impact on the relatively low self-harm ideation in the group as a whole. This should be included as a point of discussion.*
It is a fairly standard design feature of antidepressant trials that patients who are a suicide risk be excluded, as it would not be ethical to allow a suicidal patient into a placebo-controlled trial. However, as evidenced by the mean baseline CDRS-R scores, depression severity was similar to that seen in other placebo-controlled trials. The point of including the suicidality measures was not to establish what the prevalence of suicidality is in depressed adolescents, but to measure what changes occur in such measures over the course of a placebo-controlled antidepressant trial, given the reported findings of the relevant FDA analyses.

*7. In the results section the authors describe that the majority of the subjects were antidepressant-naïve. However, there were still 14.6% in the placebo group and 18.7% in the escitalopram group that were not. It would be helpful to know what and for how long they had been treated with in the past and what the response had been for a previous depressive episode.*
We have added the number of previous non-responders to the manuscript.

*8. Since in the results section the authors do describe comorbidity to be present - was there a different response between those who had "pure" MDD vs those with co-morbidity?*
The number of patients with psychiatric comorbidities was too small to allow for an analysis of differential efficacy.

*Reviewer #4:*
*1. My only major concern is the limited adverse events reporting. Are the any statistically significant differences in adverse events between placebo and escitalopram for adverse events*

*described in Table 3? If there are none, a footnote at the bottom of Table 3 stating this would be sufficient. Also, the article states that physical exams, laboratory tests and ECG were preformed at baseline and week 8. Are there any significant changes in weight, diastolic BP, systolic BP, heart rate, labs, or QTc that occurred during the study period? Are there any differences between placebo and escitalopram groups on these measures? A full disclosure of adverse events is requested.*
Adverse events are reported in Table 3 of the manuscript. We have added a paragraph at the end of the Tolerability section of the Results to mention our findings with regard to labs, vital signs and ECG. However, we did not perform statistical testing of adverse event rates or of changes in laboratory or vital sign measures due to concerns of multiple comparisons. All serious adverse events (SAEs) are described; we also took care to point out that one of the SAEs that was reported by a patient from the double-blind placebo treatment group occurred following discontinuation of study medication and following initiation of commercially-available escitalopram.

**Comment [T&TM3]:** Revise after deciding if new table of SAEs (per request from editors) is added

*2. The safety population and ITT population are clearly defined in the text and Figure 1. Please also clearly define the population for the observed cases analysis.*
We have clarified the population for the observed cases analysis in the Methods.

*3. On page 11 the article states, "The majority of patients in both treatment groups has a dose-level increase." Please clarify what is meant by a dose-level increase.*
The word "level" is deleted for clarity.

*3) In table 2, please explain abbreviations used (e.g. LSM, LS mean).*
We have amended the table accordingly.

*4) CDRS-R response is usually defined as 50% decrease in symptoms. I would prefer if this more common definition were reported in Table 2 (and not the 40% decrease.) It is acceptable to present both results in the text.*
Both were in fact presented in the manuscript as submitted. However, because the 40% decrease was the *a priori* CDRS-R response criteria for the study, we have included that definition in the table.

*Reviewer #5:*
*1. There was no mention in the Abstract of the negative finding that escitalopram did not increase suicidal symptomatology.... Was this study more aggressive in limiting those with suicide from entering the protocol?*
The abstract has been amended to include a statement about suicidality. Regarding the exclusion of actively suicidal patients, this is a standard antidepressant study design, across age groups, and the sample in this study is therefore comparable to those of many other adolescent MDD studies.

*2. The evaluation process suggested that there were two K-SADS P/L interviews done, one at the screening and the second at baseline. Did this include the complete interview each time? Were patients excluded if they met an exclusion diagnosis on only one of the interviews or did they need to meet diagnostic criteria both times? How was the K-SADS rater's reliability among the forty sites verified?*
Two independent clinicians administered the K-SADS-P/L at the two visits (Visits 1 and 3, respectively). The text has been amended to clarify that the patient could only be included in the trial if the two clinicians agreed to the diagnosis. All investigators were trained in the K-SADS-P/L at a pre-study meeting; however, no quality assurance measures were conducted

during the study, as sites were selected based on having investigators experienced with diagnosing and treating adolescent depression, and with this specific instrument.

3. *It should be noted in the text that the comorbid diagnoses which were listed on pg 9 may in fact be lifetime diagnoses and thus are not concurrent with the MDD under study in this report.*
The exclusion criteria states the exclusionary comorbid diagnoses were for current disorders; we have attempted to highlight this fact by underlining current.

*4. The exclusion diagnoses were quite extensive. It would seem that this level of "cleansing" of the study entry criteria makes this cohort a limited domain of those adolescents with MDD....*
It is true that comorbid primary Axis-I diagnoses excluded patients from entering this trial; however, this is a fairly standard design feature of many antidepressant trials, including those involving depressed youth (for example, the sertraline trials, as well as the earlier escitalopram trial). The purpose is not to claim that the results replicate routine clinical practice; it is to provide a patient population upon which a specific hypothesis can be tested concerning the antidepressant efficacy of a drug. Therefore, we believe that the concern regarding "generalizability" does not impact the basic interpretation of this trial's findings, namely that these results suggest that escitalopram is an effective treatment for depressed adolescents.

That said, we have amended the final sentence to include a caveat about the lack of data concerning the use of escitalopram in patients with co-morbid primary Axis I diagnoses.

With regard to the statement in the manuscript concerning the incidence of secondary psychiatric diagnoses (both previous and/or ongoing) -- found in the second paragraph of the Results section -- please note that we stated that ADHD, enuresis and GAD were only the most common diagnoses, not the only ones; similarly, we did not state that there were no histories of simple phobia. In fact, among patients with ongoing secondary Axis I diagnoses, there was 1 diagnosis of specific phobia, and 1 of simple phobia (both placebo treated patients).

*5. The discussion of the clinician's scoring of the CDSR stated that it was based on the rater's "synthesis of separate interviews" with the patient and parent. The standard methodology for this interview is generally to use the higher of the parent or child score. Is this what happened or did the raters make their "best estimate" from data of both interviews?*
In fact, the CDRS-R manual states that when the parent and child interviews result in different ratings for a given item, the rater must determine which informant is more reliable, and rate the item based on the most accurate reflection of the severity of the symptom. Therefore, the text has not been revised.

*6. The effect size (ES) reported as 0.27 may be comparable to prior reports, however, it should be noted that according to Cohen this is a relatively small ES. Given this small ES, there were no data to see if this level of change had any quality of life meaning.*
See response to Reviewer #1.

*7. It was not clear why the authors consider the baseline difference in the CDRS-R (~2 points) between the two treatment groups as not clinically significant even though it was statistically significant. This is confusing as the authors' then note that a CDRS-R treatment difference between the groups of ~2pts, which is statistically significant, shows efficacy. It was clear the authors controlled for these baseline severity scores but then what does a 2-point difference really mean for the adolescent? Is this a quality of life difference?*
**The primary outcome (CDRS-R) was significant but there was little discussion of why most of the secondary outcome measures were not significant. Also, the authors did not discuss the*

*meaning of the finding that the primary outcome was not significant when tested among the study completers. Was the CDRS required to be the primary outcome measure?*

As noted above, we have substantially revised the Discussion section, and include comments on the clinical vs. statistical significance.

*8. Of particular concern is the lack of a "true" discussion of the difficulties in this and the other RCTs, which find some scales show efficacy and others don't, the clinical significance of a 2-point end point difference on the CDRS-R between drug and placebo, and the methodology of the protocol, and maintaining fidelity across so many sites. Finally, one has to wonder whether the restrictive entry criteria in conjunction with the small effect size limit the utility of escitalopram in the real world of adolescent MDD. Are these results statistically significant but clinically not meaningful?*

As we have noted above, we have made revised the manuscript substantially, in order to better clarify the clinical significance of the findings of this study. As we conclude at the end of the discussion section, clearly further research to address some of these issues is warranted.

Through addressing these reviews, the authors made additional revisions, some quite substantial, to improve the flow of the manuscript; all changes have been tracked in the revised submission. We thank you for your further consideration of our manuscript, and believe the revisions have improved the paper.

Sincerely,

Graham J. Emslie, MD
Professor of Psychiatry
UT Southwestern Medical Center