The following comments are in response to:

Gibbons RD, Hur K, Brown CH, Davis JM, Mann J. Benefits from antidepressants: Synthesis of 6-week patient-level outcomes from double-blind placebo-controlled randomized trials of fluoxetine and venlafaxine. *Arch Gen Psychiatry*. 2012;69(6):572-579.

Gibbons RD, Brown CH, Hur K, Davis JM, Mann J. Suicidal thoughts and behavior with antidepressant treatment: reanalysis of the randomized placebo-controlled studies of fluoxetine and venlafaxine. *Arch Gen Psychiatry*. 2012;69(6):580-587.

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The Exaggerated Benefits from Antidepressants

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"Benefits from Antidepressants," (1) is fraught with problems and offers a misrepresentation of available evidence. For example, the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) (2), contrary to the 67% cumulative response rate reported, found that of the 4041 patients who entered the program only 108 (3%) had a sustained remission—all other patients either dropped out or relapsed (3). Moreover, the Treatment for Adolescents with Depression Study (TADS), the largest of the four trials in the current analysis of youth showing a "significant" effect at 6 weeks, demonstrated no differences between placebo and fluoxetine at both 6 and12 weeks (4).

Given the results of studies like the STAR*D and TADS, as well as other meta-analyses showing similarly small and clinically insignificant differences (5,6,7,8), the reported 2.55 point difference on the HAM-D, under the accepted 3 point criterion of clinical significance, and the 4.62 points (even less than the 6 and 12 week non-significant differences in TADS) on the CDRS-R is not front page news. But herein is the authors' main thrust: these clinically insignificant mean differences translate to large response and remission rate differences. Their analysis reported an "estimated" combined response/remission rate of 32.2% over placebo for adults and a 54.1% combined advantage over placebo for youth. How are we to interpret the findings of small mean discrepancies translating to large response/remission rate differences in the context of the findings of the STAR*D and TADS? For example, what sense do the differential response and remission estimates at 6 weeks make given the TADS reported no difference between medication and placebo at 6 and 12 weeks not only on the CDRS-R but also the Reynolds Adolescent Depression Scale?

Finally, the most dangerous misrepresentation in the study was that these findings of "benefits" should favor a reconsideration of the black box warning for suicidal thinking and antidepressants in children and adolescents. TADS recorded 15 suicidal events in fluoxetine groups compared with 9 in non-fluoxetine groups at 12 weeks, including 6 suicide attempts by fluoxetine takers compared to 1 in the cognitive behavioral therapy (CBT) group (none in placebo). After 36 weeks of treatment, there were 25 suicidal events for those taking fluoxetine compared with 7 in CBT (9). This already troubling risk benefit equation is actually an underestimate of the risk. Following the acute treatment phase, fluoxetine was prescribed to some patients in the placebo and CBT conditions and when those patients had a suicidal event, it was charged against their original non-drug assignment rather that the medication (10).

In sum, this article does not warrant the media hype it has received and certainly does not trump the large body of available evidence about antidepressant efficacy. Its major premise does not make common-sense (extremely small differences at 6 weeks translating to large response and remission differences) and its representation of the available evidence inaccurate. This assertion is only strengthened by consideration of the study's sole reliance on clinician rated measures and the problems associated with industry affiliation.

References:

1. Gibbons RD, Hur K, Brown CH, Davis JM, Mann J. Benefits from antidepressants: Synthesis of 6-week patient-level outcomes from double-blind placebo-controlled randomized trials of fluoxetine and venlafaxine. Arch Gen Psychiatry. 2012;69(6):572-579.

2. Rush AJ, Trivedi MH, Wisniewski SR, Nierenberg AA, Stewart JW, Warden D, Niederehe G, Thase ME, Lavori PW, Lebowitz BD, McGrath PJ, Rosenbaum JF, Sackheim HA, Kupfer DJ, Luther J, Fava M. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: A STAR*D report. Am J Psychiatry. 2006;163:1905-1917.

3. Pigott HE, Leventhal AM, Alter GS, Boren JJ. Efficacy and effectiveness of antidepressants: Current status of research. Psychother Psychosom. 2010;79(5):267-279.

4. March J, Silva S, Petrycki S, Curry J, Wells K, Fairbank J, Burns B, Domino M, McNulty S, Vitiello B, Severe J. Fluoxetine, cognitive-behavioral therapy, and their combination for adolescents with depression: Treatment for Adolescents With Depression Study (TADS) randomized controlled trial. JAMA. 2004;292:807–820.

5. Kirsch, I, Moore T, Scoboria A, Nichols, S. The emperor's new drugs: An analysis of antidepressant medication data submitted to the U.S. Food and Drug Administration. Prev Treat. 2002;5(23):article 33.

6. Kirsch I, Deacon B, Huedo-Medina T, Scoboria A, Moore T, Johnson B. Initial severity and antidepressant benefits: A meta-analysis of data submitted to the Food and Drug Administration. PLoS Medicine. 2008;5(2): 260-268.

7. Fournier JC, DeRubeis RJ, Hollon SD, Dimidjian S, Amsterdam JD, Shelton RC, Fawcett J. Antidepressant drug effects and depression severity: A patient-level meta-analysis. JAMA. 2007;303(1): 47–53.

8. Turner EH, Matthews AM, Eftihia Linardatos BS, Tell RA, Rosenthal R. Selective publication of antidepressant trials and its influence on apparent efficacy. N Engl J Med. 2008;358(3):252-260.

9. March JS, Silva S, Petrycki S, Curry J, Wells K, Fairbank J, Burns B, Domino M, McNulty S, Vitiello B, Severe J. The Treatment for Adolescents With Depression Study (TADS): Long-term effectiveness and safety outcomes. Arch Gen Psychiatry. 2007;64:1132–43.

10. Vitiello B, Silva SG, Rohde P, Kratochvil CJ, Kennard BD, Reinecke MA, Mayes TL, Posner K, May DE, March JS. Suicidal events in the Treatment for Adolescents With Depression Study (TADS). J Clin Psychiatry. 2009;70(5): 741-747.

Fluoxetine and Pediatric Suicidality Risk Re-analyzed

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Gibbons and colleagues (1) reanalyzed suicidality short-term data from 4 pediatric trials of fluoxetine (3 Eli Lilly-funded and the Treatment of Adolescents With Depression Study, TADS (2,3)) and found no increased risk of suicidality. The investigation, however, is fraught with problems. First, they did not solicit suicidal ideation adverse events reports (AERs), despite the fact that suicidal ideation is considered a suicide event by the Columbia Classification Algorithm of Suicide Assessment (C-CASA) (4), FDA analyses (5,6) and the TADS. Consequently, the study's AER data necessarily underestimates suicidality by only capturing suicidal behaviors (attempts or suicides).

Second, the primary analysis used one item of a clinician-rated scale. This is unusual for this type of analysis. FDA meta-analyses examining suicidality in pediatric SSRI trials have relied on coded AER narratives, with suicide item score data secondarily analyzing worsening or emergent suicidality (5), or electronic search and manual review for serious adverse event descriptions (6). The study coded AERs (7) on the CDRS-R, but, lacking ideation AERs, no other supplemental data was added to the scale scores.

Third, the authors did not describe procedures to minimize bias, especially since AER data was obtained from Ely Lilly, funder of 3 of the 4 analyzed studies. As a comparison, an evaluation of safety in 23 pediatric antidepressant trials used blinded pharmaceutical personnel to identify suicidal events; Columbia University suicidology experts then blindly analyzed that data (5). Without these types of safeguards, bias cannot be eliminated.

Fourth, coding AERs as 7 on the CDRS-R item 13 hides suicidal behaviors instead of evaluating them as separate variables. In TADS, suicide events are analyzed separately, making them accessible for contrast analysis. For example, an analysis of the 12-week TADS suicidal behavioral events reported 6 suicide attempts for SSRI groups compared with 1 for non-SSRI groups (2). Though under-powered for statistical analysis, such data becomes meaningful within multiple contexts of analysis (e.g., by week 36 in TADS, there were 17 suicide attempts for fluoxetine; 1, non-fluoxetine, counting those switched to fluoxetine from original assignment (7).

Finally, the authors failed to mention that the short time frame (12 weeks) as a limitation. In TADS, time to first suicidal event ranged from 0.4 – 31.1 weeks (7). Beyond 12 weeks, only fluoxetine groups experienced a suicidal event. Counting those switched to fluoxetine, there were 36 suicidal events for fluoxetine takers and 8 for non-fluoxetine takers (7).

In sum, this study is inconsistent with standard pediatric suicidality assessment methodology, resulting most notably in under-representation of suicide-related events. Collapsing the first two categories in item 13 may have further undercounted these by downgrading suicidal ideation when angry to a non-event, though this is unclear (a table of revised response categories is not included). As derived, the study's conclusion lacks credibility, especially given its contradiction of previous studies (5,6,8). The disclosure that Gibbons has served as an expert witness for Wyeth and Pfizer Pharmaceuticals in cases related to antidepressants and suicide further draws into question this study's credibility. Unfortunately, the media blitz in its wake stands to mislead the public and prescribers.

References

1. Gibbons RD, Brown CH, Hur K, Davis JM, Mann J. Suicidal thoughts and behavior with antidepressant treatment: reanalysis of the randomized placebo-controlled studies of fluoxetine and venlafaxine. Arch Gen Psychiatry. 2012;69(6):580-587.

2. March J, Silva S, Petrycki S, Curry J, Wells K, Fairbank J, Burns B, Domino M, McNulty S, Vitiello B, Severe J; Treatment for Adolescents With Depression Study (TADS) Team. Fluoxetine, cognitive-behavioral therapy, and their combination for adolescents with depression: Treatment for Adolescents With Depression Study (TADS) randomized controlled trial. JAMA. 2004; 292(7):807-820.

3. March JS, Silva S, Petrycki S, Curry J, Wells K, Fairbank J, Burns B, Domino M, McNulty S, Vitiello B, Severe J. The Treatment for Adolescents With Depression Study (TADS): Long-term effectiveness and safety outcomes. Arch Gen Psychiatry. 2007;64:1132–43.

4. Posner K, Oquendo MA, Gould M, Stanley B, Davies M. Columbia Classification Algorithm of Suicide Assessment (C-CASA): classification of suicidal events in the FDA's pediatric suicidal risk analysis of antidepressants. Am J Psychiatry. 2007;164(7):1035-1043.

5. Hammad TA, Laughren T, Racoosin J. Suicidality in pediatric patients treated with antidepressant drugs. Arch Gen Psychiatry. 2006;63:332-339.

6. Mosholder AD, Willy, M. Suicidal adverse events in pediatric randomized, controlled clinical trials of antidepressant drugs are associated with active drug treatment: a meta-analysis. J Child Adolesc Psychopharmacol. 2006 Feb-Apr;16 (1-2):25-32.

7. Vitiello B, Silva SG, Rohde P, Kratochvil CJ, Kennard BD, Reinecke MA, Mayes TL, Posner K, May DE, March JS. Suicidal events in the Treatment for Adolescents With Depression Study (TADS). J Clin Psychiatry. 2009;70(5):741-747.

8. Olfson M, Marcus SC, Shaffer D. Antidepressant drug therapy and suicide in severely depressed children and adults. Archives of General Psychiatry. 2006 Aug. 63:865-72.