PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Critical appraisal of adverse effects reporting in the “Treatment for Adolescents With Depression Study (TADS)” study
AUTHORS	Westergren, Tone; Narum, Sigrid; Klemp, Marianne

VERSION 1 – REVIEW

REVIEWER	Andrew J. Lewis School of Psychology Murdoch University, Perth., Australia
REVIEW RETURNED	02-Oct-2018

GENERAL COMMENTS	Thank you for the opportunity to review this important and interesting paper. The focus specifically on the TADS study initially seemed quite narrow but as the paper progressed it was apparent that a very detailed analysis was being undertaken which was interesting. However, particularly in the final paragraphs of the discussion and again at the end of the abstract I would have liked the authors to broaden their focus and draw up the wider implications for the status of the TADS study in the evidence base for treatment options of adolescent depression, and in particular, make some comments about how they think adverse events are best evaluated in RCTs, especially in complex psychiatric studies where participants break their original allocation treatment. A second point is that the abstract and in the findings makes reference to the reporting of sexual problems as an adverse event but we need to remember that these are adolescents. There is only one minor concession to this point in the discussion but earlier the abstract for example reads as if the absence of reporting of sexual problems was a limitation in TADS reporting. It is an open question in my mind as to how studies of adolescents ought to assess both the positive and negative impact of treatment on their sexual behaviour. p.5 some justification as to why only one of the two clinical trials identified in the reported Cochrane review should be added. p. 6 the issue of how an adequate definition of "clinically significant interference with functioning" should be added at this point on the intro. The issue is critical to the overall argument of the paper. p.6 the final statement in the intro about the study rationale needs to be stated much earlier. Method p.6 search terms should be added inclusion and exclusion headings are needed. The operational definition of an adverse effect should be stated here also Results

	Generally quite clear but the data in Table 2 was difficult to follow and I think its clarity could be improved. Discussion. Some very interesting points raised here such as the potential for bias within the ITT allocation given breaking of treatment allocation. Limitations of the study need development- ie is this issue likely in other clinical trials. I would have preferred to see the discussion draw out more clearly the implications in terms of the role of TADS as one of the major studies of treatment for adolescent depression as its place in the evidence base. I would have also liked to see the authors make suggestions about how future studies should best assess adverse effects in adolescent depression RCTs and more generally.

REVIEWER	Joe Kossowsky Instructor in Anesthesia, Boston Children's Hospital, Harvard Medical School., Boston, USA
REVIEW RETURNED	24-Nov-2018

GENERAL COMMENTS	This manuscript reports on a review of all publications from the "Treatment for Adolescents With Depression Study (TADS)" study with regard to reporting of adverse effects in the treatment groups both for the short-term and long-term study stages. Give the importance and relevance of the TADS study with regard to treatment recommendations and the effectiveness and risk of antidepressant therapy in adolescents, this study is both timely and important. It is likely to be of interest to both clinicians and researchers and therefore have considerable impact. There are a few issues in the results and discussion that the authors may want to consider. Introduction: Introduce the importance and controversy related to the topic of adverse events in SSRIs in youth. The authors might want to highlight and summarize findings of recent meta-analyses on side effect profiles of SSRIs in children (e.g. Locher et al., JAMA Psychiatry, 2017; Garland et al.,2016). Method: As a systematic search was conducted, if possible, please add a PRISMA Flowchart, which would complement the Figure 1 currently provided Results: Page 8, line 7: Authors mention that is unclear whether adverse events led to dropouts. Was it ever explicitly assessed/reported in any publication how many patients in total dropped out due to adverse events? If so, please report. Could the authors provide more explicit information on how adverse events other than suicidality were assessed (i.e. checklist, open questions in interview)? In this regard, in table 3, the authors report common side effects of fluoxetine either mentioned or not mentioned in publications from the TADS study. Do they have information whether these side effects were explicitly asked about and negated by patients, or were they not reported on by patients? Discussion: It could be beneficial for readers if the authors could compare and discuss their findings related the TADS study with findings of later

	SSRI studies reported in recent meta-analyses and reviews looking at side effect profiles of SSRIs in youth with depression (e.g. Locher et al., 2017; Garland et al.,2016). Given their findings, what recommendations would the authors make for future pediatric psychopharmacologic studies?

VERSION 1 – AUTHOR RESPONSE

Reviewer(s)' Comments to Author:

Reviewer: 1

Please leave your comments for the authors below
Thank you for the opportunity to review this important and interesting paper. The focus specifically on the TADS study initially seemed quite narrow but as the paper progressed it was apparent that a very detailed analysis was being undertaken which was interesting. However, particularly in the final paragraphs of the discussion and again at the end of the abstract I would have liked the authors to broaden their focus and draw up the wider implications for the status of the TADS study in the evidence base for treatment options of adolescent depression, and in particular, make some comments about how they think adverse events are best evaluated in RCTs, especially in complex psychiatric studies where participants break their original allocation treatment.

A second point is that the abstract and in the findings makes reference to the reporting of sexual problems as an adverse event but we need to remember that these are adolescents. There is only one minor concession to this point in the discussion but earlier the abstract for example reads as if the absence of reporting of sexual problems was a limitation in TADS reporting. It is an open question in my mind as to how studies of adolescents ought to assess both the positive and negative impact of treatment on their sexual behaviour.

We agree that a study in adolescents probably will not be suitable or powered to give any significant information on the risk for sexual adverse effects. However, sexual adverse effects were discussed in the Treatment for Adolescents with Depression Study (TADS) Pharmacotherapy (PT) Treatment Manual, which states that it is particularly important to inquire about sexual side effects (without parents present if necessary), as these may comprise the “real reason” for non-compliance. Procedures in case of pregnancy were established and mentioned in the patient information.
Our point was to illustrate the fact that this possible adverse effect probably was not addressed or described. The study does not provide information as to how this might affect young adults. Prescribers should be aware of the fact that this has not been addressed, especially if treatment started in young teenagers continue into adulthood.

We have amended the text in the section “Other adverse effects” to: “Effects on sexual functioning are not mentioned in this group of young patients.”

We have amended the text in the Discussion section to focus more on the young age of the patients: “Sexual adverse effects may not have been relevant to many patients at the time due to their age, or may not have been forthcoming in interviews, especially as many patients were interviewed in the company of caregivers. Risk of sexual adverse effects was discussed in the adverse event monitoring protocol (23) and procedures in case of pregnancies were established (24), so it is reasonable to assume that a certain proportion of patients were sexually active”.

p.5 some justification as to why only one of the two clinical trials identified in the reported Cochrane review should be added.

Our intention was to perform an in-depth analysis of the TADS study publications. As we have not analysed the other study that was part of the risk/benefit assessment in the Cochrane review, we have amended the text by deleting the phrase: “and is one of two clinical trials of fluoxetine included for risk/benefit assessment in the latest Cochrane systematic review of antidepressant treatment in children and adolescents”.

p. 6 the issue of how an adequate definition of "clinically significant interference with functioning" should be added at this point on the intro. The issue is critical to the overall argument of the paper.

The study protocol gives an example on what should be considered "clinically significant interference with functioning": “e.g. headache that causes school absence or otherwise restricts activity”. This example has now been added to the text.

p.6 the final statement in the intro about the study rationale needs to be stated much earlier.

The study rationale text has been moved and is now described at the beginning of the introduction.

Method
p.6 search terms should be added

The search terms have been added to the Methods section.
Search terms in Google Scholar were either «TADS team» or «Treatment for adolescents with depression study». Search term in PsycINFO was «Treatment for adolescents with depression study». Search term in PubMed was the phrase «Treatment for adolescents with depression study» and similar publications, limited to 2004 to 1. September 2017 and age group Child 0-18. Search term in Embase was «Treatment for adolescents with depression study».

inclusion and exclusion headings are needed. The operational definition of an adverse effect should be stated here also

Inclusion and exclusion criteria have been added to the Methods section, as well as our operational definition on adverse effects.

Results
Generally quite clear but the data in Table 2 was difficult to follow and I think its clarity could be improved.

Table 2 has been revised by removal of abbreviations, use of full words, use of bold characters to groups and use of n to denote number of cases.

Discussion.
Some very interesting points raised here such as the potential for bias within the ITT allocation given breaking of treatment allocation.
Limitations of the study need development- ie is this issue likely in other clinical trials.

We have made the following addition to the points concerning study limitations: “ Our findings regarding adverse effect reporting and potential for bias are based on analysis of one specific trial and

do not give information on adverse effects reporting or bias in other studies of an SSRI in adolescents. “ We have also commented more in this in the Discussion section.

I would have preferred to see the discussion draw out more clearly the implications in terms of the role of TADS as one of the major studies of treatment for adolescent depression as its place in the evidence base.

The Discussion section has been amended to include more discussion of the implications of the findings.

I would have also liked to see the authors make suggestions about how future studies should best assess adverse effects in adolescent depression RCTs and more generally.

According to the TADS study protocol, the study had in place a system of extensive monitoring and follow-up. As to the assessment of adverse events, we believe that the potential for bias would have been substantially reduced by avoiding the severity thresholds.
Reporting: We would suggest a consistent method of describing suicidal risk and mania score worsening throughout the publication series. Changes in mania and suicidality scores for individual patients could have been reported in more detail. The full spectre of adverse effects is included in the phase I results, but have not been reported in full for the rest of the study period.
Analysis: Percentage calculation of occurrence was done by analysing the number of cases relative to the number of patients originally allotted to the respective treatment groups, not taking the number of dropouts into consideration. If calculated relative to the number of patients actually receiving treatment, the percentages would have been higher. We would suggest that if risk is presented as percentages, it should be calculated based on the number of patients who were receiving treatment at the time the adverse event occurred.
The Discussion section has been amended to include the mentioned suggestions.

Reviewer: 2

Introduction:
Introduce the importance and controversy related to the topic of adverse events in SSRIs in youth. The authors might want to highlight and summarize findings of recent meta-analyses on side effect profiles of SSRIs in children (e.g. Locher et al., JAMA Psychiatry, 2017; Garland et al.,2016).

We have amended the Introduction section and included references to Locher 2017 and Garland 2016: “The safety profile of SSRIs in adolescents has been extensively debated. Several systematic reviews have analysed what is known about the risk of suicidal behaviour (1-3) as well as other psychiatric and somatic adverse risks and the perceived benefit/risk balance. The reviews have highlighted considerable variations in assessment, definitions and reporting of adverse effects in the clinical trials”.

Method:
As a systematic search was conducted, if possible, please add a PRISMA Flowchart, which would complement the Figure 1 currently provided

We have added the number of records from the database searches to the existing figure, to adjust to the PRISMA Flowchart. The PRISMA Flowchart is best suited to describe the information flow in a systematic review. In our study, we attempted to trace all publications arising from one specific clinical trial. Due to the large number of articles, including primary literature, guidelines, review articles etc. that address use of fluoxetine in adolescents, keyword searches generally resulted in too broad

results and irrelevant records. Use of text phrases gave more precise results in the literature databases, but gave a large number of unspecific and broad results in Google Scholar. Consequently, the number of records in our search results will be less informative than is the case in a regular literature search for clinical studies for a systematic review.

Results:
Page 8, line 7: Authors mention that is unclear whether adverse events led to dropouts. Was it ever explicitly assessed/reported in any publication how many patients in total dropped out due to adverse events? If so, please report.

Dropouts or premature terminations due to adverse events are not specified in the publications for the entire study group. We have added a sentence to clarify this: “It is not specified to what extent dropouts or premature terminations were due to adverse events in the initial study population”.

Could the authors provide more explicit information on how adverse events other than suicidality were assessed (i.e. checklist, open questions in interview)? In this regard, in table 3, the authors report common side effects of fluoxetine either mentioned or not mentioned in publications from the TADS study. Do they have information whether these side effects were explicitly asked about and negated by patients, or were they not reported on by patients?

Patient safety was monitored in several ways: By a screening questionnaire for affective disorders used by patient and clinician, by checklist of physical symptoms filled out by the patient, by registration forms for adverse events and serious adverse events, by logs for concomitant medications and mental health treatment. Patients were asked about any new health problems that caused the patient to alter his daily routine, seek medical care or take a new medication. We have not been able to find a published version of the questionnaires that were used and it is not available on the study website. Consequently, we do not have information as to which adverse effects were specifically asked for. This has been included in the Discussion section.

Discussion:
It could be beneficial for readers if the authors could compare and discuss their findings related the TADS study with findings of later SSRI studies reported in recent meta-analyses and reviews looking at side effect profiles of SSRIs in youth with depression (e.g. Locher et al., 2017; Garland et al.,2016). Given their findings, what recommendations would the authors make for future pediatric psychopharmacologic studies?

The review by Garland discuss physical and emotional/behavioural adverse effects in most detail. We have included a reference to the frequency of emotional/behavioural adverse effects in this review: “The risk of psychiatric adverse events such as mania, irritability, agitation and anxiety is given as 11% in the FLX group and 5,6% in the COMB group (12). In the review by Garland, the occurrence of emotional/behavioural adverse effects is given as 10-25% (3), but the numbers may not be comparable due to different inclusion criteria.”

We have amended the Discussion section to include recommendations for future studies: “In future studies, the potential for bias may be substantially reduced by avoiding severity thresholds and defining a consistent method of describing adverse effects such as suicidal risk and mania score worsening. Changes in mania and suicidality scores for individual patients should be analysed beyond the group level. We would also suggest that if risk is presented as percentages, it should be calculated based on the number of patients who were receiving treatment at the time the adverse event occurred, especially in studies with large dropout rates and treatment changes. The full spectrum of adverse effects should be reported for all study stages”.

VERSION 2 – REVIEW

REVIEWER	Joe Kossowsky Boston Children's Hospital, Harvard Medical School, USA
REVIEW RETURNED	20-Jan-2019

GENERAL COMMENTS	The authors have adequately addressed all of my concerns.