PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Suicide-related events in young people following prescription of SSRIs and other antidepressants: a self-controlled case series analysis
AUTHORS	Wijlaars, Linda; Nazareth, Irwin; Whitaker, Heather; Evans, Stephen; Petersen, Irene

VERSION 1 - REVIEW

REVIEWER	Bernadka Dubicka consultant child and adolescent psychiatrist, Lancashire care Foundation Trust, and honarary senior lecturer, University of Manchester UK Competing interests: principle investigator in HTA funded depression trial of psychological treatment in depressed adolescents
REVIEW RETURNED	03-Jun-2013

THE STUDY	research question: there is some inconsistency between the various descriptions of the research question in the abstract, article focus and pg 5 of the discussion; namely the authors need to be consistent with the term used for the population (children and adolescents/young people, not just children); consider the wording of their outcomes, and consistently state the 2 main aims which are the temporal associations with suicide-related events and ADs, and also the comparison between TCAs and SSRIs (not stated in article focus or at the end of pg 5 in the introduction). With regards to the description of their outcomes, this is a difficult issue in the literature which has not yet been resolved. the term used in the title 'suicide-related events' probably best describes the outcomes examined, since intentional (or non-suicidal?) self-harm has also been linked to completed suicide. I would suggest the authors continue to use this term instead of 'suicidal behaviour' as this doesn't cover ideation and the relationship between this term and intentional self-harm is unclear. it is also not clear from the research question whether the authors intended to only include depression or all conditions where ADs were prescribed, hence my query about inclusions/exclusions. Confusingly, much of the introduction and discussion refers to depression, but the only condition excluded is enuresis; did the authors only look at depression diagnoses or was this analysis based on all AD prescriptions including those for OCD and anxiety? The analysis remains informative irrespective of whether these conditions were included, but this would have to be made explicit throughout the paper and discussed. As the authors point out, the Bridge analysis found a difference in these outcomes according to

	the condition examined. If the authors did include OCD and anxiety as a prinary diagnosis, would it be possible to present the separate figures as in the Bridge analysis I also have a query about other newer-generation ADs, particularly venlafaxine (non-SSRIs): these were still in use in adolescents before the CSM warning, so did the authors collect data on any of these ADs? It would be helpful to have this data if available, since these will be licensed for use in 18 year olds which is still in the remit of this study. the numbers may have been too small to include; if this is the case, if would be helpful to have this included. With regards to the method, further elaboration on how suicide-related events were determined would be helpful. It is very difficult to retrospectively ascertain these outcomes (particularly for brief GP consultations), and there is no indication in the paper regarding the difficulties that may have arisen here. It should also be acknowledged that the NICE depression guidelines in 2005 stated that ADs should only be prescribed by C&A psychiatrists, hence further limiting data after this time. Could the authors also clarify how multiple events were coded for each YP, eg all attempts would be associated with ideation - would just the attempt be recorded here or would there be double-counting? Abstract: I also note that in the conclusion the authors haven't re-stated the increase in risk in the 4th week. I think there may be a typo in the 3rd to last sentence in the conclusion: should this sentance not read 'the pattern of IRRs (not death)...' as in the discussion? key messages: there needs to be a statement regarding the temporal findings overall (in preference to the key message on the registry). This finding does appear to be mixed, like much of the literature; there does seem to be a peak post-prescription at week 4, including for suicide (although the numbers are very small). Although overall I would agree with the authors that the risks appear limited and the advice for ADs should be re-considered, this data would still suggest ongoing close monitoring in the first month (the authors have succinctly summarised these issues in the discussion). My other key message from this paper which is not sufficiently highlighted is that only 14% of YP who completed suicide were on Ads and only 23% were referred to mental health services - this would suggest a strong case for under-treatment being an important factor in completed suicide, and this data would need to be considered alongside the peak at week 4 (which is difficult to interpret due to the small numbers and wide CIs). Lastly, the data suggests that there may be some differences between the SSRIs - can the authors state whether these were significantly different or not?
RESULTS & CONCLUSIONS	The key points and conclusions should be re-considered as above. The figures do not appear to have labels for outcomes. i would also have found it useful to know how many YP were treated with each AD as it would give an indication of number of events in relation to number of YP on ADs. perhaps this could be added to the tables?

	I have some hesitation in suggesting a registry, particularly as a main recommendation. I would dispute with the authors that this would be easy for clinicians and cost-neutral. ADs are still largely prescribed by C&A psychiatrists in the UK due to the NICE recommendations - there is no electonic system currently in place where this information could be recorded. Also, if all suicide-related events were to be recorded this would be cumbersome for clinicians as these events are very common in depression; there is therefore a danger that only limited data would be collected, skewing results. GP data collection would also be limited by the brevity of consultations, and limited number of contacts. Depressed YP are often difficult to engage and this is all the more difficult in brief consultations. 'hard' outcomes such as attendance for attempts in A&E could be potentially collected, however, most YP who self-harm don't go to A&E so this route would also be problematic. An easier and essential recommendation is that at least within trials, all such data should be propectively collected, although this will not answer the issue regarding completed suicide as this is a rare event. Collecting data on completed suicides and ADs remains an important source of information.
GENERAL COMMENTS	This is an informative, well-conducted analysis of a large data set and adds valuable additional data on the issue of suicide and suicide-related events in young people on anti-depressants. Most data has come from the US so this UK based study is a welcome addition to the field.

REVIEWER	***Arif Khan, MD*** ***Medical Director*** ***Northwest Clinical Research Center*** ***Bellevue, WA, USA*** ***Adjunct Professor*** ***Duke University School of Medicine*** ***Department of Psychiatry*** ***Durham, NC, USA*** ***--- No Competing Interests---***
REVIEW RETURNED	03-Jun-2013

GENERAL COMMENTS	Dr. Wiljaars and her colleagues have conducted a self-controlled case series analysis to evaluate incident rate of suicide attempts, behaviors and ideations prior to and after prescription of tricyclic and SSRI antidepressants. The results of the study are important. Specifically, the patients that received SSRI antidepressants showed very similar patterns to those prescribed tricyclic antidepressant. By using a large scale ecological design, the authors have informed the debate on association of antidepressant medication with suicidal thoughts and behaviors in the younger age group. In this case, they did not find a “smoking gun” as the patients that took SSRIs versus tricyclic antidepressants behaved very similarly over time. This suggests that other factors lead to the bump in suicidal thoughts and behaviors on prescription day. If I were to offer a suggestion, the authors should clearly spell out the method for determining a baseline rate as this will be important to general acceptance of the findings. It is not clear if this rate was determined from all patients upon entrance into the data pool, from the subset of suicidal patients upon entry into the data pool, or if the rate was determined at some other time.

VERSION 1 – AUTHOR RESPONSE

Reviewer: Bernadka Dubicka

Consultant child and adolescent psychiatrist, Lancashire care Foundation Trust, and honorary senior lecturer, University of Manchester UK Competing interests: principle investigator in HTA funded depression trial of psychological treatment in depressed adolescents

Research question:

There is some inconsistency between the various descriptions of the research question in the abstract, article focus and pg 5 of the discussion; namely the authors need to be consistent with the term used for the population (children and adolescents/young people, not just children); consider the wording of their outcomes, and consistently state the 2 main aims which are the temporal associations with suicide-related events and ADs, and also the comparison between TCAs and SSRIs (not stated in article focus or at the end of pg 5 in the introduction).

With regards to the description of their outcomes, this is a difficult issue in the literature which has not yet been resolved. The term used in the title 'suicide-related events' probably best describes the outcomes examined, since intentional (or non-suicidal?) self-harm has also been linked to completed suicide. I would suggest the authors continue to use this term instead of 'suicidal behaviour' as this doesn't cover ideation and the relationship between this term and intentional self-harm is unclear.

>We thank the reviewer for pointing out our inconsistencies in describing the population, outcomes and aims. We have clarified these by consistent use of the terms: children and adolescents, rather than just children and suicide-related events, rather than suicidal behaviour. We have also amended the description of our aims as suggested by the reviewer (p. 5).

It is also not clear from the research question whether the authors intended to only include depression or all conditions where ADs were prescribed, hence my query about inclusions/exclusions. Confusingly, much of the introduction and discussion refers to depression, but the only condition excluded is enuresis; did the authors only look at depression diagnoses or was this analysis based on all AD prescriptions including those for OCD and anxiety? The analysis remains informative irrespective of whether these conditions were included, but this would have to be made explicit throughout the paper and discussed. As the authors point out, the Bridge analysis found a difference in these outcomes according to the condition examined. If the authors did include OCD and anxiety as a primary diagnosis, would it be possible to present the separate figures as in the Bridge analysis

>We thank the reviewer for this comment. As prescriptions are not directly linked to diagnoses in THIN, excluding prescriptions based on diagnoses isn't straightforward. We were able to exclude TCA prescriptions for enuresis as in this instance TCAs are prescribed at a different dose for enuresis as compared to depression.

However, despite the lack of a direct link between prescriptions and diagnoses, we can identify what diagnoses were entered in the electronic health records. Of the 5,035 people with a record of a non-fatal suicide-related event, 65 (1.3%) had a diagnosis or symptom of OCD recorded at any time and 557 (11.1%) had a record of anxiety at any time. Most of these patients also had a diagnosis of depression. However, 25 people had a prescription for an antidepressant and a diagnosis of OCD or anxiety, but no record of a depression diagnosis. This means that a small group of people could have a primary diagnosis other than depression as an indication for their antidepressant prescription. Because of these small numbers, we feel that a sub-analysis would be inappropriate. We have added a section in the results section describing this finding (p. 12: "A small group of 25 patients had a prescription for an antidepressant and a primary diagnosis other than depression (obsessive compulsive disorder (OCD) or anxiety). Due to the small size of this group we did not perform a subgroup analysis.") and discussion (p. 17: "Due to small numbers of patients with primary diagnoses of OCD and anxiety disorders, we could not repeat the meta-analysis' sub-group comparison."

I also have a query about other newer-generation ADs, particularly venlafaxine (non-SSRIs): these were still in use in adolescents before the CSM warning, so did the authors collect data on any of these ADs? It would be helpful to have this data if available, since these will be licensed for use in 18 year olds which is still in the remit of this study. The numbers may have been too small to include; if this is the case, if would be helpful to have this included.

>We agree with the reviewer that it would be helpful to report the numbers of venlafaxine prescriptions. As with the previous comment, we did not perform a subgroup analysis on venlafaxine because of small numbers: only 107 patients were prescribed venlafaxine at any time point (80% before 2005). We have added a sentence in the results section (p. 11: Due to small numbers, we were not able to analyse antidepressants other than SSRIs or TCAs.)

With regards to the method, further elaboration on how suicide-related events were determined would be helpful. It is very difficult to retrospectively ascertain these outcomes (particularly for brief GP consultations), and there is no indication in the paper regarding the difficulties that may have arisen here.

>The reviewer raises an interesting concern. We used GP diagnoses, entered as Read codes, as indications for suicide-related events which were entered by GPs. We have not ascertained these events any further (apart from completed suicides, as described in the methods section on pages 6-7). It is possible that suicide-related events are under-reported as young people could consult another doctor or not disclose their behaviour to their GP. Therefore, we could have missed some cases. Young people who do not disclose suicide-related events to their GP could be less likely to receive antidepressants than those who do report it. The question of whether the exposures would have been different in those individuals who did not disclose the suicide related events cannot be ascertained with the data we have available. However, If cases are more likely to be prescribed AD, it would bias results toward the null (if cases see their GP soon after) or inflate the prescription day effect (if they saw their GP the same day).

It should also be acknowledged that the NICE depression guidelines in 2005 stated that ADs should only be prescribed by C&A psychiatrists, hence further limiting data after this time.

>We thank the reviewer for emphasising this and have acknowledged this in the discussion (p. 14: "As antidepressants should only be prescribed by child & adolescent psychiatrics (2005 NICE guidelines6), this artefact could also arise when GPs continue a prescription started in secondary care and record the initial indication when first prescribing this drug.").

However, we found that despite the NICE guidelines, GPs do prescribe antidepressants to children and adolescents, even after 2005 (Wijlaars et al. 2012).

Could the authors also clarify how multiple events were coded for each YP, eg all attempts would be associated with ideation - would just the attempt be recorded here or would there be double-counting?

>Multiple events were analysed separately: if a young person had records for a suicide attempt and a separate record for intentional self-harm on different dates, these would be counted separately in the stratified analyses for type of suicide-related event.

If multiple entries were made on the same day, we only counted the more severe entry.

Abstract:

I also note that in the conclusion the authors haven't re-stated the increase in risk in the 4th week. I think there may be a typo in the 3rd to last sentence in the conclusion: should this sentence not read 'the pattern of IRRs (not death)...' as in the discussion?

>We thank the reviewer for spotting the mistake in the abstract and we have corrected this accordingly.

Key messages:

There needs to be a statement regarding the temporal findings overall (in preference to the key message on the registry). This finding does appear to be mixed, like much of the literature; there does seem to be a peak post-prescription at week 4, including for suicide (although the numbers are very small). Although overall I would agree with the authors that the risks appear limited and the advice for ADs should be re-considered, this data would still suggest on-going close monitoring in the first month (the authors have succinctly summarised these issues in the discussion).

>We agree with the reviewer and have adapted our key message (p. 3: "Up to the fourth week of prescription, the IRRs for attempted suicide, suicidal ideation and self-harm remained around the levels experienced during the pre-exposure period, suggesting on-going close monitoring in the first month is important.").

My other key message from this paper which is not sufficiently highlighted is that only 14% of YP who completed suicide were on Ads and only 23% were referred to mental health services - this would suggest a strong case for under-treatment being an important factor in completed suicide, and this data would need to be considered alongside the peak at week 4 (which is difficult to interpret due to the small numbers and wide CIs).

>We agree with the reviewer that this could be an important point. We did not emphasise it in our paper as we may have missed referrals and these estimates are thus uncertain. GPs can use specific referral codes (e.g. specifying a patient was referred to mental health services), but can also use nonspecific referrals that do not mention where a patient was referred to. We did not include these nonspecific codes and are thus likely to have missed a certain amount of referrals.

Second, we could only measure drug treatment as prescribed in primary care. THIN has limited information on psychological treatments or antidepressants prescribed by psychiatrists. Hence the number of referred and treated patients might be higher than we are able to estimate.

Lastly, the data suggests that there may be some differences between the SSRIs - can the authors state whether these were significantly different or not?

>As the differences between the SSRIs are small, we would require a much larger sample size to be able to make any informative statements about differences between individual SSRIs.

The key points and conclusions should be re-considered as above.

The figures do not appear to have labels for outcomes.

>We thank the reviewer for noticing this omission. We have now labelled the figures accordingly.

I would also have found it useful to know how many YP were treated with each AD as it would give an indication of number of events in relation to number of YP on ADs. Perhaps this could be added to the tables?

>As we are likely to have missed young people with suicide-related events, we do not think our sample would be representative and think there would be too much uncertainty to extrapolate information. However, we have published a paper on trends in depression and antidepressant prescriptions in the same database that we think does represent young people (Wijlaars et al., 2012).

I have some hesitation in suggesting a registry, particularly as a main recommendation. I would dispute with the authors that this would be easy for clinicians and cost-neutral. ADs are still largely prescribed by C&A psychiatrists in the UK due to the NICE recommendations - there is no electronic system currently in place where this information could be recorded. Also, if all suicide-related events

were to be recorded this would be cumbersome for clinicians as these events are very common in depression; there is therefore a danger that only limited data would be collected, skewing results. GP data collection would also be limited by the brevity of consultations, and limited number of contacts. Depressed YP are often difficult to engage and this is all the more difficult in brief consultations. 'hard' outcomes such as attendance for attempts in A&E could be potentially collected, however, most YP who self-harm don't go to A&E so this route would also be problematic.

An easier and essential recommendation is that at least within trials, all such data should be prospectively collected, although this will not answer the issue regarding completed suicide as this is a rare event. Collecting data on completed suicides and ADs remains an important source of information.

>We agree with the reviewer's concern about a registry – it would, in the current system, only be possible to collect data from primary care, and data quality will likely be limited by the reason mentioned by the reviewer. However, suicide-screening questions could be brief, and (even if slightly biased) might be able improve the quality of the data that is currently available. Moreover, as it is possible to link primary care data to hospital data in the UK, it could be possible to asses 'hard' hospital-based outcomes as well.

Although trials would be able to collect very rich data, they will be limited in size and are likely underpowered to detect suicide-related events.

This is an informative, well-conducted analysis of a large data set and adds valuable additional data on the issue of suicide and suicide-related events in young people on anti-depressants. Most data has come from the US so this UK based study is a welcome addition to the field.

Reviewer: Arif Khan, MD

Medical Director

Northwest Clinical Research Center

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Adjunct Professor

Duke University School of Medicine

Department of Psychiatry

Durham, NC, USA

--- No Competing Interests---

Dr. Wijlaars and her colleagues have conducted a self-controlled case series analysis to evaluate incident rate of suicide attempts, behaviors and ideations prior to and after prescription of tricyclic and SSRI antidepressants. The results of the study are important. Specifically, the patients that received SSRI antidepressants showed very similar patterns to those prescribed tricyclic antidepressant.

By using a large scale ecological design, the authors have informed the debate on association of antidepressant medication with suicidal thoughts and behaviors in the younger age group. In this case, they did not find a “smoking gun” as the patients that took SSRIs versus tricyclic antidepressants behaved very similarly over time. This suggests that other factors lead to the bump in suicidal thoughts and behaviors on prescription day.

If I were to offer a suggestion, the authors should clearly spell out the method for determining a baseline rate as this will be important to general acceptance of the findings. It is not clear if this rate was determined from all patients upon entrance into the data pool, from the subset of suicidal patients upon entry into the data pool, or if the rate was determined at some other time.

>We thank the reviewer for his comments. We used a self-controlled case series study rather than an ecological study. The self-controlled case series (SCCS) method is a case-only method (i.e. people with a suicide-related event in our study) where individuals are followed over time and we compare the incidence rate during the time they were exposed to antidepressants to times they were not exposed. The strength of the SCCS is that all fixed characteristics of the individuals are accounted for in the analysis. However, the SCCS cannot be used to determine base rates.

References

Wijlaars, L.P., Nazareth, I., & Petersen, I. 2012. Trends in depression and antidepressant prescribing in children and adolescents: A cohort study in The Health Improvement Network (THIN). PLoS One

VERSION 2 – REVIEW

REVIEWER	Dr Bernadka Dubicka consultant adolescent psychiatrist and honorary senior lecturer Univeristy of Manchester and Lancashirecare Foundation Trust
REVIEW RETURNED	19-Jul-2013

THE STUDY	The authors have responded to my suggestions from my previous review and the paper has greater clarity overall. However, I have one remaining area of concern which would be important to address. The findings on suicide are likely to be taken to be of considerable importance by readers and as the abstract stands, there is no qualification for this finding. I do not think that the authors intend to send a message that SSRIs cause suicide so it would be helpful to put this finding in context in the abstract, ie the very low number which make findings difficult to interpret. Importantly, only 14% YP were on ADs at the time of their suicide and this for me is a vital finding which suggests undertreatment of depression may be related to suicide, rather than overtreatment with SSRIs. I do think that this should be incorporated in the key messages as it again places the

	suicide finding in context. Could the authors also add the word 'continued' to 'ongoing close monitoring' in the key message just to emphasise their point that suicidality is high both before and after SSRIs, as the current guidance emphasises additional close monitoring after prescribing.
RESULTS & CONCLUSIONS	Pg 16, first paragraph: negative outcomes may have decreased as SSRIs may have been stopped due to improvement – could the authors qualify the statement re negative outcomes? Could they also review the statement on benefits of SSRIs vs TCAs – the Hazell review is clear about the unfavourable risk ratio for TCAs, but evidence for SSRIs is generally more favourable than TCAs. The study below interestingly found an improvement in depression but not suicidality in youths in line with this study, but the authors analysis did not examine other outcomes. Gibbons, R. D., C. H. Brown, et al. (2012). "Suicidal Thoughts and Behavior With Antidepressant Treatment: Reanalysis of the Randomized Placebo-Controlled Studies of Fluoxetine and Venlafaxine." Arch Gen Psychiatry: archgenpsychiatry.2011.2048.
GENERAL COMMENTS	Overall this is a new and interesting analysis in a contentious field which warrants publication with a few additional considerations. As this is such a controversial area, it is important that the abstract and key messages accurately convey the findings. I have one additional minor suggestion: pg 5: the last sentence in the first main paragraph on TCAs would be better placed in the final paragraph after the second sentence.

VERSION 2 – AUTHOR RESPONSE

Reviewer: Dr Bernadka Dubicka

consultant adolescent psychiatrist and honorary senior lecturer University of Manchester and Lancashire care Foundation Trust

The authors have responded to my suggestions from my previous review and the paper has greater clarity overall. However, I have one remaining area of concern which would be important to address. The findings on suicide are likely to be taken to be of considerable importance by readers and as the abstract stands, there is no qualification for this finding. I do not think that the authors intend to send a message that SSRIs cause suicide so it would be helpful to put this finding in context in the abstract, i.e. the very low number which make findings difficult to interpret. Importantly, only 14% YP were on ADs at the time of their suicide and this for me is a vital finding which suggests undertreatment of depression may be related to suicide, rather than overtreatment with SSRIs. I do think that this should be incorporated in the key messages as it again places the suicide finding in context.

We thank the reviewer for this comment. We have now added the low number of young people on ADs in our cohort make it difficult to interpret these data (page 3: "Only a limited number of young people had a prescription for an antidepressant in the year before their suicide-related event making it difficult to interpret these data.") and mentioned it in the discussion (page 18: "Furthermore, the relatively low number of young people who had a prescription for an antidepressant at the time of their suicide-related event, limits the interpretation of our results. However, Windfuhr et al. also found that

mental health service contact is low in juveniles who committed suicide: only 14% contacted services in the year before they died29").

Finally, we have amended the abstract (page 2: "We found that a very small number of young people were prescribed antidepressants and the absence of a sustained increase in rates of suicide-related events in this group.")

Could the authors also add the word ‘continued’ to ‘ongoing close monitoring’ in the key message just to emphasise their point that suicidality is high both before and after SSRIs, as the current guidance emphasises additional close monitoring after prescribing.

We have amended the key message as suggested by the reviewer.

Please see above points. The conclusion and discussion would both benefit from emphasising these points.

Also: Pg 16, first paragraph: negative outcomes may have decreased as SSRIs may have been stopped due to improvement – could the authors qualify the statement re negative outcomes?

We have amended the statement to read: "The rate of suicide-related events decreased to below pre-exposure levels when the prescriptions were stopped."

Could they also review the statement on benefits of SSRIs vs TCAs – the Hazell review is clear about the unfavourable risk ratio for TCAs, but evidence for SSRIs is generally more favourable than TCAs.

We have adapted our statement on TCAs (page 4: "As tricyclic antidepressants (TCAs) lack efficacy for depression treatment in this age group, and have a poor side effect profile3, selective serotonin reuptake inhibitors (SSRIs) are the most commonly prescribed pharmacological treatment for children and adolescents4.")

The study below interestingly found an improvement in depression but not suicidality in youths in line with this study, but the authors' analysis did not examine other outcomes.

Gibbons, R. D., C. H. Brown, et al. (2012). "Suicidal Thoughts and Behavior With Antidepressant Treatment: Reanalysis of the Randomized Placebo-Controlled Studies of Fluoxetine and Venlafaxine." Arch Gen Psychiatry: archgenpsychiatry.2011.2048.

We thank the reviewer for highlighting this reference. However, as the online comments on the article point out, there are some methodological difficulties with this article and as such we have chosen not to cite it.

Overall this is a new and interesting analysis in a contentious field which warrants publication with a few additional considerations. As this is such a controversial area, it is important that the abstract and key messages accurately convey the findings.

I have one additional minor suggestion:

pg 5: the last sentence in the first main paragraph on TCAs would be better placed in the final paragraph after the second sentence.

We have moved the sentence as suggested.