Author’s response to reviews

Title: The association of ADHD symptoms to self-harm behaviours: A systematic PRISMA review

Authors:

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Version: 2
Date: 9 March 2014

Author’s response to reviews: see over
Dear Dr Murray,

Please find below a copy of our response to the reviewer comments on our manuscript – reference number 2002903150105035.

I have made numerous changes to the manuscript which can also be seen in the tracked-changes version and also indicated in the detailed response to the reviewers comments. I am also happy to make any further changes and additions.

I hope that you will consider my manuscript for publication in BMC Psychiatry and I look forward to hearing from you.

Yours sincerely,

Clare Allely.
Reviewer: Christopher Bushe

Compulsory revisions

Reviewer comment 1 - I have a number of aspects that should however be included within the introduction and discussion sections to give greater context. The main comments would be these. Data collected retrospectively and then analysed for suicidal related events is open to some confounding bias in studies where for example the CSRS/CCASA have not been used. Mapping any event to a specific code is possible however the potential for error is greater than if the scales were used prospectively. The ability to separate self-harm as an entity from a suicide attempt is not always easy and again this as a potential confounding bias should be discussed. The use of these scales in trials often is mandatory and should be mentioned.

Response: I have added the following to the limitation section of the discussion to address the limitations identified by the reviewer:

“Another limitation is the fact that data for the studies were collected retrospectively and then analysed for suicidal related events which exposes the studies to a degree of confounding bias, particularly in the studies where, for example, the Columbia Classification Algorithm for Suicide Assessment (C-CASA) (the standardised suicidal rating system) and the Computerized Suicide Risk Scale (CSRS) have not been delivered. Mapping any event to a specific code is possible, however, the potential for error is greater than if the scales were used prospectively. The use of these scales are often mandatory in trials. Additionally, the ability to separate self-harm as an entity from a suicide attempt is not always easy which is a potential confounding bias. In particular, Silverman, Berman, Sanddal, O'Carroll and Joiner (2007) [82] emphasised the potential complication with trying to separate self-harm and suicide attempt into two independent categories by highlighting that self-injurious intent and suicidal intent can be present simultaneously in an individual.[82] SIB and suicidal behaviours exist along the same continuum, with SIB representing a lesser form.[83,84] Research has also found that 28% to 41% of individuals who engage in SIB report suicidal thoughts at the time they were engaged in self-injury.[85]”

References added:


Reviewer comment 2: I would also like further details on the search methodologies and why these databases were chosen.

Response: The following was added to the method section: “The search criteria identified below were entered in a number of other databases including PsycINFO. However, the Medline was chosen as the primary database because it returned more relevant articles. CINAHL was also used because it is the definitive research tool for nursing and allied health professionals”.

Reviewer comment 3: In the results section there are too many words and these to some extent are replicated in the table. I would make this section much shorter and succinct.

Response: The word count in the results section was originally 2,770 words. In light of the above reviewers comment, I have now reduced this section by approximately 1,084 words (I also added some description at the beginning). Please see tracked-changes version of the manuscript to see what was removed/modified.
Reviewer comment 4: In contrast the discussion needs expanding. I would make specific reference to Barbaresi et al, Paediatrics, 2013 and their findings on increased suicide rates OR 5 in a birth cohort study.

Response: In light of the comment above, the following has been added to the discussion:

“The importance of further research into the association between ADHD and self-harm is further highlighted by the studies (outwith this review) which have investigated the increased rates of suicide in individuals with ADHD. For instance, Barbaresi, Colligan, Weaver, Voigt, Killian, and Katusic (2013) [81] investigated long-term outcomes of ADHD in a population-based sample of childhood ADHD cases (n = 367) and controls, who were all prospectively assessed as adults. Importantly, findings revealed that childhood ADHD is a chronic health problem, with significant risk for mortality, persistence of ADHD, and long-term morbidity in adulthood. The cause-specific mortality for suicide only was significantly higher among ADHD cases (standardised mortality ratios, SMR, 4.83; 95% CI, 1.14–20.46; P = .032) compared to non-ADHD controls from the same birth cohort.[81]”

Reference added:


Reviewer comment 5: I would also consider including a paragraph on the known associations of suicide related events and ADHD medications, Bushe and Savill 2013 meta-analysis atomoxetine and methylphenidate. From the EU SPCs for Methylphenidate it should also be stated that suicidal tendencies are a contraindication for this medication. Although the paper quite rightly focuses on the illness of ADHD and the outcomes, the crossover with medication is important, relevant and the readers will benefit from a short summary of what is known.

Response: I have added the following paragraph to the introduction section:
“Associations of Suicide Related Events and ADHD Medications

Although the focus of this systematic review is on ADHD and the outcomes, it is important to include a brief discussion of the crossover with medication and what is currently known. With the treatment of ADHD it is thus important to establish any associations between pharmacological treatments (such as atomoxetine and methylphenidate) and suicide-related events. Atomoxetine (Strattera®) is a selective norepinephrine (noradrenaline) reuptake inhibitor. It is not a stimulant, and is indicated for use in patients with ADHD.[31]. Methylphenidate is a central nervous system (CNS) stimulant used to treat ADHD. From the European Union (EU) Supplementary protection certificates (SPCs) for methylphenidate, it is important to highlight that suicidal tendencies have been found to be a contraindication for this medication.[32,33] The US Food and Drug Administration and Health Canada also warned of increased rates of suicidal ideation among children taking atomoxetine in placebo-controlled trials.[34] Based on fourteen identified trials in paediatric patients, Bangs and colleagues (2008) [35] found that, despite being uncommon, suicidal ideation was significantly more frequent in paediatric ADHD patients treated with atomoxetine compared to those treated with placebo.[35] One study found no evidence which suggested an increase in the risk of sudden death associated with stimulants or atomoxetine. However, there was an increased risk of suicide with the treatment.[36]

However, a recent meta-analysis, the first focusing on five studies comparing suicide-related events in comparative randomised double-blind atomoxetine and methylphenidate clinical trials, found no significant evidence of a difference in risk between the two treatments.[37] Given the limitations of meta-analyses, acknowledged by the authors [37], further research is required to establish whether there are associations between suicide-related behaviours and specific ADHD treatment medications”.

References added:


[32]. Datapharm Communications Limited Electronic Medicines Compendium: Strattera. [http://www.medicines.org.uk/EMC/medicine/14482/SPC/Strattera++10mg%2c+18mg%2c+25mg%2c+40mg%2c+60mg+or+80mg+hard+capsules].
[33]. Datapharm Communications Limited Electronic Medicines Compendium: Concerta. [http://www.medicines.org.uk/EMC/medicine/8382/SPC/Concerta+XL+18+mg++36+mg+prolonged+release+tablets/].


**Reviewer comment 6:** I would consider adding more keywords if permitted. Such as suicide-related events.

**Response:** I have added keyword: ‘suicide-related events’.

**Reviewer:** Tuula Hurtig

**Minor Essential Revisions**

**Reviewer comment 7:** ADHD is very heterogeneously defined in cited studies. That is why it would be more safe to refer to the symptoms of ADHD instead of a diagnosis, at least in conclusions. The title is ok regarding this issue.
**Response:** In the future directions and clinical implications section, the conclusion section and in the conclusion of the abstract, I have made this change from ‘ADHD diagnosis’ to ‘symptoms of ADHD’.

**Reviewer comment 8:** Self-harm behaviours are well defined, both in this manuscript and in cited studies. However, these behaviours are sometimes difficult to differentiate from suicidal behaviours, and often people have both. This is seen also in cited studies. When interpreting the results the author should clearly differentiate these behaviours.

**Response:** Please see response to Reviewer comment 1.

**Reviewer comment 9:** The manuscript would benefit from clarifications. Re-organization of the material should be made. In the Results section, the reader should be able to differentiate studies using clinical or epidemiological samples, or, is the sample basing on ADHD or self-harm. For instance, you will get different results if you study a population with ADHD and measure self-harm behaviour there, or, if you study a population hospitalized due to injury and measure symptoms of ADHD there. In addition, the age groups of the participants in cited studies should be clearly focused. As the author points out, self-harm is a health problem in young people. Some of these issues were discussed in limitations though.

**Response:** I have split the results section up into two sections – with separate sub-headings. One where the sample involved a study population with ADHD and measures of self-harm behaviour was then conducted and the second section involved studies which used a population who were hospitalised due to injury (or identified by records/self-assessment) and measures of ADHD were then conducted. The following section was added at the start of the results section to indicate this:

“In this section, the fifteen studies are split into two sections. The first section includes studies where the sample involved a study population with ADHD and measures of self-harm behaviour were then conducted. The second section includes the studies which examined a population who were hospitalised due to injury and measures of ADHD were then conducted. This was done given the possibility that different results may be obtained depending on this. Under each of these headings, studies are divided depending on whether the samples involved children and/or adolescents under the age of 18 years and adults (those above 18 years of age).”
I have also created a table (Table 2 – please see below), which indicates the gender for each of the fifteen studies for the group of interest for clarity for the reader.

**Reviewer comment 10:** In the Discussion section the author should clearly point out the most relevant and reliable studies. Some of the cited studies are referred here but there is no mention if these are the most relevant ones.

**Response:** I have removed some of the studies I had previously discussed, which were identified in the review, and have now only discussed the studies which were most relevant and reliable.

The following was added to the discussion section:

“Looking at the gender in the group of interest across all fifteen studies it is clear that there is much higher numbers of males than females. This can be seen more clearly in Table 2. Studies which include greater levels of females are required. The small number of females in a large proportion of studies is limiting the power and the ability to find any significant association between ADHD and self-harming behaviours.

The majority of the studies used samples of children (below the age of 18 years). Only three studies used a sample of adults (older than 18 years) [43-45], of which two were by the same research group.[43,44] Given what has just been described about the potential effect of age on ADHD symptoms, more studies are required which use samples to include older people in order to elucidate the effect of ADHD over the course of their lifetime.

From the 15 identified studies in this review, seven were studies using a population with ADHD and measures of self-harming behaviour were then conducted.[41,43,44,47,48,52,53] The remaining studies investigated a population who were hospitalised due to injury (or identified by records/self-assessment) and measures of ADHD were then conducted.[17,40,42,45,46,49-51]

Three of the 15 studies discussed in this systematic review were identified as the most relevant and methodologically reliable.[42,47,48] DiScala et al. [42] investigated the differences between hospital admitted injuries to children with pre-injury ADHD and injuries to those with no pre-injury conditions (NO). Compared with the NO children, the children with ADHD were more likely to inflict injury upon themselves (1.3% versus 0.1%). The importance of early identification of individuals at greater risk of self-harm is further validated by the findings of Hinshaw et al. [47] which showed that girls with childhood ADHD maintain marked impairment by early adulthood (including higher rates of suicide attempts and self-injury). Hinshaw et al. [43] found that girls with
childhood-diagnosed ADHD continued to display higher rates of ADHD and comorbid symptoms and exhibited higher rates of suicide attempts and self-injury compared with the comparison sample. Self-harm behaviour predominated in the participants originally diagnosed with ADHD-combined. Hinshaw et al. [47] indicated that individuals with the ADHD combined type are at even greater risk of self-harm behaviours which merits further attention. Lastly, Hurtig et al. [48] investigated the effect of ADHD on suicidal or self-harm behaviour in adolescents from a general population sample and found that, compared with adolescents without ADHD, those with ADHD had more suicidal ideation (57% versus 28%) and DSH (69% versus 32%)”.

I have also created the table below to make it clearer the number of males and females in the group of interest.

**Table 2.** The number of males and females in each group of interest across all 15 studies identified in this review.

<table>
<thead>
<tr>
<th>Study</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ben-Yehuda et al. [40]</td>
<td>Does not specify for the DSH individuals.</td>
<td>Does not specify for the DSH individuals.</td>
</tr>
<tr>
<td></td>
<td>Of the 39 suicidal children, 25 were males (64%).</td>
<td>Of the 39 suicidal children, 14 were females (36%).</td>
</tr>
<tr>
<td></td>
<td>Of the 227 suicidal adolescents, 58 (26%) were males.</td>
<td>Of the 227 suicidal adolescents, 169 (74%) were females.</td>
</tr>
<tr>
<td>Deane and Young (2012) [41]</td>
<td>No males (n = 0)</td>
<td>ADHD (n = 4)</td>
</tr>
<tr>
<td>DiScala et al. (1998) [42]</td>
<td>ADHD (n = 211)</td>
<td>ADHD (n = 28)</td>
</tr>
<tr>
<td>Dowson et al. (2007) [43]</td>
<td>ADHD (n = 43)</td>
<td>ADHD (n = 16)</td>
</tr>
<tr>
<td>Dowson et al. (2010) [44]</td>
<td>ADHD (n = 73)</td>
<td>No females (n = 0)</td>
</tr>
<tr>
<td>Fulwiler et al. [45]</td>
<td>Self-mutilators (n = 15)</td>
<td>Self-mutilators (n = 1)</td>
</tr>
<tr>
<td></td>
<td>Suicide-attempters (n = 11)</td>
<td>Suicide-attempters (n = 4)</td>
</tr>
<tr>
<td>Goodman et al. [46]</td>
<td>Assaultive/suicidal (83.3% of 24).</td>
<td>Assaultive/suicidal (16.7% of 24)</td>
</tr>
<tr>
<td></td>
<td>Assaultive-only (89.5% of 19)</td>
<td>Assaultive-only (10.5% of 19)</td>
</tr>
<tr>
<td>Hinshaw et al. [47]</td>
<td>No males (n = 0)</td>
<td>ADHD (n = 140)</td>
</tr>
<tr>
<td>Hurtig et al. (2012) [48]</td>
<td>ADHD and DSH (n = 15)</td>
<td>ADHD and DSH (n = 30)</td>
</tr>
<tr>
<td></td>
<td>Suicidal Acts &amp; ADHD (n = 4)</td>
<td>Suicidal Acts &amp; ADHD (n = 4)</td>
</tr>
<tr>
<td>Izutsu et al. (2006) [49]</td>
<td>DSH (n = 239)</td>
<td>DSH (n = 238)</td>
</tr>
</tbody>
</table>
States that of the types of injuries they looked at, there were 59 cases of suicide/self-harm but does not specify the gender of this group of injuries.

<table>
<thead>
<tr>
<th>Study</th>
<th>Group</th>
<th>n</th>
<th>Additional Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lam (2005) [50]</td>
<td>ADD (n = 97)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lynch et al. (2006)</td>
<td>‘At-risk’ of psychiatric disorder (n = 67)</td>
<td></td>
<td>‘At-risk of psychiatric disorder (n = 73)</td>
</tr>
<tr>
<td>Semiz et al. (2008)</td>
<td>ADHD (n = 68.25) (65% of 105)</td>
<td>No females (n = 0)</td>
<td></td>
</tr>
<tr>
<td>Wehmeier et al. (2008) [53]</td>
<td>ADHD (n = 338) (80.3%)</td>
<td>ADHD (n = 83) (19.7%)</td>
<td></td>
</tr>
</tbody>
</table>

Discretionary Revisions

**Reviewer comment 11:** The manuscript needs to be checked throughout in terms of spelling and typing.

**Response:** The manuscript has been checked throughout and some very minor corrections have been made which can be seen in the tracked changes version of the manuscript.

Reviewer: Anthony James

**Reviewer comment 12:** Major compulsory revision with regard to an improved discussion with emphasis on age and sex effects and reference to other reviews. Also there needs to be a revised written text with less emphasis upon on listing of papers.

**Response:** I have added this below to the discussion section in light of all the comments.

“It is important to consider the age of the individuals with ADHD in the studies which have been identified by this review (which investigated the association between ADHD and self-harming behaviours) given the literature which suggests that ADHD symptoms can sometimes change with age. Although ADHD symptoms frequently persist over time,[63] maturation has been found to have a significant positive effect on ADHD symptoms in many children [64]. These findings have
resulted in the hypothesis that ADHD is associated with a delay as opposed to an abnormal brain development.[65,66]. However, few studies have examined the persistence of ADHD from childhood to adulthood.[67,68] This lack of rigorous research is surprising, given the significant impact that ADHD frequently has on the individual. For instance, ADHD diagnosed at school age increases the risk for antisocial development, drug misuse, pathological aggression, and social and academic exclusion by a factor of five to ten compared to the general population.[69-71]

It is also important to highlight the gender in the studies identified by this review given the gender differences seen in individuals with ADHD.[72] The existing literature shows that although the gender difference in childhood is quite large, in adult samples this difference diminishes or disappears. Studies investigating gender differences, indicates that girls may consistently be under-identified and under-diagnosed and it is suggested that differences in the expression of ADHD between the genders might be one explanation for this.[73,74-76] Females with ADHD are reported to have less hyperactive/impulsive symptoms and more inattentive symptoms compared to males with ADHD.[73,77,78] Diagnosis of the inattentive subtype also appears to be more common in females with ADHD.[79] Boys with ADHD appear to exhibit more externalising disorders compared to boys without ADHD. Females, on the other hand, tend to exhibit more internalising disorders compared to girls without ADHD.[73,74,78,80] and to their male counterparts.[80]”

References added:


**Deleted sections:**

Numerous sections in the discussion deleted to reduce the tedious reporting of studies and instead the focus is on the five key papers found – which were the strongest methodologically.

Example of section deleted in the discussion:

“Lastly, Semiz et al. [51] found that ADHD(d) ((dimensional symptoms by means of the WURS [53] and CAARS, [54]) symptoms may be related to earlier onset of SIB, suicide attempts and criminal behaviours, in male study subjects with APD. These results therefore suggest the importance of early assessment of not only ADHDc (combined) but assessment of ADHD(d) symptoms as an early indicator of severity risk as well as onset of associated problem behaviours. A dissertation, based on a sample of 67 adults from Christchurch, New Zealand (average age 33) of whom a sample of 35 adults met criteria for ADHD (which persisted into adulthood) found a relationship between ADHD and self-destructive behaviours including self-harm and suicidal ideation and attempts. These behaviours were found to be significantly mediated by coping behaviour and psychological comorbidity.(56)”
Reviewer comment 13: …the format of listing papers, although interesting is slightly tedious. One wonders whether grouping themes or particular items together may not be more sensible.

Response: Please see reviewer comment 9.

Reviewer comment 14: The review is reasonably well conducted and thorough, however, the discussion is rather limited, and I note in particular the lack details on the grouping of papers, by for instance age. Indeed, the author has assembled a collection of papers across the age range from young children to adults, therefore, comment on this does need to be made, although not as a meta analysis as such with meta regression to delineate the influence of age upon the presentation. Self-harm presenting at differing ages does carry with it different meanings and links with suicide attempt and completed suicide. A greater emphasis upon this, and the differences between the sexes would seem important.

Response: Please see response to comments 10 and 12.

Reviewer comment 15: Discussion limited and needs expansion and linked with other reviews. Note age sex effects not highlighted

Response: Please see reviewer comment 12 in particular. However, this comment has also been addressed in other comments.

Reviewer comment 16: Are limitations of the work clearly stated? No

Response: More detail on limitations has been added in the limitation section – please see above.

Reviewer comment 17: Do the authors clearly acknowledge any work upon which they are building, both published and unpublished? yes but as noted above further reference needs to be made in the discussion with particular reference to other reviews
Response: Please see other responses across all 17 comments which address this.

Some other personal changes:

Original reference number 56 was erroneous and has now been removed – apologies for this. Reference removed - [56]. Taylor MR. Risk-taking and psychosocial functioning of adults with attention-deficit/hyperactivity disorder, 2012. http://ir.canterbury.ac.nz/handle/10092/7535

Additions to the title page: Author affiliation and other details.

Changes were made to the format of the reference list to be in line with BMC Psychiatry’s style requirements.

End of Document.