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ACTA NEUROPSYCHIATRICA

Commentary

Great boast, small roast on effects of selective serotonin reuptake inhibitors: response to a critique of our systematic review

Katakam KK, Sethi NJ, Jakobsen JC, Gluud C. Great boast, small roast on effects of selective serotonin reuptake inhibitors: response to a critique of our systematic review.

Our systematic review in *BMC Psychiatry* concluded that selective serotonin reuptake inhibitors (SSRIs) compared with placebo significantly increase the risk of serious adverse events (SAEs) in patients with major depression and the potential beneficial effects of SSRIs seem to be outweighed by the harms. Hieronymus et al. accused us of methodological inaccuracies and blatant errors. In their *post-hoc* analysis of our data, they reported that SSRIs only increase the risk of SAEs in elderly and seems safe for non-elderly patients. They also found our review misleading because our efficacy analyses were based on the 17-item Hamilton Depression Rating Scale; we included suboptimal SSRI doses; and we missed some 'pivotal trials'. We do not agree with Hieronymus et al. regarding several of the 'errors' they claim that we have made. However, we acknowledge that they have identified minor errors and that we missed some trials. After rectifying the errors and inclusion of the missed trials by us and Hieronymus et al., we re-analysed the data. The updated analyses are even more robust and confirm our earlier conclusions. SSRIs significantly increase the risk of an SAE both in non-elderly ($p = 0.045$) and elderly ($p = 0.01$) patients [overall odds ratio 1.39; 95% confidence interval (CI) 1.13 to 1.73; $p = 0.002$; $I^2 = 0\%$]. Moreover, SSRIs did not change noticeably the 17-item Hamilton Depression Rating Scale, the internationally accepted scale (mean difference −2.02 points; 95% CI −2.38 to −1.66; $p < 0.00001$). We found no differential effect of dose ($p = 0.20$).

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Hieronymus et al. raise doubts regarding our systematic review (1), which concluded that the potential small beneficial effects of selective serotonin reuptake inhibitors (SSRIs) seem to be outweighed by harmful effects in patients with major depressive disorder (2).

In the current publication, we give our clarifications to each of the doubts raised by Hieronymus et al. (2). We show that after going through all their comments, we are sure of the validity of our original review results showing that SSRIs increase the risk of serious adverse events (SAEs) without having any convincing beneficial clinical effects. Therefore, our heading 'Great boast, small roast' (in German 'Viel Geschrei und wenig Wolle'; in French 'Grande invitation, petites portions') represents our condensed reply.

This does not mean that we are unhappy with the doubts and comments raised by Hieronymus et al. (2). On the contrary, we are very thankful that they

drew our attention to two publications (3,4) and 13 study reports (5–17) (published on pharmaceutical companies' websites) that we had not identified in our searches (2). Second, we are thankful for the errors that they identified in our review (please see below). Third, we are also thankful for the other issues that they raised as they allow us to discuss the issues in greater detail.

To assess the critiques' allegations, two persons (K.K. and N.J.S.) have gone through all the included studies independently one more time. During this process, we have identified few additional trials that we already included in the original publication, but their data regarding SAEs were not reported earlier (18–25) and a few new additional trials that we and Hieronymus et al. missed (26–29). We agree that we overlooked SAEs from Kranzler et al. trial (30).

We have therefore now conducted analyses on three different sets of data: (a) data from the trials that were included in our original publication (1); (b) the latter data (a) plus the data from the trials that were reported missing by our critiques and judged eligible by us (3,4,7,10,11,13–17,30); (c) the latter data (b) plus additional data from our previously included trials where we missed to extract data on SAEs (18–25) and from four newly identified (26–29) trials. For each of these three sets of data, we conducted meta-analyses to address the impact of each issue raised by our critiques on our results (Table 1).

Below we respond point to point to the issues raised by Hieronymus et al. (2). Each number is a response to the corresponding number in the manuscript by Hieronymus et al. (2).

1. We acknowledge that for some of the trials we used the number of participants who completed the trial for the analysis of SAEs. This is not necessarily wrong. The reporting of SAEs in these trials was very poor and it was not clear whether participants discontinuing treatment prematurely were monitored for SAEs or whether they discontinued due to SAEs. If the number of randomised participants was used in the meta-analysis as the denominator, it was assumed that the participants lost to follow-up did *not* experience an SAE. If there was doubt that the SAE data for the participants discontinuing treatment were included, then we used the number of 'completers' instead of the number of randomised participants. Two independent review authors, who extracted the data, decided what data (whether it was the number of 'completers' or the number of randomised participants) should be used and included.

   Nevertheless, even if Hieronymus et al.' approach is followed the results do not change significantly. We re-calculated the number of analysed participants for SAEs in publications where the safety population or the number of analysed participants for SAEs was not reported. Instead of the number of 'completers', we calculated the number of analysed participants for SAEs by deducting the number of participants who were lost to follow-up from the number of randomised participants. For publications where there was no information on the number of participants that were lost to follow-up, we simply considered the number of randomised participants for the analysis of SAEs. With this approach, the updated meta-analysis results do not change noticeably. The odds ratio (OR) of 1.37 [95% confidence interval (CI) 1.08–1.75; $p = 0.01$; $I^2 = 0\%$] in the original publication (1) changed into 1.36 (95% CI 1.07–1.73; $p = 0.01$; $I^2 = 0\%$) in our updated meta-analysis (Table 1).
2. Referring to the Schneider et al. study (45), Hieronymus et al. claimed that we have assumed that the total number of reported SAEs corresponds to the number of participants afflicted by at least one SAE. This is not necessarily wrong. The way Schneider et al. (45) reported SAEs is unclear. We do not know if the reported number is a count and one or more of the participants experienced more than one SAE or if it is the number of participants affected by one or more SAEs (proportion). Again, two independent review authors extracted the data and then decided to include these data (number) for SAE analysis.

   Regarding the Kasper et al. study (36), we acknowledge that in the table 2 of our publication (1), we only included SAE information from the published paper (i.e. two deaths) and not from the total number of 33 participants who experienced an SAE as reported in the Lundbeck study report (46). However, we included all participants with SAE from the Lundbeck study report (46) in our analysis (1). Hence, our omission in the table does not have any influence on the meta-analysis results. We will include the SAE information from the Lundbeck study report (46) in the table in the next update of our review.
3. Hieronymus et al. claim that we have missed several trials (3–17,30,47–49). We acknowledge that we have not identified some study reports (published on pharmaceutical companies' websites) in our searches (5–17). However, published papers (50–54) for some of these missed study reports (5,7,14,15,17) were included (1), but there was no information on SAEs in the published

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Table 1. Summary of our systematic results when each of the issues raised by our critiques was been addressed

Analysis	Result	Non-elderly subgroup	Elderly subgroup	Test for heterogeneity between sub-groups
(a) Original results in our publication (1)	OR 1.37; 95% CI 1.08–1.75; $p=0.01$	–	–	–
Our results after implementation of issues raised by our critiques				
1. Intention-to-treat population if available or safety population used for analysis	OR 1.36; 95% CI 1.07–1.73; $p=0.01$	$p=0.13$	$p=0.02$	$p=0.07$
2. Pettinati et al. (31) trial excluded from analysis	OR 1.36; 95% CI 1.06–1.74: $p=0.02$	$p=0.20$	$p=0.01$	$p=0.04$
3. Ravindran et al. (32) trial excluded from analysis	OR 1.37; 95% CI 1.07–1.75; $p=0.01$	$p=0.14$	$p=0.01$	$p=0.05$
4. Serious adverse event in placebo group of Nyth et al. (33) trial corrected	OR 1.38; 95% CI 1.09–1.76; $p=0.01$	$p=0.14$	$p=0.01$	$p=0.04$
5. Female-specific serious adverse events from GSK/810 trial (34) added	OR 1.34; 95% CI 1.06–1.70; $p=0.02$	$p=0.18$	$p=0.01$	$p=0.04$
6. Number of serious adverse events in paroxetine 25-mg group of GSK/785 trial (35) corrected	OR 1.36; 95% CI 1.07–1.73; $p=0.01$	$p=0.15$	$p=0.01$	$p=0.05$
7. Different treatment groups from multi-grouped trials (34–44) combined	OR 1.37; 95% CI 1.07–1.73; $p=0.01$	$p=0.14$	$p=0.01$	$p=0.05$
8. Reciprocal of the opposite treatment group added to the number of events in the non-zero events group	OR 1.37; 95% CI 1.07–1.73; $p=0.01$	$p=0.14$	$p=0.01$	$p=0.05$
9. When all suggestions from 1 to 8 above are implemented	OR 1.35; 95% CI 1.05–1.72; $p=0.02$	$p=0.24$	$p=0.01$	$p=0.03$
10. When only valid issues are implemented (1, 4, 6 and 8)	OR 1.36; 95% CI 1.07–1.73; $p=0.01$	$p=0.13$	$p=0.02$	$p=0.07$
(b) Original data in our publication (1) plus data from the trials that were reported missing by our critiques (2) and judged eligible by us (3,4,7,10,11,13–17,30)				
When data from missed trials were added to original data	OR 1.39; 95% CI 1.11–1.73; $p=0.004$	$p=0.07$	$p=0.01$	$p=0.06$
Our results after implementation of issues raised by our critiques				
1. Intention-to-treat population if available or safety population used for analysis	OR 1.38; 95% CI 1.11–1.72; $p=0.004$	$p=0.06$	$p=0.02$	$p=0.07$
2. Pettinati et al. (31) trial excluded from analysis	OR 1.37; 95% CI 1.09–1.73: $p=0.006$	$p=0.12$	$p=0.01$	$p=0.04$
3. Ravindran et al. (32) trial excluded from analysis	OR 1.39; 95% CI 1.11–1.73; $p=0.004$	$p=0.07$	$p=0.01$	$p=0.06$
4. Serious adverse event in placebo group of Nyth et al. (33) trial corrected	OR 1.40; 95% CI 1.12–1.74; $p=0.003$	$p=0.07$	$p=0.01$	$p=0.046$
5. Female-specific serious adverse events from GSK/810 trial (34) added	OR 1.36; 95% CI 1.09–1.70; $p=0.006$	$p=0.10$	$p=0.01$	$p=0.048$
6. Number of serious adverse events in paroxetine 25-mg group of GSK/785 trial (35) corrected	OR 1.38; 95% CI 1.10–1.72; $p=0.004$	$p=0.08$	$p=0.01$	$p=0.06$
7. Different treatment groups from multi-grouped trials (3,14,15,34–44) combined	OR 1.38; 95% CI 1.11–1.72; $p=0.004$	$p=0.07$	$p=0.01$	$p=0.06$
8. Reciprocal of the opposite treatment group added to the number of events in the non-zero events group	OR 1.38; 95% CI 1.10–1.73; $p=0.004$	$p=0.07$	$p=0.01$	$p=0.06$
9. When all suggestions from 1 to 8 above are implemented	OR 1.36; 95% CI 1.08–1.71; $p=0.008$	$p=0.14$	$p=0.01$	$p=0.03$
10. When only valid issues are implemented (1, 4, 6, and 8)	OR 1.38; 95% CI 1.11–1.72; $p=0.004$	$p=0.07$	$p=0.02$	$p=0.07$
(c) Original data in our publication (1) plus data from the trials that were reported missing by our critiques (2) and judged eligible by us (3,4,7,10,11,13–17,30) plus additional data from our previously included trials where we missed to extract data on serious adverse events (18–25) and four newly identified trials (26–29)				
When data from missed trials and additional trials were added to original data	OR 1.38; 95% CI 1.12–1.71; $p=0.003$	$p=0.05$	$p=0.01$	$p=0.05$
Our results after implementation of issues raised by our critiques				
1. Intention-to-treat population if available or safety population used for analysis	OR 1.38; 95% CI 1.12–1.71; $p=0.003$	$p=0.045$	$p=0.02$	$p=0.07$
2. Pettinati et al. (31) trial excluded from analysis	OR:1.38; 95% CI 1.11–1.71: $p=0.004$	$p=0.07$	$p=0.01$	$p=0.04$
3. Ravindran et al. (32) trial excluded from analysis	OR 1.39; 95% CI 1.12–1.72; $p=0.003$	$p=0.049$	$p=0.01$	$p=0.05$
4. Serious adverse event in placebo group of Nyth et al. (33) trial corrected	OR 1.40; 95% CI 1.13–1.73; $p=0.002$	$p=0.05$	$p=0.01$	$p=0.04$
5. Female-specific serious adverse events from GSK/810 trial (34) added	OR 1.36; 95% CI 1.10–1.69; $p=0.004$	$p=0.07$	$p=0.01$	$p=0.04$
6. Number of serious adverse events in paroxetine 25-mg group of GSK/785 trial (35) corrected	OR 1.38; 95% CI 1.12–1.71; $p=0.003$	$p=0.05$	$p=0.01$	$p=0.05$
7. Different treatment groups from multi-grouped trials (3,14,15,26,34–44) combined	OR 1.38; 95% CI 1.12–1.71; $p=0.003$	$p=0.05$	$p=0.01$	$p=0.07$
8. Reciprocal of the opposite treatment group added to the number of events in the non-zero events group	OR 1.38; 95% CI 1.12–1.71; $p=0.003$	$p=0.05$	$p=0.01$	$p=0.05$
9. When all suggestions from 1 to 8 above are implemented	OR 1.36; 95% CI 1.09–1.70; $p=0.006$	$p=0.09$	$p=0.01$	$p=0.04$
10. When only valid issues are implemented (1,4,6, and 8)	OR 1.39; 95% CI 1.13–1.73; $p=0.002$	$p=0.045$	$p=0.01$	$p=0.05$

CI, confidence interval; OR, odds ratio.

papers (50–54). We thank Hieronymus et al. for raising this issue and we have now conducted an updated meta-analysis. The original analysis showed that the OR was 1.37 (95% CI 1.08–1.75; $p=0.01$; $I^2=0\%$) and the OR in the updated meta-analysis including missed data is 1.39 (95% CI 1.11–1.73; $p=0.004$; $I^2=0\%$) (Table 1). These new data do not change our results or conclusions.

We did not include some trials (47,49) because they were zero-event trials (zero events in both groups) as suggested by The Cochrane Handbook and valid systematic review methodology (55,56). However, we have now analysed the SAE data including all the zero-event trials using β-binomial regression which is the recommended analysis method if double zero-event trial data are included in the meta-analysis (57,58). When double

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zero-event trial data are included in the analysis, the results show an even larger harmful effect of SSRIs compared with our original analysis (OR 1.41; 95% CI 1.13–1.75; $p = 0.002$) (57,58).

Hieronymus et al. erroneously propose that we should include a trial that specifically randomised patients with stroke (48). In our published protocol, we describe explicitly that trials specifically randomising depressed participants with a somatic disease will be excluded (59). So, the trial that Hieronymus et al. refer to (48) has therefore correctly been excluded from our analysis.

4. Hieronymus et al.' claim that the Pettinati et al. trial (31), including depressed participants co-morbid with alcohol dependence, is an extreme outlier with respect to SAE prevalence and the most frequent SAEs in the trial were 'requiring inpatient detoxification and/or rehabilitation'. Hence, Hieronymus et al. argue that the Pettinati et al. trial (31) need to be excluded from our SAE analysis. We do not agree. The inclusion of the Pettinati et al. trial (31) does not bias our results as participants in both intervention and placebo groups experience similar SAEs that might or might not be related to SSRI treatment. Moreover, it would not be possible to compare the effects of SSRIs in depressed patients with and without alcohol dependence if such trials were excluded and hence may lead to loss of generalisability of our review results and complete overview of the available evidence. Nevertheless, we have now conducted a sensitivity analysis after exclusion of the Pettinati et al. trial (31) and this revealed no considerable difference. The original analysis showed that the OR was 1.37 (95% CI 1.08–1.75; $p = 0.01$; $I^2 = 0\%$) and the OR in the updated meta-analysis after excluding the Pettinati et al. trial (31) is 1.36 (95% CI 1.06–1.74; $p = 0.02$; $I^2 = 0\%$) (Table 1).

   Hieronymus et al. claim that the numbers reported in the Ravindran et al. trial (32) do not refer to SAEs but to severe adverse events. As Ravindran et al. (32), under the heading safety, clearly mentioned the word 'serious side effects' referring to table 2 in their publication, we still assume the severe adverse events that were reported in table 2 as SAEs. However, a sensitivity analysis after exclusion of the Ravindran et al. trial (32) revealed no considerable difference. The original analysis showed that the OR was 1.37 (95% CI 1.08–1.75; $p = 0.01$; $I^2 = 0\%$) and the OR in the updated meta-analysis is 1.37 (95% CI 1.07–1.75; $p = 0.01$; $I^2 = 0\%$) (Table 1).

5. Regarding Hieronymus et al.'s criticism of our review about the wording in the methods section and in the pre-published protocol (59), we would like to clarify that the SAEs were defined according to International Conference on Harmonization (ICH) guidelines (60), and we do not agree with their claim that the wording of method section is misleading. As mentioned, the reporting of SAEs in most of the publications was very poor and incomplete. For instance, in the Higuchi et al. trial (61), it is just mentioned that 'Other SAEs were reported in nine patients with 10 events: two in controlled-release low dose, four in controlled-release high dose, two in immediate-release low dose and one in placebo'. As it is mandatory to follow Good Clinical Practice-ICH guidelines (60) for all clinical trials, we assume that it is an SAE when trialists mention SAE even though they do not elaborate on the type of SAE. We wonder why we should not consider 'an abnormal laboratory value' as SAE when trialists report them as an SAE. Abnormal laboratory value could be an indication of serious kidney disease, liver failure, etc.

   It is true that our results do not show that the specific risk of a suicide or a suicide attempt is increased by SSRIs. However, absence of evidence is not evidence of absence of effect (62). The lack of statistical significance might be due to low statistical power. The justification of using a composite outcome such as SAEs is that a composite outcome increases the statistical power (63). Moreover, signals of SAEs do not require statistical p values below a certain level to be taken seriously (64).

6. We agree with Hieronymus et al. that the trial by Ball et al. (65) did not include a placebo group but we do not agree with them that this trial needs to be excluded. We explicitly included trials comparing SSRIs versus *no intervention*, placebo, or 'active' placebo in our review (59). As the trial (65) included three groups: (i) aprepitant + paroxetine, (ii) aprepitant and (iii) paroxetine, we correctly considered groups (i) and (ii) for our review.

   We agree with Hieronymus et al. that a case of death in the trial by Nyth et al. (33) occurred during the single-blind lead-in but was regarded as an SAE during treatment in placebo group. Hence, we have now corrected the error and the updated analysis did not change the results. The OR in the original meta-analysis was 1.37 (95% CI 1.08–1.75; $p = 0.01$; $I^2 = 0\%$) and the OR in the updated meta-analysis is 1.38 (95% CI 1.09–1.76; $p = 0.01$; $I^2 = 0\%$) (Table 1).

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We agree with Hieronymus et al. that we have not included female-specific SAEs that were reported in a separate table in the GSK/810 trial (34) in our analysis (1). This is because it was not clear whether the same participants had any other SAEs that were reported in the main table in that study report. Moreover, the two review authors who extracted data independently agreed on this assumption. However, we conducted a sensitivity analysis after including the female-specific SAEs and the results do not change significantly. The OR in the original meta-analysis was 1.37 (95% CI 1.08–1.75; $p = 0.01$; $I^2 = 0\%$) and the OR in the updated meta-analysis is 1.34 (95% CI 1.06–1.70; $p = 0.02$; $I^2 = 0\%$) (Table 1).

We agree with Hieronymus et al. that for the trial NCT01473381 (66) in table 2 of our review, we wrongly reported escitalopram instead of citalopram. We will correct this error in our update of the review. We agree with Hieronymus et al. that the paroxetine 25-mg group of the trial GSK/785 (35) was wrongly reported as having four SAEs instead of three. We have now updated the analysis with the correct figure and it does not change our results. The OR in the original meta-analysis was 1.37 (95% CI 1.08–1.75; $p = 0.01$; $I^2 = 0\%$) and the OR in the updated meta-analysis is 1.36 (95% CI 1.07–1.73; $p = 0.01$; $I^2 = 0\%$) (Table 1).

Regarding the SCT-MD 01 trial (37), Hieronymus et al. claim that we have only reported one escitalopram group instead of two. They are correct. The reason is, there were no SAEs in the escitalopram 10-mg group and placebo group.

Regarding the Kasper et al. study (36), we agree with Hieronymus et al. that there was a mismatch between figure 11 and table 2 in our review and as explained in the point 2, we will update the table in our update of the review. This has obviously no impact on our results.

We agree with Hieronymus et al. that the two studies '99001, 2005' (67), and 'Loo et al.' (68) were included in the analysis but not presented in the table in our review (1). We will rectify this error in our update of the review. As the two studies were included in the analysis in our review (1), it does not have any influence on the meta-analysis results.

We agree with Hieronymus et al. that there was a mismatch regarding the total number of SAEs and the total number of participants provided in the text and table. We will correct this error in our next update. All these typos, however, do not in any way change our results or our conclusions.

7. We agree with Hieronymus et al. that The Cochrane Handbook (55) recommends combining different treatment groups from multi-grouped trials, but The Handbook also states that a 'shared' group can be split into two or more groups with smaller sample size to allow two or more (reasonably independent) comparisons (55). It must be noted that it is not often possible to conduct subgroup analysis if treatment groups are pooled. We were interested in assessing the effects of different doses of SSRIs and if multi-grouped trials use different doses of a SSRI in different groups it is not possible to compare the effects of the different doses if these treatment groups are pooled. Another advantage of not pooling different treatment groups is that it becomes possible to investigate heterogeneity across intervention groups (55). Nevertheless, we have now conducted a sensitivity analysis after pooling different treatment groups and this revealed no considerable difference in the results. The OR in the original meta-analysis was 1.37 (95% CI 1.08–1.75; $p = 0.01$; $I^2 = 0\%$) and the OR in the updated meta-analysis is 1.37 (95% CI 1.07–1.73; $p = 0.01$; $I^2 = 0\%$).
8. Regarding reciprocal zero-cell correction, we agree with Hieronymus et al. that one should also add the reciprocal of the opposite treatment group to the number of events in the non-zero events group as suggested by Sweeting et al. (56). So, if there are five events in one group and 100 patients in the reciprocal group with zero events then '5' should be changed into '5.01'. This has obviously very little impact on the results. However, we have now updated our analysis after adding the reciprocal of the opposite treatment group to the number of events in the non-zero events group and this revision did not change the results. The OR in the original meta-analysis was 1.37 (95% CI 1.08–1.75; $p = 0.01$; $I^2 = 0\%$) and the OR in the updated meta-analysis is 1.37 (95% CI 1.07–1.73; $p = 0.01$; $I^2 = 0\%$) (Table 1).

It is true that we in our protocol planned to use 'Review Manager (RevMan) version 5.3 (69) for all meta-analyses' in our review, and we did not mention the use of reciprocal zero-cell correction for SAE analysis in our pre-published protocol (59). We did not anticipate the rare event rate of SAEs during our protocol preparation. Once it was evident that SAEs were rare events, we followed the Cochrane methodology (55) and the method recommended by Sweeting et al. (56). We used STATA software (70) for the SAE analysis and

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creation of graph (figure 11 in our review) as RevMan software (69) does not have the capability to perform reciprocal zero-cell correction.

Hieronymus et al. have conducted analyses on our data after 'correcting the errors' and 'addressing methodological issues' using RevMan 5.3 (Maentel–Haenszel random-effects model) (69) and concluded that there was no significant difference between SSRI and placebo with respect to SAEs. In addition, Hieronymus et al. have also concluded that the test for subgroup differences (elderly compared with non-elderly patients) was significant and there was an increased risk of SAEs being observed in SSRI-treated patients in studies regarding elderly patients, but no corresponding association found in the non-elderly trials. We have serious reservations against the use of RevMan 5.3 (Maentel–Haenszel random) (69) for the analysis of SAEs as explained in the previous paragraph. We think the analysis that our critiques have conducted is invalid because of the observed rare events.

Hieronymus et al. criticised our review on having missed several trials for which SAE data are readily available. However, it surprises us that Hieronymus et al. concluded that there was no significant difference between SSRI and placebo with respect to SAEs without including data from these missed trials. We have now re-analysed our data after (i) including the missed trials that our critiques reported and judged eligible by us (2,3,4,7,10,11,13–17,30); (ii) correcting the errors reported by Hieronymus et al. (2); and (iii) using safety population if available. If not, we used the number of analysed participants (number of randomised participants minus number of participants lost to follow-up) or number of randomised participants (if no information were available regarding the number of participants lost to follow-up). Our re-analysis of the second data set still fully supports our earlier findings (1) of a significant difference between SSRI compared with placebo or no intervention with respect to SAEs (OR 1.38, 1.11–1.72, $p = 0.004$; $I^2 = 0\%$) (Table 1). It also revealed that there is no significant subgroup difference between elderly and non-elderly patients with respect to occurrence of SAEs ($p = 0.07$).

A re-analysis on the third set of data, that is (i) data from trials included in our original publication (1) augmented with (ii) the data from trials that were reported missed by our critiques and judged eligible by us (3,4,7,10,11,13–17,30) plus (iii) additional data identified in our previously included trials where we missed to extract data on SAEs (18–25) and data from our newly identified trials (26–29), is even more robust than our previous result and confirm our earlier conclusions. SSRIs significantly increase the risk of an SAE both in non-elderly ($p = 0.045$) and elderly ($p = 0.01$) patients [OR in this re-analysis is 1.39 (95% CI 1.13–1.73, $p = 0.002$; $I^2 = 0\%$)] (Fig. 1). There is no significant subgroup difference between non-elderly and elderly patients ($p = 0.05$). Please see Table 1 for results for sensitivity analyses for different scenarios.

The Trial Sequential Analysis (TSA) on the updated data reveals that the trial sequential boundary for harm is still crossed (Fig. 2), the OR is 1.30 and the TSA-adjusted CI is 1.07–1.58. We have now updated the table that summarises the number and types of SAEs in the different studies (Table 2).

We have also conducted a sensitivity analysis after accepting all the suggestions of Hieronymus et al., that is (i) excluding the Pettinati et al. trial (31) and the Ravindran et al. trial (32); (ii) including missing treatment groups; (iii) correcting all identified errors regarding the number of SAEs; (iv) consistently using the intention-to-treat population for the patients at risk statistics; (v) refraining from subdividing the placebo groups in multi-group studies; (vi) adding the data from missed trials that the critiques reported; and (vii) adding the reciprocal of the opposite treatment group to the number of events in the non-zero events group. We have also included the data from additional trials that we found. The sensitivity analysis still shows that there is a highly significant difference between SSRI versus placebo or no intervention with respect to SAEs (OR 1.36, 95% CI 1.09–1.70, $p = 0.006$; $I^2 = 0\%$) but with a significant difference between elderly compared to non-elderly ($p = 0.04$) (Table 1). However, it must be noted that this analysis is performed after accepting all the suggestions even the ones we do not agree with.

We strongly disagree with Hieronymus et al.' statement that 'studies based on total rating of all 17 Hamilton Depression Rating Scale (HDRS17) items as a measure of the antidepressant effect of SSRIs parameter, including that of Jakobsen et al. (1), are grossly misleading'. Several national medicines agencies recommend HDRS17 for assessing depressive symptoms (71–73).

We therefore also disagree with Østergaard's views (74) which Hieronymus et al. (2) cited in their critique because a number of studies (75,76) have shown that HDRS17 and HDRS6 largely produce similar results. From these results, it cannot be concluded that HDRS6 is a better assessment scale than HDRS17, just considering the psychometric validities of the two scales. If the total score of HDRS17 is affected by some of the multiple severe adverse effects of SSRIs, then this might in fact better reflect the actual summed clinical effects of SSRIs in the depressed patient than

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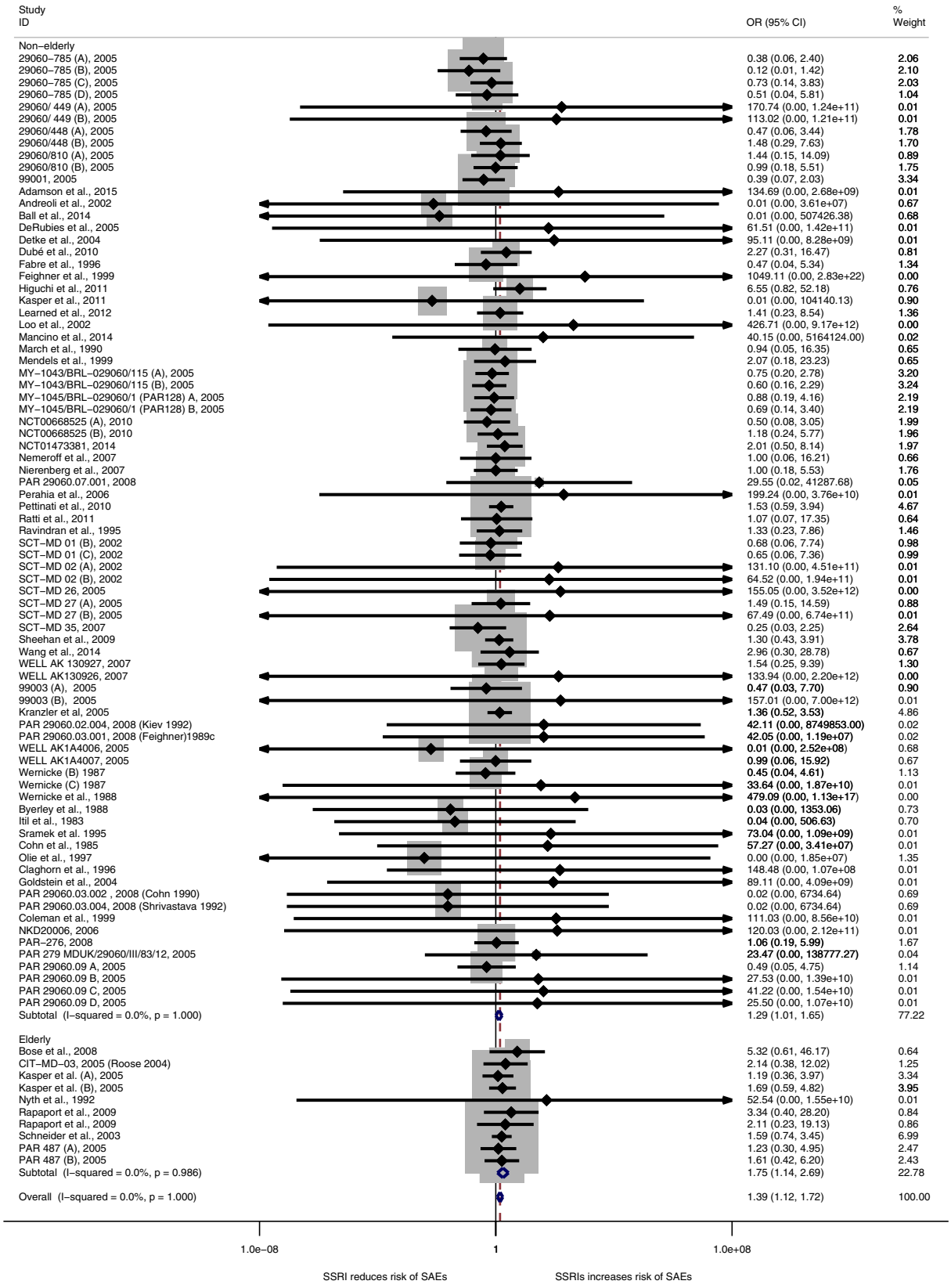

Fig. 1. Meta-analysis of serious adverse events data.

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Fig. 2. Trial Sequential Analysis of serious adverse event data.

HDRS6 ignoring these adverse effects. We think that until scales are validated against patient-centred clinically relevant outcomes (e.g. suicidality; suicide; death), such scales are merely non-validated surrogate outcomes (77).

We do not agree with Hieronymus et al.' comments on our review (1) that we are more loyal to our anti-SSRI beliefs than to our own results regarding remission and response (2). Though our results showed statistical superiority of SSRIs over placebo with respect to remission and response, we, as explained in our review (1), still believe that these results need to be interpreted cautiously due to a number of reasons: (1) the trials are all at high risk of bias; (2) the assessments of remission and response were primarily based on single HDRS scores and it is questionable whether single HDRS scores are indications of full remission or adequate response to the intervention; (3) information is lost when continuous data are transformed to dichotomous data and the analysis results can be greatly influenced by the distribution of data and the choice of an arbitrary cut-point (54,78–80) even though a larger proportion of participants cross the arbitrary cut-point in the SSRI group compared with the control group (often HDRS below 8 for remission and 50% HDRS reduction for response), the effect measured on HDRS might still be limited to a few HDRS points (less than 3 HDRS points); (4) by only focussing on how many patients cross a certain line for benefit, investigators ignore how many patients are deteriorating at the same time; and (5) (and most importantly) the effects do not seem to be clinically significant (1). If results, for example, show relatively large beneficial effects of SSRIs when remission and response are assessed but very small averaged effects (as our results show) – then it must be because similar proportions of the participants are harmed (increase on the HDRS compared with placebo) by SSRIs. Otherwise the averaged effect would not show small or no difference in effect. The clinical significance of our results on 'remission' and 'response' should therefore be questioned – especially as all trials were at high risk of bias (1). The methodological limitations of using 'response' as an outcome has been investigated in a valid study by Kirsch et al. who conclude that: 'response rates based on continuous data do not add information, and they can create an illusion of clinical effectiveness' (81).

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Table 2. Summary of serious adverse events in the included trials

		SSRI participants assessed for serious adverse events		Placebo/'no intervention' participants assessed for serious adverse events	
Trials	Experimental intervention	Numbers and types of serious adverse events	Proportion of participants with a serious adverse event	Numbers and types of serious adverse events	Proportion of participants with a serious adverse event
99001, 2005	Escitalopram	2 unspecified serious adverse events	2 out of 191	5 unspecified serious adverse events	5 out of 189
29060/449 (A), 2005	Paroxetine CR	1 abdominal pain, 1 pancreatitis, 1 accidental overdose, 1 unintended pregnancy	2 out of 108	No serious adverse event	0 out of 55
29060/449 (B), 2005	Paroxetine IR	1 emotional lability, 1 abortion, 2 unintended pregnancy	3 out of 112	No serious adverse event	0 out of 55
29060/448 (A), 2005	Paroxetine IR	1 myocardial infarction, 1 emotional lability	2 out of 104	1 uterine fibroids enlarged, 1 gall bladder disorder	2 out of 50
29060/448 (B), 2005	Paroxetine CR	3 emotional lability, 1 hepatocellular jaundice, 1 manic reaction	6 out of 105	1 dehydration, 1 accidental overdose	2 out of 51
29060/810 (A), 2005	Paroxetine CR	2 abnormal laboratory value, 1 carcinoma of lung	3 out of 153	1 cerebrovascular disorder, 1 depression	1 out of 73
29060/810 (B), 2005	Paroxetine CR	1 abnormal laboratory value, 1 gall bladder disorder, 1 anxiety,1 emotional lability	4 out of 148	1 pleura disorder, 1 sinusitis, 1 bronchitis	2 out of 73
29060-785 (A), 2005	Paroxetine CR	3 abnormal laboratory value, 1 emotional lability	3 out of 98	1 abnormal laboratory value, 1 gastrointestinal disorder	2 out of 26
29060-785 (B), 2005	Paroxetine CR	1 abnormal laboratory value	1 out of 94	1 abnormal laboratory value, 1 myocardial infarction	2 out of 26
29060-785 (C), 2005	Citalopram	5 abnormal laboratory value, 1 syncope	6 out of 105	1 abnormal laboratory value, 1 suicide	2 out of 25
29060-785 (D), 2005	Citalopram	1 abnormal laboratory value, 1 emotional lability	2 out of 97	1 abnormal laboratory value	1 out of 25
99003 (A), 2005	Citalopram	1 unspecified serious adverse event	1 out of 161	1 unspecified serious adverse event	1 out of 77
99003 (B), 2005	Escitalopram	2 unspecified serious adverse events	2 out of156	No serious adverse event	0 out of 77
Adamson, 2015	Citalopram	1 suicidal ideation, severe abdominal cramps	2 out of 73	No serious adverse event	0 out of 65
Andreoli, 2002	Fluoxetine	No serious adverse event	0 out of 127	1 suicide	1 out of 128
Ball, 2014	Paroxetine	No serious adverse event	0 out of 79	1 unspecified serious adverse event	1 out of 79
Barber, 2012	Sertraline	No serious adverse event	0 out of 51	No serious adverse event	0 out of 48
Bose, 2008	Escitalopram	1 bowel obstruction, 1 nausea, 1 arrhythmia, 1 respiratory arrest, 1 retinal detachment, 1 chest pain	5 out of 130	1 syncope	1 out of 134
Byerley, 1988	Fluoxetine	No serious adverse event	0 out of 32	1 hospitalisation	1 out of 29
CIT-MD-03, 2005	Citalopram	2 congestive heart failure, 1 cerebrovascular accident, 1 hyponatremia	4 out of 87	1 cerebrovascular accident, 1 cellulitis	2 out of 91
Claghorn, 1996	Fluvoxamine	3 clinically significant ECG deteriorations	3 out of 47	No serious adverse event	0 out of 46
Cohn, 1985	Fluoxetine	1 suicide attempt	1 out of 45	No serious adverse event	0 out of 55
Coleman, 1999	Sertraline	1 migraine headache	1 out of 108	No serious adverse event	0 out of 109
Cornelius, 1997	Fluoxetine	No serious adverse event	0 out of 25	No serious adverse event	0 out of 26
Corrigan, 2000	Fluoxetine	No serious adverse event	0 out of 34	No serious adverse event	0 out of 32
Croft, 1999	Sertraline	No serious adverse event	0 out of 111	No serious adverse event	0 out of 113
Davidson, 2002	Sertraline	No serious adverse event	0 out of 101	No serious adverse event	0 out of 109
DeRubeis, 2005	Paroxetine	1 suicide	1 out of 120	No serious adverse event	0 out of 60
Detke, 2004	Paroxetine	1 unspecified serious adverse event	1 out of 86	No serious adverse event	0 out of 93
Dube, 2010	Escitalopram	1 suicide attempt, 1 gastroenteritis/malaria	2 out of 62	1 near drowning, 1 gastroenteritis	2 out of 138
Fabre, 1996	Fluvoxamine	1 hospitalisation (non-cardiac chest pain)	1 out of 46	1 hospitalisation, 1 ruptured ectopic pregnancy, 1 hernia repair	2 out of 44
Fava, 2005	Fluoxetine	No serious adverse event	0 out of 47	No serious adverse event	0 out of 43
Feighner, 1999	Citalopram	3 suicide attempts, 1 miscarriage, 1 intestinal flu symptoms, 1 chest pain, 1 severe thinking abnormality, 1 allergic reaction	8 out of 521	No serious adverse event	0 out of 129
Goldstein, 2002	Flouxetine	No serious adverse event	0 out of 33	No serious adverse event	0 out of 70
Goldstein, 2004	Paroxetine	1 relapsed into alcohol abuse	1 out of 80	No serious adverse event	0 out of 87
Higuchi, 2011	Paroxetine	1 suicide and 8 unspecified serious adverse events	9 out of 244	1 unspecified serious adverse event	1 out of 172
Itil, 1983	Fluoxetine	No serious adverse event	0 out of 22	1 suicide attempt	1 out of 22
Kasper, 2005	Escitalopram	2 death and 7 unspecified serious adverse events	9 out of 172	1 death and 3 unspecified serious adverse events	4 out of 90
Kasper, 2005	Fluoxetine	1 death and 14 unspecified serious adverse events	15 out of 164	1 death and 4 unspecified serious adverse events	5 out of 89

Table 2 *(Continued)*

		SSRI participants assessed for serious adverse events		Placebo/'no intervention' participants assessed for serious adverse events	
Trials	Experimental intervention	Numbers and types of serious adverse events	Proportion of participants with a serious adverse event	Numbers and types of serious adverse events	Proportion of participants with a serious adverse event
Kasper, 2011	Escitalopram	No serious adverse event	0 out of 140	1 hospitalisation due to appendicitis	1 out of 70
Kranzler, 2005	Sertraline	10 unspecified serious adverse events	10 out of 160	8 unspecified serious adverse events	8 out of 171
Learned, 2012	Paroxetine	1 intentional overdose, 1 depression, 1 unspecified event	3 out of 165	2 unspecified serious adverse events	2 out of 154
Loo, 2002	Paroxetine	1 suicide, 2 suicide attempts	3 out of 147	No serious adverse event	0 out of 139
LVM-MD 06, 2013	SSRI	No serious adverse event	0 out of 77	No serious adverse event	0 out of 89
Mancino, 2014	Sertraline	1 hospitalisation	1 out of 35	No serious adverse event	0 out of 38
Mao, 2015	Sertraline	No serious adverse event	0 out of 16	No serious adverse event	0 out of 18
March, 1990	Fluvoxamine	1 hospitalisation due to worsening of depression	1 out of 18	1 suicide attempt	1 out of 17
Mendels, 1999	Citalopram	1 prostatic hyper trophy, 1 bronchitis	2 out of 89	1 suicide	1 out of 91
MY-1043/BRL-029060/115 (A), 2005	Paroxetine	1 hypertension, 1 diabetes and hypothyroidism, 1 fibrocystic disease, 1 ovarian cysts, 1 peptic ulcer haemorrhage, 1 spinal surgery, 1 hypomanic episode with suicidal tendency, 2 suicidal ideation, 1 alcoholism, 1 neoplasm	11 out of 284	1 suicidal ideation, 1 back pain, 1 trauma	3 out of 59
MY-1043/BRL-029060/115 (B), 2005	Fluoxetine	1 suicidal ideation, 1 neoplasm, 2 acute pyelonephritis, 1 thrombophlebitis, 1 ectopic pregnancy, 1 polycystic granuloma, 2 basal cell carcinomas, 1 myxoid mitral valve	9 out of 289	1 viral meningitis, 1 infection, 1 myocardial infarction, 1 mole removal	3 out of 59
MY-1045/BRL-029060/1 (A), 2005	Paroxetine	2 depression (worsening), 2 emotional lability, 1 neoplasm, 1 insomnia, 1 nervousness, 1 carcinoma, 1 epistaxis, 1 gastrointestinal disorder, 1 prostate disorder	9 out of 357	1 depression (worsening), 1 rectal disorder	2 out of 70
MY-1045/BRL-029060/1, 2005	Fluoxetine	1 depression (worsening), 2 emotional lability, 1 neoplasm, 1 coronary artery disease, 1 thrombophlebitis, 1 hypoglycaemia	7 out of 351	2 depression (worsening), 1 flu syndrome disorder	2 out of 70
NCT00668525 (A), 2010	Escitalopram	1 chest pain, 1 pharyngitis, 1 multiple sclerosis	3 out of 322	1 asthma, 1 haemothorax	2 out of 109
NCT00668525 (B), 2010	Escitalopram	1 chest pain, 1 appendicitis, 2 anxiety, 1 suicidal ideation, 1 suicide attempt, 1 peripheral vascular disorder	7 out of 324	1 injury, 1 suicidal ideation	2 out of 109
NCT01020799	Escitalopram	No serious adverse event	0 out of 50	No serious adverse event	0 out of 99
NCT01473381, 2014	Citalopram	1 haemorrhagic anaemia, 1 diverticulitis, 1 ilium fracture, 1 road traffic accident, 1 traumatic renal injury, 1 wrist fracture, 1 abortion missed, 1 suicidal ideation, 1 hospitalisation	6 out of 282	1 angina pectoris, 1 gastric disorder, 1 pneumonia, 1 neck abscess, 1 oral abscess, 1 abnormal electrocardiogram ST segment, 1 back pain, 1 suicidal ideation, 1 obstructive airways disorder	3 out of 281
Nemeroff, 2007	Flouxetine	1 unspecified serious adverse event	1 out of 102	1 unspecified serious adverse event	1 out of 102
Nierenberg, 2007	Escitalopram	1 death and 3 unspecified serious adverse events	4 out of 274	2 unspecified serious adverse events	2 out of 137
Nyth, 1992	Citalopram	1 cerebral haemorrhage and death	1 out of 98	No serious adverse events	0 out of 51
Olie, 1997	Sertraline	No serious adverse events	0 out of 129	2 suicide attempts	2 out of 129
PAR 29060.02.001, 2008	Paroxetine	No serious adverse events	0 out of 55	No serious adverse events	0 out of 56
PAR 29060.02.002, 2008	Paroxetine	No serious adverse events	0 out of 36	No serious adverse events	0 out of 35
PAR 29060.02.003, 2008 (Smith 1992)	Paroxetine	No serious adverse events	0 out of 39	No serious adverse events	0 out of 38
PAR 29060.02.004, 2008	Paroxetine	1 overdose	1 out of 38	No serious adverse events	0 out of 40
PAR 29060.03.001, 2008	Paroxetine	1 increased liver enzymes	1 out of 40	No serious adverse events	0 out of 40
PAR 29060.03.002, 2008	Paroxetine	No serious adverse events	0 out of 40	1 suicidal tendencies	1 out of 40
PAR 29060.03.003, 2008	Paroxetine	No serious adverse events	0 out of 41	No serious adverse events	0 out of 42
PAR 29060.03.004, 2008	Paroxetine	No serious adverse events	0 out of 40	1 burning in the chest	1 out of 40
PAR 29060.03.005, 2008	Paroxetine	No serious adverse events	0 out of 40	No serious adverse events	0 out of 42
PAR 29060.07.001, 2008	Paroxetine	1 acute depression, 1 acute alcohol intoxication and suicide ideation	2 out of 13	No serious adverse event	0 out of 12

Table 2 *(Continued)*

Trials	Experimental intervention	SSRI participants assessed for serious adverse events: Numbers and types of serious adverse events	SSRI participants assessed for serious adverse events: Proportion of participants with a serious adverse event	Placebo/'no intervention' participants assessed for serious adverse events: Numbers and types of serious adverse events	Placebo/'no intervention' participants assessed for serious adverse events: Proportion of participants with a serious adverse event
PAR 487 (A), 2005	Paroxetine CR	2 depression, 1 intestinal obstruction, 1 angina pectoris, 1 prostate disorder, 1 chronic lymphocytic leukaemia, 1 emotional lability (suicide ideation)	7 out of 104	1 gastroenteritis, 1 skin melanoma, 1 SGPT Increased	3 out of 54
PAR 487 (B), 2005	Paroxetine IR	2 pneumonia, 3 trauma, 1 pneumothorax, 1 bronchitis, 1 haematuria, 1 hyponatremia,	9 out of 106	1 SGOT increased, 1 chest pain, 1 cystitis	3 out of 55
Perahia, 2006	Paroxetine	1 back pain, 1 breast neoplasm	2 out of 94	No serious adverse events	0 out of 97
Pettinati, 2010	Sertraline	15 unspecified serious adverse events	15 out of 40	11 unspecified serious adverse events	11 out of 39
Rapaport (A), 2009	Paroxetine CR	2 chest pain, 1 osteoarthritis, 1 ankle fracture, 1 atrial fibrillation, 1 femur fracture	6 out of 164	1 nephrolithiasis	1 out of 89
Rapaport (B), 2009	Paroxetine CR	1 coronary artery occlusion, 1 pneumonia, 1 confusional state, 1 depression	4 out of 173	1 aortic aneurism, 1 arteriosclerosis	1 out of 90
Ratti, 2011	Paroxetine	1 haemorrhoidal haemorrhage	1 out of 112	1 rash	1 out of 120
Ravindran, 1995	Sertraline	4 unspecified serious adverse events	4 out of 40	2 unspecified serious adverse events	2 out of 26
Schneider, 2003	Sertraline	17 unspecified serious adverse events	17 out of 371	11 unspecified serious adverse events	11 out of 376
SCT-MD 01 (A), 2001	Escitalopram	No serious adverse events	0 out of 125	No serious adverse event	0 out of 40
SCT-MD 01 (B), 2002	Escitalopram	1 anaphylaxis, 1 suicide attempt	2 out of 119	1 gall bladder stones	1 out of 41
SCT-MD 01 (C), 2002	Citalopram	1 coma, 1 intestinal fistula	2 out of 125	1 non-accidental overdose	1 out of 41
SCT-MD 02 (A), 2002	Escitalopram	1 suicidal tendency, suicide attempt; 1 non-accidental overdose, suicidal attempt, tachycardia	2 out of 125	No serious adverse event	0 out of 64
SCT-MD 02 (B), 2002	Citalopram	1 cholestasis intrahepatic, dehydration	1 out of 123	No serious adverse event	0 out of 63
SCT-MD 26, 2005	Escitalopram	1 inflicted injury	1 out of 147	No serious adverse event	0 out of 153
SCT-MD 27 (A), 2005	Escitalopram	1 depression, 1 abnormal mental status, 1 malignant neoplasm	3 out of 134	1 labyrinthitis	1 out of 66
SCT-MD 27 (B), 2005	Sertraline	1 appendicitis	1 out of 137	No serious adverse event	0 out of 66
SCT-MD 35, 2007	Escitalopram	1 abnormal hepatic function	1 out of 131	1 breast cancer, 1 depression, 1 suicidal ideation, 1 suicide	4 out of 133
Sheehan, 2009	Fluoxetine	1 suicidal ideation/suicidality, 1 worsening of depression, 2 suicide attempts, 1 anxiety/agitation/racing thoughts, 1 syncope, 1 ankle fracture, 1 viral gastroenteritis	8 out of 99	2 suicidal ideation/suicidality, 2 worsening of depression, 1 nose bleed, 1 allergic reaction	6 out of 95
Sramek, 1995	Fluoxetine	1 atrial fibrillation	1 out of 70	No serious adverse event	0 out of 71
Wang, 2014	Escitalopram	3 unspecified serious adverse event	3 out of 152	1 unspecified serious adverse event	1 out of 148
WELL AK130926, 2007	Escitalopram	1 agitation	1 out of 143	No serious adverse event	0 out of 132
WELL AK130927, 2007	Escitalopram	2 suicidal ideation, 1 hepatic function abnormal	3 out of 138	1 suicidal ideation, 1 sudden cardiac death	2 out of 141
WELL AK1A4006, 2005	Fluoxetine	No serious adverse event	0 out of 155	1 abdominal pain	1 out of 154
WELL AK1A4007, 2005	Fluoxetine	1 influenza	1 out of 154	1 spontaneous abortion	1 out of 152
MD/PAR/009 (PAR-276), 2005	Paroxetine	1 agitation, 1 alcohol abuse, 1 exacerbation of depression, 1 syncope	3 out of 20	1 asthenia, 1 manic reaction, 1 overdose, 1 weight loss	3 out of 21
NKD20006, 2006	Paroxetine	1 nephrolithiasis	1 out of 117	No serious adverse event	0 out of 118
PAR279.MDUK/29060/III/83/12, 2005	Paroxetine	1 confusion, 1 dysarthria	2 out of 19	No serious adverse event	0 out of 10
PAR 29060.09 (A), 2005	Paroxetine	1 suicidal ideation, 1 increased depression, 1 myeloproliferative disorder, 1 decreased white blood cell count	4 out of 102	1 decreased white blood cell count	1 out of 13
PAR 29060.09 (B), 2006	Paroxetine	1 liver abnormalities, 1 attempted suicide	2 out of 104	No serious adverse event	0 out of 13
PAR 29060.09 (C), 2007	Paroxetine	1 suicidal ideation, 1 upper respiratory infection, increased depression	3 out of 101	No serious adverse event	0 out of 13
PAR 29060.09 (D), 2008	Paroxetine	1 overdose, 1 angina	2 out of 102	No serious adverse event	0 out of 12
Wernicke (A), 1987	Fluoxetine	No serious adverse event	0 out of 99	No serious adverse event	0 out of 16
Wernicke (B), 1987	Fluoxetine	1 chest pain and ischaemia, 1 mental status changes, 1 rash	3 out of 103	1 chest pain and ischaemia	1 out of 16
Wernicke (C), 1987	Fluoxetine	1 suicide attempt, 1 rash	2 out of 106	No serious adverse event	0 out of 16
Wernicke, 1988	Fluoxetine	1 rash, 1 urticaria, 4 worsening of depression	6 out of 285	No serious adverse event	0 out of 78

CR, controlled-release; ECG; electrocardiogram; IR, immediate-release; SSRI, selective serotonin reuptake inhibitors.

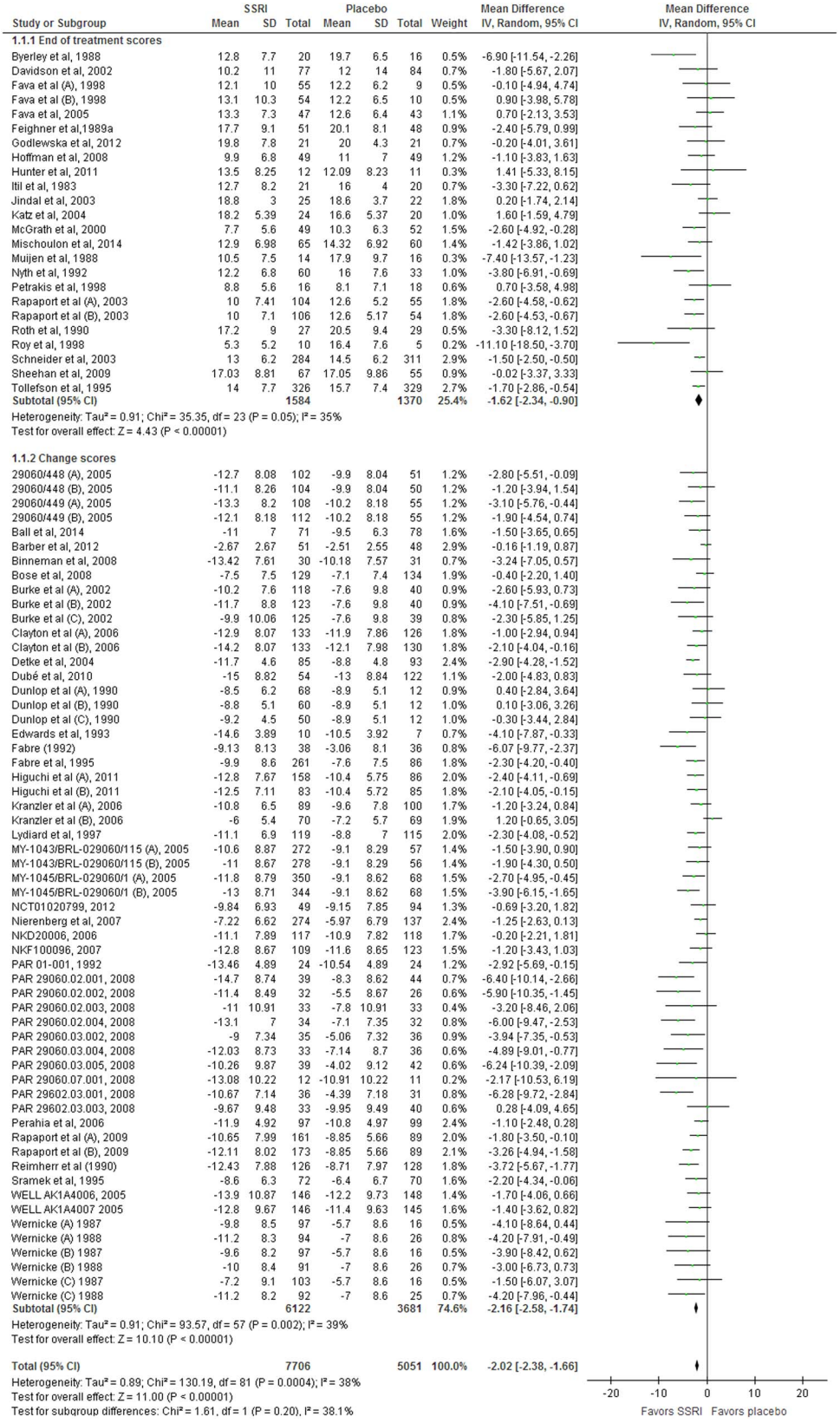

Fig. 3. Meta-analysis of Hamilton Depression Rating Scale (HDRS) data.

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With respect to the assessment of efficacy, we agree with Hieronymus et al. (2) that we had missed a few small trials (3,4). We also agree with our critiques (2) that the extremely low variance attributed to the study by Fabre et al. (82) is probably an artefact. However, after we included the missed trials (3–12) and a newly identified trial (28) and calculated the standard deviation from standard error for Fabre et al. (82), our results and conclusions just became even more robust. Random-effects meta-analysis of the updated data revealed a mean difference of −2.02 points (95% CI −2.38 to −1.66; $p < 0.00001$) (Fig. 3), which is 0.08 HDRS17 points different compared with that of our published review (1). Again, this has no impact on the results or conclusions of our review.

We do not agree with Hieronymus et al.' claim (2) that the efficacy of the SSRIs is marred by the inclusion of treatment groups that received suboptimal doses of the tested SSRI. We showed that there was no subgroup difference comparing low-dose trials (i.e. trials administrating a dose below the median dose of all trials giving this information) to the trials administrating at or above the median dose (1). We have now extended this analysis to the 64 trials that reported both HDRS17 scores and the final dose goal of SSRI. Again, we found no significant difference between low-dose and high-dose trials ($p = 0.20$).

We suggest that Hieronymus et al. in the future should critically consider what they write, when they write. Their piece (2) has had a sad influence on the Danish Medical Agency so that their experts have used it to mislead the Danish Minister of Health in her replies to a member of the Danish parliament (83). Nevertheless, the critique has also improved our systematic review, which we are very grateful of. The updated results presented here report a more valid and robust picture of the lacking efficacy and severe harmful effect of SSRIs.

In conclusion, a re-analysis of data after correcting unintentional errors, accepting valid suggestions, and including the data from the missed and newly identified trials, did not change the overall result, that is there is robust evidence showing that SSRIs increase the risk of an SAE both in non-elderly and elderly patients without having any clinically significantly beneficial effect. Moreover, in addition to SAEs, SSRI also increase a number of very many other adverse events that patients may consider severe (1).

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Conflicts of Interest

None.

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