**Supplementary Table – Justification to our (Copenhagen Trial Unit (CTU)) decisions on whether an adverse event description warranted classification as a serious adverse event (SAE) for the examples provided by the Hieronymus et al. (1).**

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| --- | --- | --- | --- |
| **Study** | **Example event description provided by Hieronymus et al. (1)** | **Classified as SAE by us (CTU)** | **Our (CTU) justification for considering or not considering an event as SAE** |
| Claghorn et al., 1996 (2) | “Minor non-specific ST-T changes”  | Yes | In the publication, it is explicitly mentined that ’patients had **clinically significant** ECG deteriorations’. According to definition of a serious adverse event, we considered it as an SAE. |
| Fabre et al., 1985 (3) | “Non-specific ST-T change” | No | In the publication, it is mentioned that "non-specific STT change" at visit 4 **that had disappeared** by visit 7. As the authors have not mentioned whether the event is clinically signficant or not, and as they reported that the event is disappeared, we did not consider it as an SAE  |
| Lydiard et al., 1997 (4) | “experimental drug (placebo) discontinued due to ECG- abnormalities” | No | It is not clear whether the ECG has any clinical significance. Partcipants may discontinue their participation in a trial even for adverse events like headache. Hence we did not consider it as an SAE  |
| Wernicke et al., 1988 (5) | “Worsening of depression considered clinically significant” | Yes | The authors clearly mentioned that participants developed worsening of depression considered **clinically significant** and this sentence is reported in a paragraph that described possible SAEs. Hence we considered it as an SAE. |
| Norton et al., 1984 (6) | “Increasing depression throughout study, withdrawal by investigator” | No | As explained above, it is not clear whether the event has any clinical significance.  |
| Adamson et al., 2015 (7) | “Unblinding […] for severe adverse reactions” | Yes | As it is reported that unblinding during the first 12 weeks was permitted for severe adverse reactions or other emergencies, and according to the definition of SAE, the event is considered as an SAE. |
| Tollefson et al., 1995 (8) | “Emergence of substantial suicidal ideation” | No | Suicidal ideation is only defined as a change in the HAMD Item 3 [suicide] score from 0 or 1 at baseline to 3 or 4 during double-blind therapy. We do not consider a score on a single HDRS item sufficient to with reasonable certainty judge that this is an SAE.  |

**Additional errata**

1. While the CTU group chose to include SAEs occurring up to nine months after withdrawal from treatment in the Lundbeck-sponsored protocol 99024 (9), the net result being an increased risk of SAEs for patients treated with an SSRI, they did not include SAEs from the double-blind continuation phase of the study by Detke and co-workers (10) in which one suicide and one SAE occurred in the placebo-group, with no pertinent events in the paroxetine group. Also other studies seem to have been treated differentially with regard to post-therapy SAEs (11, 12).

**Answer: The other studies are different from Detke and co-workers’ trial. In Detke et al.’s trial, only responders were allowed into the continuation phase.** **For the Lundbeck-sponsored protocol 99024 (9), we extracted the data presented in the table. However, in the description below the table, they reported few incidents of deaths: one suicide one week after completion of study; one death seven weeks after the patient withdrawn from the study** **due to cardiac failure; and one death nine months after the patient withdrawn from the study due to brain tumour. We do not think we made any mistake in choosing to include these incidents as SAEs as we think it takes some time from the start of development of a disease process until it leads to death. In Detke et al.’s trial (10), only responders during the treatment phase were allowed to participate in the continuation phase. As the continuation phase included only selected populations, we decided to exclude this phase and hence not extracted data from the continuation phase. They may not be compareable. Regarding other studies (11, 12), we clearly specified in our protocol that we would assess outcomes at two time points, i.e., end of treatment (our time point of primary interest) and at maximum follow-up. In the Sramek et al.’s trial (11), one patient experienced a serious adverse event 19 days after treatment stopped and because this was the only avaiable data we used this data. In the PAR 487 trial (12), SAE outcomes were reported at two time points and according to our protocol we used primarily the events duing the treatment phase.**

1. The 1998 report by Fava and colleagues (13) summarizes the results from some of the participating centers in two GlaxoSmithKline sponsored protocols, GSK/115 (14) and GSK/128 (15) (see p. 146, §5). This thus constitutes double inclusion.

**Answer: Fava et al.’s 1998 trial (13) did not report any SAE and hence it has no influence on our SAE analysis. The updated efficacy analysis does not change our results and conclusions.**

1. The efficacy statistics included for the study by Barber and co-workers (16) are slope estimates, not endpoint differences. Apart from the statistic being inaccurate for this analysis, the fact that slope estimates have lower variances than the corresponding endpoint estimates renders this negative study more weight than it should have.

**Answer: Yes, slope estimates were reported and we used them in our analyses. We now excluded Barber et al.’s trial (16) from efficacy analysis and the updated efficacy analysis does not change our results and conclusions.**

1. Similarly, in the report by Jindal et al. (17) pretreatment values are used instead of posttreatment values. Again, the low variance in the pre-treatment values renders this negative study undue weight.

**Answer: This trial investigated the impact of sertraline on the sleep of depressed patients. In table 1 of the manuscript, they reported baseline parameters and in table 2 they reported variables both presleep and postsleep. We used the data for presleep. Hence it is not a mistake.**

1. The inclusion of a one week study by Godlewska and co-workers (18) is, if not an error, still questionable, since it likely introduces a bias towards the null as SSRIs are not expected to show any significant effects versus placebo on the HDRS-17 after such short a treatment duration. For the 6-week study by Katz et al. (19), data from the second week of treatment, which finds a nominally worse effect of paroxetine as compared to placebo, is used, even though the report also states numerical superiority for paroxetine at the end of treatment (46% vs 30% responders for paroxetine and placebo, respectively). The CTU group hence has included negative data from an early evaluation while knowing that the trend was towards a positive effect of treatment at study end-point.

**Answer: Inclusion of a one week study by Godlewska and co-workers (18) is not an error.** **We assessed the outcome at the end of the treatment. In most of the trials the end of treatment is 6-18 week. As Godlewska and co-workers study (18) is a one week study, we considered it as one week study and we took the values after the end of 1 week. Regarding Katz et al. study (19), though it was a 6-week study, HDRS scores were provided at baseline, at the end of week one, and at the end of week two only. Sensitivity analysis after excluding these two studies did not change the results (The Hamilton Rating Scale for Depression (HRSD) mean difference -2.02 (95% CI -2.33 to -1.72))**

1. Regarding the Lundbeck-sponsored study 99024 (9), as in the study by Nyth et al., (20) the CTU included SAEs occurring prior to double-blind treatment in the placebo group.

**Answer: Regarding the Lundbeck 99024 study (9), we used the data given in the tables. It is a bit confusing, as authors of the report included the event in the placebo arm but in the description they mentioned that 1 patient died in the screening period prior to double-blind treatment.**  **Though the exclusion of this event is debatable as this event was reported under placebo in the table, we now excluded this event from our re-analysis and it does not change our results or conclusions. Regarding Nyth et al. trial (20), we have already corrected the error in our earlier response (21).**

1. The study by Tyrer and co-workers. (22), which is listed as having a low-risk of for profit bias (figure 3 in the *BMC Psychiatry* paper), *i)* was sponsored by GSK (23) and *ii)* is not placebo-controlled.

**Answer: i) In the manuscript (22), it is not mentioned that study is sponsored by GSK. There were no funding details. The authors were from medical school, Queen’s Medical Centre, Nottingham. Based on the avaiable data, our decision is still to list the study as a low-risk of for profit bias. ii) For week 3 and 4, it is a placebo controlled trial. Please see the design below.**



1. The study by Feighner and co-workers (24) is listed as not having any SAEs in the placebo group. The relevant passage in the published article states the following: “The serious adverse events that occurred in the citalopram-treated and placebo patients did not appear to be related to study medication or the dose of study medication administered. Serious adverse events occurred in 8 citalopram patients, including 3 suicide attempts, a miscarriage, intestinal flu symptoms, chest pain and dizziness unaccompanied by ECG abnormalities, a severe thinking abnormality, and an allergic reaction.” Thus, while the text alludes to SAEs in placebo-treated patients, such events are not explicitly provided and have thus been missed by the CTU. As we have access to AE data for this particular trial, we can confirm that one case of suicidal ideation, which was classified as an SAE, occurred in a placebo-treated patient.

**Answer: We extracted the data as reported in the publication and hence it is not an error commited by us. Anyhow, as the Hieronymus et al. claim they have access to the data and there was an SAE in placebo, we have now updated our analysis and it does not change our results or conclusions.**

1. The GSK-sponsored protocol GSK/279 (25) was only placebo-controlled at one of two centers as the independent review board at one of the participating centers refused to administer placebo. As it is impossible to disentangle site-related differences from treatment-related differences in the published report, the inclusion of this partly uncontrolled study is questionable.

**Answer: The methdology is definitely poorly described, but as we understood the methodlogy then it was described that only one of the centres TREATED patients with placebo. We have tried to contact the authors to clarify this unclear methdology but we have received no answer. Although the exclusion of this trial (25) is debatable as the SAEs were reported intervention wise, we now excluded this trial from our re-analysis. It does not change our results or conclusions.**

1. The odds ratio reported for the trial by Mathews et al. (NCT01473381) was erroneous; this has, however, been corrected without further comment in the response from the CTU group) (26, 27).

**Anwer: As it was corrected earlier, we do not think this is an error.**

1. In table 2 in the response from CTU group (21) it is stated that Kranzler and co-workers (28) did not specify the type of SAEs in their study on co-occuring alcohol dependence and major depression. This is not correct, the type of SAE is explicitly given in the study report: “Among sertraline treated patients, serious adverse events consisted of a worsening of clinical condition because of alcoholic relapse (n = 7; 2 patients required hospitalization), depression (n = 1), suicidal ideation (n =1), or blood in the stool (n = 1). Among placebo-treated patients, serious adverse events consisted of a worsening of clinical condition because of suicidal ideation or attempt (n = 3), alcoholic relapse (n = 2), depression (n = 1), chest pain (n = 1), or syncope (n = 1).” Notably, the numerical overrepresentation of SAEs with sertraline is entirely driven by alcoholic relapses; with these events included the OR is 1.36 (0.52 – 3.53), if excluded the odds ratio drops to 0.53 (0.13 – 2.14).

**Answer: We acknowledge that we wrongly stated that Kranzler and co-workers did not specify the type of SAEs in their study (28). However, we do not agree with Hieronymus et al.’s argument that SAEs in sertraline is entirely driven by alcoholic relapses. As alcoholic relapse is considered as an SAE by the authors of the manuscript (28) themselves, we cannot separate alcoholic relapse from other SAEs and reanalyse.**

1. In reference to the study by Schneider and co-workers (29), the CTU group states in their reply that “[w]e 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).” In fact, we are reasonably certain that it is a count as this is what the manuscript states: “There were 28 serious adverse events in the study: 17 among the patients in the sertraline group and 11 in the placebo group […] Four patients left the study because of serious adverse events; all were receiving sertraline. These events included depression and fecal impaction in one patient and syncope, diverticulitis, and accidental bone fracture in one patient each.”

**Answer: We disagree. Please see our text. We agree that it is poorly described but we still believe that it is valid to consider these data as proportions. We have contacted the authors to clarify but have received no response.**

1. The study by Itil and co-workers (30) concerns fluvoxamine, not fluoxetine.

**We acknowledge that instead of fluvoxamine, we misreported it as fluoxetine. Thank you. But it does not has any influence on our results or conclusions, as fluvoxamine is still an SSRI.**

1. The study by Pettinati and co-workers (31) is not included in the efficacy evaluations.

**We acknowledge that this study is not included in the efficacy analysis. Inclusion of this study does not change the efficacy results.**

1. In the *BMC psychiatry* paper, the author state that “[w]hen the four trials with low risk of bias of financial bias were analysed separately then there was no significant difference between the SSRI group and the placebo group (−0.92 points; 95% CI −2.42 to 0.58; I2 26%) (Additional file 4: Figure S1).” However Additional file 4: Figure S1 reveals that that five, not four, trials were included in the analysis; one of these has a duration of merely one week and another erroneously uses pre-treatment values rather than post-treatment ones (see points 4 and 5 above).

**Answer: We acknowledge that it is an error, but it does not effect our results or conclusions. See our explanation to points 4 and 5 above regarding a study (18) with duration of one week and the other study (17) which Hieronymus et al. mistakenly considered pre-sleep values as pre-treatment values.**

1. *The BMC Psychiatry* paper (32) states that “[t]here were no significant differences between participants randomised to SSRIs versus placebo on number of suicides (RR 0.68; 95% CI 0.16 to 2.81; P = 0.59; Trial Sequential Analysis-adjusted CI 0.01 to 226.85; 6 trials [60, 71, 108, 113, 151, 155]).” Table 2, however, shows that suicides occurred in 7 of the tabulated trials. Moreover, there was a suicide in the study by Loo and co-workers (33) which was included in the SAE analysis but not tabulated.

**Answer: We acknowledge that in Table 2 of our original review we reported that suicides occurred in seven trials but by mistake we included only six trials in meta-analysis of suicides. We also acknowledge that we included a trial by Loo et al. (33), in which there was a suicide, in the SAE analysis, but did not include in the table and meta-analysis of suicides. However, the updated meta-analysis does not change the results on suicides (RR 0.70; 95% CI 0.26 to 1.88; P = 0.51).**

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