Letter to the Editor / Reply

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Reply to the Letter to the Editor: "Newer-Generation Antidepressants and Suicide Risk: Thoughts on Hengartner and Plöderl's Re-Analysis"

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We thank Hayes et al. [1] for their interest in our work and the opportunity to address important issues, which were not covered in our original paper [2]. We decided to replicate the findings from Khan et al. [3] without a meta-analytic method because, first, the statistical model should be comparable to the one Khan et al. used for this particular data table [3], and second, it should also closely resemble the model Khan et al. used in their previous analysis of the FDA database [4].

Hayes et al. [1] demonstrate that different meta-analytic methods produce varying results when events are very rare. However, some of their models (e.g., inverse-variance and DerSimonian-Laird) are inappropriate for data with rare events and many zero-events in both arms [5, 6]. We further acknowledge that an ideal meta-analytic method would not only account for differences between new drug application programs, but also for differences within programs, as every program consists of varying numbers of different trials, including placebo-controlled, active-controlled, and even few open-label (safety extension) trials. Perhaps the most important issue we had not addressed in our original letter due to space limitations and firm opposition from a reviewer are systematic biases in industry-sponsored trials. These include misclassification of suicides, miscoding suicide attempts as emotional lability, and misreporting the true number of events [7, 8].

Healy and Whitaker [9] show that two suicides in the paroxetine program that occurred during the lead-in phase were incorrectly recorded as placebo suicides. Sharma et al. [8] document that 4 out of 16 deaths recorded in 70 antidepressant trials were misreported by the drug manufacturer, in all cases favoring the active treatment. For example, a patient on venlafaxine who attempted suicide during the randomized treatment phase and who died 5 days later in hospital was recorded as a post-study event because death occurred in the hospital when treatment was discontinued. These flaws in industry-sponsored antidepressant trials also question the reliability of the highly cited FDA analysis, which was not based on the FDA's own safety reviews but on the evaluations obtained from the drug manufacturers [10].

To demonstrate that misreported suicides can substantially bias the results, we show in Table 1 that the suicide risk according to a Bayesian random-effects meta-analysis (the method recommended by Ren et al. [6]) of the uncorrected data table was OR = 2.49, 0.82–45.32 (note the discrepancy to Hayes et al. [1]). With the two misclassified placebo suicides from the paroxetine program removed, the association was OR = 5.72, 1.36–427.45, and with data from the fluoxetine and bupropion programs included (which increases power), it was OR = 6.34, 1.55–365.83. Finally, Hayes et al. [1] did not present meta-analytic results for suicide attempts, the single most important determinant of suicide. Even when based on the uncorrected data table, our analyses reveal a significantly increased risk of suicides and suicide attempts combined in antidepressant arms relative to placebo that was largely consistent across methods (e.g. Bayesian random-effects meta-analysis: OR = 1.80, 1.19–3.33). The R-code is available online via https://osf.io/qzjva. These meta-analytic findings indicate that there is an increased suicide risk with antidepressants.

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Table 1. Summary estimates for different meta-analytic methods

	Suicides			Suicides and suicide attempts		
	original	corrected[a]	corrected[a] plus fluoxetine and bupropion	original	corrected[a]	corrected[a] plus fluoxetine and bupropion
Peto[b]	1.74 (0.78–3.90)	2.41 (1.06–5.48)	2.48 (1.13–5.44)	1.57 (1.15–2.16)	1.65 (1.20–2.27)	1.72 (1.26–2.34)
Mantel-Haenszel[c]	1.98 (0.71–5.50)	3.96 (0.97–16.20)	4.37 (1.07–17.82)	1.70 (1.17–2.49)	1.83 (1.24–2.70)	1.94 (1.32–2.87)
Arcsine (risk difference in %)[d]	0.05 (0.00–0.17)	0.09 (0.02–0.21)	0.09 (0.02–0.20)			
Exact[e]	1.91 (0.62–14.96)	3.49 (0.77–768.57)	3.71 (0.81–1491.41)	1.70 (1.17–2.57)	1.81 (1.23–2.78)	1.93 (1.31–2.97)
Bayesian random-effects[f]	2.49 (0.82–45.32)	5.72 (1.36–427.45)	6.34 (1.55–365.83)	1.80 (1.19–3.33)	1.92 (1.27–3.36)	2.07 (1.36–4.06)
Original analysis	2.83 (1.13–9.67)			2.49 (1.74–3.70)		

Figures are OR with 95% CI in parentheses. Our results for the Peto method are identical to those reported by Hayes et al. [1], but our results for both the Mantel-Haenszel and the Bayesian method differ due to different model specifications. OR, odds ratio; CI, confidence interval or credible interval (for the Bayesian meta-analysis).

[a] Two suicides erroneously recorded in the placebo group from the paroxetine approval program removed. [b] With metafor package. [c] With metafor package. Contrary to the method applied by Hayes et al. [1], drug approval programs with zero events in both arms were included in the analysis and a continuity correction is thus not necessary with metafor. According to Bradburn et al. [5], common Mantel-Haenszel models with constant 0.5 continuity correction introduce bias when events are rare. [d] With metafor package. The arcsine transformation has the advantage that no continuity correction is necessary. [e] With gmeta package. Using the approach suggested by Liu et al. [11]. [f] With JAGS program for R, using a model based on the parameters given by Hayes et al. [1]. The estimates are the medians of the posterior distribution. In our analysis, we used 8 chains, 1,000,000 burn-in samples, and 5,000,000 resamples. All analyses were conducted with R, version 3.6.1 (R Core Team, 2019). See R-Code for details https://osf.io/qzjva.

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