Appendix 3

[Appendix Tables 2](#_Toc492388320)

[*Appendix Table 1* 2](#_Toc492388321)

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[*Appendix Table 4* 8](#_Toc492388324)

[*Appendix Table 5 Results from multivariate meta-regression for the impact of placebo-controlled trials in response and dropout with active antidepressant drugs. The active drugs are included as covariates. Results are adjusted for differences in the availability of the unpublished report (for response and dropout) and the use of placebo run-in phase (in dropout). π: Probability of being allocated to placebo arm. Heterogeneity standard deviations are τ=0.19 (response), τ=0.35 (all-cause dropout).* 9](#_Toc492388325)

# Appendix Tables

Appendix Table 1 Average log-transformed response and dropout rates (logP) together with their standard errors (selogP) by drug and study design (PC2: studies with π=50%, PC3: studies with 20%≤π<50%, HTH: studies with π=0%). These data is used to produce Figures 1a and 1b and the Appendix Figure 2.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Response** | | | | |
| **Drug** | **Design** | **logP** | **SElogP** | **P** |
| fluv | PC2 |  |  |  |
| fluv | PC3 | -0.76 | 0.06 | 0.47 |
| fluv | HTH | -0.67 | 0.07 | 0.51 |
| bupr | PC2 | -0.74 | 0.08 | 0.48 |
| bupr | PC3 | -0.77 | 0.05 | 0.46 |
| bupr | HTH | -0.64 | 0.05 | 0.53 |
| nefa | PC2 | -0.74 | 0.13 | 0.48 |
| nefa | PC3 | -0.71 | 0.08 | 0.49 |
| nefa | HTH | -0.63 | 0.06 | 0.53 |
| rebo | PC2 | -0.63 | 0.20 | 0.53 |
| rebo | PC3 | -0.67 | 0.05 | 0.51 |
| rebo | HTH | -0.62 | 0.12 | 0.54 |
| dulo | PC2 | -0.83 | 0.04 | 0.44 |
| dulo | PC3 | -0.65 | 0.05 | 0.52 |
| dulo | HTH | -0.60 | 0.07 | 0.55 |
| amit | PC2 | -0.32 | 0.13 | 0.72 |
| amit | PC3 | -0.61 | 0.04 | 0.54 |
| amit | HTH | -0.60 | 0.04 | 0.55 |
| traz | PC2 | -0.60 | 0.05 | 0.55 |
| traz | PC3 | -0.76 | 0.10 | 0.47 |
| traz | HTH | -0.59 | 0.09 | 0.55 |
| paro | PC2 | -0.87 | 0.07 | 0.42 |
| paro | PC3 | -0.65 | 0.03 | 0.52 |
| paro | HTH | -0.57 | 0.03 | 0.57 |
| sert | PC2 | -0.85 | 0.17 | 0.43 |
| sert | PC3 | -0.74 | 0.06 | 0.48 |
| sert | HTH | -0.55 | 0.06 | 0.58 |
| mirt | PC2 | -0.92 | 0.11 | 0.40 |
| mirt | PC3 | -0.75 | 0.07 | 0.47 |
| mirt | HTH | -0.51 | 0.06 | 0.60 |
| venl | PC2 | -0.60 | 0.08 | 0.55 |
| venl | PC3 | -0.61 | 0.03 | 0.54 |
| venl | HTH | -0.48 | 0.04 | 0.62 |
| vort | PC2 | -0.80 | 0.06 | 0.45 |
| vort | PC3 | -0.72 | 0.04 | 0.49 |
| vort | HTH | -0.43 | 0.05 | 0.65 |
| cita | PC2 | -0.94 | 0.13 | 0.39 |
| cita | PC3 | -0.69 | 0.03 | 0.50 |
| cita | HTH | -0.37 | 0.05 | 0.69 |
| esci | PC2 | -0.82 | 0.13 | 0.44 |
| esci | PC3 | -0.68 | 0.05 | 0.50 |
| esci | HTH | -0.37 | 0.05 | 0.69 |
| agom | PC2 | -0.62 | 0.04 | 0.54 |
| agom | PC3 | -0.72 | 0.04 | 0.49 |
| agom | HTH | -0.36 | 0.04 | 0.70 |
| All drugs | PC2 | -0.70 | 0.05 | 0.50 |
| All drugs | PC3 | -0.66 | 0.04 | 0.51 |
| All drugs | HTH | -0.53 | 0.02 | 0.59 |

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Dropout for any cause** | | | | |
| **Drug** | **Design** | **logP** | **SElogP** | **P** |
| cita | PC2 | -1.42 | 0.19 | 0.24 |
| cita | PC3 | -1.51 | 0.10 | 0.22 |
| cita | HTH | -1.99 | 0.14 | 0.14 |
| esci | PC2 | -1.50 | 0.15 | 0.22 |
| esci | PC3 | -1.59 | 0.10 | 0.20 |
| esci | HTH | -1.95 | 0.12 | 0.14 |
| agom | PC2 | -1.84 | 0.15 | 0.16 |
| agom | PC3 | -1.79 | 0.11 | 0.17 |
| agom | HTH | -1.85 | 0.12 | 0.16 |
| vort | PC2 | -1.68 | 0.12 | 0.19 |
| vort | PC3 | -1.82 | 0.07 | 0.16 |
| vort | HTH | -1.72 | 0.15 | 0.18 |
| sert | PC2 | -1.48 | 0.08 | 0.23 |
| sert | PC3 | -1.04 | 0.07 | 0.35 |
| sert | HTH | -1.64 | 0.11 | 0.19 |
| mirt | PC2 | -0.98 | 0.11 | 0.37 |
| mirt | PC3 | -1.09 | 0.09 | 0.34 |
| mirt | HTH | -1.46 | 0.10 | 0.23 |
| venl | PC2 | -1.33 | 0.14 | 0.26 |
| venl | PC3 | -1.30 | 0.08 | 0.27 |
| venl | HTH | -1.42 | 0.07 | 0.24 |
| nefa | PC2 | -0.71 | 0.13 | 0.49 |
| nefa | PC3 | -1.06 | 0.17 | 0.35 |
| nefa | HTH | -1.40 | 0.10 | 0.25 |
| dulo | PC2 | -1.19 | 0.12 | 0.30 |
| dulo | PC3 | -1.44 | 0.09 | 0.24 |
| dulo | HTH | -1.39 | 0.09 | 0.25 |
| paro | PC2 | -0.89 | 0.06 | 0.41 |
| paro | PC3 | -1.25 | 0.06 | 0.29 |
| paro | HTH | -1.37 | 0.06 | 0.26 |
| traz | PC2 | -1.29 | 0.10 | 0.27 |
| traz | PC3 | -1.09 | 0.10 | 0.34 |
| traz | HTH | -1.33 | 0.17 | 0.26 |
| amit | PC2 |  |  |  |
| amit | PC3 | -1.06 | 0.06 | 0.35 |
| amit | HTH | -1.29 | 0.09 | 0.28 |
| fluv | PC2 |  |  |  |
| fluv | PC3 | -0.83 | 0.12 | 0.44 |
| fluv | HTH | -1.27 | 0.10 | 0.28 |
| rebo | PC2 | -1.35 | 0.25 | 0.26 |
| rebo | PC3 | -1.33 | 0.12 | 0.26 |
| rebo | HTH | -1.24 | 0.10 | 0.29 |
| bupr | PC2 | -1.43 | 0.15 | 0.24 |
| bupr | PC3 | -0.94 | 0.08 | 0.39 |
| bupr | HTH | -1.14 | 0.13 | 0.32 |
| all | PC2 | -1.32 | 0.08 | 0.27 |
| all | PC3 | -1.30 | 0.10 | 0.27 |
| all | HTH | -1.47 | 0.04 | 0.23 |

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Dropout for AE** | | | | |
| **Drug** | **Design** | **logP** | **SElogP** | **P** |
| esci | PC2 | -2.64 | 0.24 | 0.07 |
| esci | PC3 | -2.86 | 0.13 | 0.06 |
| esci | HTH | -2.96 | 0.12 | 0.05 |
| agom | PC2 | -2.74 | 0.18 | 0.06 |
| agom | PC3 | -3.29 | 0.18 | 0.04 |
| agom | HTH | -2.91 | 0.15 | 0.05 |
| sert | PC2 | -2.54 | 0.25 | 0.08 |
| sert | PC3 | -2.22 | 0.20 | 0.11 |
| sert | HTH | -2.73 | 0.25 | 0.07 |
| cita | PC2 | -2.07 | 0.28 | 0.13 |
| cita | PC3 | -2.77 | 0.21 | 0.06 |
| cita | HTH | -2.73 | 0.20 | 0.07 |
| vort | PC2 | -3.51 | 0.33 | 0.03 |
| vort | PC3 | -2.80 | 0.10 | 0.06 |
| vort | HTH | -2.72 | 0.26 | 0.07 |
| bupr | PC2 | -2.58 | 0.25 | 0.08 |
| bupr | PC3 | -2.46 | 0.13 | 0.09 |
| bupr | HTH | -2.36 | 0.33 | 0.09 |
| mirt | PC2 | -2.08 | 0.36 | 0.12 |
| mirt | PC3 | -1.94 | 0.15 | 0.14 |
| mirt | HTH | -2.24 | 0.13 | 0.11 |
| paro | PC2 | -2.33 | 0.17 | 0.10 |
| paro | PC3 | -2.17 | 0.07 | 0.11 |
| paro | HTH | -2.21 | 0.10 | 0.11 |
| dulo | PC2 | -2.14 | 0.10 | 0.12 |
| dulo | PC3 | -2.46 | 0.10 | 0.09 |
| dulo | HTH | -2.17 | 0.13 | 0.11 |
| venl | PC2 | -2.31 | 0.25 | 0.10 |
| venl | PC3 | -2.06 | 0.11 | 0.13 |
| venl | HTH | -2.17 | 0.11 | 0.11 |
| traz | PC2 | -2.45 | 0.37 | 0.09 |
| traz | PC3 | -1.56 | 0.17 | 0.21 |
| traz | HTH | -2.15 | 0.22 | 0.12 |
| fluv | PC2 |  |  |  |
| fluv | PC3 | -1.64 | 0.16 | 0.19 |
| fluv | HTH | -2.11 | 0.18 | 0.12 |
| rebo | PC2 | -2.45 | 0.69 | 0.09 |
| rebo | PC3 | -2.18 | 0.16 | 0.11 |
| rebo | HTH | -2.05 | 0.23 | 0.13 |
| amit | PC2 |  |  |  |
| amit | PC3 | -1.68 | 0.08 | 0.19 |
| amit | HTH | -1.92 | 0.13 | 0.15 |
| nefa | PC2 | -2.03 | 0.33 | 0.13 |
| nefa | PC3 | -1.84 | 0.12 | 0.16 |
| nefa | HTH | -1.85 | 0.14 | 0.16 |
| all | PC2 | -2.33 | 0.15 | 0.10 |
| all | PC3 | -2.22 | 0.12 | 0.11 |
| all | HTH | -2.30 | 0.05 | 0.10 |

Appendix Table 2 Risk Ratios (RR) for response, all-cause dropout and dropout due to adverse events together with 95% Confidence Intervals (CI) estimated from multivariate model after excluding Amitriptyline and Trazodone. The model includes all other drugs as covariates.

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Response to active treatment** | **All-cause dropout** | **Dropout due to adverse events** |
| **π=0%**  **π>0%** | 1  0.85 (0.81, 0.86) | 1  1.19 (1.09 1.30) | 1  1.03 (0.90, 0.17) |

Appendix Table 3 Odds-ratios (OR) for response, all-cause dropout and dropout due to adverse events together with 95% Confidence Intervals (CI) estimated from multivariate model with the logit link function. The model includes all drugs as covariates.

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Response** | | | **All-cause dropout** | | | **Dropout due to adverse events** | | |
| **Variable** | **OR** | **95% CI** | | **OR** | **95% CI** | | **OR** | **95% CI** | |
| **π=0%** | 1 | | | 1 | | | 1 | | |
| **π> 0%** | 0.73 | 0.65 | 0.83 | 1.29 | 1.12 | 1.47 | 1.09 | 0.94 | 1.28 |
| **π=0%** | 1 | | | 1 | | |  | | |
| **π=50%** | 0.70 | 0.57 | 0.84 | 1.41 | 1.17 | 1.70 |  |  |  |
| **20%≤π<50%** | 0.74 | 0.65 | 0.84 | 1.37 | 1.24 | 1.51 |  | - |  |
| **10% increase π** | 0.93 | 0.89 | 0.96 | 2.31 | 1.75 | 3.05 |  |  |  |

Appendix Table 4 Risk-ratios (RR) together with 95% Confidence Intervals (CI) estimated from the multivariate model that includes variables that are correlated with the presence of a placebo arm as suggested in Table 1 and Table 2. Blinding of the outcome assessor and attrition bias relevant only for response. The impact of the variable “Percentage of female participants” was not significant for both response and all-cause dropout (for a 10% increase in the percentage of female participants we obtained RR for response: 1.01 95% CI (0.98,1.04) and RR for dropout 0.99 ( 95% CI 0.94,1.04) ) and is omitted from the analysis below in order to increase the sample size (missing values from 374 arms). The active drugs are also included as covariates.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | **Response** | | | **All-cause dropout** | | |
|  | RR | 95% CI | | RR | 95% CI | |
| Sponsorship bias (high versus low risk) | 1.01 | 0.99 | 1.03 | 1.00 | 0.99 | 1.00 |
| Blinding of outcome assessor stated versus unclear | 1.03 | 0.96 | 1.10 | - | **-** | **-** |
| Attrition bias  High risk vs low  Unclear risk vs low | 1.00  1.00 | 0.90  0.90 | 1.11  1.11 | - | - | **-** |
| Availability of unpublished report | 1.13 | 1.07 | 1.19 | 0.90 | 0.82 | 0.99 |
| Placebo run-in phase (yes versus no) | 0.97 | 0.92 | 1.03 | 1.11 | 1.01 | 1.22 |
| π=0% versus π>0% | 0.89 | 0.84 | 0.94 | 1.13 | 1.03 | 1.25 |

Appendix Table 5 Results from multivariate meta-regression for the impact of placebo-controlled trials in response and dropout with active antidepressant drugs. The active drugs are included as covariates. Results are adjusted for differences in the availability of the unpublished report (for response and dropout) and the use of placebo run-in phase (in dropout). π: Probability of being allocated to placebo arm. Heterogeneity standard deviations are τ=0.19 (response), τ=0.35 (all-cause dropout).

|  |  |  |
| --- | --- | --- |
|  | Response to active treatment | All-cause dropout |
| Number of active arms (studies) | 647 (386) | 641 (378) |
| Risk Ratios (95% CI) | | |
| π=0%  π> 0% | 1  0.89 (0.84, 0.94) | 1  1.19 (1.076, 1.306) |
| π=0%  20%≤π<50%  π=50% | 1  0.89 (0.85, 0.94)  0.87 (0.80, 0.94) | 1  1.19 (1.08,1.31)  1.15 (0.99,1.34) |
| For π increase by 10% | 0.97 (0.96, 0.99) | 1.04 (1.01, 1.07) |