Appendix 2

[Details on statistical models 2](#_Toc492388224)

[1. Analysis strategy 2](#_Toc492388225)

[2. Preliminary analysis: Regression models for the effect of placebo on various characteristics 2](#_Toc492388226)

[For patient-level characteristics summarized by arm 2](#_Toc492388227)

[For trial-level characteristics 3](#_Toc492388228)

[Arm-level characteristics 3](#_Toc492388229)

[3. Main analysis: Meta-regression models for the effect of placebo on response and dropout 4](#_Toc492388230)

# Details on statistical models

The covariate $P\_{i}$ (probability of receiving placebo) has been studied in three different formats; Dichotomous taking 0 if placebo is not included in the *i* trial and 1 otherwise, categorical at three levels (head-to-head study versus two-arm study with placebo versus multi-arm study with placebo) and finally continuous with the probability of being allocated to a placebo arm (defined as 1/(the number of study arms)). The number of study arms includes also arms that are excluded from our analysis; for example a study that compares placebo, sertaline and hypericum has probability of being allocated to placebo 1/3 despite the fact that the hypericum arm is not included in our analysis.

## Analysis strategy

We first compare patient, trial and arm characteristics between arms and trials with π>0% (placebo-controlled trials) and π=0% (head-to-head trials) as described in section 5 below. Those variables that appear to differ between the two groups were consider to be potential confounders of the association between π and the study outcomes. We then estimated the impact of π and the study outcomes adjusting for the type of antidepressant using multivariate multivariable meta-regression as described in section 6. Then we entered into the model all variables identified as potential confounders. Then the final model was re-run retaining only those variables that appear to be significantly associated with the outcome.

## Preliminary analysis: Regression models for the effect of placebo on various characteristics

We denote with $x\_{ij}$ patient-level characteristics summarized by arm (mean age of the participants, disease severity at baseline). There are also trial-level characteristics; we denote them by $m\_{i}$ the continuous (year of publication) and with $y\_{i}=0, 1$ the dichotomous (the unavailability of unpublished data, low risk of bias, use of placebo run-in phase and use of rescue medication). The arm-specific variables sample size and the sponsoring of the arm (0 if the arm was not sponsored or received independent sponsoring) were denoted by $m\_{ij}$ and $y\_{ij}$ respectively.

To estimate whether the various characteristics differ between placebo-controlled and head-to-head trials we fit the following models. $P\_{i} $refers to the inclusion of placebo in the trial (dichotomous variable as described above).

### **For patient-level characteristics summarized by arm**

*(mean age of the participants, disease severity at baseline and mean percentage of females)*

For $x\_{ij}$ the mean age in each study arm we consider the following meta-regression model

$$x\_{ij}=α+βP\_{i}+γT\_{i}+δ\_{i}+e\_{i}$$

where $γ$ is a vector of the 15 coefficients referring to the interventions (Fluoxetine is represented in the intercept). The term $δ\_{i}$ is a random-effects term and $e\_{i}$ is a random error term that reflects the precision with which $x\_{ij}$ is measured in study $i$. We assume that $δ\_{i}\~N(0,σ^{2})$ and $e\_{i}\~N(0,SE(x\_{ij})^{2})$.

Then the estimated coefficient $β$ measures the difference in the average value of the age of participants between placebo-controlled and head-to-head studies averaged over the 16 possible drugs. For the percentage of female participants we used $x\_{ij}=logit(P\_{F})$ where $P\_{F}$ is the observed proportion of women.

For the disease severity at baseline and sample size we employed a simple linear regression model.

### For trial-level characteristics

*(Low risk of bias, use of placebo run-in phase, year of study publication and use of rescue medication, reporting of outcomes, availability of unpublished data)*

For continuous trial level characteristics we employ a linear regression model

$$m\_{i}=α+βP\_{i }+e\_{i}$$

Consider now that $y\_{i }$is a trial-level dichotomous characteristic that takes the values 1 and 0 for each study. Then the model is a logistic regression model

$$logit (y\_{i})=α+βP\_{i}+e\_{i}$$

Because we are interested on the impact that the differences between placebo-controlled and head-to-head studies will have in a meta-analysis context, we fit both unweighted and weighted regressions for study size.

### Arm-level characteristics

*(sample size and sponsoring)*

For sample size we used the linear regression model

$$m\_{ij}=α+βP\_{i }+γT\_{i}+e\_{ij}$$

And for sponsoring

$$logit (y\_{ij})=α+βP\_{i}+γT\_{i}+e\_{i}$$

## Main analysis: Meta-regression models for the effect of placebo on response and dropout

 Each arm is identified with index $j$ and each study with $i$. For each study arm, we denote the probability of responding, to dropout for any cause and to dropout for adverse events with $p\_{ij}$. Each study includes at least one active treatment (out of 16 active interventions in total) which is identified with a vector $T\_{i}$ of length 17: this vector takes 1 for the drugs reported in study $i$ and the rest is filled with zeros. From the list of interventions we exclude Fluoxetine which is used as the reference treatment and its outcome is identified in the constant of the model. Then the multivariable multivariate meta-regression model is

$$log (p\_{ij})=α+βP\_{i}+γT\_{i}+δ\_{ij}+e\_{ij}$$

The random effects $δ\_{ij}$ follow a multivariate normal distribution with zero expectation and with unknown variance-covariance matrix to account for the correlations induced by the arms belonging to the same study. The random errors $e\_{ij}$ follow a univariate normal distribution with zero expectation and variance the sample variance of $log (p\_{ij})$.

The model was extended to include other potential patient- or study-level covariates.

Estimation of model parameters was done using the Restricted Maximum Likelihood Approach in mvmeta command in Stata.