# National Institute for Health and Care Excellence

Consultation draft

## Depression in adults: treatment and management

Appendix N2: Network meta-analysis - bias adjustment methods and results

NICE Guideline Appendices May 2018

Consultation draft

Developed by the National Guideline Alliance, hosted by the Royal College of Obstetricians and Gynaecologists

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# 21 Appendix N2: Network meta-analysis - bias 22 adjustment methods and results

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### 2.14 Introduction

5 Publication bias is known to affect results of meta-analyses in several clinical areas,
6 including Depression (Trinquart et al. 2012; Moreno et al. 2011; Moreno et al. 2009, Driessen
7 et al. 2015, Turner et al. 2008). It has been shown that published smaller studies tend to
8 overestimate the relative treatment effect of interventions vs control, compared to larger
9 studies (Moreno et al. 2011; Driessen et al. 2015, Turner et al. 2008, Chaimani et al.,2013). It
10 is thought that these "small study effects" are a consequence of publication bias, where

11 results from smaller, less precise, studies are unlikely to get published unless they show a

- 12 large effect in the expected direction, whereas large studies tend to be published quickly,
- 13 regardless of the magnitude and direction of effect.
- 14 When it is suspected that publication bias (small study effects) is present in a dataset, it is 15 important to try to account for its impact on the results. A regression using a measure of
- 16 study precision can be used to adjust for small study effects in meta-analysis, with the study
- 17 variance being typically used to adjust for study size (Moreno et al. 2011; Chaimani et al.
- 18 2013). Similar regression methods can be used to estimate and adjust for bias in network
- 19 meta-analysis (NMA) for a variety of risk of bias indicators (Dias et al. 2010).

The NMAs carried out for the Depression guideline were thought to be at risk of bias due to
small study effects. A bias adjustment analysis based on the variance of the relative
treatment effects was carried out to assess (1) whether there is evidence of small study bias,
and (2) the sensitivity of the estimated relative effects to this bias, where it is present.

We focused on the main outcomes included in the economic model and informing the clinical decisions: the log odds ratio (OR) of discontinuation for any reason, the log OR of response in those who did not discontinue and the standardized mean difference (SMD) in depression

27 scores.

28 The models for the main NMAs are reported separately (see Appendix N1). These models

29 were adapted to estimate and adjust for potential small study/publication bias. The data

30 informing the bias adjustment models are the same as in the main NMAs.

### 2.2 Methods

### 2.2.82 Assumptions on the direction of bias

33 The effect of small studies will be characterised by the variance of the effect of the treatment

34 in arms 2, 3, ... of each trial, relative to the treatment in arm 1 of that trial. The Guideline

35 Committee expressed the opinion that bias would act to favour active interventions when

36 compared to a control, but that there would be no systematic preference for active

37 interventions when compared to each other. These assumptions were supported by empirical

- 38 evidence of the direction and magnitude of small study bias in meta-analyses of
- 39 psychological interventions vs control (Driessen et al. 2015) and of antidepressants vs
- 40 placebo (Turner et al. 2008).
- 41 The model therefore estimates a (possibly) non-zero mean bias, with an estimated variance,
- 42 for comparisons of active interventions to controls, but forces the mean bias to be zero in
- 43 active vs active comparisons, whilst still allowing a non-zero variance around this mean. This
- 44 allows for the fact that small studies may exaggerate effects of one active intervention over

5

1 another, but that this may cancel out across multiple studies, with no particular intervention

- 2 being favoured across all studies (Dias et al. 2010). Further details on the bias model for
- 3 each of the outcomes considered are given in Sections 2.2.3 to 2.2.5.

4 The treatments defined as controls by the Guideline Committee were those in the following5 classes

- 6 1. Pill placebo
- 7 2. No treatment
- 8 3. Attention Placebo
- 9 4. TAU

while all other interventions were defined as active. See Appendix N1 for details on classesand treatment definitions.

12 The data were coded so that treatments are in ascending order by study arm, therefore 13 control treatments are always in arm 1 of studies included in the NMA, although they may 14 also be in arms 2, 3, etc., depending on the interventions considered in the trials. Treatment 15 comparisons within a trial were defined as being of three types:

- 16 1. Control vs Control
- 17 2. Control vs Active
- 18 3. Active vs Active

19 Comparisons of types 1 and 3 are assumed to have zero mean bias, whilst comparisons of 20 type 2 estimate a possibly non-zero mean bias, *b*.

For each of the outcomes, the bias is assumed to exaggerate the relative treatment effect on the scale that is being estimated. So for SMD outcomes the bias, if present, is expected to be negative as that would indicate an overestimation of the reduction in depression scores in active interventions compared to controls in studies with larger variances (i.e. smaller studies). For OR outcomes the bias will be assumed to act on the log OR scale and is expected to be positive for the response outcome (increasing of the odds of response in active interventions compared to controls in studies with larger variances, i.e. favouring the active interventions) and negative for the discontinuation outcome (decreasing the odds of discontinuation).

A Bayesian framework is used to estimate all parameters, using Markov chain Monte Carlo
simulation methods implemented in WinBUGS 1.4.3 (Lunn et al. 2013). Convergence was
assessed using the Brooks-Gelman-Rubin diagnostic (Brooks et al. 1998 Gelman and Rubin
1992). Further iterations post-convergence were obtained on which all reported results were
based. Sample WinBUGS code for each outcome is provided at the end of this document, in

35 Appendix 6.

### 2.2.26 Reporting of results

For each of the NMAs considered, the median of the small study bias and the standarddeviation around the mean bias are reported along with their 95% Credible Intervals (CrIs).

39 Networks for which the 95%Crl for the mean bias *b* does not contain zero will be considered

40 to have evidence of small study bias. In random effects models, a substantial reduction of the

41 between-study heterogeneity in relative treatment effects in the bias-adjusted model will also

42 indicate evidence of bias. If bias adjustment explains a substantial amount of the observed

43 between-study heterogeneity, then there is evidence that some of this heterogeneity was due

44 to the different effects reported by small studies and bias adjusted results should be

45 considered.

46 The direction of the estimated bias will also be assessed. As it is expected that bias will

47 favour active interventions, if the sign of the bias estimate suggests favouring the control

6

1 interventions we will interpret these results with caution as they go against informed clinical2 opinion (see Section 2.2.1.).

3 Adjusted relative intervention effects will also be reported as posterior median OR or SMD
4 and 95% Crl compared to Pill placebo. However, these should be interpreted with caution for
5 networks where there is no evidence of bias.

6 We also report the posterior median rank of each class (and 95% Crls), with the convention
7 that the lower the rank the better the class. Rank of interventions are presented in Appendix
8 7. Only interventions and classes of interest were included in the calculations of the rankings
9 (see Appendix N1 for a list of these).

### 2.2.30 Bias adjustment methods for SMD

11 The bias model acts to change the relative treatment effects of the treatment in arm *k* 

12 compared to the treatment in arm 1, for each study *i* on the SMD scale,  $\delta_{ik}$ . This applies to

13 the relative effects estimated from all included studies, whether the data are reported as

14 change form baseline in measures of depression, depression measured at follow-up or as

15 the number of responders to treatment. The model to pool these data is described in full in

16 Section 1.2.5 of Appendix N1. The only change required to incorporate the bias adjustment is

17 to change equation (3) of Appendix N1 to

18 
$$\theta_{ik} = \gamma_i + \delta_{ik} + (\beta_{ik} \times V_{ik})$$
(1)

19 where  $\delta_{i1} = \beta_{i1} = V_{i1} = 0$ ,  $V_{ik}$  is the variance of the relative effect measure calculated for arm

20 *k* of study *i* compared to arm 1, and  $\beta_{ik}$  represents the bias coefficient for the comparison of 21 the treatment in arm *k* to the treatment in arm 1 of study *i* which is assumed to follow a

22 Normal distribution

23 
$$\beta_{ik} \sim \operatorname{Normal}(B, \kappa_{SMD}^2)$$
 (2)

 $V_{ik} = \frac{3}{\pi^2} V_{ik}^*$  (3)

where B=b if the treatment in arm 1 of trial *i* is a control and the treatment in arm *k* is not (type 2) and B=0 if the comparison of treatment 1 to treatment *k* is active vs active or control vs control (types 1 and 3). The mean differences between the change from baseline for the

treatment in arm *k* and the treatment in arm 1 of trial *i*,  $\delta_{ik}$ , are modelled as in equation (4) of Appendix N1.

For trials reporting continuous measures of effect,  $V_{ik}$  is the variance of the SMD, calculated as the sum of the variances of the means in arms 1 and *k*, divided by the square of the standardising constant (i.e. the pooled variance for that trial). For trials reporting the number

of responders, the variance of the logOR of response in arm *k* compared to arm 1,  $V_{ik}^{*}$ , is calculated for each trial and transformed to a variance on the SMD scale using the relationship (Chinn 2009, Higgins and Green 2008)

36 The mean bias *b* is given a non-informative normal prior distribution  $b \sim \text{Normal}(0, 100^2)$ .

The between-study standard deviation around the mean bias,  $\kappa_{SMD}$ , is given a Uniform prior distribution with a lower bound of zero and upper bound chosen to capture all the observed

- 1 variability. For the less severe network the upper bound was 5 and for the more severe
- 2 network the upper bound was 50 as greater variability was observed.

### 2.2.43 Bias adjustment methods for OR of response

4 The bias model acts to change the relative treatment effects of the treatment in arm k

5 compared to the treatment in arm 1, for each study *i* on the logOR scale,  $\eta_{ik}$ . This applies to

6 the relative effects estimated from all included studies, whether the data are reported as the

7 number of responders to treatment, change form baseline in measures of depression or

8 depression measured at follow-up. The model to pool these data is described in full in

- 9 Section 1.2.6 of Appendix N1.
- 10 For studies reporting the number of responders, the only change required to incorporate the 11 bias adjustment is to write

12 
$$\operatorname{logit}(p_{ik}) = \alpha_i + \eta_{ik} + \left(\beta_{ik}^* \times V_{ik}^*\right)$$
(4)

13 where  $\eta_{i1} = \beta_{i1}^* = V_{i1}^* = 0$ , the logOR for the treatment in arm *k* compared to the treatment in

14 arm 1 of trial *i*,  $\eta_{ik}$ , are modelled as before and  $V_{ik}^*$  is the variance of the logOR calculated for 15 arm *k* of study *i* compared to arm 1.

16 Trials reporting continuous measures of effect provide information on SMDs which are then 17 converted to logORs as described in Section 1.2.6 of Appendix N1 (Chinn 2000; Higgins and 18 Green 2008). The variances of the logORs can be obtained by inverting the relationship in 19 equation (3), where the variance of the SMD is calculated as describe in Section 2.2.3. The 20 bias adjustment then acts on the converted logOR for arm *k* compared to arm 1 of each 21 study.

22 Parameter  $\beta_{ik}^{*}$  represents the bias coefficient for the comparison of the treatment in arm *k* to 23 the treatment in arm 1 of study *i* which is assumed to follow a Normal distribution

24  $\beta_{ik}^* \sim \operatorname{Normal}(B^*, \kappa_{LOR}^2)$  (5)

25 where  $B^*=b^*$  if the treatment in arm 1 of trial *i* is a control and the treatment in arm *k* is not 26 (type 2) and  $B^*=0$  if the comparison of treatment 1 to treatment *k* is active vs active or control 27 vs control (types 1 and 3).

28 The mean bias  $b^*$  is given a non-informative normal prior distribution  $b^* \sim \text{Normal}(0, 100^2)$ .

29 The between-study standard deviation around the mean bias is given a Uniform prior

30 distribution with a lower bound of zero and upper bound of 5 which was sufficient to capture

31 all the observed variability in the less severe and more severe networks.

### **2.2.5**<sup>2</sup> Bias adjustment methods for OR of discontinuation

33 The bias model acts to change the relative treatment effects of the treatment in arm *k* 

34 compared to the treatment in arm 1 of each study *i* on the logOR scale. Only data on the

- 35 number of discontinuations were included so the bias model is as described in equations (4)
- 36 and (5), with  $V_{ik}^*$  the variance of the logOR calculated for arm *k* of study *i* compared to arm 1.

### 2.31 Results: population with less severe depression

### 2.3.12 Outcome: SMD – less severe depression

3 A burn-in of 70,000 iterations was used after which a further 140,000 iterations were taken

4 from 2 independent chains (total of 280,000 iterations). High autocorrelation is present in 5 some parameters.

6 We therefore conclude that there is strong evidence of small study bias in this network.

7 The bias adjusted NMA model showed a substantially improved fit compared to the

8 unadjusted NMA model and the DIC favours the bias adjusted NMA model (Section 1.8 of

9 Appendix N1). The bias adjusted model better predicted the data for Hermat-Far 2012 and

10 Dunn 2005, compared to the unadjusted NMA model. These studies were poorly predicted

11 by the unadjusted NMA model. There was a small reduction in the between-study

12 heterogeneity in the bias adjusted NMA model (see Section 1.8 in Appendix N1). The median

13 of the posterior distribution of the mean bias is negative (as expected) and the 95% Crl

14 excludes the possibility of zero bias (Table 1). However there is considerable variability in

15 mean bias (Figure 1). We therefore conclude that there is strong evidence of small study bias 16 in this network.

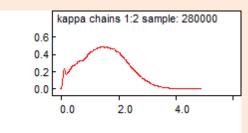
17 We therefore conclude that there is strong evidence of small study bias in this network.

#### 18 Table 1: Median and 95%Crl for the mean bias and its between study standard

#### 19 deviation for the SMD in the population with less severe depression.

	Median	95%Crl
mean bias, b	-2.23	(-4.31, -0.36)
Standard deviation of bias, $\kappa$	1.49	(0.15, 3.07)

### Figure 1: Between-study variability in mean bias for the SMD in the population with less severe depression



22

The SMD of interventions and classes for the bias adjusted model shows a small reduction is
 some relative effects (Figure 7Error! Reference source not found. and Figure 8Error!
 Reference source not found.).

Adjusted ranks for classes show no meaningful changes in class ranking compared to the unadjusted NMA, although there is added uncertainty in some rankings (Table 2).

### Table 2: Posterior median rank and 95%Crl from the bias adjusted analysis of the SMD for the population with less severe depression.

Class	Posterior median rank	95% Crl
Combined (Counselling + AD)	2	(1, 21)
Combined (IPT + AD)	2	(1, 8)
Combined (Short-term psychodynamic psychotherapies + AD)	3	(1, 15)
Combined (Exercise + AD/CBT)	3	(1, 15)

Class	Posterior median rank	95% Crl
Behavioural therapies (individual)	5	(1, 19)
Combined (Cognitive and cognitive behavioural therapies individual + AD)	6	(2, 16)
Self-help with support	8	(3, 15)
Cognitive and cognitive behavioural therapies (individual)	8	(4, 16)
TCAs	10	(5, 18)
Exercise	12	(5, 21)
SSRIs	12	(7, 19)
Short-term psychodynamic psychotherapies	12	(3, 22)
Behavioural, cognitive, or CBT groups	14	(8, 20)
Combined (Self-help + AD)	14	(3, 23)
Psychoeducational interventions	15	(6, 21)
Interpersonal psychotherapy (IPT)	15	(4, 23)
Counselling	15	(5, 22)
Self-help without support	16	(9, 20)
Pill placebo	17	(12, 20)
Attention placebo	17	(6, 22)
TAU	21	(13, 23)
No treatment	22	(15, 23)
Problem solving	23	(11, 23)

1 We conclude that although there is some evidence of bias, the overall conclusions from the

2 NMA for SMD in the population with less severe depression is robust to small

3 study/publication bias.

4 Relative intervention and class effects versus pill placebo as well as the posterior median 5 rank of each intervention are reported in the *'Bias adjustment'* worksheet of the respective

6 excel file in Appendix N3.

### 2.3.27 Outcome: discontinuation for any reason – less severe depression

8 A burn-in of 30,000 iterations was used after which a further 60,000 iterations were taken 9 form 2 independent chains (total of 120,000 iterations).

10 The NMA with bias adjustment showed a slightly improved fit to the data compared to the

11 unadjusted NMA. The DIC for the adjusted and unadjusted model were similar although

12 slightly smaller for the unadjusted NMA model. There was a small reduction in the between-

13 study heterogeneity when adjusting for bias (see Section 1.8 in Appendix N1).

14 The mean bias had a negative median (which is in the expected direction) but the 95%Crl

15 included the possibility of a zero bias although with moderate variability (Table 3 and Figure

16 2). We therefore conclude that there is no evidence of small study bias in this network.

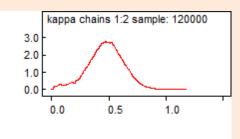
### 17 Table 3: Median and 95%Crl for the mean bias and its between study standard18 deviation for the logOR of discontinuation in the population with less severe

19

	Modian	95% Crl
depression.		
deviation for the logOR of discontinuation	on in the popula	ation with less severe

	Median	95%Crl
mean bias, b	-0.12	(-0.46, 0.20)
Standard deviation of bias, K	0.48	(0.13, 0.77)

## Figure 2: Between-study variability in mean bias for the logOR of discontinuation in the population with less severe depression.



3

4 The OR of interventions and classes for the bias adjusted model show some very small5 changes is relative effects (Figure 9 and Figure 10).

6 Adjusted ranks for classes (Table 4) show only small changes in class ranking when

7 compared to the unadjusted NMA ranks. Since there was no evidence of bias these should8 be interpreted with caution.

### 9 Table 4: Posterior median rank and 95%Crl from the bias adjusted analysis of the 10 logOR of discontinuation for the population with less severe depression

logert et discontinuation fer the population		001011
Class	Posterior median rank	95% Crl
Combined (Problem solving + AD)	3	(1, 24)
Mirtazapine	4	(1, 23)
No treatment	5	(1, 17)
Psychoeducational interventions	6	(1, 19)
Behavioural therapies (individual)	6	(1, 22)
Interpersonal psychotherapy (IPT)	9	(2, 21)
Problem solving	9	(2, 22)
Cognitive and cognitive behavioural therapies (individual)	9	(3, 17)
Combined (psych + placebo)	9	(1, 23)
Behavioural, cognitive, or CBT groups	10	(3, 21)
TAU	11	(3, 22)
Counselling	12	(3, 22)
Combined (IPT + AD)	12	(1, 25)
Exercise	14	(3, 23)
SSRIs	14	(6, 20)
Short-term psychodynamic psychotherapies	15	(3, 24)
Pill placebo	16	(9, 22)
Combined (Cognitive and cognitive behavioural therapies individual + AD)	16	(3, 25)
Combined (Counselling + AD)	16	(1, 25)
Attention placebo	18	(5, 25)
Self-help without support	19	(10, 24)
TCAs	20	(11, 24)
Self-help with support	21	(11, 25)
Combined (Short-term psychodynamic psychotherapies + AD)	23	(6, 25)
Combined (Behavioural, cognitive, or CBT groups + AD)	25	(4, 25)

11 We conclude that the NMA for discontinuation for any reason in the population with less

12 severe depression presented in Appendix N1 is robust to small study/publication bias.

1 Relative intervention and class effects versus pill placebo as well as the posterior median

2 rank of each intervention are reported in the '*Bias adjustment*' worksheet of the respective
3 excel file in Appendix N3.

### 2.3.34 Outcome: response in completers

5 A burn-in of 121,000 iterations was used after which a further 200,000 iterations were taken

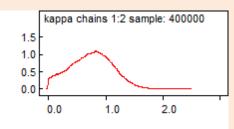
6 form 2 independent chains (total of 400,000 iterations). High autocorrelation is present in7 some parameters.

8 The NMA with bias adjustment showed a substantially improved fit to the data compared to 9 the unadjusted NMA with the DIC favouring the bias adjusted NMA model (see Section 1.8 in 10 Appendix N1). There was also a substantial reduction in the between-study heterogeneity in 11 the bias adjusted model (see Section 1.8 in Appendix N1). The mean bias had a positive 12 median (as expected) and the 95%Crl excluded the possibility of a zero bias although with 13 moderate variability (Table 5 and Figure 3). We therefore conclude that there is strong 14 evidence of small study bias in this network.

## Table 5: Median and 95%Crl for the mean bias and its between study standard deviation for the logOR of responses in completers in the population with less severe depression.

	median	95%Crl
mean bias, <i>b</i>	1.54	(0.54, 2.53)
Standard deviation of bias, K	0.76	(0.07, 1.45)

### Figure 3: Between-study variability in mean bias for the logOR of response in completers in the population with less severe depression.



#### 20

The OR of interventions and classes for the bias adjusted model show some reduction in magnitude of relative effects, which suggests that some classes no longer have evidence of a beneficial effect, compared to Pill Placebo Figure 11 and Figure 12). This reduction in class effects is due to the down-weighting and adjustment of the effects estimated in small studies to account for the bias (Dias et al. 2010).

Adjusted ranks for classes show some changes in class ranking (Table 6). The highest ranked class is unchanged but there are changes to the top 5 class rankings and their uncertainty.

## Table 6: Posterior median rank and 95%Crl from the bias adjusted analysis of the logOR of response in completers for the population with less severe depression.

depression. Class

Class	Posterior median rank	95% Crl
Combined (IPT + AD)	2	(1, 17)
Combined (Cognitive and cognitive behavioural therapies individual + AD)	3	(1, 12)
Combined (Counselling + AD)	4	(1, 24)

Class	Posterior median rank	95% Crl
Combined (Short-term psychodynamic psychotherapies + AD)	4	(1, 18)
Self-help without support	7	(2, 17)
Behavioural therapies (individual)	7	(2, 20)
Behavioural, cognitive, or CBT groups	8	(2, 17)
Cognitive and cognitive behavioural therapies (individual)	9	(3, 18)
TCAs	11	(4, 19)
SSRIs	11	(5, 18)
Exercise	12	(4, 21)
Mirtazapine	13	(1, 24)
Self-help with support	13	(3, 22)
Attention placebo	14	(3, 23)
Counselling	15	(4, 23)
Combined (Problem solving + AD)	15	(2, 24)
Short-term psychodynamic psychotherapies	16	(5, 23)
Interpersonal psychotherapy (IPT)	16	(5, 23)
TAU	17	(6, 23)
Problem solving	17	(7, 23)
Combined (Exercise + AD/CBT)	19	(5, 24)
Pill placebo	20	(15, 24)
Psychoeducational interventions	21	(8, 24)
No treatment	23	(15, 24)

1 We conclude that the results of the NMA for response in completers in the population with

2 less severe depression presented in Appendix N1 are sensitive to small study effects and the 3 impact of the bias on conclusions should be assessed.

4 Relative intervention and class effects versus pill placebo as well as the posterior median

5 rank of each intervention are reported in the 'Bias adjustment' worksheet of the respective

6 excel file in Appendix N3.

### 2.47 Results: population with more severe depression

#### 2.4.18 Outcome: SMD – more severe depression

9 A burn-in of 120,000 iterations was used after which a further 240,000 iterations were taken

10 form 2 independent chains (total of 480,000 iterations). High autocorrelation is present in 11 some parameters.

12 The bias adjusted NMA model showed a substantially improved fit compared to the

13 unadjusted NMA model and the DIC favours the bias adjusted NMA model (see Section 1.8

14 in Appendix N1). The bias adjusted model better predicted the data for Rush 1977, Torkan

15 2014, and Shamsaei 2008, compared to the unadjusted NMA model. These studies were

16 poorly predicted by the unadjusted NMA model. There was a substantial reduction in the

17 between-study heterogeneity in the bias adjusted NMA model (Section 1.8 of Appendix N1). 18 The median of the posterior distribution of mean bias is negative (as expected), however the

19 95% Crl includes the possibility of zero bias (Table 7) and there is large between-study

20 variability in bias (Table 7 and Figure 4). However, there is a large probability that the bias is

21 indeed negative. There is not enough evidence to conclude the presence of small study bias

22 in this network. However, results of the unadjusted model should be interpreted with caution

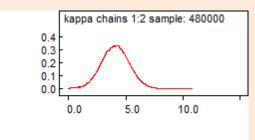
23 due to the lack of adequate fit to the data.

1.0

## 1 Table 7Median and 95%Crl for the mean bias and its between study standard2deviation for the SMD in the population with more severe depression.

	median	95%Crl
mean bias, b	-4.28	(-10.19, 0.94)
Standard deviation of bias, K	4.11	(1.7, 6.56)

## Figure 4: Between-study variability in mean bias for the SMD in the population with more severe depression.



5

6 The SMD of interventions and classes for the bias adjusted model shows a small reduction is7 some relative effects and increased uncertainty (Figure 13 and Figure 14).

8 Adjusted ranks for classes show some changes in class ranking (Table 8). The highest

9 ranked class is unchanged but there are changes to the top 5 classes and to the uncertainty

10 in rankings.

## 11 Table 8Posterior median rank and 95%Crl from the bias adjusted analysis of the12SMD for the population with more severe depression

Sind for the population with more severe depression					
Class	Posterior median rank	95% Crl			
Combined (Exercise + AD/CBT)	1	(1, 2)			
Combined (Cognitive and cognitive behavioural therapies individual + AD)	3	(1, 14)			
TCAs	4	(2, 11)			
SSRIs	5	(2, 11)			
Mirtazapine	6	(3, 13)			
Pill placebo	7	(4, 13)			
Interpersonal psychotherapy (IPT)	7	(2, 16)			
Behavioural therapies (individual)	8	(2, 16)			
Short-term psychodynamic psychotherapies	10	(2, 17)			
Self-help with support	10	(2, 16)			
Cognitive and cognitive behavioural therapies (individual) [CBT/CT]	10	(4, 16)			
Self-help without support	12	(6, 16)			
Counselling	13	(3, 17)			
No treatment	14	(3, 17)			
Attention placebo	14	(4, 17)			
TAU	14	(7, 17)			
Exercise	16	(3, 17)			

13 We conclude that the results of the NMA for SMD in the population with more severe

depression presented in Appendix N1 may be sensitive to small study effects although thereis no clear evidence of bias.

1 Relative intervention and class effects versus pill placebo as well as the posterior median

2 rank of each intervention are reported in the 'Bias' adjustment' worksheet of the respective
3 excel file in Appendix N3.

### 2.4.24 Outcome: discontinuation for any reason – more severe depression

5 A burn-in of 60,000 iterations was used after which a further 200,000 iterations were taken 6 from 2 independent chains (total of 400,000 iterations).

7 The NMA with bias adjustment showed an improved fit to the data compared to the

8 unadjusted NMA, but there was no difference in the DIC and there was only a small

9 reduction in the between-study heterogeneity when adjusting for bias (see Section 1.8 in

10 Appendix N1). The mean bias had a positive median (as expected) but the 95%Crl included

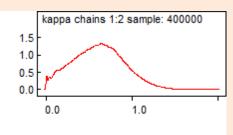
11 the possibility of a zero bias (Table 9). There was a large variability around the mean bias12 (Table 9 and Figure 5). We therefore conclude that there is no evidence of small study bias

13 in this network.

## Table 9 Median and 95%Crl for the mean bias and its between study standard deviation for any reason for the logOR of discontinuation for any reason in the population with more severe depression.

	median	95%Crl
mean bias, <i>b</i>	0.19	(-0.54, 0.94)
Standard deviation of bias, $\kappa$	0.61	(0.07, 1.21)

## Figure 5: Between-study variability in mean bias for the logOR of discontinuation for any reason in the population with more severe depression.



#### 19

20 The OR of interventions and classes for the bias adjusted model show only small changes in 21 relative effects (Figure 15 and Figure 16).

22 Adjusted ranks for classes show some changes in class ranking but also increased

23 uncertainty when compared to the unadjusted NMA results (Table 10).

## Table 10: Posterior median rank and 95%Crl from the bias adjusted analysis of the logOR of discontinuation for any reason for the population with more severe depression.

Class	Posterior median rank	95% Crl
Problem solving	1	(1, 21)
Exercise	3	(1, 20)
Interpersonal psychotherapy (IPT)	5	(1, 19)
No treatment	6	(2, 18)
Counselling	7	(1, 21)
Cognitive and cognitive behavioural therapies (individual) [CBT/CT]	8	(3, 16)
Self-help with support	9	(2, 19)

15

Class	Posterior median rank	95% Crl
Mirtazapine	10	(2, 18)
Combined (Cognitive and cognitive behavioural therapies individual + AD)	10	(2, 19)
TAU	11	(4, 19)
TCAs	11	(3, 19)
SSRIs	12	(3, 19)
Behavioural therapies (individual)	13	(3, 21)
Behavioural, cognitive, or CBT groups	13	(3, 21)
Pill placebo	14	(5, 20)
Attention placebo	14	(3, 21)
Long-term psychodynamic psychotherapies	14	(2, 21)
Short-term psychodynamic psychotherapies	16	(2, 21)
Self-help without support	16	(8, 21)
Combined (Short-term psychodynamic psychotherapies + AD)	16	(2, 21)
Combined (Long-term psychodynamic psychotherapies + AD)	20	(5, 22)
Psychoeducational interventions	22	(20, 22)

1 We conclude that the results of the NMA for discontinuation in the more population with more

2 severe depression presented in Appendix N1 are unlikely to be sensitive to small study
 3 effects.

4 Relative intervention and class effects versus pill placebo as well as the posterior median

- 5 rank of each intervention are reported in the 'Bias adjustment' worksheet of the respective
- 6 excel file in Appendix N3.

### 2.4.37 Outcome: response in completers – more severe depression

8 A burn-in of 50,000 iterations was used after which a further 200,000 iterations were taken 9 from 2 independent chains (total of 400,000 iterations).

The NMA with bias adjustment showed a small reduction in the between-study heterogeneity
but there was similar model fit and DIC for the adjusted and unadjusted models (see Section
1.8 of Appendix N1). The mean bias had a positive median (as expected) with moderate
variance (Table 11 and Figure 6) but the 95%Crl included the possibility of a zero bias (Table
11), although with a high probability that it is indeed positive. There is therefore only weak
evidence of small study bias in this network.

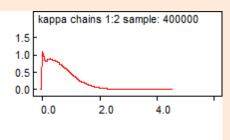
### 16 Table 11: Median and 95%Crl for the mean bias and its between study standard

17 18

### deviation for the logOR of responses in completers in the population with more severe depression.

	median	95%Crl
mean bias, b	1.41	(-0.17, 2.98)
Standard deviation of bias, K	0.57	(0.02, 1.88)

#### 1 Figure 6: Between-study variability in mean bias for the logOR of response in 2 completers in the population with more severe depression.



3

4 The OR of interventions and classes for the bias adjusted model shows some reduction in 5 magnitude of relative effects (Figure 17 and Figure 18).

6 Adjusted ranks for classes show small changes in ordering for the highest ranked classes, 7 although with added uncertainty in class ranking (Table 12).

#### 8 Table 12: Posterior median rank and 95%Crl from the bias adjusted analysis of the 9 logOR of response in completers for the population with more severe 10 depression.

Class	Posterior median rank	95% Crl
Problem solving	1	(1, 2)
Behavioural, cognitive, or CBT groups	2	(1, 3)
No treatment	3	(2, 5)
Combined (IPT + AD)	5	(3, 19)
Interpersonal psychotherapy (IPT)	7	(4, 20)
Exercise	8	(4, 20)
Short-term psychodynamic psychotherapies	9	(4, 20)
Behavioural therapies (individual)	9	(4, 18)
Cognitive and cognitive behavioural therapies (individual) [CBT/CT]	9	(5, 14)
Self-help with support	10	(4, 20)
Counselling	10	(5, 19)
Combined (Short-term psychodynamic psychotherapies + AD)	11	(4, 20)
Combined (Cognitive and cognitive behavioural therapies individual + AD)	12	(5, 19)
Attention placebo	13	(5, 20)
TCAs	13	(7, 18)
TAU	15	(8, 20)
Mirtazapine	15	(7, 19)
Self-help without support	16	(8, 20)
SSRIs	17	(10, 19)
Placebo	19	(14, 20)

11 We conclude that the results of the NMA for response in completers in the population with

12 more severe depression presented in Appendix N1 are unlikely to be sensitive to small study 13 effects.

14 Relative intervention and class effects versus pill placebo as well as the posterior median

15 rank of each intervention are reported in the 'Bias adjustment' worksheet of the respective

16 excel file in Appendix N3.

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### 2.61 Forest plots (bias adjusted results): population with less 2 severe depression

### Figure 7: SMD of each intervention compared to Pill Placebo from the bias adjusted and unadjusted models – less severe depression.

📕 unadjusted 🔶 blas ad	ljusted	
SMD Intervention (vs. Pill Placebo)		SMD 95%Crl
Waitlist		0.56 (0.26, 0.87)
No treatment		0.72 (0.24, 1.24)
Attention placebo	H + + +	0.05 (-0.3, 0.42)
Attention placebo + TAU	F - F - 1	0.19 (-0.47, 0.91)
TAU	<b>1</b>	0.3 (0.01, 0.59)
Enhanced TAU		0.54 (0, 1.2)
Exercise		-0.26 (-0.52, 0)
Exercise + TAU	H	-0.35 (-1.06, 0.3)
Internet-delivered therapist-guided physical activity	F	-0.21 (-0.77, 0.42)
Any TCA	H	-0.33 (-0.71, 0.13)
Amitriptyline		-0.48 (-0.74, -0.24
Imipramine	H -	-0.37 (-0.62, -0.12
Lofepramine		-0.42 (-0.84, -0.01
Citalopram		-0.26 (-0.55, 0.05)
Escitalopram		-0.22 (-0.45, 0.05)
Fluoxetine	H-1	-0.34 (-0.55, -0.15
Sertraline		-0.26 (-0.44, -0.07
Any AD	H 4	-0.66 (-1.02, -0.29
Short-term psychodynamic psychotherapy individual		-0.32 (-0.71, 0.08)
Cognitive bibliotherapy with support	<u> </u>	-0.26 (-0.67, 0.16)
Computerised behavioural activation with support	<u> </u>	-0.44 (-0.95, 0.06)
Computerised psychodynamic therapy with support	F I	-0.82 (-1.49, -0.23
Computerised-CBT (CCBT) with support	<u> </u>	-0.49 (-0.87, -0.11
Computerised-CBT (CCBT) with support + TAU	F - + 4	-0.29 (-0.81, 0.28)
Cognitive bibliotherapy	F- F- 1	-0.11 (-0.46, 0.23)
Cognitive bibliotherapy + TAU	<u> </u>	0.15 (-0.35, 0.69)
Computerised mindfulness intervention	► <u></u>	-0.15 (-0.76, 0.41)
Computerised-CBT (CCBT)		-0.25 (-0.59, 0.1)
Online positive psychological intervention		0.12 (-0.36, 0.65)
Psychoeducational website	F =	-0.16 (-0.66, 0.32)
Tailored computerised psychoeducation and self-help strategies Lifestyle factors discussion		0.26 (-0.3, 0.93)
Psychoeducational group programme	<u></u>	0.06 (-0.43, 0.58)
	<u> </u>	-0.08 (-0.51, 0.36)
Psychoeducational group programme + TAU Interpersonal psychotherapy (IPT)	<u> </u>	-0.13 (-0.65, 0.37) -0.16 (-0.51, 0.19)
Non-directive counselling		-0.15 (-0.6, 0.31)
Wheel of wellness counselling	<u></u>	-0.1 (-0.68, 0.48)
Problem solving individual + enhanced TAU		0.72 (-0.07, 1.58)
Behavioural activation (BA)		-0.83 (-1.24, -0.43
CBT individual (under 15 sessions)		-0.56 (-0.97, -0.16
CBT individual (under 15 sessions) + TAU		-0.56 (-1, -0.12)
CBT individual (over 15 sessions)		-0.53 (-0.82, -0.24
CBT individual (over 15 sessions) + TAU		0.15 (-0.61, 1.07)
Rational emotive behaviour therapy (REBT) individual		-0.52 (-0.98, -0.07
Third-wave cognitive therapy individual		-0.64 (-1.09, -0.21
Third-wave cognitive therapy individual + TAU		-0.63 (-1.23, -0.1)
CBT group (under 15 sessions)		-0.2 (-0.56, 0.15
CBT group (under 15 sessions) + TAU		-0.26 (-0.74, 0.16
Coping with Depression course (group)	1	-0.08 (-0.5, 0.4)
Third-wave cognitive therapy group		-0.08 (-0.48, 0.35
Third-wave cognitive therapy group + TAU		-0.18 (-0.72, 0.36
CBT individual (over 15 sessions) + any TCA		-0.73 (-1.21, -0.24
CBT individual (over 15 sessions) + imipramine	<u> </u>	-0.77 (-1.32, -0.22
Supportive psychotherapy + any SSRI		-1.3 (-2.77, 0.18
Interpersonal psychotherapy (IPT) + any AD		-1.42 (-2.09, -0.74
Short-term psychodynamic psychotherapy individual + Any AD	F 1	-1.07 (-1.74, -0.4)
Short-term psychodynamic psychotherapy individual + any SSRI	<u> </u>	-1.07 (-2.3, 0.16)
CBT individual (over 15 sessions) + Pill placebo		-1.26 (-1.93, -0.59
Exercise + Sertraline	F	-1.08 (-1.66, -0.45
Cognitive bibliotherapy + escitalopram		-0.2 (-0.85, 0.44)
4		3
	SMD	

5

#### 1 Figure 8: SMD of each class compared to Pill Placebo from the bias adjusted and 2 unadjusted models – less severe depression.

#### 🔳 unadjusted 🔹 blas adjusted

SMD		
Class (vs Placebo)	SMD	95%Crl
No treatment	0.64	(0.07, 1.25)
Attention placebo	0.12	(-0.51, 0.8)
TAU	0.41	(-0.15, 1.08)
Exercise	-0.27	(-0.84, 0.29)
TCA	-0.4	(-0.75, -0.03)
SSRI	-0.27	(-0.56, 0.04)
Any AD	-0.66	(-1.5, 0.19)
Short-term psychodynamic psychotherapies	-0.32	(-1.18, 0.52)
Self-help with support	-0.46	(-0.93, 0)
Self-help	-0.02	(-0.43, 0.41)
Psychoeducational interventions	-0.05	(-0.59, 0.5)
Interpersonal psychotherapy (IPT)	-0.16	(-1, 0.68)
Counselling	-0.13	(-0.82, 0.56)
Problem solving	0.72	(-0.37, 1.85)
Behavioural therapies (individual)	-0.83	(-1.7, 0.04)
Cognitive and cognitive behavioural therapies (individual)	-0.47	(-0.87, -0.04)
Behavioural, cognitive, or CBT groups	-0.16	(-0.56, 0.24)
Combined (Cognitive and cognitive behavioural therapies individual + AD)	-0.75	(-1.42, -0.07)
Combined (Counselling + AD)	-1.3	(-2.94, 0.35)
Combined (IPT + AD)	-1.42	(-2.4, -0.43)
Combined (Short-term psychodynamic psychotherapies + AD)	-1.07	(-2.04, -0.09)
Combined (psych + placebo)	-1.26	(-2.26, -0.26)
Combined (Exercise + AD/CBT)	-1.06	(-1.98, -0.12)
Combined (Self-help + AD)	-0.2	(-1.17, 0.76)
-3 -2 -1 0 1 2	3	
-3 -2 -1 0 1 2 SMD	3	

3

Update 2018

## Figure 9: OR of discontinuation for any reason of each intervention compared to Pill Placebo from the bias adjusted and unadjusted models (on a log scale) – less severe depression.

unadjusted 🔶	blas adjusted		
Discontinuation		a dala metia	050/ 0-1
Intervention (vs Pill Placebo)	- <b>-</b>	odds ratio	
Waitlist		0.52	(0.3, 0.88)
No treatment		0.57	(0.29, 1.11)
Attention placebo	F-4-1	0.93	(0.48, 1.74)
Attention placebo + TAU		1.23	(0.55, 3)
TAU	<b></b> )	0.68	(0.45, 1.04)
Enhanced TAU	<b></b> 1	0.82	(0.43, 1.68)
Exercise	<b>F • -</b>	0.76	(0.45, 1.27)
Exercise + TAU	<u></u>	0.93	(0.46, 2)
Yoga + TAU	<b>⊢−−</b> +−+	0.64	(0.19, 1.6)
Any TCA	P P P	1.24	(0.78, 2.08)
Amitriptyline	<b>H</b>	1.03	(0.71, 1.46)
Imipramine		1.26	(0.92, 1.75)
Lofepramine		1.24	(0.76, 2.11)
Any SSRI	H-4-1	0.82	(0.5, 1.26)
Any SSRI + Enhanced TAU	<b>F • 4</b>	0.83	(0.45, 1.4)
Citalopram	F	0.85	(0.56, 1.31)
Escitalopram		0.85	(0.58, 1.26)
Fluoxetine		0.82	(0.58, 1.13)
Sertraline	<b>F</b>	0.89	(0.66, 1.2)
Any AD	E F F	1.06	(0.64, 1.75)
Mirtazapine	F	0.48	(0.13, 1.74)
Short-term psychodynamic psychotherapy individual	<b>F</b> • •	0.87	(0.49, 1.55)
Short-term psychodynamic psychotherapy group	H	0.87	(0.33, 2.3)
Cognitive bias modification with support + TAU	H I	1.23	(0.5, 2.85)
Cognitive bibliotherapy with support	<b>--</b> +	1.35	(0.67, 2.63)
Cognitive bibliotherapy with support + TAU		1.24	(0.49, 2.95)
Computerised behavioural activation with support	H 1	1.06	(0.4, 2.37)
Computerised psychodynamic therapy with support	F	1.45	(0.6, 3.92)
Computerised third-wave cognitive therapy with support	F - + - +	1.16	(0.41, 2.81)
Computerised-CBT (CCBT) with support	H	1.71	(0.9, 3.3)
Computerised-CBT (CCBT) with support + TAU		1.08	(0.54, 2.05)
Tailored computerised-CBT (CCBT) with support	H I	1.17	(0.48, 2.58)
Behavioural bibliotherapy	H	1.11	(0.55, 2.35)
Cognitive bibliotherapy	F	1	(0.55, 1.79)
Cognitive bibliotherapy + TAU		1.04	(0.53, 1.98)
Computerised cognitive bias modification	F	1.07	(0.53, 2.12)
Computerised mindfulness intervention	F	1.08	(0.53, 2.23)
Computerised-CBT (CCBT)	E E E	1.09	(0.63, 1.86)
Computerised-CBT (CCBT) + TAU	F -	1.12	(0.63, 2.02)
Online positive psychological intervention		1.11	(0.57, 2.22)
Psychoeducational website	H	1.03	(0.54, 1.91)
Tailored computerised psychoeducation and self-help strategie	es + +	1.02	(0.5, 1.95)
Lifestyle factors discussion	<u></u>	0.51	(0.22, 1.18)
Psychoeducational group programme	<b>F - F - 1</b>	0.45	(0.18, 1.02)
Psychoeducational group programme + TAU	F	0.6	(0.29, 1.26)
Interpersonal psychotherapy (IPT)		0.73	(0.44, 1.2)
Interpersonal psychotherapy (IPT) + TAU		0.62	(0.24, 1.32)
Emotion-focused therapy (EFT)	F	0.67	(0.28, 1.42)
Interpersonal counselling		0.69	(0.33, 1.37)
Non-directive counselling		0.85	(0.42, 1.78)
-			(continues)
	0.02 0.5 1 2 20 5	0	
	odds ratio		

4

#### 🔳 unadjusted 🔹 blas adjusted

Discontinuation			
Intervention (vs Pill Placebo)		odds ratio	95%Crl
			(continued)
Non-directive counselling + TAU	F	0.82	(0.38, 1.82)
Psychodynamic counselling + TAU	<b>F</b>	0.75	(0.32, 1.69)
Relational client-centered therapy	<b>F</b> - <b>6</b> - <b>1</b>	0.73	(0.28, 1.78)
Wheel of wellness counselling		0.69	(0.26, 1.6)
Problem solving group	F +	0.7	(0.29, 1.86)
Problem solving individual	F	0.64	(0.33, 1.25)
Problem solving individual + TAU	F I	0.59	(0.24, 1.33)
Problem solving individual + enhanced TAU	F	0.72	(0.3, 1.86)
Behavioural activation (BA)	F	0.49	(0.22, 1.08)
Behavioural activation (BA) + TAU	F I	0.63	(0.22, 1.91)
Behavioural therapy (Lewinsohn 1976)	F	0.75	(0.27, 2.48)
Coping with Depression course (individual)	F	0.63	(0.21, 1.96)
CBT individual (under 15 sessions)	<b>H</b>	0.7	(0.42, 1.17)
CBT individual (under 15 sessions) + TAU	F - I	0.73	(0.4, 1.51)
CBT individual (over 15 sessions)	<b>-</b>	0.66	(0.43, 1)
CBT individual (over 15 sessions) + TAU	F 1	0.64	(0.29, 1.3)
Rational emotive behaviour therapy (REBT) individual		0.64	(0.3, 1.25)
Third-wave cognitive therapy individual	F I	0.61	(0.32, 1.09)
Third-wave cognitive therapy individual + TAU	F	0.63	(0.29, 1.27)
CBT group (under 15 sessions)	F - 1	0.83	(0.43, 1.63)
CBT group (under 15 sessions) + TAU	F	0.41	(0.14, 0.98)
CBT group (over 15 sessions)	<u>⊢</u>	0.7	(0.29, 1.63)
Coping with Depression course (group)		0.72	(0.33, 1.55)
Coping with Depression course (group) + TAU		0.95	(0.43, 2.35)
Rational emotive behaviour therapy (REBT) group		0.55	(0.18, 1.36)
Third-wave cognitive therapy group		0.84	(0.37, 2.07)
Third-wave cognitive therapy group + TAU	<b>F F F F F</b>	0.61	(0.22, 1.5)
CBT individual (over 15 sessions) + any AD	F	1.05	(0.39, 3.07)
CBT individual (over 15 sessions) + any TCA	<u>⊢</u> –	0.96	(0.42, 2.19)
CBT individual (over 15 sessions) + imipramine	F	0.94	(0.38, 2.32)
CBT group (under 15 sessions) + imipramine	F	2.24	(0.52, 9.89)
Problem solving individual + any SSRI	F	0.42	(0.1, 1.62)
Supportive psychotherapy + any SSRI	F	0.89	(0.14, 5.54)
Interpersonal psychotherapy (IPT) + any AD		0.77	(0.22, 2.62)
Interpersonal psychotherapy (IPT) + imipramine	<b>H - - - - - - - - - -</b>	0.69	(0.17, 2.69)
Short-term psychodynamic psychotherapy individual + Any A	D + -	1.48	(0.62, 3.46)
Short-term psychodynamic psychotherapy individual + any S		1.43	(0.48, 4.29)
CBT individual (over 15 sessions) + Pill placebo	F	0.3	(0.08, 0.97)
Interpersonal psychotherapy (IPT) + Pill placebo	F	0.35	(0.11, 1.07)
Exercise + CBT individual (under 15 sessions)	F	0.63	(0.22, 1.67)
Exercise + Sertraline		0.7	(0.34, 1.47)
	0.02 0.51 2 20 5	1 0	
	odds ratio	~	

1 2

## Figure 10: OR of discontinuation for any reason of each class compared to Pill Placebo from bias adjusted and unadjusted models (on a log scale) – less severe depression.

Discontinuation			
Class (vs Placebo)		odds ratio	95%Crl
No treatment		0.54	(0.26, 1.12
Attention placebo	<b>H</b>	1.07	(0.48, 2.45
TAU	<b>F 4 - 1</b>	0.75	(0.39, 1.53
Exercise	P	0.77	(0.34, 1.6)
TCA		1.19	(0.78, 1.85
SSRI		0.84	(0.59, 1.17
Any AD	<b>H</b> - <b>H</b> - <b>H</b>	1.06	(0.41, 2.72
Mirtazapine	h	0.48	(0.13, 1.74
Short-term psychodynamic psychotherapies	P	0.87	(0.38, 2.02
Self-help with support		1.26	(0.66, 2.3)
Self-help	<b>F F 1</b>	1.07	(0.62, 1.82
Psychoeducational interventions	1	0.51	(0.23, 1.14
Interpersonal psychotherapy (IPT)	5 - <b>5</b> - 5	0.67	(0.31, 1.34
Counselling	F	0.74	(0.38, 1.39
Problem solving		0.66	(0.31, 1.41
Behavioural therapies (individual)	F - F + 1	0.62	(0.26, 1.55
Cognitive and cognitive behavioural therapies (individual)		0.66	(0.39, 1.09
Behavioural, cognitive, or CBT groups	F 4 - 1	0.68	(0.35, 1.26
Combined (Cognitive and cognitive behavioural therapies individual + AD)	)	0.98	(0.41, 2.39
Combined (Behavioural, cognitive, or CBT groups + AD)		2.25	(0.44, 11.6
Combined (Problem solving + AD)	····	0.42	(0.09, 1.89
Combined (Counselling + AD)	·····	0.89	(0.12, 6.27
Combined (IPT + AD)	b b 1	0.72	(0.19, 2.72
Combined (Short-term psychodynamic psychotherapies + AD)		1.45	(0.52, 3.98
Combined (psych + placebo)	· · · · · · · · · · · · · · · · · · ·	0.32	(0.09, 1.03
Combined (Exercise + AD/CBT)	P	0.66	(0.26, 1.65
0	0.02 0.512 2	0 50	

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## Figure 11: OR of response in completers of each intervention compared to Pill Placebo from the bias adjusted model and unadjusted models (on a log scale) – less severe depression

📕 unadjusted 🔶 blas adjusted		
Response (completers)		
Intervention (vs Pill Placebo)	odds ratio	95%Crl
		(continued)
Behavioural therapy (Lewinsohn 1976)	<b>♦</b> -⊣ 4.87	(1.97, 13.14)
Coping with Depression course (individual)	♦  4.66	(1.8, 13.25)
CBT individual (under 15 sessions)	2.98	(1.61, 5.53)
CBT individual (over 15 sessions)	3.14	(1.79, 5.55)
Third-wave coopitive thereavy individual	3.24	(1.37, 8.27)
CBT group (updor 15 coscions)		(1.38, 6.7)
CBT group (under 15 sessions) + TAU	3.23	(1.32, 8.55)
CBT group (over 15 sessions)	2.56	(1.08, 5.73)
	2.77	(1.12, 6.53)
Coping with Depression course (group) + TAU	3.44	(1.58, 7.75)
Detional exertive behavious thereasy (DEDT) errors	→ -1 3.27	(1.38, 8.16)
CBT individual (over 15 sessions) + any AD	7.09	(2.49, 21.2)
CBT individual (over 15 sessions) + any TCA	- <b>•</b> 5.39	(1.9, 14.57)
CBT individual (over 15 sessions) + imipramine	6.53	(2.4, 17.64)
Problem solving individual + any SSRI	2.02	(0.63, 6.61)
Supportive psychotherapy + any SSRI	4.83	(0.92, 25.33)
Interpersonal psychotherapy (IPT) + any AD	7.44	(1.97, 28.19)
Interpersonal psychotherapy (IPT) + imipramine	6.81	(1.34, 30.75)
Short-term psychodynamic psychotherapy individual + Any AD	<mark>-∳ - </mark> 4.74	(1.8, 12.85)
Short-term psychodynamic psychotherapy individual + any SSRI	4.31	(1.35, 13.78)
CBT individual (over 15 sessions) + Pill placebo	♦I 4.41	(1.5, 12.95)
Interpersonal psychotherapy (IPT) + Pill placebo	3.41	(1.1, 9.95)
Exercise + CBT individual (under 15 sessions)	-1 1.44	(0.47, 4.42)
Exercise + Sertraline		(0.63, 4.67)
0.02 0.51 2 odds rat		

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## Figure 12: OR of response in completers of each class compared to Pill Placebo from the bias adjusted model and unadjusted models (on a log scale) – less severe depression.

🛛 unadjusted 🔶 bias adjusted			
Response (completers)			
Class (vs Placebo)		odds ratio	95%Crl
No treatment	F	0.59	(0.24, 1.44)
Attention placebo	F	1.37	(0.47, 4.03)
TAU	H	1.27	(0.56, 2.91)
Exercise	H	2.62	(1.13, 6.05)
TCA	H-0-1	2.77	(1.69, 4.47)
SSRI	101	2.5	(1.71, 3.71)
Any AD	H	3.35	(1.12, 10.32
Mirtazapine	H	3.22	(0.69, 16.95
Short-term psychodynamic psychotherapies	F	2.2	(0.88, 5.81)
Self-help with support	F	2.67	(1.05, 6.97)
Self-help		2.62	(1.25, 5.45
Psychoeducational interventions	F 1	1.36	(0.49, 4.01)
Interpersonal psychotherapy (IPT)	F	2.05	(0.9, 4.81)
Counselling	F	2.19	(0.84, 5.75)
Problem solving	F - I	1.7	(0.79, 3.61)
Behavioural therapies (individual)	F	4.19	(1.77, 10.39
Cognitive and cognitive behavioural therapies (individual)		3.12	(1.56, 6.36)
Behavioural, cognitive, or CBT groups	F - F	3.04	(1.48, 6.28
Combined (Cognitive and cognitive behavioural therapies individual + AD)	<b>⊢ −+ −</b> 1	6.29	(2.35, 16.73
Combined (Problem solving + AD)	F	2.03	(0.5, 8.62)
Combined (Counselling + AD)	F	4.82	(0.77, 30.51
Combined (IPT + AD)	F	7.01	(1.59, 29.76
Combined (Short-term psychodynamic psychotherapies + AD)	H	4.51	(1.49, 13.97
Combined (psych + placebo)	H	3.87	(1.29, 11.34
Combined (Exercise + AD/CBT)		1.56	(0.52, 4.81)
0.02	0.5 1 2 20 5 odds ratio	0	

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## 2.71 Forest plots (bias adjusted results): population with more severe depression

### Figure 13: SMD of each intervention compared to Pill Placebo from the bias adjusted and unadjusted models – more severe depression.

SMD			
ntervention (vs Pill Placebo)		SMD	95%Crl
Vaitlist		0.63	(-0.09, 1.33
lo treatment		0.77	(-0.14, 1.68
Attention placebo	F	0.69	(-0.31, 1.72
Attention placebo + TAU		0.65	(-0.13, 1.4
AU		0.66	(0.05, 1.25
inhanced TAU		0.6	(-0.06, 1.24
xercise	F	0.26	(-0.82, 1.3)
exercise + TAU		0.31	(-0.6, 1.2)
mitriptyline		-0.29	(-0.52, -0.0
mipramine	÷.	-0.41	(-0.64, -0.1
ofepramine		-0.59	(-1.08, -0.1
Ditalopram	-	-0.27	(-0.43, -0.1
scitalopram	141 	-0.33	(-0.47, -0.2
luoxetine		-0.28	(-0.42, -0.1
Sertraline	-	-0.25	(-0.44, -0.0
Any AD		1.38	(-0.06, 2.8
/irtazapine		-0.2	(-0.53, 0.1)
hort-term psychodynamic psychotherapy individual + TAU	<u> </u>	0.05	(-0.77, 0.8
cognitive bibliotherapy with support + TAU		-0.02	(-0.74, 0.6
Computerised-CBT (CCBT) with support		0.21	(-0.65, 1.1
Cognitive bibliotherapy + TAU		0.49	(-0.24, 1.2
computerised cognitive bias modification		0.3	(-0.57, 1.1
Computerised-CBT (CCBT)		0.36	(-0.38, 1.0
Computerised-CBT (CCBT) + TAU		0.33	(-0.33, 0.9)
computerised-problem solving therapy		0.33	(-0.44, 1.0
nterpersonal psychotherapy (IPT)		-0.5	(-1.19, 0.1
motion-focused therapy (EFT)	· · · · · · · · · · · · · · · · · · ·	0.19	(-1.03, 1.3
lon-directive counselling		0.37	(-0.27, 0.9
elational client-centered therapy		0.56	(-0.58, 1.7
Behavioural activation (BA)		-0.43	(-1.06, 0.2
Behavioural activation (BA) + TAU		-0.31	(-1.21, 0.5
BT individual (under 15 sessions)		0.48	(-0.05, 0.9
BT individual (under 15 sessions) + TAU		0.31	(-0.45, 1.0
BT individual (over 15 sessions)		-0.55	(-1.12, 0.0
hird-wave cognitive therapy individual		-0.81	(-1.79, 0.0
BT individual (under 15 sessions) + citalopram		-0.68	(-1.23, -0.1
BT individual (over 15 sessions) + any AD		-0.42	(-1.6, 0.9)
hird-wave cognitive therapy individual + any AD		-0.96	(-2.27, 0.2
xercise + Fluoxetine	'	1 77	(-2.35, -1.2

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### Figure 14: SMD of each class compared to Pill Placebo from the bias adjusted and unadjusted models – more severe depression.

🗖 unadjusted 🔶 blas adjusted	
SMD	
Class (vs Placebo)	SMD 95%Crl
No treatment	0.7 (-0.18, 1.58)
Attention placebo	0.67 (-0.25, 1.61)
	0.63 (-0.1, 1.36)
Exercise	0.29 (-0.76, 1.31)
TCA	-0.42 (-0.9, 0)
SSRI	-0.28 (-0.52, -0.04)
Any AD	1.38 (-0.24, 3.04)
Mirtazapine He I	-0.2 (-0.53, 0.13)
Short-term psychodynamic psychotherapies	0.05 (-1.09, 1.17)
Self-help with support	0.09 (-0.79, 0.98)
Self-help	0.36 (-0.36, 1.04)
Interpersonal psychotherapy (IPT)	-0.49 (-1.74, 0.69)
Counselling	0.38 (-0.63, 1.36)
Behavioural therapies (individual)	-0.37 (-1.35, 0.6)
Cognitive and cognitive behavioural therapies (individual) [CBT/CT]	-0.14 (-0.89, 0.57)
Combined (Cognitive and cognitive behavioural therapies individual + AD)	-0.69 (-1.7, 0.34)
Combined (Exercise + AD/CBT)	-1.77 (-2.8, -0.74)
-3 -2 -1 0 1	2 3
SMD	

3

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## Figure 15: OR of discontinuation for any reason of each intervention compared to Pill Placebo from the bias adjusted and unadjusted models – more severe depression.

unadjusted 🔶 blas adjusted			
Discontinuation		odda ratio	05% C d
Intervention (vs Pill Placebo) Waitlist	F	odds ratio 0.32	95%Crl (0.07, 1.39)
Attention placebo		0.83	(0.14, 4.72
Attention placebo + TAU		0.65	(0.12, 3.29
TAU	F	0.51	(0.12, 1.93
Enhanced TAU		0.53	(0.12, 1.33
Exercise		0.33	(0.02, 2.23
Exercise + TAU		0.24	(0.02, 2.23)
Yoga + TAU		0.24	(0.02, 2.57
Any TCA		0.24	(0.39, 1.8)
Amitriptyline		0.84	(0.64, 1.1)
Imipramine	<b>.</b>	0.86	(0.65, 1.13
Lofepramine		0.78	(0.43, 1.3)
Citalopram		0.91	(0.67, 1.27
	南	0.89	(0.65, 1.27
Escitalopram Fluoxetine	3	0.83	
Settraline	<b>±</b>		(0.64, 1.07
		0.87	(0.61, 1.26
Any AD	·····	0.2	(0.02, 2.56
Mirtazapine		0.76	(0.51, 1.14
Short-term psychodynamic psychotherapy individual + TAU	+- <u></u> +	0.88	(0.12, 6.28
Long-term psychodynamic psychotherapy individual	F	1.06	(0.31, 3.67
Cognitive bibliotherapy with support + TAU	<u> </u>	0.42	(0.08, 2.01
Computerised-CBT (CCBT) with support	F	0.3	(0.05, 1.67
Computerised-problem solving therapy with support	F	0.4	(0.07, 2.05
Cognitive bibliotherapy + TAU		0.86	(0.18, 3.88
Computerised cognitive bias modification	► <b>-</b>	0.81	(0.16, 3.78
Computerised-CBT (CCBT)	F	0.79	(0.17, 3.37
Computerised-CBT (CCBT) + TAU	F	1.07	(0.24, 4.46
Computerised-CBT (CCBT) + enhanced TAU	F	0.72	(0.15, 3.22
Computerised-problem solving therapy	F	0.85	(0.18, 3.88
Psychoeducational group programme	F	12.69	(1.87, 85.8
Interpersonal psychotherapy (IPT)		0.34	(0.06, 1.81
Counselling (any type)	H4	0.38	(0.04, 3.31
Emotion-focused therapy (EFT)	H4	0.38	(0.04, 3.27
Non-directive counselling	F4	0.38	(0.05, 2.51
Relational client-centered therapy	F4	0.38	(0.04, 3.27
Problem solving group	**	0.12	(0.01, 2.05
Behavioural activation (BA)		0.89	(0.16, 4.75
Behavioural activation (BA) + TAU	H	0.55	(0.09, 3.14
CBT individual (under 15 sessions)	+	0.46	(0.11, 1.8)
CBT individual (under 15 sessions) + TAU		0.36	(0.08, 1.41
CBT individual (under 15 sessions) + enhanced TAU	F	0.49	(0.11, 2.15
CBT individual (over 15 sessions)		0.44	(0.11, 1.54
Third-wave cognitive therapy individual	F	0.35	(0.07, 1.51
CBT group (under 15 sessions)	F	0.63	(0.12, 3.26
CBT group (over 15 sessions) + TAU	F4	0.57	(0.1, 3.09)
Coping with Depression course (group)	<b></b>	0.64	(0.12, 3.48
Third-wave cognitive therapy group	<b>F</b>	0.64	(0.11, 3.62
CBT individual (under 15 sessions) + escitalopram	F	0.79	(0.24, 2.59
CBT individual (over 15 sessions) + amitriptyline	<b>F</b>	0.6	(0.14, 2.34
CBT individual (over 15 sessions) + any SSRI	<b>F</b>	0.47	(0.1, 1.8)
Short-term psychodynamic psychotherapy individual + any TCA	F	1.27	(0.27, 5.88
Long-term psychodynamic psychotherapy individual + fluoxetin		2.16	(0.66, 7.19
	0.02 0.5 1 2 20 5 odds ratio	D	

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## Figure 16 OR of discontinuation for any reason of each class compared to Pill Placebo from the bias adjusted and unadjusted models – more severe depression.

Intervention (vs Pill Placebo) Waitlist	· · · · · · · · · · · · · · · · · · ·		
	`	odds ratio	
	-+	416.13	(17.06, 14371.47)
No treatment	++	416.55	(19.69, 11884.62)
Attention placebo + TAU		2.98	(0.37, 24.43)
TAU	F + - + 1	2.44	(0.56, 11.42)
Enhanced TAU		2.13	(0.41, 11.91)
Exercise	····	18.14	(0.91, 409.12)
Exercise + TAU	+	19.03	(1.18, 372.78)
Yoga + TAU		17.06	(0.89, 378.8)
Any TCA	F	4.33	(2, 10.69)
Amitriptyline	H + 4	3.98	(2.6, 6.12)
Imipramine	F+++	4.22	(2.83, 6.37)
Lofepramine	<u>⊢ → = 4</u>	4.34	(2.22, 9.27)
Citalopram	+ +	2.02	(1.13, 3.38)
Escitalopram	H + 1	2.54	(1.58, 4.24)
Fluoxetine	++-1	2.4	(1.61, 3.63)
Sertraline	+ + +	2.09	(1.19, 3.47)
Any AD	►	6.38	(0.4, 106.91)
Mirtazapine	<u></u>	3.39	(1.55, 7.46)
Short-term psychodynamic psychotherapy individual + TAU	FF	8.47	(0.71, 108.09)
Cognitive bibliotherapy with support + TAU		5.64	(0.59, 52.98)
Cognitive bibliotherapy + TAU	F	2.4 2.59	(0.41, 15.12)
Computerised-CBT (CCBT) Computerised-CBT (CCBT) + TAU	F	2.38	(0.44, 16.3) (0.39, 14.76)
Computerised-CBT (CCBT) + TAD Computerised-CBT (CCBT) + enhanced TAU		2.39	(0.35, 14.76)
Interpersonal psychotherapy (IPT)		12.17	(0.47, 338.66)
Counselling (any type)		6.22	(0.71, 56,94)
Non-directive counselling		6.22	(0.87, 46.67)
Problem solving group		144/2.42	
Behavioural activation (BA)	<b>_</b>	12.38	(2.05, 77.63)
Behavioural activation (BA) + TAU		11.53	(1.76, 80.24)
CBT individual (under 15 sessions)		8.46	(2.17, 33.68)
CBT individual (under 15 sessions) + TAU		8.15	(1.84, 36.53)
CBT individual (under 15 sessions) + enhanced TAU		9.84	(2.24, 45.51)
CBT individual (over 15 sessions)		9.07	(2.36, 35.73)
Third-wave cognitive therapy individual		10.06	(2.29, 48.23)
CBT group (under 15 sessions)		3789.54	(377.66, 38177.44)
Third-wave cognitive therapy group		3710.79	(328.32, 41772.77)
CBT individual (under 15 sessions) + escitalopram		4.67	(1.06, 21.43)
CBT individual (over 15 sessions) + amitriptyline		4.85	(1, 24.93)
CBT individual (over 15 sessions) + any SSRI		4.95	(1.03, 25.58)
Interpersonal psychotherapy (IPT) + any AD		20.7	(0.78, 588.16)
Short-term psychodynamic psychotherapy individual + any TCA	F F I	6.01	(0.86, 43.6)
Interpersonal psychotherapy (IPT) + Pill placebo		14.78	(0.57, 418.22)
0.02	0.51 2 20 50		
	odds ratio		

3

## Figure 17: OR of response in completers of each intervention compared to Pill Placebo from the bias adjusted and unadjusted models – more severe depression.

🔲 unadjusted 🗢 blas adjusted			
Response (completers)			
Intervention (vs Pill Placebo)		odds ratio	95%Crl
Waitlist	F.*	416.13	(17.06, 14371.47)
No treatment	E E E E E E E E E E E E E E E E E E E	416.55	(19.69, 11884.62)
Attention placebo + TAU	F	2.98	(0.37, 24.43)
TAU	F	2.44	(0.56, 11.42)
Enhanced TAU	F1	2.13	(0.41, 11.91)
Exercise	► <b>-</b>	18.14	(0.91, 409.12)
Exercise + TAU	·	19.03	(1.18, 372.78)
Yoga + TAU	····	17.06	(0.89, 378.8)
Any TCA		4.33	(2, 10.69)
Amitriptyline	He H	3.98	(2.6, 6.12)
Imipramine	H • +	4.22	(2.83, 6.37)
Lofepramine	<b>H</b>	4.34	(2.22, 9.27)
Citalopram	H • -	2.02	(1.13, 3.38)
Escitalopram	H . H	2.54	(1.58, 4.24)
Fluoxetine	H.	2.4	(1.61, 3.63)
Sertraline	F • 1	2.09	(1.19, 3.47)
Any AD	·····	6.38	(0.4, 106.91)
Mirtazapine		3.39	(1.55, 7.46)
Short-term psychodynamic psychotherapy individual + TAU	F	8.47	(0.71, 108.09)
Cognitive bibliotherapy with support + TAU	·····	5.64	(0.59, 52.98)
Cognitive bibliotherapy + TAU	F	2.4	(0.41, 15.12)
Computerised-CBT (CCBT)	F	2.59	(0.44, 16.3)
Computerised-CBT (CCBT) + TAU	F	2.38	(0.39, 14.76)
Computerised-CBT (CCBT) + enhanced TAU	F	2.39	(0.41, 14.5)
Interpersonal psychotherapy (IPT)	·	12.17	(0.47, 338.66)
Counselling (any type)		6.22	(0.71, 56.94)
Non-directive counselling		6.27	(0.87, 46.67)
Problem solving group	:	-14472.42	(377.28, 814231.5)
Behavioural activation (BA)		12.38	(2.05, 77.63)
Behavioural activation (BA) + TAU	·	11.53	(1.76, 80.24)
CBT individual (under 15 sessions)	F	8.46	(2.17, 33.68)
CBT individual (under 15 sessions) + TAU	F	8.15	(1.84, 36.53)
CBT individual (under 15 sessions) + enhanced TAU	F	9.84	(2.24, 45.51)
CBT individual (over 15 sessions)	F	9.07	(2.36, 35.73)
Third-wave cognitive therapy individual	F	10.06	(2.29, 48.23)
CBT group (under 15 sessions)	-	3789.54	(377.66, 38177.44)
Third-wave cognitive therapy group	:	-3710.79	(328.32, 41772.77)
CBT individual (under 15 sessions) + escitalopram	H	4.67	(1.06, 21.43)
CBT individual (over 15 sessions) + amitriptyline	F 01	4.85	(1, 24.93)
CBT individual (over 15 sessions) + any SSRI	I	4.95	(1.03, 25.58)
Interpersonal psychotherapy (IPT) + any AD	·•-•	20.7	(0.78, 588.16)
Short-term psychodynamic psychotherapy individual + any TC	A +	6.01	(0.86, 43.6)
Interpersonal psychotherapy (IPT) + Pill placebo	·	14.78	(0.57, 418.22)
	0.02 0.51 2 20 50	0	
	odds ratio		

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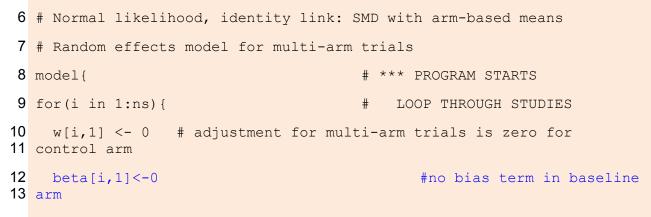
### Figure 18: OR of response in completers of each class compared to Pill Placebo from the bias adjusted and unadjusted models – more severe depression.

Response (completers) Intervention (vs Pill Placebo)		odds ratio	o 95%Crl
Waitlist	-+	416.13	(17.06, 14371.47)
No treatment	++	416.55	(19.69, 11884.62)
Attention placebo + TAU	F	2.98	(0.37, 24.43)
TAU	F 1	2.44	(0.56, 11.42)
Enhanced TAU		2.13	(0.41, 11.91)
Exercise	F	18.14	(0.91, 409.12)
Exercise + TAU	+	19.03	(1.18, 372.78)
Yoga + TAU	+	17.06	(0.89, 378.8)
Any TCA	F	4.33	(2, 10.69)
Amitriptyline	H + +	3.98	(2.6, 6.12)
Imipramine	<b>H</b> +++	4.22	(2.83, 6.37)
Lofepramine	F → - 4	4.34	(2.22, 9.27)
Citalopram	- + -	2.02	(1.13, 3.38)
Escitalopram		2.54	(1.58, 4.24)
Fluoxetine		2.4	(1.61, 3.63)
Sertraline	+++	2.09	(1.19, 3.47)
Any AD	►- <u></u> →	6.38	(0.4, 106.91)
Mirtazapine	<u>+ -+</u>	3.39	(1.55, 7.46)
Short-term psychodynamic psychotherapy individual + TAU		8.47	(0.71, 108.09)
Cognitive bibliotherapy with support + TAU	<u></u>	5.64	(0.59, 52.98)
Cognitive bibliotherapy + TAU	+	2.4	(0.41, 15.12)
Computerised-CBT (CCBT)	F	2.59	(0.44, 16.3)
Computerised-CBT (CCBT) + TAU	F	2.38 2.39	(0.39, 14.76)
Computerised-CBT (CCBT) + enhanced TAU Interpersonal psychotherapy (IPT)	F-+	12.35	(0.41, 14.5)
Counselling (any type)		6.22	(0.47, 338.66)
Non-directive counselling		6.22	(0.71, 56.94) (0.87, 46.67)
Problem solving group	F		(377.28, 814231.5
Behavioural activation (BA)		12.38	(2.05, 77.63)
Behavioural activation (BA) + TAU		11.53	(1.76, 80.24)
CBT individual (under 15 sessions)		8.46	(2.17, 33.68)
CBT individual (under 15 sessions) + TAU		8.15	(1.84, 36.53)
CBT individual (under 15 sessions) + enhanced TAU		9.84	(2.24, 45.51)
CBT individual (over 15 sessions)		9.07	(2.36, 35.73)
Third-wave cognitive therapy individual		10.06	(2.29, 48.23)
CBT aroup (under 15 sessions)		3789.54	(377.66, 38177.44
Third-wave cognitive therapy group		3710.79	(328.32, 41772.77
CBT individual (under 15 sessions) + escitalopram		4.67	(1.06, 21.43)
CBT individual (over 15 sessions) + amitriptyline		4.85	(1, 24.93)
CBT individual (over 15 sessions) + any SSRI		4.95	(1.03, 25.58)
Interpersonal psychotherapy (IPT) + any AD		20.7	(0.78, 588.16)
Short-term psychodynamic psychotherapy individual + any TCA	F F 1	6.01	(0.86, 43.6)
Interpersonal psychotherapy (IPT) + Pill placebo		14.78	(0.57, 418.22)
			,
0.02	0.51 2 20 50	)	
	odds ratio		

3

### 2.84 Appendix 6: Sample WinBugs code

### 2.8.15 Sample WinBugs code - SMD bias analysis



31

```
1
                                                 #no variance term in
         V[i,1]<-0
 2 baseline arm
 3
                                               # treatment effect is zero
         delta[i,1] <- 0
 4 for control arm
 5
   mu[i] ~ dnorm(0,.0001)
                                         # vague priors for all trial
 6 baselines
 7 }
8 # (1) CFB DATA
9 for(i in 1:nsCFB) {
10
    # calculate pooled.sd and adjustment for SMD
11
     df[i] <- sum(nCFB[i,1:naCFB[i]]) - naCFB[i] # denominator for
12 pooled.var
13
     Pooled.var[i] <- sum(nvar[i,1:naCFB[i]])/df[i]</pre>
14
        # pooled sd for study i, for SMD
15
     Pooled.sd[i] <- sqrt(Pooled.var[i])</pre>
16 # H[i] <- 1 - 3/(4*df[i]-1) # use Hedges' g
17
     H[i] <- 1
                                         # use Cohen's d (ie no
18 adjustment)
19
     for (k in 1:naCFB[i]) {
20
       se[i,k] <- sdCFB[i,k]/sqrt(nCFB[i,k])</pre>
21
       var[i,k] <- pow(se[i,k],2)</pre>
                                         # calcultate variances
22
       prec[i,k] <- 1/var[i,k]</pre>
                                         # set precisions
23
       y[i,k] ~ dnorm(phi[i,k], prec[i,k]) # normal likelihood
24
       phi[i,k] <- theta[i,k] * (Pooled.sd[i]/H[i]) # theta is stand</pre>
25 mean
26 # model for linear predictor, delta is SMD
27
       theta[i,k] <- mu[i] + delta[i,k] + (beta[i,k]*V[i,k])</pre>
28
       dev[i,k] <- (y[i,k]-phi[i,k])*(y[i,k]-phi[i,k])*prec[i,k]</pre>
29
       nvar[i,k] <- (nCFB[i,k]-1) * pow(sdCFB[i,k],2) # for pooled.sd</pre>
30
      }
31
     # summed residual deviance contribution for this trial
32
     resdev[i] <- sum(dev[i,1:naCFB[i]])</pre>
33
    }
34 # (2) BASELINE + FOLLOW-UP DATA (no CFB)
35 for(i in 1:nsBF) {
                                           # LOOP THROUGH STUDIES
36
   # calculate pooled.sd and adjustment for SMD
```

32

```
1
    df[i+nsCFB] <- sum(n[i,1:na[i]]) - na[i] # denominator for
2 pooled.var
3
     Pooled.var[i+nsCFB] <- sum(nvarBF[i,1:na[i]])/df[i+nsCFB]</pre>
4
         # pooled sd for study i, for SMD
5
     Pooled.sd[i+nsCFB] <- sqrt(Pooled.var[i+nsCFB])</pre>
6 # H[i] <- 1 - 3/(4*df[i]-1)
                                            # use Hedges' g
7
     H[i+nsCFB] <- 1
                                           # use Cohen's d (ie no
8 adjustment)
9
     for (k in 1:na[i]) {
10
       yBF[i,k] <- yF[i,k] - yB[i,k] # calculate mean CFB</pre>
11
       seF[i,k] <- sdF[i,k]/sqrt(n[i,k]) # se at followup</pre>
12
       seB[i,k] <- sdB[i,k]/sqrt(n[i,k]) # se at baseline</pre>
13
       # variance of mean CFB, assuming correlation corr[i]
14
       var[i+nsCFB,k] <- pow(seF[i,k],2)+ pow(seB[i,k],2)</pre>
15 -2*(seF[i,k]*seB[i,k]*corr[i])
16
       prec[i+nsCFB,k] <- 1/var[i+nsCFB,k] # set CFB precisions</pre>
17
       yBF[i,k] ~ dnorm(phi[i+nsCFB,k], prec[i+nsCFB,k]) # normal
18 likelihood
19
       # theta is standardised mean
20
       phi[i+nsCFB,k] <- theta[i+nsCFB,k] *</pre>
21 (Pooled.sd[i+nsCFB]/H[i+nsCFB])
22
       # model for linear predictor, delta is SMD
23
       theta[i+nsCFB,k] <- mu[i+nsCFB] + delta[i+nsCFB,k]</pre>
24 + (beta[i+nsCFB,k]*V[i+nsCFB,k])
25
       # residual deviance contribution
       dev[i+nsCFB,k] <- (yBF[i,k]-phi[i+nsCFB,k]) * (yBF[i,k]-</pre>
26
27 phi[i+nsCFB,k])
                                                 * prec[i+nsCFB,k]
28
       # variance of CFB, assuming correlation corrBF[i] (var is sd
29 squared)
30
       varBF[i,k] \le pow(sdF[i,k],2) + pow(sdB[i,k],2)
31 - 2*(sdF[i,k]*sdB[i,k]*corr[i])
32
       nvarBF[i,k] <- (n[i,k]-1) * varBF[i,k] # for pooled.sd</pre>
33
      }
34
     # summed residual deviance contribution for this trial
35
     resdev[i+nsCFB] <- sum(dev[i+nsCFB,1:na[i]])</pre>
36
    }
37 # (3) RESPONSE DATA (no CFB or BL+follow-up)
```

33

```
1 for(i in 1:nsR) {
                                          #
                                              LOOP THROUGH STUDIES
 2
    # calculate pooled.sd and adjustment for SMD
 3
     df[i+nsCFB+nsBF] <- sum(nR[i,1:naR[i]]) - naR[i] # denominator for
 4 pooled.var
 5
     Pooled.var[i+nsCFB+nsBF] <-</pre>
 6 sum(nvarR[i,1:naR[i]])/df[i+nsCFB+nsBF]
 7
         # pooled sd for study i, for SMD
 8
     Pooled.sd[i+nsCFB+nsBF] <- sqrt(Pooled.var[i+nsCFB+nsBF])</pre>
9 # H[i] <- 1 - 3/(4*df[i]-1)
                                         # use Hedges' g
10
     H[i+nsCFB+nsBF] <- 1
                                         # use Cohen's d (ie no
11 adjustment)
12
     for (k in 1:naR[i]) {
13
       r[i,k] ~ dbin(R[i,k], nR[i,k]) # binomial likelihood
14
       R[i,k] <- phi.adj[i,k]</pre>
15
       x[i,k] <- -(q[i]*yBR[i,k]+ phi[i+nsCFB+nsBF,k])/(sdBR[i,k] *</pre>
16 sqrt(1+(1-q[i])*(1-q[i]-2*corrR[i])))
17
       # adjust link function phi(x) for extreme values that can give
18 numerical
19
       # errors when x < -5, phi(x)=0, when x > 5, phi(x)=1
20
       phi.adj[i,k] <- (step(5+x[i,k]) * step(x[i,k]-5)</pre>
21
              + step(5-x[i,k])* step(x[i,k]+5) * phi(x[i,k]))*(1-
22 equals(x[i,k],5))
23
              + equals(x[i,k],5) # correct for x=5
24
       # theta is standardised mean
25
       phi[i+nsCFB+nsBF,k] <- theta[i+nsCFB+nsBF,k]</pre>
26
                     * (Pooled.sd[i+nsCFB+nsBF]/H[i+nsCFB+nsBF])
27
       # model for linear predictor, delta is SMD
28
       theta[i+nsCFB+nsBF,k] <- mu[i+nsCFB+nsBF] +</pre>
29 delta[i+nsCFB+nsBF,k] + (beta[i+nsCFB+nsBF,k] *V[i+nsCFB+nsBF,k])
30
       # residual deviance contribution
31
       rhat[i,k] <- R[i,k] * nR[i,k]
32
       dev[i+nsCFB+nsBF,k] <- 2 * (r[i,k] * (log(r[i,k])-</pre>
33 log(rhat[i,k]))
34
            + (nR[i,k]-r[i,k]) * (log(nR[i,k]-r[i,k]) - log(nR[i,k]-
35 rhat[i,k])))
36 # Sensitivity analysis
37 #
        sdR[i,k] <- 4.24 + sdBR[i,k] * 0.73 # sd for response</pre>
```

34

```
1
       sdR[i,k] <- sdBR[i,k]</pre>
                                         # sd for response
 2
       nvarR[i,k] <- (nR[i,k]-1) * pow(sdR[i,k],2) # for pooled.sd</pre>
 3
      }
 4
     # summed residual deviance contribution for this trial
 5
     resdev[i+nsCFB+nsBF] <- sum(dev[i+nsCFB+nsBF,1:naR[i]])</pre>
 6
    }
7 #
8 # RE MODEL (CFB data)
9 for(i in 1:nsCFB) {
                                            # LOOP THROUGH STUDIES WITH
10 CFB DATA
11
     for (k in 2:naCFB[i]) {
                                            # LOOP THROUGH ARMS
12
       # model for bias parameter beta
13
       beta[i,k] ~ dnorm(mb[i,k], Pkappa)
14
       mb[i,k] <- A[CCFB[i,k]]</pre>
15
       V[i,k] <- (var[i,k]+var[i,1])/Pooled.var[i]</pre>
16
       # trial-specific RE distributions
17
       delta[i,k] ~ dnorm(md[i,k], taud[i,k])
18
       md[i,k] <- d[tCFB[i,k]] - d[tCFB[i,1]] + sw[i,k]</pre>
19
       # precision of RE distributions (with multi-arm trial
20 correction)
21
       taud[i,k] <- tau *2*(k-1)/k
22
       #adjustment, multi-arm RCTs
23
       w[i,k] <- delta[i,k] - d[tCFB[i,k]] + d[tCFB[i,1]]</pre>
24
       # cumulative adjustment for multi-arm trials
25
       sw[i,k] <-sum(w[i,1:k-1])/(k-1)</pre>
26
      }
27
    }
28 # RE MODEL (BL and F-up data)
29 for(i in 1:nsBF) {
                                            # LOOP THROUGH STUDIES WITH
30 BL+FUP DATA
31
     for (k in 2:na[i]) {
                                            # LOOP THROUGH ARMS
32
       # model for bias parameter beta
33
       beta[i+nsCFB,k] ~ dnorm(mb[i+nsCFB,k], Pkappa)
34
       mb[i+nsCFB,k] <- A[CBF[i,k]]</pre>
```

```
1
       V[i+nsCFB,k] <-</pre>
2 (var[i+nsCFB,k]+var[i+nsCFB,1])/Pooled.var[i+nsCFB]
3
       # trial-specific RE distributions
4
       delta[i+nsCFB,k] ~ dnorm(md[i+nsCFB,k], taud[i+nsCFB,k])
5
       md[i+nsCFB,k] <- d[t[i,k]] - d[t[i,1]] + sw[i+nsCFB,k]</pre>
6
       # precision of RE distributions (with multi-arm trial
7 correction)
8
       taud[i+nsCFB,k] <- tau *2*(k-1)/k</pre>
9
       #adjustment, multi-arm RCTs
10
       w[i+nsCFB,k] <- delta[i+nsCFB,k] - d[t[i,k]] + d[t[i,1]]
11
       # cumulative adjustment for multi-arm trials
12
       sw[i+nsCFB,k] <-sum(w[i+nsCFB,1:k-1])/(k-1)</pre>
13
      }
14
    }
15 # RE MODEL (Response data)
16 for(i in 1:nsR) {
                                      # LOOP THROUGH STUDIES WITH
17 RESPONSE DATA
18
     for (k in 2:naR[i]) {
                                      # LOOP THROUGH ARMS
19
        # model for bias parameter beta
20
       beta[i+nsCFB+nsBF,k] ~ dnorm(mb[i+nsCFB+nsBF,k], Pkappa)
21
       mb[i+nsCFB+nsBF,k] <- A[C[i,k]]</pre>
22
       #
23
       # calculate variance of log odds ratio for comparisons with arm
24 1
25
       # check for zero or 100% events in arm k
26
       aux.a[i,k] <- equals(r[i,k],0)+equals(r[i,k],nR[i,k])</pre>
27
       # check for zero or 100% events in arm 1
28
       aux.b[i,k] <- equals(r[i,1],0)+equals(r[i,1],nR[i,1])</pre>
29
       aux[i,k] <- max(aux.a[i,k],aux.b[i,k]) # any zero or 100%</pre>
30 events?
31
       # add 0.5 if zero or 100% events
32
       VLOR[i,k] <- 1/(r[i,k]+(0.5*aux[i,k])) +</pre>
33 1/(r[i,1]+(0.5*aux[i,k]))
                                                            + 1/(nR[i,k]-
34 r[i,k]+(0.5*aux[i,k]))
35 + 1/(nR[i,1]-r[i,1]+(0.5*aux[i,k]))
36
       V[i+nsCFB+nsBF,k] <- 0.30396 * VLOR[i,k] # convert to var of</pre>
37 SMD
```

36

```
1
       # trial-specific RE distributions
 2
       delta[i+nsCFB+nsBF,k] ~ dnorm(md[i+nsCFB+nsBF,k],
 3 taud[i+nsCFB+nsBF,k])
 4
       md[i+nsCFB+nsBF,k] <- d[tR[i,k]] - d[tR[i,1]] +</pre>
 5 sw[i+nsCFB+nsBF,k]
6
       # precision of RE distributions (with multi-arm trial
 7 correction)
8
       taud[i+nsCFB+nsBF,k] <- tau *2*(k-1)/k</pre>
9
       #adjustment, multi-arm RCTs
10
       w[i+nsCFB+nsBF,k] <- delta[i+nsCFB+nsBF,k] - d[tR[i,k]] +
11 d[tR[i,1]]
12
       # cumulative adjustment for multi-arm trials
13
       sw[i+nsCFB+nsBF,k] <-sum(w[i+nsCFB+nsBF,1:k-1])/(k-1)</pre>
14
    }
15
    }
16 #
17 totresdev <- sum(resdev[])
                                            # Total Residual Deviance
18 (all data)
19 # Partial Residual Deviance
20 totresdev.p[1] <- sum(resdev[1:nsCFB])</pre>
                                                                  # CFB
21 data
22 totresdev.p[2] <- sum(resdev[nsCFB+1:nsCFB+nsBF])</pre>
                                                                 # BL +
23 Fup data
24 totresdev.p[3] <- sum(resdev[nsCFB+nsBF+1:nsCFB+nsBF+nsR]) #</pre>
25 Response data
26 #
27 # Priors and model assumptions (classes)
28 d[1] <- 0
                               # treatment effect is zero for reference
29 treatment
30
31
         # vague prior for treatment effects (mirtazapine)
32
        d[18] ~ dnorm(0, .0001)
33
34
         # treatments borrowing variance
35
         # Variance from 'No treatment'
36
         for(k in 4:7) { d[k] ~ dnorm(m[D[k]], prec2[2]) }
37
         # Variance from 'Self-help with support'
```

37

```
1
        for(k in 8:9) { d[k] ~ dnorm(m[D[k]], prec2[11]) }
 2
        # Any AD, variance from SSRIs & TCAS
 3
        d[17] ~ dnorm(m[D[17]], prec2[8])  #prec2[8]=precision of
 4
  any AD class
 5
        z <- (1/prec2[7]) + (1/prec2[6]) # sum of SSRI & TCA variances
        prec2[8] <- 1/z
 6
 7
        # Variance from Counselling
 8
        d[19] ~ dnorm(m[D[19]], prec2[14])
 9
        # Variance from CBT/CT
10
        d[27] ~ dnorm(m[D[27]], prec2[16])
11
        for(k in 31:32) { d[k] ~ dnorm(m[D[k]], prec2[16]) }
12
        # Variance from Combined (CBT/CT + AD)
13
        d[40] ~ dnorm(m[D[40]], prec2[17])
14
15
        # treatment effects from Class
16
        # No treatment
17
        for (k in 2:3) { d[k] ~ dnorm(m[D[k]], prec2[D[k]]) }
18
        # TCA, SSRI
19
        for(k in 10:16) { d[k] ~ dnorm(m[D[k]], prec2[D[k]]) }
20
        # Self-help with support, Self-help
21
        for(k in 20:26) { d[k] ~ dnorm(m[D[k]], prec2[D[k]]) }
22
        # Counselling
23
        for(k in 28:30) { d[k] ~ dnorm(m[D[k]], prec2[D[k]]) }
24
        # CBT/CT, Combined (CBT/CT + AD)
25
        for(k in 33:39){ d[k] ~ dnorm(m[D[k]], prec2[D[k]]) }
26
27 #
28 m[1] <- 0
29 #treatments not belonging to a class
30 m[9] < - d[18]
                          #mirtazapine
31
32 # priors for mean class effect
33 for (k in 2:8) { m[k] ~ dnorm(0, .0001) }
34 for (k in 10:nc) { m[k] ~ dnorm(0, .0001) }
```

38

```
1 # priors for within-class variability
 2
        for (k in 2:7) {
 3
        sd2[k] ~ dnorm(0,tau2)I(0,) # prior for class variance
 4
         prec2[k] <- pow(sd2[k], -1)</pre>
 5
        }
 6
        for (k in 9:nc) {
 7
        sd2[k] ~ dnorm(0,tau2)I(0,) # prior for class variance
 8
        prec2[k] <- pow(sd2[k], -1)</pre>
9
        }
10
11 tau2 <- pow(0.19, -2)
                                        # informative prior precision
12 #
13 sdev ~ dunif(0, 5)
                                         # vague prior for between-trial
14 SD
15 tau <- pow(sdev, -2)
                                          # between-trial precision
16
17 #
18 # mean bias: assumptions
19 A[1] <- 0
                    # control v control
20 A[2] <- b
                         # control v Active
21 A[3] <- 0
                         # Active v Active
22 # bias model prior for variance
23 kappa ~ dunif(0,50)
24 kappa.sq <- pow(kappa,2)</pre>
25 Pkappa <- 1/kappa.sq</pre>
26 # bias model prior for mean
27 b ~ dnorm(0,.0001)
28
29 # all pairwise differences
30 for (c in 1:(nt-1)) { for (k in (c+1):nt) { diff[c,k] <- d[k] -
31 d[c] } }
32 # pairwise SMDs for all possible class comparisons
33 for (c in 1: (nt-1)) {
34
    for (k in (c+1):nc) { diffClass[c,k] <- (m[k]-m[c]) }</pre>
```

```
1 }
    2 #
    3 for (k in 1:nt) {
        rk[k] <- rank(d[],k)  # lower values are "good"</pre>
    4
    5
        best[k] <- equals(rk[k],1) # Smallest is best (i.e. rank 1)</pre>
    6
        # prob treat k is h-th best, prob[1,k]=best[k]
    7
      for (h in 1:nt) { prob[h,k] <- equals(rk[k],h)  }
    8
      }
    9 #
   10 # rank classes
   11 for (k in 1:nc) {
   12
       rkClass[k] <- rank(m[],k)  # lower values are "good"</pre>
   13
       bestClass[k] <- equals(rkClass[k],1) # Smallest is best (i.e. rank</pre>
   14 1)
       # prob class k is h-th best, prob[1,k]=best[k]
   15
   16
       for (h in 1:nc) { probClass[h,k] <- equals(rkClass[k],h) }</pre>
   17 }
   18 }
                                        # *** PROGRAM ENDS
2.8.29 Sample WinBugs code - Response bias analysis
   20 # Random effects model for multi-arm trials
   21 model {
                                          # *** PROGRAM STARTS
   22 for(i in 1:ns) {
                                          # LOOP THROUGH ALL STUDIES
   23
      w[i,1] <- 0 # adjustment for multi-arm trials is zero for</pre>
   24 control arm
   25
      beta[i,1] <- 0
                                          # no bias term in baseline arm
   26
      V[i,1] <- 0
                                          # no variance term in baseline
   27 arm
   28
        # RESPONSE DATA
   29
       delta[i,1] <- 0
                                        # treatment effect is zero for
   30 control arm
       mu[i] ~ dnorm(0,.0001)
   31
                                        # vague priors for all trial
   32 baselines
   33
      # CONTINUOUS DATA
   34
      deltaX[i,1] <- 0
                                     # treatment effect is zero for
   35 control arm
```

```
Update 2018
```

```
1 muX[i] ~ dnorm(0,.0001)
                                # vague priors for all trial
 2 baselines
 3
   }
 4 #
 5 # RESPONSE DATA
                                 # LOOP THROUGH STUDIES WITH RESPONSE
 6 for(i in 1:nsR){
 7 DATA
 8
   r[i,k] ~ dbin(p[i,k],nR[i,k]) # binomial likelihood
 9
10
   # model for linear predictor
11
      logit(p[i,k]) <- mu[i] + delta[i,k] + beta[i,k] * V[i,k]# model</pre>
12 for linear predictor
13
      rhat[i,k] <- p[i,k] * nR[i,k] # expected value of the</pre>
14 numerators
15
      #Deviance contribution
16
      dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k]))</pre>
17
            + (nR[i,k]-r[i,k]) * (log(nR[i,k]-r[i,k]) - log(nR[i,k]-
18 rhat[i,k])))
19
     }
20
     # Summed residual deviance contribution for this trial
21
    resdev[i] <- sum(dev[i,1:naR[i]])</pre>
22
    }
23 #
24 # (1) CFB DATA
25 for(i in 1:nsCFB) {
                                    # LOOP THROUGH STUDIES WITH CFB
26 DATA
27
    # calculate pooled.sd and adjustment for SMD
28
    df[i] <- sum(nCFB[i,1:naCFB[i]]) - naCFB[i] # denominator for
29 pooled.var
30
    Pooled.var[i] <- sum(nvar[i,1:naCFB[i]])/df[i]</pre>
31
    Pooled.sd[i] <- sqrt(Pooled.var[i]) # pooled sd for study i, for</pre>
32 SMD
33
   # H[i] <- 1 - 3/(4*df[i]-1)
                                    # use Hedges' g
34
    H[i] <- 1
                                     # use Cohen's d (ie no
35 adjustment)
36
   for (k in 1:naCFB[i]){
                                    # LOOP THROUGH ARMS
```

Update 2018

41

```
1
       se[i,k] <- sdCFB[i,k]/sqrt(nCFB[i,k]) # calculate st error of</pre>
 2 CFB
 3
       var[i,k] <- pow(se[i,k],2)</pre>
                                        # calcultate variances of CFB
 4
       prec[i,k] <- 1/var[i,k]</pre>
                                       # set precisions of CFB
 5
       y[i,k] ~ dnorm(phi[i,k], prec[i,k]) # normal likelihood
 6
       phi[i,k] <- theta[i,k] * (Pooled.sd[i]/H[i]) # theta is stand</pre>
7 mean
 8
       # model for linear predictor, deltaX is SMD
       theta[i,k] <- muX[i] + deltaX[i,k]</pre>
9
10
       dev[i+nsR,k] <- (y[i,k]-phi[i,k])*(y[i,k]-phi[i,k])*prec[i,k]</pre>
11
       nvar[i,k] <- (nCFB[i,k]-1) * pow(sdCFB[i,k],2) # for pooled.sd</pre>
12
      }
     # summed residual deviance contribution for this trial
13
14
     resdev[i+nsR] <- sum(dev[i+nsR,1:naCFB[i]])</pre>
15
    }
16 # (2) BASELINE + FOLLOW-UP DATA (no CFB)
17 for(i in 1:nsBF) {
                                      # LOOP THROUGH STUDIES WITH BL + F-
18 UP DATA
19
     # calculate pooled.sd and adjustment for SMD
20
     df[i+nsCFB] <- sum(n[i,1:na[i]]) - na[i] # denominator for
21 pooled.var
22
     Pooled.var[i+nsCFB] <- sum(nvarBF[i,1:na[i]])/df[i+nsCFB]</pre>
23
     Pooled.sd[i+nsCFB] <- sqrt(Pooled.var[i+nsCFB])# pooled sd for</pre>
24 study i,for SMD  # H[i+nsCFB] <- 1 - 3/(4*df[i]-1) # use Hedges' g
25
     H[i+nsCFB] <- 1
                                          # use Cohen's d (ie no
26 adjustment)
27
                                          # LOOP THROUGH ARMS
     for (k in 1:na[i]) {
28
       yBF[i,k] <- yF[i,k] - yB[i,k] # calculate mean CFB</pre>
29
       seF[i,k] <- sdF[i,k]/sqrt(n[i,k]) # se at followup</pre>
30
       seB[i,k] <- sdB[i,k]/sqrt(n[i,k]) # se at baseline</pre>
31
       # variance of mean CFB, assuming correlation corr[i]
32
       var[i+nsCFB,k] <- pow(seF[i,k],2)+ pow(seB[i,k],2)</pre>
33 -2*(seF[i,k]*seB[i,k]*corrBF[i])
34
       prec[i+nsCFB,k] <- 1/var[i+nsCFB,k] # set CFB precisions</pre>
35
       yBF[i,k] ~ dnorm(phi[i+nsCFB,k], prec[i+nsCFB,k]) # normal
36 likelihood
37 # theta is standardised mean
```

```
Update 2018
```

```
1
       phi[i+nsCFB,k] <- theta[i+nsCFB,k] *</pre>
2 (Pooled.sd[i+nsCFB]/H[i+nsCFB])
3
       # model for linear predictor, deltaX is SMD
4
       theta[i+nsCFB,k] <- muX[i+nsCFB] + deltaX[i+nsCFB,k]</pre>
5
       # residual deviance contribution
6
       dev[i+nsR+nsCFB,k] <- (yBF[i,k]-phi[i+nsCFB,k]) * (yBF[i,k]-</pre>
7 phi[i+nsCFB,k])
                                                * prec[i+nsCFB,k]
8
       # variance of CFB, assuming correlation corrBF[i] (var is sd
9 squared)
10
       varBF[i,k] \le pow(sdF[i,k],2) + pow(sdB[i,k],2)
11
                    - 2*(sdF[i,k]*sdB[i,k]*corrBF[i])
12
       nvarBF[i,k] <- (n[i,k]-1) * varBF[i,k] # for pooled.sd</pre>
13
      }
14
     # summed residual deviance contribution for this trial
15
     resdev[i+nsR+nsCFB] <- sum(dev[i+nsR+nsCFB,1:na[i]])</pre>
16
    }
17 #
18 # RE MODEL (Response data)
19 for(i in 1:nsR) {
                                     # LOOP THROUGH STUDIES WITH RESPONSE
20 DATA
21
     for (k in 2:naR[i]) {
                                     # LOOP THROUGH ARMS
22
    # calculate variance of log odds ratio for comparisons with arm 1
23
       # check for zero or 100% events in arm k
24
       aux.a[i,k] <- equals(r[i,k],0)+equals(r[i,k],nR[i,k])</pre>
25
       # check for zero or 100% events in arm 1
26
       aux.b[i,k] <- equals(r[i,1],0)+equals(r[i,1],nR[i,1])</pre>
27
       aux[i,k] <- max(aux.a[i,k],aux.b[i,k]) # any zero or 100%</pre>
28 events?
29
       # add 0.5 if zero or 100% events
30
       V[i,k] < -1/(r[i,k]+(0.5*aux[i,k])) + 1/(r[i,1]+(0.5*aux[i,k]))
31 + 1/(nR[i,k]-r[i,k]+(0.5*aux[i,k]))
32 + 1/(nR[i,1]-r[i,1]+(0.5*aux[i,k]))
33
       # model for bias parameter beta
34
       beta[i,k] ~ dnorm(mb[i,k], Pkappa)
35
       mb[i,k] <- A[CR[i,k]]
36
       delta[i,k] ~ dnorm(md[i,k], taud[i,k]) # trial-specific LOR
37 distributions
```

43

```
1
       # mean of LOR distributions (with multi-arm trial correction)
2
       md[i,k] <- d[tR[i,k]] - d[tR[i,1]] + sw[i,k]</pre>
3
       # precision of LOR distributions (with multi-arm trial
4 correction)
5
       taud[i,k] <- tau *2*(k-1)/k
6
       # adjustment for multi-arm RCTs
7
       w[i,k] <- (delta[i,k] - d[tR[i,k]] + d[tR[i,1]])
8
       # cumulative adjustment for multi-arm trials
9
       sw[i,k] <- sum(w[i,1:k-1])/(k-1)</pre>
10
      }
11
    }
12 # RE MODEL (CFB data)
13 for(i in 1:nsCFB) {
                                        # LOOP THROUGH STUDIES WITH CFB
14 DATA
15
     for (k in 2:naCFB[i]) {
                                        # LOOP THROUGH ARMS
16
       # convert SMD to LOR
17
       deltaX[i,k] <-</pre>
   (delta[i+nsR,k]+beta[i+nsR,k]*V[i+nsR,k])*((sqrt(3))/-3.1416)
18
19
    # convert variance of SMD to variance of LOR for bias model
20
       VSMD[i,k] <- (var[i,k]+var[i,1])/Pooled.var[i]</pre>
21
       V[i+nsR,k] <- 3.2899 * VSMD[i,k]</pre>
22
       # model for bias parameter beta
23
       beta[i+nsR,k] ~ dnorm(mb[i+nsR,k], Pkappa)
24
       mb[i+nsR,k] <- A[CCFB[i,k]]</pre>
25
       # trial-specific RE distributions
26
       delta[i+nsR,k] ~ dnorm(md[i+nsR,k], taud[i+nsR,k])
27
       md[i+nsR,k] <- d[tCFB[i,k]] - d[tCFB[i,1]] + sw[i+nsR,k]
28
       # precision of RE distributions (with multi-arm trial
29 correction)
30
       taud[i+nsR,k] < - tau *2*(k-1)/k
31
       # adjustment, multi-arm RCTs
32
       w[i+nsR,k] <- delta[i+nsR,k] - d[tCFB[i,k]] + d[tCFB[i,1]]
33
       # cumulative adjustment for multi-arm trials
34
       sw[i+nsR,k] <-sum(w[i+nsR,1:k-1])/(k-1)</pre>
35
      }
```

```
1
  }
2 # RE MODEL (BL and F-up data)
3 for(i in 1:nsBF) {
                                        # LOOP THROUGH STUDIES WITH BL +
4 F-UP DATA
5
     for (k in 2:na[i]) {
                                        # LOOP THROUGH ARMS
6
       # convert SMD to LOR
7
       deltaX[i+nsCFB,k] <- (delta[i+nsR+nsCFB,k]+</pre>
8 beta[i+nsR+nsCFB,k]*V[i+nsR+nsCFB,k]) * ((sqrt(3))/-3.1416)
9
       # convert variance of SMD to variance of LOR for bias model
10
       VSMD[i+nsCFB,k] <-
11
   (var[i+nsCFB,k]+var[i+nsCFB,1])/Pooled.var[i+nsCFB]
       V[i+nsR+nsCFB,k] <- 3.2899 * VSMD[i+nsCFB,k]</pre>
12
13
       # model for bias parameter beta
14
       beta[i+nsR+nsCFB,k] ~ dnorm(mb[i+nsR+nsCFB,k], Pkappa)
       mb[i+nsR+nsCFB,k] <- A[C[i,k]]</pre>
15
16
       # trial-specific RE distributions
17
       delta[i+nsCFB+nsR,k] ~ dnorm(md[i+nsCFB+nsR,k],
18 taud[i+nsCFB+nsR,k])
19
       md[i+nsCFB+nsR,k] <- d[t[i,k]] - d[t[i,1]] + sw[i+nsCFB+nsR,k]</pre>
20
       # precision of RE distributions (with multi-arm trial
21 correction)
22
       taud[i+nsCFB+nsR,k] <- tau *2*(k-1)/k</pre>
23
       #adjustment, multi-arm RCTs
24
       w[i+nsCFB+nsR,k] <- delta[i+nsR+nsCFB,k] - d[t[i,k]] + d[t[i,1]]</pre>
25
       # cumulative adjustment for multi-arm trials
26
       sw[i+nsCFB+nsR,k] < -sum(w[i+nsCFB+nsR,1:k-1])/(k-1)
27
      }
28
    }
29 #
30 # Calculate residual deviance
31 totresdev <- sum(resdev[])</pre>
                                           # Total Residual Deviance (all
32 data)
33 totresdev.p[1] <- sum(resdev[1:nsR]) # Response data
34 totresdev.p[2] <- sum(resdev[nsR+1:nsR+nsCFB]) # CFB data
35 totresdev.p[3] <- sum(resdev[nsR+nsCFB+1:nsCFB+nsBF+nsR]) # BL + FL
36 data
```

```
1 d[1] <- 0
                                # treatment effect is zero for
2 reference treatment
3 m[1] < - 0
                                # treatment effect is zero for
4 reference class
5 #
6 # Priors and model assumptions (classes)
7 # treatment effects from Class
8 for (k in 2:3) { d[k] ~ dnorm(m[D[k]], prec2[D[k]]) }
9 for (k in 10:19) { d[k] ~ dnorm(m[D[k]], prec2[D[k]]) }
10 for (k in 24:39) { d[k] ~ dnorm(m[D[k]], prec2[D[k]]) }
11 for (k in 42:65) { d[k] ~ dnorm(m[D[k]], prec2[D[k]]) }
12
13 # variance from no treatment
14 for (k in 4:7) { d[k] ~ dnorm(m[D[k]], prec2[D[2]]) }
15 # variance from self-help with support
16 for (k in 8:9) { d[k] ~ dnorm(m[D[k]], prec2[D[11]]) }
17 # sum of variances from SSRI/TCAs
18 d[20] ~ dnorm(m[D[20]], prec2[8])
19 x <- (1/prec2[6]) + (1/prec2[7])
20 prec2[8] <- 1/x
21 # variance from counselling
22 for (k in 22:23) { d[k] ~ dnorm(m[D[k]], prec2[D[15]]) }
23 # variance from CBT/CT
24 for (k in 40:41) { d[k] ~ dnorm(m[D[k]], prec2[D[18]]) }
25 for (k in 72:73) { d[k] ~ dnorm(m[D[k]], prec2[D[18]]) }
26 # variance from CBT/CT + AD
27 for (k in 66:71) { d[k] ~ dnorm(m[D[k]], prec2[D[20]]) }
28 for (k in 74:75) { d[k] ~ dnorm(m[D[k]], prec2[D[20]]) }
29
30 # no class treatments [mirtazapine]
31 d[21] ~ dnorm(0, .0001) # vague prior for treatment effects
32 m[9] <- d[21]
                                  # class effect = treat effect
33
34 for (k in 2:8) { m[k] ~ dnorm(0, .0001) }
```

46

```
1 for (k in 10:nc) { m[k] ~ dnorm(0, .0001) }
 2 # priors for class precision
 3 \text{ tau2} < - \text{pow}(0.19, -2)
 4 for (k in 1:7) {
 5
   sd2[k] ~ dnorm(0,tau2)I(0,) # informative prior for within-class
 6 st dev
 7
   prec2[k] <- pow(sd2[k], -1) # within-class precision</pre>
 8
   }
9 for (k in 9:nc) {
10
   sd2[k] ~ dnorm(0,tau2)I(0,) # informative prior for within-class
11 st dev
12
   prec2[k] <- pow(sd2[k], -1) # within-class precision</pre>
13 }
14 #
15 sdev \sim dunif(0,5)
                                    # vague prior for between-trial SD
16 tau <- pow(sdev, -2)
                                    # between-trial precision
17 # mean bias: assumptions
18 A[1] <- 0
                         # control v control
19 A[2] <- b
                         # control v Active
20 A[3] <- 0
                         # Active v Active
21 # bias model prior for variance
22 kappa ~ dunif(0,5)
23 kappa.sq <- pow(kappa,2)</pre>
24 Pkappa <- 1/kappa.sq
25 # bias model prior for mean
26 b ~ dnorm(0,.0001)
27 # pairwise ORs and LORs for all possible pair-wise comparisons
28 for (c in 1: (nt-1)) {
29
    for (k in (c+1):nt) {
30
      or[c,k] <- exp(d[k] - d[c])
31
       lor[c,k] <- (d[k]-d[c])
32
      }
33
   }
34 #
```

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47

```
1 # pairwise differences for classes
    2 for (c in 1:(nc-1)) {
    3
       for (k in (c+1):nc) {
    4
          diffClass[c,k] <- m[k] - m[c]
    5
          orClass[c,k] <- exp(m[k] - m[c])</pre>
    6
         1
    7
       }
    8 #
    9 # rank treatments
   10 #
   11 for (k in 1:nt) {
   12
        rk[k] <- nt+1-rank(d[],k)  # assumes events are "good"</pre>
                                             # assumes events are "bad"
   13 # rk[k] <- rank(d[],k)
   14
        best[k] <- equals(rk[k],1) # Smallest is best (i.e. rank 1)</pre>
   15
        # prob treat k is h-th best, prob[1,k]=best[k]
   16
        for (h in 1:nt) { prob[h,k] <- equals(rk[k],h) }</pre>
   17
       }
   18 #
   19 # rank classes
   20 for (k in 1:nc) {
   21
        rkClass[k] <- nc+1-rank(m[],k)  # assumes events are "good"</pre>
   22
        bestClass[k] <- equals(rkClass[k],1) # Smallest is best (i.e. rank</pre>
   23 1)
   24
        # prob class k is h-th best, prob[1,k]=best[k]
   25
        for (h in 1:nc) { probClass[h,k] <- equals(rkClass[k],h) }</pre>
   26
      }
   27 }
                                             # *** PROGRAM ENDS
2.8.38 Sample WinBugs code - Discontinuation bias analysis
   29 # RE - random class effect model with bias adjustment for sample
   30 size
   31 # all active treatments same bias when compared to inactive
   32 controls:
   33 # TAU, Waitlist, Placebo, attention placebo, no treatment
   34 # active-active comparisons have zero mean bias (but shared
   35 variance)
```

48

```
1
2 model{
3 for(i in 1:ns) {
                                     # LOOP OVER ALL STUDIES
4
    w[i,1] <- 0 # adjustment for multi-arm trials is zero for control
5 arm
6
                                     # no bias term in baseline arm
    beta[i,1] <- 0
7
    V[i, 1] < - 0
                                     # no variance term in baseline arm
8
    delta[i,1] <- 0 # treatment effect is zero for control arm
    mu[i] ~ dnorm(0,.0001)
9
                                     # vague priors for all trial
10 baselines
                                    # LOOP OVER ARMS
11
    for (k in 1:na[i]) {
12
       r[i,k] ~ dbin(p[i,k],n[i,k]) # binomial likelihood
13
       # model for linear predictor
14
       logit(p[i,k]) <- mu[i] + delta[i,k] + beta[i,k] * V[i,k]</pre>
15
       rhat[i,k] <- p[i,k] * n[i,k] # expected value of the numerators</pre>
16
       #Deviance contribution
17
       dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k]))</pre>
18
          + (n[i,k]-r[i,k]) * (log(n[i,k]-r[i,k]) - log(n[i,k]-
19 rhat[i,k]))
20
     }
21
     # Summed residual deviance contribution for this trial
22
    resdev[i] <- sum(dev[i,1:na[i]])</pre>
23
     24
       # calculate variance of log odds ratio for comparisons with arm
25 1
26
       # check for zero or 100% events in arm k
27
       aux.a[i,k] <- equals(r[i,k],0)+equals(r[i,k],n[i,k])</pre>
28
       # check for zero or 100% events in arm 1
29
       aux.b[i,k] <- equals(r[i,1],0)+equals(r[i,1],n[i,1])</pre>
30
       aux[i,k] <- max(aux.a[i,k],aux.b[i,k]) # any zero or 100%</pre>
31 events?
32
       # add 0.5 if zero or 100% events
33
      V[i,k] < -1/(r[i,k]+(0.5*aux[i,k])) + 1/(r[i,1]+(0.5*aux[i,k]))
34 + 1/(n[i,k]-r[i,k]+(0.5*aux[i,k]))
35 + 1/(n[i,1]-r[i,1]+(0.5*aux[i,k]))
36
       # model for bias parameter beta
```

49

```
1
       beta[i,k] ~ dnorm(mb[i,k], Pkappa)
 2
       mb[i,k] <- A[C[i,k]]
 3
       delta[i,k] ~ dnorm(md[i,k],taud[i,k]) # trial-specific LOR
 4
  distributions
 5
       # mean of LOR distributions (with multi-arm trial correction)
 6
       md[i,k] < - d[t[i,k]] - d[t[i,1]] + sw[i,k]
 7
       # precision of LOR distributions (with multi-arm trial
 8
  correction)
9
       taud[i,k] <- tau *2*(k-1)/k
10
       # adjustment for multi-arm RCTs
11
       w[i,k] <- (delta[i,k] - d[t[i,k]] + d[t[i,1]])</pre>
12
       # cumulative adjustment for multi-arm trials
13
       sw[i,k] <- sum(w[i,1:k-1])/(k-1)</pre>
14
      }
15
    }
16 totresdev <- sum(resdev[])</pre>
                                      # Total Residual Deviance
17 d[1]<-0
                 # treatment effect is zero for reference treatment
18 #
19
20
         # own class treatments with zero variance
21
         # vague prior for treatment effects (mirtazapine)
22
        d[22] \sim dnorm(0, .0001)
23
24
         # class treatments borrowing variance
25
         #Variance from 'No treatment'
26
         for(k in 4:7) { d[k] ~ dnorm(m[D[k]], prec2[2]) }
27
         #Any AD, variance from SSRIs & TCAs
28
        d[21] ~ dnorm(m[D[21]], prec2[8]) # prec2[8]=precision of Any
29 AD class
30
         x <- (1/prec2[7]) + (1/prec2[6]) # sum of SSRI & TCA variances
31
        prec2[8] <- 1/x
32
         #Variance from Counselling
33
         for(k in 23:24) { d[k] ~ dnorm(m[D[k]], prec2[15]) }
34
         #Variance from CBT/CT
```

```
Update 2018
```

```
1
        for(k in 47:48) { d[k] ~ dnorm(m[D[k]], prec2[18]) }
 2
        for(k in 89:90) { d[k] ~ dnorm(m[D[k]], prec2[18]) }
 3
        #Variance from Combined [CBT/CT + AD]
 4
        for(k in 82:88) { d[k] ~ dnorm(m[D[k]], prec2[20]) }
 5
        for(k in 91:92) { d[k] ~ dnorm(m[D[k]], prec2[20]) }
 6
 7
        # treatment effects from Class
 8
        #No treatment
9
        for (k in 2:3) { d[k] ~ dnorm(m[D[k]], prec2[D[k]]) }
10
        #Exercise; TCA; SSRI
11
        for (k in 8:20) { d[k] ~ dnorm(m[D[k]], prec2[D[k]]) }
12
        #Self-help with support; Self-help; psychoeducational
13 interventions
14
        for (k in 25:46) { d[k] ~ dnorm(m[D[k]], prec2[D[k]]) }
15
        #Counselling, Problem solving, behavioural therapies
16 (individual),
17
        #CBT/CT; Behavioural, cognitive, or CBT groups; Combined
18 (CBT/CT + AD)
19
        for (k in 49:81) { d[k] ~ dnorm(m[D[k]], prec2[D[k]]) }
20
21
22 #
23 m[1]<-0 # treatment effect is zero for reference class
24 #treatments not belonging to a class
25 m[9] <- d[22]
                        #mirtazapine
26
27 # priors for mean class effect
28 for(k in 2:8) { m[k] ~ dnorm(0, .0001) }
29 for (k in 10:nc) { m[k] ~ dnorm(0, .0001)
                                              }
30 #
31 # priors for within-class variability
32
     sd2[2] ~ dnorm(0,tau2)I(0,) # informative prior for within-class
33 variance
34
     prec2[2] <- pow(sd2[2], -1) # within-class precision</pre>
35
        for (k in 5:7) {
```

```
1
        sd2[k] ~ dnorm(0,tau2)I(0,) # informative prior for within-
 2 class variance
 3
        prec2[k] <- pow(sd2[k], -1) # within-class precision</pre>
 4
        }
 5
        for (k in 11:13) {
 6
        sd2[k] ~ dnorm(0,tau2)I(0,) # informative prior for within-
 7 class variance
8
        prec2[k] <- pow(sd2[k], -1) # within-class precision</pre>
 9
        }
10
        for (k in 15:20) {
11
        sd2[k] ~ dnorm(0,tau2)I(0,) # informative prior for within-
12 class variance
13
        prec2[k] <- pow(sd2[k], -1) # within-class precision</pre>
14
        - }
15 tau2 <- pow(0.19, -2)
16
17 #
18 sd ~ dunif(0,5)
                      # vague prior for between-trial SD
19 tau <- pow(sd, -2)
                      # between-trial precision = (1/between-trial
20 variance)
21 # mean bias: assumptions
22 A[1] <- 0
                         # control v control
23 A[2] <- b
                         # control v Active
24 A[3] <- 0
                          # Active v Active
25 # bias model prior for variance
26 kappa ~ dunif(0,5)
27 kappa.sq <- pow(kappa,2)</pre>
28 Pkappa <- 1/kappa.sq
29 # bias model prior for mean
30 b ~ dnorm(0,.0001)
31 #
32 # pairwise ORs and LORs for all possible pair-wise comparisons
33 for (c in 1: (nt-1)) {
34
    for (k in (c+1):nt) {
35
       or[c,k] <- exp(d[k] - d[c])</pre>
```

52

```
1
       lor[c,k] <- (d[k]-d[c])
 2
      }
 3
    }
 4
  #
 5 # pairwise differences for classes
 6 for (c in 1:(nc-1)) {
 7
     for (k in (c+1):nc) {
 8
       diffClass[c,k] <- m[k] - m[c]</pre>
 9
       orClass[c,k] <- exp(m[k] - m[c])</pre>
10
      }
11
    }
12 #
13 # ranking on relative scale
14 for (k in 1:nt) {
15
     rk[k] <- rank(d[],k)
                                       # assumes events are "bad"
16
     best[k] <- equals(rk[k],1) #calculate probability that treat k</pre>
17 is best
18
     # calculate probability that treat k is h-th best
19
     for (h in 1:nt) { prob[h,k] <- equals(rk[k],h) }</pre>
20
    }
21 # rank classes
22 for (k in 1:nc) {
23
     rkClass[k] <- rank(m[],k)</pre>
24
     bestClass[k] <- equals(rkClass[k],1) # Smallest is best (i.e. rank</pre>
25 1)
26
     # prob class k is h-th best, prob[1,k]=best[k]
27
     for (h in 1:nc) { probClass[h,k] <- equals(rkClass[k],h) }</pre>
28
    }
29 }
30
```

Update 2018