Melancholic and atypical depression as predictor and moderator of outcome in cognitive behavior therapy and pharmacotherapy for adult depression.

Cuijpers, Pim; Weitz, E.; Lamers, F.; Penninx, B.W.; Twisk, J.; DeRubeis, R.J.; Dimidjian, S.; Dunlop, B.W.; Jarrett, R.B.; Segal, Z.V.; Hollon, S.D.

published in
Depression and Anxiety
2017

DOI (link to publisher)
10.1002/da.22580

document version
Publisher's PDF, also known as Version of record

Received: 13 August 2015 | Revised: 25 September 2016 | Accepted: 27 September 2016

DOI: 10.1002/da.22580

RESEARCH ARTICLE

WILEY AD/AA

Melancholic and atypical depression as predictor and moderator of outcome in cognitive behavior therapy and pharmacotherapy for adult depression

Pim Cuijpers, Ph.D.[1,2] | **Erica Weitz, M.A.**[1,2] | **Femke Lamers, Ph.D.**[2,3] | **Brenda W. Penninx, Ph.D.**[2,3] | **Jos Twisk, Ph.D.**[2] | **Robert J. DeRubeis, Ph.D.**[4] | **Sona Dimidjian, Ph.D.**[5] | **Boadie W. Dunlop, M.D., M.S.**[6] | **Robin B. Jarrett, Ph.D.**[7] | **Zindel V. Segal, Ph.D.**[8] | **Steven D. Hollon, Ph.D.**[9]

[1]Department of Clinical, Neuro and Developmental Psychology, Vrije Universiteit Amsterdam, The Netherlands

[2]EMGO Institute for Health and Care Research, VU University Amsterdam, Amsterdam, The Netherlands

[3]Department of Psychiatry, VU University Medical Center, Amsterdam, The Netherlands

[4]Department of Psychology, University of Pennsylvania, Philadelphia, PA, USA

[5]Department of Psychology and Neuroscience, University of Colorado, Boulder, CO, USA

[6]Department of Psychiatry and Behavioral Sciences, Emory University School of Medicine, Atlanta, GA, USA

[7]Department of Psychiatry, University of Texas Southwestern Medical Center, Dallas, TX, USA

[8]Department of Psychology, University of Toronto—Scarborough, Toronto, Canada

[9]Department of Psychology, Vanderbilt University, Nashville, TN, USA

Correspondence
Pim Cuijpers, Department of Clinical Psychology, VU University Amsterdam, Van der Boechorststraat 1, 1081 BT Amsterdam, The Netherlands.
Email: p.cuijpers@vu.nl

Background: Melancholic and atypical depression are widely thought to moderate or predict outcome of pharmacological and psychological treatments of adult depression, but that has not yet been established. This study uses the data from four earlier trials comparing cognitive behavior therapy (CBT) versus antidepressant medications (ADMs; and pill placebo when available) to examine the extent to which melancholic and atypical depression moderate or predict outcome in an "individual patient data" meta-analysis.

Methods: We conducted a systematic search for studies directly comparing CBT versus ADM, contacted the researchers, integrated the resulting datasets from these studies into one big dataset, and selected the studies that included melancholic or atypical depressive subtyping according to DSM-IV criteria at baseline ($n = 4$, with 805 patients). After multiple imputation of missing data at posttest, mixed models were used to conduct the main analyses.

Results: In none of the analyses was melancholic or atypical depression found to significantly moderate outcome (indicating a better or worse outcome of these patients in CBT compared to ADM; i.e., an interaction), predict outcome independent of treatment group (i.e., a main effect), or predict outcome within a given modality. The outcome differences between patients with melancholia or atypical depression versus those without were consistently very small (all effect sizes $g < 0.10$).

Conclusions: We found no indication that melancholic or atypical depressions are significant or relevant moderators or predictors of outcome of CBT and ADM.

KEYWORDS
antidepressants, atypical depression, cognitive behavior therapy, melancholia, meta-analysis

1 | INTRODUCTION

Major depressive disorders are considered by many to be a heterogeneous condition, with many different symptoms constellations, clinical representations, and varying levels of severity and course (Baumeister, & Gordon, 2012). Furthermore, many different psychological and pharmacological treatments are available and effective (National Institute for Health & Clinical Excellence [NICE], 2009), and the effects of these treatments are very comparable, with no one treatment being much more effective than the others (Cuijpers et al., 2016). At the same time there are hardly any indications for which treatment is effective in a given individual (Cuijpers et al., 2012).

Over the past few decades, several subtypes of major depressive disorder have been proposed (Baumeister & Gordon, 2012). Subtypes not only may help in differentiating the large group of patients with major depression, but may also help determine whether a specific treatment is more effective than others within one or more specific subtypes of depression.

One important subtype of major depressive disorder is melancholia (American Psychiatric Association 2013). In major depression with melancholic features, the patient either has anhedonia or a lack of mood reactivity, and at least three of six other symptoms (depression that is subjectively different from grief, severe weight loss or loss of appetite, psychomotor agitation or retardation, early

morning awakening; excessive guilt, worse mood in the morning). It has been suggested that melancholic depression should be treated with antidepressant medication (ADM), and that response to psychotherapies in general is poor (Brown, 2007; Leventhal & Rehm, 2005).

Another important subtype of major depressive disorders that has attracted considerable attention is atypical depression. This subtype is characterized by mood reactivity and two or more specific secondary symptoms (hyperphagia, hypersomnia, weight gain or increased appetite, hypersomnia, leaden paralysis, and long-standing interpersonal sensitivity to rejection; American Psychiatric Association 2013; Jarrett et al., 1999; Thase, 2007).

The first observations of differential treatment response go back to the 1950s, with atypical depression responding better to MAOIs than TCAs (Stewart, McGrath, Quitkin, & Klein, 2007). There is evidence suggesting that patients have preferential response to monoamine oxidase inhibitors (MAOIs) relative to tricyclic antidepressants (TCAs; Henkel et al., 2006). Jarrett et al. (1999) showed that depressive adults with atypical depression responded more to either cognitive behavior therapy (CBT) or phenelzine (an MAOI) alone than to pill placebo. The response to the two active modalities did not differ. It is unclear what other psychotherapies or other medications, if any, should be preferred or avoided in these patients (Stewart et al., 2007).

Although the hypothesis that diagnostic subtypes such as melancholic and atypical depressive moderate or predict treatment outcomes is popular, few studies exist to test it. An important reason for this void is that most trials focus on patients with major depression in general and are only powered to determine whether treatment is effective in the overall patient group. Few studies have been designed to examine whether a clinical characteristic, such as a diagnosis of a melancholic or atypical depressive subtype, moderates outcome (Cuijpers et al., 2012; Uher et al., 2011); and secondary analyses of trials typically do not have sufficient statistical power to identify significant moderators (Brookes et al., 2004).

In the current "individual patient data" (IPD) meta-analysis, we pooled the data from four randomized trials examining melancholia and atypical depressive subtypes as moderators and predictors of outcome in trials comparing CBT versus ADM and also included data regarding response to pill placebo if the trial contained one. *Moderators* indicate whether certain subsets of participants respond better to one treatment than to another (examined in trials in which two treatments are directly compared with each other; in our case CBT and ADM). In these data, we also can examine melancholia and atypical depression as *nonspecific predictors*, which indicate whether these characteristics are related to improvement, regardless of comparison or control groups (common within-group improvement). Because we also included some studies in which CBT and ADM were compared with a pill placebo, we also could examine whether melancholia and atypical depression are *specific predictors*, and predict specificity of response (the extent to which melancholia and atypical depression predict change over and above what is produced simply by going into generic treatment).

2 | METHODS

2.1 | Identification and inclusion of studies

The methods for this "IPD" meta-analysis have been reported elsewhere (Cuijpers et al., 2014b). To identify potential studies for inclusion, we turned to an existing database of trials on the psychological treatment of adult depression, which also includes all trials directly comparing psychological treatments and ADM. This database has been described in detail elsewhere (Cuijpers, van Straten, Warmerdam, & Andersson, 2008), and has been used in a series of published meta-analyses (www.evidencebasedpsychotherapies.org). This database has been continuously updated through comprehensive literature searches (through January 2014) and the update is used here. Abstracts were identified by combining terms indicative of psychological treatment and depression (both MeSH terms and text words). For this database, we also checked the primary studies from earlier meta-analyses of psychological treatment for depression to ensure that no published studies were missed.

For the current study, we included (a) randomized controlled trials in which (b) CBT (c) was compared with ADM (d) for patients with a depressive disorder, (e) based on an established standardized diagnostic interview, and (f) in which atypical or melancholic depression according to one of the versions of the DSM was measured. We considered a psychological intervention to be CBT when cognitive restructuring was the core component of the treatment for adults (Cuijpers et al., 2013b). We excluded studies in children or adolescents (<18 years). Studies specifically aimed at depressed patients with comorbid general medical or psychiatric disorders were included.

After identifying potential trials for inclusion, the corresponding authors of each were contacted by e-mail and invited to participate in this project by providing the data from their trials, including depression scores pre- and posttreatment, and the sociodemographic and clinical characteristics of participants. When the authors did not respond within 2 weeks, we sent a reminder. If no answer was received to that reminder, we considered the trial unavailable.

2.2 | Quality assessment and data extraction

We assessed the quality of the 24 trials comparing CBT versus ADM using four criteria of the "Risk of bias" assessment tool, developed by the Cochrane Collaboration (Higgins, & Altman, 2008). This tool assesses possible sources of bias in randomized trials, including the adequate generation of allocation sequence, the concealment of allocation to conditions, the prevention of knowledge of the allocated intervention (masking of assessors), and dealing with incomplete outcome data (this was assessed as positive when intention-to-treat analyses were conducted, meaning that all randomized patients were included in the analyses).

In the assessment of trial quality, we only used the data reported in the published papers (and not the information provided by the participating authors), because we considered this to be the most conservative estimate. Because we also tested whether the studies included

in the IPD meta-analysis differed from the studies that did not participate, personal information from the participating authors also might lead to differences between those studies included and those studies not included.

We also coded additional aspects of the included studies, including participant characteristics, aspects of the CBT and the type of ADM, and trial characteristics. Two independent researchers conducted the quality assessments and data extraction.

2.3 | Differences between included and not-included studies in the IPD meta-analysis

In order to examine whether the studies from which the primary data were included in the IPD meta-analysis differed from the other studies, we first calculated the effect sizes indicating the difference between CBT versus ADM at posttest based on the data reported in the published papers. We calculated effect sizes by subtracting (at posttest) the average score of the CBT group from the average score of the ADM group, and dividing the result by the pooled standard deviation. Because several studies had small samples, we corrected the effect size for small sample bias according to the procedures suggested by Hedges and Olkin (Hedges' *g*; Hedges, & Olkin, 1985).

In the calculations of effect sizes, we focused mainly on the HAM-D-17 as outcome instrument. If only dichotomous outcomes for the HAM-D-17 were reported without means and standard deviations, we used the procedures described by Borenstein, Hedges, Higgins, and Rothstein (2009) to calculate the standardized mean difference.

Then we conducted a univariate metaregression analysis with the effect size (based on the published data) as the dependent variable, and as the predictor a dummy variable indicating whether or not the primary data were included in the IPD meta-analysis. These analyses were conducted using Comprehensive Meta-analysis software (version 2.2.057).

Publication bias was tested in the full set of studies meeting inclusion criteria and also separately in the set of studies that were included in the IPD meta-analyses. This was done by inspecting the funnel plot on primary outcome measures and by Duval and Tweedie's (2000) trim and fill procedure that yields an estimate of the effect size after publication bias has been taken into account (as implemented in Comprehensive Meta-Analysis, version 2.2.021). We also conducted Egger's test of the intercept to quantify the bias captured by the funnel plot and test whether it was significant.

2.4 | Missing data

In the IPD dataset, we first imputed missing depression scores at posttest with a multivariate imputation algorithm ("mi impute mvn," in Stata MP 13.1 for Mac). In this multiple imputation method, several datasets are generated, and the analyses are conducted separately in each dataset, after which the results are combined into one outcome. Multiple imputations are currently considered to be the most sophisticated method for handling missing data in randomized trials (Donders, van der Heiden, Stijnen, & Moons, 2012). We generated 100 new datasets with the observed and imputed scores for posttest depression scores from trial, depression score at baseline, age, gender, and time from baseline to follow-up.

2.5 | IPD meta-analyses

We first examined baseline differences between patients with melancholia or atypical depression and patients not meeting criteria for a subtype. We examined differences in baseline depression and sociodemographics, while accounting for clustering of patients within studies. We conducted multilevel mixed-effects logistic regression analyses with the dummy variables of the subtypes (melancholic vs. not; atypical vs. not) as dependent variables and the baseline characteristics as predictors.

In order to examine the extent to which melancholia and atypical depression moderated outcome, we conducted a series of so-called "one-step" IPD meta-analyses (Riley, Lambert, & Abo-Zaid, 2010). In these analyses, a mixed effects model is used to examine whether a moderator or predictor is associated with the outcome, while accounting for clustering of patients within studies. One-step IPD meta-analyses allow for the most sophisticated modeling of covariates. It affords greater power and is less affected by bias than the "two-step" IPD meta-analyses, in which IPD are used to estimate the treatment–moderator interaction within each trial, followed by a standard inverse variance meta-analysis (Bower et al., 2013).

In the first series of main analysis, we examined whether melancholic and atypical depression *moderated* outcome, looking for differential outcomes for CBT relative to ADM in patients with or without melancholia and in patients with or without atypical depression. In these analyses, we used the (imputed) posttest HAM-D-17 scores as the dependent variable. As predictors, we used the baseline HAM-D-17 scores, the treatment dummy (CBT = 1 and ADM = 0), melancholia/atypical (yes/no), and the interaction between melancholia/atypical and the treatment dummy, while adjusting for the clustering of patients within studies.

In addition, we performed the same analysis adjusted for other sociodemographic indices that were available in the majority of studies (age, gender, minority status, married or not, more than 12 years of education or less), trial characteristics (type of ADM; whether or not the trial was conducted in the United States), the preceding four quality criteria for each trial as predictors in the model, and time to follow-up.

We also conducted the same analysis for the trial completers only (the patients for whom posttest data were available, so not the intention-to-treat sample).

In the second series of analyses, we examined whether melancholia/atypical features were *nonspecific predictors* of outcome, by examining whether melancholia/atypical features were associated with the posttest HAM-D-17 score within the CBT group, and separately, within the ADM group. In these analyses, posttest HAM-D-17 score was again used as the dependent variable and melancholia and atypical depression, as well as baseline HAM-D-17 scores, were entered into

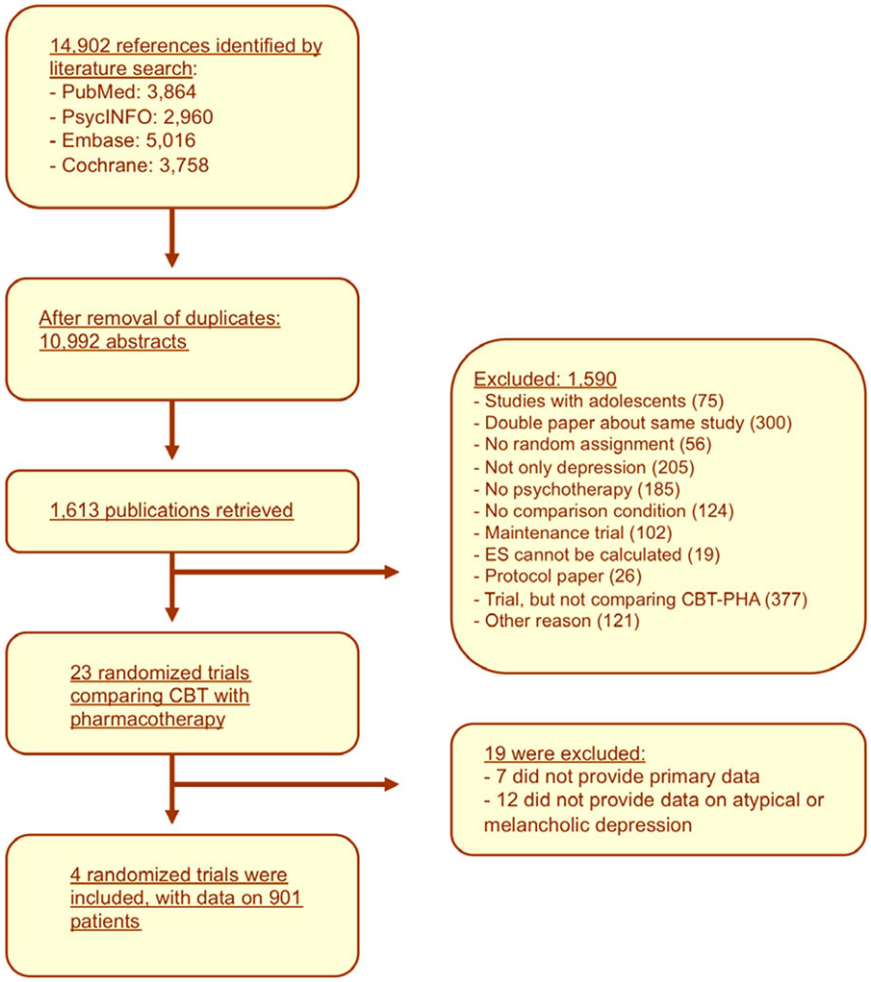

FIGURE 1 Flowchart of inclusion of studies

the model as predictors. We then repeated the analyses adjusted for the sociodemographics indices and the four trial quality criteria previously described, along with melancholia/atypical features and baseline HAM-D-17 scores. These analyses were repeated once more with the completers only.

In the third series of analyses, we examined whether melancholia/atypical features predicted specificity of response (was a *specific predictor*), through examining whether melancholia/atypical features predicted differential outcome for CBT compared to pill placebo controls, and separately for ADM compared to pill placebo controls (Such specific prediction is a special case of moderation vis-à-vis nonspecific factors common to all treatments.) Again, we used posttest HAM-D-17 scores as the dependent variable, and baseline HAM-D-17 scores as the treatment dummy (CBT vs. pill placebo; and separately, ADM vs. pill placebo) melancholia/atypical features, and melancholia/atypical by treatment interaction as predictors. This same model was analyzed again adjusting for the sociodemographics, trial characteristics, and quality criteria, along with melancholia/atypical features, and then repeated again with completers only.

3 | RESULTS

3.1 | Selection of studies

Of the 1,613 full-text papers retrieved, 1,589 were excluded (details are given in Fig. 1). Twenty-three studies met inclusion criteria for the current meta-analysis (see also our earlier reports on this IPD meta-analyses). One other study was only aimed at patients with atypical depression and was not included in the current set of studies, because only nonatypical patients were included and comparisons with other patients were therefore impossible (Jarrett et al., 1999). Of these 23 studies, 16 provided patient-level data (70%). Four studies of those 16 studies collected data on the presence of melancholia and atypical depression, as well as on baseline and posttest depression scores using the HAM-D-17 (DeRubeis et al., 2005; Dimidjian et al., 2006; Dunlop et al., 2012; Segal et al., 2006). In a previous meta-analysis, we identified five studies in which CBT was compared with pill placebo (Cuijpers et al., 2014a). Two of these (40%) also provided data on melancholia and atypical depression (DeRubeis et al., 2005; Dimidjian et al., 2006).

The four studies included 805 patients, 402 in the ADM conditions, 290 in the CBT conditions, and 113 in the pill placebo conditions. Of these 805 patients, 298 met criteria for melancholia (37.0%), 140 had atypical depression (17.4%), and 367 did not meet criteria for either subtype (45.6%). Sixteen patients met criteria for both melancholia and atypical depression, but because one of the criteria for atypical depression is that the criteria for melancholia are not met at the same time, these patients were considered to have only melancholia and included in the 37.0% above.

3.2 | Characteristics of included studies

In all the four included studies, patients were recruited (in part) through the community, all were aimed at adults in general (none at specific populations). Three studies were conducted in the United States, one in Canada. All four studies used an selective serotonin reuptake inhibitor as ADM, defined major depressive disorder according to the DSM-IV, and applied CBT in an individual treatment format. The number of treatment sessions in CBT varied from 16 to 28.

The quality of the included studies based on the published reports varied (Table 1). Two of the four studies reported an adequate sequence generation and one reported allocation to conditions by an independent (third) party. Three studies reported blinding of outcome assessors, and in three studies intention-to-treat analyses were conducted. One study met all four of the quality criteria, two others met two or three criteria; and the remaining study had a lower quality (0 of the four criteria).

3.3 | Available and unavailable data

We compared the four studies from which the primary data were included in the current IPD meta-analysis study with the 19 trials that met our inclusion criteria, but which did not contribute their primary data to the current study (11 studies did provide data, but had not measured melancholic and atypical subtypes). We calculated the effect sizes from all published studies and pooled them. The results for the included studies and the nonincluded studies are presented in Figure 2. We found no significant difference between the 19 studies that did not contribute primary data to the current meta-analysis and the four studies that were included ($P = .47$).

For all 23 studies meeting our inclusion criteria, as well as for the subgroup of four studies included in the IPD meta-analysis and the subgroup of 19 studies not included in the IPD meta-analysis, we found no indication of publication bias. For all three groups of studies, Duvall and Tweedie's trim and fill procedure suggested that no trials were missing and that the adjusted effect size was identical to the unadjusted effects size. Egger's test of the intercept also did neither point at significant publication bias in the total group of studies, nor in the included and not-included studies ($P > .1$).

3.4 | Baseline differences between patients with melancholia or atypical depression and other patients

We compared patients with melancholia to all other patients (including those with atypical depression) and separately to those who did

TABLE 1 Selected characteristics of studies comparing CBT with ADM

Trial	Mean Baseline HAM-D	Proportion of Men	Pharmacotherapy	*N* Pharmacotherapy	CBT Sessions	*N* CBT	*N* Placebo	Quality[a]	Country
DeRubeis et al. (2005)	21.53	0.42	Paroxetine	120	28	60	60[b)]	−−++	United States
Dimidjian et al. (2006)	18.48	0.30	Paroxetine	100	24	45	53[b)]	+−++	United States
Dunlop et al. (2012)	19.70	0.44	Escitalopram	39	16	41	–	++++	United States
Segal et al. (2006)	19.47	0.44	Citalopram	149	20	152	–	−−−−	Canada

[a] In this column a positive (+), or negative (−) sign is given for four quality criteria, respectively: allocation sequence, concealment of allocation to conditions, blinding of assessors, and intention-to-treat analyses.
[b] In these studies the patients in the pill placebo condition received antidepressant medication after 8 weeks.

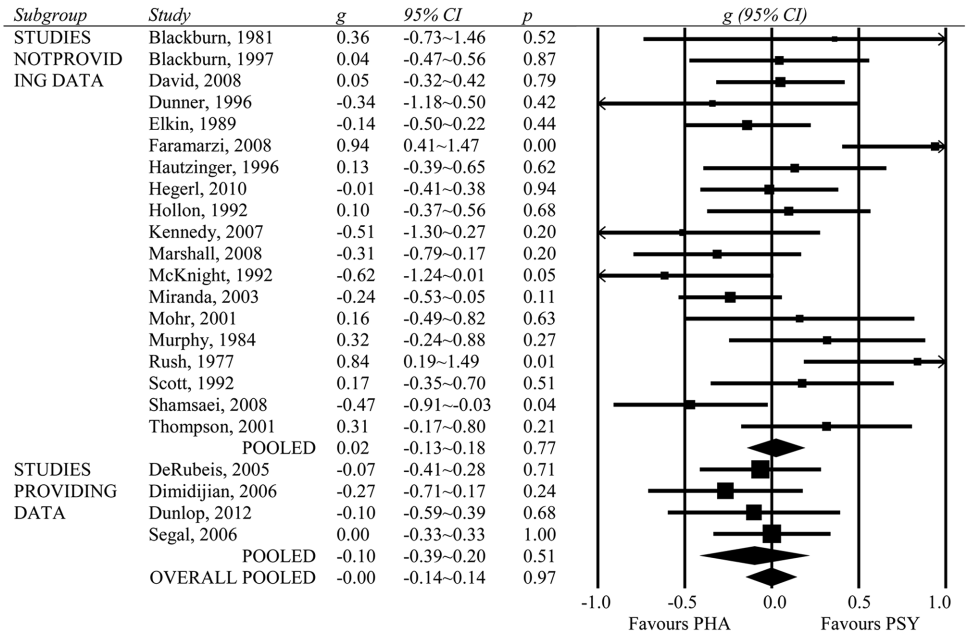

FIGURE 2 Direct comparisons of CBT and ADM for adult depression: Hedges' *g* of studies providing data and those not providing primary data

TABLE 2 Differences between atypical and melancholic depressive subtypes and other depressed patients ($N = 805$)[a]

	Baseline Characteristics		Melancholia versus All Other		Atypical versus All Other[a]		Melancholia versus No Subtype		Atypical versus No Subtype [a]	
	n/N/M (SE)	Percentage	Coefficient	*SE*	Coefficient	*SE*				
Baseline HAMD (*M* [*SE*])	19.88 (0.64)[b]	-	0.12	0.02***	−0.07	0.02**	0.11	0.02***	−0.03	0.03
Age (*M* [*SE*])	39.67 (0.95)[b]	-	−0.00	0.01	0.01	0.01	0.00	0.01	0.01	0.01
Female gender	483/805	60.0	−0.22	0.16	0.20	0.20	−0.20	0.17	0.10	0.22
Married	295/800	36.9	0.14	0.16	−0.23	0.21	0.04	0.18	−0.20	0.22
>12 Years education	627/773	81.1	0.25	0.22	−0.01	0.26	0.31	0.23	0.17	0.27
Minority status	174/631	21.6	−0.16	0.20	0.42	0.22 º	−0.06	0.21	0.47	0.25º
Employed	288/781	36.9	−0.16	0.60	0.10	0.20	−0.04	0.19	0.06	0.23

º$P < .1$; *$P < .05$; **$P < .001$.

[a]All analyses were done separately for each variable in univariate analyses and with all variables together in multivariate analyses. Only the results for the multivariate analyses are presented here. The only difference in terms of significant findings was that minority status was significant ($P < .05$) in the univariate and not significant ($P < .1$) in the multivariate analyses comparing atypical to all other patients, while there was only a trend in the multivariate analyses ($P < .1$).

[b]All categorical variables are coded as 1 (having that characteristics such as female gender, or being married) or 0 (not having this characteristic), and melancholia and atypical depression are also coded as 1 (melancholia/atypical depression present) or 0 (not present).

not meet criteria for atypical depression for baseline depression and sociodemographic variables. We did the same analyses for atypical depression. The results are presented in Table 2. We found that patients with melancholia were significantly more depressed at baseline than other patients ($P < .001$). Patients with atypical depression were significantly less depressed than other patients ($P < .01$), but when the melancholia patients were excluded from the analyses, the difference was no longer significant (Table 2). No other variable was significant, except that minority status was significantly associated with having melancholic depression in the univariate analyses ($P < .05$). In the multivariate analyses this association was no longer significant, although there was a trend ($P < .1$).

The effect size indicating the difference between patients with melancholic depression and those not meeting criteria for a subtype at baseline was $g = 0.40$ (95% CI: 0.23~0.57), which corresponds with 1.48 points difference on the HAM-D-17 (95% CI: 0.85~2.11). The effect size indicating the difference between patients with atypical depression and those with no subtype was $g = -0.13$ (95% CI: −0.40~0.14), or 0.51 points on the HAM-D-17 (95% CI: −1.49~0.46).

3.5 | Melancholia as moderator of outcome in CBT versus ADM

The results of the mixed effects models are presented in Table 3. As can be seen, none of the analyses showed that melancholia significantly

TABLE 3 Melancholic depression as predictor and moderator of outcome in studies comparing CBT with ADM for adult depression: HAM-D-17

	Intention to Treat (itt)			Adjusted (itt)[b]			Completers Only		
Melancholia As	**Coefficient**	***SE***	***p***	**Coefficient**	***SE***	***p***	**Coefficient**	***SE***	***p***
Moderator of CBT versus PHA[a]	(*N* = 703)			(*N* = 652)			(*N* = 443)		
Baseline HAM-D	0.24	0.07	<.001	0.25	0.07	<.001	0.25	0.07	<.001
CBT versus pharmacotherapy	0.12	0.62	.85	0.13	0.63	.83	0.36	0.66	.59
Melancholic depression	0.08	0.68	.90	−0.05	0.70	.94	0.06	0.72	.93
Melancholic × treatment	−0.42	1.12	.71	−0.38	1.13	.74	−0.25	1.17	.83
Constant	2.86	1.39	.04	1.65	2.05	.34	2.71	1.41	.06
Predictor of improvement within CBT	(*N* = 295)			(*N* = 277)			(*N* = 171)		
Baseline HAM-D	0.29	0.10	.004	0.29	0.10	.005	0.33	0.11	.002
Melancholic depression	−0.29	0.86	.74	−0.32	0.87	.71	−0.10	0.92	.91
Constant	2.26	2.06	.27	2.00	3.19	.53	1.54	2.22	.49
Predictor of improvement within PHA	(*N* = 408)			(*N* = 375)			(*N* = 272)		
Baseline HAM-D	0.22	0.09	.01	0.23	0.09	.01	0.19	0.09	.03
Melancholic depression	0.13	0.69	.86	−0.01	0.71	.99	0.23	0.74	.76
Constant	3.22	1.73	.06	1.35	2.69	.62	3.69	1.75	.04
Predictor of CBT compared with pill placebo	(*N* = 217)			(*N* = 196)			(*N* = 176)		
Baseline HAM-D	0.40	0.10	<.001	0.42	0.12	<.001	0.42	0.10	<.001
CBT versus Pill placebo	−1.98	1.03	.06	−1.73	1.50	.12	−2.21	1.04	.03
Melancholic depression	−1.06	1.29	.41	−1.58	1.36	.25	1.08	1.29	.40
Melancholic × treatment	0.96	1.88	.61	1.14	1.97	.56	0.90	1.86	.63
Constant	5.40	2.19	.01	1.94	3.66	.60	5.25	2.16	.02
Predictor of PHA compared with pill placebo	(*N* = 333)			(*N* = 293)			(*N* = 266)		
Baseline HAM-D	0.33	0.09	.001	0.38	0.10	<.001	0.31	0.09	.001
Pharmacotherapy versus pill placebo	−2.31	0.95	.02	−2.52	0.95	.01	−2.74	0.97	.01
Melancholic depression	−0.93	1.38	.50	−1.57	1.39	.26	−0.97	1.42	.50
Melancholic × treatment	0.54	1.75	.76	1.30	1.77	.46	0.42	1.79	.81
Constant	6.78	1.97	.001	0.94	3.15	.77	7.42	1.96	<.001

[a]CBT = 1; ADM is 0.
[b]Adjusted for sociodemographics (gender, minority status, married or not, more than 12 years of education or less) and the four quality criteria for each trial.

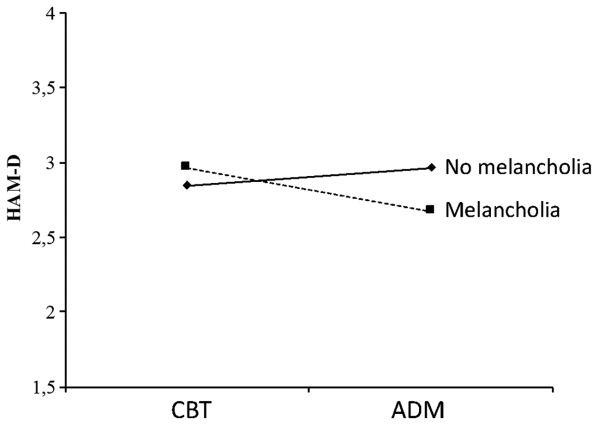

FIGURE 3 Interaction between melancholia and nonmelancholia in CBT and ADM

moderated outcome of CBT versus ADM. The interaction between melancholia and nonmelancholia in CBT and ADM is presented in Figure 3. As can be seen, ADM was a little more effective in melancholic patients compared to CBT, but that did not approach significance.

We also found no evidence that melancholia was a nonspecific predictor of outcome (melancholia was not significantly associated with improvement or the lack of same within the CBT group or within the ADM group). Finally, we found no evidence that melancholia was a specific predictor, as it did not significantly predict differential response for either CBT or ADM compared to pill placebo controls.

We conducted a series of sensitivity analyses. First, we ran the analyses comparing CBT and ADM one more time while leaving out the baseline depression score on the HAM-D-17. Second, we ran the analyses comparing CBT and ADM four more times, leaving out one of the studies in each of the analyses. Third, we selected the patients with melancholic depression and examined within that group whether CBT and ADM resulted in differential outcomes. Fourth, we excluded the patients with atypical depression, so that we directly compared those with melancholia and those not meeting criteria for a subtype. Because the mixed model may not estimate the random intercept correctly, we added three dummy variables for each of the studies (the fourth study was used as reference group) to the model, but again found very comparable outcomes (results not reported in the tables). We also ran the analyses separately for each of the studies. None of these analyses indi-

TABLE 4 Atypical depression as predictor and moderator of outcome in studies comparing CBT with ADM for adult depression: HAM-D-17

	Intention to Treat (itt)			Adjusted (itt)[b]			Completers Only		
Model: Atypical As	**Coefficient**	***SE***	***p***	**Coefficient**	***SE***	***p***	**Coefficient**	***SE***	***p***
Moderator of CBT versus PHA[a]	(*N* = 692)			(*N* = 641)			(*N* = 436)		
Baseline HAM-D	0.25	0.07	<.001	0.26	0.07	<.001	0.27	0.07	<.001
CBT versus pharmacotherapy	0.25	0.59	.67	0.34	0.61	.57	0.85	0.62	.17
Atypical depression	0.90	0.80	.27	1.14	0.83	.17	1.31	0.84	.11
Atypical × treatment	−1.55	1.25	.21	−1.83	1.28	.15	−2.71	1.37	.048
Constant	2.52	1.44	.08	1.12	2.07	.59	1.91	1.45	.19
Predictor of improvement within CBT	(*N* = 290)			(*N* = 272)			(*N* = 169)		
Baseline HAM-D	0.29	0.10	.004	0.29	0.10	.005	0.35	0.11	.001
Atypical depression	−0.65	0.93	.48	−0.49	0.96	.61	−1.38	1.06	.19
Constant	2.22	2.05	.28	1.80	3.17	.57	1.41	2.17	.52
Predictor of improvement within PHA	(*N* = 402)			(*N* = 369)			(*N* = 267)		
Baseline HAM-D	0.22	0.09	.01	0.24	0.09	.009	0.22	0.09	.01
Atypical depression	0.94	0.88	.28	1.33	0.88	.13	1.44	0.91	.12
Constant	2.99	1.78	.09	0.80	2.75	.77	2.96	1.84	.11
Predictor of CBT compared with pill placebo	(*N* = 217)			(*N* = 196)			(*N* = 176)		
Baseline HAM-D	0.38	0.10	<.001	0.38	0.11	<.001	0.42	0.10	<.001
CBT versus Pill placebo	−1.55	0.95	.10	−1.36	0.99	.17	−1.96	0.93	.04
Atypical depression	1.53	1.58	.33	1.73	1.64	.29	1.28	1.57	.41
Atypical × treatment	0.04	2.42	.99	0.45	2.52	.86	0.81	2.42	.74
Constant	5.01	2.23	.03	2.04	3.63	.57	4.71	2.18	.03
Predictor of PHA compared with pill placebo	(*N* = 333)			(*N* = 293)			(*N* = 266)		
Baseline HAM-D	0.31	0.09	.001	0.35	0.10	<.001	0.31	0.09	.001
Pharmacotherapy versus pill placebo	−1.83	0.87	.04	−1.64	0.87	.06	−2.27	0.89	.01
Atypical depression	1.36	1.70	.43	1.30	1.68	.44	1.14	1.74	.51
Atypical × treatment	−1.71	2.10	.41	−2.48	2.10	.24	−1.74	2.16	.41
Constant	6.54	2.01	.001	0.70	3.10	.82	6.87	1.98	.001

[a]CBT=1; ADM is 0.
[b]Adjusted for sociodemographics (gender, minority status, married or not, more than 12 years of education or less) and the four quality criteria for each trial.

cated that melancholia was a significant moderator of outcome for CBT and ADM ($P > .1$ for all analyses).

Three of the four studies also used the Beck Depression Inventory-II (BDI-II) as an outcome instrument. We imputed missing scores at posttest and examined whether the BDI-II was a moderator of outcome, but again no significant association was found ($P > .1$).

3.6 | Atypical depression as moderator of outcome in CBT versus ADM

The results of atypical depression as a moderator, nonspecific and specific predictor of outcome in CBT and ADM are presented in Table 4. As can be seen, we found no evidence that atypical depression is a significant moderator, specific predictor, or nonspecific predictor of outcome. The interaction between atypical depression and other depressive disorders across CBT and ADM is presented in Figure 4. As can be seen, ADM was a little more effective in patients with atypical depression compared to CBT (but this was not significant).

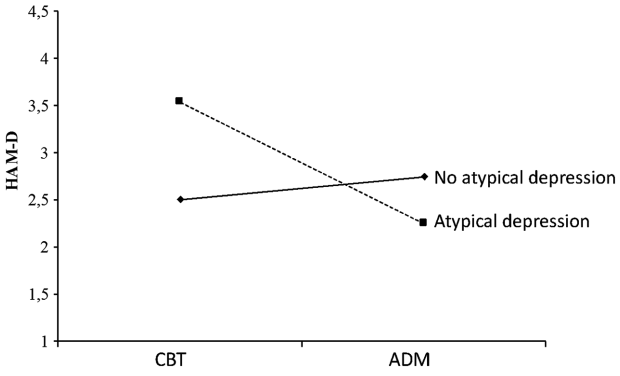

FIGURE 4 Interaction between atypical depression and no atypical depression in CBT and ADM

We only found one significant outcome, indicating that the interaction between atypical depression and the treatment dummy was significant in the completers sample (patients with atypi-

TABLE 5 Differences between patients with and without melancholic or atypical depression for posttest HAM-D-17: within and between group effect sizes (Hedges' *g*) and differences in means[a]

Within Conditions[a]	N_{st}[b]	Effect	95% CI	*p*	Effect	95% CI	*p*	Effect	95% CI	*p*
		Melancholic Depression versus Other Patients			Atypical Depression versus Other Patients			Atypical Depression versus Other Patients (Melancholia Excl.)		
Hedges' *g*[c]										
• CBT	4	−0.09	−0.43~0.25	.60	−0.08	−0.37~0.20	.56	0.02	−0.29~0.33	.91
• ADM	4	0.09	−0.11~0.29	.39	0.06	−0.19~0.31	.63	0.15	−0.13~0.43	.29
• Pill placebo	2	−0.04	−0.43~0.34	.83	0.09	−0.42~0.60	.73	0.09	−0.45~0.63	.73
Difference in means[d]										
• CBT	4	−0.62	−2.88~1.64	.59	−0.62	−2.60~1.36	.54	0.14	−1.93~2.21	.89
• ADM	4	0.59	−0.74~1.91	.38	0.40	−1.27~2.06	.64	0.97	−0.82~2.76	.29
• Pill placebo	2	−0.33	−3.12~2.47	.82	0.64	−3.10~4.38	.74	0.65	−3.14~4.43	.74
Within diagnostic groups[e]		**Within group of patients with melancholia**			**Within group of patients with atypical depression**			**Within group of patients with atypical depression (melancholia excl.)**		
• CBT versus ADM[f]	4	0.12	−0.14~0.38	.36	0.12	−0.22~0.46	.48	0.13	−0.23~0.48	.48
• CBT versus pill placebo	2	1.00	0.45~1.56	.00	0.80	0.17~1.43	.01	0.77	0.13~1.40	.02
• ADM versus pill placebo	2	0.68	0.28~1.08	.00	0.76	0.19~1.33	.01	0.77	0.18~1.35	.01
Difference in means[d]										
• CBT versus ADM[f]	4	0.85	−0.96~2.66	.36	0.82	−1.37~3.01	.46	0.87	−1.43~3.16	.46
• CBT versus pill placebo	2	7.29	3.53~11.05	.00	5.61	1.35~9.87	.01	5.46	1.10~9.82	.01
• ADM versus pill placebo	2	4.96	2.10~7.83	.00	5.38	1.55~9.20	.01	5.41	1.52~9.30	.01

[a]These effect sizes indicate the difference within each of the conditions, between those with and those without a depressive subtype.
[b]Number of studies.
[c]Lower score in melancholic/atypical depression indicates a negative effect.
[d]The difference in means indicates the difference between men and women within each condition in HAM-D-17 score.
[e]These effect sizes indicate the difference between conditions within the group of patients with a specific subtype of depression
[f]A positive effect indicates that CBT is superior to ADM.

cal depression responding better to ADM). However, because the *P*-value was just below the 0.05 threshold ($P = .048$) despite the large sample, and because the number of analyses we conducted was considerable, this finding should be considered with caution.

We ran the same sensitivity analyses as we did for melancholic depression, as well as the analyses with the BDI-II as outcome, but again found no indication that atypical depression is a moderator of outcome.

3.7 | Effect sizes indicating the differences between melancholic and atypical depression

In order to examine the size of the difference between those with melancholia and those without at posttest, we calculated the effect sizes indicating these differences within each of the condition (separately for the groups receiving CBT, ADM, and pill placebo; Table 5). We also calculated the differences between CBT and ADM within the group of patients with melancholia, as well the differences between CBT and placebo and ADM and placebo. We calculated standardized

effect sizes (Hedges' *g*) as well as differences in means (indicating the difference in scores on the HAM-D-17).

As can be seen, all effect sizes indicating the difference between those with and without melancholia were smaller than $g = 0.10$ and not significant ($P > .1$) in all three treatment groups, the effect size indicating the difference between CBT and ADM within melancholia patients was also small (g = 0.12) and the difference between CBT and ADM compared to placebo were both large and significant.

In the same way, we calculated the effect sizes for atypical depression and again found few small effects for the within condition effect sizes, as well as small differential effects for CBT versus ADM within this group, and large effects of both conditions versus placebo (Table 5). Because these outcomes may be affected by patients with melancholia (who were more depressed at baseline and could also be more depressed at posttest), we also calculated these effect sizes, while excluding melancholic patients, and again found comparable results.

4 | DISCUSSION

We integrated the data of four randomized trials comparing CBT and ADM with or without a pill placebo condition and examined the extent to which melancholic and atypical depression moderated or predicted outcome within or between modalities. None of the analyses showed that melancholic or atypical depressive subtypes were a significant moderator of outcome, a nonspecific or a specific predictor. The posttest differences between patients with melancholia or atypical depression and those without were very small. We did find that severity was significantly higher in melancholic patients at baseline, but we did not find that melancholia was a moderator of outcome, even when we did not adjust for baseline severity of depression.

These results may appear surprising since there is increasing evidence that the melancholic and atypical depressive subtypes not only differ in symptom presentation, but also in biological correlates and somatic consequences (Lamers et al., 2013; Penninx, Milaneschi, Lamers, & Vogelzangs, 2013). Inflammatory and metabolic dysregulation have been found to be more pronounced in atypical depression, while HPA-axis hyperactivity is stronger in melancholic depression. There also is evidence that the determinants of the long-term course of melancholic and atypical depression differ from each other and from other depressive disorders (Lamers et al., 2012).

Since our study did not find any indication, however, that melancholic and atypical depression were moderators or predictors of outcome, the findings are in line with the hypothesis that both treatment modalities include effective mechanisms, which could influence the biopsychosocial systems similarly or differentially. The distinct subtypes of depression may have different etiologies and course of illness, but our findings suggest that the effects of CBT and ADM do not differ, nor does either modality work better or worse in these subtypes. It is possible that when the exact processes leading to depression and its subtypes are understood, more focused treatments, with known mechanisms, can be developed that focus on the core elements underlying these processes.

This analysis has several important strengths and limitations that have to be considered. Strengths include the relatively high statistical power, related to the large sample size, and that the analyses were conducted in a uniform way across all included studies. There are also some limitations, however. We could include only a relatively small number of studies, and most studies either did not provide primary data or no data on melancholic or atypical depression were collected in the study. It is possible that our selection was not representative of all available studies in this field. Another limitation is that it is not clear whether melancholic and atypical depression are valid diagnostic subtypes and whether they were diagnosed appropriately in the studies, despite the fact that it was measured in all studies according the DSM criteria. Furthermore, the quality of the included studies as reported in the published papers was not consistently optimal (although most quality ratings would have been positive after receiving additional information from the authors). The studies also varied from each other in terms of type of antidepressant, maximal dose, average dose, and duration of treatment, and it was not possible to categorize this in a uniform way. It also was not possible to categorize the delivery of CBT in a uniform way. A more general limitation of these studies is that patients cannot be blinded when randomized to psychotherapy, which may result in bias in favor of psychotherapy. A final limitation is that we only examined short-term outcomes, while there are indications that CBT has enduring effects that are clearly detectable up to 1 year after treatment (Cuijpers et al., 2013a).

Adults with atypical depression can be optimal candidates for efficient CBT because their reactive mood maps right onto the mood shifts, which trigger application of the cognitive model. On the other hand, the unreactive mood, anhedonia, and psychomotor retardation that are cardinal features of melancholic depression can make CBT laborious for both patients and clinicians, which can prompt considering the benefits of using ADM before CBT, switching to ADM if CBT is inefficient or adding ADM to CBT. The data we provide do not speak to clinical efficiency, patient or clinician preferences, or other important process relevant to daily functioning in patient and clinicians' lives.

Despite these limitations, the finding that neither melancholic nor atypical depression was found to be significant moderator or predictor of outcome between or within CBT versus ADM is important from a clinical as well as a scientific perspective. Specifically, the null findings support clinicians and patients in selecting either modality based on availability, preferences, and other considerations. Although melancholic and atypical depression may be valid subtypes of depression, there is no reason to assume that these patients respond differently to CBT and ADM for depression in general.

FUNDING

No funding was received for this project.

CONFLICT OF INTERESTS

The authors declare no conflicts of interests or financial disclosures related to this work.

REFERENCES

American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders (DSM5)* (5th ed.). Washington DC: Author.

Baumeister, H., & Gordon, P. (2012). Meta-review of depressive subtyping models. *Journal of Affective Disorders*, *139*, 126–140.

Borenstein, M., Hedges, L. V., Higgins, J. P. T., & Rothstein, H. R. (2009). *Introduction to meta-analysis*. Chichester, UK: Wiley.

Bower, P., Kontopantelis, E., Sutton, A., Kendrick, T., Richards, D., & Gilbody, S. . . . Liu, E.T.H. (2013). Who should get low-intensity treatments for depression? An individual patient data meta-analysis. *BMJ*, *346*, f540.

Brookes, S. T., Whitely, E., Egger, M., Smith, G. D., Mulheranc, P. A., & Peters, T. J. (2004). Subgroup analyses in randomized trials: Risks of subgroup-specific analyses; power and sample size for the interaction test. *Journal of Clinical Epidemiology*, *57*, 229–236.

Brown, W. A. (2007). Treatment response in melancholia. *Acta Psychiatrica Scandinavica*, *433S*, 125–129.

Cuijpers, P., Berking, M., Andersson, G., Quigley, L., Kleiboer, A., & Dobson, K. S. (2013b). A meta-analysis of cognitive behavior therapy for adult depression, alone and in comparison to other treatments. *Canadian Journal of Psychiatry*, *58*, 376–385.

Cuijpers, P., Hollon, S. D., van Straten, A., Bockting, C., Berking, M., & Andersson, G. (2013a). Does cognitive behaviour therapy have an enduring effect that is superior to keeping patients on continuation pharmacotherapy? A meta-analysis. *BMJ Open*, *3*, e002542. doi:10.1136/bmjopen-2012-002542

Cuijpers, P., Reynolds, C. F., Donker, T., Li, J., Andersson, G., & Beekman, A. (2012). Personalized treatment of adult depression: Medication, psychotherapy or both? A systematic review. *Depression and Anxiety*, *29*, 855–864.

Cuijpers, P., Sijbrandij, M., Koole, S. L., Andersson, G., Beekman, A. T., & Reynolds, C. F. (2016). The efficacy of psychotherapy and pharmacotherapy in treating depressive and anxiety disorders: A meta-analysis of direct comparisons. *World Psychiatry*, *12*, 137–148.

Cuijpers, P., Turner, E. H., Mohr, D. C., Hofmann, S. G., Andersson, G., Berking, M., & Coyne, J. (2014a). Comparison of psychotherapies for adult depression to pill placebo control groups: A meta-analysis. *Psychological Medicine*, *44*, 685–695.

Cuijpers, P., van Straten, A., Warmerdam, L., & Andersson, G. (2008). Psychological treatment of depression: A meta-analytic database of randomized studies. *BMC Psychiatry*, *8*, 36. doi:10.1186/1471-244X-8-36.

Cuijpers, P., Weitz, E., Twisk, J., Kuehner, C., Cristea, I., & David, D. . . . Hollon, S.D. (2014b). Gender as predictor and moderator of outcome in cognitive behavior therapy and pharmacotherapy for adult depression: An "individual patient data" meta-analysis. *Depression and Anxiety*, *31*, 941–951.

DeRubeis, R. J., Hollon, S. D., Amsterdam, J. D., Shelton, R. C., Young, P. R., & Salomon, R. M. et al. (2005). Cognitive therapy vs. medications in the treatment of moderate to severe depression. *Archives of General Psychiatry*, *62*, 409–416.

Dimidjian, S., Hollon, S. D., Dobson, K. S., Schmaling, K. B., Kohlenberg, R. J., & Addis, M. E. et al. (2006). Randomized trial of behavioral activation, cognitive therapy, and antidepressant medication in the acute treatment of adults with major depression. *Journal of Consulting and Clinical Psychology*, *74*, 658–670.

Donders, A., van der Heiden, G., Stijnen, T., & Moons, K. (2012). A gentle introduction to imputation of missing values. *Journal of Clinical Epidemiology*, *59*, 1087–1091.

Dunlop, B. W., Kelley, M. E., Mletzko, T. C., Velasquez, C. M., Craighead, E., & Mayberg, H. S. (2012). Depression beliefs, treatment preference, and outcomes in a randomized trial for major depressive disorder. *Journal of Psychiatric Research*, *46*, 375–381.

Duval, S., & Tweedie, R. (2000). Trim and fill: A simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. *Biometrics*, *56*, 455–463.

Hedges, L. V., & Olkin, I. (1985). *Statistical methods for meta-analysis*. San Diego, CA: Academic Press.

Henkel, V., Mergl, R., Allgaier, A. K., Kohnen, R., Möller, H. J., & Hegerl, U. (2006). Treatment of depression with atypical features: A meta-analytic approach. *Psychiatry Res*, *141*, 89–101.

Higgins, J. P. T., & Altman, D. G. (2008). Chapter 8: Assessing risk of bias in included studies. In J. P. T. Higgins & S. Green (Eds.), *Cochrane handbook for systematic reviews of interventions*. Version 5.0.1. Retrieved from http://www.cochranehandbook.org

Jarrett, R. B., Schaffer, M., McIntire, D., Witt-Browder, A., Kraft, D., & Risser, R. C. (1999). Treatment of atypical depression with cognitive therapy or phenelzine: A double-blind, placebo-controlled trial. *Archives of General Psychiatry*, *56*, 431–437.

Lamers, F., Rhebergen, D., Merikangas, K. R., de Jonge, P., Beekman, A. T. F., & Penninx, B. W. J. H. (2012). Stability and transitions of depressive subtypes over a 2-year follow-up. *Psychological Medicine*, *42*, 2083–2093.

Lamers, F., Vogelzangs, N., Merikangas, K. R., de Jonge, P., Beekman, A. T. F., & Penninx, B. W. J. H. (2013). Evidence for a differential role of HPA-axis function, inflammation and metabolic syndrome in melancholic versus atypical depression. *Molecular Psychiatry*, *18*, 692–699.

Leventhal, A. M., & Rehm, L. P. (2005). The empirical status of melancholia: Implications for psychology. *Clinical Psychology Review*, *25*, 25–44.

National Institute for Health and Clinical Excellence (NICE). (2009). *Depression: The treatment and management of depression in adults*. Holborn: Author.

Penninx, B. W., Milaneschi, Y., Lamers, F., & Vogelzangs, N. (2013). Understanding the somatic consequences of depression: Biological mechanisms and the role of depression symptom profile. *BMC Medicine*, *15*, 129.

Riley, R., Lambert, P., & Abo-Zaid, G. (2010). Meta-analysis of individual participant data: Rationale, conduct, and reporting. *BMJ*, *340*, c221.

Segal, Z. V., Kennedy, S., Gemar, M., Hood, K., Pedersen, R., & Buis, T. (2006). Cognitive reactivity to sad mood provocation and the prediction of depressive relapse. *Archives of General Psychiatry*, *63*, 749–755.

Stewart, J. W., McGrath, P. J., Quitkin, F. M., & Klein, D. F. (2007). Atypical depression: Current status and relevance to melancholia. *Acta Psychiatrica Scandinavica 115*, (Suppl. 433), 58–71.

Thase, M. E. (2007). Recognition and diagnosis of atypical depression. *Journal of Clinical Psychiatry*, *68*(Suppl. 8), 11–16.

Uher, R., Dernovsek, Z., Mors, O., Hauser, J., Souery, D., & Zobel, A. . . . Farmer, A. (2011). Melancholic, atypical and anxious depression subtypes and outcome of treatment with escitalopram and nortriptyline. *Journal of Affective Disorders*, *132*, 112–120.