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The effectiveness of off-label dopamine stimulating agents in depressive disorder: A systematic review and meta-analysis

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ABSTRACT

The chronicity of depressive disorders is a major problem. Dopamine stimulating agents (DSA) are suggested to hold a promising potential in depression management, particularly in older adults, in whom dopamine deficiency due to aging may be an underlying cause. More evidence is needed to support these drugs in the management of depression. Therefore, we conducted a systematic literature review and meta-analysis. Data was extracted from eighteen randomized-controlled-trials and eight open-label-studies. Additional meta-regression-analyses were performed to examine superiority of monotherapy versus augmentation, and to rule out a putative age effect. DSA were found to reduce depressive symptoms (SMD=-0.26, 95%CI[-0.43;-0.10]). Heterogeneity was high and a significant Egger's test indicated publication bias. Adjustment for missing studies, using trim-and-fill-methodology, reduced the effect size (SMD=-0.17, 95%CI[-0.39;0.05]), which lost statistical significance. Removing the outlier study from the analysis, the effect size remained marginally small, but was statistically-significant (SMD=-0.17, 95%CI[-0.31;-0.02]). Neither augmentation nor monotherapy was superior. No age effect was found. It can be concluded that off-label DSA are overall effective in reducing depressive symptoms. However, the evidence is weak, regarding the publication bias, and modest-to-weak treatment effects. Well-designed high-quality trials are highly needed, before dopamine stimulating agents can be adequately positioned in future depression treatment protocols.

1. Introduction

Depression is a prevalent and disabling disorder at any age, affecting more than 264 million people worldwide (James et al., 2018). The prognosis of depression worsens with age (Schaakxs et al., 2018), which is partly explained by an increase in physical health problems, higher prevalence of suffering losses – such as the death of a spouse or dear friend – and a diminished response to conventional antidepressants (Blazer, 2003). Current treatment protocols for depression contain an 'one-size-fits-all' regimen and are little age-specific, while more specific and personalized treatments are needed to improve the prognosis of patients with depression and reduce chronicity.

Growing evidence has indicated a reciprocal relationship between depression and frailty (Oude Voshaar et al., 2021), which can be seen as a marker of accelerated aging within individuals. Inflammation and dopamine depletion are among the two most important aging

mechanisms, with the latter leading to a gradual depletion of the dopaminergic tonus across the lifespan (Felger et al., 2016), leading to reduced dopamine levels in the brain. Moreover, inflammation can inhibit key components of dopamine synthesis and availability even more (Taylor et al., 2022). A previous study has demonstrated age to be a mediating factor in antidepressant response, with those aged 65 and older experiencing lower efficacy of conventional antidepressant treatment (Calati et al., 2013). A major problem is that current antidepressant treatment protocols have not yet incorporated the consequences of (accelerated) aging within individuals (Rutherford et al., 2016), while it may be assumed that the effectiveness of conventional antidepressants is hindered by a reduced dopaminergic tone, particularly later in life.

Clinically, diminished dopamine brain levels, manifest itself as inertia in thought processes (Bäckman et al., 2006), slowness in movement (Stahl and Albert, 2017), and other cognitive changes such as apathy. These manifestations partly overlap with symptoms of

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depression, including anhedonia, and psychomotor retardation. There has been increasing interest in the so-called ‘slow-phenotype’ depression, which is associated with an increased inflammation and dopaminergic deficiency (Rutherford et al., 2019). This slow-phenotype depression tends to have a poor response to conventional antidepressants, including selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), and tricyclic antidepressants (TCAs) (Bäckman et al., 2006). Furthermore, new evidence indicates that MDD patients with high inflammation, as measured by CRP, exhibit a greater antidepressant response to SSRIs used in combination with a dopamine enhancer (bupropion) compared to SSRI monotherapy (Jha and Trivedi, 2018). Pharmacological strategies that increase dopamine availability or signaling may effectively treat MDD, particularly in patients with slow-phenotype depression and/or high inflammation. However, few dopamine stimulating agents are currently registered or available for the treatment of depressive disorder (Tundo et al., 2019).

Dopamine agonists such as pramipexole have already been proven effective in reducing depressive symptoms in Parkinson’s disease (Bxarone et al., 2010), a disease caused by severe dopaminergic deficiency (Aiken, 2007). Despite the tentative evidence that dopamine stimulating agents are also effective in improving the outcome of depressive disorder (Tundo et al., 2019; Aiken, 2007), it has not been part of clinical guidelines yet. The literature lacks a comprehensive overview of studies evaluating the effectiveness of a broad range of dopamine stimulating agents in depressive disorder, which are currently not registered (off-label) for depression management in Europe. These include dopamine agonists, stimulants, selective MAO-B-inhibitors, and levodopa. Studies to date usually focus on the effectiveness of one dopamine stimulating agent in particular (Tundo et al., 2019), hereby neglecting the theory of the existence of an overall triad between aging – inflammation and dopamine depletion – and depressive disorder (Taylor et al., 2022; Bäckman et al., 2006).

The current systematic literature review and meta-analysis aims to determine whether DSA are of added value in depression treatment by investigating the effectiveness of a broad range dopamine stimulating agents in depressive disorder, and by confirming a putative age effect. Specifically, the study will focus on drugs that are currently not registered (off-label) for depression management in Europe, including stimulants (e.g. methylphenidate, dexamphetamine, modafinil), dopamine agonists (e.g. pramipexole, ropinirole, bromocriptine), selective MAO-B-inhibitors (selegiline), and levodopa in major depressive disorder. We hypothesize that dopamine stimulating agents as a group are overall effective in reducing depressive symptoms, particularly later in life.

2. Methods

The meta-analysis was conducted using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Page et al., 2021). The review protocol was registered in advance at the international prospective register of systematic reviews (PROSPERO), registration number CRD42021258330. Reference management software Mendeley (Holt Zaugg Isaku and Randall, 2011) was used to manage retrieved articles and screening- and labeling tool Rayyan (Ouzzani et al., 2016) was used to screen articles.

2.1. Eligibility criteria

2.1.1. Population

Full-text articles written in English were considered eligible if they met the following criteria: 1) experimental/intervention studies (randomized controlled trials, case studies with more than 5 participants) 2) including participants over the age of 18, and 3) studying the effects of one or more of the selected medications in relation to depression. Both augmentation and monotherapy studies were included. Studies were excluded if they included participants younger than the age of 18, or

participants without clinically relevant symptoms of unipolar depression. A formal diagnosis of depression according to DSM-criteria with a validated diagnostic interview (e.g., SCID, MINI) had to have been made. Studies including participants with bipolar depression and from whom the results could not be separated from participants with unipolar depression were also excluded.

2.1.2. Interventions

All medications with dopamine stimulating properties were included, except for the partial dopamine agonists (antipsychotics) and antidepressant drugs with a current registration for depression treatment in Europe. Bupropion, non-selective MAO-inhibitors (tranylcypromine), and MAO-A-inhibitors (moclobemide) were left out the review, because these drugs are currently registered as antidepressant drugs in Europe. The most important reason to exclude the partial dopamine agonists (i.e. aripiprazole, brexpiprazole, and cariprazine) is that these drugs (being antipsychotics) have a predominantly antagonistic effect on dopamine-2-receptors. Even aripiprazole, being the partial agonist with the most agonistic action, inhibits roughly 80% of dopamine-2-transmission (Stahl, 2016). Despite the already proven clinical effectiveness of aripiprazole in the treatment of depressive disorder (Lenze et al., 2015), these drugs were therefore excluded. Furthermore, as the partial agonists have strong serotonergic modulatory properties (e.g. by 5HT1A partial agonism) it would also be difficult to attribute their antidepressant efficacy to dopamine.

Dopamine Stimulating Agents (DSA) were subsequently divided into four groups, i) dopamine agonists (e.g. pramipexole, ropinirole, bromocriptine), ii) stimulants (e.g. methylphenidate, dexamphetamine, modafinil), iii) MAO-B-inhibitors (selegiline), and iv) levodopa.

2.1.3. Predictor and outcome variables

The main outcome measured was the severity of depressive symptoms before and after exposure to the selected medications. Different validated measurement types of depression were included: most commonly the Hamilton Depression Rating Scale (HAM-D) (Hamilton, 1960) and Montgomery Asberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979). Non-validated scales were not included.

2.2. Search strategy

A comprehensive literature search of PubMed (Medline), Embase, Cochrane Library, and PsycINFO was carried out to find peer-reviewed articles on the topic of dopamine stimulating agents for the treatment of depression using a combination of search terms (see Appendix I). Search terms were identified in the title, abstract, and keyword fields. A search profile was developed with the help of a qualified librarian and performed up until July 9th, 2021. Reference lists of retrieved articles were examined for other related studies. After first selection on title and abstract by the first author, all possible eligible studies were evaluated on inclusion and exclusion criteria by two researchers. Differences in judgment were settled by discussion and in case no consensus could be reached, a third author decided.

2.3. Study selection

A flow diagram of the study selection process is presented in Fig. 1. The systematic literature search was carried out until July 9th, 2021. Searching the four databases resulted in a total of 7540 potential articles, of which 1893 duplicates were removed. Title and abstract of 6547 articles were screened based on the inclusion and exclusion criteria, excluding 6436 articles. Of the remaining 65 articles another eleven could not be retrieved, most of which were trial registrations. Finally, 54 articles were assessed for eligibility. Of these, another nine articles were excluded because they turned out to be reviews. Another eighteen articles did not present suitable data. This resulted in a total of 27 included

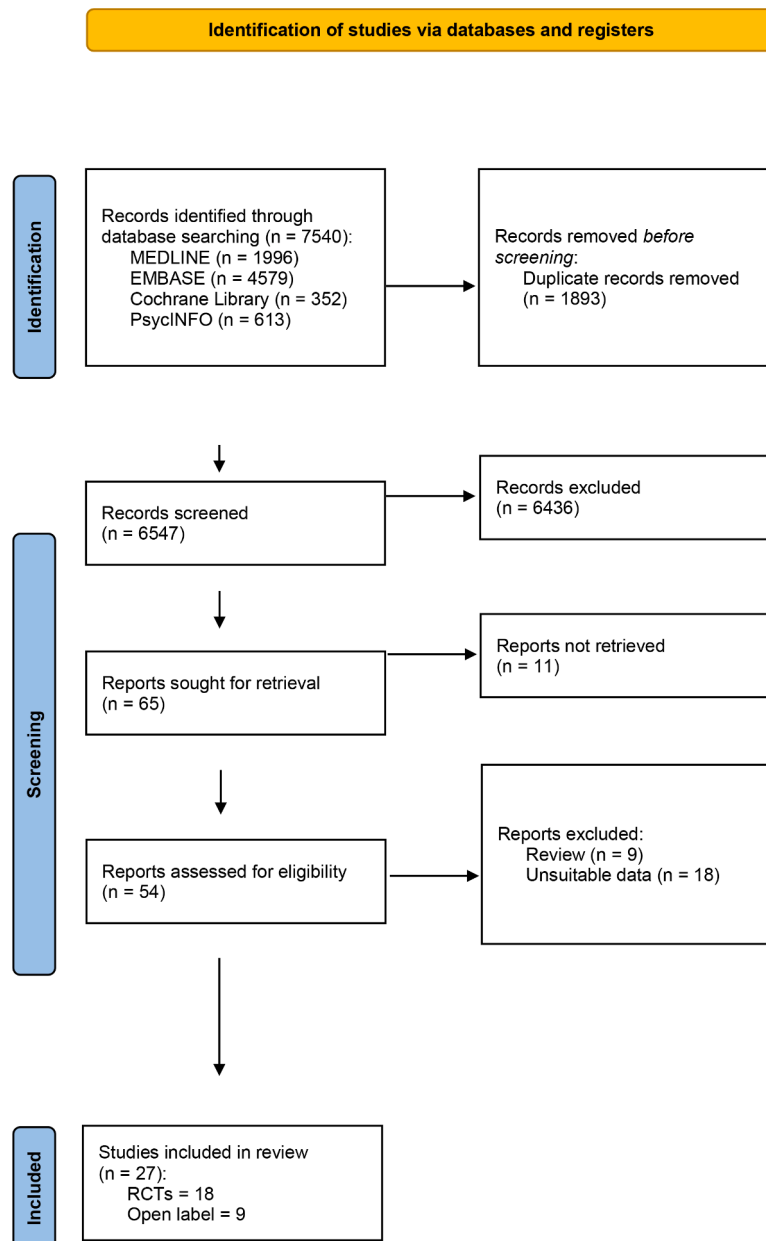


Fig. 1. Flow of information through the different phases of the systematic search (HAMILTON, 1960).

articles (see Fig. 1). Seventeen were RCTs, of which one article presented two RCT studies (Richards et al., 2016). One was an open trial but had a control group matched from a different study (Quitkin et al., 1984), and nine were uncontrolled studies.

2.4. Data extraction procedure

Data extraction about key study characteristics including bibliographic details (publication year, country), setting, diagnosis of depression, intervention characteristics (type, duration, dosage), study population (mean age and age range, percentage of women), sample size, definition of severity (including baseline severity), methodology (type of statistical analysis, mean, standard deviation, effect measures) and reporting, and summary of quantitative findings and conclusions were collected. Data extraction was evaluated by two different researchers, and disagreements were settled by discussion.

2.5. Risk of bias assessment

To assess the characteristics of the studies for risk of bias, the Cochrane Risk of Bias tool (version 2) was used, the most common tool used for RCT studies (Higgins et al., 2011). The risk of bias was assessed by the first author and a second author was consulted only in case of uncertainty. Potential bias was assessed through five mandatory domains, based on information reported in the manuscripts (Appendix III):

- (1) bias arising from the randomization process.
- (2) bias due to deviations from intended interventions.
- (3) bias due to missing outcome data.
- (4) bias in measurement of the outcome.
- (5) bias in selection of the reported result.

2.6. Data analysis

All analyses were performed in R version 4.1.2 (Team, 2013), using

an online handbook . If studies contained different treatment arms (e.g., multiple dosages), these groups were combined in the meta-analysis by pooling the data applying the following formulas:

$$n_{pooled} = n_1 + n_2$$

$$m_{pooled} = \frac{n_1 m_1 + n_2 m_2}{n_1 + n_2}$$

$$SD_{pooled} = \sqrt{\frac{(n_1 - 1)SD_1^2 + (n_2 - 1)SD_2^2 + \frac{n_1 n_2}{n_1 + n_2} (m_1^2 + m_2^2 - 2m_1 m_2)}{n_1 + n_2 - 1}}$$

Treatment effects (TE) and the standard errors of the treatment effect (seTE) for each study were calculated using Cohen's d to indicate the standardized mean differences (SMD) based on the mean change and corresponding standard deviations (SDs) or the pre- and post-treatment means and SDs. For RCTs, SMD refers to the difference of means between the intervention and control group. This can be either the mean change score or the mean end-of-treatment score. For uncontrolled trials, SMD refers to the difference between the mean end-of-treatment score and the mean baseline score, which is equal to the change score. Placebo-controlled and uncontrolled studies were separated in the analyses. For RCTs, end-of-treatment scores were used for SMD calculation, if no change score was presented. These two types of results can be validly combined, according to Da Costa and colleagues (2013) (Da Costa et al., 2013). Sensitivity analyses were performed to check for inconsistencies between the different result types. If neither change scores or end-of-treatment scores were available, F-scores were used to calculate the TE. For analyses of uncontrolled studies, average baseline and end-of-treatment scores and their SDs were used, if no change score was presented. For calculation of the seTE of the within-group SMD, the correlation coefficient was estimated at 0.5. If neither means were available, F-scores were used to calculate the TEs. Treatment effect sizes were pooled by applying a random-effects model using the DerSimonian-Laird estimator to calculate a mean weighted SMD of all included studies by estimating the variance of the distribution of true effects sizes. Hartung-Knapp adjustments were used in the random-effects model, which estimate the between-study variance like the DerSimonian-Laird estimator but do not base further calculations on a standard distribution (Jackson et al., 2017). This modified method has been argued to outperform the standard DerSimonian-Laird method (Int'Hout et al., 2014) and is therefore recommended to apply in random-effects meta-analysis (Van Aert and Jackson, 2019). A mean weighted SMD of $p < 0.05$ (two-tailed) was regarded as statistically significant, with 0.2 reflecting a small effect, 0.5 a medium one and ≥ 0.8 a large effect. Heterogeneity was assessed by evaluating Q -values and the I^2 -statistic. The Q -statistic shows a Chi-square distribution with $k-1$ degrees of freedom (k = number of studies). High between-studies variability was indicated by Q -values higher than the degrees of freedom (df). The I^2 -statistic indicates the percentage of total variation due to heterogeneity (Huedo-Medina et al., 2006). An I^2 -value of 25% was regarded as low, 50% as moderate, and 75% as high heterogeneity. The funnel plot and Egger's test ($p < 0.01$, two-tailed) were inspected to investigate the possibility of a publication bias, which is the tendency to publish only significant results and can thus create bias in favor of positive results (Joober et al., 2012). An asymmetrical plot and significant Egger's test would indicate potential publication bias. In case of publication bias, the trim-and-fill method was performed to adjust the effect estimates for missing studies (Duval and Tweedie, 2000). Finally, leave-one-out analyses were performed, to investigate the influence of each study on the overall effect-size estimate and to identify influential studies.

2.6.1. Additional subgroup analyses

Analyses were performed to investigate differences between studies with and without a control group, and for monotherapy versus

augmentation therapy. Finally, a meta-regression comparing the effect sizes against mean age was created to investigate a potential age effect.

3. Results

3.1. Characteristics of included studies

The 27 studies included a total of 3387 patients (see Table 1). All articles were published between 1972 and 2019. One study was performed in Iran, eighteen in the United States of America, one in the United Kingdom, two in Italy, one in Israel, one in Japan, one in Turkey, one in Canada, and one in Germany. Almost all studies were performed using outpatient participants (inpatient = 2; inpatient & outpatient = 1; outpatient = 24).

3.2. Overall meta-analysis and heterogeneity

The forest plot below (Fig. 2) presents the overall results from the placebo-controlled ($n = 19$ trials in 18 articles) studies included in the meta-analysis. The model showed a significant effect of DSA on reducing depressive symptoms (SMD = -0.26 , 95% CI [-0.43 ; -0.10]). Heterogeneity was relatively high [$Q(18) = 42.2$, $p < 0.001$; $I^2 = 57\%$].

To investigate heterogeneity, studies were separated into those with a sample size above 50 and those with a sample size below or equal to 50, as small studies tend to be more heterogeneous than larger ones (Abolfazli et al., 2011). Heterogeneity reduced drastically for studies with a large sample size to a nonsignificant level [$Q(11) = 12.54$, $p = 0.32$; $I^2 = 12\%$]. The treatment effect remained statistically significant in both groups.

Meta-analysis of the nine uncontrolled studies revealed a significant pre-post decrease in depression scores (SMD = -1.75 , 95% CI [-2.77 ; -0.73]), also with a high level of heterogeneity [$Q(8) = 110.5$, $p < 0.001$; $I^2 = 93\%$]. Appendix II shows results when uncontrolled studies ($n = 9$) are included.

3.3. Additional subgroup analysis

3.3.1. Monotherapy versus augmentation

The forest plot in Fig. 3 below shows the results of the first additional analysis comparing treatment effects between monotherapy and augmentation strategies in RCT studies. Augmentation effects were not significant (SMD = -0.23 , 95% CI [-0.52 ; 0.06], $p = 0.106$), but monotherapy effects were (SMD = -0.31 , 95% CI [-0.53 ; -0.09], $p = 0.012$), although there was no significant difference between both subgroups ($p = 0.62$).

3.3.2. Medication group effect

Separating medication groups yielded only a significant effect for the selective MAO-B-inhibitor (selegiline), but there was no difference between the different subgroups ($p = 0.23$), as can be seen in Fig. 2.

3.3.3. Age effect

Only two RCT studies from the total of 19 placebo-controlled studies included an older patient population. A bubble plot with mean age as independent variable is presented in Fig. 4. There was no significant effect of age observed ($p = 0.79$).

3.4. Study quality and risk of bias

Methodological quality was assessed for RCT studies only, given the probable higher risk of bias for pre-post open label studies which are non-randomized or non-blinded. RCT studies generally had relatively high dropout rates, hence a higher risk on bias due to missing outcome data. In total, ten studies indicated possible risk of bias.

Table 1
Characteristics of included studies.

Author	Design	Participants (female)	Mean age (years)	Intervention	Outcome measures
Albolfazli et al., 2011	Double-blind placebo-controlled RCT	Active: N = 23 (12) Control: N = 23 (11)	33; 33	400 mg/d modafinil augmentation 6 weeks	HAM-D
Amsterdam, 2003	Double-blind placebo-controlled RCT	Active: N = 149 (94) Control: N = 152 (99)	41; 44	20 mg/d STS patch monotherapy 8 weeks	HAM-D
Bodkin and Amsterdam, 2002	Double-blind placebo-controlled RCT	Active: N = 89 (53) Control: N = 88 (53)	41; 43	20 mg/d STS patch monotherapy 6 weeks	HAM-D
Bouras & Bridges, 1982	Double-blind placebo-controlled RCT	Active: N = 4 (3) Control: N = 5 (5)	45; 42	15 mg/d (3 × 5 mg) bromocriptine monotherapy 10 weeks	HAM-D
Cassano et al., 2005	Open label	N = 10 (7)	51	Between 0.75 mg/d and 2 mg/d ropinirole augmentation 16 weeks	MADRS
Cusin et al., 2013	Double-blind placebo-controlled RCT	Active: N = 30 (16) Control: N = 30 (18)	47; 46	Between 0.5 mg/d (2 × 0.25) to 1.5 mg/d pramipexole augmentation 8 weeks	MADRS
Dunlop et al., 2007	Double-blind placebo-controlled RCT	Active: N = 37 Control: N = 36	44	Between 100 mg/d to 300 mg/d modafinil augmentation 6 weeks	MADRS
Fava et al., 2005	Double-blind placebo-controlled RCT	Active: N = 158 (110) Control: N = 153 (110)	42; 42	100 mg/d modafinil (day 1–3), 200 mg/d (day 4–56) augmentation; 8 weeks	HAM-D
Feiger et al., 2006	Double-blind placebo-controlled RCT	Active: N = 132 (81) Control: N = 133 (71)	42; 42	Between 6 mg/d to 12 mg/d STS patch monotherapy 8 weeks	HAM-D
Gershon et al., 2019	Double-blind placebo-controlled RCT	Active: N = 11 (9) Control: N = 10 (6)	52; 51	0.5 mg/d until max. 2 mg/d ropinirole monotherapy 8 weeks	HAM-D
Hori & Kunugi, 2012	Open label	N = 12 (10)	36	0.25 mg/d up to 3 mg/d pramipexole augmentation 12 weeks	HAM-D
Konuk et al., 2006	Open label	N = 25 (8)	32	100 mg/d to 200 mg/d modafinil augmentation 6 weeks	HAM-D
Lattanzi et al., 2002	Open label	N = 16	54	0.375 mg/d to max. 1 mg/d pramipexole augmentation 16 weeks	MADRS
Lavretsky & Kumar, 2001	Open label	N = 10 (5)	80	Between 0.25 mg/d and 20 mg/d methylphenidate augmentation 8 weeks	HAM-D
Lavretsky et al., 2006	Double-blind placebo-controlled RCT	Active: N = 10 (5) Control: N = 6 (4)	74; 74	5 mg/d up to 20 mg/d methylphenidate augmentation 10 weeks	HAM-D
Lavretsky et al., 2015	Double-blind placebo-controlled RCT	Active: N = 48 (19) Control: N = 47 (28)	70; 70	Between 5 mg and 50 mg of methylphenidate daily 16 weeks	HAM-D
Markovitz & Wagner, 2003	Open label	N = 27 (21)	45	200 mg/d modafinil augmentation 38 weeks	GAF
Mattes, 1997	Double-blind placebo-controlled RCT	Active: N = 3 Control: N = 5	45	From 0.05 mg up to 2 mg of pergolide augmentation 3 weeks	HAM-D
Nasr, 2004	Open label	N = 99 (49)	44	Mean dosage of 265 mg/d modafinil augmentation 4 to 5 weeks	CDRS
Quitkin et al., 1984	Placebo-controlled open trial	Active: N = 22 (12) Control: N = 24 (14)	38; 38	10 mg/d (week 1–4), 20 mg/d (week 5), 30 mg/d (week 6) selegiline monotherapy 6 weeks	HAM-D
Ravindran et al., 2008	Double-blind placebo-controlled RCT	Active: N = 73 (47) Control: 72 (47)	46; 42	18 mg/d up to 54 mg/d OROS methylphenidate monotherapy 5 weeks	MADRS
Richards et al., 2016	Double-blind placebo-controlled RCT	Study 1 Active: N = 201 (129) Control: N = 201 (133) Study 2 Active: N = 211 (141) Control: N = 213 (143)	42; 42 42; 43	30, 50, or 70 LDX daily augmentation 16 weeks	MADRS
Richards et al., 2017	Double-blind placebo-controlled RCT	Active: N = 314 Control: N = 280 (53)	42; 44	10, 30, 50, or 70 mg LDX once daily (combined in meta-analysis) 8 weeks	
Rickels et al., 1972	Double-blind placebo-controlled RCT	Active: N = 50 Control: N = 51	33	30 mg/d methylphenidate monotherapy 4 weeks	PDS
Rutherford et al., 2019	Open label	N = 36 (20)	75	150 mg up to 450 mg L-DOPA or up to 3 × 36.5 mg carbidopa 3 weeks	HAM-D
Sunderland et al., 1994			66		HAM-D

(continued on next page)

Table 1 (continued)

Author	Design	Participants (female)	Mean age (years)	Intervention	Outcome measures
Szegedi et al., 1997	Double-blind placebo-controlled RCT	Active: N = 16 (12)	45	60 mg/d selegiline monotherapy	MADRS
	Open label	Control: N = 16 N = 26 (12)		3 weeks Up to 9 mg/d pramipexole monotherapy 4 weeks (up to 75 weeks)	

Note. STS = selegiline transdermal system.

Note. GAF = Global Assessment Functioning; CDRS = Carroll Depression Rating Scale; PDS = Physician Depression Scale.

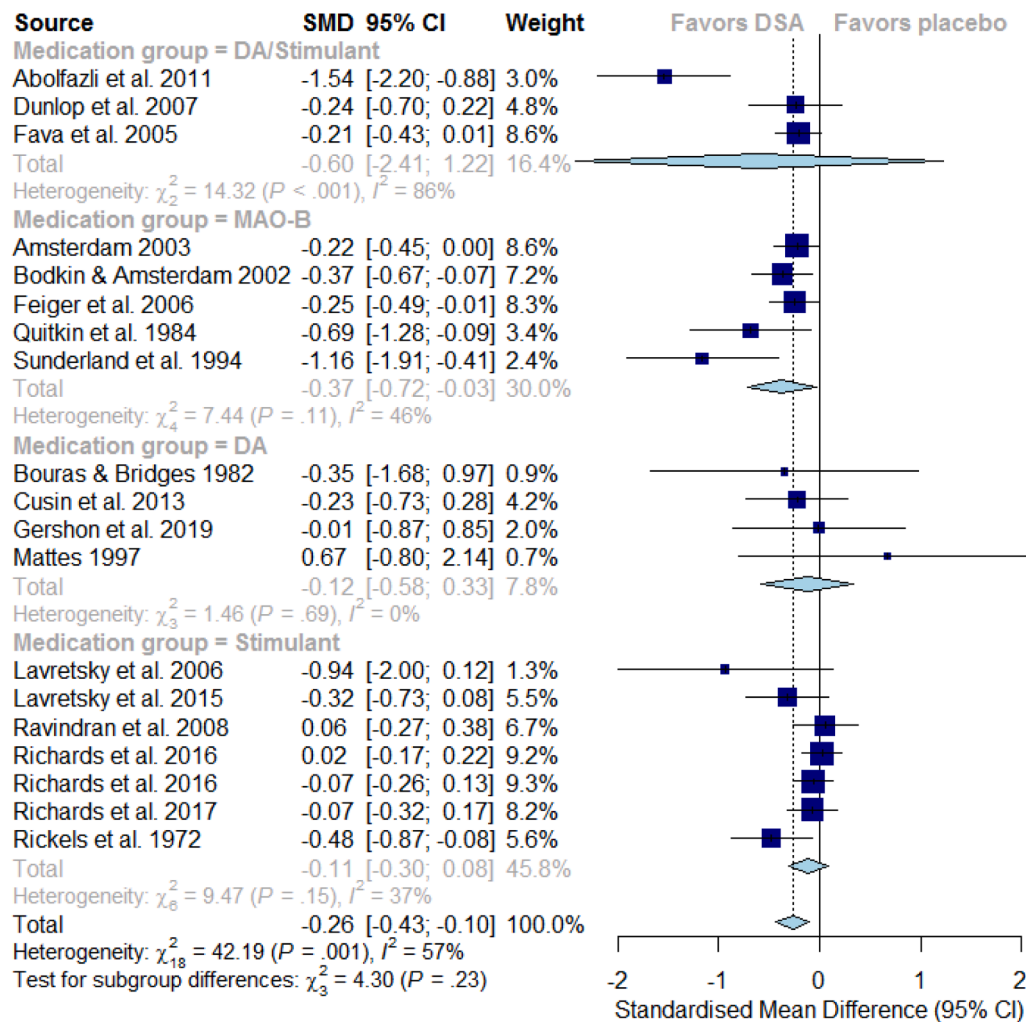


Fig. 2. Meta-analysis: overall results.

3.5. Risk of publication bias and sensitivity analyses

Visual inspection of the funnel plot of the RCT studies suggested potential publication bias, indicated by asymmetry (Appendix Va). A significant Egger's test indicated potential publication bias for placebo-controlled studies ($t = -2.391$, 95% CI [-2.83; -0.28], $p = 0.0286$). When uncontrolled studies were included, this effect increased ($t = -4.282$, 95% CI [-4.19; -1.56], $p = 0.0002$).

Adjusting the effect estimates for missing studies, using the trim-and-fill method (Duval and Tweedie, 2000), the results show a slightly decreased treatment effect (SMD = -0.17, 95% CI [-0.39; 0.05]), which was no longer statistically significant ($p = 0.128$). Leave-one-out analyses (Appendix IV) specifically revealed that the study by Abolfazli et al. (2011) (Abolfazli et al., 2011) is an outlier, and largely influenced the main finding. Omitting the trial by Abolfazli et al. (2011) in a

sensitivity analysis slightly reduced the treatment effect (SMD = -0.20, 95% CI [-0.32; -0.09]), but also reduced heterogeneity to a non-significant level [$Q(17) = 25.8$, $p = 0.079$; $I^2 = 34\%$]. Moreover, the trim-and-fill analysis excluding this outlier demonstrated that the main treatment effect remained statistically significant (SMD = -0.17, 95% CI [-0.31; -0.02], $p = 0.026$). A funnel plot including the imputed studies was added to the appendix (Appendix Vb). Sensitivity analyses ruled out inconsistencies between the use of end-of-treatment scores versus change scores (Appendix VI).

4. Discussion

The most important finding from the meta-analysis is a small-sized, but significant, overall effect favoring dopamine stimulating agents (DSA) in reducing depressive symptoms in major depressive disorder.

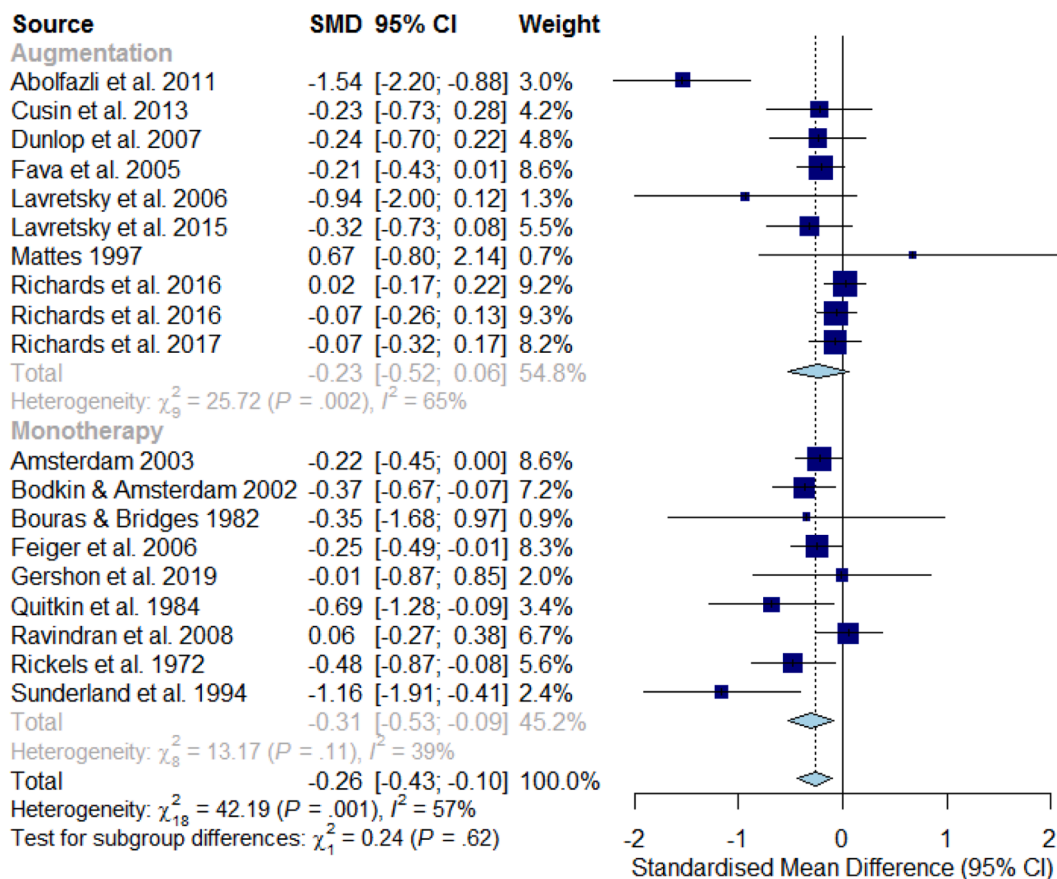


Fig. 3. Comparing augmentation versus monotherapy strategies in RCTs.

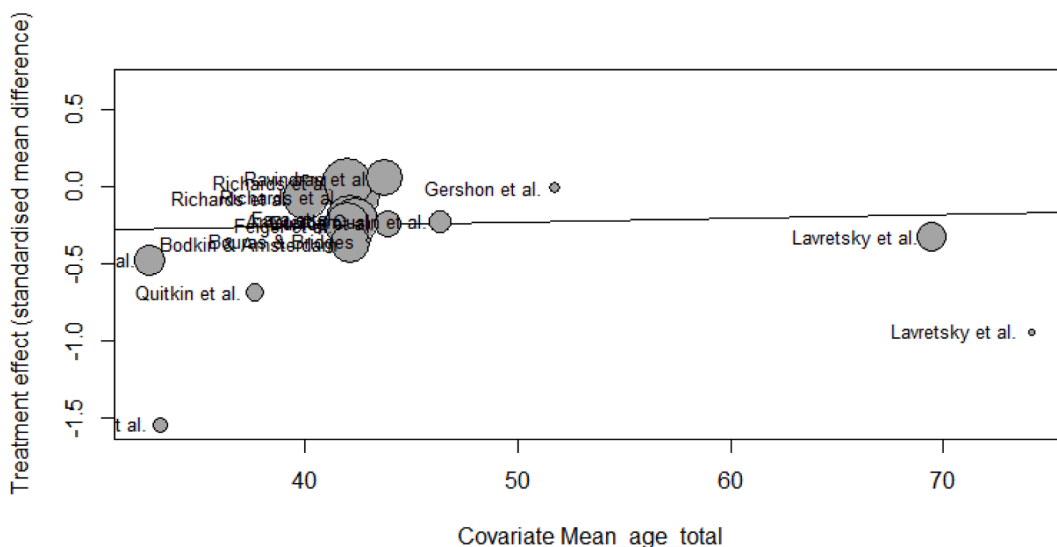


Fig. 4. Bubble plot comparing age effects in RCTs.

The meta-analysis included eighteen articles, comprising nineteen RCT studies. Separating placebo-controlled and uncontrolled studies yielded both significant effects. Given the indications for a publication bias, and the potential risk of bias in certain studies due to high dropout rates, results must be interpreted with caution.

Nevertheless, the main finding may indicate a promising potential for the use of DSA in the management of depression. In-depth analysis, in which medication groups were distinguished, showed a slight preference for the use of the selective MAO-B-inhibitor (selegiline), although

no subgroup differences were found. For the other dopaminergic drug classes we found no supporting evidence. In contrast to the non-selective MAO-inhibitor (e.g. tranylcypromine), selegiline has far fewer adverse effects. Also the possibility of transdermal administration (plaster) (Bodkin and Amsterdam, 2002; Amsterdam, 2003), eases its use in certain situations where oral administration is hindered. Contrary to Europe, in the USA a transdermal patch containing selegiline (Emsam) has already been approved by the FDA for treatment of major depressive disorder (MDD) in adults.

From a historical perspective, in the development of antidepressants, much attention has been paid to the reuptake of neurotransmitters serotonin (SSRIs), and noradrenalin (TCAs), or a combination of these two (SNRIs), whereas little attention has been paid to the reuptake of dopamine in depression management. Electroconvulsive therapy (ECT) respectively non-selective MAO-inhibitors (e.g. tranylcypromine) both exhibit dopamine stimulating properties, and are highly effective treatment strategies for treatment-resistant depressive disorder, but not used until late in the treatment process. We found some first evidence that off-label DSA might be effective as monotherapy and as augmentation strategy. These findings indirectly support a role for dopamine in recovery from depression. A recent review has described the molecular pathways underlying the potential antidepressant effects of D1-like-receptors and D2-like-receptors (Zhao et al., 2022). Given the high degree of chronicity of depressive disorder, there is an urgent need for more effective, tailored, treatment strategies earlier in the disease course. Whether DSA could have a place as (first-line) antidepressants and for what type of patients deserves further study.

In addition, the so-called placebo-reward hypothesis states that placebos can induce dopamine release due to the expectation of reward (de la Fuente-Fernández, 2009). This could mean that true treatment effects in RCTs may be even larger than currently presented. The results of the current study are largely in accordance with those found in meta-analyses on the working of certain dopamine treatments in patients with bipolar depression, (Tundo et al., 2019) and Parkinson's disease (Ives et al., 2004). Another meta-analysis conducted on the efficacy of 21 antidepressants, including SSRIs, SNRIs, and TCAs, found a moderate effect favoring treatment over placebo (Cipriani et al., 2018). These results are similar to those found in the current meta-analysis on monotherapy placebo-controlled studies (SMD = 0.31, 95% CI [-0.53; -0.09], $p = 0.012$), and hence suggest that DSA may have comparable treatment effects as conventional antidepressants.

Despite these indications, only six out of the twenty-seven studies included were conducted within the last ten years (Rutherford et al., 2019; Richards et al., 2016; Cusin et al., 2013; Gershon et al., 2019; Lavretsky et al., 2015; Richards et al., 2017). As there are no notable differences between earlier and later studies, the idea seems to have become less popular nowadays despite indications of the efficacy of DSA in the treatment of depressive disorder. Similarly, only two RCT studies were conducted among older adults, (Lavretsky et al., 2015; Lavretsky et al., 2006) which makes interpretation of a possible age effect difficult. However, the mean age of participants in all included studies combined was approximately 47.5 years old. It has been suggested that dopamine levels decline by around 10% every ten years since early adulthood (Mukherjee et al., 2002), which implicates that dopamine depletion effects may already play a role in middle-aged adulthood. The results in this study did not support our hypothesis that DSA are more effective later in life. However, more research specifically in the older adult population needs to be done.

4.1. Implications for clinical practice

Though effects found were largest in uncontrolled studies, significant effects were also present in randomized controlled trials, suggesting there may be clinical benefits in the prescription of DSA for depressed patients as placebos are not fully responsible for the effects. As there are ample differences in tolerability between dopaminergic agents, it will be important to gain more insight into particular dopaminergic compounds. Case study effects emphasize the importance of a more individual approach to treatment of clinical depression. Important reasons to consider DSA for depressive patients are 1) intolerable side-effects from conventional antidepressant agents in which case monotherapy with DSA could be considered; and 2) insufficient effects from conventional antidepressants – which, unfortunately is common – in which case augmentation with DSA could be a relevant option.

4.2. Limitations and further research

The current meta-analysis and systematic review presents an important overview of a promising research field that unfortunately seems to have been neglected in recent years. Its primary strengths therefore include the extensive overview of the literature on the topic of dopamine agonists for depression, highlighting the importance of future research in this field. The different types of studies, and dopamine stimulating agents were included to find as many trials as possible and to provide evidence for a role of dopamine in depression. Specifically, the slow-phenotype depression associated with dopaminergic depletion has hardly been investigated in individual studies, which underlines the addition to the literature of the current study. The findings of the current study may therefore hopefully act as a catalyst for future research to be conducted on this topic.

The current systematic literature review and meta-analysis is not without limitations. First, high heterogeneity was found between studies, even among the placebo-controlled studies. Variance likely occurred in several domains, including different measurement scales of depression severity, varying sample sizes, different treatments and dosages, baseline severity of depression symptoms and other individual differences in participants. Though heterogeneity is expected when conducting a meta-analysis, a high between-study variability may influence the strength of the results. However, when separating results for studies with a large and small sample size, heterogeneity for those with a big sample size reduced to a nonsignificant level while the effectiveness of DSA for treatment of depression remained significant in large studies. Second, several studies had a high risk of bias, particularly bias due to missing outcome data. Although it is common for participants to dropout of clinical trials for a variety of reasons, results must still be interpreted with caution, given that it cannot always be excluded these reasons are related to the true values of outcome data. This means systematic differences could exist between participants who adhered to protocol or did not. Still, very few dropouts occurred due to severe adverse effects, indicating that treatments were generally well-tolerated. Third, several studies could not be included due to a lack of data, despite fitting other inclusion criteria. This resulted in a lower number of included studies in the meta-analysis than could have potentially been included, which might have affected the outcome. Moreover, for RCTs, SMDs based on end-of-treatment scores were combined with SMDs based on change scores, which is a limitation according to the Cochrane Handbook. However, Da Costa and colleagues (2013) (Da Costa et al., 2013) showed that it is valid to combine these two types of results. Sensitivity analyses comparing both result types confirmed that our main finding was consistent and robust. Finally, the studies included in this meta-analysis did not include comparable data regarding inflammation status and specific symptom decreases, such as apathy and slowness in movement, even though earlier research suggests that augmentation of DSA with conventional antidepressants has a higher response on an increased inflammation status (Jha and Trivedi, 2018).

5. Conclusion

The results of this systematic review and meta-analysis suggest the overall effectiveness of off-label dopamine stimulating agents in the treatment of major depressive disorder, indicated by a significant small-sized effect in RCTs. However, the evidence is weak, regarding the publication bias, and modest to weak treatment effects. Adjustment for missing studies reduced the effect size, and it was no longer statistically significant. By removing the inflated outlier study from the analysis, the overall effect size remained marginally small, but statistically significant. The clinical practice may thus benefit from dopamine-related treatments in addition to or instead of registered antidepressant medication. DSA may be considered off-label when conventional antidepressants are ineffective. Considering the potential publication bias, and poor methodological quality of certain studies included in the current

meta-analysis, future clinical trials are highly advised to better investigate the role and positioning of dopamine stimulating drugs in the management of depression.

Trials investigating the effects of DSA on depression, also in older adults (aged > 65) remains interesting, considering the triad between aging – inflammation & dopamine depletion – depression (Rutherford et al., 2016), and poor outcome of late-life depression (Jeuring et al., 2018). The use of DSA in patients nonresponsive to conventional antidepressants (e.g. treatment-resistant depression), and in other populations, such as minor depression have to be further investigated. Also,

collecting and combining data of psychomotor retardation, inflammation, and dopamine levels are important to consider in designing studies. Rutherford and colleagues have embarked on a promising path (Rutherford et al., 2016), our findings support that the field is on the right track.

Declaration of Competing Interest

none.

Appendix I. Search Strategy

Medline (PubMed)

("Depressive Disorder"[Mesh] OR "Depression"[Mesh] OR depress*[ti]) AND ("Dopamine Agonists"[Mesh] OR "Dopamine Agents"[Mesh:NoExp] OR "Dopamine Agents" [Pharmacological Action] OR "dopamine agonist*[tiab] OR "dopaminergic agonist*[tiab] OR "dopamine receptor agonist*[tiab] OR "dopaminergic receptor agonist*[tiab] OR "dopamine agent*[tiab] OR "dopaminergic-agent*[tiab] OR "dopamine stimulat*[tiab] OR "dopamine deplet*[tiab] OR "dopaminergic deplet*[tiab] OR "dopaminergic stimulat*[tiab] OR "d3 agonist*[tiab] OR Bromocriptin*[tiab] OR Bromocryptin*[tiab] OR carbidopa[tiab] OR modafinil[tiab] OR dexamphetamin*[tiab] OR levodopa[tiab] OR l-dopa[tiab] OR pramipexole[tiab] OR ropinirole[tiab] OR methylphenidate[tiab] OR selegiline[tiab] OR rasagiline[tiab] OR safinamide[tiab]) AND ("Clinical Trial" [Publication Type] OR "Clinical Trials as Topic"[Mesh] OR "Treatment Outcome"[Mesh:NoExp] OR "clinical trial*[tiab] OR clinicaltrial* OR "clinical study"[tiab] OR "controlled trial*[tiab] OR "controlled study"[tiab] OR random*[tiab] OR trial[ti]) NOT ("Child"[Mesh] OR "Adolescent"[Mesh]) NOT "Adult"[Mesh] NOT ("Animals"[Mesh] NOT "Humans"[Mesh]) NOT ("Parkinson Disease"[Mesh]) NOT ("Schizophrenia"[Mesh]) NOT ("Neoplasms"[Mesh])

1996 results

Embase

('chronic depression'/exp OR 'late life depression'/exp OR 'major depression'/exp OR depress*:ti,ab OR antidepress*:ti, kw) AND ('dopamine receptor stimulating agent'/exp OR 'methylphenidate'/exp OR 'carbidopa'/exp OR 'dexamphetamine'/exp OR 'levodopa'/exp OR 'modafinil'/exp OR (dopamin* NEXT/3 (agonist* OR agent* OR stimulat* OR deplet*):ab,ti,kw) OR 'd3 agonist*':ab,ti,kw OR bromocriptin*:ab,ti,kw OR bromocryptin*:ab,ti,kw OR carbidopa:ab,ti,kw OR modafinil:ab,ti,kw OR dexamphetamin*:ab,ti,kw OR levodopa:ab,ti,kw OR pramipexole:ab,ti,kw OR ropinirole:ab,ti,kw OR methylphenidate:ab,ti,kw OR selegiline:ab,ti,kw OR rasagiline:ab,ti,kw OR safinamide:ab,ti,kw) NOT 'parkinson disease':ab,ti,kw NOT 'schizophrenia':ab,ti,kw NOT 'cancer':ab,ti,kw AND ('clinical trial'/exp OR 'major clinical study'/exp OR 'intervention study'/exp OR 'treatment outcome'/de OR 'clinical outcome'/exp OR 'clinical trial*':ab,ti,kw OR clinicaltrial*:ab,ti,kw OR 'clinical study':ab,ti,kw OR 'controlled trial*':ab,ti,kw OR 'controlled study':ab,ti,kw OR random*:ab,ti,kw OR trial:ti) NOT ('child'/exp OR 'adolescent'/exp) NOT 'adult'/exp) NOT ('animal'/exp NOT 'human'/exp OR 'conference abstract'/it)

4579 results

Cochrane Library

([mh "Depressive Disorder"] OR [mh Depression] OR depression:ti OR depressive:ti OR depressed:ti OR antidepress*:ti) AND ([mh "Dopamine Agonists"] OR [mh "Dopamine Agents"] OR [mh Levodopa] OR [mh Bromocriptine] OR [mh Carbidopa] OR [mh Dextroamphetamine] OR [mh Methylphenidate] OR [mh Modafinil] OR [mh Pramipexole] OR (dopamin* NEAR/3 agonist*):ti,ab OR (dopamin* NEAR/3 agent*):ti,ab OR (dopamin* NEAR/3 stimulat*):ti,ab OR (dopamin* NEAR/3 deplet*):ti,ab OR ("d3" NEAR/3 agonist*):ti,ab OR Bromocriptin*:ti,ab OR Bromocryptin*:ti,ab OR carbidopa:ti,ab OR modafinil:ti,ab OR dexamphetamin*:ti,ab OR levodopa:ti,ab OR l-dopa:ti,ab OR pramipexole:ti,ab OR ropinirole:ti,ab OR methylphenidate:ti,ab OR selegiline:ti,ab OR rasagiline:ti,ab OR safinamide:ti,ab) NOT [mh "Parkinson Disease"]

362 results

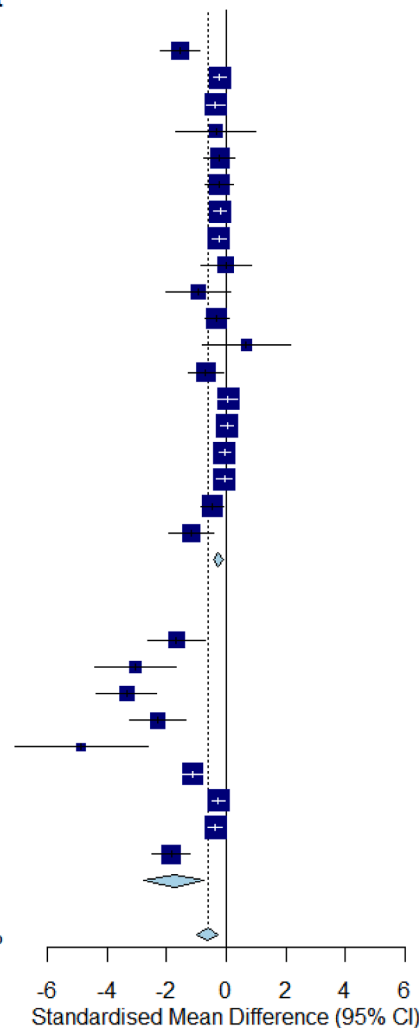
PsycINFO (EBSCO)

(DE "Major Depression" OR DE "Late Life Depression" OR TI (depress* OR antidepress*)) AND (DE "Dopamine Agonists" OR DE "Amphetamine" OR DE "Apomorphine" OR DE "Cabergoline" OR DE "Morphine" OR DE "Quinpirole" OR DE "Dextroamphetamine" OR DE "Bromocriptine" OR DE "Carbidopa" OR DE "Levodopa" OR DE "Methylphenidate" OR TI (dopamin* N3 (agonist* OR agent* OR stimulat* OR deplet*) OR "d3 agonist*" OR bromocriptin* OR Bromocryptin* OR carbidopa OR modafinil OR dexamphetamin* OR levodopa OR pramipexole OR ropinirole OR methylphenidate) OR AB (dopamin* N3 (agonist* OR agent* OR stimulat* OR deplet*) OR "d3 agonist*" OR bromocriptin* OR Bromocryptin* OR carbidopa OR modafinil OR dexamphetamin* OR levodopa OR pramipexole OR ropinirole OR methylphenidate) AND (DE "Experimental Design" OR DE "Between Groups Design" OR DE "Clinical Trials" OR DE "Cohort Analysis" OR DE "Followup Studies" OR DE "Hypothesis Testing" OR DE "Longitudinal Studies" OR DE "Repeated Measures" OR DE "Retrospective Studies" OR DE "Single-Case Experimental Design" OR DE "Randomized Controlled Trials" OR DE "Randomized Clinical Trials" OR DE "Drug Therapy" OR DE "Treatment Outcomes" OR DE "Treatment Effectiveness Evaluation" OR TI ("clinical trial*" OR clinicaltrial* OR "clinical study" OR "controlled trial*" OR "controlled study" OR random* OR trial OR study) OR AB ("clinical trial*" OR clinicaltrial* OR "clinical study" OR "controlled trial*" OR "controlled study" OR random*) NOT "Parkinson disease" NOT "neoplasms"

613 results

Appendix II. Inclusion of uncontrolled studies

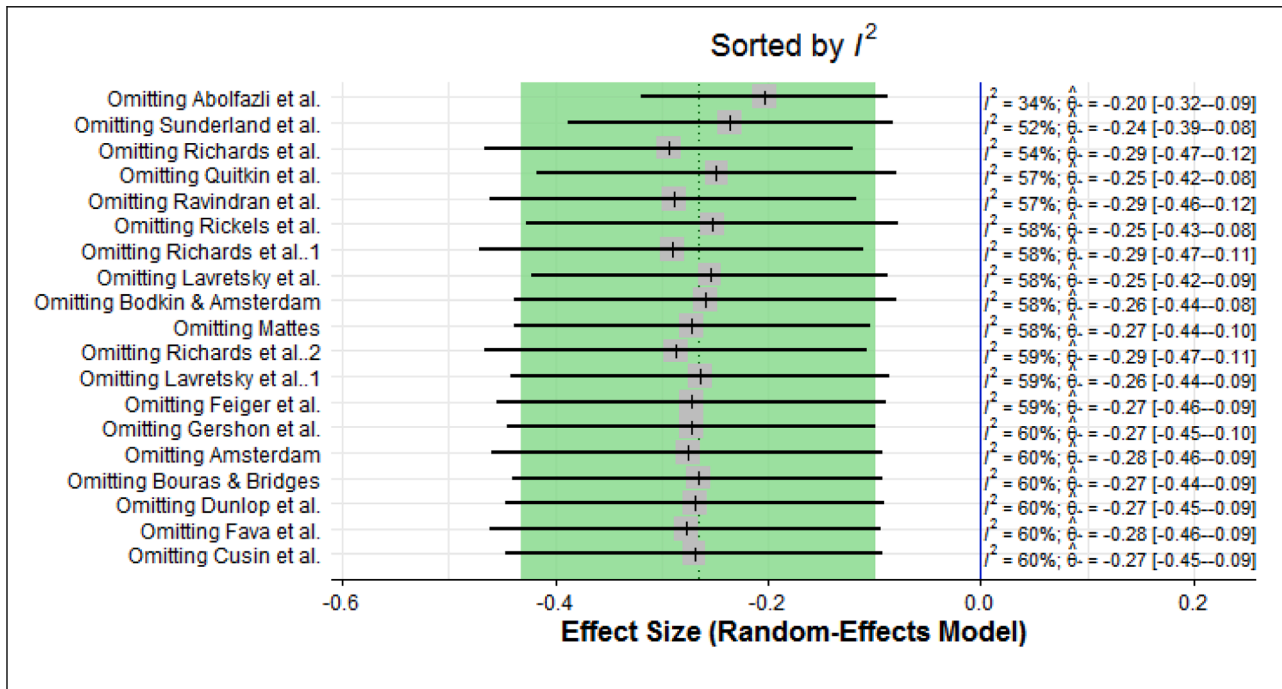
Source	SMD	95% CI	Weight
Control Group = Placebo			
Abolfazli et al. 2011	-1.54	[-2.20; -0.88]	3.3%
Amsterdam 2003	-0.22	[-0.45; 0.00]	4.9%
Bodkin & Amsterdam 2002	-0.37	[-0.67; -0.07]	4.7%
Bouras & Bridges 1982	-0.35	[-1.68; 0.97]	1.6%
Cusin et al. 2013	-0.23	[-0.73; 0.28]	3.9%
Dunlop et al. 2007	-0.24	[-0.70; 0.22]	4.1%
Fava et al. 2005	-0.21	[-0.43; 0.01]	4.9%
Feiger et al. 2006	-0.25	[-0.49; -0.01]	4.9%
Gershon et al. 2019	-0.01	[-0.87; 0.85]	2.6%
Lavretsky et al. 2006	-0.94	[-2.00; 0.12]	2.1%
Lavretsky et al. 2015	-0.32	[-0.73; 0.08]	4.3%
Mattes 1997	0.67	[-0.80; 2.14]	1.3%
Quitkin et al. 1984	-0.69	[-1.28; -0.09]	3.6%
Ravindran et al. 2008	0.06	[-0.27; 0.38]	4.6%
Richards et al. 2016	0.02	[-0.17; 0.22]	5.0%
Richards et al. 2016	-0.07	[-0.26; 0.13]	5.0%
Richards et al. 2017	-0.07	[-0.32; 0.17]	4.8%
Rickels et al. 1972	-0.48	[-0.87; -0.08]	4.3%
Sunderland et al. 1994	-1.16	[-1.91; -0.41]	3.0%
Total	-0.26	[-0.43; -0.10]	73.0%
Heterogeneity: $\chi^2_{18} = 42.19$ ($P = .001$), $I^2 = 57\%$			
Control Group = Not controlled			
Cassano et al. 2005	-1.67	[-2.63; -0.71]	2.3%
Hori & Kunugi 2012	-3.05	[-4.40; -1.70]	1.5%
Konuk et al. 2006	-3.34	[-4.35; -2.34]	2.2%
Lattanzi et al. 2002	-2.31	[-3.25; -1.37]	2.4%
Lavretsky & Kumar 2001	-4.87	[-7.09; -2.65]	0.7%
Markovitz & Wagner 2003	-1.13	[-1.46; -0.80]	4.6%
Nasr 2004	-0.27	[-0.48; -0.07]	5.0%
Rutherford et al. 2019	-0.37	[-0.61; -0.14]	4.9%
Szegedi et al. 1997	-1.85	[-2.49; -1.22]	3.4%
Total	-1.75	[-2.77; -0.73]	27.0%
Heterogeneity: $\chi^2_8 = 110.46$ ($P < .001$), $I^2 = 93\%$			
Total	-0.63	[-0.97; -0.29]	100.0%
Heterogeneity: $\chi^2_{27} = 190.62$ ($P < .001$), $I^2 = 86\%$			
Test for subgroup differences: $\chi^2_1 = 11.02$ ($P < .001$)			



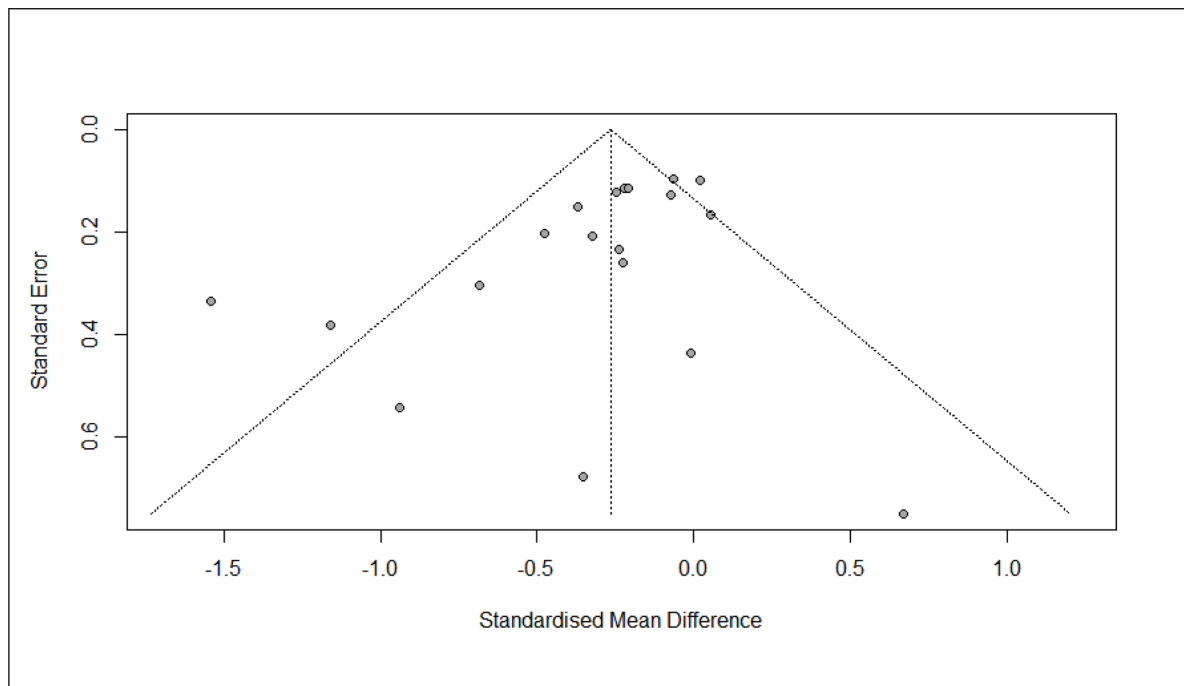
Appendix III. Risk of Bias

Study	Random-ization process	Deviations from intended interventions	Missing outcome data	Measure-ment of the outcome	Selection of the reported result	Overall bias
Albolfazli et al., 2011	+	+	+	+	+	+
Amsterdam, 2003	+	+	-	+	+	-
Bodkin and Amsterdam, 2002	+	+	-	+	+	-
Bouras & Bridges, 1982	+	+	+	+	!	!
Cusin et al., 2013	+	+	-	+	+	-
Dunlop et al., 2007	+	+	+	+	+	+
Fava et al., 2005	+	+	-	+	+	-
Feiger et al., 2006	+	+	-	+	+	-
Gershon et al., 2019	+	+	-	+	+	-
Lavretsky et al., 2006	+	+	+	+	+	+
Lavretsky et al., 2015	+	+	-	+	+	-
Mattes, 1997	+	+	+	+	+	+
Ravindran et al., 2008	+	+	-	+	+	-
Richards et al., 2016	+	+	-	+	+	-
Richards et al., 2017	+	+	+	+	+	+
Rickels et al., 1972	+	+	+	+	+	+
Sunderland et al., 1994	+	+	+	+	+	+

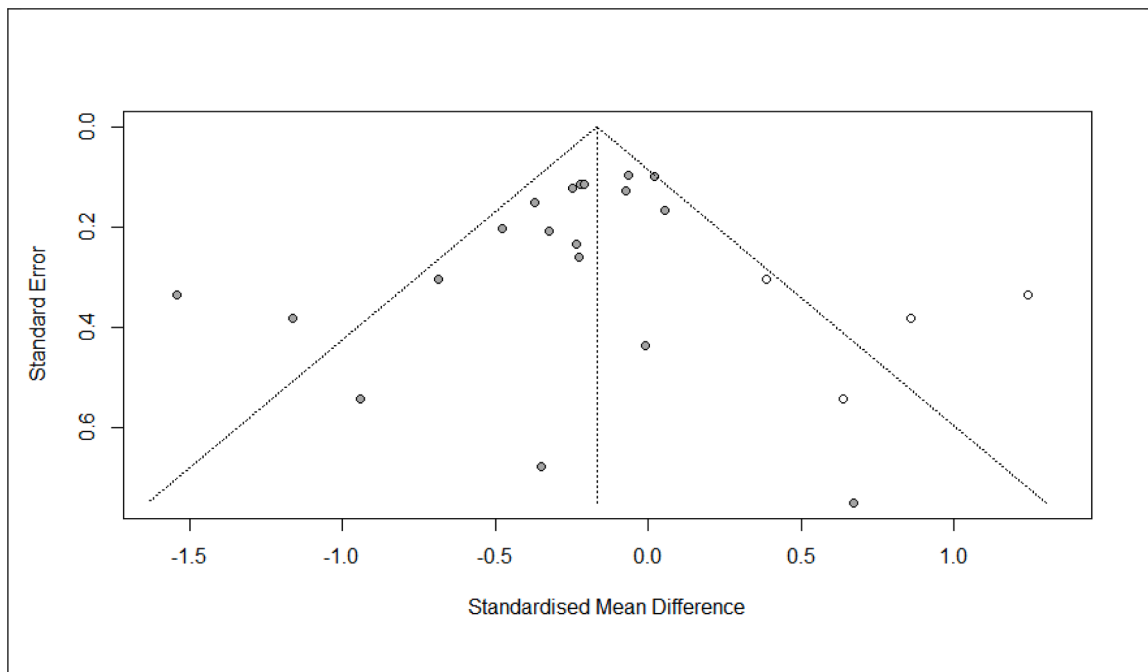
Appendix IV. Leave-one-out analyses



Appendix Va. Funnel plot for publication bias



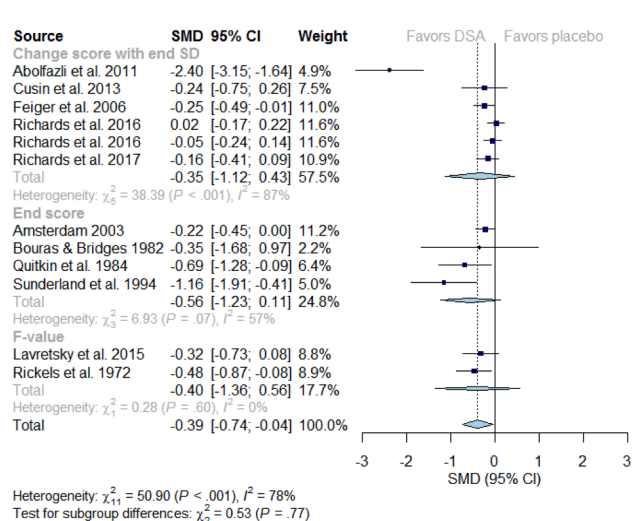
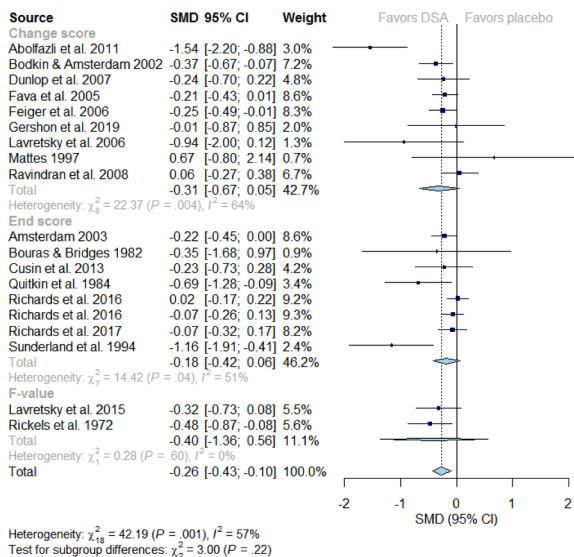
Appendix Vb. Funnel plot for publication bias including imputed data points



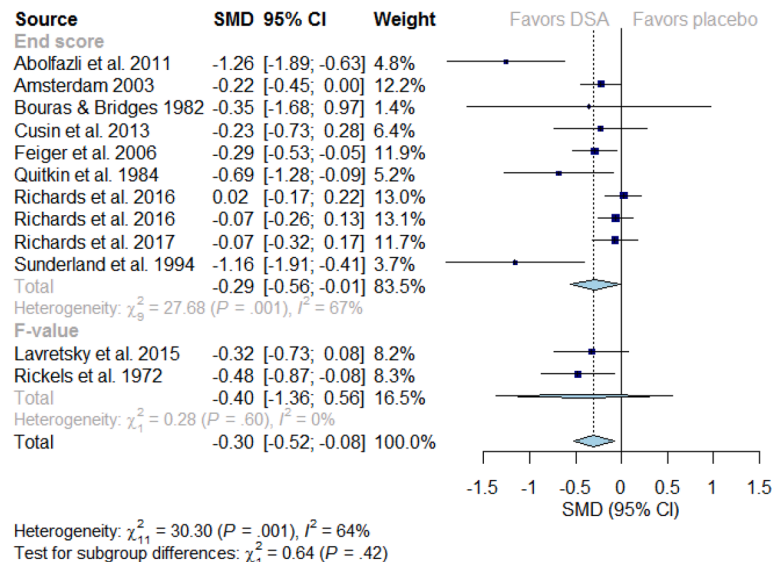
Appendix VI. Sensitivity analyses comparing change scores versus end-of-study scores

a) Forest plot subdivided by change score or end-of-study score

b) PostSD-plot



c) Postscores-plot



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