The Effectiveness of Dopamine Stimulating Agents in Late-Life Depression

A Systematic Review and Meta-Analysis

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Abstract

Background. Depression is a prevailing disorder at any age. Existing literature suggests the use of dopamine stimulating agents (DSAs) may be effective in the treatment of clinical depression, particularly in older adults in whom dopamine depletion may occur as part of the natural ageing process. Currently, most DSAs are not registered for the treatment of depression.

Research aim. This study aims to present a systematic overview of the existing literature on the effectiveness of DSAs on depression. It is hypothesized that DSAs are effective in reducing depressive symptoms, specifically in later life.

Methods. A systematic literature search was conducted in PubMed, Embase, Cochrane Library, and PsycINFO until July 9th, 2021. Data was extracted from randomized controlled trials, open label, and case studies with over five participants to perform meta-analyses of either a pre-post effect-size (uncontrolled studies) or placebo-adjusted effect-size (randomized controlled trials). Additional analyses investigated monotherapy versus augmentation treatment effects and a meta-regression was conducted to investigate an age effect.

Results. An overall small-sized effect was found for DSAs in reducing depressive symptoms (SMD = -0.26, 95% CI [-0.43; -0.10]), analyzing eighteen RCT studies. Heterogeneity was high and a significant Egger's test indicated potential publication bias. Meta-regression did not show a significant age effect, but only two RCT studies included an elderly population.

Conclusion. Results indicate that DSAs are effective in the treatment for depression. Future research should not only replicate these findings but generate more data on the position of DSAs for clinical treatment guidelines.

Keywords. Depression, dopamine, prognosis, slowing, aging, treatment.

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1 – Introduction

Depression. Depression is a prevalent and disabling disorder at any age, affecting more than 264 million people worldwide (World Health Organization, 2022). The prognosis of depression is remarkably worse among older adults (Schaaks, et al., 2018), which might be explained by an increase of physical health problems in later life, 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 may be better suited to improve the prognosis of depressed patients.

Aging. A major problem is that current biological treatments for depression do not take into account the consequences of 'normal' physiological aging of individuals (Rutherford, Taylor, Brown, Sneed, & Roose, 2017). Aging has been associated with depletion of the dopaminergic system (Bäckman, Nyberg, Lindenberger, Li, & Farde, 2006), leading to a decrease of dopamine levels in the brain. This decrease can manifest itself in many ways, for example causing inertia in thought processes (Bäckman, Nyberg, Lindenberger, Li, & Farde, 2006), slowness in movement (Stahl & Albert, 2017), and cognitive changes such as apathy (Yuen et al., 2015). These manifestations partly overlap with symptoms of depression. Indeed, the so-called 'slow type' depression – often seen in elderly patients – has been linked to dopamine deficiency (Rutherford, et al., 2019); (Stahl & Albert, 2017), and tends to have a poor response to conventional antidepressants, such as selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), and tricyclic antidepressants (TCAs) (Lattanzi, et al., 2002). In fact, a recent meta-regression analysis showed age to be a mediating factor in antidepressant response, with those aged 65 and older resulting in lower efficacy of conventional antidepressant treatment (Calati, et al., 2013). However, few pharmacological alternatives are available in current clinical practice (Tundo, de

Filippis, & De Crescenzo, 2019). Considering the ongoing increase of the older adult population in the coming decades (Christensen, Doblhammer, Rau, & Vaupel, 2009), it is important to evaluate other pharmacological options that may be beneficial for the treatment of depression, particularly among older adults.

Dopamine stimulating agents. There are several ways to enhance dopaminergic functioning in the brain by dopamine stimulating agents (DSAs), through exogenous and endogenous stimulation (Dunlop & Nemeroff, 2007). Dopamine agonists such as pramipexole have already been proven effective in reducing depressive symptoms in Parkinson's disease (Aiken, 2007), a disease caused by severe dopaminergic deficiency (Barone, et al., 2010). Despite the tentative evidence that dopamine stimulating agents have also been effective in improving the outcome of late-life depression (Barone, et al., 2010); (Rutherford, et al., 2019), it has not been part of clinical guidelines yet. The literature lacks comprehensive overview of studies evaluating the effectiveness of a broad range of dopamine stimulating agents in depression that are not currently registered for depression treatment. Studies to date usually focus on the effectiveness of one dopamine stimulating agent in particular (Tundo, de Filippis, & De Crescenzo, 2019), hereby neglecting the existence of an overall triad between aging – dopamine depletion – and depression.

Aims of the study. The current systematic literature review and meta-analysis will contribute to the evidence by investigating whether dopamine stimulating agents may have a role in the treatment of depression, and investigate the efficacy of these agents for the elderly. Specifically, this review and meta-analysis will focus on the treatment effects of stimulants (e.g. methylphenidate, dexamphetamine, modafinil), dopamine agonists (e.g. pramipexole, ropinirole, bromocriptine), MAO-B inhibitors (selegiline), and levodopa on (late-life) depression.

The primary aim of the study is to systematically review the literature on the effectiveness of dopamine stimulants in people with depression. Secondly, this study aims to investigate the putative role of age-related decline of dopaminergic functioning in late-life depression. It is hypothesized that dopamine stimulating agents are effective in reducing depressive symptoms, in particular among older adults.

The following chapter will give a more detailed description of the expected working of said treatments.

2 – Theoretical Background

Dopamine. Dopamine is a neurotransmitter important for functions of the nervous system, including movement, attention, mood, and pleasure (Iversen & Iversen, 2007). It also inhibits the secretion of prolactin in the pituitary gland. Individual dopamine neurons together can form dopaminergic pathways in the brain – certain routes – responsible for behavioral as well as physiological processes (Alcaro, Huber, & Panksepp, 2007). Aging of the dopaminergic system likely contributes to the 'slow-type' depression (Bäckman, Nyberg, Lindenberger, Li, & Farde, 2006). A logical step is therefore to investigate different means of administering dopamine to try and achieve normal levels again. Primarily, this is done through the administration of so-called dopamine agonists (Dunlop & Nemeroff, 2007). These are chemicals that bind to a receptor in order to activate it and produce a biological response, in this case, releasing dopamine.

Five types of dopamine receptors exist in the body's central nervous system, each responsible for a set of functions. Though functions partly overlap, the D1- and D5-receptors are mostly responsible for cognitive functions; the D2-receptor for motor skills and salience; and the D3- and D4-receptor's main functions concern sleep (Bhatia, Lenchner, & Saadabadi, 2021).

There are several different ways in which these receptors can be activated. Firstly, dopamine can be administered directly in the form of dopamine precursors, such as levodopa or carbidopa, which are converted into dopamine through the enzyme DOPA-decarboxylase. The increased dopamine availability that follows may increase the effectiveness of remaining neurons. Secondly, receptors can be activated indirectly through dopamine agonists which act directly on the dopamine receptors and therefore mimic the effect of the neurotransmitter dopamine itself (Dunlop & Nemeroff, 2007). Stimulants such as amphetamine inhibit a protein that normally transports monoamines into vesicles, thereby increasing the levels of dopamine.

Dopamine Stimulating Agents (DSAs).

Dopamine agonists. The following presents a brief examination of the pharmacological aspects of dopamine-related medications.

Pergolide. A dopamine agonist generally used to treat Parkinson's disease, acting on dopamine receptors to increase activity. It may also be used to enhance cognitive processes in other conditions in which dopamine depletion occurs (McClure, et al., 2010).

Bromocriptine. A partial dopamine agonist, particularly on the D2-receptor (de Leeuw van Weenen, et al., 2010). Used among other conditions for treatment of Parkinson's disease or to suppress prolactin production.

Ropinirole. A medication used to treat Parkinson's disease and restless legs syndrome. It is a dopamine receptor agonist, acting mainly on the D3-receptor, but also on the D2 and D4-receptors (Shill & Stacy, 2009).

Pramipexole. Used mainly in the treatment of Parkinson's disease, sometimes together with L-DOPA. It acts as an agonist on the D2, D3 and D4-receptors (Tundo, de Filippis, & De Crescenzo, 2019).

Psychostimulants.

Modafinil. Generally used to treat narcolepsy or to lose weight. It has been found to elevate dopamine levels in animals (Ishizuka, Murakami, & Yamatodani, 2008). Modafinil has been described as an atypical dopamine transporter inhibitor, as it shows different effects from other dopaminergic stimulants (Reith, et al., 2015).

Methylphenidate. Also known under the brand name Ritalin. It is generally used to treat ADHD. It is an indirect agonist, indirectly activating the D1-receptor. In healthy people, it may cause modest improvements in cognition (Spencer, Devilbiss, & Berridge, 2015).

Lisdexamfetamine. A derivative of amphetamine and an indirect dopamine agonist. It is mainly used to treat ADHD. In the body, it becomes converted into dextroamphetamine,

releasing dopamine in the central nervous system (Parker, Lamichhane, Caetano, & Narayanan, 2013).

MAO-B inhibitors.

Selegiline. Also known as L-deprenyl. It is a monoamine oxidase inhibitor, particularly of monoamine oxidase B (MAO-B), which increases levels of dopamine in the brain. It is generally used to treat Parkinson's disease, sometimes in combination with L-DOPA (Ives, et al., 2004).

L-DOPA. An amino acid that acts as a precursor to dopamine. Unlike dopamine, it can cross the blood-brain barrier, and therefore has the ability to increase dopamine concentrations (Hardebo & Owman, 1980). It is mainly used to treat Parkinson's disease.

Measures of depression. Besides a diagnosis of major depressive disorder based on DSM criteria, severity of depressive symptoms can be assessed through commonly used and well-validated scales. The first is the Hamilton Depression Rating Scale (HAM-D). The most used version consists of 21 items and scoring is based on the first 17 items (Williams, 1988). The HAM-D assesses depressive symptoms across the following domains: depressed mood, feelings of guilt, suicide, insomnia, work and interests, retardation, agitation, anxiety, somatic symptoms, genital symptoms, hypochondriasis, weight loss, and insight. The higher the score, the more severe the depression, with a score of 14-17 being classified as mild to moderate and a score over 17 as moderate to severe (Hamilton, 1967). Another frequently used scale is the Montgomery Asberg Depression Rating Scale (MADRS) (Carmody, et al., 2006). It assesses the severity of symptoms rather than being diagnostic of a major depressive disorder. Domains include apparent and reported sadness, inner tension, reduced sleep, reduced appetite, concentration difficulty, lassitude, inability to feel, pessimistic thoughts, and suicidal thoughts. Higher scores reflect more severe symptoms, with 20-34 being classified as moderate and 35-60 as severe depression (Asberg, Montgomery, Perris, Schalling, & Sedvall, 1978).

3 – Methods

Search strategy. The review is conducted according to the Preferred Reporting for Systematic Reviews and Meta-analyses (Moher, Liberati, Tetzlaff, Altman, & PRISMA Group, 2010). Prior to conducting the current study, it was registered in PROSPERO (registration number CRD42021258330). 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.

In- and exclusion criteria. Reference management software package EndNote X9 (The EndNote Team, 2013) was used to manage retrieved articles and screening- and labelling tool Rayyan (Ouzzani, Hammady, Fedorowicz, & Elmagarmid, 2016) was used to screen articles. 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 an official diagnostic interview (e.g., DSM, 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.

Outcome measures. 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) (Williams, 1988) and Montgomery Asberg Depression Rating Scale (MADRS) (Carmody, et al., 2006). Non-validated scales were not included. Medications were divided into dopamine agonists, stimulants, MAO-B, and levodopa groups.

Data extraction. 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.

Risk of bias. 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, Savović, Page, Elbers, & Sterne, 2021). 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:

(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.

4 – Data Analysis

Meta-analysis. All analyses were performed in R version 4.1.2 (R Core Team, 2021). If studies contained different treatment arms (e.g., multiple dosages), these groups were combined in the meta-analysis by pooling the data. 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. Placebo-controlled and uncontrolled studies were separated in the analyses. For RCT studies, end-of-treatment scores were compared. Average baseline and end-of-treatment scores and their SDs were used for analyses of uncontrolled studies. For calculation of the SD of mean change, 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. This model incorporates adjusted standard errors that include a measure of heterogeneity among intervention effects, which are referred to as tau-squared (τ^2) (Higgins, et al., 2021). 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. 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, Law, Rücker, & Schwarzer, 2017). This modified method has been argued to outperform the standard DerSimonian-Laird method (IntHout, Ioannidis, & Borm, 2014) and is therefore recommended to apply in random-effects meta-analysis (van Aert & Jackson, 2019). 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, Sánchez-Meca, Marín-Martínez, & Botella, 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, Schmitz, Annable, & Boksa, 2012). An asymmetrical plot and significant Egger's test would indicate potential publication bias.

Additional analyses. Subgroup 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.

5 – Results

Search results. 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 enough data. This resulted in a total of 27 included articles (see Figure 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.

Quality assessment. 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. Results are presented in Table 1 below.

Table 1. Risk of bias assessment: + = low risk; ! = some concerns; - = high risk

Study	Random-ization process	Deviations from intended interven-tions	Missing outcome data	Measure-ment of the outcome	Selection of the reported result	Overall bias
Albolfazli et al., 2011	+	+	+	+	+	+
Amsterdam, 2003	+	+	-	+	+	-
Bodkin & 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	+	+	+	+	+	+

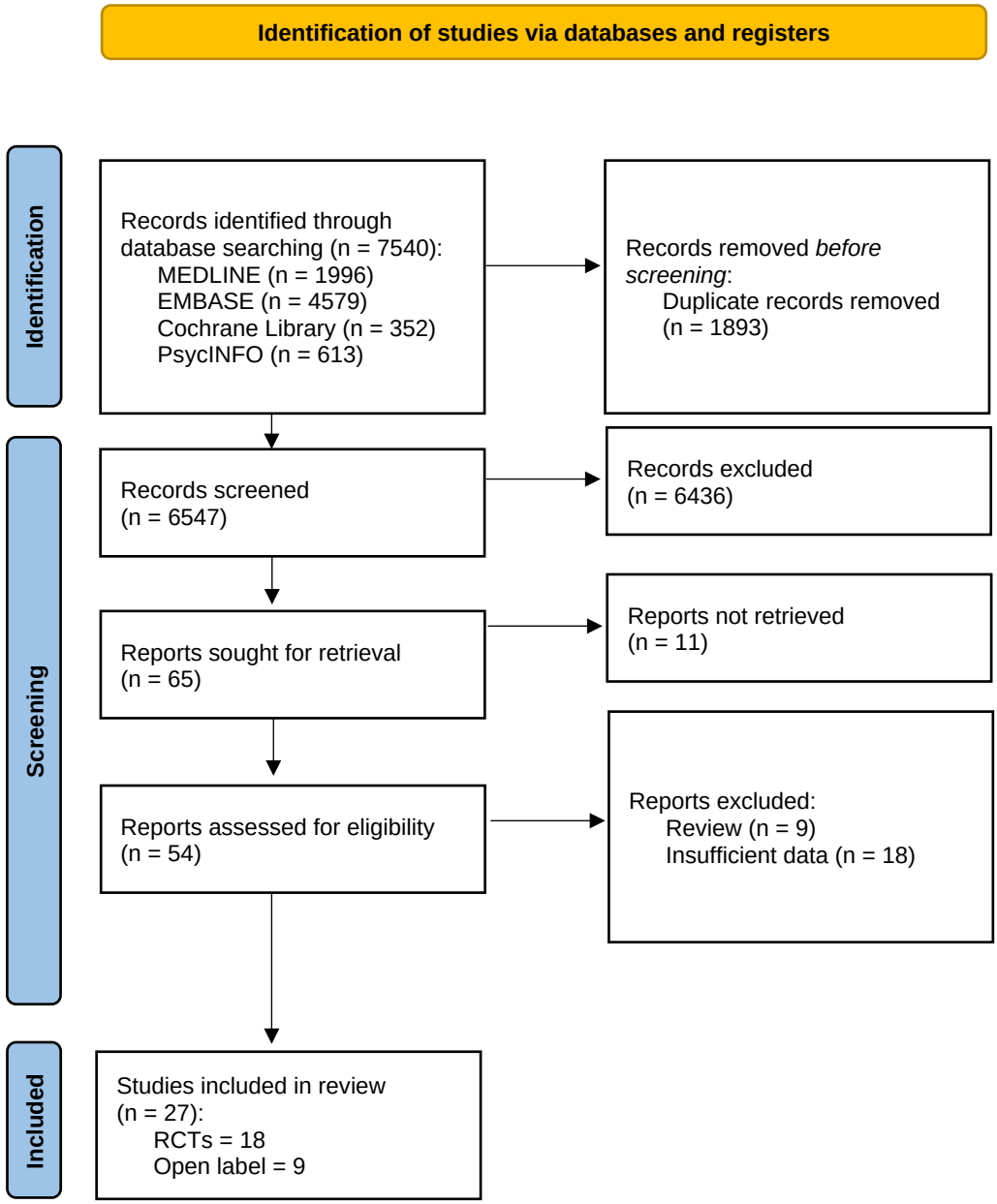

Figure 1. Flow of information through the different phases of the systematic search (Page, et al., 2021).

Study characteristics. An overview of included studies can be found in Table 2. 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).

Table 2. 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	400mg/d modafinil augmentation 6 weeks	HAM-D
Amsterdam, 2003	Double-blind placebo-controlled RCT	Active: N = 149 (94) Control: N = 152 (99)	41; 44	20mg/d STS patch monotherapy 8 weeks	HAM-D
Bodkin & Amsterdam, 2002	Double-blind placebo-controlled RCT	Active: N = 89 (53) Control: N = 88 (53)	41; 43	20mg/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	15mg/d (3x5mg) bromocriptine monotherapy 10 weeks	HAM-D
Cassano et al., 2005	Open label	N = 10 (7)	51	Between 0.75mg/d and 2mg/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 0.5mg/d (2x0.25) to 1.5mg/d pramipexole augmentation 8 weeks	MADRS
Dunlop et al., 2007	Double-blind placebo-controlled RCT	Active: N = 37 Control: N = 36	44	Between 100mg/d to 300mg/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	100mg/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 6mg/d to 12mg/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	0.5mg/d until max. 2mg/d ropinirole monotherapy 8 weeks	HAM-D
Hori & Kunugi, 2012	Open label	N = 12 (10)	36	0.25mg/d up to 3mg/d pramipexole augmentation 12 weeks	HAM-D
Konuk et al., 2006	Open label	N = 25 (8)	32	100mg/d to 200mg/d modafinil augmentation 6 weeks	HAM-D
Lattanzi et al., 2002	Open label	N = 16	54	0.375mg/d to max. 1mg/d pramipexole augmentation 16 weeks	MADRS
Lavretsky & Kumar, 2001	Open label	N = 10 (5)	80	Between 0.25mg/d and 20mg/d methylphenidate augmentation 8 weeks	HAM-D

Note. STS = selegiline transdermal system.

Table 2. Continued

Author	Design	Participants (female)	Mean age (years)	Intervention	Outcome measures
Lavretsky et al., 2006	Double-blind placebo-controlled RCT	Active: N = 10 (5) Control: N = 6 (4)	74; 74	5mg/d up to 20mg/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 5mg and 50mg 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 0.05mg up to 2mg of pergolide augmentation 3 weeks	HAM-D
Nasr, 2004	Open label	N = 99 (49)	44	Mean dosage of 265mg/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	10mg/d (week 1-4), 20mg/d (week 5), 30mg/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 54mg/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)	42; 42	30, 50, or 70 LDX daily augmentation 16 weeks	MADRS
		Study 2 Active: N = 211 (141) Control: N = 213 (143)	42; 43		
Richards et al., 2017	Double-blind placebo-controlled RCT	Active: N = 314 Control: N = 280 (53)	42; 44	10, 30, 50, or 70mg 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	30mg/d methylphenidate monotherapy 4 weeks	PDS
Rutherford et al., 2019	Open label	N = 36 (20)	75	150mg up to 450mg L-DOPA or up to 3x 36,5mg carbidopa 3 weeks	HAM-D
Sunderland et al., 1994	Double-blind placebo-controlled RCT	Active: N = 16 (12) Control: N = 16	66	60mg/d selegiline monotherapy 3 weeks	HAM-D
Szegedi et al., 1997	Open label	N = 26 (12)	45	Up to 9mg/d pramipexole monotherapy 4 weeks (up to 75 weeks)	MADRS

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

Overall effects. The forest plot below (Figure 2) presents the overall results from the placebo-controlled (n = 19 trials in 18 articles) studies included in the meta-analysis. Appendix II shows results when uncontrolled studies (n = 9) are included. The model showed a significant effect of DSAs on reducing depressive symptoms (SMD = -0.26, 95% CI [-0.43; -0.10]). Heterogeneity was relatively high [$Q(18) = 42.2$, $p < 0.001$; $I^2 = 57\%$]. When looking at only uncontrolled studies (Appendix II), a larger significant decrease in depression scores was observed (SMD = -1.75, 95% CI [-2.77; -0.73]) and heterogeneity was high as well [$Q(8) = 110.5$, $p < 0.001$; $I^2 = 93\%$].

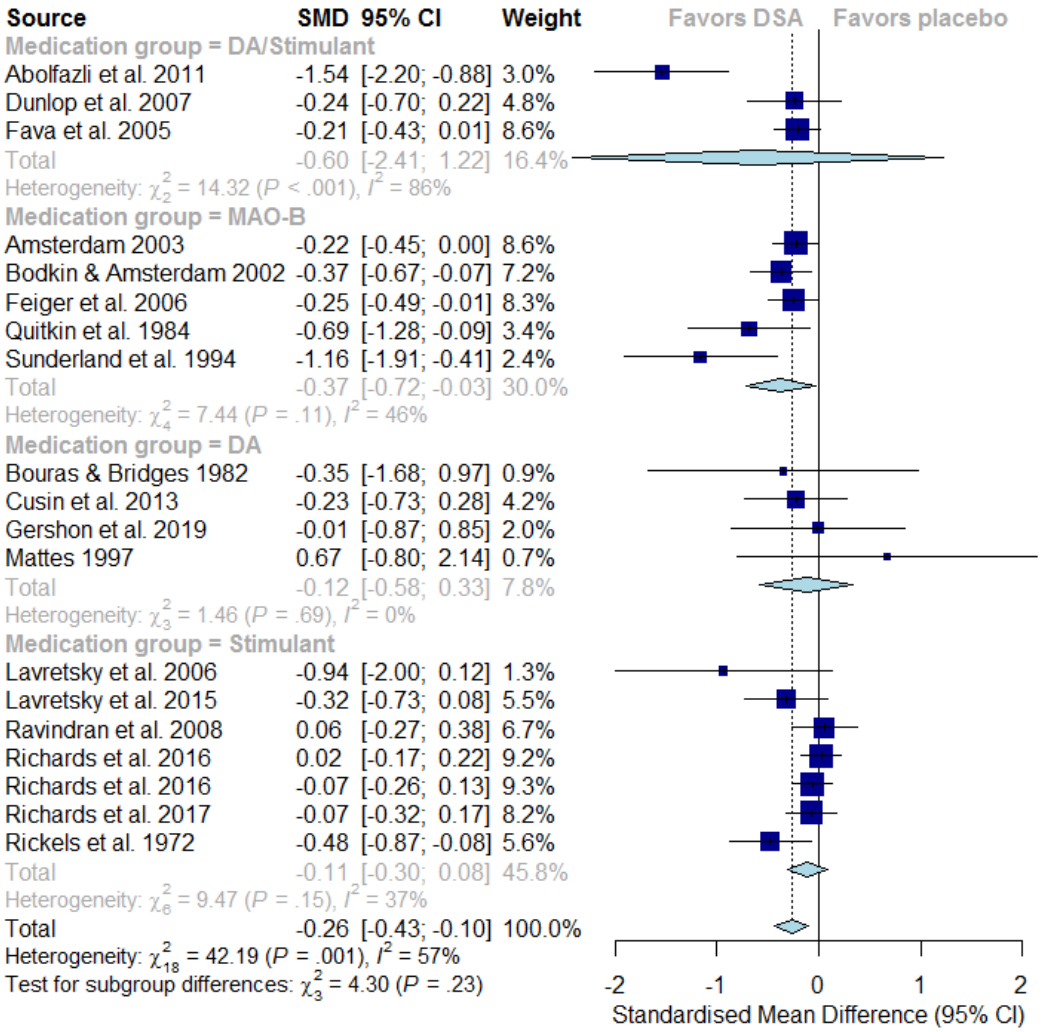

Figure 2. Meta-analysis: overall results

Visual inspection of the funnel plot of the RCT studies suggested potential publication bias (see Figure 3).

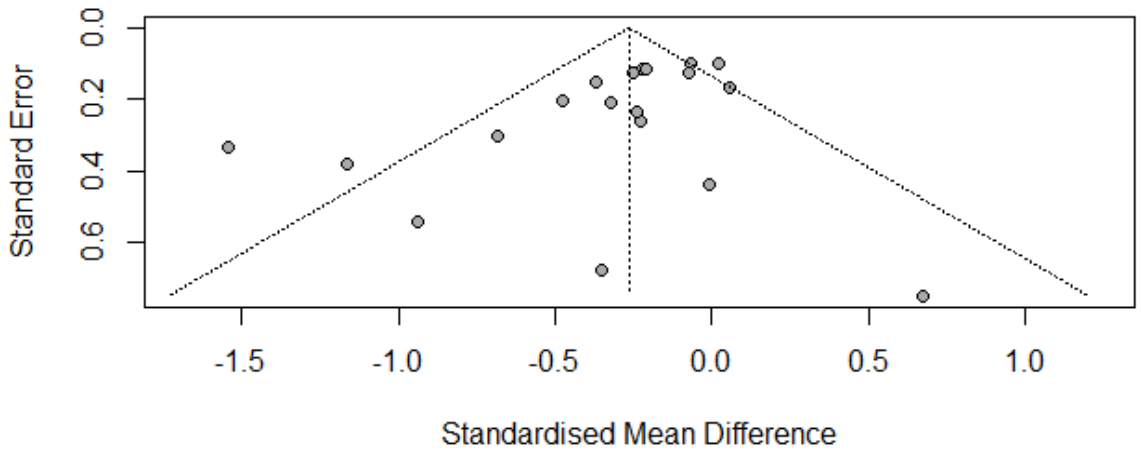

Figure 3. Funnel plot. Asymmetry indicates potential publication bias.

A significant Egger's test indicated potential publication bias for placebo-controlled studies. When uncontrolled studies were included, this effect increased (Table 3).

Table 3. Egger's test for placebo-controlled alone and combined with uncontrolled studies.

	Intercept	95% CI	*t*	*p*
Placebo-controlled	-1.554	-2.83 – -0.28	-2.391	0.0286
Uncontrolled	-2.875	-4.19 – -1.56	-4.282	0.0002

Monotherapy versus augmentation effects. The forest plot in figure 4 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], $p = 0.012$).

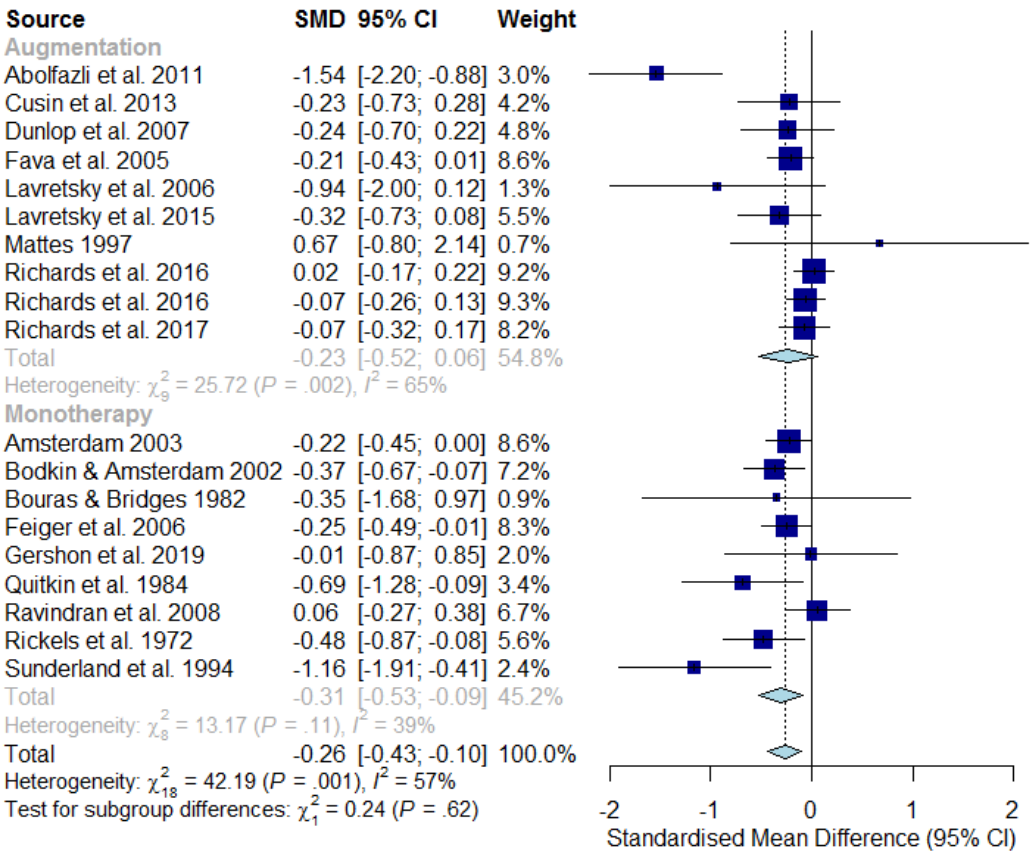

Figure 4. Sub-analyses of augmentation versus monotherapy strategies in RCTs.

Sample size effects. 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 (IntHout, Ioannidis, Borm, & Goeman, 2015). Heterogeneity reduced drastically for studies with a large sample size to a nonsignificant level [$Q(11) = 12.54$, $p = 0.32$; $I^2 = 12\%$].

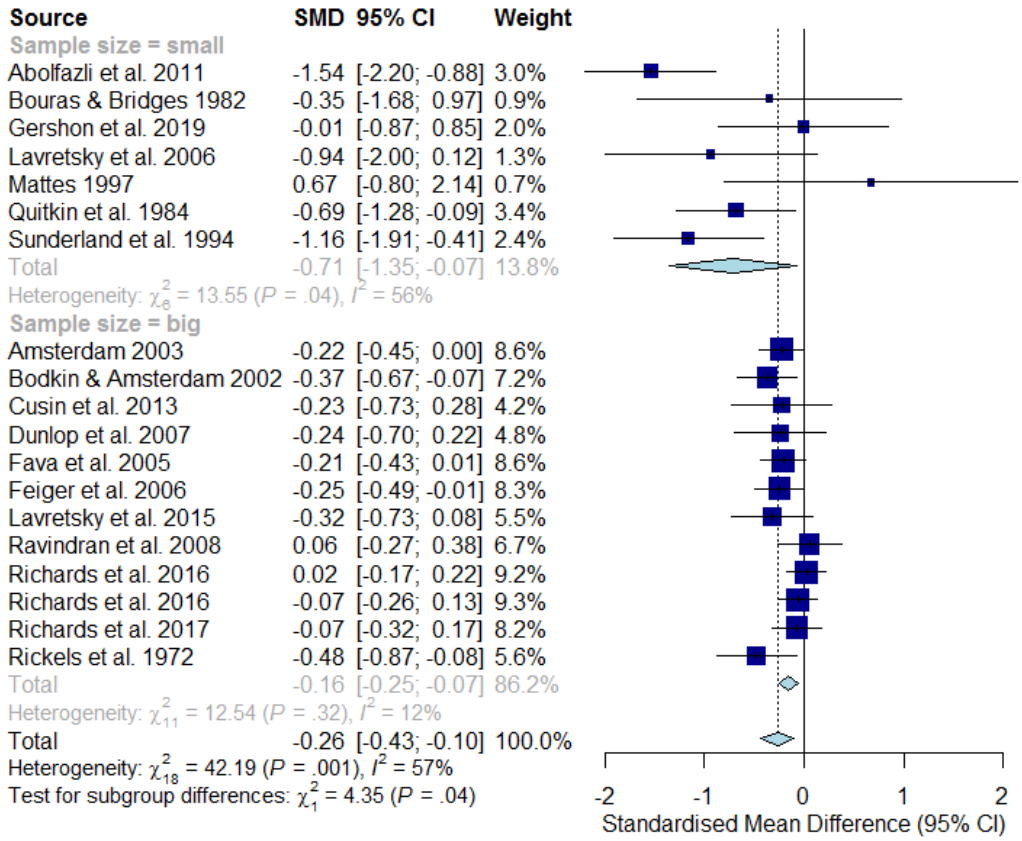

Figure 5. Exploration of heterogeneity. Sub-analyses per sample size with a large sample size defined as > 50 and a small sample size < 50 participants.

Medication group effects. Separating medication groups did not yield significant effects, as can be seen in Figure 2.

Age effects. Only two RCT studies from the total of 19 placebo-controlled studies included an older sample. As presented in the bubble plot below (Figure 6), there did not seem to be any significant results concerning age effects.

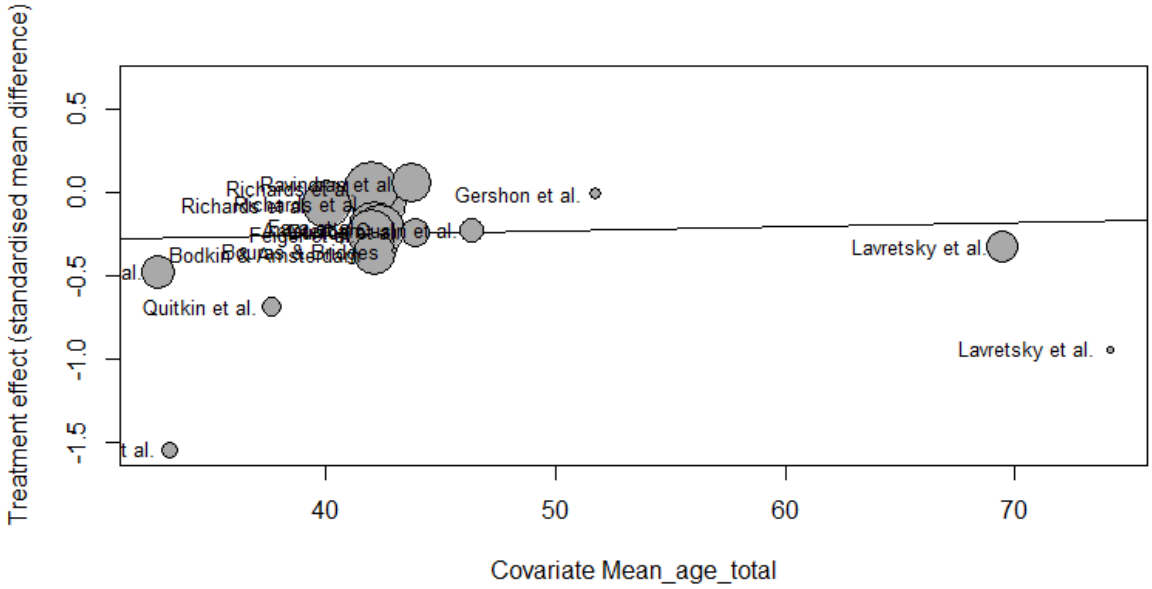

Figure 6. Bubble plot comparing age effects in RCTs.

The next chapter discusses the implications of the results presented above.

6 – Discussion

This systematic review and meta-analysis aimed to present an overview of the current literature on dopamine stimulating agents (DSAs) and related medication groups and their effects on depression. It was hypothesized that dopamine stimulating agents are effective in reducing depressive symptoms, particularly among older adults. A total of twenty-seven studies with a total sample size of 3387 participants were included in the systematic review. Eighteen articles comprising nineteen RCT studies showed small-sized significant results of DSAs on reducing depressive symptoms. Separating placebo-controlled and uncontrolled studies showed significant effects for both groups, with uncontrolled studies having larger significant effects, as can be expected. The different types of studies were included to find as many trials as possible on DSAs for depression to be included in the review. In the meta-analysis, only RCT studies were included as combining both types of studies in the same model likely overestimates effects due to the higher risks of bias in uncontrolled studies. Given the indications of a potential publication bias as well as the potential risk of bias in certain studies due to high dropout rates, results must be interpreted with some caution. However, current findings indicate promising results for the use of dopamine agonists, stimulants, and MAO-B medications, all of which are not registered for the use in clinical depression at the time of the present 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-Fernandez, 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 bipolar depression (e.g., (Tundo, de Filippis, & De Crescenzo, 2019)) and Parkinson's disease (e.g., (Ives, et al., 2004)), all disorders that show great overlap with clinical unipolar depression. 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 DSAs may have comparable treatment effects as conventional antidepressants. Cipriani et al. (2018) did however include unpublished trials, which the current study did not. This may cause the current study's SMD to be overestimated compared to the study of Cipriani et al. (2018), which is an important difference to keep in mind. However, it is likely that some of those studies have been published in the meantime. Results show that it seems worthwhile to further investigate the use of these medications in clinical practice. Despite these indications, only six out of the twenty-seven studies included were conducted within the last ten years (Cusin, et al., 2013); (Gershon, Amiaz, Shem-David, & Grunhaus, 2019); (Lavretksy, et al., 2015); (Richards, et al., 2016); (Richards, et al., 2017) (Rutherford, et al., 2019). 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 DSAs in the treatment of depression. Similarly, only two RCT studies were conducted with an elderly sample (Lavretsky, Park, Siddarth, Kumar, & Reynolds, 2006); (Lavretksy, et al., 2015), 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 age effects as investigated through the bubble-plot in the current study, however, showed almost horizontal lines. This is therefore not supportive of the proposed hypothesis that DSAs are particularly effective in the elderly.

Separating medication groups did not yield significant effects, which suggests the absence of a superior treatment group. Although effects were small, monotherapy treatment

effects reached the significance level, underlining once more the importance of DSAs as an alternative treatment for depressive outcomes.

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 DSAs 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 DSAs for depressive patients are 1) intolerable side-effects from conventional antidepressant agents in which case monotherapy with DSAs could be considered; and 2) insufficient effects from conventional antidepressants – which, unfortunately is common – in which case augmentation with DSAs could be a relevant option.

Strengths, limitations, and recommendations for future 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. It's 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. Specifically, the slow-type depression caused by dopaminergic depletion has hardly been investigated as such 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. As discussed earlier, recent research was barely available, and up to date research should be conducted to further investigate results.

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 DSAs for treatment of depression remained significant in large studies. Certain included studies had rather small sample sizes, which may have reduced power in those studies. However, the weight of each study has been clearly indicated in the meta-analysis, indicating the influence per study on the final results. Third, 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 some 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 not. Still, very few dropouts occurred due to severe adverse effects, indicating that treatments were generally well-tolerated. Fourth, several studies could not be included due to a lack of data, despite fitting other inclusion criteria. This results in a lower number of included studies in the meta-analysis than could have potentially been included, which might have affected the outcome.

7 – Conclusion

The results of this systematic review and meta-analysis suggest that the use of dopamine stimulating agents may be effective in the treatment of clinical unipolar depression, indicated by a significant small-sized effect in RCTs. The clinical practice may thus benefit from dopamine-related treatments in addition to or instead of registered antidepressant medication. Particularly monotherapy effects were found to be significant. Specifically, DSAs may be the next choice of treatment when conventional antidepressants seem to have no treatment effect on the patient. However, considering the potential publication bias and poor methodological quality of certain studies included in the current meta-analysis, future clinical trials are advised to be conducted in this promising field. Trials investigating the effects of DSAs on depression in elderly people (aged > 65) would be of particular interest, considering the effects of dopaminergic depletion. Moreover, studies could further investigate the use of DSAs in patients nonresponsive to conventional antidepressants. Finally, the current meta-analysis did not discover a superior medication group of DSAs, indicating that currently all DSAs seem to be equally effective. It would therefore be recommended to more closely look at the effects of individual medication groups to investigate whether there are any circumstances under which certain groups are more effective.

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Appendix I. Search terms

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