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REVIEW

Functioning outcomes with adjunctive treatments for major depressive disorder: a systematic review of randomized placebo-controlled studies

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Objective: Patients with major depressive disorder (MDD) with inadequate response to antidepressant treatment (ADT) may suffer a prolonged loss of functioning. This review aimed to determine if self-rated functional measures are informative in randomized placebo-controlled studies of adjunctive therapy in patients with MDD and inadequate response to ADT.

Methods: This was a systematic literature review of articles in any language from the MEDLINE database published between January 1990 and March 2017. Eligible studies met the following criteria: patients with MDD; inadequate response to at least one ADT; adjunctive therapy (pharmacological or otherwise) to ADT; placebo control group; randomized controlled trial or a post hoc analysis of a randomized controlled trial; reported a self-rated functioning scale. Study characteristics and functioning efficacy data were extracted.

Results: A total of 2,090 discrete records were screened, 293 full-text articles were assessed for eligibility, and 26 studies were included. All studies were acute (6–12 weeks) except for one 52-week study. The only self-rated functioning scale used in the included studies was the Sheehan Disability Scale (SDS). Of the 13 adjunctive agents identified, aripiprazole, brexpiprazole, edivoxetine, and risperidone improved functioning versus placebo ($p<0.05$), as measured by the SDS total or mean score. On the SDS "work/studies" item, only aripiprazole had a statistically significant benefit, in one study out of four. Thus, where a benefit was observed on the SDS total or mean, this was generally driven by improvement on the "social life" and "family life" items. A limitation of the review is that it only considered published literature from one database.

Conclusion: The SDS, a self-rated functional measure, is informative in acute randomized placebo-controlled studies of adjunctive therapy in patients with MDD and inadequate response to ADT. However, the item that measures work performance may be less relevant to this population than the items that measure social and family life.

Keywords: depression, antidepressant, adjunct, Sheehan Disability Scale, functional, work

Introduction

Major depressive disorder (MDD) is characterized by symptoms including depressed mood and a loss of interest or pleasure in activities.[1] As a consequence of depressive symptoms, patients with MDD typically have impaired functioning across multiple domains, including work, social, and family functioning.[2,3] For example, depressive symptoms are associated with reduced marital quality, reduced work performance, and lower earnings.[2]

Key goals for patients with MDD experiencing a depressive episode are remission and full recovery.[4,5] Recovery should be considered in broad terms, encompassing work, social, and family functioning as well as improvement of depressive symptoms.[6,7]

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Indeed, patients with MDD consider a return to normal levels of functioning as one of the most important factors in defining remission from depression.[8] Although numerous standardized assessments are available to monitor functioning outcomes in the clinic and in research, functioning scales are used less frequently and less consistently than symptom severity scales.[9] Furthermore, functioning may be less responsive to treatment than symptoms, meaning that functional improvement can lag behind symptomatic outcomes.[10,11]

Despite being the mainstay of pharmacological treatment for MDD, more than half of patients do not respond to antidepressant treatment (ADT), as shown by the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study.[12] Patients with inadequate response to ADT have a prolonged loss of functioning and a lower likelihood of employment than those patients who do respond.[13,14] Treatment strategies for patients with inadequate response to an optimized dose of ADT include switching to another antidepressant, combining the initial antidepressant with a second antidepressant that has a different mode of action, or augmenting the antidepressant with a non-antidepressant drug.[4,15–18] Of the various options for augmentation, second-generation antipsychotics are best supported by the evidence.[19] However, the effects of different adjunctive therapies on patient functioning have not been consistently studied, and it is not clear whether existing measures of functioning are useful among patients with MDD and inadequate response to ADT.

A recent systematic review investigated the effect of ADT (selective serotonin reuptake inhibitors, serotonin–norepinephrine reuptake inhibitors, other antidepressants, and psychotherapies such as cognitive behavior therapy [CBT]) on functional outcomes in MDD.[20] The review, which excluded clinical studies of adjunctive pharmacotherapies, concluded that functioning improves together with depressive symptoms, but that functional deficits often remain, even among patients who achieve symptomatic remission.[20] Given the importance of functioning to the overall well-being of patients, the aim of the present systematic literature review was to determine if self-rated functional measures are informative in randomized placebo-controlled studies of adjunctive therapy in patients with MDD and inadequate response to ADT.

Methods

This systematic review adheres to PRISMA.[21]

Eligibility criteria

Studies were included if they were published, randomized, placebo-controlled studies of adjunctive therapy to ADT in patients with MDD and inadequate response to at least one ADT, and reported a self-rated scale of functioning. The literature search was performed on 8 March 2017. Reports were limited to those published on or after 1 January 1990. No language exclusions were applied.

Search strategy

The aim of the initial top-level search strategy was to identify studies that satisfied three criteria: 1) the study included patients with MDD; 2) the study was of antidepressant augmentation (with any pharmacological or non-pharmacological approach, such as CBT or deep brain stimulation); and 3) the study included a placebo or sham control group. The US National Library of Medicine's MEDLINE database was searched, via PubMed, using the terms: (depress* OR MDD) AND (adjunct* OR "add-on" OR augment* OR resist* OR refractory OR inadequate OR incomplete OR suboptimal) AND (placebo).

Following the initial search it became apparent that these terms were likely to miss some publications of olanzapine–fluoxetine combination (OFC) studies. OFC is indicated for the treatment of treatment-resistant depression in the US,[22] and, due to its availability as a single tablet, has been tested against fluoxetine with no need for placebo. Consequently, a second search was performed on 21 March 2017 to capture OFC studies, using the terms: (depress* OR MDD) AND ((olanzapine AND fluoxetine) OR OFC).

Study selection

Following the top-level database searches, duplicates were excluded and records were screened to exclude unsuitable articles based on titles and abstracts (Figure 1). At this stage, studies were not excluded based on a lack of functioning outcomes, because these are often secondary outcomes not mentioned in abstracts.

After screening, full-text articles for the remaining records were assessed for eligibility, defined as meeting all of the following criteria: 1) the study included patients with MDD; 2) the patients had inadequate response (by any definition) to at least one ADT; 3) the study investigated an adjunctive therapy to ADT; 4) the study included a placebo or sham control group (or a fluoxetine control group, for OFC); 5) the study was a randomized controlled trial or a post hoc analysis of a randomized controlled trial; and 6) the study reported self-rated functioning scale (or subscale) outcomes. Any self-rated functioning scale was eligible, defined as a scale that reflects the user's actual behavior in the world and is assessed in ways that emphasize doing, performing,

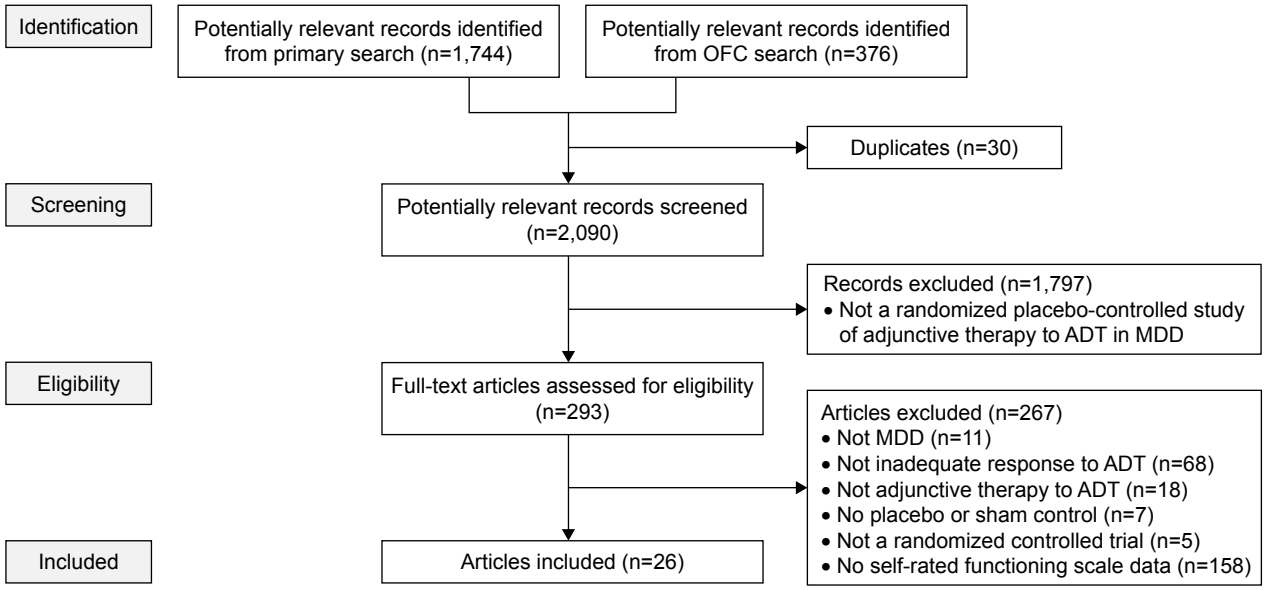

Figure 1 Flow diagram of published articles examined for inclusion in a systematic review.
Abbreviations: ADT, antidepressant treatment; MDD, major depressive disorder; OFC, olanzapine–fluoxetine combination.

maintaining, etc (this is distinct from quality of life – a measure based on self-perception and context with an emphasis on satisfaction, contentment, or enjoyment in various aspects of life).[9] Eligibility assessment was performed in duplicate by two reviewers (split between CPW, CE and JARM), and disagreements were resolved by consensus.

Data extraction

The following data were extracted for each study, where available: 1) the definition of inadequate response to ADT, both historical (prior to study enrollment) and prospective/ongoing (during the study); 2) the adjunctive treatment (type, dose, and duration); 3) the number of randomized patients; 4) the primary efficacy endpoint and whether or not it was met (in order that failed or negative studies might be identified); 5) the name of the self-rated functioning scale/subscale/items used; 6) self-rated functioning scale scores at baseline (ie, randomization to adjunctive therapy) and the mean change from baseline to the study endpoint (including error measurements, *p*-values versus placebo, and patient numbers); 7) the setting; and 8) the source of funding. Published data were supplemented with data from ClinicalTrials.gov and study protocols/reports, where available. One reviewer extracted the data from included studies (CPW) and a second reviewer checked the extracted data (CE). Disagreements were resolved by checking the original data source. To assess the risk of bias in individual studies, one reviewer (CPW) judged the adequacy of randomization, blinding, and outcome reporting for each study.

Results

Study characteristics

A total of 2,090 discrete records were identified and screened (Figure 1).

Of the 293 full-text articles assessed for eligibility, 26 articles were included, of which 20 reported one or more primary study, and six reported post hoc analyses of already identified studies. In total, these articles described 26 different studies, the characteristics of which are shown in Table 1. Five of the post hoc analyses were pooled analyses of aripiprazole, and are not discussed further.[23–27] The sixth post hoc analysis reported self-rated functioning data from a risperidone study in more detail than in the primary manuscript.[28] No sources of bias were identified in individual studies.

The only self-rated functioning scale used in the included studies was the Sheehan Disability Scale (SDS),[49–51] which was always a secondary or exploratory outcome. The SDS comprises three visual analog scales on which patients self-rate the extent to which symptoms have disrupted their: 1) work/studies (including paid and unpaid volunteer work and training); 2) social life or leisure activities; and 3) family life or home responsibilities. Each of these items is scored from 0 (not at all) to 10 (extremely). Patients can skip the work/studies item if they have not worked/studied in the last week for reasons unrelated to their disorder (eg, retirement); the instructions are unclear for patients who have stopped working because of their depression. The majority of studies calculated the SDS total score, obtained by summing the scores for the three items (range 0 to 30).[37–43,45,46,48]

Table 1 Characteristics of included studies

Reference (ClinicalTrials.gov identifier)	Adjunctive treatment	Adjunctive treatment duration	Randomized patients	Inadequate response to (current episode)	Inadequate response definition		Primary efficacy measure	Setting	Source of funding
					Historical ADT[a]	Prospective/ongoing ADT[b]			
Berman et al, 2007[29] (NCT00095823)	Aripiprazole 2–20 mg	6 weeks	362	1–3 historical ADTs + 1 prospective SSRI/SNRI	<50% improved on ATRQ	<50% reduction in HAM-D_{17} total score from start of prospective treatment to week 8; HAM-D_{17} total score ≥14 and CGI-I score ≥3 at week 8	MADRS total	24 outpatient sites in the US	Bristol-Myers Squibb and Otsuka
Marcus et al, 2008[30] (NCT00095758)	Aripiprazole 2–20 mg	6 weeks	381	1–3 historical ADTs + 1 prospective SSRI/SNRI	<50% improved on ATRQ	<50% reduction in HAM-D_{17} total score from start of prospective treatment to week 8; HAM-D_{17} total score ≥14 and CGI-I score ≥3 at week 8	MADRS total	36 outpatient sites in the US	Bristol-Myers Squibb and Otsuka
Berman et al, 2009[31] (NCT00105196)	Aripiprazole 2–20 mg	6 weeks	349	1–3 historical ADTs + 1 prospective SSRI/SNRI	<50% improved on ATRQ	<50% reduction in HAM-D_{17} total score from start of prospective treatment to week 8; HAM-D_{17} total score ≥14 at week 8; CGI-I score ≥3 at weeks 6 and 8	MADRS total	36 outpatient sites in the US	Bristol-Myers Squibb and Otsuka
Kamijima et al, 2013[32] (NCT00876343)	Aripiprazole 3 mg/3–15 mg	6 weeks	586	1–3 historical ADTs + 1 prospective ADT	Not specified	<50% reduction in HAM-D_{17} total score from start of prospective treatment to week 8; HAM-D_{17} total score ≥14 and CGI-I score ≥3 at week 8[c]	MADRS total	169 sites in Japan	Otsuka
Quiroz et al, 2016[33] (NCT01437657)	Basimglurant MR 0.5 mg/1.5 mg	6 weeks	333	1–3 historical ADTs (1 ongoing SSRI/SNRI)	Investigator judgment	MADRS total score ≥25 and CGI-S score ≥4 at screening[d]	MADRS total	59 outpatient sites in Chile, Europe, Japan, Mexico, and the US	Hoffmann-La Roche
Thase et al, 2015[34] (NCT01360645)	Brexpiprazole 2 mg	6 weeks	379	1–3 historical ADTs + 1 prospective SSRI/SNRI	<50% improved on ATRQ	<50% reduction in HAM-D_{17} total score from start of prospective treatment to week 8; HAM-D_{17} total score ≥14 at week 8; <50% reduction in MADRS total score from start of prospective treatment to weeks 2, 4, 6, and 8; CGI-I score ≥3 at weeks 2, 4, 6, and 8[e]	MADRS total	59 outpatient sites in Canada, Europe, and the US	Otsuka and Lundbeck
Thase et al, 2015[35] (NCT01360632)	Brexpiprazole 1 mg/3 mg	6 weeks	677	1–3 historical ADTs + 1 prospective SSRI/SNRI	<50% improved on ATRQ	<50% reduction in HAM-D_{17} total score from start of prospective treatment to week 8; HAM-D_{17} total score ≥14 at week 8; <50% reduction in MADRS total score from start of prospective treatment to weeks 2, 4, 6, and 8; CGI-I score ≥3 at weeks 2, 4, 6, and 8[e]	MADRS total	92 outpatient sites in Canada, Europe, Russia, and the US	Otsuka and Lundbeck
Fava et al, 2016[36] (NCT01500200)	Buprenorphine + samidorphan 2 mg + 2 mg/ 8 mg + 8 mg	Stage 1: 5 weeks; stage 2: 5 weeks[f]	142	1–2 historical ADTs (1 ongoing)	<50% improved on ATRQ	For entry into stage 2[f]: <50% reduction in HAM-D_{17} total score from start of stage 1 to week 5; HAM-D_{17} total score ≥14 at week 5	HAM-D_{17} total	31 sites in the US	Alkermes

Durgam et al, 2016[37] (NCT01469377)	Cariprazine 1–2 mg/ 2–4.5 mg	8 weeks	819	1–2 historical ADTs (1 ongoing)	Not specified	ATHF resistance rating ≥3 with global confidence ≥3 at screening[e]	MADRS total	76 outpatient sites in Europe and the US	Forest Laboratories (Allergan) and Gedeon Richter
Fava et al, 2015[38] (NCT01098240)	CP-601,927 2–4 mg	6 weeks	162	1–3 historical ADTs + 1 prospective SSRI	<50% improved on ATRQ	<50% reduction in HAM-D_{17} total score from start of prospective treatment to week 8; HAM-D_{17} total score ≥16 at week 8	MADRS total	25 outpatient sites in the US	Pfizer
Vieta et al, 2014[39] (NCT01157078, NCT01180400)	Dexmecamylamine 2–8 mg (2 studies)	8 weeks	319, 295	0–1 historical ADTs + 1 prospective SSRI/SNRI	Not specified	<50% reduction in HAM-D_{17} total score from start of prospective treatment to week 8; HAM-D_{17} total score ≥16 and CGI-S score ≥4 at week 8	MADRS total	70 outpatient sites in India and the US; 80 outpatient sites in Europe	AstraZeneca and Targacept
Möller et al, 2015[40] (NCT01153347, NCT01197508)	Dexmecamylamine 0.2 mg/1 mg/2 mg/ 4 mg/8 mg (across 2 studies)	8 weeks	641, 696	0–1 historical ADTs + 1 prospective SSRI/SNRI	Not specified	<50% reduction in HAM-D_{17} total score from start of prospective treatment to week 8; HAM-D_{17} total score ≥16 and CGI-S score ≥4 at week 8	MADRS total	114 outpatient sites in India and the US; 132 outpatient sites in Europe, South Africa, and South America	AstraZeneca and Targacept
Tummala et al, 2015[41] (NCT01152554)	Dexmecamylamine 2–8 mg	52 weeks	813 (769 de novo[g])	0–1 historical ADTs + 1 prospective SSRI/SNRI	Not specified	De novo patients[g]: HAM-D_{17} total score ≥10 and CGI-S score ≥3 at week 6 of prospective treatment	Not applicable (safety)	115 outpatient sites in the US	AstraZeneca
Ball et al, 2014[42] (NCT00840034)	Edivoxetine 6–18 mg	8 weeks	227	1 ongoing SSRI	Not applicable	Investigator judgment at screening; <25% reduction in QIDS-SR_{16} score from start of adjunctive placebo phase to week 2	MADRS total	25 outpatient sites in the US	Eli Lilly and Company
Ball et al, 2016[43] (NCT01173601, NCT01187407, NCT01185340)	Edivoxetine 6 mg/ 12 mg/12–18 mg/ 18 mg (across 3 studies)	8 weeks	701, 689, 449	1 ongoing SSRI	Not applicable	Investigator judgment at screening and start of adjunctive placebo phase; <25% reduction in MADRS total score from start of adjunctive placebo phase to week 3; MADRS total score ≥14 at week 3	MADRS total	Multiple outpatient sites in Australia, Europe, Japan, Russia, South Africa, and the US	Eli Lilly and Company
Barbee et al, 2011[44] (NCT00901407)	Lamotrigine 100–400 mg	10 weeks	96	≥1 historical ADT + 1 prospective paroxetine/ paroxetine CR	Not specified	HAM-D_{17} total score ≥15 at week 8 of prospective treatment	MADRS total	19 sites in the US	GlaxoSmithKline
Sanacora et al, 2017[45] (NCT01482221)	Lanicemine 50 mg/100 mg (IV regimen)	12 weeks (primary analysis at week 6)	302	≥1 historical ADT (1 ongoing)	Investigator judgment	Investigator judgment	MADRS total	49 outpatient sites in Chile, Europe, South Africa, and the US	AstraZeneca
Richards et al, 2016[46] (NCT01436149, NCT01436162)	Lisdexamfetamine dimesylate 20–70 mg (2 studies)	8 weeks	404, 426	0–2 historical ADTs + 1 prospective SSRI/SNRI	Not specified	<50% reduction in MADRS total score from start of prospective treatment to week 8; MADRS total score ≥18 at week 8	MADRS total	76 sites in Canada, Europe, Mexico and the US; 94 sites in Europe, South Africa, and the US	Shire

(*Continued*)

Table 1 (*Continued*)

Reference (ClinicalTrials.gov identifier)	Adjunctive treatment	Adjunctive treatment duration	Randomized patients	Inadequate response to (current episode)	Inadequate response definition		Primary efficacy measure	Setting	Source of funding
					Historical ADT[a]	Prospective/ongoing ADT[b]			
Thase et al, 2007[47] (NCT00035321)	Olanzapine 6–18 mg (as OFC; 2 studies pooled)	8 weeks	605 (pooled)	1 historical ADT + 1 prospective fluoxetine	Investigator judgment	<25% reduction in HAM-D_{17} total score from start of prospective treatment to week 8; HAM-D_{17} total score ≥18 at week 8; ≤15% reduction in HAM-D_{17} total score from week 7 to week 8	MADRS total	Multiple outpatient sites in Canada and the US	Eli Lilly and Company
Mahmoud et al, 2007[48] (NCT00095134)	Risperidone 1–2 mg	6 weeks	274	1 ongoing ADT	Not applicable	CGI-S score ≥4 and CDS score ≥20 at week 4 of prospective phase	HAM-D_{17} total	75 outpatient sites in the US	Ortho-McNeil-Janssen

Notes: [a]"Historical" describes an ADT that was discontinued prior to study enrollment. [b]"Prospective" describes an ADT that was initiated during the study, whereas "ongoing" describes an ADT that was initiated prior to study enrollment and was continued during the study. [c]The manuscript states that any one of these criteria is sufficient; however, by comparison with the other aripiprazole studies, we assume this is an error. [d]In addition, where available, a patient-rated MADRS total score ≥23 at screening, with a permitted discrepancy of ≤7 points versus the clinician-rated MADRS total score. [e]Revised criteria following a protocol amendment. [f]Two-stage study design: 1) patients were randomized to placebo or active treatment; 2) placebo non-responders in stage 1 were re-randomized to placebo or active treatment. [g]Study also rolled-over a small number of patients from two acute studies (NCT01157078 and NCT01153347).

Abbreviations: ADT, antidepressant treatment; ATHF, Antidepressant Treatment History Form; ATRQ, Massachusetts General Hospital Antidepressant Treatment Response Questionnaire; CDS, Carroll Depression Scale; CGI-I/S, Clinical Global Impressions – Improvement/Severity of illness; CR, controlled release; HAM-D_{17}, 17-item Hamilton Depression Rating Scale; IV, intravenous; MADRS, Montgomery–Åsberg Depression Rating Scale; MR, modified release; OFC, olanzapine–fluoxetine combination; QIDS-SR_{16}, 16-item Quick Inventory of Depressive Symptomatology (Self-Report); SNRI, serotonin–norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.

If the work/studies item was unrated, as was the case for 10%–35% of patients (in studies where patient numbers by item were available), it was generally unclear whether these patients were excluded from the SDS total score, or whether the SDS total score was calculated by imputing the mean of the other two items in place of the work/studies item. One study calculated the SDS sum of items 2 and 3 score (range 0 to 20), since a large proportion of patients (25%–35%) had no work/studies rating.[33] Six studies calculated the SDS mean score, obtained by taking an average of the item scores for all items that were rated (range 0 to 10).[29–32,34,35] Finally, four studies did not specify how SDS scores were calculated.[36,44,47]

As can be seen in Table 1, 13 different adjunctive agents were used across the studies, of which five were second-generation antipsychotics. All were short-term studies (6–12 weeks), except for one 52-week study. The minimum number of ADTs (historical plus prospective) to which patients were required to show inadequate response prior to randomization ranged from one to two. Definitions of inadequate response varied, from "investigator judgment", to strict definitions with qualifying scores on multiple rating scales at multiple time points.

Efficacy

Each of the second-generation antipsychotics (aripiprazole, brexpiprazole, cariprazine, olanzapine as OFC [pooled data], and risperidone) had at least one dose that met the primary efficacy endpoint of their respective studies (improvement of depressive symptoms, measured by either Montgomery–Åsberg Depression Rating Scale total score or 17-item Hamilton Depression Rating Scale total score; Table 1).[29–32,34,35,37,47,48] The combination of buprenorphine and samidorphan also met its primary efficacy endpoint at one dose.[36] All other agents failed to meet the primary efficacy endpoint of their respective studies, and were therefore failed or negative studies.

A summary of the SDS results from the included studies is given in Table 2. Baseline SDS scores were similar between treatment groups in each study. All groups (active and control) improved numerically from baseline to endpoint, as measured by the SDS total or SDS mean. Most active treatments showed a numerically greater improvement than placebo (except for dexmecamylamine, which had inconsistent results). However, the majority of agents, and studies, failed to show a statistically significant benefit versus placebo on the SDS total or SDS mean. Only four agents demonstrated efficacy ($p<0.05$ versus placebo) on the SDS total or SDS mean in at least one study: aripiprazole, brexpiprazole,

Table 2 Change from baseline to endpoint in self-rated functioning scale scores (for the population who received ≥1 dose of randomized treatment and had ≥1 post-baseline efficacy evaluation)

Reference	Treatment arm	SDS summary score					SDS work/studies		SDS social life		SDS family life	
		Baseline		Change to endpoint			Change to endpoint		Change to endpoint		Change to endpoint	
		n	Mean (SD)	n	Mean (SE)	*p*-value versus placebo	Mean (SE)	*p*-value versus placebo	Mean (SE)	*p*-value versus placebo	Mean (SE)	*p*-value versus placebo
Aripiprazole		**SDS mean**										
Berman	Placebo	164	5.4 (0.2)[a]	164	−0.7 (0.2)		−0.7 (0.3)[b]		−0.8 (0.2)		−0.5 (0.2)	
et al, 2007[29]	2–20 mg	167	5.7 (0.2)[a]	167	−1.1 (0.2)	0.055	−0.7 (0.2)[c]	0.98	−1.4 (0.2)	0.030	−1.1 (0.2)	0.017
Marcus et al,	Placebo	168	5.4 (0.2)[a]	168	−0.7 (0.2)		−0.4 (0.2)[d]		−0.6 (0.2)[e]		−1.0 (0.2)[e]	
2008[30]	2–20 mg	180	5.1 (0.2)[a]	180	−1.3 (0.2)	0.012	−0.5 (0.2)[f]	0.62	−1.4 (0.2)[g]	0.002	−1.8 (0.2)[g]	0.002
Berman	Placebo	160	5.9 (0.2)[a]	160	−0.8 (0.2)		−0.7 (0.3)[h]		−0.7 (0.2)		−0.8 (0.2)	
et al, 2009[31]	2–20 mg	160	5.7 (0.2)[a]	160	−1.2 (0.2)	0.075	−0.8 (0.3)[i]	0.79	−1.2 (0.2)	0.052	−1.4 (0.2)	0.037
Kamijima	Placebo	195	5.3 (0.1)[a]	193	−0.5 (0.1)		−0.4 (0.1)		−0.6 (0.1)		−0.3 (0.1)	
et al, 2013[32]	3 mg	197	5.0 (0.1)[a]	197	−1.0 (0.1)	0.001	−0.9 (0.1)	0.003	−1.1 (0.1)	0.003	−0.9 (0.1)	0.003
	3–15 mg	194	5.0 (0.1)[a]	193	−1.0 (0.1)	<0.001	−1.0 (0.1)	<0.001	−1.2 (0.1)	<0.001	−0.9 (0.1)	0.003
Basimglurant MR		**SDS sum of items 2 and 3**										
Quiroz et al,	Placebo	109[j]	13.2 (3.7)	109	−5.1 (0.6)							
2016[33]	0.5 mg	112[j]	13.8 (4.0)	112	−5.1 (0.6)	0.94						
	1.5 mg	111[j]	13.5 (3.6)	111	−6.4 (0.6)	0.09						
Brexpiprazole		**SDS mean**										
Thase et al,	Placebo	191[j]	6.3 (2.1)	178	−0.9 (0.2)		−1.0 (0.2)		−1.0 (0.2)		−0.7 (0.2)	
2015[34]	2 mg	188[j]	6.0 (2.0)	175	−1.4 (0.2)	0.035	−1.1 (0.2)	0.61	−1.6 (0.2)	0.022	−1.3 (0.2)	0.011
Thase et al,	Placebo	221[k]	5.6 (1.9)	203	−0.8 (0.2)		−0.7 (0.2)		−0.9 (0.2)		−0.8 (0.2)	
2015[35]	1 mg	226[k]	5.9 (2.0)	211	−1.3 (0.2)	0.016	−1.1 (0.2)	0.082	−1.3 (0.2)	0.035	−1.3 (0.2)	0.019
	3 mg	230[k]	5.7 (2.2)	213	−1.3 (0.2)	0.019	−0.9 (0.2)	0.30	−1.4 (0.2)	0.028	−1.4 (0.2)	0.0077
Buprenorphine + samidorphan												
Fava et al,	Placebo											
2016[36]	2 mg + 2 mg					NS						
	8 mg + 8 mg					NS						
Cariprazine		**SDS total**										
Durgam	Placebo	264	18.5 (4.7)	264	−6.6 (0.5)						−2.3	
et al, 2016[37]	1–2 mg	273	18.7 (4.7)	273	−7.7 (0.5)	0.24		NS		NS		NS
	2–4.5 mg	271	18.8 (4.8)	271	−8.0 (0.5)	0.11		NS		NS	−2.9	0.014
CP-601,927		**SDS total**										
Fava et al,	Placebo	85	18.5 (5.3)	85	−5.7 (8.2)[l]							
2015[38]	2–4 mg	77	19.0 (5.9)	77	−6.6 (8.0)[l]	NS		NS		NS		NS

(*Continued*)

Table 2 (*Continued*)

Reference	Treatment arm	SDS summary score					SDS work/studies		SDS social life		SDS family life	
		Baseline		Change to endpoint			Change to endpoint		Change to endpoint		Change to endpoint	
		n	Mean (SD)	n	Mean (SE)	*p*-value versus placebo	Mean (SE)	*p*-value versus placebo	Mean (SE)	*p*-value versus placebo	Mean (SE)	*p*-value versus placebo
Dexmecamylamine		**SDS total**										
Vieta et al, 2014[39]	Placebo			151	−5.5 (0.7)		−1.7 (0.2)[m]		−1.9 (0.2)		−2.0 (0.3)	
	2–8 mg			143	−6.1 (0.7)	0.42	−2.0 (0.2)[n]	0.21	−1.9 (0.2)	0.93	−2.1 (0.3)	0.76
	Placebo			142	−5.8 (0.5)		−1.8 (0.2)[o]		−1.9 (0.2)		−2.0 (0.2)	
	2–8 mg			138	−5.8 (0.5)	0.96	−2.2 (0.3)[p]	0.20	−2.0 (0.2)	0.76	−1.9 (0.2)	0.62
Möller et al, 2015[40]	Placebo			153	−4.9 (0.6)		−1.7 (0.2)[q]		−1.9 (0.2)		−1.6 (0.2)	
	1 mg			152	−5.5 (0.6)	0.42	−1.7 (0.2)[r]	0.95	−1.9 (0.2)	0.92	−1.9 (0.2)	0.21
	4 mg			148	−5.5 (0.6)	0.49	−1.8 (0.2)[s]	0.87	−1.9 (0.2)	0.97	−1.8 (0.2)	0.34
	8 mg			149	−4.5 (0.7)	0.60	−1.7 (0.2)[t]	0.79	−1.6 (0.2)	0.24	−1.6 (0.2)	0.97
	Placebo			172	−7.1 (0.6)		−2.1 (0.2)[u]		−2.4 (0.2)		−2.3 (0.2)	
	0.2 mg			171	−6.1 (0.6)	0.18	−2.0 (0.2)[v]	0.91	−2.1 (0.2)	0.25	−2.0 (0.2)	0.17
	2 mg			168	−6.3 (0.6)	0.33	−1.8 (0.2)[w]	0.45	−2.2 (0.2)	0.50	−2.1 (0.2)	0.40
	8 mg			163	−6.2 (0.6)	0.27	−1.9 (0.2)[x]	0.66	−2.2 (0.2)	0.44	−2.0 (0.2)	0.20
Tummala et al, 2015[41]	Placebo			70	−7.4 (7.5)[l]							
	2–8 mg			185	−7.0 (7.9)[l]							
Edivoxetine		**SDS total**[y]										
Ball et al, 2014[42]	Placebo	71[k]	19.2 (6.8)	68	−2.6		−0.4		−1.0		−1.0	
	6–18 mg	67[k]	17.9 (6.9)	63	−6.0	0.039	−1.9	0.10	−2.1	0.046	−1.9	0.11
Ball et al, 2016[43]	Placebo	P: 690[k]	P: 18.1 (6.1)	240	−4.5 (0.4)							
	12 mg	E: 1,149[k]	E: 18.2 (5.8)	231	−5.4 (0.4)	NS						
	18 mg	(pooled)	(pooled)	230	−5.3 (0.4)	NS						
	Placebo			231	−4.3 (0.4)							
	6 mg			226	−6.3 (0.4)	≤0.05						
	12–18 mg			232	−5.3 (0.4)	NS						
	Placebo			219	−4.4 (0.5)							
	12–18 mg			230	−4.5 (0.5)	NS						
Lamotrigine												
Barbee et al, 2011[44]	Placebo											
	100–400 mg					NS						
Lanicemine (IV regimen)		**SDS total**										
Sanacora et al, 2017[45]	Placebo			97	−6.9 (1.0)							
	50 mg			101	−7.1 (1.0)	0.89						
	100 mg			100	−6.9 (1.0)	0.99						

Lisdexamfetamine dimesylate		**SDS total**										
Richards et al, 2016[46]	Placebo	198	15.6 (5.7)	164	−4.3 (−5.3, −3.3)[z]							
	20–70 mg	198	15.9 (6.0)	162	−4.7 (−5.6, −3.7)[z]	0.58		NS		NS		NS
	Placebo	213	16.8 (5.8)	189	−4.3 (−5.2, −3.4)[z]							
	20–70 mg	209	16.8 (5.3)	180	−4.9 (−5.8, −4.0)[z]	0.35		NS		NS		NS
Olanzapine (as OFC; 2 studies pooled)												
Thase et al, 2007[47]	Fluoxetine			203					−1.1 (2.6)[l]		−1.2 (2.6)[l]	
	6–18 mg			198				0.46	−1.6 (2.8)[l]	0.027	−1.7 (2.7)[l]	0.047
Risperidone		**SDS total**										
Mahmoud et al, 2007[48]	Placebo	113	20.2 (0.6)[a]	101	−3.9		−0.8		−1.5		−1.4	
	1–2 mg	110	19.9 (0.6)[a]	100	−7.6	<0.001	−1.7	0.12	−2.9	<0.001	−2.5	<0.001
Pandina et al, 2009[28]												

Notes: Highlighted cells indicate $p \leq 0.05$ versus placebo. [a]SE. [b]n=130. [c]n=127. [d]n=136. [e]n=170. [f]n=142. [g]n=181. [h]n=126. [i]n=115. [j]For the population who received ≥1 dose of randomized treatment. [k]For the randomized population. [l]SD. [m]n=134. [n]n=124. [o]n=120. [p]n=115. [q]n=137. [r]n=132. [s]n=123. [t]n=134. [u]n=137. [v]n=141. [w]n=140. [x]n=126. [y]If the work/studies item was missing, the mean of the other two items was imputed to calculate the total score. [z]95% CI.
Abbreviations: E, edivoxetine; IV, intravenous; MR, modified release; NS, not statistically significant (and *p*-value not reported); OFC, olanzapine–fluoxetine combination; P, placebo; SDS, Sheehan Disability Scale.

edivoxetine, and risperidone. A large variation in placebo response was seen between studies.

Considering the individual SDS items, only one agent (aripiprazole) in one study had a statistically significant benefit on the SDS work/studies item. The study in question (Kamijima et al)[32] investigated two doses (3 mg and 3–15 mg) of adjunctive aripiprazole in a 6-week randomized treatment phase, and both doses showed a benefit on the work/studies item. Three other studies of aripiprazole were included in the review; none of these showed efficacy on the SDS work/studies item, despite having almost identical designs to Kamijima et al.

On the SDS social life item, aripiprazole, brexpiprazole, edivoxetine, olanzapine (as OFC), and risperidone showed a benefit over placebo ($p<0.05$) in at least one study. On the SDS family life item, a benefit ($p<0.05$) was observed for aripiprazole, brexpiprazole, cariprazine, olanzapine (as OFC), and risperidone in at least one study.

Discussion

This review of 26 randomized placebo-controlled studies showed that, of the 13 adjunctive agents identified, only aripiprazole, brexpiprazole, edivoxetine, and risperidone statistically significantly improved functioning versus placebo, as measured by the SDS total or mean, in patients with MDD and inadequate response to at least one ADT. In a previous meta-analysis of adjunctive second-generation antipsychotics in MDD, which was conducted prior to the availability of brexpiprazole data, only aripiprazole and risperidone were found to provide a benefit based on a composite endpoint of patient-reported functioning and quality of life.[52] Furthermore, a systematic review in patients with MDD who received ADT (but no adjunctive pharmacotherapy) found that many patients, particularly partial responders, continued to experience functional impairments after treatment, highlighting an unmet need in MDD.[20]

Other than edivoxetine, a selective norepinephrine reuptake inhibitor, the only agents to show statistically significant benefits on any SDS items in the present review were second-generation antipsychotics. Of these agents, aripiprazole and brexpiprazole have an indication for the adjunctive treatment of MDD, and OFC has an indication for the treatment of treatment-resistant depression (all in the US).[22,53,54] The development of edivoxetine as an adjunctive treatment for MDD was halted in 2013 because it failed to meet the primary endpoint in three Phase 3 studies.[55] Indeed, more than half of the adjunctive agents identified in this review failed to meet the primary efficacy endpoint of their respective studies. Nonetheless, the findings of this review suggest that the SDS

as a whole is a useful scale to track changes in functioning among patients with inadequate response to ADTs, and that adjunctive second-generation antipsychotics or edivoxetine may improve functioning in such patients.

The SDS was the only self-rated measure of functional impairment that was used in the retrieved records. This observation is in line with a meta-analysis of second-generation antipsychotics for the adjunctive treatment of MDD.[52] Indeed, the SDS appears to be the most widely used functioning measure in studies of MDD.[20] The SDS is considered to be a reliable and valid measure of functioning impairment, originally developed in 1981 for use in treatment outcome studies in psychiatry.[49–51] To the authors' knowledge, no minimal clinically important difference has been established for the SDS. Sheehan selected the three items of work/studies, social life, and family life after reviewing other impairment instruments and consulting with patients and colleagues.[51] In general, all three items, including the work/studies item, are sensitive to treatment effects across a variety of psychological disorders.[51] In the present review, however, in the population of patients with MDD and inadequate response to ADTs, only aripiprazole had a statistically significant benefit on the SDS work/studies item, and this was only in one study out of four. Thus, where a benefit was observed on the SDS total or mean, this was generally driven by improvement on the social life and family life items.

There are several possible reasons for a lack of effect on the work/studies item in this population. Since the work/studies item is not rated for patients who are not working, one possibility is that the studies were underpowered to measure this item. In general, as shown in a US nationwide survey of patients with MDD, inadequate responders to ADT (based on self-reports) are less likely to be employed than responders.[14] Unfortunately, the majority of studies in the present review did not separate out the number of patients who rated each item of the SDS. Where such data were available, 10%–35% of patients across the studies with a rating on the social life and family life items did not rate the work/studies item. Thus, the power to show a difference between treatment groups was reduced for the work/studies item compared with the other items.

Nevertheless, 65%–90% of patients did rate the work/studies item, and therefore were in employment or studying. In general, studies have shown that people with depression who are in employment are less severely ill than those who are unemployed.[56,57] Thus, on average, the subset of patients who rated the work/studies item may be less severely ill than the total population in each study. Meta-analyses have investigated the question of whether or not antidepressant efficacy increases with baseline illness severity, with varying results.[58,59] If, as some have suggested, antidepressants are more efficacious in more severely ill patients, then the drug–placebo difference may be expected to be greater in the total population (ie, on the social life and family life items) than in the subset of patients in employment (ie, on the work/studies item).

Finally, it is possible that the studies were too short to show a benefit on the work/studies item. With a few exceptions, the included studies assessed functioning after 6 or 8 weeks of adjunctive treatment. In general, job performance deficits can still remain after 18 months among patients whose depressive symptoms have improved,[60] and patients with inadequate response to ADT are particularly at risk of persisting impairment.[61] Thus, acute studies may not be able to detect a benefit in occupational functioning in this population of inadequate responders. Only one of the included studies was a long-term study, and, over 52 weeks, adjunctive dexmecamylamine did not show a notable difference to adjunctive placebo on the SDS total.[41] However, dexmecamylamine failed as an adjunctive agent in MDD, having shown no differences to placebo on the primary efficacy outcome in four acute studies,[39,40] and thus no benefit on the SDS might be expected.

Recent literature has acknowledged the difficulty in using the work/studies item among populations with a high proportion of non-workers, and attempts have been made to modify the SDS accordingly. Sonne et al proposed a rewording of the first item from "work/studies" to "work/daily tasks", so that patients without a job could still rate the item.[62] Similarly, Bech reported a modified version of the SDS in which the work/studies item was replaced by an overall rating, "Your daily activities all things considered".[63]

The present review is limited because it only considered published literature, leading to a risk of publication bias (as positive studies are more likely to be published than failed or negative studies). However, even with the risk of publication bias, fewer than a third of the included studies reported a treatment benefit on the SDS. In addition, the review is limited since MEDLINE (via PubMed) was the only database searched. Nonetheless, the 26 studies identified had a consistent message, that the work/studies item is less informative in this population than the other two items.

Conclusion

The SDS, a self-rated functional measure, is informative in acute randomized placebo-controlled studies of adjunctive

therapy in patients with MDD and inadequate response to ADT. However, the item that measures work performance may be less relevant to this population than the items that measure social and family life.

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Author contributions

CPW and CE performed data collection and analysis. All authors contributed toward data analysis, drafting and revising the paper, and agree to be accountable for all aspects of the work.

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