Remission, dropouts, and adverse drug reaction rates in major depressive disorder: a meta-analysis of head-to-head trials

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ABSTRACT

Objective: To summarize remission rates and dropouts due to adverse drug reactions (ADRs) or lack of efficacy (LoE) of serotonin-norepinephrine reuptake inhibitors (SNRIs), selective serotonin-reuptake inhibitors (SSRIs), and tricyclic antidepressants (TCAs) in treating major depressive disorder.

Methods: We searched MEDLINE, EMBASE, IPA, and the Cochrane International Library from 1980–2005. Meta-analysis summarized outcomes from head-to-head randomized clinical trials comparing ≥ 2 drugs from three antidepressants classes (SNRIs, and/or SSRIs, and/or TCAs) followed by ≥ 6 weeks of treatment. Remission was a final Hamilton Depression Rating Scale (HAMD) score ≤ 7 or Montgomery-Åsberg Depression Rating Scale (MADRS) ≤ 12. Intent-to-treat data were combined across study arms using random effects models, producing point estimates with 95% confidence intervals.

Results: We obtained data from 30 arms of 15 head-to-head trials with 2458 patients. SNRIs had the highest ITT remission rate (49.0%), then TCAs (44.1%), and SSRIs (37.7%) ($p > 0.05$ for SNRIs versus TCAs; $p < 0.001$ for TCAs versus SSRIs and SNRIs versus SSRIs). When categorized as inpatients ($n = 582$) and outpatients ($n = 1613$), SNRIs had the highest remission rates (52.0% for 144 inpatients and 49.3% for 559 outpatients). SNRIs had lowest overall dropouts (26.1%), followed by SSRIs (28.4%), and TCAs (35.7%). Dropouts due to ADRs and LoE were 10.3% and 6.2% for SNRIs, 8.3% and 7.2% for SSRIs, and 19.8% and 9.9% for TCAs, respectively ($p > 0.05$ for ADR dropouts only). One limitation was the inclusion of only venlafaxine-XR; results may not be the same for immediate release forms. In addition, few studies reported remission rates.

Conclusions: SNRIs had the highest efficacy remission rates (statistically significant for inpatients and outpatients), and the lowest overall dropout rates, suggesting clinical superiority in treating major depression.

Introduction

Major depressive disorder (MDD) is a severe, debilitating illness affecting 121 million people worldwide. On a yearly basis, 9.5% of all women and 5.8% of all men will develop a depressive episode[1]. The consequences of the disease can be substantial, in terms of morbidity[2], mortality[3], and economic impact[4].

Several agents have been introduced, but not all patients respond to pharmacotherapy, and research

continues for newer and improved therapies[5]. The first drugs that were demonstrated to exert an antidepressant effect were those that inhibited monoamine oxidase. Later, tricyclic antidepressants (TCAs) were introduced, but the lack of selectivity (i.e., anticholinergic and anti-alpha-adrenergic effects) resulted in a decreased tolerability for this group of drugs[5]. Antidepressants selectively affecting one receptor, such as selective serotonin-reuptake inhibitors (SSRIs), have been shown to be as effective[6], and better tolerated than TCAs[7]. Also, a theoretical basis exists for antidepressants selectively affecting both serotonin and norepinephrine systems to be superior in terms of improved efficacy and tolerability. In fact, there is growing clinical evidence that drugs acting on these two systems, i.e., serotonin-norepinephrine reuptake inhibitors (SNRIs), have clinical superiority compared with SSRIs[8].

Rates of success and dropout for the three pharmacological classes (i.e., SNRIs, SSRIs, and TCAs) have been reported in previous studies[9,10]. Those studies analyzed clinical outcomes in placebo-controlled randomized clinical trials, using response to treatment (i.e., 50% reduction in depression scales) as therapeutic success. However, that measure of outcome is flawed, since a patient could experience a response, yet still remain clinically depressed. For example, a person whose Hamilton Depression Rating Scale (HAMD) score was decreased from a baseline of 30 to 15 would be rated as a success, but may remain above the accepted threshold of 7, and clinically still be defined as depressed. Hence, that person could, in fact, be enrolled in a trial for depression that admits patients having a score of ≥ 15, which is not uncommon, and be considered a responder while still being clinically depressed. A more valid measure of antidepressant efficacy would be remission as defined as a score ≤ 7 on the HAMD or ≤ 12 on the Montgomery-Åsberg Depression Rating Scale (MADRS); a more stringent measure of antidepressant efficacy, characterized by resolution of the depression with minimal residual symptoms[11].

The primary aim of our study was to summarize remission rates from head-to-head clinical trials of remission for three classes of antidepressants; the SNRIs, SSRIs and TCAs. Secondary aims were to quantify clinical dropout rates due to adverse drug reactions (ADRs) or lack of efficacy (LoE), and incidences of important ADRs.

Methods

The target disease was moderate-to-severe MDD. Patients had to be adults aged ≥ 18 years with MDD, diagnosed using any standard scale, such as the Diagnostic and Statistical Manual of Mental Disorders (version III or higher)[12]. They must have scored ≥ 18 on the MADRS[13], or ≥ 15 on any version of the HAMD[14], and have no concomitant psychiatric, endocrine, or metabolic disease, as reported in the original study articles.

We attempted to locate all head-to-head randomized clinical trials involving at least two active treatment arms comparing SNRIs (venlafaxine, duloxetine, or milnacipran), SSRIs (citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, or sertraline), and/or TCAs (doxepin, clomipramine, amitriptyline, nortriptyline, maprotiline, desipramine, trimipramine, imipramine, or protriptyline). There must have been at least two active drugs being compared; however, there could be additional arms involving placebo or other types of treatment (e.g., psychotherapy). For a study to be incorporated into the meta-analysis, it had to entail a 1–2-week washout period, followed by at least 6 weeks of oral administration of a relevant drug in therapeutic doses. Patients should not have been taking antidepressants, other than those already named, or drugs that could interfere with the interpretation of study data, such as thyroid hormones or lithium. Hypnotic agents and tranquilizers were allowed. No restriction was placed on language or time of publication.

The outcome of primary interest was remission, defined as a score ≤ 7 on the HAMD or ≤ 12 on the MADRS scale. A secondary interest was tolerability, which was defined in terms of dropouts due to ADRs and LoE. Also, rates of occurrence of important ADRs were analyzed. Clinical rates for inpatients and outpatients were examined separately.

We searched computerized databases including Medline, Embase, International Pharmaceutical Abstracts, and the Cochrane International Library from 1980, the decade during which SNRIs were introduced, through December 2005. Medical subject headings used included 'serotonin norepinephrine reuptake inhibitors', 'selective serotonin reuptake inhibitors', 'tricyclic antidepressants', 'major depression', and 'clinical remission'.

Two reviewers independently identified studies to be included in the analysis and performed the data extraction. Disagreements in both study selection and data extraction were resolved through consensus. The rationale for decisions was discussed until reviewers agreed on a final decision.

From the clinical trials, we summarized patient parameters such as age, weight, HAMD and MADRS scores, as well as clinical outcome rates. We used a random effects model, weighted by inverse variance, and modified for use in combining data from individual arms of trials[15]. Results were summarized across

the arms of studies to arrive at a single estimate of remission, dropout, and ADR occurrence rates, along with a 95% confidence interval (CI). Data were combined separately for all antidepressant classes (i.e., SNRIs, SSRIs, and TCAs). It was assumed that all drugs within a class were essentially equivalent and, in equipotent doses used continuously over several weeks, would act similarly. Subgroup analyses were performed for individual drugs whenever possible. When only one study was reported for a particular drug, we calculated rates and CIs by using the proportion score method. Data were analyzed using both intent-to-treat (ITT) and per-protocol (PP) models.

To examine the rates statistically, we calculated Z-scores using the method described by Rosenthal[16], where the summary mean rate was divided by its standard error. The significance of the difference between rates was then calculated using the following formula:

$$Z = (Z_1 - Z_2) / \sqrt{2}$$

where subscripts 1 and 2 represent comparator 1 and comparator 2, respectively. Since this test strictly requires homogeneity of variances between comparators, we first tested for the presence of heterogeneity using Box's variant of the Bartlett test, which is valid for small sample sizes. In the case of heterogeneity, the test becomes invalid, yielding improbable or impossible results (e.g., it could show that a small value is statistically higher than a large value). In such cases, a Mann-Whitney U test would be done to contrast the rates between studies.

Heterogeneity of effects was tested using the Q-statistic[17]. In the case where potential heterogeneity was detected, we identified the responsible studies and inspected them in attempt to identify moderator variables. Publication bias was assessed using visual inspection of funnel plots and by calculating the Begg-Mazumdar statistic[18]. For all statistical tests, a p-value of ≤ 0.05 was considered statistically significant.

Results

A total of 55 studies were identified in the literature search. Of those studies, 40 (72.7%) were excluded; 24 for having different outcome measures (i.e., did not present remission rates)[19-42], 10 were not randomized controlled trials[43-52], two identified in the search could not be located[53,54], one each for being a duplicate publication[55], having a different treatment duration[56], data not extractable[57], and for including patients with comorbidities[58]. As a result, 15 randomized clinical trials[59-73], yielding 30 study arms, were used in the analysis of remission rates. Article selection and data extraction were resolved with full consensus (100%).

The funnel plot for success rates was suggestive of the possibility of a potential problem (data not shown), but there were few studies. On the other hand, the Begg-Mazumdar test found a small and non-significant correlation for all three pharmacological groups. It was therefore concluded that publication bias was probably not present to any great extent.

When we calculated the Q-statistic for heterogeneity, the analytic rates across trials for remission and dropout rates showed the presence of heterogeneity in all pharmacological groups. A search for moderator variables could find no systematic differences in the (presumed) responsible studies. Further examination (as presented below in the Discussion) suggested that the studies were not different in any way, so we proceeded to combine them.

From the 30 study arms ($n = 2458$), 10 involved SNRIs ($n = 836$), 11 examined SSRIs ($n = 916$), and nine studied TCAs ($n = 706$). The patients' mean ages were 52.5 years (SD = 10.9), 40.9 (SD = 12.0), and 53.7 (SD = 10.0) in the groups treated with SNRIs, SSRIs, and TCAs, respectively ($p > 0.05$ for TCAs versus SNRIs; $p < 0.05$ for TCAs versus SSRIs and for SNRIs versus SSRIs). Also, a significant difference was found between patients' weights ($p < 0.05$ for SSRIs versus TCAs, only). All other categories (i.e., HAMD-17, HAMD-21, and MADRS scores) showed non-significant results between groups. Comprehensive demographics from the selected studies are presented in Table 1.

Table 2 presents meta-analytic remission rates across study arms using ITT and PP models. For the ITT analysis, the maximum and minimum observed meta-analytic remission rates for individual drugs was 0.536 (SE = 0.037) and 0.234 (SE = 0.031) for citalopram and fluoxetine, respectively. By drug class and using an ITT approach, SNRIs had the highest overall remission rate of 49.0%, followed by TCAs with 44.1%, and SSRIs with 37.7%. The difference was not significant ($p > 0.05$) between SNRIs and TCAs. However, both were superior to SSRIs ($p < 0.001$ for both contrasts). If we consider a difference of 10% to be clinically important, then only SNRIs would be considered clinically superior to SSRIs.

Using the PP approach, clomipramine and sertraline had the highest and lowest meta-analytic remission rates (0.765, SE = 0.093; 0.356, SE = 0.071, respectively). TCAs produced significantly higher remission rates compared to SNRIs and SSRIs ($p < 0.001$ for both comparisons), while the other two did not differ among themselves ($p > 0.05$). In this case, there is a clinical difference (14.6%) between TCAs and SSRIs, but not SNRIs (5.4%).

Table 1. Demographic and clinical details of accepted studies

Drug class	Reference	Drug	Setting	Treatment duration, weeks	Dosage range, mg	*n* (ITT)	Mean age, years (SD)	Mean weight, kg (SD)	Women, %	Remission definition	Mean HAMD-17 (SD)	Mean HAMD-21 (SD)	Mean MADRS (SD)
SNRIs	60	MIL	In	6	100*	53	46.7 (ND)	61.5 (ND)	70.6	HAMD ≤ 7	NA (NA)	26.5 (6.8)	36.5 (7.9)
	64	VEN	Out	8	75–225	100	37.5 (11.6)	ND (ND)	47.0	HAMD ≤ 7	NA (NA)	ND (ND)	30.0 (ND)
	65	DUL	Out	8	80*	93	43.1 (11.1)	71.0 (14.8)	73.3	HAMD ≤ 7	19.9 (3.6)	NA (NA)	21.8 (5.8)
	63	VEN	Out	8	75–150	57	37.9 (10.1)	65.4 (13.5)	80.0	HAMD ≤ 7	NA (NA)	23.9 (3.0)	25.6 (5.2)
	67	DUL	Out	8	80–120	70	42.3 (10.8)	83.6 (20.0)	62.9	HAMD ≤ 7	18.4 (4.0)	NA (NA)	22.9 (6.1)
	66	DUL	In	8	80*	91	41.0 (12.0)	82.0 (21.0)	62.0	HAMD ≤ 7	17.9 (4.7)	NA (NA)	22.2 (6.5)
	69	MIL	Both	24	200*	52	49.2 (9.8)	ND (ND)	65.0	HAMD ≤ 7	23.7 (3.1)	NA (NA)	ND (ND)
	70	VEN	Out	8	75–150	142	47.0 (14.0)	71.0 (17.0)	71.0	MADRS ≤ 12	20.4 (5.8)	NA (NA)	29.0 (5.4)
	71	VEN	Out	8	75–225	95	40.0 (ND)	ND (ND)	73.0	HAMD ≤ 7	NA (NA)	25.0 (ND)	28.0 (ND)
	73	MIL	Both	8	75–100	83	74.0 (6.2)	63.3 (11.9)	83.9	HAMD ≤ 7	25.8 (4.5)	NA (NA)	32.0 (4.8)
	Total SNRIs					836	52.5 (10.9)	69.9 (16.7)	69.0		21.3 (4.4)	24.3 (5.3)	27.0 (6.0)
SSRIs	61	PAR	In	12	20–40	25	ND (ND)	ND (ND)	64.0	HAMD ≤ 7	ND (ND)	NA (NA)	ND (ND)
	62	FLU	In	6	20–80	56	42.1 (12.9)	ND (ND)	79.0	HAMD ≤ 7	NA (NA)	28.0 (5.3)	ND (ND)
	64	ESC	Out	8	10–20	98	37.3 (12.3)	ND (ND)	69.4	HAMD ≤ 7	NA (NA)	ND (ND)	30.7 (ND)
	59	PAR	In	6	30*	62	ND (ND)	ND (ND)	ND	HAMD ≤ 7	ND (ND)	ND (ND)	ND (ND)
	65	PAR	Out	8	20*	85	42.0 (10.6)	70.4 (15.0)	75.3	HAMD ≤ 7	20.3 (4.1)	NA (NA)	22.3 (6.2)
	67	FLU	Out	8	20*	30	39.7 (10.5)	78.5 (17.8)	57.6	HAMD ≤ 7	17.9 (4.3)	NA (NA)	22.6 (6.9)
	66	PAR	In	8	20*	82	40.0 (11.0)	89.0 (29.0)	64.0	HAMD ≤ 7	17.9 (5.2)	NA (NA)	23.3 (7.8)
	68	CIT	Out	8	20–40	179	73.4 (ND)	ND (ND)	73.0	MADRS ≤ 12	ND (ND)	ND (ND)	ND (ND)
	70	ESC	Out	8	10–20	146	49.0 (15.0)	74.0 (19.0)	73.0	MADRS ≤ 12	19.9 (5.7)	NA (NA)	28.7 (5.0)
	71	FLU	Out	8	20–60	103	40.0 (ND)	ND (ND)	69.0	HAMD ≤ 7	NA (NA)	26.0 (ND)	29.0 (ND)
	72	SER	Out	12	50–200	50	39.6 (11.1)	ND (ND)	78.4	HAMD ≤ 7	NA (NA)	25.0 (ND)	14.9 (11.0)
	Total SSRIs					916	40.9 (12.0)	75.4 (20.9)	71.8		19.0 (4.9)	26.7 (5.7)	24.2 (7.7)
TCAs	60	IMI	In	6	150*	56	45.9 (ND)	66.1 (ND)	71.0	HAMD ≤ 7	NA (NA)	25.5 (5.3)	36.5 (6.4)
	61	IMI	In	12	100–200	32	ND (ND)	ND (ND)	47.0	HAMD ≤ 7	ND (ND)	NA (NA)	ND (ND)
	62	IMI	In	6	75–300	62	43.3 (13.1)	ND (ND)	84.0	HAMD ≤ 7	NA (NA)	27.0 (5.8)	ND (ND)
	59	CLO	In	6	150*	58	ND (ND)	ND (ND)	ND	HAMD ≤ 7	ND (ND)	ND (ND)	ND (ND)
	63	AMI	Out	8	50–150	59	39.1 (8.7)	61.3 (11.0)	81.0	HAMD ≤ 7	NA (NA)	24.5 (3.2)	24.9 (6.0)
	68	AMI	Out	8	50–100	186	74.1 (ND)	ND (ND)	74.0	MADRS ≤ 12	ND (ND)	ND (ND)	ND (ND)
	69	CLO	Both	24	150*	55	47.1 (10.6)	ND (ND)	62.0	HAMD ≤ 7	23.1 (3.5)	NA (NA)	ND (ND)
	72	IMI	Out	12	100–300	117	40.9 (9.8)	ND (ND)	61.5	HAMD ≤ 7	NA (NA)	24.6 (6.4)	24.8 (8.4)
	73	IMI	Both	8	75–100	81	74.2 (6.8)	64.4 (12.7)	76.6	HAMD ≤ 7	25.1 (4.7)	NA (NA)	31.0 (5.3)
	Total TCAs					706	53.7 (10.0)	62.6 (11.9)	72.3		23.8 (4.1)	25.1 (5.3)	29.8 (6.6)

*Fixed dosage

AMI = amitriptyline; CIT = citalopram; CLO = clomipramine; DUL = duloxetine; ESC = escitalopram; FLU = fluoxetine; HAMD = Hamilton depression scale; IMI = imipramine; ITT = intent-to-treat; MIL = milnacipran; MADRS = Montgomery-Åsberg depression scale; PAR = paroxetine; NA = not applicable; ND = not described; SD = standard deviation; SER = sertraline; SNRIs = serotonin norepinephrine reuptake inhibitors; SSRIs = selective serotonin reuptake inhibitors; TCAs = tricyclic antidepressants; VEN = venlafaxine

TCAs had the highest overall dropout rate (35.7%), followed by SSRIs (28.4%), and SNRIs (26.1%). In this case, the rate for TCAs was significantly greater than the other two classes ($p < 0.05$ for both comparisons). The SNRIs and SSRIs did not differ ($p > 0.05$). These rates have important implications for the clinical management of patients.

Table 3 presents meta-analytic dropout rates by drug and by drug class. Rates of dropout due to ADRs and LoE were 10.3% and 6.2% for SNRIs, 8.3% and 7.2% for SSRIs, and 19.8% and 9.9% for TCAs, respectively. A p-value of less than 0.05 was reached when we compared TCAs to both SNRIs and SSRIs with respect to dropout rates due to ADRs. However, statistical significance was not achieved when we compared SNRIs, SSRIs, and TCAs dropout rates caused by LoE.

When patients were categorized by level of care, there were 582 inpatients and 1613 outpatients. Generally, inpatient rates were greater than outpatient rates. Among the inpatients, SNRIs had the highest

Table 2. Meta-analytic remission rates by drug and drug class under intent-to-treat and per-protocol models

Model	Drug class	Drug	Authors	Number of successes	Number of failures	Meta-analytic remission rates	95% CI, LL	95% CI, UL
ITT	SNRIs	Duloxetine	Detke *et al.*[65]	47	46	0.505	0.406	0.605
			Goldstein *et al.*[66]	46	45	0.505	0.357	0.653
			Goldstein *et al.*[67]	37	33	0.529	0.310	0.737
			Total duloxetine	130	124	0.512	0.450	0.573
		Milnacipran	Amerongen *et al.*[60]	30	23	0.566	0.314	0.788
			Leinonen *et al.*[69]	21	31	0.404	0.189	0.663
			Tignol *et al.*[73]	36	47	0.434	0.246	0.642
			Total milnacipran	87	101	0.465	0.373	0.557
		Venlafaxine	Benedictis[63]	33	24	0.579	0.332	0.792
			Bielski *et al.*[64]	31	69	0.310	0.164	0.508
			Montgomery *et al.*[70]	99	43	0.697	0.531	0.824
			Rudolph and Feiger[71]	35	60	0.368	0.205	0.570
			Total venlafaxine	198	196	0.489	0.292	0.686
		Total SNRIs		415	421	0.490	0.407	0.573
	SSRIs	Citalopram	Kyle *et al.*[68]	96	83	0.536	0.463	0.608
		Escitalopram	Bielski *et al.*[64]	35	63	0.357	0.198	0.556
			Montgomery *et al.*[70]	102	44	0.699	0.535	0.824
			Total escitalopram	137	107	0.529	0.195	0.864
		Fluoxetine	Beasley *et al.*[62]	12	44	0.214	0.075	0.479
			Goldstein *et al.*[67]	10	20	0.333	0.108	0.673
			Rudolph and Feiger[71]	23	80	0.223	0.104	0.416
			Total fluoxetine	45	144	0.234	0.174	0.295
		Paroxetine	Arminen *et al.*[61]	11	14	0.440	0.154	0.772
			Danish University[59]	12	50	0.194	0.067	0.443
			Detke *et al.*[65]	39	46	0.459	0.268	0.662
			Goldstein *et al.*[66]	30	52	0.366	0.193	0.582
			Total paroxetine	92	162	0.357	0.227	0.488
		Sertraline	Thase *et al.*[72]	16	34	0.320	0.208	0.458
		Total SSRIs		386	530	0.377	0.269	0.486
	TCAs	Amitriptyline	Benedictis[63]	32	27	0.542	0.305	0.762
			Kyle *et al.*[68]	99	87	0.532	0.391	0.669
			Total amitriptyline	131	114	0.535	0.472	0.597
		Clomipramine	Danish University[59]	26	32	0.448	0.230	0.689
			Leinonen *et al.*[69]	29	26	0.527	0.286	0.756
			Total clomipramine	55	58	0.487	0.395	0.578
		Imipramine	Amerongen *et al.*[60]	29	27	0.518	0.280	0.748
			Arminen *et al.*[61]	12	20	0.375	0.135	0.697
			Beasley *et al.*[62]	21	41	0.339	0.156	0.586
			Thase *et al.*[72]	27	90	0.231	0.114	0.411
			Tignol *et al.*[73]	38	43	0.469	0.273	0.675
			Total imipramine	127	221	0.382	0.266	0.498
		Total TCAs		313	393	0.441	0.354	0.527

Table 2. Contd.

Model	Drug class	Drug	Authors	Number of successes	Number of failures	Meta-analytic remission rates	95% CI, LL	95% CI, UL
PP	SNRIs	Duloxetine	Detke *et al.*[65]	47	46	0.505	0.315	0.695
			Goldstein *et al.*[66]	46	7	0.868	0.602	0.966
			Goldstein *et al.*[67]	37	9	0.804	0.513	0.941
			Total duloxetine	130	62	0.726	0.501	0.951
		Milnacipran	Amerongen *et al.*[60]	30	12	0.714	0.413	0.899
			Leinonen *et al.*[69]	21	20	0.512	0.246	0.772
			Tignol *et al.*[73]	36	37	0.493	0.284	0.705
			Total milnacipran	87	69	0.572	0.432	0.712
		Venlafaxine	Benedictis[63]	31	35	0.470	0.257	0.694
			Bielski *et al.*[64]	33	15	0.688	0.407	0.876
			Montgomery *et al.*[70]	99	24	0.805	0.633	0.908
			Rudolph and Feiger[71]	35	41	0.461	0.261	0.674
			Total venlafaxine	198	115	0.608	0.421	0.796
		Total SNRIs		415	246	0.635	0.528	0.741
	SSRIs	Citalopram	Kyle *et al.*[68]	96	39	0.711	0.630	0.781
		Escitalopram	Bielski *et al.*[64]	35	37	0.486	0.277	0.700
			Montgomery *et al.*[70]	102	23	0.816	0.647	0.915
			Total escitalopram	137	60	0.654	0.331	0.978
		Fluoxetine	Beasley *et al.*[62]	12	11	0.522	0.195	0.831
			Goldstein *et al.*[67]	10	11	0.476	0.160	0.813
			Rudolph and Feiger[71]	23	52	0.307	0.145	0.535
			Total fluoxetine	45	74	0.411	0.264	0.558
		Paroxetine	Arminen *et al.*[61]	11	1	0.917	0.366	0.995
			Danish University[59]	12	38	0.240	0.084	0.520
			Detke *et al.*[65]	39	37	0.513	0.304	0.718
			Goldstein *et al.*[66]	30	17	0.638	0.361	0.847
			Total paroxetine	92	93	0.573	0.312	0.835
		Sertraline	Thase *et al.*[72]	16	29	0.356	0.232	0.502
		Total SSRIs		386	297	0.543	0.409	0.676
	TCAs	Amitriptyline	Benedictis[63]	32	20	0.615	0.353	0.824
			Kyle *et al.*[68]	99	31	0.762	0.591	0.876
			Total amitriptyline	131	51	0.699	0.558	0.841
		Clomipramine	Danish University[59]	26	13	0.667	0.362	0.876
			Leinonen *et al.*[69]	29	5	0.853	0.513	0.970
			Total clomipramine	55	18	0.765	0.583	0.947
		Imipramine	Amerongen *et al.*[60]	29	3	0.906	0.559	0.987
			Arminen *et al.*[61]	12	5	0.706	0.276	0.938
			Beasley *et al.*[62]	21	3	0.875	0.471	0.982
			Thase *et al.*[72]	27	61	0.307	0.154	0.518
			Tignol *et al.*[73]	38	36	0.514	0.302	0.720
			Total imipramine	127	108	0.660	0.403	0.916
		Total TCAs		313	177	0.689	0.548	0.829

CI = confidence interval; ITT = intent-to-treat; LL = lower limit; PP = per-protocol; SE = standard error; SNRIs = serotonin norepinephrine reuptake inhibitors; SSRIs = selective serotonin reuptake inhibitors; TCAs = tricyclic antidepressants; UL = upper limit

remission rate (52.0% in 144 patients), followed by TCAs (46.1% in 146 patients), and SSRIs (28.6% in 292 patients). In treating outpatients, SNRIs were again highest (49.3% in 559 patients), followed by SSRIs (43.8% in 692 patients), and TCAs (43.2% in 362 patients). All pair-wise comparisons of remission rates between inpatients and outpatients for SNRIs, SSRIs, and TCAs were statistically significant (i.e., $p < 0.05$).

Table 4 shows meta-analytic rates of occurrence of selected adverse drug reactions by drug and drug class. TCAs had the highest rates of occurrence (57.7% and 25.9% for dry mouth and constipation, respectively). There were only four categories in which TCAs did

Table 3. *Meta-analytic dropout rates due to all reasons, lack of efficacy, and adverse drug reactions by drug and drug class*

Reasons for dropouts	Drug class	Drug	Authors	Number of dropouts	Number of completers	Meta-analytic dropout rates	95% CI LL	95% CI UL
All reasons	SNRIs	Duloxetine	Goldstein *et al.*[66]	24	46	0.343	0.242	0.460
			Goldstein *et al.*[67]	38	53	0.418	0.322	0.520
			Total duloxetine	62	99	0.384	0.309	0.459
		Milnacipran	Amerongen *et al.*[60]	11	42	0.208	0.120	0.335
			Tignol *et al.*[73]	33	50	0.398	0.299	0.505
			Total milnacipran	44	92	0.303	0.117	0.489
		Venlafaxine	Benedictis[63]	9	48	0.158	0.085	0.274
			Montgomery *et al.*[70]	19	123	0.134	0.087	0.200
			Rudolph and Feiger[71]	19	76	0.200	0.132	0.291
			Total venlafaxine	47	247	0.156	0.115	0.197
		Total SNRIs		153	438	0.261	0.172	0.350
	SSRIs	Citalopram	Kyle *et al.*[68]	44	135	0.246	0.189	0.314
		Escitalopram	Montgomery *et al.*[70]	21	125	0.144	0.096	0.210
		Fluoxetine	Beasley *et al.*[62]	33	23	0.589	0.459	0.708
			Goldstein *et al.*[67]	4	26	0.133	0.053	0.297
			Rudolph and Feiger[71]	28	75	0.272	0.195	0.365
			Total fluoxetine	65	124	0.330	0.094	0.565
		Paroxetine	Arminen *et al.*[61]	13	12	0.520	0.335	0.700
			Danish University[59]	12	50	0.194	0.114	0.309
			Goldstein *et al.*[66]	38	44	0.463	0.360	0.571
			Total paroxetine	63	106	0.383	0.172	0.595
		Sertraline	Thase *et al.*[72]	5	45	0.100	0.043	0.214
		Total SSRIs		198	535	0.284	0.188	0.380
	TCAs	Amitriptyline	Benedictis[63]	7	52	0.119	0.059	0.225
			Kyle *et al.*[68]	56	130	0.301	0.240	0.370
			Total amitriptyline	63	182	0.212	0.033	0.390
		Clomipramine	Danish University[59]	19	39	0.328	0.221	0.456
		Imipramine	Amerongen *et al.*[60]	24	32	0.429	0.308	0.559
			Arminen *et al.*[61]	15	17	0.469	0.309	0.636
			Beasley *et al.*[62]	38	24	0.613	0.488	0.724
			Thase *et al.*[72]	29	88	0.248	0.178	0.333
			Tignol *et al.*[73]	33	48	0.407	0.307	0.516
			Total imipramine	139	209	0.428	0.294	0.562
		Total TCAs		221	430	0.357	0.256	0.459
LoE	SNRIs	Duloxetine	Goldstein *et al.*[66]	6	85	0.066	0.031	0.136
			Goldstein *et al.*[67]	2	68	0.029	0.008	0.098
			Total duloxetine	8	153	0.044	0.008	0.079
		Milnacipran	Amerongen *et al.*[60]	5	48	0.094	0.041	0.203
			Tignol *et al.*[73]	16	67	0.193	0.122	0.290
			Total milnacipran	21	115	0.142	0.046	0.239
		Venlafaxine	Montgomery *et al.*[70]	6	136	0.042	0.020	0.089
			Rudolph and Feiger[71]	3	92	0.032	0.011	0.089
			Total venlafaxine	9	228	0.037	0.013	0.061
		Total SNRIs		38	496	0.062	0.028	0.096
	SSRIs	Citalopram	Kyle *et al.*[68]	2	177	0.011	0.003	0.040
		Escitalopram	Montgomery *et al.*[70]	3	143	0.021	0.007	0.059
		Fluoxetine	Beasley *et al.*[62]	12	44	0.214	0.127	0.338
			Goldstein *et al.*[67]	3	27	0.100	0.035	0.256
			Rudolph and Feiger[71]	7	96	0.068	0.033	0.134
			Total fluoxetine	22	167	0.118	0.033	0.204
		Paroxetine	Arminen *et al.*[61]	3	22	0.120	0.042	0.300

Table 3. Contd.

Reasons for dropouts	Drug class	Drug	Authors	Number of dropouts	Number of completers	Meta-analytic dropout rates	95% CI LL	95% CI UL
			Goldstein *et al.*[66]	11	71	0.134	0.077	0.224
			Total paroxetine	14	93	0.131	0.067	0.194
		Total SSRIs		41	580	0.072	0.032	0.111
	TCAs	Amitriptyline	Kyle *et al.*[68]	3	183	0.016	0.006	0.046
		Imipramine	Amerongen *et al.*[60]	9	47	0.161	0.087	0.278
			Arminen *et al.*[61]	3	29	0.094	0.032	0.242
			Beasley *et al.*[62]	10	52	0.161	0.090	0.272
			Tignol *et al.*[73]	8	73	0.099	0.051	0.183
			Total imipramine	30	201	0.111	0.059	0.162
		Total TCAs		33	384	0.099	0.029	0.169
ADRs	SNRIs	Duloxetine	Goldstein *et al.*[66]	14	77	0.154	0.094	0.242
			Goldstein *et al.*[67]	7	63	0.100	0.049	0.192
			Detke *et al.*[65]	4	89	0.043	0.017	0.105
			Total duloxetine	25	229	0.093	0.027	0.160
		Milnacipran	Amerongen *et al.*[60]	1	52	0.019	0.003	0.099
			Leinonen *et al.*[69]	9	43	0.173	0.094	0.297
			Tignol *et al.*[73]	15	68	0.181	0.113	0.277
			Total milnacipran	25	163	0.118	0.000	0.242
		Venlafaxine	Bielski *et al.*[64]	16	84	0.160	0.101	0.244
			Montgomery *et al.*[70]	16	126	0.113	0.071	0.175
			Rudolph and Feiger[71]	6	89	0.063	0.029	0.131
			Total venlafaxine	38	299	0.107	0.055	0.159
		Total SNRIs		88	691	0.103	0.063	0.143
	SSRIs	Citalopram	Kyle *et al.*[68]	31	148	0.173	0.125	0.235
		Escitalopram	Bielski *et al.*[64]	4	94	0.041	0.016	0.100
			Montgomery *et al.*[70]	11	135	0.075	0.043	0.130
			Total escitalopram	15	229	0.057	0.023	0.091
		Fluoxetine	Beasley *et al.*[62]	12	44	0.214	0.127	0.338
			Goldstein *et al.*[67]	1	29	0.033	0.006	0.167
			Rudolph and Feiger[71]	9	94	0.087	0.047	0.158
			Total fluoxetine	22	167	0.101	0.017	0.184
		Paroxetine	Arminen *et al.*[61],	6	19	0.240	0.115	0.434
			Danish University[59]	1	61	0.016	0.003	0.086
			Detke *et al.*[65]	3	85	0.034	0.012	0.095
			Goldstein *et al.*[66]	8	74	0.098	0.050	0.181
			Total paroxetine	18	239	0.059	0.008	0.110
		Total SSRIs		74	739	0.083	0.047	0.119
	TCAs	Amitriptyline	Kyle *et al.*[68]	48	138	0.258	0.201	0.325
		Clomipramine	Danish University[59]	11	47	0.190	0.109	0.309
			Leinonen *et al.*[69]	15	40	0.273	0.173	0.402
			Total clomipramine	26	87	0.225	0.145	0.306
		Imipramine	Amerongen *et al.*[60]	5	51	0.089	0.039	0.193
			Arminen *et al.*[61]	7	25	0.219	0.110	0.388
			Beasley *et al.*[62]	14	48	0.226	0.140	0.344
			Thase *et al.*[72]	11	106	0.094	0.053	0.161
			Tignol *et al.*[73]	23	58	0.284	0.197	0.390
			Total imipramine	60	288	0.173	0.093	0.253
		Total TCAs		134	513	0.198	0.136	0.261

ADRs = adverse drug reactions; CI = confidence interval; LL = lower limit; LoE = lack of efficacy; SE = standard error; SNRIs = serotonin norepinephrine reuptake inhibitors; SSRIs = selective serotonin reuptake inhibitors; TCAs = tricyclic antidepressants; UL = upper limit

Table 4. Meta-analytic rates of occurrence of selected adverse drug reactions by drug class

Drug*	Ref.	Adverse drug reactions											
		Dry mouth	Nausea	Dizziness	Headache	Fatigue	Constipation	Diarrhea	Somnolence	Insomnia	Nervousness	Sweating	Anorexia
DUL	65	0.032	0.126	ND	0.053	ND	0.126	ND	ND	0.053	ND	0.042	ND
DUL	67	0.300	0.129	0.157	0.200	ND	0.114	0.143	0.186	0.200	ND	0.186	ND
DUL	66	0.154	0.253	0.165	ND	ND	0.088	ND	0.110	0.198	ND	0.121	0.110
MIL	60	0.264	0.132	ND	ND	ND	0.057	ND	ND	ND	ND	ND	ND
MIL	69	0.333	ND	ND	ND	ND	ND	ND	ND	0.170	ND	ND	ND
MIL	73	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
VEN	64	0.160	0.240	ND	0.140	ND	ND	ND	0.170	ND	ND	0.110	ND
VEN	61	NE	NE	NE	NE	NE	NE	ND	NE	ND	ND	ND	ND
VEN	70	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	ND
VEN	71	ND	0.379	0.274	ND	ND	ND	0.147	0.084	ND	0.126	0.105	0.095
SNRIs		0.199	0.207	0.196	0.124	–	0.093	0.145	0.130	0.150	0.126	0.104	0.097
*(± 95% CI)**		(± 0.102)	(± 0.076)	(± 0.071)	(± 0.086)		(± 0.032)	(± 0.054)	(± 0.047)	(± 0.088)	(± 0.067)	(± 0.046)	(± 0.010)
CIT	68	0.073	0.128	0.067	0.061	0.034	0.045	ND	0.078	ND	ND	ND	ND
ESC	64	0.122	0.061	ND	0.153	ND	ND	ND	0.092	ND	ND	0.051	ND
ESC	70	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	ND
FLU	62	0.286	0.143	0.143	0.125	ND	0.179	0.107	0.179	0.071	0.107	0.054	ND
FLU	67	0.212	0.182	0.061	0.333	ND	0.152	0.303	0.212	0.091	ND	0.091	ND
FLU	71	ND	0.194	0.058	ND	ND	ND	0.184	0.117	ND	0.097	0.078	0.097
PAR	59	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
PAR	65	NE	NE	NE	NE	NE	NE	ND	NE	ND	ND	ND	ND
PAR	66	0.070	0.116	ND	0.047	ND	0.070	ND	ND	0.035	ND	0.058	ND
PAR	72	0.080	0.161	0.103	ND	ND	0.138	ND	0.080	0.080	ND	0.069	0.034
SER	61	0.314	0.275	0.176	0.412	0.196	0.098	0.255	0.157	0.392	0.118	0.078	ND
SSRIs		0.142	0.144	0.085	0.163	0.106	0.099	0.094	0.106	0.114	0.104	0.113	0.062
*(± 95% CI)**		(± 0.057)	(± 0.042)	(± 0.030)	(± 0.080)	(± 0.158)	(± 0.044)	(± 0.054)	(± 0.003)	(± 0.008)	(± 0.041)	(± 0.015)	(± 0.006)
AMI	68	NE	NE	NE	NE	NE	NE	ND	NE	ND	ND	ND	ND
AMI	59	0.344	0.048	0.086	0.048	0.059	0.091	ND	0.161	ND	ND	ND	ND
CLO	69	NE	NE	NE	NE	NE	NE	ND	NE	ND	ND	ND	ND
CLO	62	0.6	ND	ND	ND	ND	ND	ND	ND	0.04	ND	ND	ND
IMI	60	0.51786	0.05357	ND	ND	ND	0.25	ND	ND	ND	ND	ND	ND
IMI	61	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
IMI	61	0.581	0.097	0.21	0.226	ND	0.323	0.065	0.129	0.016	0.177	0.177	ND
IMI	72	0.838	0.239	0.333	0.393	0.154	0.385	0.085	0.308	0.188	0.068	0.385	ND
IMI	73	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
TCAs		0.577	0.104	0.206	0.220	0.102	0.259	0.077	0.197	0.076	0.114	0.282	–
(± 95% CI)*		(± 0.216)	(± 0.075)	(± 0.160)	(± 0.227)	(± 0.093)	(± 0.163)	(± 0.015)	(± 0.098)	(± 0.088)	(0.106)	(± 0.204)	

*Adding this value to the mean gives the upper limit of the 95% confidence interval, and subtracting it from the mean gives the lower limit of the interval

ADRs = adverse drug reactions; AMI = amitriptyline; CI = confidence interval; CIT = citalopram; CLO = clomipramine; DUL = duloxetine; ESC = escitalopram; FLU = fluoxetine; IMI = imipramine; MIL = milnacipran; PAR = paroxetine; NE = not extractable; ND = not described; Refs = references; SNRIs = serotonin norepinephrine reuptake inhibitors; SSRIs = selective serotonin reuptake inhibitors; TCAs = tricyclic antidepressants; VEN = venlafaxine

not have the highest overall ADR rate (i.e., nausea, diarrhea, insomnia, and nervousness); in all of these categories, SNRIs had the highest rates of occurrence. The highest meta-analytic rates for SNRIs and SSRIs were for nausea (20.7% and 14.4%) followed by dry mouth (19.9% and 14.2%), respectively.

Discussion

A literature search identified one meta-analysis that used clinical remission as the outcome of interest[4]. However, only venlafaxine was considered as the SNRI in that paper. We have included the other two SNRIs currently available in many countries. Most meta-analyses and pharmacoeconomic analyses reported in the literature comparing antidepressants have used response rates. Response is defined as a 50% reduction in depression score, which is of limited use. Another aspect of the present research is that we utilized data only from head-to-head trials of active drugs.

Furthermore, despite a great volume of literature on the subject, our systematic review could only identify 15 articles that matched our inclusion/exclusion criteria. Unfortunately, not all drugs from the selected antidepressants matched our search criteria and, therefore, some could not be evaluated in this meta-analysis (i.e., fluvoxamine, doxepin, nortriptyline, maprotiline, desipramine, trimipramine, and protriptyline). One clinical trial[30], comparing fluvoxamine and maprotiline in the treatment of major depression, was found in our search strategy, but was excluded from our analysis because it used HAMD scores ≥ 8 as main outcome measure. We believe that the drugs analyzed in our study represented the selected pharmacological groups reasonably. However, the non-inclusion of the above-listed TCAs might have an influence on the clinical outcomes presented in our study, mainly due to the occurrence of ADRs.

Before data can be legitimately combined, one must ensure their combinability. Despite our use of inclusion/exclusion criteria intended to minimize bias across study arms, this possibility still exists when using outcomes from single arms. Therefore, heterogeneity of effects was somewhat expected across study arms. If it is assumed that all drugs within selected pharmacological classes were essentially the same, the use of a random effects model makes it permissible to combine the original results.

Since we detected heterogeneity of effects among the studies, we performed a one-way sensitivity analysis by systematically excluding those studies that contributed most to that heterogeneity. When statistical non-significance (i.e., homogeneity) was obtained from the sensitivity analysis, the final meta-analytic remission rates using ITT model changed to 50.1% from 49.0% for SNRIs, to 35.7% from 37.7% for SSRIs, and to 46.0% from 44.1% for TCAs. Thus, their removal did not result in major differences from the original results. Although higher rates were observed in the sensitivity analysis (except for SSRIs), the relative ranking of the remission rates remained unchanged for the three pharmacological groups (i.e., SNRIs > TCAs > SSRIs).

When subgroup analyses were performed on individual drugs, the highest meta-analytic remission rates using the ITT approach was that of citalopram (0.536, 95% CI 0.463 to 0.608, $n = 179$), followed by amitriptyline (0.535, 95% CI 0.472 to 0.597, $n = 245$), and escitalopram (0.529, 95% CI 0.195 to 0.864, $n = 244$), respectively. Under the PP approach, clomipramine (0.765, 95% CI 0.583 to 0.947, $n = 73$), followed by duloxetine (0.726, 95% CI 0.501 to 0.951, $n = 0192$), and citalopram (0.711, 95% CI 0.630 to 0.781, $n = 135$) had the highest meta-analytic remission. rates. These findings did not match with our overall results categorized by pharmacological groups (i.e., SNRIs > TCAs > SSRIs) indicating that generalization of clinical results must be done carefully. The same was observed by Machado *et al.*[8], in a previous meta-analysis, where escitalopram showed similar efficacy rates compared to SNRIs, and therefore increased the overall clinical effects of SSRIs. For formulary management, clinical information concerning the individual drug should be taken into consideration, not only that of the pharmacological class. Moreover, this information should be accompanied by well-designed full pharmacoeconomic analyses for future decision-making.

Different results were observed for ITT and PP approaches. Since ITT analysis is intended to mimic real life results – described as clinical effectiveness data by including patients who dropped out from therapy, considering them as drug failures – this type of data should be utilized by clinicians in their clinical practice. PP analysis, by not including dropouts, is considered to reflect clinical efficacy data. Those rates should be used by those intending to perform pharmacoeconomic analyses (i.e., modeling studies), if they also incorporate dropouts and rates of ADRs into their analyses, since they can impact costs.

Inpatient and outpatient efficacy rates were also analyzed. SNRIs showed statistically significant clinical superiority over SSRIs in treating inpatients. Clinical rates varied among pharmacological classes for inpatients and outpatients. SNRIs and TCAs both had slightly higher inpatient rates, whereas SSRIs had substantially greater efficacy for outpatients (43.8%) than for inpatients (28.6%). These results may reflect issues such as compliance and/or emergence of side effects. Dropout rates reflected a better tolerance for SNRIs and SSRIs, compared with TCAs. When we

analyzed meta-analytic rates of occurrence of ADRs from pharmacological classes, SSRIs had the lowest meta-analytic rate for four out of 10 different types of ADRs. This could partially explain (i.e., ADR-related severity was not evaluated) why fewer patients receiving SSRIs dropped out due to ADRs from their treatment compared to those receiving drugs from other pharmacological classes.

Since we used a different approach for clinical outcomes in our meta-analysis, direct comparison between the data of previous studies could not be performed. Previous meta-analyses using single arms[9,10] generated similar overall results for clinical efficacy and safety of pharmacological classes of antidepressants, where the rankings of clinical outcomes between them maintained unchanged.

One issue to be addressed is the statistical difference in demographics found in our study. The average age for patients in the SSRI group was significantly lower than in the groups taking SNRIs and TCAs. In some cases, age may impact upon the treatment of depression[75]. Therefore we tested such impact by performing a sensitivity analysis and combined the remission rates of studies that included patients with similar age presented by the SSRIs. In this case we excluded the study by Tignol *et al.*[73], which included patients with an average age of 74 years in both SNRIs and TCAs arms. This exclusion decreased the average age of SNRIs and TCAs to 42.6 and 42.1, respectively, now comparable to the average 40.9 years of SSRIs. However, this exclusion did not cause any real change in the meta-remission analytic rates under ITT analysis. Meta-analytic rates changed to 49.6% for SNRIs, and 43.7% for TCAs.

One limitation in the interpretation of the overall results is the fact that all of the venlafaxine trials involved the extended release formula while the other two drugs in that group were immediate release products. Since the immediate release form of all members of the SNRI group have short half-lives, they must be given twice daily. Actual results in practice may vary due to differences in adherence to prescribed regimens.

Another limitation is the small number of published trials that have used remission as an outcome. That is especially true with the older drugs (e.g., tricyclics) which have long been genericized and appear only as comparators in trials. We believe that we have found the majority of the available studies using this outcome and that, with time, it will become the standard for reporting outcomes from trials of antidepressants.

Conclusion

In this study, SNRIs had the highest remission rates, and the lowest overall dropout rates, suggesting clinical superiority for this class in treating major depression. However, for the selection of a drug of choice, one must also identify consequences other than clinical ones (i.e., economic and humanistic). To our knowledge, the present study represents the most comprehensive source of clinical outcomes (targeting remission) of SNRIs, SSRIs, and TCAs for the treatment of major depressive disorder. Future research should analyze the economic consequences of antidepressant therapy using the data presented in this meta-analysis.

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