Does Randomized Evidence Support Sertraline as First-Line Antidepressant for Adults With Acute Major Depression? A Systematic Review and Meta-Analysis

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Objective: Preliminary evidence suggested that sertraline might be slightly superior to other antidepressant medications in terms of efficacy. The aim of this study was to carry out a systematic review and meta-analysis to compare sertraline with any other antidepressant in the acute phase treatment of major depression at 8 weeks.

Data Sources: MEDLINE; EMBASE; the Cochrane Collaboration Depression, Anxiety and Neurosis Controlled Trials Register; and the Cochrane Central Register of Controlled Trials up to August 2007. No language restriction. The following search strategy was used: diagnosis = *depress** or *dysthymi** or *adjustment disorder** or *mood disorder** or *affective disorder* or *affective symptoms*, and intervention (or free text) = *sertraline*. Reference lists of relevant papers and previous systematic reviews were hand-searched. Pharmaceutical companies and experts in this field were contacted for supplemental data.

Study Selection: Only randomized controlled trials allocating patients with major depression to sertraline versus any other antidepressant agent.

Data Extraction: Three reviewers independently extracted data. A double-entry procedure was employed by 2 reviewers. To analyze data, a very conservative approach with a 99% confidence interval (CI) and a random effects model was used. Information extracted included study characteristics, participant characteristics, intervention details, and outcome measures, such as the number of patients who responded to treatment and the number of patients who failed to complete the study by any cause at 8 weeks.

Data Synthesis: This systematic review and meta-analysis found that sertraline is statistically significantly better than fluoxetine (relative risk [RR] = 0.85, 99% CI = 0.74 to 0.98; number needed to treat [NNT] = 12) and other SSRIs as a class (RR = 0.88, 99% CI = 0.78 to 0.99; NNT = 17) and highlighted a consistent even though not statistically significant trend in favor of sertraline over many other antidepressants both in terms of efficacy and acceptability in a homogeneous and clinically relevant time frame of 8 weeks.

Conclusions: The results of this review suggest that sertraline may be a candidate as the initial choice of antidepressant for people with major depression.

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MANGA Study group: the Meta-Analyses of New Generation Antidepressants (MANGA) project is a research project in which a group of researchers agreed to systematically review all available evidence for specific newer antidepressants, in order to inform clinical practice and mental health policies.

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The National Institute for Health and Clinical Excellence (NICE) clinical practice guideline on the treatment of depressive disorder recommended that a selective serotonin reuptake inhibitor (SSRI) should be the first-line option when drug therapy is indicated for a depressive episode.[1] Some preliminary evidence on SSRIs has found sertraline to have modestly but statistically significantly superior efficacy to fluoxetine.[2,3] As part of an ongoing program to update and improve the Cochrane Database reviews of SSRIs, we report a systematic review

and meta-analysis of all randomized studies that compared sertraline with any other antidepressant in the acute phase treatment of major depression, taking into account time to response.

METHOD

Inclusion Criteria

Randomized controlled trials (RCTs) comparing sertraline with all other active antidepressant agents as monotherapy in the acute phase treatment of depression were included. Quasi-randomized trials (such as those allocating by using alternate days of the week) were excluded. Study participants were of either sex and any age (more than 18 years) with a primary diagnosis of major depression. Studies adopting any standardized criteria to define patients suffering from depression were included. A concurrent diagnosis of a medical disorder was considered an exclusion criteria. Randomized controlled trials of women with postpartum depression were also excluded, because postpartum depression appears to be clinically different from major depression.[4,5]

Search Strategy

We conducted a comprehensive literature search of EMBASE and MEDLINE from 1966 through August 2007. The Cochrane Collaboration for Depression, Anxiety and Neurosis (CCDAN) Controlled Trial Register was searched using the following search strategy: diagnosis = *depress** or *dysthymi** or *adjustment disorder** or *mood disorder** or *affective disorder* or *affective symptoms*, and intervention (or free text) = *sertraline*. The search included also non–English-language articles. Trial databases of the following drug-approving agencies (the Food and Drug Administration [FDA] in the United States, the Medicines and Healthcare products Regulatory Agency [MHRA] in the United Kingdom, the European Medicines Agency [EMEA] in the European Union, the Pharmaceuticals and Medical Devices Agency [PMDA] in Japan, the Therapeutic Goods Administration [TGA] in Australia) and ongoing trial registers (clinicaltrials.gov in the United States, International Standard Randomised Controlled Trial Number Register [ISRCTN] and National Research Register in the United Kingdom, Nederlands Trial Register in The Netherlands, the European Union Drug Regulating Authorities Clinical Trials [EudraCT] database in the European Union, University Hospital Medical Information Network clinical trial entry system [UMIN-CTR] in Japan and the Australian Clinical Trials Registry in Australia) were hand searched for published, unpublished, and ongoing controlled trials. Pharmaceutical companies and experts in this field were asked if they knew of any study that met the inclusion criteria of this review. Reference lists of the included studies, previous systematic reviews, and major textbooks of affective disorder written in English were checked for published reports and citations of unpublished research. The references of all included studies were checked via Science Citation Index for articles that cited the included study.

Data Extraction

Using a standardized data extraction form, 3 independent investigators (A.C., L.M., and A.S.) extracted all data from included studies. Discrepancies were resolved via referencing the original article and via group discussions with a fourth member of the team (C.B.). A double-entry procedure was employed by 2 reviewers (A.C. and C.B.). Information extracted included study characteristics (such as lead author, publication year, journal), participant characteristics (such as diagnostic criteria for depression, age range), intervention details (such as dose ranges, mean doses of study drugs), and outcome measures (such as the number of patients who responded to treatment and the number of patients who failed to complete the study by any cause). When dichotomous efficacy outcomes were not reported but baseline mean and endpoint mean and standard deviation of the Hamilton Rating Scale for Depression (HAM-D) (or any other depression scale) were provided, we calculated the number of responding patients employing a validated imputation method.[6] We examined the validity of this imputation in the sensitivity analyses. Where outcome data or standard deviations were not recorded, authors were asked to supply the data. When only the standard error, t statistics, or p values were reported, standard deviations were calculated according to Altman and Bland.[7] In the absence of data from the authors, the mean value of known standard deviations was calculated from the group of included studies according to Furukawa and colleagues.[8]

Outcome Measures

In many systematic reviews, the ability to provide valid estimates of treatment effect, applicable to the real world, is limited because trials with different durations of follow-up are combined.[9–11] Clinically, the assessment of efficacy after 6 weeks of treatment or after 16 to 24 weeks or more may lead to wide differences in terms of treatment outcome. Clinicians need to know whether (and to which extent) treatments work within a clinically reasonable period of time. One recent systematic review of antidepressant clinical trial data, which investigated the issue of early response to antidepressants, employed a common definition of early response across all included studies.[12] Apart from this review, however, no systematic reviews have studied the comparative efficacy of antidepressants in individuals with major depression employing a common definition of acute response that includes a predefined follow-up duration. In the present review, acute treatment was defined as an 8-week treatment in both the

efficacy and acceptability analyses.[13] If 8-week data were not available, we used data ranging between 6 to 12 weeks.

Response was defined as the proportion of patients who showed a reduction of at least 50% on the HAM-D[14] or Montgomery-Asberg Depression Rating Scale,[15] or who scored "much improved" or "very much improved" on the Clinical Global Impressions scale,[16] out of the total number of patients randomly assigned to sertraline or control antidepressant. Treatment discontinuation (acceptability) was defined as the proportion of patients who left the study early by any cause during the first 8 weeks of treatment, out of the total number of patients randomly assigned to sertraline or control antidepressant. In the present review, we reported efficacy data as "failure to respond" in order to be consistent with the graphical presentation of both efficacy and acceptability outcomes. In all the forest plots, values scoring less than 1 favored sertraline.

Study Quality

Two reviewers (A.C. and L.M.) independently assessed trial quality in accordance with the Cochrane Handbook.[17] Studies were given a quality rating ranging from C (poorest quality) to A (best quality). C = inadequately concealed (e.g., via alternation or reference to an open random number table). B = no adequate details about how the randomization procedure was carried out were given. A = trials that were reported to have taken adequate measures to conceal allocation (e.g., serially numbered, opaque, sealed envelopes; numbered or coded bottles or containers).

Data Analysis

Data were initially entered and analyzed using the Cochrane Collaboration's Review Manager software (RevMan, version 4.2.10, Cochrane Collaboration, Oxford, England) and subsequently entered into a spreadsheet and reanalyzed using the "metan2" command of STATA 8.0 (STATA Corp, College Station, Tex.). Outputs were cross-checked for internal consistency. Three 3-arm placebo trials were converted into 2-arm trials (Table 1). One trial comparing different doses of sertraline with fluoxetine was converted into a 2-arm trial by summing samples and averaging doses according to Cipriani and colleagues.[18]

Responders to treatment were calculated on an intention-to-treat basis, using as denominator the number of participants who were initially randomized: dropouts were always included in this analysis. When data on dropouts were carried forward and included in the efficacy evaluation (last observation carried forward,), they were analyzed according to the primary studies; when dropouts were excluded from any assessment in the primary studies, they were considered as drug failures.

For all analyses, the relative risk (RR) was calculated. Relative risk is usually expressed as a proportion or as a percentage: its meaning is usually clear and it has been shown that serious divergence between the odds ratio (OR) and the RR can occur with large effects on groups at high initial risk.[19] The DerSimonian and Laird random effects method[20] was also routinely used to incorporate the assumption that the different studies were estimating different, yet related, treatment effects.[18] Where there is heterogeneity in the results from the individual trials, confidence intervals for the average treatment effect are wider if the DerSimonian and Laird method is used rather than a fixed-effect method, and corresponding claims of statistical significance are more conservative.[18] When the overall results were significant, we calculated the number needed to treat (NNT) as the inverse of the risk difference.

A 99% confidence interval (CI) was calculated for all efficacy estimates according to Cipriani and colleagues.[3] This approach, instead of a 95% CI approach, was adopted to have the widest estimate of likely true effect. We set the level of significance at .01, as we were making multiple comparisons and we reasoned that only robust differences between treatments should inform clinical practice. In fact, when comparing 2 active treatments and trying to find which is the most effective from a clinical point of view, it was more important to avoid the possibility of showing a difference in the absence of a true difference than to avoid the possibility of not showing a difference in the presence of a true difference. As we previously did in similar circumstances, we gave priority to avoid a type I than a type II error.[3]

Visual inspection of graphs was used to investigate the possibility of statistical heterogeneity. This was supplemented using, primarily, the I^2 statistic. This provides an estimate of the percentage of variability due to heterogeneity rather than a chance of showing that heterogeneity alone. When the I^2 estimate was greater than or equal to 50%, we interpreted this as indicating the presence of high levels of heterogeneity.[21]

RESULTS

The search yielded 154 studies: after reading the abstracts, 55 articles were excluded for at least 1 of the following criteria: wrong diagnosis (7 articles), wrong population (12 articles), reviews (9 articles), or nonrandomized design (25 articles). A total of 99 articles were considered potentially relevant (Figure 1). Pfizer, the manufacturer of sertraline, responded to our request to provide a comprehensive list of trials that they had sponsored worldwide. In a second round of screening, 35 articles were excluded for the following reasons: no outcome data available (16 articles) or multiple publication (19 articles). A total of 64 articles were included in the

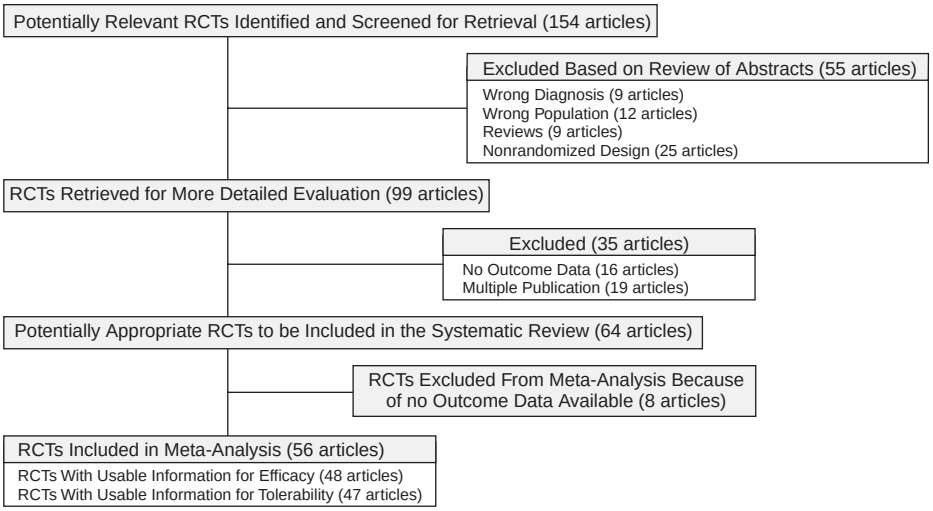
Table 1. Characteristics of Studies Included in the Systematic Review

Study	Year	Comparison	Follow-up Duration, wk	Setting	Diagnostic Criteria	Sample, N		Quality[a]	Dose, mg		Sponsored by Pfizer?
						Sertraline	Other		Sertraline	Other	
Bersani et al[28]	1994	Amitriptyline	8	Out	DSM-III-R	37	34	B	50–150	50–150	Unclear
Cohn et al[33]	1990	Amitriptyline	8	Out	DSM-III	161	80	B	50–200	50–150	Unclear
Kamijima et al[47]	1997	Amitriptyline	6	In & out	DSM-IV	93	94	B	25–75	50–150	Yes
Lee et al[49]	1994	Amitriptyline	6	In & out	DSM-III-R	25	23	B	50–200	50–200	Yes
Lydiard et al[52]	1997	Amitriptyline	8	Out	DSM-III-R	132	131	B	50–200	50–150	Yes
Möller et al[54]	2000	Amitriptyline	6	Out	DSM-III-R	116	124	B	50–100	75–150	Yes
Reimherr et al[63]	1990	Amitriptyline	8	Out	DSM-III	149	149	B	50–200	50–150	Unclear
Behan and Hannifah[25]	1995	Clomipramine	8	Out	DSM-III-R	20	20	B	50–150	50–150	Yes
Edwards and Newburn[38]	1996	Clomipramine	10	Out	DSM-III-R	17	15	B	50–150	50–150	Unclear
Lepine et al[50]	2000	Clomipramine	8	Out	DSM-III-R	82	84	B	50–200	50–250	Yes
Moon et al[55]	1994	Clomipramine	6	In	DSM-III-R	51	55	B	50–150	50–150	Yes
Ravindran et al[62]	1995	Desipramine	8	Out	DSM-III-R	40	37	B	50–200	50–225	Yes
Doogan and Langdon[37]	1994	Dothiepin	6	GP	DSM-III-R	99	108	B	50–100	75–150	Yes
Baca et al[24]	2003	Imipramine	8	Out	DSM-III-R	116	123	B	50–200	75–225	Yes
Chen et al[32]	2001	Imipramine, venlafaxine	6	NS	Other	45	44, 44	B	50–100	25–75, 25–100	No
Forlenza et al[44]	2001	Imipramine	8	Out	DSM-IV	27	28	B	50	150	Yes
Fournier et al[45]	1997	Imipramine	24	Out	DSM-III-R	54	50	B	50–200	50–200	Yes
Murasaki et al[56]	1997	Imipramine	6	In & out	DSM-III-R	106	48	B	50–150	50–150	No
Bondareff et al[29]	2000	Nortriptyline	12	Out	DSM-III-R	105	105	B	50–150	25–100	Yes
Ekselius et al[40]	1997	Citalopram	24	GP	DSM-III-R	200	200	B	50–150	20–60	Yes
Stahl[69]	2000	Citalopram	24	NS	DSM-IV	106	103	B	50–150	20–60	No
Ventura et al[76]	2007	Escitalopram	8	Out	DSM-IV	108	107	B	50	10	No
Aguglia et al[23]	1993	Fluoxetine	8	Out	DSM-III-R	56	52	B	50–150	20–60	Unclear
Bennie et al[27]	1995	Fluoxetine	6	Out	DSM-III-R	144	142	A	50–100	20–40	Yes
Boyer et al[30]	1998	Fluoxetine	26	GP	DSM-IV	120	122	B	50–150	20–60	Yes
Fava et al[42]	2000	Fluoxetine, paroxetine	16	Out	DSM-IV	35	30, 43	B	50–200	20–60, 20–60	No
Fava et al[41]	2002	Fluoxetine, paroxetine	10	Out	DSM-IV	92	96, 96	B	50–200	20–60, 20–60	No
Newhouse et al[59]	2000	Fluoxetine	12	Out	DSM-III-R	119	117	B	50–100	20–40	Yes
Sechter et al[65]	1999	Fluoxetine	24	Out	DSM-III-R	120	118	A	50–150	20–60	Yes
Suri et al[70]	2000	Fluoxetine	6	Out	DSM-IV	18	35	B	50–150	20	No
Van Moffärt et al[75]	1995	Fluoxetine	8	In & out	DSM-III-R	82	83	B	50–100	20–40	Yes
Nemeroff et al[58]	1995	Fluvoxamine	7	Out	DSM-III-R	48	49	B	50–200	50–150	No
Rossini et al[64]	2005	Fluvoxamine	10	Out	DSM-III-R	48	40	B	50–150	50–150	Unclear
Aberg-Wistedt et al[22]	2000	Paroxetine	24	Out	DSM-III-R	176	177	B	50–150	20–40	Yes
Zanardi et al[77]	1996	Paroxetine	6	In	DSM-III-R	24	22	B	50–150	20–50	Unclear
Li et al[51]	2001	Maprotiline	6	In	Other	32	32	B	50	75–250	No
Coleman et al[34]	1999	Bupropion	8	NS	DSM-IV	118	122	B	50–200	150–400	No
Croft et al[35]	1999	Bupropion	8	Out	DSM-IV	119	120	B	50–200	50–400	No
Kavoussi et al[48]	1997	Bupropion	16	Out	DSM-IV	126	122	B	50–200	100–300	No
Brenner et al[31]	2000	Hypericum	7	Out	DSM-IV	15	15	B	50–75	600–900	No
Davidson et al[36]	2002	Hypericum	8	Out	DSM-IV	111	113	A	50–150	900–1800	Yes
Gastpar et al[46]	2005	Hypericum	12	Out	DSM-IV	118	123	B	50	612	No
Van Gurp et al[74]	2002	Hypericum	12	GP	DSM-IV	43	44	B	50–100	900–1800	Yes
Behnke et al[26]	2003	Mirtazapine	8	NS	DSM-IV	170	176	B	50–150	30–45	No
Thase et al[72]	2000	Mirtazapine	12	In & out	DSM-III-R	126	124	B	50–100	30–45	No
Orsel Donbak et al[60]	1995	Moclobemide	13	In & out	DSM-III-R	27	28	B	50–200	300–600	Unclear
Søgaard et al[68]	1999	Moclobemide	12	Out	DSM-III-R	100	97	B	50–100	300–450	Yes
Feiger et al[43]	1996	Nefazodone	6	Out	DSM-IV	82	78	B	50–200	100–600	No
Eker et al[39]	2005	Reboxetine	11	Out	DSM-IV	24	25	B	NS	NS	Unclear
Szádóczky and Füredi[71]	2002	Tianeptine	6	In & out	DSM-IV	109	103	B	50	37.5	Unclear
Tsutsui et al[73]	1997	Trazodone	6	GP	Other	112	106	A	25–75	75–225	Yes
Munizza et al[57]	2006	Trazodone	8	Out	DSM-IV	60	62	B	25–75	75–225	No
Mehtonen et al[53]	2000	Venlafaxine	8	Out	DSM-IV	72	75	B	50–100	37.5–150	No
Oslin et al[61]	2003	Venlafaxine	10	Out	DSM-IV	25	27	B	25–100	37.5–150	No
Sir et al[67]	2005	Venlafaxine	8	Out	DSM-IV	79	84	B	50–100	75–150	Yes
Shelton et al[66]	2006	Venlafaxine	12	Out	DSM-IV	82	78	B	50–100	75–150	Yes

[a]According to Cochrane Handbook criteria (Higgins and Green[17]): A = trials that were reported to have taken adequate measures to conceal allocation (e.g., serially numbered, opaque, sealed envelopes; numbered or coded bottles or containers); B = no adequate details about how the randomization procedure was carried out were given; and C = inadequately concealed (e.g., via alternation or reference to an open random number table).

Abbreviations: DSM-III = *Diagnostic and Statistical Manual of Mental Disorders*, Third Edition; DSM-III-R = *Diagnostic and Statistical Manual of Mental Disorders*, Third Edition, Revised; DSM-IV = *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition; GP = general practice (primary care); In = inpatient; In & out = both inpatient and outpatient; NS = not stated; Out = outpatient.

Figure 1. Included and Excluded Studies With Reasons: The QUOROM Flow Diagram (from Moher et al.[93])



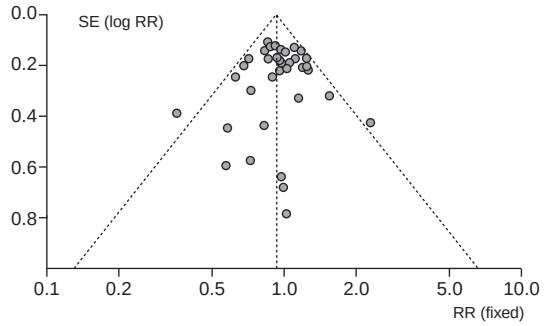
Abbreviation: RCTs = randomized controlled trials.

systematic review. Attempts to contact authors for additional information were unsuccessful in 17 cases, successful in 5 but authors were unable to provide additional data, and successful in 8 other cases with additional data provided by authors. Pfizer did not provide us with unpublished material, but we were able to implement information from published reports with supplemental data from study authors and also Web sites of other pharmaceutical companies (GlaxoSmithKline, Eli Lilly).

At the end of the reviewing process, 56 RCTs providing data on efficacy and/or tolerability outcomes were included.[22–77] Overall, 8507 patients were available for examining efficacy (4333 participants randomly assigned to sertraline and 4174 randomly assigned to another antidepressant), and 8387 were available for examining acceptability of treatments (4207 participants randomly assigned to sertraline and 4180 randomly assigned to another antidepressant) in the meta-analysis. The descriptive characteristics of included studies are presented in Table 1. The great majority of studies comparing sertraline with a tricyclic antidepressant were sponsored by Pfizer, about one half of trials (7 of 16) comparing sertraline with other SSRIs were funded by the sertraline manufacturer, and the majority of studies comparing sertraline with newer antidepressants were not sponsored by Pfizer (see Table 1).

Sixteen studies recruited fewer than 100 participants, and almost all (51 RCTs) were reported to be double-blind. The majority of trials enrolled outpatients (44 RCTs), with a diagnosis of major depression based on DSM-III, DSM-III-R, DSM-IV, or ICD-10 criteria in 56 RCTs. Elderly subjects (over 65 years old) were not excluded in 35 studies. In 53 studies, individuals with moderate to severe depression were enrolled, while in 3 studies, individuals suffered from mild to moderate depressive symptoms. Nine studies of 56 had a duration of follow-up longer than 12 weeks, and therefore, for these studies, we used mid-trial data instead of data at endpoint (primary outcome). Description of concealment of allocation was rated as B in all but 4 studies. Funnel plots did not suggest evidence of publication bias (Figure 2). Sensitivity analyses to examine the validity of data imputation (see Method section) did not materially change results (data not shown in the paper, but available on request).

Figure 2. Funnel Plot: Efficacy Measured as at Least 50% Reduction on Rating Scale Score

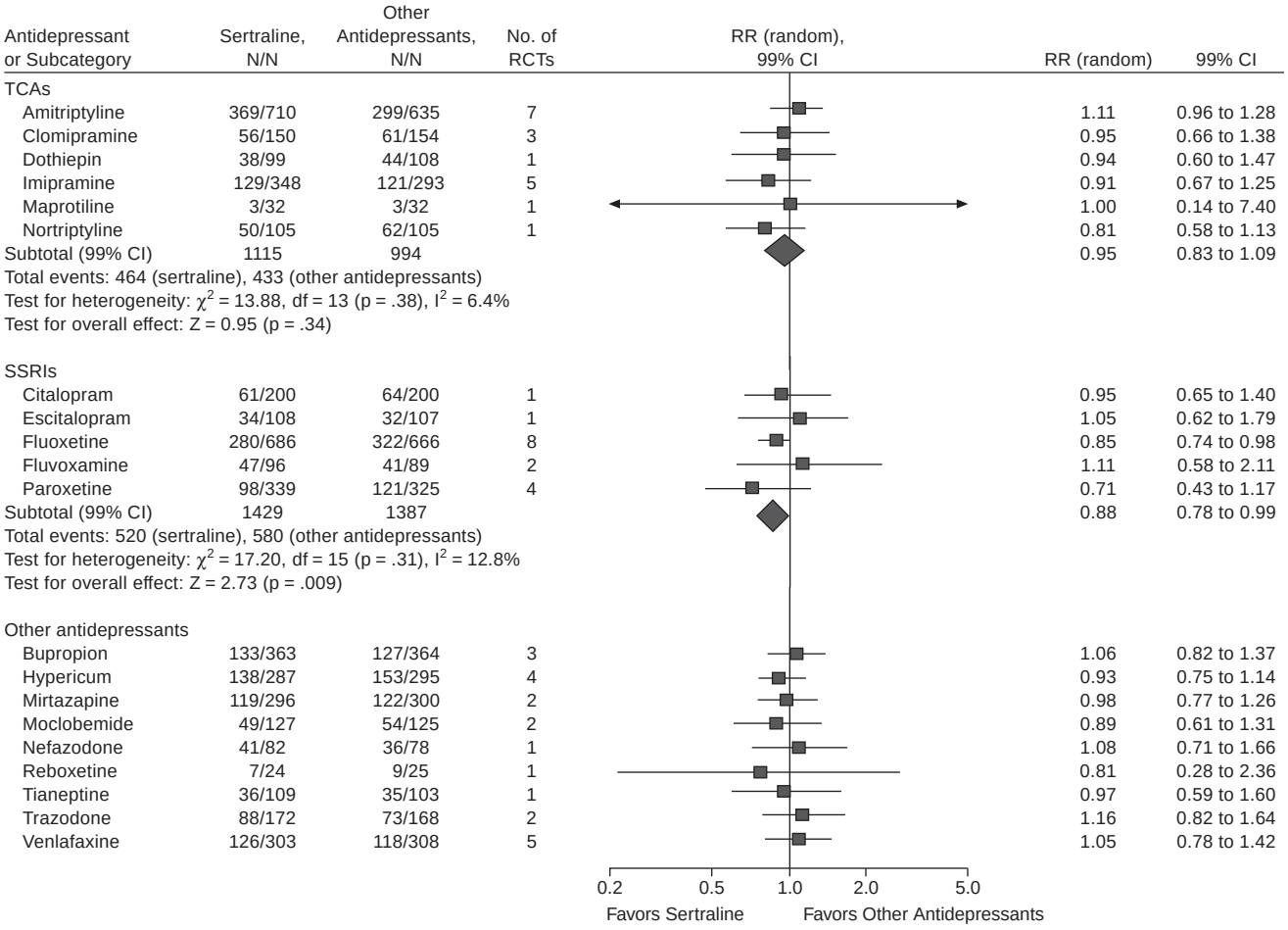


Abbreviation: RR = relative risk.

Comparative Efficacy

Tricyclics. The analysis found no statistically significant difference in terms of efficacy between sertraline and tricyclics neither as a class (RR = 0.95, 99% CI = 0.83 to

Figure 3. Efficacy (at least 50% reduction on rating scale score) Measured as Failure to Respond, Considering Relative Risk (RR) With Random-Effects Model



Abbreviations: RCTs = randomized controlled trials, SSRIs = selective serotonin reuptake inhibitors, TCAs = tricyclic antidepressants.

1.09; p = .34; 14 studies, 2109 participants) nor in head-to-head comparisons (Figure 3).

SSRIs. A statistically significant difference in terms of efficacy between sertraline and SSRIs as a class (RR = 0.88, 99% CI = 0.78 to 0.99; p = .009; 16 studies, 2816 participants; NNT = 17) was found. There was also a statistically significant difference in terms of efficacy in favor of sertraline over fluoxetine (RR = 0.85, 99% CI = 0.74 to 0.98; p = .004; 8 studies, 1352 participants; NNT = 12). We found no statistically significant difference between sertraline and the remaining SSRIs in head-to-head comparisons (Figure 3).

Other antidepressants. We found no statistically significant difference in terms of efficacy between sertraline and remaining antidepressants in head-to-head comparisons (Figure 3).

Comparative Acceptability

Tricyclics. We found no statistically significant difference in terms of acceptability between sertraline and tricyclics neither as a class nor in head-to-head comparisons (Figure 4).

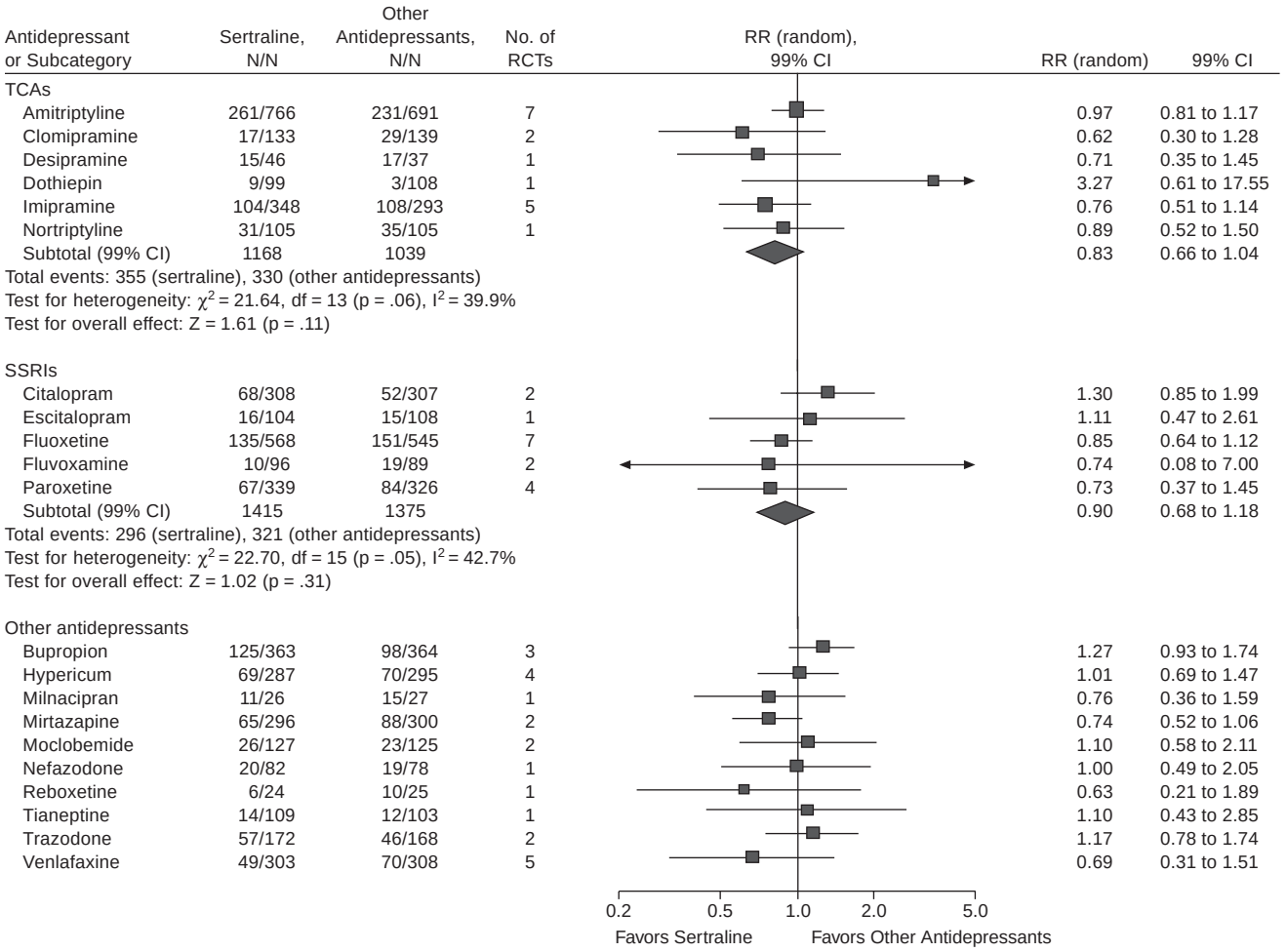
SSRIs. No statistically significant differences in terms of efficacy between sertraline and SSRIs neither as a class (RR = 0.90, 99% CI = 0.68 to 1.18; p = .31; 16 studies, 2790 participants) nor in head-to-head comparisons were found (Figure 4).

Other antidepressants. We found no statistically significant difference in terms of acceptability between sertraline and remaining antidepressants in head-to-head comparisons (Figure 4).

Heterogeneity

The I^2 estimate was greater than 50% and was interpreted as indicating the presence of high levels of heterogeneity in 2 comparisons of efficacy and acceptability: sertraline versus fluvoxamine (I^2 = 53.4% and 57.9%, respectively) and sertraline versus paroxetine (I^2 = 64.2% and 59.3%, respectively). The I^2 estimate indicated the potential for high levels of heterogeneity when comparing

Figure 4. Acceptability Measured as All-Cause Dropout Rate, Considering Relative Risk (RR) With Random-Effects Model



Abbreviations: RCTs = randomized controlled trials, SSRIs = selective serotonin reuptake inhibitors, TCAs = tricyclic antidepressants.

sertraline with all other SSRIs in terms of acceptability (I^2 = 42.7%).

CONCLUSIONS

This systematic review and meta-analysis highlighted a consistent although not statistically significant trend in favor of sertraline over many other antidepressants (most of all, SSRIs and in particular fluoxetine) both in terms of efficacy and acceptability in a homogeneous and clinically relevant time frame of 8 weeks, using a very conservative approach with a 99% confidence interval and a random effects analysis. Notwithstanding the well-known problem of study quality in antidepressant trials, the risk of publication bias, and the potentially confounding effect of sponsorship, our results are surprisingly consistent in favor of sertraline. The effect of these and other potential confounders (such as differences in study design, i.e., the inclusion of studies with a placebo arm) cannot be assessed with precision and can affect the real estimate of our findings introducing greater heterogeneity. However, the direction of the effect favored sertraline in the great majority of the trials, which implies that the heterogeneity is quantitative rather than qualitative. Even though funnel plots did not suggest evidence of publication bias, we are aware that some unpublished information might exist and be at the disposal of other reviewing groups. We tried to retrieve as much information as possible, and all new data (either published or unpublished) will be collected to be included in the update of the present review.

Some limitations should be borne in mind. First, even though differences in this review were robust in terms of statistical significance, evidence coming from randomized trials may be of limited applicability to everyday clinical practice.[78] Second, even if the funnel plots did not show any evidence of publication bias, this possibility cannot be ruled out.[79] For the meta-analyses of tricyclic antidepressants and SSRIs, the funnel plots have

generally been symmetrical, suggesting publication bias is absent. However, a review of trial data on children and adolescents with major depression suggested that publication bias may remain a very serious limitation to the entire literature comparing SSRIs and tricyclic antidepressants.[79] If important information is concealed, the funnel plot (and other formal statistical tests that work on the same principle) will not be able to detect publication bias under these circumstances. In this review, we tried to include all available evidence either published or unpublished, searching trial databases of drug-approving agencies and trial registers and also contacting pharmaceutical companies. Recently, one meta-analysis found that serotonergic-noradrenergic antidepressant drugs seem to have a modest efficacy advantage compared with SSRIs in major depression (that is, around 24 patients would need to be treated with dual-action antidepressant drugs instead of SSRIs in order to obtain 1 additional responder).[80] This study analyzed dual-action and serotonergic antidepressants as a class, and the focus of the present review is to assess whether differences among individual agents in terms of efficacy and acceptability may have a clinical meaning. In our systematic review, serotonergic-noradrenergic antidepressant drugs (venlafaxine, mirtazapine) were not different from sertraline. Further research is needed to assess efficacy and tolerability of each serotonergic-noradrenergic antidepressant (and other newer drugs) to systematically answer this compelling issue.

Two other relevant issues to be addressed are dosing and cost-effectiveness. In the field of antidepressant studies, the dose issue is an important issue because it may affect results.[81] However, it is a real complex issue because information about the dosing schedule is present in the method section of each study, but often authors do not report in the results of the article the overall mean dose for each comparison (and we do not know the most informative value, the mean dose at the individual patient level). For this reason, in the present review, we included only studies using antidepressants within the therapeutic range, either as fixed or flexible dose type, to draw general but clinically sound conclusions. In terms of cost-effectiveness, in this systematic review only 1 RCT reported economic outcomes. Considering that several SSRIs are now available as generic versions, this perspective should be considered to have more comprehensive estimates of antidepressant treatment effect to inform heath care policy.

Another complex issue about antidepressants is the increased risk for suicidality.[82] In 2007, the FDA licensed a comprehensive report about the occurrence of suicidality in the course of treatment of adult patients with various antidepressants.[83] This individual patient data analysis showed that the odds ratios for suicidality and suicidal behavior attributable to antidepressant treatment in adults with psychiatric disorders were 0.83 (95% CI = 0.69 to 1.00) and 1.10 (95% CI = 0.77 to 1.56), respectively. Among all antidepressants (SSRIs, tricyclics, or newer antidepressants such as duloxetine, venlafaxine, bupropion, mirtazapine, and nefazodone) sertraline was the only one with a favorable statistically significant risk over placebo (OR = 0.51, 95% CI = 0.29 to 0.91 for suicidality risk and OR = 0.25, 95% CI = 0.07 to 0.90 for suicidal behavior risk).[84]

Findings from the present analysis expand previous evidence supporting the use of sertraline as the drug of choice in the first-line treatment of individuals with major depression. NICE guidelines issued that sertraline should be considered the treatment of choice when initiating treatment in a patient with a recent myocardial infarction or unstable angina, as it has the most evidence for safe use in this situation.[1] NICE recommendations are consistent with what has been observed in other systematic reviews.[85] More recently, the report of the Canadian Cardiac Randomized Evaluation of Antidepressant and Psychotherapy Efficacy trial concluded that the first step in the treatment of patients with major depression and coronary artery disease should begin with sertraline or citalopram (plus clinical management).[86] These findings are backed by some observational evidence. In a national survey of cardiovascular physicians' beliefs and clinical care practices when diagnosing and treating depression in patients with cardiovascular disease, sertraline was the most frequently prescribed antidepressant.[87] Recently, some evidence discussed other antidepressants as being the drug of choice for major depression.[88–91] However, these were not large scale systematic reviews, but individual studies, surveys, or pooled analysis on an individual patient data basis of a selection of studies (and, consistently, of comparisons). To address larger questions regarding comparisons across multiple drugs, newer meta-analytic methods such as network meta-analysis (or multiple treatment meta-analysis) are needed and welcome.[92]

Taken together with this other evidence, the results of this review suggest that sertraline may be a candidate as the initial choice of antidepressant treatment for people with major depression.

Drug names: bupropion (Wellbutrin and others), citalopram (Celexa and others), clomipramine (Anafranil and others), desipramine (Norpramin and others), duloxetine (Cymbalta), escitalopram (Lexapro and others), fluoxetine (Prozac and others), fluvoxamine (Luvox and others), imipramine (Tofranil and others), mirtazapine (Remeron and others), nortriptyline (Pamelor and others), paroxetine (Paxil and others), sertraline (Zoloft and others), venlafaxine (Effexor and others).

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REFERENCES

1. National Institute for Clinical Excellence. Depression (amended): Management of Depression in Primary and Secondary Care. Clinical Guideline 23. London, England: NICE; 2007. Available at: http://www.nice.org.uk/nicemedia/pdf/CG23NICEguidelineamended.pdf. Accessibility verified July 29, 2008
2. Hansen AR, Gartlehner G, Lohr KN, et al. Efficacy and safety of second-generation antidepressants in the treatment of major depressive disorder. Ann Int Med 2005;143:415–426
3. Cipriani A, Barbui C, Brambilla P, et al. Are all antidepressants really the same? the case of fluoxetine: a systematic review. J Clin Psychiatry 2006;67:850–864
4. Cooper PJ, Murray L. Postnatal depression. BMJ 1998;316:1884–1886
5. Nonacs RM, Soares CN, Viguera AC, et al. Bupropion SR for the treatment of postpartum depression: a pilot study. Int J Neuropsychopharmacol 2005;8:445–449
6. Furukawa TA, Cipriani A, Barbui C, et al. Imputing response rates from means and standard deviations in meta-analysis. Int Clin Psychopharmacol 2005;20:49–52
7. Altman DG, Bland JM. Detecting skewness from summary information. BMJ 1996 Nov;313(7066):1200
8. Furukawa TA, Barbui C, Cipriani A, et al. Imputing missing standard deviations in meta-analyses can provide accurate results. J Clin Epidemiol 2006;59:7–10
9. Edwards JG, Anderson I. Systematic review and guide to selection of selective serotonin reuptake inhibitors. Drugs 1999;57:507–533
10. Geddes JR, Freemantle N, Mason J, et al. SSRIs versus other antidepressants for depressive disorder. Cochrane Database Syst Rev 2000; 2:CD001851
11. Zimmerman M, Posternak MA, Chelminski I. Symptom severity and exclusion from antidepressant efficacy trials. J Clin Psychopharmacol 2002;22:610–614
12. Taylor MJ, Freemantle N, Geddes JR, et al. Early onset of selective serotonin reuptake inhibitor antidepressant action: systematic review and meta-analysis. Arch Gen Psychiatry 2006;63:1217–1223
13. Bauer M, Whybrow PC, Angst J, et al. World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for Biological Treatment of Unipolar Depressive Disorders, pt 1: acute and continuation treatment of major depressive disorder. World J Biol Psychiatry 2002;3:5–43
14. Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry 1960;23:56–62
15. Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. Br J Psychiatry 1979;134:382–389
16. Guy W, Bonato RR. Manual for the ECDEU Assessment Battery 2. Chevy Chase, Md: National Institute of Mental Health; 1970
17. Higgins JPT, Green S, eds. Cochrane Handbook for Systematic Reviews of Interventions 4.2.6 [updated September 2006]. In: The Cochrane Library, Issue 4, 2006. Chichester, United Kingdom: John Wiley & Sons, Ltd; 2006
18. Cipriani A, Brambilla P, Furukawa T, et al. Fluoxetine versus other types of pharmacotherapy for depression. Cochrane Database Syst Rev 2005; 4:CD004185
19. Davies HT, Crombie IK, Tavakoli M. When can odds ratios mislead? BMJ 1998;316:989–991
20. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986;7:177–188
21. Higgins JP, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. BMJ 2003;327:557–560
22. Aberg-Wistedt A, Agren H, Ekselius L, et al. Sertraline versus paroxetine in major depression: clinical outcome after 6 months of continuous therapy. J Clin Psychopharmacol 2000;20:645–652
23. Aguglia E, Casacchia M, Cassano GB, et al. Double-blind study of the efficacy and safety of sertraline versus fluoxetine in major depression. Int Clin Psychopharmacol 1993;8:197–202
24. Baca E, Gonzalez de Chavez M, Garcia-Toro M, et al. Sertraline is more effective than imipramine in the treatment of non-melancholic depression: results from a multicentre, randomized study. Prog NeuroPsychopharmacol Biol Psychiatry 2003;27:493–500
25. Behan PO, Hannifah H. 5-HT reuptake inhibitors in CFS. J Immunol Immunopharmacol 1995;15:66–69
26. Behnke K, Søgaard J, Martin S, et al. Mirtazapine orally disintegrating tablet versus sertraline: a prospective onset of action study. J Clin Psychopharmacol 2003;23:358–364
27. Bennie EH, Mullin JM, Martindale JJ. A double-blind multicenter trial comparing sertraline and fluoxetine in outpatients with major depression. J Clin Psychiatry 1995;56:229–237
28. Bersani G, Rapisarda V, Ciani N, et al. A double-blind comparative study of sertraline and amitriptyline in outpatients with major depressive episodes. Hum Psychopharmacol 1994;9:63–68
29. Bondareff W, Alpert M, Friedhoff AJ, et al. Comparison of sertraline and nortriptyline in the treatment of major depressive disorder in late life. Am J Psychiatry 2000;157(5):729–736
30. Boyer P, Danion JM, Bisserbe JC, et al. Clinical and economic comparison of sertraline and fluoxetine in the treatment of depression: a 6-month double-blind study in a primary-care setting in France. PharmacoEconomics 1998;13:157–169
31. Brenner R, Azbel V, Madhusoodanan S, et al. Comparison of an extract of hypericum (LI 160) and sertraline in the treatment of depression: a double-blind, randomized pilot study. Clin Ther 2000;22:411–419
32. Chen ZM, Zhang JH, Li ZW, et al. Venlafaxine vs imipramine, sertraline in treating depression. Chinese J New Drug Clin Remedies 2001;20: 109–111
33. Cohn CK, Shrivastava R, Mendels J, et al. Double-blind, multicenter comparison of sertraline and amitriptyline in elderly depressed patients. J Clin Psychiatry 1990;51(Suppl B):28–33
34. Coleman CC, Cunningham LA, Foster VJ, et al. Sexual dysfunction associated with the treatment of depression: a placebo-controlled comparison of bupropion sustained release and sertraline treatment. Ann Clin Psychiatry 1999;11:205–215
35. Croft H, Settle E Jr, Houser T, et al. A placebo-controlled comparison of the antidepressant efficacy and effects on sexual functioning of sustained-release bupropion and sertraline. Clin Ther 1999;21:643–658
36. Davidson JR, Gadde KM, Fairbank JA, et al, Hypericum Depression Trial Study Group. Effect of hypericum perforatum (St John's Wort) in major depressive disorder: a randomized controlled trial. JAMA 2002; 287:1807–1814
37. Doogan DP, Langdon CJ. A double-blind, placebo-controlled comparison of sertraline and dothiepin in the treatment of major depression in general practice. Int Clin Psychopharmacol 1994;9:95–100
38. Edwards RA, Newburn GL. A double-blind trial comparing clomipramine and sertraline in the treatment of major depression. Psychiatry Online, Priory Lodge Education; 1996. Available at http://www.priory.com/serttri.htm. Accessibility verified July 1, 2008
39. Eker SS, Akkaya C, Akgoz S, et al. Comparison of reboxetine and sertraline in terms of efficacy and safety in major depressive disorder [in Turkish]. Turk Psikiyatri Derg 2005;16:153–163
40. Ekselius L, von Knorring L, Eberhard G. A double-blind multicenter trial comparing sertraline and citalopram in patients with major depression treated in general practice. Int Clin Psychopharmacol 1997;12:323–331
41. Fava M, Hoog SL, Judge RA, et al. Acute efficacy of fluoxetine versus sertraline and paroxetine in major depressive disorder including effects of baseline insomnia. J Clin Psychopharmacol 2002;22:137–147
42. Fava M, Rosenbaum JF, Hoog SL, et al. Fluoxetine versus sertraline and paroxetine in major depression: tolerability and efficacy in anxious depression. J Aff Disord 2000;59:119–126
43. Feiger A, Kiev A, Shrivastava RK, et al. Nefazodone versus sertraline in outpatients with major depression: focus on efficacy, tolerability, and effects on sexual function and satisfaction. J Clin Psychiatry 1996; 57(suppl 2):53–62
44. Forlenza OV, Almeida OP, Stoppe A Jr, et al. Antidepressant efficacy and safety of low-dose sertraline and standard-dose imipramine for the treatment of depression in older adults: results from a double-blind, randomized, controlled clinical trial. Int Psychogeriatr 2001;13:75–84
45. Fournier JP, Lane RM, Chouinard G, et al. A double-blind comparison of sertraline and imipramine in outpatients with major depression: acute (8 weeks) and continuation (16 weeks) treatment. Hum Psychopharmacol 1997;12:203–215
46. Gastpar M, Singer A, Zeller K. Efficacy and tolerability of hypericum

extract STW3 in long-term treatment with a once-daily dosage in comparison with sertraline. Pharmacopsychiatry 2005;38:78–86
47. Kamijima K, Koyama T, Mita T, et al. A double-blind, group comparison study of sertraline by hydrochloride vs amitriptyline hydrochloride. Japan J Neuropsychopharmacol 1997;19:529–548
48. Kavoussi RJ, Segraves RT, Hughes AR, et al. Double-blind comparison of bupropion sustained release and sertraline in depressed outpatients. J Clin Psychiatry 1997;58:532–537
49. Lee MS, Kim SH, Suh KY, et al. Efficacy of sertraline in dysthymia. Neuropsychopharmacol 1994;10:222S
50. Lepine JP, Goger J, Blashko C, et al. A double-blind study of the efficacy and safety of sertraline and clomipramine in outpatients with severe major depression. Int Clin Psychopharmacol 2000;15:263–271
51. Li JH, Kong QR, Li SM. A comparative study of sertraline and maprotiline in the treatment of depression. Shandong J Psych Med 2001;14: 173–175
52. Lydiard RB, Stahl SM, Hertzman M, et al. A double-blind, placebo-controlled study comparing the effects of sertraline versus amitriptyline in the treatment of major depression. J Clin Psychiatry 1997;58:484–491
53. Mehtonen OP, Søgaard J, Roponen P, et al. Randomized, double-blind comparison of venlafaxine and sertraline in outpatients with major depressive disorder. J Clin Psychiatry 2000;61:95–100
54. Möller HJ, Glaser K, Leverkus F, et al. Double-blind, multicenter comparative study of sertraline versus amitriptyline in outpatients with major depression. Pharmacopsychiatry 2000;33:206–212
55. Moon CA, Jago W, Wood K, et al. A double-blind comparison of sertraline and clomipramine in the treatment of major depressive disorder and associated anxiety in general practice. J Psychopharmacol 1994;8: 171–176
56. Murasaki M, Kamijima K, Yamashita I, et al. Clinical evaluation of sertraline hydrochloride, a selective serotonin reuptake inhibitor for depression and depressive state: a double-blind study compared with imipramine hydrochloride. Japan J Neuropsychopharmacol 1997;19: 505–527
57. Munizza C, Olivieri L, Di Loreto G, et al. A comparative, randomized, double-blind study of trazodone prolonged-release and sertraline in the treatment of major depressive disorder. Curr Med Res Opin 2006;22: 1703–1713
58. Nemeroff CB, Ninan PT, Ballenger JC, et al. Double-blind multicenter comparison of fluvoxamine versus sertraline in the treatment of depressed outpatients. Depression 1995;3:163–169
59. Newhouse PA, Krishnan KR, Doraiswamy PM, et al. A double-blind comparison of sertraline and fluoxetine in depressed elderly outpatients. J Clin Psychiatry 2000;61:559–568
60. Orsel Donbak S, Turkcapar MH, Ozturk Kilic EZ, et al. Moclobemide and sertraline in the treatment of depressive disorders: a comparative study. Acta Psychiatr Belg 1995;95:139–151
61. Oslin DW, Ten Have TR, Streim JE, et al. Probing the safety of medications in the frail elderly: evidence from a randomized clinical trial of sertraline and venlafaxine in depressed nursing home residents. J Clin Psychiatry 2003;64:875–882
62. Ravindran AV, Teehan MD, Bakish D, et al. The impact of sertraline, desipramine, and placebo on psychomotor functioning in depression. Hum Psychopharmacol 1995;10(4):273–281
63. Reimherr FW, Chouinard G, Cohn CK, et al. Antidepressant efficacy of sertraline: a double-blind, placebo- and amitriptyline-controlled, multicenter comparison study in outpatients with major depression. J Clin Psychiatry 1990;51(Suppl B):18–27
64. Rossini D, Serretti A, Franchini L, et al. Sertraline versus fluvoxamine in the treatment of elderly patients with major depression: a double-blind, randomized trial. J Clin Psychopharmacol 2005;25(5):471–475
65. Sechter D, Troy S, Paternetti S, et al. A double-blind comparison of sertraline and fluoxetine in the treatment of major depressive episode in outpatients. Eur Psychiatry 1999;14:41–48
66. Shelton RC, Haman KL, Rapaport MH, et al. A randomized, double-blind, active-control study of sertraline versus venlafaxine XR in major depressive disorder. J Clin Psychiatry 2006;67(11):1674–1681
67. Sir A, D'Souza RF, Uguz S, et al. Randomized trial of sertraline versus venlafaxine XR in major depression: efficacy and discontinuation symptoms. J Clin Psychiatry 2005;66(10):1312–1320
68. Søgaard J, Lane R, Latimer P, et al. A 12-week study comparing moclobemide and sertraline in the treatment of outpatients with atypical depression. J Psychopharmacol 1999;13:406–414
69. Stahl SM. Placebo-controlled comparison of the selective serotonin reuptake inhibitors citalopram and sertraline. Biol Psychiatry 2000;48: 894–901
70. Suri RA, Altshuler LL, Rasgon NL, et al. Efficacy and response time to sertraline versus fluoxetine in the treatment of unipolar major depressive disorder. J Clin Psychiatry 2000;61:942–946
71. Szádóczky E, Füredi J. Efficacy and acceptability of tianeptine and sertraline in the acute treatment phase of depression [in French]. Encephale 2002;28:343–349
72. Thase ME, Kremer C, Rodrigues H. Mirtazapine versus sertraline after SSRI nonresponse. Presented at the 52nd annual Institute on Psychiatric Services, American Psychiatric Association Meeting; October 25–29, 2000; Philadelphia, Pa
73. Tsutsui S, Okuse S, Sasaki D, et al. Clinical evaluation of sertraline hydrochloride, a selective serotonin reuptake inhibitor in the treatment of depression and depressive state: a double-blind, group comparison study of sertraline hydrochloride vs trazodone hydrochloride. Japan J Neuropsychopharmacol 1997;19:549–568
74. Van Gurp G, Meterissian GB, Haiek LN, et al. St John's wort or sertraline? randomized controlled trial in primary care. Can Fam Physician 2002;48:905–912
75. Van Moffärt M, Bartholome F, Cosyns P, et al. A controlled comparison of sertraline and fluoxetine in acute and continuation treatment of major depression. Hum Psychopharmacol 1995;10:393–405
76. Ventura D, Armstrong EP, Skrepnek GH, et al. Escitalopram versus sertraline in the treatment of major depressive disorder: a randomized clinical trial. Curr Med Res Opin 2007;23(2):245–250
77. Zanardi R, Franchini L, Gasperini M, et al. Double-blind controlled trial of sertraline versus paroxetine in the treatment of delusional depression. Am J Psychiatry 1996;153:1631–1633
78. Zwarenstein M, Oxman A. Pragmatic Trials in Health Care Systems (PRACTIHC): why are so few randomized trials useful, and what can we do about it? J Clin Epidemiol 2006;59:1125–1126
79. Whittington CJ, Kendall T, Fonagy P, et al. Selective serotonin reuptake inhibitors in childhood depression: systematic review of published versus unpublished data. Lancet 2004;363:1341–1345
80. Papakostas GI, Thase ME, Fava M, et al. Are antidepressant drugs that combine serotonergic and noradrenergic mechanisms of action more effective than the selective serotonin reuptake inhibitors in treating major depressive disorder? a meta-analysis of studies of newer agents. Biol Psychiatry 2007 Dec;62(11):1217–1227
81. Barbui C, Hotopf M, Garattini S. Fluoxetine dose and outcome in antidepressant drug trials. Eur J Clin Pharmacol 2002;58:379–386
82. Cipriani A, Barbui C, Geddes JR. Suicide, depression, and antidepressants. BMJ 2005;330:373–374
83. Friedman RA, Leon AC. Expanding the black box: depression, antidepressants, and the risk of suicide. N Engl J Med 2007;356:2343–2346
84. Laughren TP. Memorandum: Overview for December 13 Meeting of Psychopharmacologic Drugs Advisory Committee (PDAC). Department of Health and Human Services, Public Health Service, Food and Drug Administration, Center for Drug Evaluation and Research; 2006. Available at http://www.fda.gov/ohrms/dockets/ac/06/briefing/2006-4272b1-01-fda.pdf. Accessibility verified September 11, 2008
85. Davies SJ, Jackson PR, Potokar J, et al. Treatment of anxiety and depressive disorders in patients with cardiovascular disease. BMJ 2004;328: 39–43
86. Lespérance F, Frasure-Smith N, Koszycki D, et al, CREATE Investigators. Effects of citalopram and interpersonal psychotherapy on depression in patients with coronary artery disease: the Canadian Cardiac Randomized Evaluation of Antidepressant and Psychotherapy Efficacy (CREATE) trial. JAMA 2007 Jan;297(4):367–379
87. Feinstein RE, Blumenfield M, Orlowski B, et al. A national survey of cardiovascular physicians' beliefs and clinical care practices when diagnosing and treating depression in patients with cardiovascular disease. Cardiol Rev 2006;14:164–169
88. Clayton AH, Croft HA, Horrigan JP, et al. Bupropion extended release compared with escitalopram: effects on sexual functioning and antidepressant efficacy in 2 randomized, double-blind, placebo-controlled studies. J Clin Psychiatry 2006;67:736–746
89. Papakostas GI, Montgomery SA, Thase ME, et al. Comparing the rapidity of response during treatment of major depressive disorder with bupropion and the SSRIs: a pooled survival analysis of 7 double-blind, randomized clinical trials. J Clin Psychiatry 2007;68:1907–1912

90. Zimmerman M, Posternak MA, Attiullah N, et al. Why isn't bupropion the most frequently prescribed antidepressant? J Clin Psychiatry 2005; 66:603–610
91. Nemeroff CB, Entsuah R, Benattia I, et al. Comprehensive analysis of remission (COMPARE) with venlafaxine versus SSRIs. Biol Psychiatry 2008;63(4):424–434
92. Lumley T. Network meta-analysis for indirect treatment comparisons. Stat Med 2002;21:2313–2324
93. Moher D, Cook DJ, Eastwood S, et al. Improving the quality of reports of meta-analyses of randomized controlled trials: the QUOROM statement. Lancet 1999;354:1896–1900. Available at http://www.consort-statement.org/mod_product/uploads/QUOROM%20Statement%201999.pdf. Accessibility verified July 15, 2008