Sponsorship, Antidepressant Dose, and Outcome in Major Depressive Disorder: Meta-Analysis of Randomized Controlled Trials

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ABSTRACT

Objective: Differences in dosing may influence results of pharmaceutical industry–sponsored medication trials. This study aims to determine the relationship between sponsorship and antidepressant dosing and efficacy in randomized controlled trials for major depressive disorder.

Data Sources: Trials were identified through English-language searches of MEDLINE and PsycINFO (January 1996–June 2010) using specific drug names and classes and *depressive disorder* or *major depression* and *double blind* or *double-blind method*. Other limitations included human subjects and treatment study designs using the clinical queries option. Other sources were also searched following a strict set of inclusion and exclusion criteria.

Study Selection: Randomized controlled trials were included if they examined antidepressant treatment for major depressive disorder, reported mean final medication dosages, acknowledged an association with industry, and included study arms of medications produced by the associated manufacturer and a competitor ("sponsor" and "nonsponsor" arms) (58 trials involving 15,026 patients from 101 citations identified).

Data Extraction: Data on dosing, efficacy, baseline severity, and adverse events were extracted by 2 of the authors.

Results: Meta-analyses were used to examine dosing and efficacy data. Using consensus guidelines for medication dosing, we determined that sponsor medication was dosed relatively higher than nonsponsor medication, in 37% (22/60) of comparisons as opposed to 5% (3/60) in which the nonsponsor medication was dosed higher ($\chi^2_2 = 25.9$, $P < .001$). Trials in which sponsor drugs were dosed higher than nonsponsor drugs demonstrated higher remission rates for the sponsor drug (OR = 1.28, 95% CI = 1.11–1.47, $P < .001$). These results were confirmed using regulatory dosing guidelines. There was no significant correlation between dosing or outcome with baseline severity or adverse events.

Conclusions: Sponsor drugs are dosed higher than nonsponsor drugs in antidepressant randomized controlled trials, and higher dosing is associated with better sponsor drug outcomes in some cases.

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Recent literature reviews and meta-analyses have demonstrated inconsistent findings regarding differences in efficacy between antidepressants.[1,2] While individual studies may favor one drug over another, overall the literature indicates roughly equivalent efficacy among antidepressants. One reason for this apparent inconsistency, which has not been well studied, may be differences in relative dosing between comparator drugs.[3,4] It has been argued in the broad medical literature that studies with large relative dose differences between comparators may erroneously skew results in favor of specific drugs and that this disparity is particularly relevant in pharmaceutical industry–sponsored trials.[3,5] In the psychiatric literature, several studies have examined the issue of sponsorship and outcome for antipsychotics in schizophrenia and have speculated about the role of dosing. Montgomery and colleagues[6] found that outcomes of industry-funded trials were more likely to favor second-generation than first-generation antipsychotics when compared to those not funded by industry. Another study[7] examining head-to-head trials of second-generation antipsychotics argued that subtle differences between trials in terms of entry criteria, patient population, methods, and reporting of results may explain the finding that outcomes favored the sponsor drug in 90% of trials. Authors of both studies[6,7] noted that asymmetric dosing strategies between sponsor and nonsponsor medications may have influenced the results, though they did not directly test this hypothesis. No studies have quantitatively examined the issue of dosing, sponsorship, and outcome in the antidepressant literature. Indeed, the only such study[8] we could identify looked at trials of nonsteroidal anti-inflammatory drugs (NSAIDs) for arthritis. It found that in 48.2% of trials, the sponsor drug was dosed significantly higher than the nonsponsor drug compared to only 3.6% where the opposite was true, and it speculated that this might explain why sponsor NSAIDs were more likely to have positive outcomes.[8] Here, we examine randomized controlled trials (RCTs) of antidepressants to determine whether sponsor drugs are dosed relatively differently than nonsponsor drugs and what, if any, impact this has on RCT outcomes.

METHOD

Data Sources and Study Selection

We used the following search strategy on MEDLINE and PsycINFO to obtain antidepressant RCTs from January 1996 to June 2010:

We entered the Boolean search string *"antidepressive agents* OR *antidepressant drugs* OR *agomelatine* OR *amitriptyline* OR *amoxapine* OR *bupropion* OR *citalopram* OR *clomipramine* OR *desipramine* OR *doxepin* OR *duloxetine* OR *escitalopram* OR *s-citalopram* OR *fluoxetine* OR *fluvoxamine* OR *imipramine*

Clinical Points

- Clinicians need to be aware that trial design factors may influence randomized controlled trial results.
- Dosing is an important factor.
- Clinicians looking to trial results to decide whether they want to use a new medication should pay attention to comparator medication dosing and whether patients were dosed adequately.

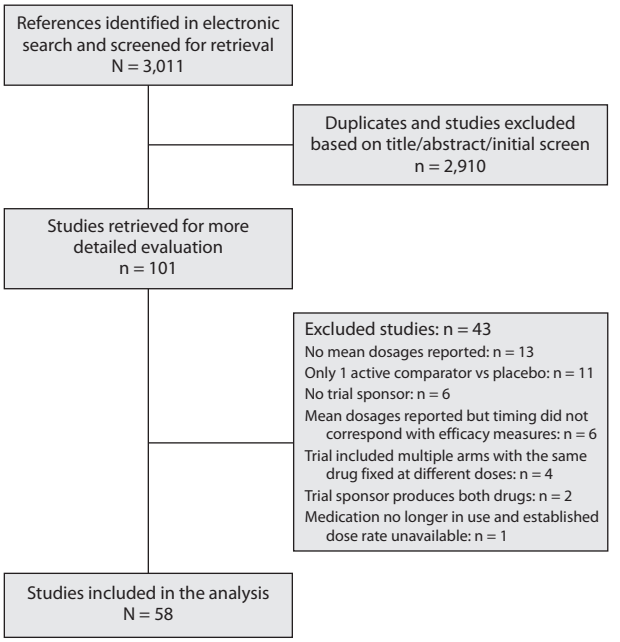
OR *lofepramine* OR *maprotiline* OR *milnacipran* OR *mirtazapine* OR *moclobemide* OR *nefazodone* OR *nk1 antagonist* OR *nk2 antagonist* OR *nortriptyline* OR *paroxetine* OR *reboxetine* OR *sertraline* OR *tianeptine* OR *trazodone* OR *trimipramine* OR *venlafaxine* OR *serotonin uptake inhibitors* OR *tricyclic* OR *serotonin norepinephrine reuptake inhibitors* OR *dopamine uptake inhibitors* OR *monoamine oxidase inhibitors* OR *heterocyclic drugs* OR *mixed re-uptake inhibitors* OR *reversible monoamine oxidase inhibitors* OR *placebo*" AND *"depressive disorder"* (MEDLINE)/"*major depression*" (PsycINFO) AND "*double blind*" (MEDLINE and PsycINFO) OR *"double-blind method"* (MEDLINE only).

The search was limited to human subjects, English language, and treatment study designs using the clinical queries option.

Pharmaceutical Web sites were also searched for unpublished RCTs examining the use of antidepressant medication for major depressive disorder (MDD), though no studies meeting inclusion criteria were identified. To be included, studies had to (*a*) report double-blind RCT data, (*b*) examine adult subjects (≥ 16 years old) given a diagnosis of MDD, (*c*) include data on response and/or remission rates within the first 120 days of treatment (ie, acute treatment), (*d*) report mean final dosages for each medication arm, (*e*) have at least 2 active antidepressant comparators, and (*f*) have at least 1 sponsor drug and 1 nonsponsor drug within the comparators. A medication was considered a sponsor drug if the pharmaceutical company who produced it provided funding for the trial and/or had one of its employees as an author. A study was excluded if it examined subjects with bipolar or psychotic depression or if some or all subjects were pregnant or had a comorbid psychiatric diagnosis, except anxiety disorders. Studies with subjects who were suffering or had recently suffered from a major medical condition were excluded. Studies were also excluded if they tested drugs that are no longer in use or for which no established dose range could be identified. The study extraction and selection process is shown in Figure 1. Fifty-eight studies met criteria and were included in the analysis.[9–66]

Three trials conducted with funding from H. Lundbeck A/S comparing its products escitalopram and citalopram were included in the analysis with only escitalopram being considered the sponsor drug since the trials were published after Lundbeck's patent on citalopram had expired.[20,23,35]

Figure 1. Flow Diagram of Randomized Controlled Trials Included and Excluded in Meta-Analysis of Dosing and Efficacy in Industry-Sponsored Antidepressant Trials



Two trials compared a sponsor drug to 2 nonsponsor drugs.[41,42] Each comparison was treated separately, resulting in 60 sponsor-nonsponsor comparisons for the 58 trials. Forty-two of the 58 trials had flexible dosing strategies for both comparator arms, and 4 had flexible dosing strategies for 1 comparator arm. These were considered flexible-dosing trials. The 12 remaining trials used a purely fixed-dose design. Finally, 13 of the 58 trials had a placebo comparator arm.

Data Extraction and Synthesis

Mean medication doses and dose ranges were gleaned from each trial by the investigators (M.S. and N.H.G.). For the primary analyses, standard medication doses for each drug were obtained from American Psychiatric Association (APA) guidelines[67] (Table 1). Several drugs, particularly newer antidepressants, were not listed in the APA guidelines, so dose ranges for these were taken from the more recent Canadian Network for Mood and Anxiety Treatments (CANMAT) guidelines.[1] Post hoc confirmatory analyses were likewise conducted using regulatory-approved dose ranges taken from the *Physicians' Desk Reference* (PDR)[68] or, where unavailable, the Canadian Electronic-Compendium of Pharmaceuticals and Specialties (CPS).[69] Neither guideline had dose ranges for 3 medications. In these cases, consensus values were again used.

Each medication arm was assigned 2 descriptors based on the mean final dose: each was assigned a categorical value of "underdosed," corresponding to a dose below the recommended minimum dose; "low dose," "intermediate dose," or "high dose," respectively corresponding to doses

0%–33.2%, 33.3%–66.6%, and 66.7%–100% between the recommended minimum and maximum doses; or "overdosed," corresponding to a dose above the recommended maximum dose. This categorical approach, following the method of Rochon et al,[8] was used because it gives a clinically meaningful measure of the level at which a medication was dosed compared to its usual minimum/maximum dose. However, the categorical approach involves somewhat arbitrary thresholds for what constitutes low, medium, and high doses. For example, 2 drugs dosed at 20% and 40% of their maximum dose would be in different categories and 2 drugs dosed at 40% and 60% of their maximum dose would be in the same category despite the same absolute difference in dosing. To account for this issue, a continuous measure employing a "percentage dose" (within dose range) was also assigned to each medication arm. Percentage doses were calculated using the following equation:

$$\%\ \text{dose} = \frac{[\text{mean study dose}] - [\text{minimum usual dose}]}{[\text{maximum usual dose}] - [\text{minimum usual dose}]} \times 100$$

By using this formula, we determined that a drug dosed at the minimum usual dose would have a percentage dose of 0% and a drug dosed at the maximum usual dose would have a percentage dose of 100%. A "dose difference" was then calculated for each study using the following equation:

$$\text{dose difference} = \%\ \text{dose (sponsor)} - \%\ \text{dose (nonsponsor)}$$

A positive dose difference therefore indicates a study in which the sponsor drug is dosed higher within its typical dose range than the nonsponsor drug, and a negative dose difference occurs when the reverse is true. Dose differences close to 0% reflect studies in which both sponsor and nonsponsor drugs are dosed similarly within their dose ranges. In addition to examining mean final doses, we also examined % doses and dose differences on the basis of the minimum and maximum doses allowed by studies for each medication arm.

Baseline severity ratings, total number of discontinuations, adverse events, and discontinuations due to adverse events were also extracted from each study to determine whether these factors influenced or were influenced by dosing and sponsorship.

Table 1. Standard Antidepressant Medication Doses (mg/d)[a]

	Consensus Guidelines		Regulatory Guidelines	
Medication	Minimum Usual Dose	Maximum Usual Dose	Minimum Usual Dose	Maximum Usual Dose
Agomelatine*	25*	50*	…	…
Amitriptyline	100	300	75	150
Bupropion XL	150	300	150	450
Bupropion SR	150	300	150	400
Citalopram	20	60	20	60
Clomipramine	100	250	150†	200†
Doxepin	100	300	75	300
Duloxetine	60*	120*	60	120
Escitalopram	10*	20*	10	20
Fluoxetine	20	60	20	80
Fluvoxamine	50	300	100†	300†
Imipramine	100	300	75	200
Maprotiline	100	225	75	225
Milnacipran	100*	200*	…	…
Mirtazapine	15	45	15	45
Moclobemide	300	600	300†	600†
Nefazodone	150	300	200	600
Paroxetine	20	60	20	50
Reboxetine	8*	12*	…	…
Sertraline	50	200	50	200
Trazodone	75	300	150	400
Venlafaxine	75	225	75	375 (XR = 225)

[a]Consensus guideline values were obtained from American Psychiatric Association Practice Guideline[67] with the exception of those with an asterisk (*), which were obtained from Canadian Network for Mood and Anxiety Treatments (CANMAT) guidelines.[1] Regulatory guideline values were obtained from the American *Physicians' Desk Reference*[68] with the exception of those with a dagger (†), which were obtained from the Canadian Electronic-Compendium of Pharmaceuticals and Specialties.[69] Where regulatory values were not available, consensus values were used instead.

Abbreviations: SR = sustained release, XL = extended release, XR = extended release.

Symbol: … = regulatory guideline unavailable.

Statistical Analysis

A Shapiro-Wilk test was used to assess if mean percentage doses were normally distributed. Because they were not ($W = 0.905$, $P < .001$), a χ^2 test was used to examine the difference in the number of studies with higher sponsor-drug dosing relative to the nonsponsor drug and those with higher nonsponsor dosing relative to the sponsor drug. Mann-Whitney *U* tests were used to examine dose differences between sponsor and nonsponsor arms of all studies.

To test our hypothesis, the numbers of subjects who responded and remitted were extracted from each study and assessed relative to the total number in each treatment arm using a Mantel-Haenszel (M-H) fixed-effects meta-analytic model. Studies were divided into subgroups of those with higher categorical sponsor drug dosing (n = 22) and those with equivalent dosing or higher nonsponsor drug dosing (n = 38). Effect size comparing sponsor to nonsponsor group was expressed in an odds ratio with 95% CI for each study. Studies were weighted according to their variance. Overall weighted effect size with confidence intervals was determined for each dose difference subgroup and assessed for significance using a standard (*z*) score with *P* value. Tau-square and χ^2 tests were used to assess heterogeneity, also reported in the I^2 statistic.

Mann-Whitney *U* tests were also used to compare dose differences between fixed and flexible dosing designs. In order to examine the effect of baseline depression severity on the relationship between dosing and outcome, Spearman rho (ρ) partial correlations were calculated to determine the bivariate relationship between % dose and response rates accounting for baseline scores on the Hamilton Depression Rating Scale (HDRS) and Montgomery-Asberg Depression Rating Scale (MADRS) in studies that reported them. Differences in the frequency of adverse events as well as discontinuations of sponsor versus nonsponsor drugs overall and due to adverse events were assessed using (1) Mann-Whitney *U* tests, (2) a meta-analytic model examining discontinuations in sponsor and nonsponsor groups using dose-difference subgroups as

mentioned, and (3) Spearman rho correlation coefficients of discontinuation rates and % doses.

RESULTS

Dosing and Sponsorship

Study characteristics for the 58 trials included in the meta-analysis are shown in Table 2. Using consensus guidelines, we determined that the mean dose of sponsor medication was higher within its dose range than the nonsponsor medication in 37% (22/60) of comparisons, significantly more than the 5% (3/60) in which the nonsponsor medication was dosed higher ($\chi^2_2 = 25.9$, $P < .001$). The same pattern was observed for maximum and minimum allowed doses across studies. Sponsor drugs also had a mean % dose that was, on average, 22% higher than nonsponsor drugs (mean % doses = 51 vs 29, respectively; $U = 1{,}231.5$, $P < .01$). Post hoc analyses using regulatory guidelines showed sponsor medication was dosed higher within its dose range in 35% (21/60) of comparisons, compared to 15% (9/60) in which the nonsponsor medication was dosed higher ($\chi^2_2 = 11.1$, $P < .01$), with a mean % dose difference of 13% (mean % doses = 40 vs 27, respectively; $U = 1{,}487.5$, $P = .173$).

Dose Differences and Antidepressant Efficacy

Examining efficacy data, we further assessed whether the magnitude of dose differences had any influence on response and remission rates (Figures 2 and 3). Studies with dose differences favoring sponsor drugs showed sponsor drugs to have significantly higher remission rates (OR = 1.28, 95% CI = 1.11–1.47, $P < .001$) (Figure 2). There was no statistical difference in remission rates for studies with no categorical dose differences or studies with differences favoring nonsponsor drugs (OR = 1.06, 95% CI = 0.96–1.17, $P = .23$). Response rates favoring sponsor medication were observed for both dose difference groups (comparable dosing or nonsponsor dosed higher: OR = 1.10, 95% CI = 1.01–1.21, $P = .03$; sponsor dosed higher: OR = 1.14, 95% CI = 1.02–1.27, $P = .02$) (Figure 3).

Continuous meta-analyses were also performed to detect smaller effects and to account for the artificial thresholds necessarily imposed by the categorical analyses. The pattern of sponsor drugs demonstrating better efficacy than nonsponsor drugs in trials with dose differences favoring the sponsor drug but not in others was observed for both remission and response in the continuous meta-analyses (remission: comparable dosing or nonsponsor dosed higher: OR = 1.06, 95% CI = 0.96–1.18, $P = .22$; sponsor dosed higher: OR = 1.26, 95% CI = 1.10–1.45, $P = .001$; response: comparable dosing or nonsponsor dosed higher: OR = 1.04, 95% CI = 0.95–1.14, $P = .4$; sponsor dosed higher: OR = 1.23, 95% CI = 1.11–1.37, $P = .0001$). None of the meta-analyses had significant heterogeneity (remission: $\chi^2_{36} = 35.8$, $P = .48$, $I^2 = 0\%$; response: $\chi^2_{59} = 76.5$, $P = .06$, $I^2 = 20\%$), justifying our choice of a fixed-effects model. These analytic strategies were repeated, using regulatory dosing guidelines in place of consensus dosing guidelines. The same significant findings were replicated.

Dosing Strategy, Baseline Severity, and Adverse Events

Four other post hoc analyses were conducted examining the impact of dosing strategy, baseline severity, adverse events (AEs), and discontinuations. Dose differences were statistically equivalent for fixed- and flexible-dosing designs (mean fixed-dose difference: sponsor 40% – nonsponsor 27% = 13%; mean flexible-dose difference: sponsor 54% – nonsponsor 30% = 24%; $U = 239.5$, $P = .37$). Baseline severity scores had no significant influence on the correlation between dose difference and outcome (MADRS: $\rho = -0.132$, $P = .275$ initially and $\rho = -0.097$, $P = .43$ controlling for baseline severity scores; HDRS: $\rho = 0.157$, $P = .27$ initially and $\rho = 0.121$, $P = .40$ controlling for baseline severity). Total discontinuation rates and those due to adverse events were not significantly different between sponsor and nonsponsor drugs (all discontinuations: $U = 1{,}266$, $P = .381$; discontinuations due to AEs: $U = 1{,}431$, $P = .273$) or between dose-difference groups (total discontinuations: low difference OR = 1.00, 95% CI = 0.84–1.19, $P = .99$; high difference OR = 0.84, 95% CI = 0.71–1.00, $P = .05$; discontinuations due to AEs: low difference OR = 0.92, 95% CI = 0.71–1.18, $P = .50$; high difference OR = 0.92, 95% CI = 0.67–1.27, $P = .61$). Discontinuations were also not correlated with % dose (all discontinuations: $\rho = 0.031$, $P = .754$; discontinuations due to AEs: $\rho = -0.082$, $P = .388$). The rate of adverse events was not different between sponsor and nonsponsor drugs (any AE: $U = 651.5$, $P = .721$) or between dose-difference groups (any AE: low difference OR = 1.00, 95% CI = 0.82–1.21, $P = .97$; high difference OR = 0.88, 95% CI = 0.77–1.01, $P = .06$).

DISCUSSION

No study to date has quantitatively examined the issue of dosing, sponsorship, and outcome in RCTs involving antidepressants. The analyses conducted here suggest that sponsor drugs are dosed relatively higher than nonsponsor drugs in more than one-third of antidepressant trials. Examining maximum- and minimum-allowed doses, it seems that a substantial portion of this observation occurred because permitted dose ranges were relatively higher for sponsor drugs. Asymmetric dosing favoring the sponsor drug was generally associated with better efficacy of the sponsor drug. One potential explanation for these results is sponsorship bias. The fact that sponsorship can bias findings of specific trials and of the literature in general has been well documented.[5,70–75] A specific way in which bias can be introduced is inadequate dosing of comparator drugs.[4,5] Findings of the current meta-analysis highlight the importance of dosing strategies employed in sponsored trials, or indeed any RCTs.

However, there are other possible explanations for the observation that sponsor drugs are dosed higher. For example, nonsponsor drugs often have well-established dose ranges, whereas there may be more flexibility in dosing or uncertainty about optimal dosing of sponsor drugs, particularly if they have yet to attain full regulatory approval, which could result in the use of higher doses of sponsor drugs.

Table 2. Study Characteristics of Sponsored[a] Trials of Antidepressants for Major Depression

Authors	Duration (wk)[b]	Sponsor Medication	Nonsponsor Medication	Sponsor n	Sponsor Mean Dose (mg/d)	Sponsor % Dose[c]	Sponsor Dose Category[c]	Nonsponsor n	Nonsponsor Mean Dose (mg/d)	Nonsponsor % Dose[c]	Nonsponsor Dose Category[c]
Sponsor dosed higher											
Behnke et al, 2003[9]	8	Mirtazapine	Sertraline	171	38.3	78	High	168	92.7	29	Low
Benkert et al, 2000[10]	6	Mirtazapine	Paroxetine	127	32.7	59	Intermediate	123	22.9	7	Low
Clayton et al, 2006[11]	8	Bupropion XL	Escitalopram	263	316	111	Overdosed	266	13.0	30	Low
Cohn et al, 1996[12]	8	Nefazodone	Imipramine	39	321	114	Overdosed	38	126	13	Low
Coleman et al, 2001[13]	8	Bupropion SR	Fluoxetine	136	319	113	Overdosed	146	26.0	15	Low
Coleman et al, 1999[14]	8	Bupropion SR	Sertraline	118	290	93	High	109	106	37	Intermediate
Croft et al, 1999[15]	8	Bupropion SR	Sertraline	116	293	95	High	116	121	47	Intermediate
Goldstein et al, 2002[16]	8	Duloxetine	Fluoxetine	66	110	84	High	33	20.0	0	Low
Hong et al, 2003[17]	6	Mirtazapine	Fluoxetine	60	34.1	64	Intermediate	59	30.7	27	Low
Kennedy et al, 2008[18]	12	Agomelatine	Venlafaxine XR	137	50.0	100	High	139	150	50	Low
Leinonen et al, 1999[19]	8	Mirtazapine	Citalopram	136	35.9	70	High	133	36.6	42	Intermediate
Lepola et al, 2003[20]	8	Escitalopram	Citalopram	155	14.0	40	Intermediate	159	28.4	21	Low
Lydiard et al, 1997[21]	8	Sertraline	Amitriptyline	130	139	59	Intermediate	129	103	2	Low
Möller et al, 2000[22]	6	Sertraline	Amitriptyline	100	55.0	3	Low	105	87.0	−7	Underdosed
Moore et al, 2005[23]	8	Escitalopram	Citalopram	138	20.0	100	High	142	40.0	50	Intermediate
Munizza et al, 2006[24]	6	Trazodone PR	Sertraline	62	297	99	High	59	59.0	6	Low
Poirier and Boyer, 1999[25]	4	Venlafaxine	Paroxetine	60	269	129	Overdosed	62	36.3	41	Intermediate
Ravindran et al, 1997[26]	12	Paroxetine	Clomipramine	479	28.2	21	Low	474	98.0	−1	Underdosed
Sauer et al, 2003[27]	6	Venlafaxine ER	Amitriptyline ER	76	85.4	7	Low	75	84.1	−8	Underdosed
Thase et al, 2006[28]	12	Bupropion XL	Venlafaxine XR	160	300	100	High	164	150	50	Intermediate
Wade et al, 2007[29]	8	Escitalopram	Duloxetine	141	20.0	100	High	146	60.0	0	Low
Zohar et al, 2003[30]	8	Fluvoxamine	Clomipramine	42	186	54	Intermediate	42	148	32	Low
Comparable dosing											
Benkert et al, 1996[31]	6	Venlafaxine	Imipramine	85	149	49	Intermediate	82	196	48	Intermediate
Berzewski et al, 1997[32]	6	Reboxetine	Imipramine	127	8.3	8	Low	121	159	29	Low
Bielski et al, 2004[33]	8	Escitalopram	Venlafaxine XR	97	20.0	100	High	98	225	100	High
Chouinard et al, 1999[34]	12	Paroxetine	Fluoxetine	100	25.5	14	Low	98	27.5	19	Low
Colonna et al, 2005[35]	8	Escitalopram	Citalopram	165	10.0	0	Low	174	20.0	0	Low
Costa e Silva, 1998[36]	8	Venlafaxine	Fluoxetine	196	91.5	11	Low	186	25.8	15	Low
Dalery and Honig, 2003[37]	6	Fluvoxamine	Fluoxetine	86	100	20	Low	91	20.0	0	Low
De Nayer et al, 2002[38]	12	Venlafaxine	Fluoxetine	64	103	19	Low	67	30.6	27	Low
Dierick et al, 1996[39]	6	Venlafaxine	Fluoxetine	148	111	24	Low	159	20.0	0	Low
Ekselius et al, 1997[40]	12	Sertraline	Citalopram	200	83.5	22	Low	200	33.0	33	Low
Fava et al, 2002[41]	10–16	Fluoxetine	Sertraline	88	42.0	55	Intermediate	96	108	39	Intermediate
			Paroxetine					93	37.0	43	Intermediate
Fava et al, 2000[42]	10	Fluoxetine	Sertraline	35	44.0	60	Intermediate	43	104	36	Intermediate
			Paroxetine					30	36.0	40	Intermediate
Gentil et al, 2000[43]	8	Venlafaxine	Amitriptyline	57	103	19	Low	58	103	2	Low
Guelfi et al, 2001[44]	8	Mirtazapine	Venlafaxine	77	49.5	115	Overdosed	75	255	120	Overdosed
Hewett et al, 2009[45]	8	Bupropion XR	Venlafaxine XR	187	170	13	Low	182	86.3	8	Low
Keller et al, 2007[46]	10	Venlafaxine ER	Fluoxetine	781	280	89	High	266	49.8	75	High
Khan et al, 2007[47]	8	Escitalopram	Duloxetine	136	13.0	30	Low	126	60.0	0	Low
Lapierre et al, 1997[48]	6	Moclobemide	Fluoxetine	61	440	47	Intermediate	60	35.0	38	Intermediate
Lee et al, 2007[49]	8	Duloxetine	Paroxetine	238	60.0	0	Low	240	20.0	0	Low
Mao et al, 2008[50]	8	Escitalopram	Fluoxetine	118	10.0	0	Low	113	20.0	0	Low
Mehtonen et al, 2000[51]	8	Venlafaxine	Sertraline	59	121	31	Low	60	82.5	22	Low
Möller et al, 1998[52]	6	Sertraline	Amitriptyline	62	77.0	18	Low	59	111	6	Low
Montgomery et al, 2004[53]	8	Escitalopram	Venlafaxine XR	146	12.1	21	Low	142	95.2	14	Low
Nierenberg et al, 2007[54]	8	Duloxetine	Escitalopram	273	60.0	0	Low	274	10.0	0	Low
Patris et al, 1996[55]	8	Citalopram	Fluoxetine	153	20.0	0	Low	161	20.0	0	Low
Rudolph and Feiger, 1999[56]	8	Venlafaxine XR	Fluoxetine	95	175	67	High	103	47.0	68	High
Samuelian and Hackett, 1998[57]	6	Venlafaxine	Clomipramine	52	105	20	Low	46	105	3	Low
Sandor et al, 1998[58]	6	Fluoxetine	Doxepin	18	36.8	42	Intermediate	17	169	35	Intermediate
Schnyder and Koller-Leiser, 1996[59]	6	Paroxetine	Maprotiline	37	32.2	31	Low	34	108	6	Low
Sechter et al, 2004[60]	6	Milnacipran	Paroxetine	148	100	0	Low	151	20.0	0	Low
Sheehan et al, 2009[61]	6	Venlafaxine	Fluoxetine	95	325	167	Overdosed	99	71.0	128	Overdosed
Sir et al, 2005[62]	8	Sertraline	Venlafaxine XR	79	105	37	Intermediate	79	161	58	Intermediate
Tzanakaki et al, 2000[63]	6	Venlafaxine	Fluoxetine	55	225	100	High	54	60.0	1	High
Nonsponsor dosed higher											
Fabre et al, 1996[64]	6	Fluvoxamine	Imipramine	46	117	27	Low	48	180	40	Intermediate
Perahia et al, 2008[65]	12	Duloxetine	Venlafaxine XR	330	79.4	32	Low	337	190	76	High
Ventura et al, 2007[66]	8	Escitalopram	Sertraline	104	10.0	0	Low	107	144	63	Intermediate

[a]A medication was considered a sponsor drug if the pharmaceutical company who produced it provided funding for the trial and/or had one of its employees as an author. [b]Duration of the acute-phase of each trial. [c]Each medication arm was assigned 2 descriptors based on the mean final dose: a % dose and a dose category. ***% Dose:*** A continuous measure employing a "percentage dose" (within dose range) was also assigned to each medication arm. Percentage doses were calculated using the following equation: % dose = [mean study dose] – [minimum usual dose]/[maximum usual dose] – [minimum usual dose] × 100. By using this formula, a drug dosed at the minimum usual dose would have a percentage dose of 0% and a drug dosed at the maximum usual dose would have a percentage dose of 100%. ***Dose category:*** Each was assigned a categorical value of "underdosed," corresponding to a dose below the recommended minimum dose; "low dose," "intermediate dose," or "high dose," corresponding to doses 0%–33.2%, 33.3%–66.6%, and 66.7%–100% between the recommended minimum and maximum doses, respectively; or "overdosed," corresponding to a dose above the recommended maximum dose.

Abbreviations: ER = extended release, PR = prolonged release, SR = sustained release, XL = extended release, XR = extended release.

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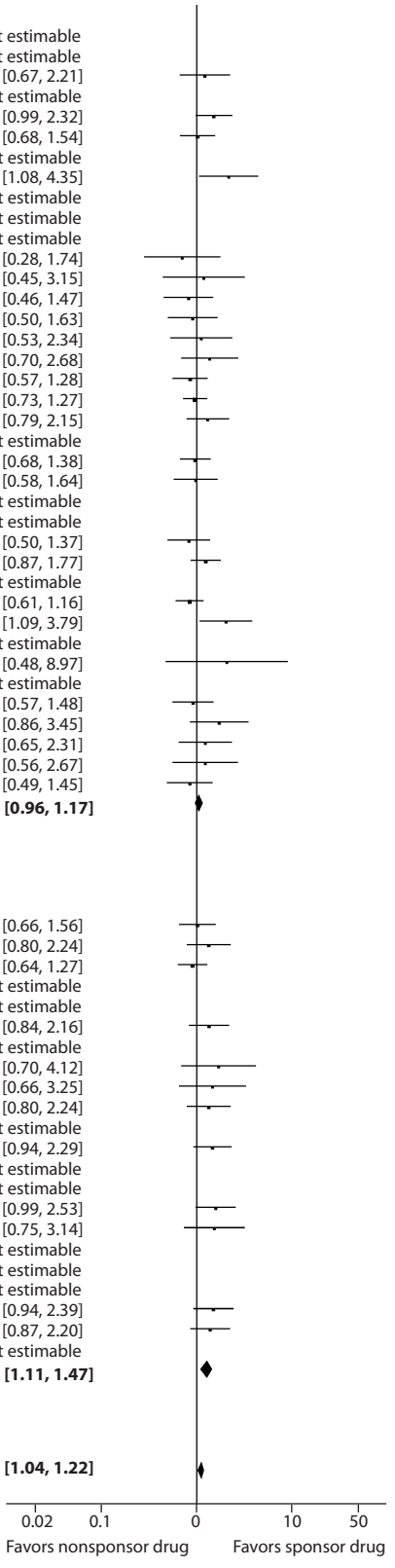
Figure 2. Forest Plot of Antidepressant Remission Rates for Studies of Major Depression With Categorical Differences in Dosing Favoring Nonsponsor Medication, Neither Medication, and Sponsor Medication, With Overall Effect (black diamond), Based on Meta-Analysis

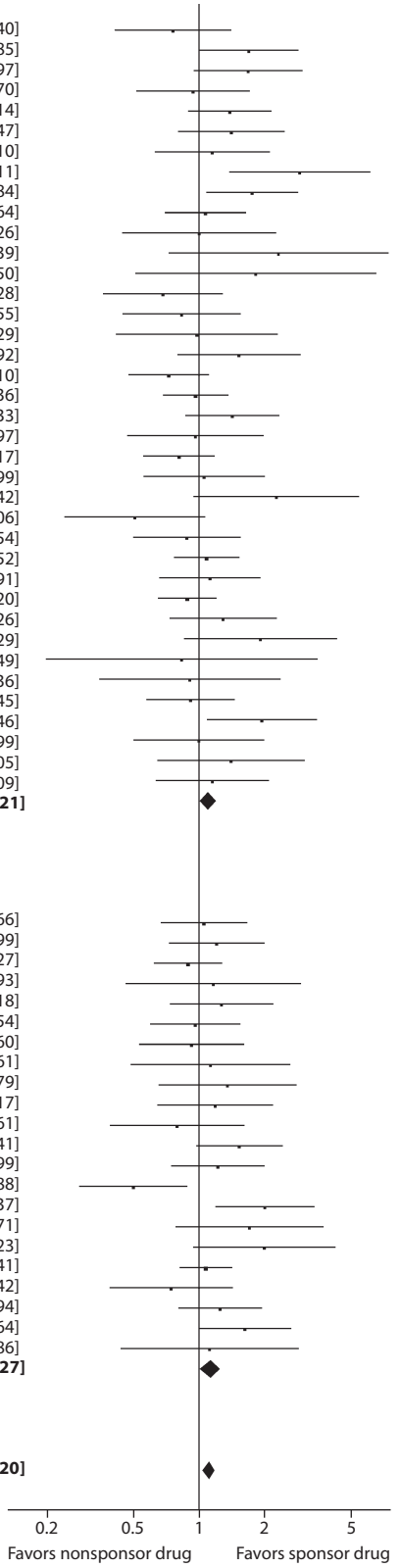
Study or Subgroup	Sponsor Events	Sponsor Total	Nonsponsor Events	Nonsponsor Total	Weight	Odds Ratio[a] M-H, Fixed, 95% CI
3.2.1 Comparable dosing or nonsponsor dosed higher						
Benkert et al, 1996[31]						Not estimable
Berzewski et al, 1997[32]						Not estimable
Bielski et al, 2004[33]	35	97	31	98	1.8%	1.22 [0.67, 2.21]
Chouinard et al, 1999[34]						Not estimable
Colonna et al, 2005[35]	91	165	78	174	3.1%	1.51 [0.99, 2.32]
Costa e Silva, 1998[36]	118	196	111	186	4.1%	1.02 [0.68, 1.54]
Dalery and Honig, 2003[37]						Not estimable
De Nayer et al, 2002[38]	38	64	27	67	1.0%	2.17 [1.08, 4.35]
Dierick et al, 1996[39]						Not estimable
Ekselius et al, 1997[40]						Not estimable
Fabre et al, 1996[64]						Not estimable
Fava et al,[b] 2000[42] (i)	19	35	27	43	1.0%	0.70 [0.28, 1.74]
Fava et al,[b] 2000[42] (ii)	19	35	15	30	0.7%	1.19 [0.45, 3.15]
Fava et al,[b] 2002[41] (i)	48	88	57	96	2.3%	0.82 [0.46, 1.47]
Fava et al,[b] 2002[41] (ii)	48	88	53	93	2.1%	0.91 [0.50, 1.63]
Gentil et al, 2000[43]	33	57	32	58	1.2%	1.12 [0.53, 2.34]
Guelfi et al, 2001[44]	29	77	23	75	1.3%	1.37 [0.70, 2.68]
Hewett et al, 2009[45]	88	187	93	182	4.5%	0.85 [0.57, 1.28]
Keller et al, 2007[46]	380	781	132	266	9.2%	0.96 [0.73, 1.27]
Khan et al, 2007[47]	56	136	44	126	2.4%	1.30 [0.79, 2.15]
Lapierre et al, 1997[48]						Not estimable
Lee et al, 2007[49]	118	238	121	240	5.5%	0.97 [0.68, 1.38]
Mao et al, 2008[50]	64	118	62	113	2.6%	0.97 [0.58, 1.64]
Mehtonen et al, 2000[51]						Not estimable
Möller et al, 1998[52]						Not estimable
Montgomery et al, 2004[53]	99	146	102	142	3.0%	0.83 [0.50, 1.37]
Nierenberg et al, 2007[54]	101	273	88	274	5.0%	1.24 [0.87, 1.77]
Patris et al, 1996[55]						Not estimable
Perahia et al, 2008[65]	104	330	119	337	7.3%	0.84 [0.61, 1.16]
Rudolph and Feiger, 1999[56]	35	95	23	103	1.3%	2.03 [1.09, 3.79]
Samuelian and Hackett, 1998[57]						Not estimable
Sandor et al, 1998[58]	7	18	4	17	0.2%	2.07 [0.48, 8.97]
Schnyder and Koller-Leiser, 1996[59]						Not estimable
Sechter et al, 2004[60]	49	148	53	151	3.2%	0.92 [0.57, 1.48]
Sheehan et al, 2009[61]	25	95	17	99	1.1%	1.72 [0.86, 3.45]
Sir et al, 2005[62]	47	79	43	79	1.6%	1.23 [0.65, 2.31]
Tzanakaki et al, 2000[63]	22	55	19	54	1.0%	1.23 [0.56, 2.67]
Ventura et al, 2007[66]	51	104	57	107	2.6%	0.84 [0.49, 1.45]
Subtotal (95% CI)		**3,705**		**3,210**	**69.3%**	**1.06 [0.96, 1.17]**
Total events	1,724		1,431			
Heterogeneity: $\chi^2_{24} = 23.81$, $P = .47$; $I^2 = 0\%$						
Test for overall effect: $Z = 1.20$, $P = .23$						
3.2.2 Sponsor dosed higher						
Behnke et al, 2003[9]	76	171	74	168	3.8%	1.02 [0.66, 1.56]
Benkert et al, 2000[10]	52	127	42	123	2.3%	1.34 [0.80, 2.24]
Clayton et al, 2006[11]	113	263	121	266	6.2%	0.90 [0.64, 1.27]
Cohn et al, 1996[12]						Not estimable
Coleman et al, 1999[14]						Not estimable
Coleman et al, 2001[13]	64	136	58	146	2.7%	1.35 [0.84, 2.16]
Croft et al, 1999[15]						Not estimable
Goldstein et al, 2002[16]	28	66	10	33	0.7%	1.69 [0.70, 4.12]
Hong et al, 2003[17]	20	60	15	59	0.9%	1.47 [0.66, 3.25]
Kennedy et al, 2008[18]	100	137	93	139	2.3%	1.34 [0.80, 2.24]
Leinonen et al, 1999[19]						Not estimable
Lepola et al, 2003[20]	81	155	68	159	2.9%	1.46 [0.94, 2.29]
Lydiard et al, 1997[21]						Not estimable
Möller et al, 2000[22]						Not estimable
Moore et al, 2005[23]	75	138	61	142	2.5%	1.58 [0.99, 2.53]
Munizza et al, 2006[24]	37	62	29	59	1.1%	1.53 [0.75, 3.14]
Poirier and Boyer, 1999[25]						Not estimable
Ravindran et al, 1997[26]						Not estimable
Sauer et al, 2003[27]						Not estimable
Thase et al, 2006[28]	59	160	46	164	2.6%	1.50 [0.94, 2.39]
Wade et al, 2007[29]	79	141	70	146	2.7%	1.38 [0.87, 2.20]
Zohar et al, 2003[30]						Not estimable
Subtotal (95% CI)		**1,616**		**1,604**	**30.7%**	**1.28 [1.11, 1.47]**
Total events	784		687			
Heterogeneity: $\chi^2_{11} = 7.59$, $P = .75$; $I^2 = 0\%$						
Test for overall effect: $Z = 3.40$, $P = .0007$						
Total (95% CI)		**5,321**		**4,814**	**100.0%**	**1.13 [1.04, 1.22]**
Total events	2,508		2,118			
Heterogeneity: $\chi^2_{36} = 35.84$, $P = .48$; $I^2 = 0\%$						
Test for overall effect: $Z = 2.94$, $P = .003$						
Test for subgroup differences: $\chi^2_1 = 4.42$, $P = .04$; $I^2 = 77.4\%$						



[a]M-H, Fixed = Mantel-Haenszel (M-H) fixed effects meta-analytic model. [b]Two trials by Fava et al (2000[42] and 2002[41]) compared a sponsor drug to 2 nonsponsor drugs. Each comparison was treated separately and is represented in the figure as "i" and "ii."

Figure 3. Forest Plot of Antidepressant Response Rates for Studies of Major Depression With Categorical Differences in Dosing Favoring Nonsponsor Medication, Neither Medication, and Sponsor Medication, With Overall Effect (black diamond), Based on Meta-Analysis

Study or Subgroup	Sponsor Events	Sponsor Total	Nonsponsor Events	Nonsponsor Total	Weight	Odds Ratio[a] M-H, Fixed, 95% CI
3.1.2 Comparable dosing or nonsponsor dosed higher						
Benkert et al, 1996[31]	44	85	48	82	1.5%	0.76 [0.41, 1.40]
Berzewski et al, 1997[32]	87	127	68	121	1.4%	1.70 [1.01, 2.85]
Bielski et al, 2004[33]	59	97	47	98	1.2%	1.68 [0.95, 2.97]
Chouinard et al, 1999[34]	67	100	67	98	1.4%	0.94 [0.52, 1.70]
Colonna et al, 2005[35]	104	165	96	174	2.2%	1.39 [0.90, 2.14]
Costa e Silva, 1998[36]	170	196	153	186	1.3%	1.41 [0.81, 2.47]
Dalery and Honig, 2003[37]	53	86	53	91	1.3%	1.15 [0.63, 2.10]
De Nayer et al, 2002[38]	48	64	34	67	0.5%	2.91 [1.39, 6.11]
Dierick et al, 1996[39]	107	148	95	159	1.6%	1.76 [1.09, 2.84]
Ekselius et al, 1997[40]	139	200	136	200	2.7%	1.07 [0.70, 1.64]
Fabre et al, 1996[64]	24	46	25	48	0.8%	1.00 [0.45, 2.26]
Fava et al,[b] 2000[42] (i)	30	35	31	43	0.3%	2.32 [0.73, 7.39]
Fava et al,[b] 2000[42] (ii)	30	35	23	30	0.2%	1.83 [0.51, 6.50]
Fava et al,[b] 2002[41] (i)	57	88	70	96	1.5%	0.68 [0.36, 1.28]
Fava et al,[b] 2002[41] (ii)	57	88	64	93	1.4%	0.83 [0.45, 1.55]
Gentil et al, 2000[43]	43	57	44	58	0.7%	0.98 [0.42, 2.29]
Guelfi et al, 2001[44]	48	77	39	75	1.0%	1.53 [0.80, 2.92]
Hewett et al, 2009[45]	107	187	118	182	3.3%	0.73 [0.48, 1.10]
Keller et al, 2007[46]	612	781	210	266	4.4%	0.97 [0.69, 1.36]
Khan et al, 2007[47]	83	136	66	126	1.7%	1.42 [0.87, 2.33]
Lapierre et al, 1997[48]	33	61	33	60	1.0%	0.96 [0.47, 1.97]
Lee et al, 2007[49]	144	238	157	240	4.0%	0.81 [0.56, 1.17]
Mao et al, 2008[50]	94	118	89	113	1.2%	1.06 [0.56, 1.99]
Mehtonen et al, 2000[51]	49	59	41	60	0.4%	2.27 [0.95, 5.42]
Möller et al, 1998[52]	32	62	40	59	1.3%	0.51 [0.24, 1.06]
Montgomery et al, 2004[53]	113	146	113	142	1.7%	0.88 [0.50, 1.54]
Nierenberg et al, 2007[54]	117	273	112	274	4.1%	1.08 [0.77, 1.52]
Patris et al, 1996[55]	120	153	123	161	1.7%	1.12 [0.66, 1.91]
Perahia et al, 2008[65]	170	330	184	337	5.7%	0.88 [0.65, 1.20]
Rudolph and Feiger, 1999[56]	54	95	52	103	1.4%	1.29 [0.74, 2.26]
Samuelian and Hackett, 1998[57]	31	52	20	46	0.6%	1.92 [0.86, 4.29]
Sandor et al, 1998[58]	12	18	12	17	0.3%	0.83 [0.20, 3.49]
Schnyder and Koller-Leiser, 1996[59]	22	37	21	34	0.6%	0.91 [0.35, 2.36]
Sechter et al, 2004[60]	86	148	91	151	2.4%	0.91 [0.58, 1.45]
Sheehan et al, 2009[61]	49	95	35	99	1.1%	1.95 [1.10, 3.46]
Sir et al, 2005[62]	56	79	56	79	1.1%	1.00 [0.50, 1.99]
Tzanakaki et al, 2000[63]	36	55	31	54	0.7%	1.41 [0.65, 3.05]
Ventura et al, 2007[66]	75	104	74	107	1.3%	1.15 [0.64, 2.09]
Subtotal (95% CI)		**4,921**		**4,429**	**60.8%**	**1.10 [1.01, 1.21]**
Total events	3,262		2,771			
Heterogeneity: $\chi^2_{37} = 49.97$, $P = .08$; $I^2 = 26\%$						
Test for overall effect: $Z = 2.22$, $P = .03$						
3.1.3 Sponsor dosed higher						
Behnke et al, 2003[9]	115	171	111	168	2.4%	1.05 [0.67, 1.66]
Benkert et al, 2000[10]	74	127	66	123	1.8%	1.21 [0.73, 1.99]
Clayton et al, 2006[11]	163	263	172	266	4.2%	0.89 [0.63, 1.27]
Cohn et al, 1996[12]	25	39	23	38	0.5%	1.16 [0.46, 2.93]
Coleman et al, 1999[14]	78	118	66	109	1.5%	1.27 [0.74, 2.18]
Coleman et al, 2001[13]	76	136	83	146	2.3%	0.96 [0.60, 1.54]
Croft et al, 1999[15]	77	116	79	116	1.7%	0.92 [0.53, 1.60]
Goldstein et al, 2002[16]	32	66	15	33	0.7%	1.13 [0.49, 2.61]
Hong et al, 2003[17]	35	60	30	59	0.8%	1.35 [0.66, 2.79]
Kennedy et al, 2008[18]	113	137	111	139	1.2%	1.19 [0.65, 2.17]
Leinonen et al, 1999[19]	116	136	117	133	1.1%	0.79 [0.39, 1.61]
Lepola et al, 2003[20]	98	155	84	159	2.0%	1.54 [0.98, 2.41]
Lydiard et al, 1997[21]	72	130	65	129	1.9%	1.22 [0.75, 1.99]
Möller et al, 2000[22]	51	100	71	105	2.2%	0.50 [0.28, 0.88]
Moore et al, 2005[23]	105	138	87	142	1.3%	2.01 [1.20, 3.37]
Munizza et al, 2006[24]	46	62	37	59	0.6%	1.71 [0.79, 3.71]
Poirier and Boyer, 1999[25]	27	60	18	62	0.6%	2.00 [0.95, 4.23]
Ravindran et al, 1997[26]	328	479	317	474	6.5%	1.08 [0.82, 1.41]
Sauer et al, 2003[27]	30	76	35	75	1.4%	0.75 [0.39, 1.42]
Thase et al, 2006[28]	87	160	80	164	2.3%	1.25 [0.81, 1.94]
Wade et al, 2007[29]	97	141	84	146	1.7%	1.63 [1.00, 2.64]
Zohar et al, 2003[30]	30	42	29	42	0.5%	1.12 [0.44, 2.86]
Subtotal (95% CI)		**2,912**		**2,887**	**39.2%**	**1.14 [1.02, 1.27]**
Total events	1,875		1,780			
Heterogeneity: $\chi^2_{21} = 26.38$, $P = .19$; $I^2 = 20\%$						
Test for overall effect: $Z = 2.29$, $P = .02$						
Total (95% CI)		**7,833**		**7,316**	**100.0%**	**1.12 [1.04, 1.20]**
Total events	5,137		4,551			
Heterogeneity: $\chi^2_{59} = 76.51$, $P = .06$; $I^2 = 23\%$						
Test for overall effect: $Z = 3.17$, $P = .002$						
Test for subgroup differences: $\chi^2_1 = 0.15$, $P = .70$; $I^2 = 0\%$						



[a]M-H, Fixed = Mantel-Haenszel (M-H) fixed effects meta-analytic model. [b]Two trials by Fava et al (2000[42] and 2002[41]) compared a sponsor drug to 2 nonsponsor drugs. Each comparison was treated separately and is represented in the figure as "i" and "ii."

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Another possibility involves the issue of side effects.[1,2] While many newer antidepressants may not be more efficacious than older ones, they may be associated with fewer or more tolerable side effects. One crucial factor that influences dose escalations in antidepressant RCTs is the emergence of side effects. Study clinicians may have been able to use relatively higher doses of newer, sponsor drugs, as compared to older, nonsponsor drugs, due to improved tolerability, especially in flexible-dose studies. This supposition is supported by the fact that higher % doses did not lead to higher rates of adverse events or dropouts for sponsor drugs.

Higher sponsor drug dosing was associated with higher sponsor drug remission rates relative to the nonsponsor drug in the categorical analysis. This result suggests that dosing differences are having some impact on efficacy results in antidepressant RCTs. Even in trials in which there were no efficacy differences between medications, dosing may have been an important factor. Table 2 shows that there were 11 trials that compared a new, sponsor drug to a tricyclic antidepressant (TCA). The newer drugs were commonly dosed higher than the TCAs, with the TCAs frequently dosed at or below their minimum recommended dose despite the fact that TCAs are thought to have linear dose-response curves.[76] Therefore, one might suspect that TCAs would have demonstrated better efficacy in these trials had their doses been higher.

It is worth noting that it may be a perfectly legitimate research practice to compare a new antidepressant with a relatively low dose of an established medication in a non-inferiority design. This approach may explain some or all of the results seen here. However, although such studies yield important results from a research standpoint, they can lead to erroneous conclusions if interpreted clinically. In other words, clinicians use individual studies and meta-analyses to decide which medications to use. But by potentially handicapping the comparator drug, these sorts of non-inferiority designs may lead to the false conclusion that a new drug is the same or better than an optimally dosed comparator when all that can be said is that it is the same or better than a low-dose comparator.

There have been few studies examining sponsorship and outcomes in the antidepressant literature. A pharmacoeconomic study[77] demonstrated that industry-sponsored antidepressant trials were more likely to have outcomes favoring the sponsor drug. Moreover, Turner and colleagues[78] concluded that selective reporting of antidepressant trials resulted in the overrepresentation of positive trials in the literature. These studies taken in the context of the present research underscore the point that methodological factors including medication dosing influence outcomes in antidepressant RCTs. Clinical trial registries now attempt to mitigate the effects of publication bias. Similar efforts at transparency may be called for within individual trials. As part of the literature search strategy employed in the current study, several trials were reviewed that did not report mean final dosages. At a minimum, all trials ought to include basic dosing information that may be relevant to the outcome, including such measures as dose range, titration schedule followed, and mean final dose.

This study has several important limitations. Both the dosing categories and the % dose values allowed for the comparison of drugs with different dose ranges; however, this approach does not account for the fact that a similar incremental dose escalation for a particular drug may yield a different change in dose category or % dose than for another drug. Although findings were replicated with both consensus and regulatory guidelines, it should also be noted that these analyses depended on anchoring standard minimum and maximum doses and that differences in these values could produce different % doses and dose differences. Given that this research compared numerous antidepressants with different dose ranges, dose increments, and titration steps, our approach was the best available for a standardized comparison. In addition, the dose escalation strategies used in individual studies were not specifically addressed. Nonetheless, the current analysis did not find a different pattern of outcome between flexible-dose studies, which permitted dose escalations, and fixed-dose studies, which did not.

Another important issue that we cannot examine from the available data is the percentage of patients in each trial arm that receives an adequate dose of medication (ie, at least the minimum usual dose). Future RCT publications should ideally include this information and provide justification if a greater proportion of subjects in the nonsponsor arm receive inadequate doses. Dosing guidelines also evolve with time, and it is possible that more stringent requirements on newer drugs have recently resulted in relatively lower dose ranges and relatively higher apparent dosing of sponsor drugs. However, results were muted somewhat when newer PDR guidelines were used compared to results using older APA guidelines, which is the opposite of what one would expect if such a shift in dosing guidelines was occurring.

The 58 studies included in the meta-analysis did not have identical subject characteristics or experimental protocols, which may have influenced the differences in outcome measures between studies. Furthermore, quantitative information was extracted from studies without any assessment or statistical weighting based on the quality of the individual study design so that sources of bias between studies were not controlled for. The current analysis also relied on the definitions of response and remission used by each group of investigators, which were similar across studies but not always identical. Finally, 2 other analyses would have strengthened our findings but were not possible with this dataset. First, it would have been useful to examine differences between classes of antidepressants rather than individual medications, but due to small sample size and a large variety of sponsor/nonsponsor combinations, this comparison was only possible in the special case of nonsponsor TCA trials. Second, our data do not include a sufficient number of trials comparing the same sponsor and nonsponsor drugs at different doses, meaning that we are unable to test directly the observation that large dose differences are associated with sponsor drug efficacy.

This study demonstrates that asymmetric dosing between sponsor and nonsponsor medications is occurring in antidepressant RCTs for major depression and may influence efficacy outcomes in some cases. This issue is crucial given that the results of any medication RCT ought to reflect an accurate comparison and the true efficacy of the drugs involved rather than an artifact of the study design. We agree with Heres et al[7] that, when possible, study investigators should obtain a dose range and titration schedule from an independent body/group of experts or the comparator company, though it should be noted that the latter option could potentially result in bias favoring the nonsponsor drug. Given that medication dosing requires a balance between many factors, most crucially efficacy and tolerability, dosing decisions will always be complex. From our perspective, the key point is that studies be more transparent about the issue of dosing. We therefore suggest that journals ask authors to include mean final doses for each medication arm as a prerequisite for publication of RCTs. Furthermore, if one drug was dosed relatively higher in its dose range than its comparator, articles should explicitly state that this has occurred and include a discussion of this issue in the main text. This research highlights the need for pharmaceutical industry sponsors, journal editors, peer reviewers, and clinicians to pay greater attention to dosing in antidepressant trials.

Drug names: bupropion (Wellbutrin, Aplenzin, and others), citalopram (Celexa and others), clomipramine (Anafranil and others), doxepin (Silenor and others), duloxetine (Cymbalta), escitalopram (Lexapro and others), fluoxetine (Prozac and others), fluvoxamine (Luvox and others), imipramine (Tofranil and others), milnacipran (Savella), mirtazapine (Remeron and others), nortriptyline (Pamelor, Aventyl, and others), paroxetine (Paxil, Pexeva, and others), sertraline (Zoloft and others), trazodone (Oleptro and others), trimipramine (Surmontil and others), venlafaxine (Effexor and others).

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REFERENCES

1. Lam RW, Kennedy SH, Grigoriadis S, et al; Canadian Network for Mood and Anxiety Treatments (CANMAT). Canadian Network for Mood and Anxiety Treatments (CANMAT) clinical guidelines for the management of major depressive disorder in adults, 3: pharmacotherapy. *J Affect Disord*. 2009;117(suppl 1):S26–S43.
2. Sartorius N, Baghai TC, Baldwin DS, et al. Antidepressant Medications and Other Treatments of Depressive Disorders: A CINP Task Force Report Based on a Review of Evidence. *Int J Neuropsychopharmacol*. 2007;10(suppl 1):S1–S207.
3. Lieberman JA, Greenhouse J, Hamer RM, et al. Comparing the effects of antidepressants: consensus guidelines for evaluating quantitative reviews of antidepressant efficacy. *Neuropsychopharmacology*. 2005; 30(3):445–460.
4. Bero LA, Rennie D. Influences on the quality of published drug studies. *Int J Technol Assess Health Care*. 1996;12(2):209–237.
5. Bodenheimer T. Uneasy alliance—clinical investigators and the pharmaceutical industry. *N Engl J Med*. 2000;342(20):1539–1544.
6. Montgomery JH, Byerly M, Carmody T, et al. An analysis of the effect of funding source in randomized clinical trials of second generation antipsychotics for the treatment of schizophrenia. *Control Clin Trials*. 2004;25(6):598–612.
7. Heres S, Davis J, Maino K, et al. Why olanzapine beats risperidone, risperidone beats quetiapine, and quetiapine beats olanzapine: an exploratory analysis of head-to-head comparison studies of second-generation antipsychotics. *Am J Psychiatry*. 2006;163(2):185–194.
8. Rochon PA, Gurwitz JH, Simms RW, et al. A study of manufacturer-supported trials of nonsteroidal anti-inflammatory drugs in the treatment of arthritis. *Arch Intern Med*. 1994;154(2):157–163.
9. 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(4):358–364.
10. Benkert O, Szegedi A, Kohnen R. Mirtazapine compared with paroxetine in major depression. *J Clin Psychiatry*. 2000;61(9):656–663.
11. 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(5):736–746.
12. Cohn CK, Robinson DS, Roberts DL, et al. Responders to antidepressant drug treatment: a study comparing nefazodone, imipramine, and placebo in patients with major depression. *J Clin Psychiatry*. 1996;57(suppl 2): 15–18.
13. Coleman CC, King BR, Bolden-Watson C, et al. A placebo-controlled comparison of the effects on sexual functioning of bupropion sustained release and fluoxetine. *Clin Ther*. 2001;23(7):1040–1058.
14. 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(4):205–215.
15. 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(4):643–658.
16. Goldstein DJ, Mallinckrodt C, Lu Y, et al. Duloxetine in the treatment of major depressive disorder: a double-blind clinical trial. *J Clin Psychiatry*. 2002;63(3):225–231.
17. Hong CJ, Hu WH, Chen CC, et al. A double-blind, randomized, group-comparative study of the tolerability and efficacy of 6 weeks' treatment with mirtazapine or fluoxetine in depressed Chinese patients. *J Clin Psychiatry*. 2003;64(8):921–926.
18. Kennedy SH, Rizvi S, Fulton K, et al. A double-blind comparison of sexual functioning, antidepressant efficacy, and tolerability between agomelatine and venlafaxine XR. *J Clin Psychopharmacol*. 2008;28(3): 329–333.
19. Leinonen E, Skarstein J, Behnke K, et al; Nordic Antidepressant Study Group. Efficacy and tolerability of mirtazapine versus citalopram: a double-blind, randomized study in patients with major depressive disorder. *Int Clin Psychopharmacol*. 1999;14(6):329–337.
20. Lepola UM, Loft H, Reines EH. Escitalopram (10–20 mg/day) is effective and well tolerated in a placebo-controlled study in depression in primary care. *Int Clin Psychopharmacol*. 2003;18(4):211–217.
21. 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(11): 484–491.
22. 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(6):206–212.
23. Moore N, Verdoux H, Fantino B. Prospective, multicentre, randomized, double-blind study of the efficacy of escitalopram versus citalopram in outpatient treatment of major depressive disorder. *Int Clin Psychopharmacol*. 2005;20(3):131–137.

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24. 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(9): 1703–1713.
25. Poirier MF, Boyer P. Venlafaxine and paroxetine in treatment-resistant depression: double-blind, randomised comparison. *Br J Psychiatry*. 1999; 175(1):12–16.
26. Ravindran AV, Judge R, Hunter BN, et al; Paroxetine Study Group. A double-blind, multicenter study in primary care comparing paroxetine and clomipramine in patients with depression and associated anxiety. *J Clin Psychiatry*. 1997;58(3):112–118.
27. Sauer H, Huppertz-Helmhold S, Dierkes W. Efficacy and safety of venlafaxine ER vs amitriptyline ER in patients with major depression of moderate severity. *Pharmacopsychiatry*. 2003;36(5):169–175.
28. Thase ME, Clayton AH, Haight BR, et al. A double-blind comparison between bupropion XL and venlafaxine XR: sexual functioning, antidepressant efficacy, and tolerability. *J Clin Psychopharmacol*. 2006;26(5):482–488.
29. Wade A, Gembert K, Florea I. A comparative study of the efficacy of acute and continuation treatment with escitalopram versus duloxetine in patients with major depressive disorder. *Curr Med Res Opin*. 2007;23(7): 1605–1614.
30. Zohar J, Keegstra H, Barrelet L. Fluvoxamine as effective as clomipramine against symptoms of severe depression: results from a multicentre, double-blind study. *Hum Psychopharmacol*. 2003;18(2): 113–119.
31. Benkert O, Gründer G, Wetzel H, et al. A randomized, double-blind comparison of a rapidly escalating dose of venlafaxine and imipramine in inpatients with major depression and melancholia. *J Psychiatr Res*. 1996; 30(6):441–451.
32. Berzewski H, Van Moffaert M, Gagiano CA. Efficacy and tolerability of reboxetine compared with imipramine in a double-blind study in patients suffering from major depressive episodes. *Eur Neuropsychopharmacol*. 1997;(7, suppl 1):S37–S47, S71–S73.
33. Bielski RJ, Ventura D, Chang CC. A double-blind comparison of escitalopram and venlafaxine extended release in the treatment of major depressive disorder. *J Clin Psychiatry*. 2004;65(9):1190–1196.
34. Chouinard G, Saxena B, Bélanger MC, et al. A Canadian multicenter, double-blind study of paroxetine and fluoxetine in major depressive disorder. *J Affect Disord*. 1999;54(1–2):39–48.
35. Colonna L, Andersen HF, Reines EH. A randomized, double-blind, 24-week study of escitalopram (10 mg/day) versus citalopram (20 mg/day) in primary care patients with major depressive disorder. *Curr Med Res Opin*. 2005;21(10):1659–1668.
36. Costa e Silva J. Randomized, double-blind comparison of venlafaxine and fluoxetine in outpatients with major depression. *J Clin Psychiatry*. 1998;59(7):352–357.
37. Dalery J, Honig A. Fluvoxamine versus fluoxetine in major depressive episode: a double-blind randomised comparison. *Hum Psychopharmacol*. 2003;18(5):379–384.
38. De Nayer A, Geerts S, Ruelens L, et al. Venlafaxine compared with fluoxetine in outpatients with depression and concomitant anxiety. *Int J Neuropsychopharmacol*. 2002;5(2):115–120.
39. Dierick M, Ravizza L, Realini R, et al. A double-blind comparison of venlafaxine and fluoxetine for treatment of major depression in outpatients. *Prog Neuropsychopharmacol Biol Psychiatry*. 1996; 20(1):57–71.
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(6): 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(2):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 Affect Disord*. 2000;59(2):119–126.
43. Gentil V, Kerr-Correa F, Moreno R, et al. Double-blind comparison of venlafaxine and amitriptyline in outpatients with major depression with or without melancholia. *J Psychopharmacol*. 2000;14(1):61–66.
44. Guelfi JD, Ansseau M, Timmerman L, et al; Mirtazapine-Venlafaxine Study Group. Mirtazapine versus venlafaxine in hospitalized severely depressed patients with melancholic features. *J Clin Psychopharmacol*. 2001;21(4):425–431.
45. Hewett K, Chrzanowski W, Schmitz M, et al. Eight-week, placebo-controlled, double-blind comparison of the antidepressant efficacy and tolerability of bupropion XR and venlafaxine XR. *J Psychopharmacol*. 2009;23(5):531–538.
46. Keller MB, Trivedi MH, Thase ME, et al. The Prevention of Recurrent Episodes of Depression with Venlafaxine for Two Years (PREVENT) study: outcomes from the acute and continuation phases. *Biol Psychiatry*. 2007;62(12):1371–1379.
47. Khan A, Bose A, Alexopoulos GS, et al. Double-blind comparison of escitalopram and duloxetine in the acute treatment of major depressive disorder. *Clin Drug Investig*. 2007;27(7):481–492.
48. Lapierre YD, Joffe R, McKenna K, et al. Moclobemide versus fluoxetine in the treatment of major depressive disorder in adults. *J Psychiatry Neurosci*. 1997;22(2):118–126.
49. Lee P, Shu L, Xu X, et al. Once-daily duloxetine 60 mg in the treatment of major depressive disorder: multicenter, double-blind, randomized, paroxetine-controlled, non-inferiority trial in China, Korea, Taiwan and Brazil. *Psychiatry Clin Neurosci*. 2007;61(3):295–307.
50. Mao PX, Tang YL, Jiang F, et al. Escitalopram in major depressive disorder: a multicenter, randomized, double-blind, fixed-dose, parallel trial in a Chinese population. *Depress Anxiety*. 2008;25(1):46–54.
51. Mehtonen OP, Søgaard J, Roponen P, et al. Randomized, double-blind comparison of venlafaxine and sertraline in outpatients with major depressive disorder. Venlafaxine 631 Study Group. *J Clin Psychiatry*. 2000;61(2):95–100.
52. Möller HJ, Gallinat J, Hegerl U, et al. Double-blind, multicenter comparative study of sertraline and amitriptyline in hospitalized patients with major depression. *Pharmacopsychiatry*. 1998;31(5):170–177.
53. Montgomery SA, Huusom AK, Bothmer J. A randomised study comparing escitalopram with venlafaxine XR in primary care patients with major depressive disorder. *Neuropsychobiology*. 2004;50(1):57–64.
54. Nierenberg AA, Greist JH, Mallinckrodt CH, et al. Duloxetine versus escitalopram and placebo in the treatment of patients with major depressive disorder: onset of antidepressant action, a non-inferiority study. *Curr Med Res Opin*. 2007;23(2):401–416.
55. Patris M, Bouchard JM, Bougerol T, et al. Citalopram versus fluoxetine: a double-blind, controlled, multicentre, phase III trial in patients with unipolar major depression treated in general practice. *Int Clin Psychopharmacol*. 1996;11(2):129–136.
56. Rudolph RL, Feiger AD. A double-blind, randomized, placebo-controlled trial of once-daily venlafaxine extended release (XR) and fluoxetine for the treatment of depression. *J Affect Disord*. 1999;56(2–3): 171–181.
57. Samuelian JC, Hackett D. A randomized, double-blind, parallel-group comparison of venlafaxine and clomipramine in outpatients with major depression. *J Psychopharmacol*. 1998;12(3):273–278.
58. Sandor P, Baker B, Irvine J, et al. Effectiveness of fluoxetine and doxepin in treatment of melancholia in depressed patients. *Depress Anxiety*. 1998; 7(2):69–72.
59. Schnyder U, Koller-Leiser A. A double-blind, multicentre study of paroxetine and maprotiline in major depression. *Can J Psychiatry*. 1996;41(4):239–244.
60. Sechter D, Vandel P, Weiller E, et al; study co-coordinators. A comparative study of milnacipran and paroxetine in outpatients with major depression. *J Affect Disord*. 2004;83(2–3):233–236.
61. Sheehan DV, Nemeroff CB, Thase ME, et al; EPIC 016 Study Group. Placebo-controlled inpatient comparison of venlafaxine and fluoxetine for the treatment of major depression with melancholic features. *Int Clin Psychopharmacol*. 2009;24(2):61–86.
62. 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.
63. Tzanakaki M, Guazzelli M, Nimatoudis I, et al. Increased remission rates with venlafaxine compared with fluoxetine in hospitalized patients with major depression and melancholia. *Int Clin Psychopharmacol*. 2000; 15(1):29–34.
64. Fabre L, Birkhimer LJ, Zaborny BA, et al. Fluvoxamine versus imipramine and placebo: a double-blind comparison in depressed patients. *Int Clin Psychopharmacol*. 1996;11(2):119–127.
65. Perahia DGS, Pritchett YL, Kajdasz DK, et al. A randomized, double-blind comparison of duloxetine and venlafaxine in the treatment of patients with major depressive disorder. *J Psychiatr Res*. 2008;42(1): 22–34.
66. 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.
67. American Psychiatric Association. Practice Guideline for the Treatment of Patients With Major Depressive Disorder (revision).

Am J Psychiatry. 2000;157(suppl):1–45.
68. Physicians' Desk Reference. http://www.pdr.net. Accessed April 4, 2011.
69. Electronic-Compendium of Pharmaceuticals and Specialties. http://e-therapeutics.ca. Accessed April 4, 2011.
70. Bekelman JE, Li Y, Gross CP. Scope and impact of financial conflicts of interest in biomedical research: a systematic review. *JAMA*. 2003;289(4): 454–465.
71. Friedman LS, Richter ED. Relationship between conflicts of interest and research results. *J Gen Intern Med*. 2004;19(1):51–56.
72. Jørgensen AW, Maric KL, Tendal B, et al. Industry-supported meta-analyses compared with meta-analyses with non-profit or no support: differences in methodological quality and conclusions. *BMC Med Res Methodol*. 2008;8(1):60.
73. Jørgensen AW, Hilden J, Gøtzsche PC. Cochrane reviews compared with industry supported meta-analyses and other meta-analyses of the same drugs: systematic review. *BMJ*. 2006;333(7572):782.
74. Lexchin J, Bero LA, Djulbegovic B, et al. Pharmaceutical industry sponsorship and research outcome and quality: systematic review. *BMJ*. 2003;326(7400):1167–1170.
75. Okike K, Kocher MS, Mehlman CT, et al. Industry-sponsored research. *Injury*. 2008;39(6):666–680.
76. Corruble E, Guelfi JD. [Is there a relationship between clinical efficacy and antidepressant dosage in major depression?]. *Encephale*. 1999; 25(Spec No 2):39–43, discussion 44–46.
77. Baker CB, Johnsrud MT, Crismon ML, et al. Quantitative analysis of sponsorship bias in economic studies of antidepressants. *Br J Psychiatry*. 2003;183(6):498–506.
78. Turner EH, Matthews AM, Linardatos E, et al. Selective publication of antidepressant trials and its influence on apparent efficacy. *N Engl J Med*. 2008;358(3):252–260.

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