Detecting Antidepressant Efficacy: The Impact of Study Design and the Value of Academic Sites

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Abstract

Introduction: Placebo response, defined as demonstrable symptomatic improvement despite inactive treatment, varies widely in clinical trials employing subjective outcomes, particularly in psychiatric disorders. In antidepressant studies, placebo effects complicate the detection of true treatment effects and appear to be increasing over time. This meta-analysis of placebo-controlled studies of venlafaxine and desvenlafaxine (administered as desvenlafaxine succinate) was conducted to identify trial and patient characteristics that may impact placebo response and signal detection in studies of major depressive disorder (MDD).

Methods: Trial design characteristics and patient-level data from all phase 2 to 4 clinical trials of MDD performed by the manufacturers of venlafaxine and desvenlafaxine were analyzed. Trials were selected if they were conducted with adult outpatients, used a double-blind, placebo-controlled design, and were 6 to 12 weeks in duration. Trials limited to inpatients or geriatric patients were excluded. Data that could potentially affect treatment outcomes were analyzed. Study design characteristics included number of postbaseline study visits, treatment arms, and assessments per visit, duration of the trial, fixed vs flexible dosing, and drug. Characteristics of the research environment included year of study, percent of US and academic sites, and proportion of completers. Patient characteristics included age, sex, race, and mean and median baseline MDD severity. Treatment outcomes included differences in standardized mean in the 17-item Hamilton Rating Scale for Depression ($HAM\text{-}D_{17}$) score and the risk ratio for response (ie, ≥50% reduction in HAM-D at end point) between antidepressant and placebo, mean change in HAM-D and response in placebo patients, and study outcome (significant drug-placebo separation at end point). Univariate meta-regression models assessed the effect of predictor variables that may be associated with the defined outcomes. To adjust for confounding effects among predictor variables, multivariate meta-regression models also were performed.

Results: Thirty trials that comprised 8933 depressed patients were included. Drug-placebo separation was most strongly predicted (β=3.74, *P*=0.0002) by the proportion of academic sites in the trial. Other factors predicting significant drug-placebo separation included lower completion rate, greater number of postbaseline visits, earlier year of study, greater percentage of whites, and studies conducted with venlafaxine vs desvenlafaxine. Lower median baseline depression severity predicted significant separation in response rates. Only the proportion of academic sites stayed as a significant predictor in the multivariate meta-regression modeling for both continuous change scores and response rates.

Conclusions: Academic sites provide significant value to clinical trials of psychiatric disorders. Recent efforts to reduce placebo response through increasing minimum severity criteria may be misguided.

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- Approximately half of the trials of newer marketed antidepressants in the US Food and Drug Administration (FDA) database failed to demonstrate superiority over placebo[1-4]
  - The mean drug-placebo difference was approximately 1.8 on the $HAM\text{-}D_{17}$[5,6] which is below the 3-point difference the National Institute for Clinical Excellence uses to denote clinical significance[7]
- A commonly cited reason for failed MDD trials is the increase in placebo response observed over the last 3 decades[6,8]
- Placebo response has been attributed to a variety of factors: regression to the mean, spontaneous recovery, expectation bias,[9] clinical attention,[10] unreliable measurement, and inclusion of inappropriate patients[11]
- Greater severity and longer duration of illness also have been associated with greater drug-placebo separation in some,[3,4,12] but not all[13] studies
- Trial design factors associated with greater placebo effects include greater numbers of treatment arms[14] and trial visits,[15] and flexible rather than fixed dosing[13]
- We performed a meta-analysis to examine factors associated with placebo response and the detection of antidepressant efficacy using data from all short-term trials of 2 marketed antidepressant medications (ie, venlafaxine and desvenlafaxine)
- Variables related to 3 aspects of clinical trial design and conduct (patient, study design, and research environment characteristics) were assessed

Method

Trial Selection

- We identified all phase 2 to 4, placebo-controlled trials of venlafaxine or desvenlafaxine in the Pfizer database as of March 1, 2011
- Inclusion criteria
  - Studies were required to be conducted with outpatients 18 to 65 years of age with a primary diagnosis of MDD
  - All trials were required to be 6 to 12 weeks in duration, to administer treatment in a double-blind manner, and to use the $HAM\text{-}D_{17}$[16] as a depression severity measure
- Exclusion criteria
  - Lifetime diagnosis of bipolar disorder or a psychotic disorder
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- Fifteen variables that could potentially predict placebo response and drug-placebo separation were assessed (**Table 1**)

Table 1. Potential Predictors of Drug-Placebo Separation and Placebo Response

Patient Characteristics	Study Design Characteristics	Research Environment Characteristics
Age, mean	Treatment arms, #	Study initiation, year
Sex	Assessments/visit, #	US sites, %
Race (white vs other)	Postbaseline visits, #	Academic sites, %
Baseline depression severity, mean; median	Trial duration, weeks	Study completers, %
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	Study drug (VEN vs DVS)	

Abbreviations: DVS, desvenlafaxine; VEN, venlafaxine.

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- For both placebo treatment effect and drug-placebo difference, the following outcomes were calculated
  - $HAM\text{-}D_{17}$ baseline to end point change score, mean
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  - $HAM\text{-}D_{17}$ response rate
    - ≥50% reduction in $HAM\text{-}D_{17}$ score from baseline to end point
  - Probability of positive study outcome
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- All analyses were based on the last-observation-carried-forward approach

Statistical Analysis

- All analyses were performed using the intent-to-treat sample
- All statistical tests were 2-sided with a significance level of α=0.05
  - No adjustments were made for multiple comparisons
- Meta-analyses and univariate meta-regression models were performed using the Comprehensive Meta-Analysis Software System, Version 2 (Biostat, Inc., Englewood, NJ)
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Assessed Studies

- The sponsor's database contained 131 phase 2, 3, or 4 studies of either venlafaxine or desvenlafaxine. After removing the studies that did not meet the inclusion criteria, 30 double-blind, placebo-controlled trials were eligible (**Figure 1**)

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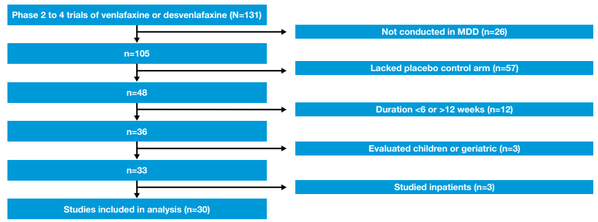

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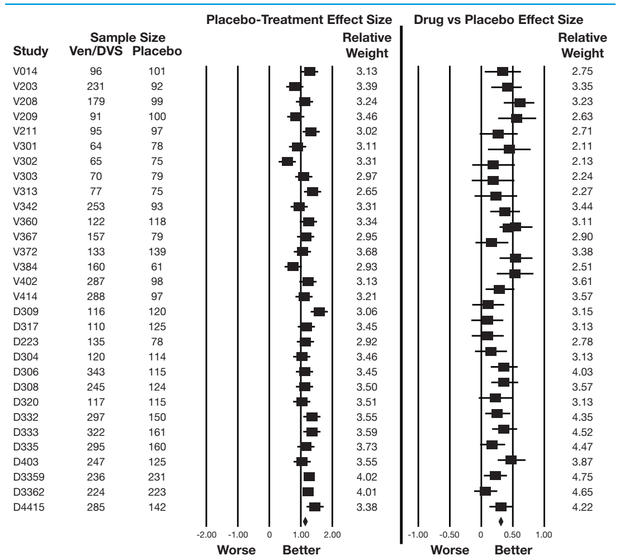

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	$HAM\text{-}D_{17}$ Change Score					$HAM\text{-}D_{17}$ Response Rate			
	Univariate Meta-Regression		Multivariate Meta-Regression			Univariate Meta-Regression		Multivariate Meta-Regression	
Predictor	Standardized β	*P*-value	Standardized β	*P*-value	**Predictor**	Standardized β	*P*-value	Standardized β	*P*-value
Completion Rate, %	3.67	0.0002	1.96	0.062	US Sites, %	-3.09	0.0020	-1.31	0.207
Year of Study	3.57	0.0004	1.52	0.141	Completion Rate, %	3.07	0.0021	0.83	0.423
Study Drug (DVS vs VEN)	2.53	0.0113	-1.22	0.240	Median Baseline $HAM\text{-}D_{17}$ Score	2.85	0.0043	0.66	0.513
Assessments per Visit	2.47	0.0134	1.27	0.219	Academic Sites, %	-2.06	0.0390	-1.63	0.119

Abbreviations: DVS, desvenlafaxine; $HAM\text{-}D_{17}$, 17-item Hamilton Rating Scale for Depression; VEN, venlafaxine.

Table 3. Significant Predictors of Differences in $HAM\text{-}D_{17}$ Score and Response Rates in Patients Treated With Venlafaxine or Desvenlafaxine vs Placebo

	$HAM\text{-}D_{17}$ Change Score					$HAM\text{-}D_{17}$ Response Rate			
	Univariate Meta-Regression		Multivariate Meta-Regression			Univariate Meta-Regression		Multivariate Meta-Regression	
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Academic Sites, %	3.74	0.0002	2.24	**0.034**	Academic Sites, %	3.71	0.0002	2.26	**0.035**
Study Drug (DVS vs VEN)	-3.00	0.0027	-0.89	0.387	Completion Rate, %	-3.55	0.0004	0.29	0.781
Completion Rate, %	-2.94	0.0033	-0.15	0.884	Study Drug (DVS vs VEN)	-2.77	0.0056	0.55	0.591
Postbaseline Visits, #	2.72	0.0066	1.32	0.201	Year of Study	-2.64	0.0083	-1.01	0.331
Year of Study	-2.14	0.0323	0.31	0.760	Median Baseline $HAM\text{-}D_{17}$ Score	-2.22	0.0266	-2.30	**0.030**
White Race, %	2.03	0.0429	—	—	Postbaseline Visits, #	2.09	0.0363	1.71	0.103

Abbreviations: DVS, desvenlafaxine; $HAM\text{-}D_{17}$, 17-item Hamilton Rating Scale for Depression; VEN, venlafaxine.

Figure 3. Effect Sizes of Placebo Treatment and Drug-Placebo Differences Over Time

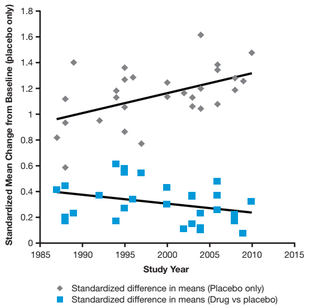
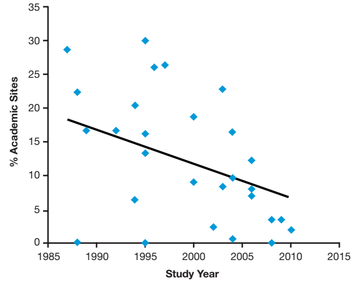


Figure 4a. Relationship Between the Percentage of Academic Sites in a Trial and the Year of Study Initiation



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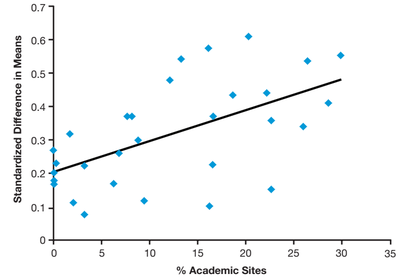

Discussion

- Completion rate, year of study, study drug, and assessments per visit emerged as significant predictors of $HAM\text{-}D_{17}$ change score in the placebo group, while US and academic sites, completion rate, and median baseline $HAM\text{-}D_{17}$ were significant predictors of placebo response (univariate analyses)
- In the univariate analyses significant predictors of drug-placebo separation in $HAM\text{-}D_{17}$ change score were academic site, study drug, completion rate, number of postbaseline visits, year of study, and white race, while for drug vs placebo separation in response rate academic sites, study drug, completion rate, postbaseline visits, year of study, and median baseline $HAM\text{-}D_{17}$ were significant predictors
- However, only academic site and median baseline $HAM\text{-}D_{17}$ maintained significance in the multivariate analyses of drug-placebo separation
- The most consistent predictor of statistical drug-placebo separation was the percentage of trial sites based in an academic institution
- Specifically, a higher proportion of academic sites predicted lower placebo response rate, greater drug-placebo separation, and a greater likelihood of positive study outcome
- We believe this is the first published analysis to document the potentially negative impact of the decreasing use of academic sites in industry-sponsored clinical trials
- We also found that the percentage of academic sites participating in MDD trials has declined over the past 20 years
  - Until the 1990s, nearly all studies were conducted at academic centers
- Today, with the large number of trials that require rapid recruitment, academic sites represent a small fraction and contribute an even smaller number of the total enrolled patients
- Strengths of this analysis are the inclusion of all trials conducted for this indication with these medications, thus eliminating the possibility of publication bias that can reduce the validity of meta-analyses. We were also able to evaluate a large number of variables, and thereby allow for more comprehensive multivariable analyses
- Limitations include the restriction to only two antidepressants studied by a single company. Unique characteristics of these medications, or aspects of trial design and administration by the sponsor, may limit generalizability of our findings

Conclusion

- Public trust in the results of clinical trials for new treatments may be enhanced through greater involvement of academic research sites

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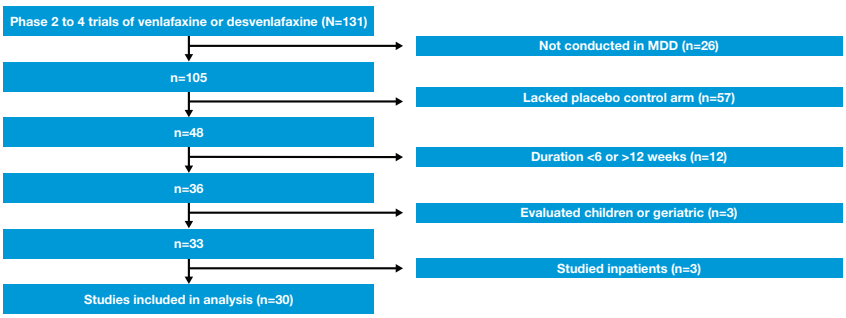

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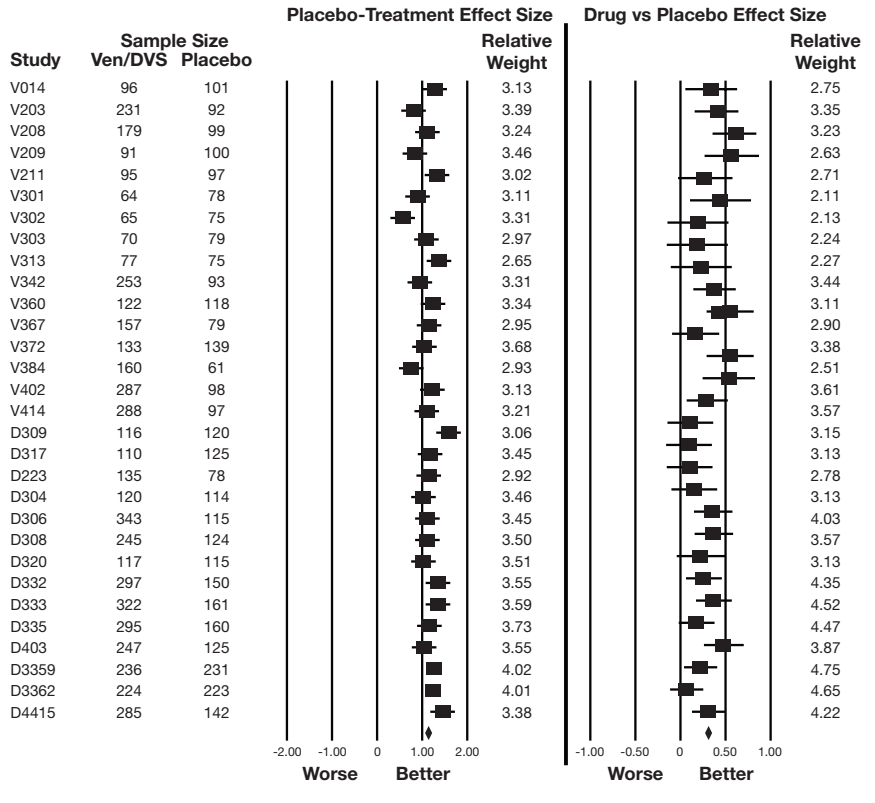

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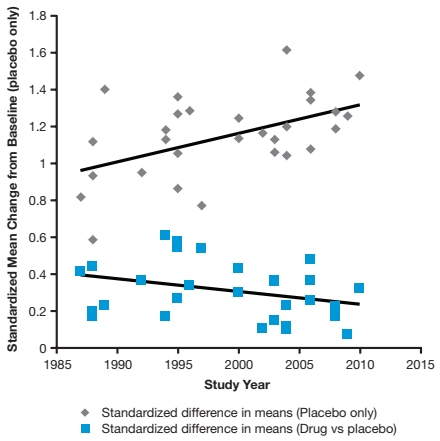

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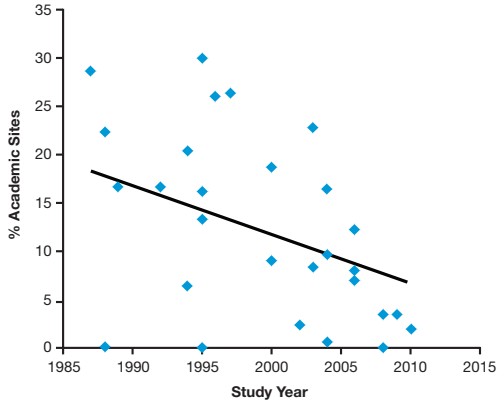

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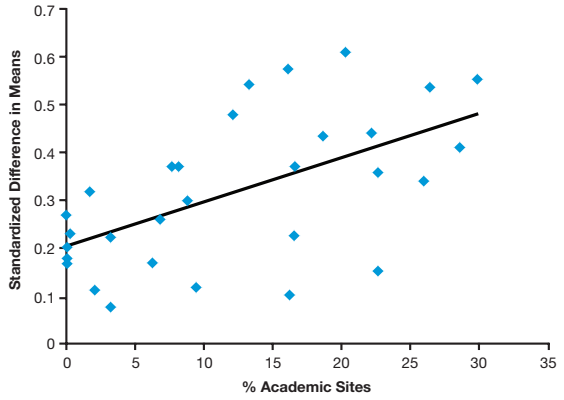

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- Specifically, a higher proportion of academic sites predicted lower placebo response rate, greater drug-placebo separation, and a greater likelihood of positive study outcome
- We believe this is the first published analysis to document the potentially negative impact of the decreasing use of academic sites in industry-sponsored clinical trials
- We also found that the percentage of academic sites participating in MDD trials has declined over the past 20 years
  - Until the 1990s, nearly all studies were conducted at academic centers
- Today, with the large number of trials that require rapid recruitment, academic sites represent a small fraction and contribute an even smaller number of the total enrolled patients
- Strengths of this analysis are the inclusion of all trials conducted for this indication with these medications, thus eliminating the possibility of publication bias that can reduce the validity of meta-analyses. We were also able to evaluate a large number of variables, and thereby allow for more comprehensive multivariable analyses
- Limitations include the restriction to only two antidepressants studied by a single company. Unique characteristics of these medications, or aspects of trial design and administration by the sponsor, may limit generalizability of our findings

Conclusion

- Public trust in the results of clinical trials for new treatments may be enhanced through greater involvement of academic research sites

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