JAMA®

Online article and related content current as of May 5, 2009.

Clinical Response and Risk for Reported Suicidal Ideation and Suicide Attempts in Pediatric Antidepressant Treatment: A Meta-analysis of Randomized Controlled Trials

Jeffrey A. Bridge; Satish Iyengar; Cheryl B. Salary; et al.

JAMA. 2007;297(15):1683-1696 (doi:10.1001/jama.297.15.1683)

http://jama.ama-assn.org/cgi/content/full/297/15/1683

Supplementary material	JAMA News Video http://jama.ama-assn.org/cgi/content/full/297/15/1683/DC1
Correction	Contact me if this article is corrected.
Citations	This article has been cited 95 times. Contact me when this article is cited.
Topic collections	Pediatrics; Adolescent Medicine; Pediatrics, Other; Psychiatry; Anxiety Disorders; Depression; Obsessive-Compulsive Disorder; Suicide; Quality of Care; Evidence-Based Medicine; Randomized Controlled Trial; Drug Therapy; Adverse Effects Contact me when new articles are published in these topic areas.
Related Letters	Benefits and Harms of Pediatric Antidepressant Medications Bruce Waslick. *JAMA*. 2007;298(6):626. Jonathan L. Edwards et al. *JAMA*. 2007;298(6):626.
	Tailoring Treatment to Parental Values: A Comment on TADS David Antonuccio. *JAMA*. 2008;65(6):723.
	In Reply: John S. March et al. *JAMA*. 2008;65(6):723.

Subscribe
http://jama.com/subscribe

Email Alerts
http://jamaarchives.com/alerts

Permissions
permissions@ama-assn.org
http://pubs.ama-assn.org/misc/permissions.dtl

Reprints/E-prints
reprints@ama-assn.org

Downloaded from www.jama.com at Ohio State University on May 5, 2009

Clinical Response and Risk for Reported Suicidal Ideation and Suicide Attempts in Pediatric Antidepressant Treatment

A Meta-analysis of Randomized Controlled Trials

Jeffrey A. Bridge, PhD
Satish Iyengar, PhD
Cheryl B. Salary, MD
Rémy P. Barbe, MD
Boris Birmaher, MD
Harold Alan Pincus, MD
Lulu Ren, PhD
David A. Brent, MD

Context The US Food and Drug Administration (FDA) has issued warnings that use of antidepressant medications poses a small but significantly increased risk of suicidal ideation/suicide attempt for children and adolescents.

Objective To assess the efficacy and risk of reported suicidal ideation/suicide attempt of antidepressants for treatment of pediatric major depressive disorder (MDD), obsessive-compulsive disorder (OCD), and non-OCD anxiety disorders.

Data Sources and Study Selection PubMed (1988 to July 2006), relevant US and British regulatory agency reports, published abstracts of important scientific meetings (1998-2006), clinical trial registries, and information from authors. Studies were published and unpublished randomized, placebo-controlled, parallel-group trials of second-generation antidepressants (selective serotonin reuptake inhibitors, nefazodone, venlafaxine, and mirtazapine) in participants younger than 19 years with MDD, OCD, or non-OCD anxiety disorders.

Data Extraction Information was extracted on study characteristics, efficacy outcomes, and spontaneously reported suicidal ideation/suicide attempt.

Data Synthesis Twenty-seven trials of pediatric MDD (n=15), OCD (n=6), and non-OCD anxiety disorders (n=6) were selected, and risk differences for response and for suicidal ideation/suicide attempt estimated by random-effects methods. Pooled risk differences in rates of primary study-defined measures of responder status significantly favored antidepressants for MDD (11.0%; [95% confidence interval {CI}, 7.1% to 14.9%]), OCD (19.8% [95% CI, 13.0% to 26.6%), and non-OCD anxiety disorders (37.1% [22.5% to 51.7%]), corresponding to a number needed to treat (NNT) of 10 (95% CI, 7 to 15), 6 (4 to 8), and 3 (2 to 5), respectively. While there was increased risk difference of suicidal ideation/suicide attempt across all trials and indications for drug vs placebo (0.7%; 95% CI, 0.1% to 1.3%) (number needed to harm, 143 [95% CI, 77 to 1000]), the pooled risk differences within each indication were not statistically significant: 0.9% (95% CI, –0.1% to 1.9%) for MDD, 0.5% (–1.2% to 2.2%) for OCD, and 0.7% (–0.4% to 1.8%) for non-OCD anxiety disorders. There were no completed suicides. Age-stratified analyses showed that for children younger than 12 years with MDD, only fluoxetine showed benefit over placebo. In MDD trials, efficacy was moderated by age, duration of depression, and number of sites in the treatment trial.

Conclusions Relative to placebo, antidepressants are efficacious for pediatric MDD, OCD, and non-OCD anxiety disorders, although the effects are strongest in non-OCD anxiety disorders, intermediate in OCD, and more modest in MDD. Benefits of antidepressants appear to be much greater than risks from suicidal ideation/suicide attempt across indications, although comparison of benefit to risk varies as a function of indication, age, chronicity, and study conditions.

JAMA. 2007;297:1683-1696 www.jama.com

Author Affiliations are listed at the end of this article.
Corresponding Author: David A. Brent, MD, Western Psychiatric Institute & Clinic, Child and Adolescent Psychiatry, 3811 O'Hara St, BFT 311, Pittsburgh, PA 15213-2592 (brentda@upmc.edu).

The US Food and Drug Administration (FDA), in its review and meta-analysis of 24 placebo-controlled trials assessing use of antidepressant medications among more than 4400 children and adolescents, concluded that these medications pose a 2-fold (4% vs 2%) increased risk for "suicidal behavior or suicidal ideation," although no suicides were reported.[1,2] In the FDA analysis, suicidal behavior comprised actual suicide attempts and preparatory actions toward imminent suicidal behavior (Box). Subsequently, the FDA mandated that a boxed warning be put on the labels of all antidepressants indicating an increased risk of suicidal thoughts and behavior in youth taking these medications but stopped short of prohibiting their use.

The concern about antidepressants must be considered in the context of possible benefit. The extant evidence supports the efficacy of antidepressant treatment for pediatric major depressive disorder (MDD),

©2007 American Medical Association. All rights reserved.

Downloaded from www.jama.com at Ohio State University on May 5, 2009

Box. Study Definitions[a]

Suicidal ideation[3]

Passive thoughts about wanting to be dead or active thoughts about killing oneself, not accompanied by preparatory behavior

Suicide attempt[3]

Self-injurious behavior associated with some intent to die
Intent can be stated or inferred by rater
No injury needed

Preparatory actions toward imminent suicidal behavior[3]

Person takes steps to injure self but is stopped by self or other (eg, a person tries to hang self but is prevented from doing so by family members)
Intent to die is either stated or inferred

Suicidal ideation/suicide attempt

Occurrence of suicidal ideation, suicide attempt, or preparatory actions toward imminent suicidal behavior

[a]Suicidal ideation and suicidal behaviors that occurred during the double-blind acute-treatment period or within 1 day of the end of this period.[1]

obsessive-compulsive disorder (OCD), and non-OCD anxiety disorders, although the strength of the treatment effect varies by indication and by the specific antidepressants.[4-19] A prior meta-analysis[20] examined the risk-benefit profile of selective serotonin reuptake inhibitors (SSRIs) in pediatric depression, but not other indications, and predated the publication of 2 large clinical trials of pediatric depression among more than 700 children and adolescents.[5,18] We therefore conducted a more current review and meta-analysis of pediatric trials assessing use of antidepressants across the indications of MDD, OCD, and non-OCD anxiety disorders and also examined patient- and trial-level moderators of benefit and risk.

METHODS

Search Strategy

A PubMed literature search was conducted (from January 1988 through July 2006) using the MeSH keywords *SSRI*; *serotonin reuptake inhibitors*; *antidepressive agents: second-generation*; *child*; *adolescent*; *randomized controlled trial*; specific names of antidepressant medications; and names of researchers known to the investigators for having conducted at least 1 clinical trial of pediatric antidepressants. Tricyclic antidepressants and monoamine oxidase inhibitors were not included in our search, because the FDA report specifically targeted the newer classes of antidepressants.[1,2] Relevant studies were also identified through (1) references of originally identified articles; (2) FDA and British Medicines and Healthcare Products Regulatory Agency reports[1,2,21,22]; (3) scientific proceedings of the American Psychiatric Association (2000-2005), the American Academy of Child and Adolescent Psychiatry (1998-2005), and the New Clinical Drug Evaluation Unit (2001-2006); (4) clinical trial registries (primarily www.clinicaltrials.gov); and (5) contact with individual investigators.

Study Selection

We included randomized, placebo-controlled, parallel-group trials that studied SSRIs as well as other second-generation agents in children and adolescents (<19 years) with MDD, OCD, or non-OCD anxiety disorders (TABLE 1). Trials were included if efficacy or treatment-emergent data on suicidal ideation/suicide attempt were available for both antidepressant-treated and placebo-treated participants. For the majority of studies, data on suicidal ideation/suicide attempt were obtained from the FDA report.[1,2] For studies not included in the FDA review, data on suicidal ideation/suicide attempt were obtained either from the principal investigators of each study[11,12,30,31,33] or from study reports.[10,18]

We excluded trials that used a crossover design[35]; had only an active comparator group[36]; only randomized treatment responders[37]; provided adjunctive cognitive behavioral therapy to all patients[38]; were currently recruiting patients (www.clinicaltrials.gov NCT00107120, NCT00352768, NCT00150306, and NCT00052078); studied anxiety-related indications other than separation, social, or generalized anxiety disorder[39,40]; or for which the primary author could not provide data.[41]

Methodological Quality Assessment

The quality of published trial reports for which data were available was independently rated by 2 coauthors (J.A.B., C.B.S.) according to the criteria of Detsky et al,[42] with final quality ratings based on consensus (intraclass correlation coefficient between raters, 0.94; 95% confidence interval [CI], 0.92 to 0.95) (Table 1).

Outcomes

The primary study-defined measure of treatment response and the prospectively identified scalar variable assessing change in symptoms from baseline to the end of treatment were the efficacy outcomes used for this meta-analysis. For studies that were included in the FDA analysis,[1,2] the primary risk outcome was suicidal ideation/suicide attempt (Box), as rated from suicidal adverse event narratives by an independent panel of suicide experts assembled by Columbia University on behalf of the FDA[3]; a breakdown of suicidal ideation/suicide attempt by age and type (suicidal ideation, suicide attempt/preparatory actions toward imminent suicidal behavior) was provided by the study author (T.A. Hammad, MD, PhD, MSc, MS, US Food and Drug Administration, written communication, October 3 and December 19, 2006). For studies not included in the FDA analysis,[10-12,18,30,31,33] we rated suicidal ideation/suicide attempt according to the Columbia coding scheme.[3]

Data Analysis

Trial characteristics were compared among treatment indications by using standard parametric and nonparametric

 ©2007 American Medical Association. All rights reserved.

Downloaded from www.jama.com at Ohio State University on May 5, 2009

statistics. The primary dichotomous outcomes (eg, symptomatic response) were expressed as Mantel-Haenszel risk differences, indicating the drug-placebo difference in the proportion of participants with each specific outcome. Use of risk differences permits all trials, including those with no events, to be included in analyses.

Table 1. Characteristics of Placebo-Controlled Trials of Antidepressants in Children and Adolescents, by Indication

Source	Intervention	No. of Patients Randomized	Age Range, y	No. of Treatment wk	No. of Study Sites	Country	Published	Quality[a]	Placebo Run-in Period	Funding Source	Average Duration of Illness, mo	Female, %
						Major Depressive Disorder						
Simeon et al,[23] 1990	Fluoxetine (20-60 mg/d) or placebo	40	13-18	6	1	Canada	Yes	0.40	Yes	Industry	NA	55
Emslie et al,[4] 1997	Fluoxetine (20 mg/d) or placebo	96	7-17	8	1	United States	Yes	0.93	Yes	NIMH	3	46
Keller et al,[14] 2001	Paroxetine (20-40 mg/d) or placebo	180[b]	12-18	8	12	United States, Canada	Yes	0.85	No	Industry	14	64
Emslie et al,[24] 2002	Fluoxetine (10 mg/d for 1 wk, then 20 mg/d) or placebo	219	8-17	9	16	United States	Yes	0.88	Yes	Industry	14	49
Wagner et al,[15] 2003	Sertraline (50-200 mg/d) or placebo	376	6-17	10	53	United States, India, Canada, Costa Rica, Mexico	Yes	0.95	No	Industry	NA	51
TADS Study Team,[5] 2004	Fluoxetine (10-40 mg/d) or placebo	221[c]	12-17	12	13	United States	Yes	1.00	No	NIMH[d]	8 (median)	54
Berard et al,[17] 2006	Paroxetine (20-40 mg/d) or placebo	286	13-18	12	33	International[e]	Yes	0.97	Yes	Industry	NA	66
Emslie et al,[16] 2006	Paroxetine (10-50 mg/d) or placebo	206	7-17	8	41	United States, Canada	Yes	0.98	No	Industry	26	47
von Knorring et al,[25] 2006	Citalopram (10-40 mg/d) or placebo	244	13-18	12	31	International[f]	Yes	0.49	No	Industry	NA	74
Wagner et al,[19] 2004	Citalopram (20-40 mg/d) or placebo	178	7-17	8	21	United States	Yes	0.66	Yes	Industry	20	53
Wagner et al,[18] 2006	Escitalopram (10-20 mg/d) or placebo	268	6-17	8	25	United States	Yes	0.90	Yes	Industry	16	52
CN104-141[26][g]	Nefazodone (100-600 mg/d) or placebo	206	12-17[h]	8	15	United States	No	ND	No	Industry	17	59
CN104-187[2,27]	Nefazodone (100-300 or 200-600 mg/d) or placebo	284	7-17	8	28	United States	No	ND	No	Industry	NA	49
003-045[27,28][i]	Mirtazapine (15-45 mg/d) or placebo	259	7-17	8	34	United States	No	ND	No	Industry	NA	52
Emslie et al[29]	Venlafaxine (37.5-225 mg/d) or placebo	367	7-17	8+taper	51[j]	United States	In press	0.80	Yes	Industry	21	46

(continued)

©2007 American Medical Association. All rights reserved.

Downloaded from www.jama.com at Ohio State University on May 5, 2009

Table 1. Characteristics of Placebo-Controlled Trials of Antidepressants in Children and Adolescents, by Indication (cont)

Source	Intervention	No. of Patients Randomized	Age Range, y	No. of Treatment wk	No. of Study Sites	Country	Published	Quality[a]	Placebo Run-in Period	Funding Source	Average Duration of Illness, mo	Female, %
Obsessive-Compulsive Disorder												
March et al,[7] 1998	Sertraline (25-200 mg/d) or placebo	189	6-17	12	12	United States	Yes	0.86	Yes	Industry	56	47
Geller et al,[8] 2001	Fluoxetine (20-60 mg/d) or placebo	103	7-17	13	21	United States	Yes	0.91	No	Industry	NA	52
Riddle et al,[9] 2001	Fluvoxamine (50-200 mg/d) or placebo	120	8-17	10	17	United States	Yes	0.84	Yes	Industry	43	47
Liebowitz et al,[30] 2002	Fluoxetine (20-80 mg/d) or placebo	43	6-18	8	2	United States	Yes	0.72	No	NIMH/ industry	NA	42
Geller et al,[6] 2004	Paroxetine (10-50 mg/d) or placebo	207	7-17	10	39	United States, Canada	Yes	0.96	No	Industry	51	42
POTS Study Team,[10] 2004	Sertraline (25-200 mg/d) or placebo	56[k]	7-17	12	3	United States	Yes	1.00	No	NIMH[d]	NA	45
Non–Obsessive-Compulsive Anxiety Disorder												
Generalized Anxiety Disorder												
Rynn et al,[31] 2001	Sertraline (25 mg/d for 1 wk, then 50 mg/d) or placebo	22	5-17	9	1	United States	Yes	0.91	No	NIMH	NA	23
Rynn et al,[32] 2007	Venlafaxine (37.5-225 mg/d) or placebo	323	6-17	8+taper	59	United States	Yes	0.83	Yes	Industry	39	43
Social Anxiety Disorder/Social Phobia												
Wagner et al,[13] 2004	Paroxetine (10-50 mg/d) or placebo	322	8-17	16	38	United States, Canada, Belgium, South Africa	Yes	0.95	No	Industry	NA	50
March et al[33,34]	Venlafaxine (37.5-225 mg/d) or placebo	293	8-17	16+taper	44	United States	In press	ND	No	Industry	58	57
Social Phobia or Separation/Generalized Anxiety Disorder												
RUPP Anxiety Study Group,[11] 2001	Fluvoxamine (50-300 mg/d) or placebo	128	6-17	8	5	United States	Yes	0.80	No	NIMH/ industry	NA	49
Birmaher et al,[12] 2003	Fluoxetine (10 mg/d for 1 wk, then 20 mg/d) or placebo	74	7-17	12	1	United States	Yes	0.88	No	NIMH[d]	NA	54

Abbreviations: NA, not available; ND, not determined; NIMH, National Institute of Mental Health.
[a] Based on adequacy of randomization, study entry criteria, outcome measures, therapeutic and placebo procedures, and statistical analyses. Individual items were summed and divided by the total number of applicable items to produce a total score ranging from 0 to 1, where higher scores denote greater methodological quality.
[b] No. of patients randomized to paroxetine and placebo groups (275 patients in total randomized).
[c] No. of patients randomized to fluoxetine only and placebo groups (439 patients in total randomized).
[d] Study medication and matching placebo provided by the drug manufacturer.
[e] 33 centers in Belgium, Italy, Spain, United Kingdom, the Netherlands, Canada, South Africa, United Arab Emirates, Argentina and Mexico.
[f] Thirty-one centers in Sweden, Denmark, Estonia, Finland, Germany, Norway, and Switzerland.
[g] Reported as abstract/poster.
[h] Patients aged 18 years were included prior to a protocol amendment; 7 nefazodone and 4 placebo patients were aged 18 years at baseline.[27]
[i] Trial comprised 2 studies. Study 1 randomized 126 patients; study 2, 133 patients.
[j] Data from 1 study site were excluded from efficacy analyses.
[k] No. of patients randomized to sertraline only and placebo groups (112 patients in total randomized).

 ©2007 American Medical Association. All rights reserved.

Downloaded from www.jama.com at Ohio State University on May 5, 2009

We used the DerSimonian and Laird random-effects model[43] to obtain a pooled estimate of the risk difference and corresponding 95% CIs. For the primary scalar measure of efficacy, we calculated the pooled random-effects mean difference and 95% CI between the treated and placebo groups, divided by the pooled standard deviation (Hedges *g*).[43,44] The random-effects approach to meta-analysis assumes that there is heterogeneity across studies that is not fully accounted for by observed covariates, such as age, and provides more conservative estimates of effect by incorporating within- and between-study heterogeneity, whereas the fixed-effects approach assumes that the effect size is constant across studies. To test the validity of the DerSimonian and Laird model, we performed a sensitivity analysis comparing inferences of the random-effects model with those of a fixed-effects model. Estimates, CIs, and *P* values based on the 2 models were very close when the test for homogeneity did not reject; when it did, the random-effects approach gave wider CIs and larger *P* values, as expected (data available on request). When outcomes were significant, we calculated the number needed to treat to benefit (NNT) and number needed to treat to harm (NNH) according to the methods of Sackett et al,[45] with 95% CIs computed using the method of Altman.[46]

To provide a common effect-size comparison between the primary categorical and scalar efficacy outcomes, we computed *g* for the dichotomous response variable of each study by means of transformation from the original log odds ratio scale to the standardized mean difference and then from this difference to *g*.[47] Heterogeneity between trials was assessed by the Cochran *Q* statistic ($P \leq .10$) and the I^2 statistic, a transformation of *Q* that indicates the percentage of variation in the effect-size estimate attributable to heterogeneity rather than sampling error.[48] Sensitivity analyses were conducted by iteratively deleting each study and calculating the resulting effect sizes. As a comparison with the FDA's analyses,[1,2] we also used fixed- and random-effects models to compute the pooled risk differences and risk ratios (RRs) of suicidal ideation/suicide attempt, where an RR greater than 1 indicates a higher relative risk for patients treated with antidepressants than for those treated with placebo. In contrast to the FDA report, we estimated pooled risk differences for each indication and combined 6 trials into 3, because these trials were pooled for publication.[15,29,32] In trials in which no suicidal ideation/suicide attempt occurred in 1 of the trial groups, 0.5 was added to each of the 4 cells to reduce bias and variance of the RR estimates, but trials without any events could not be included in the pooled estimate. We tested for a treatment × indication × suicidal ideation/suicide attempt interaction using an exact homogeneity test.

Secondary analyses included age-grouped (<12 or 13 years [depending on study definition] vs ≥12 or 13 years) comparisons of efficacy and suicidal ideation/suicide attempt, and tests of continuous and categorical moderators. For ease of interpretation, we refer to the younger age group as younger than 12 years and to the older age group as 12 years or older for all comparisons. For continuous moderators, regression was used to explore whether methodological quality, number of treatment sites, proportion of female participants, and duration of illness at baseline influenced outcome. Continuous moderators that showed an association with outcome were dichotomized by median split and reanalyzed as categorical variables. Trial-level categorical moderators of outcome, namely publication status, primary funding source, study location, drug class, and use of placebo run-in period were also examined. Publication bias was assessed visually using a funnel plot and quantitatively using an adjusted rank correlation test[49] and a regression procedure to measure funnel plot asymmetry.[50] To reduce heterogeneity in anxiety disorders trials, we excluded 1 small study[31] with very large treatment effects from all regression and moderator analyses of efficacy outcomes. Statistical analyses were performed with Comprehensive Meta-analysis version 2.1 (Biostat, Englewood, NJ), SPSS version 13.1 (SPSS Inc, Chicago, Ill), and StatXact-7 (Cytel Software Corp, Cambridge, Mass). We present *P* values and CIs unadjusted for the multiple primary and secondary hypotheses tested. $P < .05$ was used to determine statistical significance. The reader can make adjustments with such methods as Bonferroni.

RESULTS

Data Flow

Our search identified 27 prospective, randomized, placebo-controlled clinical trials that compared the relative efficacy of antidepressants against placebo in patients younger than 19 years for the treatment of MDD (15 trials, n=3430), OCD (6 trials, n=718), and non-OCD anxiety disorders (6 trials, n=1162) (FIGURE). Response rates were available for all but 2 MDD trials,[23,51] and a primary scalar measure of efficacy was available for all trials. Complete data with regard to suicidal ideation/suicide attempt were available except in 1 trial, in which data on suicidal ideation/suicide attempt were obtained from only 1 of 2 treatment sites.[30]

Study Characteristics

Characteristics of the 27 included trials are shown in Table 1. The median number of treatment weeks for MDD, OCD, and non-OCD anxiety disorders was 8, 11, and 11, respectively. Almost half (7/15 [47%]) of the MDD trials used a placebo run-period, compared with 2 (33%) of 6 OCD trials, and 1 of 6 (17%) non-OCD anxiety disorders trials ($P = .51$). All but 4 of the studies used a flexible dosing schedule. The majority (23/27 [85%]) of studies were multisite (median No. of sites, 21; interquartile range, 5-36), with no differences in number of study sites by treatment indication ($P = .63$). Most studies were conducted solely in the United States

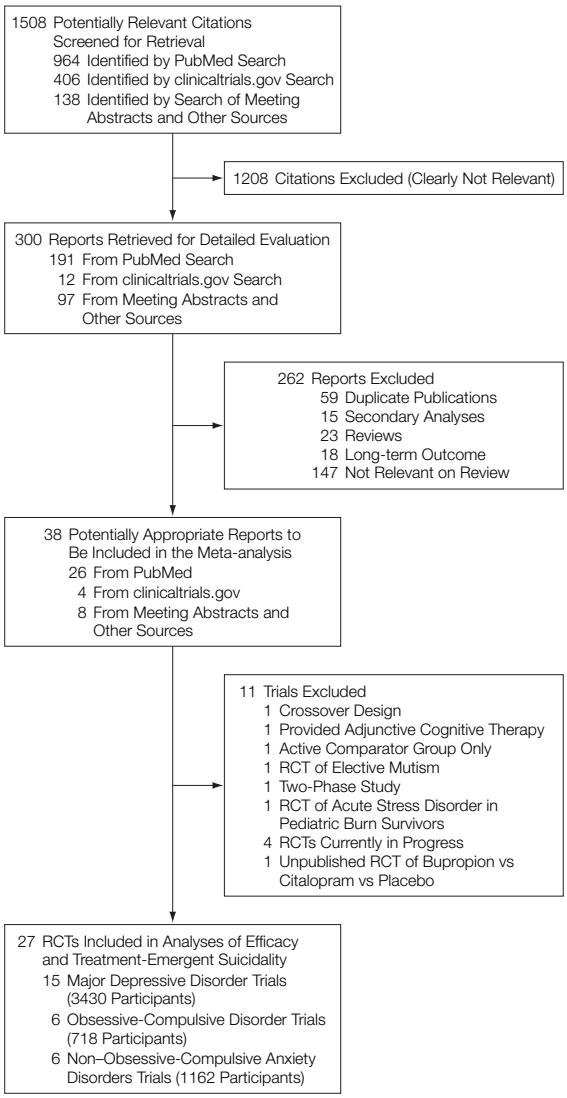
©2007 American Medical Association. All rights reserved.

Downloaded from www.jama.com at Ohio State University on May 5, 2009

(19/27 [70%]). All OCD and non-OCD anxiety disorders trials were published or in press, compared with 12 (80%) of 15 MDD trials ($P=.38$). The median overall Detsky score for the 23 trials in which quality was assessed was 0.88 (interquartile range, 0.80-0.95), indicating generally good methodological quality. Failure to analyze data on a strictly intent-to-treat basis and an inadequate description of the randomization and exclusionary procedures were the most common methodological flaws. There were no differences in methodological quality by treatment indication ($P=.91$).

In MDD trials, the Clinical Global Inventory–Improvement scale[52] was used as a primary measure of response in 8 (53%) of 15 trials. The Children's Depression Rating Scale–Revised[53] was used as the primary scalar measure of efficacy in 11 (73%) of 15 trials. In OCD trials, a reduction of 25% or more on scores from the Children's Yale-Brown Obsessive Compulsive Scale[54,55] was used as the primary measure of response in 3 of 6 trials. All OCD trials used change in the score from this latter scale, from baseline to end of treatment, as the primary scalar measure of efficacy. In non-OCD anxiety disorders trials, the Clinical Global Inventory–Improvement scale was used as the primary measure of response in all 6 trials, and the Pediatric Anxiety Rating Scale[56] was used as the primary scalar measure of efficacy in 2 (33%) of 6 studies.[11,12]

Figure. Study Selection



RCT indicates randomized controlled trial.

Treatment Efficacy and Risk of Suicidal Ideation/Suicide Attempts

Efficacy outcome data are summarized in eTable 1,[57,58] eTable 2 (http://www.jama.com), and **Table 2**. Treatment-emergent suicidal ideation/suicide attempt data are summarized in **Table 3** and **Table 4**, where separate analyses of suicidal ideation and suicide attempt/preparatory actions are presented for comparison with the overall rates of suicidal ideation/suicide attempt.

Major Depressive Disorder. Based on data from 13 trials and 2910 participants, pooled absolute rates of response were 61% (95% CI, 58% to 63%) in participants treated with antidepressants and 50% (95% CI, 47% to 53%) in those treated with placebo, yielding a pooled risk difference of 11% (95% CI, 7% to 15%), an NNT of 10 (95% CI, 7 to 15), and a g of 0.25 (95% CI, 0.16 to 0.34). A similar effect was found in pooled analyses of continuous measures of mean improvement in depression symptomatology ($g=0.20$; 95% CI, 0.12 to 0.29). Pooled absolute rates of suicidal ideation/suicide attempt were 3% (95% CI, 2% to 4%) in antidepressant-treated participants and 2% (95% CI, 1% to 2%) in those receiving placebo. The pooled risk difference was 1% (95% CI, –0.1% to 2%; $P=.08$), so the NNH was 112.

Obsessive-Compulsive Disorder. In 6 OCD trials of 705 participants, pooled rates of response were 52% (95% CI, 46% to 57%) in SSRI-treated participants and 32% (95% CI, 27% to 37%) in those receiving placebo, and the pooled risk difference was 20% (95% CI, 13% to 27%), yielding an NNT of 6 (95% CI, 4 to 8), and a g of 0.48 (95%

 ©2007 American Medical Association. All rights reserved.

Downloaded from www.jama.com at Ohio State University on May 5, 2009

CI, 0.30 to 0.65). The pooled estimate of *g* for the scalar measure of efficacy was 0.41 (95% CI, 0.26 to 0.56). Pooled absolute rates of suicidal ideation/suicide attempt were 1% (95% CI, 0% to 2%) in SSRI-treated participants and 0.3% (95% CI, –0.3% to 1%) in those receiving placebo, and the pooled risk difference was 0.5% (95% CI, –1% to 2%; $P=.57$), for an NNH of 200.

Non-OCD Anxiety Disorders. In 6 non-OCD anxiety disorders trials of 1136 participants, pooled rates of response were 69% (95% CI, 65% to 73%) in antidepressant-treated participants and 39% (95% CI, 35% to 43%) in those receiving placebo, and the pooled risk difference was 37% (95% CI, 23% to 52%), yielding an NNT of 3 (95% CI, 2 to 5). While all studies favored antidepressant treatment, there was large variation in the degree of benefit across trials (risk difference range, 19%-82%; $Q_5=32.88$; $P<.001$). One small pilot study[31] had the highest point estimate. Exclusion of this trial diminished the prior result to a risk difference of 30% (95% CI, 19% to 41% [NNT, 4; 95% CI, 3 to 6]); however, significant heterogeneity remained ($Q_4=14.71$, $P=.01$). For the primary scalar measure of efficacy, we calculated the pooled estimate of *g* after excluding the pilot study (0.69; 95% CI, 0.47 to 0.91; $Q_4=12.19$; $P=.02$), which was similar to the primary risk difference of response expressed as *g* (0.65; 95% CI, 0.52 to 0.79). Pooled absolute rates of suicidal ideation/suicide attempt were 1% (95% CI, 0.2% to 2%) in antidepressant-treated participants and 0.2% (95% CI, –0.2% to 0.5%) in those receiving placebo, and the pooled risk difference was 0.7% (95% CI, –0.4% to 2%; $P=.21$), yielding an NNH of 143.

Suicidal Ideation/Suicide Attempts in Placebo-Treated Participants

Among participants treated with placebo, the risk of suicidal ideation/suicide attempt was greater in MDD trials compared with non-OCD anxiety disorders trials (odds ratio, 9.9; 95% CI, 1.6 to 406.3) and OCD trials (odds ratio, 5.8; 95% CI, 0.9 to 237.3); these effects were limited to adolescent participants. There was no evidence of a treatment × indication × suicidal ideation/suicide attempt interaction ($P=.53$).

Suicidal Ideation/Suicide Attempts in the FDA and Present Analyses

As shown in TABLE 5, our estimates of the risk difference for suicidal ideation/suicide attempt are lower than those reported by the FDA because we used a random-effects model to combine data, whereas the FDA used a fixed-effects model, and because we included 7 additional studies,[10-12,18,30,31,33] 3 of which were not available at the time of the FDA report.[10,18,33] The FDA used primarily fixed-effects models to combine data from the randomized trials but also conducted random-effects models as part of a sensitivity analysis. The estimates derived from the latter analyses were more similar to our results, since random-effects models tended to yield smaller RRs and risk differences.

Continuous Moderators of Outcome

In MDD trials, the number of trial sites was inversely associated with risk differences in response ($\beta=-.002$, $Q_1=3.8$, $P=.05$) and the scalar measure of efficacy ($\beta=-.01$, $Q_1=3.7$, $P=.05$), suggesting a decrease in the magnitude of antidepressant treatment effects as the number of study sites increased. In 9 of 15 MDD trials for which data were available, duration of the depressive episode at intake was inversely associated with risk differences in response ($\beta=-.01$, $Q_1=5.4$, $P=.02$) and the scalar measure of efficacy ($\beta=-.02$, $Q_1=9.4$, $P=.002$), indicating less effi-

Table 2. Overall and Age-Grouped Effects of Antidepressant Medication on Pooled Measures of Efficacy, by Indication[a]

		Within Group							Effect of Age		
		No. Responses/ No. of Participants (%)				Heterogeneity					
Age Grouping	No. of Trials	Treatment	Placebo	Risk Difference, % (95% CI)[b]	*P* Value	Q_{df} Within	*P* Value	Variance Explained, %	Q_{df} Between	*P* Value	Variance Explained, %
Major Depressive Disorder											
All participants	13	944/1552 (61)	678/1358 (50)	11 (7 to 15)	<.001	14.3_{12}	.28	16	NT	NT	NT
Children	5	175/269 (65)	156/270 (58)	7 (–1 to 15)	.08	3.8_4	.43	0	1.25	.26	7
Adolescents	10	563/901 (62)	391/790 (49)	13 (8 to 17)	<.001	13.4_9	.14	33			
Obsessive-Compulsive Disorder											
All participants	6	187/363 (52)	110/342 (32)	20 (13 to 27)	<.001	1.2_5	.94	0	NT	NT	NT
Children	4	98/157 (62)	55/137 (40)	24 (13 to 35)	<.001	0.1_3	.99	0	0.40	.53	17
Adolescents	4	59/121 (49)	37/114 (32)	18 (5 to 30)	.01	1.8_3	.61	0			
Non–Obsessive-Compulsive Anxiety Disorders											
All participants	6	387/562 (69)	223/574 (39)	37 (23 to 52)	<.001	32.9_5	<.001	85	NT	NT	NT
Children	3	62/88 (70)	37/88 (42)	29 (15 to 43)	<.001	1.6_2	.45	0	3.71	.054	58
Adolescents	3	134/173 (77)	54/168 (32)	46 (36 to 55)	<.001	1.1_2	.58	0			

Abbreviations: CI, confidence interval; NT, not tested.
[a] Depending on study criteria, children were defined as being younger than 12 years or younger than 13 years; adolescents, as 12 years or older or 13 years or older.
[b] Overall risk difference estimated using the DerSimonian and Laird method,[43] which may vary from the difference in the pooled response rates.

©2007 American Medical Association. All rights reserved.

Downloaded from www.jama.com at Ohio State University on May 5, 2009

cacy with longer duration of illness. Study quality and proportion of female participants were not associated with outcome.

In OCD and non-OCD anxiety disorders trials, no patient characteristics or elements of trial design were associated with outcome ($P \geq .20$ for all).

Categorical Moderators of Outcome

In the 10 MDD trials for which age-grouped data were available,[4,5,14-17,24-26,29] the pooled risk difference in response was lower in children than in adolescents and not significantly different than zero, in part related to a higher placebo response in children ($\chi^2_1 = 5.5$, $P = .02$) (Table 2). Limiting trials to only fluoxetine studies resulted in statistically significant pooled risk differences in response that were similar for children (21%; 95% CI, 4% to 37%; $P = .01$) as well as adolescents (20%; 95% CI, 7% to 33%; $P = .002$). The trial-

Table 3. Differences in Rates of Treatment-Emergent Suicidal Ideation, Suicide Attempt, or Preparatory Actions Toward Imminent Suicidal Behavior for Antidepressant-Treated and Placebo-Treated Groups, by Indication

Drug	Source	Rate of Suicidal Ideation or Suicide Attempt/Preparatory Actions, No. Events/Total (%)		Risk Difference, % (95% CI)
		Treatment	Placebo	
	Major Depressive Disorder			
Fluoxetine	Simeon et al,[23] 1990	0/21 (0)	1/19 (5)	–5 (–18 to 8)
	Emslie et al,[4] 1997	2/48 (4)	2/48 (4)	0 (–8 to 8)
	Emslie et al,[24] 2002	6/109 (6)	6/110 (6)	0 (–6 to 6)
	TADS Study Team,[5] 2004	9/109 (8)	2/112 (2)	7 (1 to 12)[a]
	Pooled estimates	17/287 (6)	11/289 (4)	2 (–3 to 6)
Paroxetine	Keller et al,[14] 2001	4/93 (4)	1/88 (1)	3 (–2 to 8)
	Berard et al,[17] 2006	6/180 (3)	2/95 (2)	1 (–3 to 5)
	Emslie et al,[16] 2006	2/104 (2)	1/102 (1)	1 (–2 to 4)
	Pooled estimates	12/377 (3)	4/285 (1)	2 (–1 to 4)
Sertraline	Wagner et al,[15] 2003	5/189 (3)	2/184 (1)	2 (–1 to 4)
Citalopram	von Knorring et al,[25] 2006	9/124 (7)	5/120 (4)	3 (–3 to 9)
	Wagner et al,[19] 2004	1/93 (1)	2/85 (2)	–1 (–5 to 3)
Escitalopram	Wagner et al,[18] 2006[b]	1/131 (1)	2/133 (2)	–1 (–3 to 2)
Citalopram/escitalopram	Pooled estimates	11/348 (3)	9/338 (3)	–0 (–3 to 2)
Venlafaxine	Emslie et al[29]	8/182 (4)	0/179 (0)	4 (1 to 8)[c]
Nefazodone	CN104-141[26]	0/95 (0)	0/95 (0)	0 (–2 to 2)
	CN104-187	0/184 (0)	0/94 (0)	0 (–2 to 2)
	Pooled estimates	0/279 (0)	0/189 (0)	0 (–1 to 1)
Mirtazapine	003-045	1/170 (1)	0/89 (0)	1 (–2 to 3)
	Obsessive-Compulsive Disorder			
Fluoxetine	Geller et al,[8] 2001	1/71 (1)	0/32 (0)	1 (–4 to 7)
	Liebowitz et al,[30] 2002[b,d]	0/15 (0)	0/14 (0)	0 (–13 to 13)
	Pooled estimates	1/86 (1)	0/46 (0)	1 (–4 to 6)
Fluvoxamine	Riddle et al,[9] 2001	2/57 (4)	0/63 (0)	4 (–2 to 9)
Paroxetine	Geller et al,[6] 2004	1/99 (1)	0/107 (0)	1 (–2 to 4)
Sertraline	March et al,[7] 1998	0/92 (0)	1/95 (1)	–1 (–4 to 2)
	POTS Study Team,[10] 2004[b]	0/28 (0)	0/28 (0)	0 (–7 to 7)
	Pooled estimates	0/120 (0)	1/123 (1)	–1 (–4 to 2)
	Non–Obsessive-Compulsive Anxiety Disorders			
Fluoxetine	Birmaher et al,[12] 2003[b]	0/37 (0)	0/37 (0)	0 (–5 to 5)
Fluvoxamine	RUPP Anxiety Study Group,[11] 2001[b]	0/63 (0)	0/65 (0)	0 (–3 to 3)
Paroxetine	Wagner et al,[13] 2004	3/165 (2)	0/156 (0)	2 (–1 to 4)
Sertraline	Rynn et al,[31] 2001[b]	0/11 (0)	0/11 (0)	0 (–16 to 16)
Venlafaxine	Rynn et al,[32] 2007	1/157 (1)	1/163 (1)	0 (–2 to 2)
	March et al[33,34,b]	2/140 (1)	0/150 (0)	1 (–1 to 4)
	Pooled estimates	3/297 (1)	1/313 (0)	1 (–1 to 2)

Abbreviation: CI, confidence interval.
[a] Number needed to treat to harm = 16 (95% CI, 9 to 125).
[b] Data not from Hammad et al.[1]
[c] Number needed to treat to harm = 23 (95% CI, 14 to 77).
[d] Suicidal ideation/suicide attempt data were obtained from 1 of 2 study sites.

 ©2007 American Medical Association. All rights reserved.

Downloaded from www.jama.com at Ohio State University on May 5, 2009

level variables of drug class, publication status, and placebo run-in period were not significant moderators (eTable 3 [http://www.jama.com]). The potential role of funding source was not examined, because trials funded by the National Institute of Mental Health all investigated the efficacy of fluoxetine.

In OCD trials, the pooled measures of efficacy outcome were comparable in children and adolescents, and the use of a placebo run-in period was not a significant moderator of outcome.

In the 3 non-OCD anxiety disorders studies for which age stratification was possible,[11-13] there was a trend for the risk difference to be larger among adolescents (46% vs 29%, Q_1=3.71, P=.05) (Table 2). Trials of SSRIs were associated with larger effect sizes of efficacy favoring antidepressants compared with non-SSRI trials and with eliminating intertrial heterogeneity (eTable 3 [http://www.jama.com]).

With respect to suicidal ideation/suicide attempt, none of the patient

Table 4. Overall Within-Group Effects of Antidepressant Medication on Pooled Measures of Suicidal Ideation and Suicide Attempt/Preparatory Actions Toward Imminent Suicidal Behavior, by Indication[a]

Indication Type	Age Grouping	Rate of Suicidal Ideation or Suicide Attempts/Preparatory Acts, No. Events/Total (%)		Risk Difference, % (95% CI)[b]	P Value	Hetrogeneity		
		Treatment	Placebo			Q_{df}	P Value	Variance Explained, %
Major Depressive Disorder[c]								
Suicidal ideation or suicide attempt/preparatory actions	All participants	54/1832 (3)[d]	26/1553 (2)[d]	1 (–0 to 2)	.08	19.4_{14}	.15	28
	Children	12/567 (2)	5/478 (1)	1 (–1 to 3)	.20	5.5_{8}	.71	0
	Adolescents	42/1271 (3)	21/1077 (2)	1 (–0 to 2)	.17	13.1_{14}	.52	0
Suicide attempt/preparatory actions	All participants	24/1832 (1)	10/1553 (1)	0 (–0 to 1)	.26	9.1_{14}	.83	0
	Children	4/567 (1)	2/478 (0)	0 (–1 to 2)	.53	1.7_{8}	.99	0
	Adolescents	20/1271 (2)	8/1077 (1)	0 (–0 to 1)	.32	7.8_{14}	.90	0
Suicidal ideation	All participants	30/1832 (2)	16/1553 (1)	0 (–0 to 1)	.23	15.0_{14}	.38	7
	Children	8/567 (1)	3/478 (1)	1 (–1 to 2)	.29	2.9_{8}	.94	0
	Adolescents	22/1271 (2)	13/1077 (1)	0 (–0 to 1)	.32	9.8_{14}	.77	0
Obsessive-Compulsive Disorder[e]								
Suicidal ideation or suicide attempt/preparatory actions	All participants	4/362 (1)	1/339 (0)	1 (–1 to 2)	.57	2.6_{5}	.76	0
	Children	0/206 (0)	1/185 (1)	–0 (–3 to 2)	.74	0.4_{5}	.99	0
	Adolescents	4/156 (3)	0/154 (0)	2 (–2 to 5)	.38	1.9_{5}	.87	0
Suicide attempt/preparatory actions	All participants	1/362 (0)	0/339 (0)	0 (–1 to 1)	.91	0.3_{5}	>.99	0
	Children	0/198 (0)	0/180 (0)	0 (–2 to 2)	>.99	0.0_{5}	>.99	0
	Adolescents	1/164 (1)	0/159 (0)	0 (–3 to 3)	.91	0.3_{5}	>.99	0
Suicidal ideation	All participants	3/362 (1)	1/339 (0)	0 (–1 to 2)	.69	2.5_{5}	.78	0
	Children	0/198 (0)	1/180 (1)	–0 (–3 to 2)	.73	0.4_{5}	>.99	0
	Adolescents	3/164 (2)	0/159 (0)	1 (–2 to 5)	.44	1.7_{5}	.89	0
Non–Obsessive-Compulsive Anxiety Disorders[f]								
Suicidal ideation or suicide attempt/preparatory actions	All participants	6/573 (1)	1/582 (0)	1 (–0 to 2)	.21	2.2_{5}	.82	0
	Children	1/199 (1)	0/213 (0)	1 (–2 to 3)	.61	0.3_{4}	.99	0
	Adolescents	5/360 (1)	1/356 (0)	1 (–1 to 3)	.25	2.9_{4}	.54	0
Suicide attempt/preparatory actions	All participants	1/573 (0)	1/582 (0)	0 (–1 to 1)	.99	0.0_{5}	>.99	0
	Children	1/199 (1)	0/213 (0)	1 (–2 to 3)	.61	0.3_{4}	.99	0
	Adolescents	0/360 (0)	1/356 (0)	–0 (–1 to 1)	.83	0.6_{4}	.97	0
Suicidal ideation	All participants	5/573 (1)	0/582 (0)	1 (–0 to 1)	.29	3.2_{5}	.67	0
	Children	0/199 (0)	0/213 (0)	0 (–2 to 2)	>.99	0.0_{4}	>.99	0
	Adolescents	5/360 (1)	0/356 (90)	1 (–1 to 3)	.17	2.1_{4}	.73	0

Abbreviation: CI, confidence interval.
[a] Depending on study criteria, children were defined as being younger than 12 years or younger than 13 years; adolescents, as 12 years or older or 13 years or older. Effect of age was not statistically significant (P≥.35 for all).
[b] Overall risk difference estimated using the DerSimonian and Laird method,[43] which may vary from the difference in the pooled risk rates.
[c] No. of trials: n = 15, all participants; n = 9, children; n = 15, adolescents.
[d] Sum of children and adolescents does not equal sum of all participants because in several trials numbers for age-grouped data were based on intent-to-treat population instead of safety population.
[e] No. of trials: n = 6, all participants; n = 6, children; n = 6, adolescents.
[f] No. of trials: n = 6, all participants; n = 5, children; n = 5, adolescents.

©2007 American Medical Association. All rights reserved.

Downloaded from www.jama.com at Ohio State University on May 5, 2009

characteristics or trial features was an important moderator in MDD, OCD, and non-OCD anxiety disorders trials.

Publication Bias

Separate analyses of publication bias were conducted for MDD, OCD, and non-OCD anxiety disorders trials. For each treatment indication, there was no evidence of publication bias based on visual analysis of the funnel plots, the adjusted rank correlation tests, and the regression intercept approach (data available on request).

COMMENT

This meta-analysis of all available randomized clinical trials of antidepressant treatment of pediatric MDD, OCD, and non-OCD anxiety disorders shows evidence of efficacy for all 3 indications, although the effects were strongest for non-OCD anxiety disorders, intermediate for OCD, and more modest in MDD. We found some evidence that age moderated outcome both for the treatment of depression and anxiety, and duration of depression was also a moderator. One trial-level moderator was found in studies of MDD, in which efficacy was inversely proportional to the number of trial sites. Consistent with the analyses of the FDA,[1] we found evidence of an overall small but increased risk of treatment-emergent suicidal ideation/suicide attempt. However, the pooled random-effects risk differences of suicidal ideation/suicide attempt for each indication were all less than 1%. There were no completed suicides in these trials. Before we discuss each of these findings, we first place these results within the limitations of this study.

Table 5. Differences in Risk of Treatment-Emergent Suicidal Ideation and Suicide Attempt/Preparatory Actions Toward Imminent Suicidal Behavior for Antidepressant-Treated and Placebo-Treated Groups: FDA Review and Present Meta-analysis, by Indication[a]

Measure of Effect	Source	No. of Trials	Pooled Effect-Size Estimate of Suicidal Ideation/Suicide Attempt/Preparatory Actions, % (95% CI)	
			Fixed-Effects Model	Random-Effects Model
		Overall		
Risk ratio	Hammad et al,[1] 2006	20	2.0 (1.3 to 3.0)	1.8 (1.1 to 2.8)
	Present analysis[b,c]	20	1.9 (1.3 to 2.9)	1.7 (1.1 to 2.7)
Risk difference	Hammad et al,[1] 2006	23	1.5 (0.6 to 2.4)	0.8 (0.1 to 1.5)
	Present analysis[b,c]	27	1.3 (0.5 to 2.0)	0.7 (0.1 to 1.3)[d]
		Major Depressive Disorder		
Risk ratio	Hammad et al,[1] 2006	14	1.9 (1.2 to 3.0)	1.7 (1.1 to 2.8)
	Present analysis[b]	13	1.9 (1.2 to 2.9)	1.6 (1.0 to 2.7)
Risk difference	Hammad et al,[1] 2006	16	1.7 (0.5 to 2.8)	1.1 (0.0 to 2.1)
	Present analysis[b]	15	1.5 (0.4 to 2.6)	0.9 (–0.1 to 1.9)
		Obsessive-Compulsive Disorder		
Risk ratio	Hammad et al,[1] 2006	4	1.8 (0.5 to 7.1)	1.8 (0.4 to 8.5)
	Present analysis	4	1.8 (0.5 to 7.1)	1.8 (0.4 to 8.5)
Risk difference	Hammad et al,[1] 2006	4	0.9 (–1.0 to 2.8)	0.5 (–1.2 to 2.3)
	Present analysis	6	0.8 (–1.0 to 2.7)	0.5 (–1.2 to 2.2)
		Non–Obsessive-Compulsive Disorder		
Risk ratio	Hammad et al,[1] 2006	2	2.9 (0.5 to 18.8)	2.4 (0.3 to 18.3)
	Present analysis[c]	3	3.5 (0.7 to 17.1)	3.1 (0.6 to 16.8)
Risk difference	Hammad et al,[1] 2006	3	0.9 (–0.7 to 2.5)	0.7 (–0.8 to 2.3)
	Present analysis[c]	6	0.9 (–0.3 to 2.0)	0.7 (–0.4 to 1.8)

Abbreviations: CI, confidence interval; FDA, US Food and Drug Administration.
[a] Risk differences are presented as percentages. Wellbutrin trial 75 was not included in any analysis.
[b] Sertraline trials A0501001/A0501017 and venlafaxine trials 382/394 were pooled for analysis.
[c] Venlafaxine trials 396/397 were pooled for analysis.
[d] Number needed to treat to harm = 143 (95% CI, 77-1000).

The main limitations are those imposed on the meta-analytic venture, which is the quality and quantity of data available for meta-analysis. With relatively few trials in any of the 3 diagnostic categories, our ability to draw inferences about design and diagnostic moderators of treatment response and of suicidal ideation/suicide attempt are limited to major effects. Moreover, data on factors that might explain differences in outcome between trials relative to baseline differences in participants, dosing, or adherence to treatment are not consistently accrued in clinical trials and therefore were not routinely available for this meta-analysis. We did not adjust the *P* values for multiple comparisons, because the contrasts for the primary outcomes were planned and the secondary analyses were exploratory and should be regarded with caution. No study was designed to examine suicidal ideation/suicide attempt as a study outcome, and in fact most trials were conducted in patients who had been carefully screened to exclude youths at risk. Thus, unlike efficacy data for which the outcome is defined a priori, most studies only collected data on suicidal ideation/suicide attempt as part of adverse events reporting, which is generally retrospective and not systematically assessed. Finally, our risk analysis was limited to only suicidal ideation/suicide attempt. We did not consider other common adverse effects, such as activation, insomnia, and gastrointestinal tract symptoms, that may be more common in children than in adolescents,[59] or other adverse effects of the medication, such as disinhibition, mania, irritability, and agitation, any of which may precipitate suicidal ideation/suicide attempt.[60]

Adolescents appeared to respond better than children to antidepressants in trials of both depression and anxiety. While there was evidence of efficacy for antidepressant treatment for depressed adolescents across several antidepressant types, only 1 agent, fluoxetine, outperformed placebo in depressed children younger than 12

 ©2007 American Medical Association. All rights reserved.

Downloaded from www.jama.com at Ohio State University on May 5, 2009

years. The reason why depressed children seemed to respond better to fluoxetine compared with other agents is unclear but could be due to study quality, location, or properties of the medication itself, such as its long half-life. These results are consistent with recent reports examining the age-stratified performance of fluoxetine and other antidepressants in pediatric major depressive disorder[29,61-64] and suggest that the lack of a significant treatment effect may be due in part to a higher placebo response in children. The Treatment of Adolescent Depression Study (TADS)[5] found that fluoxetine showed a larger effect relative to placebo in more severely depressed individuals (effect size, 0.69 vs 0.39), so perhaps greater separation between drug and placebo would be expected in more severely ill children. Adolescents also showed a vigorous response to antidepressants for the treatment of anxiety compared with children, although children still showed a significant and positive effect. This may be because separation anxiety is more common in children than in adolescents and, at least in 1 study, did not appear to respond as well to antidepressant treatment as did the other anxiety disorders.[12] Despite some age differences in response, antidepressants appear to be more efficacious in the treatment of pediatric anxiety in both children and adolescents, compared with the effects found for depression. This may be due to chronicity and stability of anxiety disorders relative to depression[65] and greater homogeneity of children with anxiety disorders, compared with depressed children, some of whom do not go on to have recurrent depressive disorders.[66]

In depression trials, efficacy was inversely proportional to the duration of the depressive disorder. While these results should be interpreted with caution because there was a large amount of missing data (6/15 trials [40%]) for this variable, these findings were also reported in 1 large individual trial,[61] as well as in the Sequenced Treatment Alternatives to Relieve Depression (STAR-D) study in adults.[67] This suggests that efforts to identify depressed youth earlier in their depressive course may improve outcome. Given that anxiety is a frequent precursor of depression and that the efficacy of antidepressants for non-OCD anxiety disorders is larger than those for depression, identification and treatment of anxiety disorders may be another strategy to reduce the public health burden of child and adolescent depression.[65]

Effect sizes for efficacy outcomes in depression trials were inversely proportional to the number of sites. This suggests the need to either limit studies to fewer, larger sites, or to improve quality control if a study requires a larger number of sites, perhaps by centralizing the determination of eligibility and the assessment and monitoring of treatment quality to a central site.[68]

Similar to the FDA's analysis, we found an overall increased risk of suicidal ideation/suicide attempt associated with antidepressant treatment. Our pooled estimates of risk differences are smaller than those from the FDA report, because we used random-effects rather than fixed-effects models for combining studies and also because we included 7 additional studies not covered in the FDA report.[10-12,18,30,31,33] When we reanalyzed the data using fixed-effects models, our results were more similar to those of Hammad et al.[1] While either approach to meta-analysis is defensible, we believe that a random-effects approach is more appropriate for pooling data because it does not assume that there is a common effect across all studies. In light of quantitative and qualitative evidence of heterogeneity among trials, this is a more conservative assumption and provides estimates of risk differences that are less vulnerable to heterogeneity among studies. Moreover, we deemphasized the use of the metric of relative risk because it excludes studies in which there were no events in either cell, which then is not an accurate reflection of the risk found in the population of all studies. Our findings are also consistent with those of a recent reanalysis[69] of the data from the study by Hammad et al[1] that used Bayesian meta-analysis to include all available trials and found an increased risk of suicidal ideation/suicide attempt in the subset of MDD trials only. Using the metric of relative risk, the risk of suicidal ideation/suicide attempt in our analysis is increased at least as much in the OCD and non-OCD anxiety disorders groups as in the depressed group. However, a 2-fold increase in suicidal ideation/suicide attempt is of potentially greater clinical significance in depression, because the base rate of incident suicidal ideation/suicide attempt is much higher in the placebo-treated depressed group compared with the OCD or non-OCD anxiety disorders placebo groups.

This meta-analysis cannot shed light on exactly what characteristics of patient, medication, or trial might affect incident suicidal ideation/suicide attempt, but at a study level we did not find any effect of sex or use of a placebo run-in period. While there has been some speculation that emergent suicidal ideation/suicide attempt might be induced by withdrawal effects found particularly in those drugs with shorter half-lives, we found no such association when comparing the risk of suicidal ideation/suicide attempt in fluoxetine, a drug with a longer half-life (5 days) than those of the other drugs (all substantially shorter than 24 hours) ($P=.58$). Furthermore, the risk of incident suicidal ideation/suicide attempt does not appear to be a consequence of lack of efficacy, insofar as the magnitude of increased risk is as similar for anxiety as it is for depression in adolescents, even though antidepressants are more efficacious for anxiety than for depression.

A prior meta-analysis of SSRIs in pediatric depression[20] showed that published trials produced a more favorable risk-to-benefit profile than unpublished reports. In contrast, we found no evidence of a publication bias for studies of depression, because many of the negative trials that were unpub-

©2007 American Medical Association. All rights reserved.

Downloaded from www.jama.com at Ohio State University on May 5, 2009

lished at the time of the first report were either published or in press by the time of the current meta-analysis. Nevertheless, there is a need for mandatory clinical trial registration at a study's inception, because trial registries provide a step toward greater transparency.[70] To promote full disclosure, performance and outcome data from clinical trials should also be made publicly available and published in a timely manner, regardless of results.

There are several recommendations for future studies that emerge from what could not be gleaned from this meta-analysis. Baseline characteristics that are likely to be related to treatment response, as well as emergent suicidal ideation/suicide attempt, should be assessed and publicly available so that future analyses can elucidate the impact of these variables on outcome. For example, self-reported suicidal ideation and irritability at intake have been found to predict future suicidal ideation/suicide attempt.[71,72] Future research should focus on identifying the most efficient methods for systematically monitoring children and adolescents taking antidepressant medications for both clinical response and for adverse events. An effective monitoring system could increase the confidence of clinicians and parents in the use of these medications. Finally, although it would increase the cost of drug trials, assays of drug and metabolites levels could identify those who are nonadherent or who have either very slow or very rapid metabolism and thus are not responding to the treatment for reasons other than intrinsic properties of the medication. Pharmacogenetic predictors of response and adverse events may also hold promise.[73,74]

In summary, depending on treatment indication, the NNT ranges from 3 to 10, while the NNH via emergence of suicidal ideation/suicide attempt ranges from 112 to 200, indicating a favorable overall risk-to-benefit profile for antidepressants in the treatment of pediatric MDD, OCD, and non-OCD anxiety disorders. Although our meta-analysis of antidepressant treatment found an overall increased risk for suicidal ideation/suicide attempt compared with placebo, the pooled risk differences for each specific treatment indication, while in the direction of increased risk, were not statistically significant. Some may argue that any risk of suicidal ideation/suicide attempt cannot possibly justify treatment with antidepressants for children and adolescents. Instead, we believe that the strength of evidence presented here supports the cautious and well-monitored use of antidepressant medications as one of the first-line treatment options, with the recognition that efficacy appears greatest for non-OCD anxiety disorders, intermediate for OCD, and more modest for MDD. Since the choice of treatment should be the result of a collaborative discussion between clinician, family, and patient, the information presented in this report should allow for an informed evaluation of the potential benefits and risks of these medications vs no treatment and provide a framework for their comparison with nondrug treatments as well.[75,76]

Author Affiliations: Department of Pediatrics and Columbus Children's Research Institute, The Ohio State University, Columbus (Dr Bridge); Department of Psychiatry and Western Psychiatric Institute & Clinic (Drs Iyengar, Salary, Barbe, Birmaher, and Brent) and Department of Statistics (Drs Iyengar and Ren), University of Pittsburgh, Pittsburgh, Pa; Department of Psychiatry, University Hospital of Geneva, Geneva, Switzerland (Dr Barbe); Department of Psychiatry, Columbia University College of Physicians and Surgeons, New York-Presbyterian Hospital, New York, NY (Dr Pincus); and the RAND Corporation, Santa Monica, Calif (Dr Pincus). Dr Ren is now with Amgen Inc, San Francisco, Calif.

Author Contributions: Dr Bridge had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Bridge, Brent.
Acquisition of data: Bridge, Salary, Barbe, Birmaher, Brent.
Analysis and interpretation of data: Bridge, Iyengar, Barbe, Birmaher, Pincus, Ren, Brent.
Drafting of the manuscript: Bridge, Brent.
Critical revision of the manuscript for important intellectual content: Bridge, Iyengar, Salary, Barbe, Birmaher, Pincus, Ren, Brent.
Statistical analysis: Bridge, Iyengar, Ren, Brent.
Obtained funding: Bridge, Brent.
Administrative, technical, or material support: Bridge.
Study supervision: Birmaher, Pincus, Brent.
Financial Disclosures: Dr Bridge reports having received honoraria for an invited paper from *Current Opinion in Psychiatry*/Lippincott Williams & Wilkins and that from 2001-2004 he participated as a coinvestigator of an open-label trial of citalopram for treatment of pediatric recurrent abdominal pain. The study was funded by an investigator-initiated grant from Forest Labs (John V. Campo, MD, principal investigator); Dr Bridge reports having received no financial support of any kind from Forest or from Dr Campo for his participation. Salary support to Dr Bridge was provided by National Institute of Mental Health grants MH55123 and subsequently MH66371, Advanced Center for Interventions and Services Research for Early-Onset Mood and Anxiety Disorder (Dr Brent, principal investigator). Dr Birmaher reports having received royalties for publication of *New Hope for Children and Teens with Bipolar Disorder* from Random House Inc; and having received remuneration from the University of Cincinnati for participation in the writing of algorithms for the treatment of children with bipolar disorder (Kowatch RA, Fristad M, Birmaher B, et al. Treatment guidelines for children and adolescents with bipolar disorder. *J Am Acad Child Adolesc Psychiatry*. 2005;44:213-235), sponsored by the Child and Adolescent Bipolar Foundation and supported by unrestricted educational grants from Abbott Laboratories, AstraZeneca Pharmaceuticals, Eli Lilly and Co, Forest Pharmaceuticals, Janssen Pharmaceuticals, Novartis, and Pfizer. Dr Pincus reports having served as a consultant to Bristol-Myers Squibb, Cisco Systems, Community Care Behavioral Health Organization/UPMC Health Plan, Magellan Health Care, and the Urban Institute; having received royalties for publications (none of which involved specific products) from American Psychiatric Press and *Current Opinion in Psychiatry*/Lippincott William and Wilkins; and having received payments for speaking from Bimark Medical Education, Comprehensive Neuroscience Inc, Medical Information Technologies, Academy of Managed Care Pharmacy (AMCP) Horizons LLC, Cardinal Health Inc, Disease Management Association of America, Institute for Health Productivity Management, and Health Partners. No other financial disclosures were reported.
Funding/Support: Dr Bridge was supported by grant K01-MH069948 from the National Institute of Mental Health (NIMH), National Institutes of Health (NIH). Dr Pincus was supported by grant 51814 from the Robert Wood Johnson Foundation and grant 1UL1RR024156-01 from the NIMH. Dr Brent was supported by grant P30-MH066371 from the NIMH.
Role of the Sponsor: The NIMH had no role in the design and conduct of the study; the collection, analysis, and interpretation of the data; or the preparation, review, or approval of the manuscript.
Additional Information: The eTables are available at http://www.jama.com.
Acknowledgment: We thank the following individuals for providing additional details and/or access to their respective study data: Moira Rynn, MD (Columbia University, New York, NY); Anne-Liis von Knorring, MD, PhD (University Hospital, Uppsala, Sweden); Graham J. Emslie, MD, and Taryn L. Mayes, MS (University of Texas Southwestern Medical Center, Dallas); Karen Wagner, MD, PhD (University of Texas Medical Branch, Galveston); Tarek Hammad, MD, PhD, MSc, MS, and Thomas Laughren, MD (US Food and Drug Administration, Rockville, Md); Karen A. Tourian, MD (Wyeth Research, Philadelphia, Pa); Helen Blair Simpson, MD, PhD, and Andrew B. Schmidt, CSW (Columbia University, New York, NY), Daniel A. Geller, MD (Harvard Medical School, Boston, Mass); John March, MD (Duke University Medical Center, Durham, NC); and Benedetto Vitiello, MD, Daniel Pine, MD (National Institute of Mental Health, Bethesda, Md), and John T. Walkup, MD, and Mark A. Riddle, MD (Johns Hopkins Medical Institutions, Baltimore, Md), on behalf of the Fluvoxamine Treatment of Anxiety Disorders in Children and Adolescents: Multi-center study (RUPP Anxiety Study). The RUPP Anxiety Study was conducted and supported by the NIMH and the National Center for Complementary and Alternative Medi-

 ©2007 American Medical Association. All rights reserved.

Downloaded from www.jama.com at Ohio State University on May 5, 2009

cine (NCCAM) in collaboration with the study investigators. This manuscript reflects the views of the authors and may not reflect the opinions or views of all the RUPP Anxiety Study investigators, the NIMH, or the NCCAM. We also thank Holly Irvine, BS, for support with study retrieval and data management. Ms Irvine received hourly compensation for her work; none of the other acknowledged individuals received compensation for their contributions.

REFERENCES

1. Hammad TA, Laughren T, Racoosin J. Suicidality in pediatric patients treated with antidepressant drugs. *Arch Gen Psychiatry*. 2006;63:332-339.
2. US Food and Drug Administration. Relationship between psychotropic drugs and pediatric suicidality: review and evaluation of clinical data. http://www.fda.gov/ohrms/dockets/ac/04/briefing/2004-4065b1-10-TAB08-Hammads-Review.pdf. Accessed January 10, 2005.
3. Posner K, Oquendo M, Stanley B, Gould M. Suicidality classification project. http://www.fda.gov/ohrms/dockets/ac/04/slides/4006S1_08_Posner_files/frame.htm. Accessed February 19, 2007.
4. Emslie GJ, Rush AJ, Weinberg WA, et al. A double-blind, randomized, placebo-controlled trial of fluoxetine in children and adolescents with depression. *Arch Gen Psychiatry*. 1997;54:1031-1037.
5. March J, Silva S, Petrycki S, et al; Treatment for Adolescents With Depression Study (TADS) Team. Fluoxetine, cognitive-behavioral therapy, and their combination for adolescents with depression: Treatment for Adolescents With Depression Study (TADS) randomized controlled trial. *JAMA*. 2004;292:807-820.
6. Geller DA, Wagner KD, Emslie G, et al. Paroxetine treatment in children and adolescents with obsessive-compulsive disorder: a randomized, multicenter, double-blind, placebo-controlled trial. *J Am Acad Child Adolesc Psychiatry*. 2004;43:1387-1396.
7. March JS, Biederman J, Wolkow R, et al. Sertraline in children and adolescents with obsessive-compulsive disorder: a multicenter randomized controlled trial. *JAMA*. 1998;280:1752-1756.
8. Geller DA, Hoog SL, Heiligenstein JH, et al. Fluoxetine treatment for obsessive-compulsive disorder in children and adolescents: a placebo-controlled clinical trial. *J Am Acad Child Adolesc Psychiatry*. 2001;40:773-779.
9. Riddle MA, Reeve EA, Yaryura-Tobias JA, et al. Fluvoxamine for children and adolescents with obsessive-compulsive disorder: a randomized, controlled, multicenter trial. *J Am Acad Child Adolesc Psychiatry*. 2001;40:222-229.
10. The Pediatric OCD Treatment Study (POTS) Team. Cognitive-behavior therapy, sertraline, and their combination for children and adolescents with obsessive-compulsive disorder: the Pediatric OCD Treatment Study (POTS) randomized controlled trial. *JAMA*. 2004;292:1969-1976.
11. Research Unit on Pediatric Psychopharmacology Anxiety Study Group. Fluvoxamine for the treatment of anxiety disorders in children and adolescents. *N Engl J Med*. 2001;344:1279-1285.
12. Birmaher B, Axelson DA, Monk K, et al. Fluoxetine for the treatment of childhood anxiety disorders. *J Am Acad Child Adolesc Psychiatry*. 2003;42:415-423.
13. Wagner KD, Berard R, Stein MB, et al. A multicenter, randomized, double-blind, placebo-controlled trial of paroxetine in children and adolescents with social anxiety disorder. *Arch Gen Psychiatry*. 2004;61:1153-1162.
14. Keller MB, Ryan ND, Strober M, et al. Efficacy of paroxetine in the treatment of adolescent major depression: a randomized, controlled trial. *J Am Acad Child Adolesc Psychiatry*. 2001;40:762-772.
15. Wagner KD, Ambrosini P, Rynn M, et al. Efficacy of sertraline in the treatment of children and adolescents with major depressive disorder: two randomized controlled trials. *JAMA*. 2003;290:1033-1041.
16. Emslie GJ, Wagner KD, Kutcher S, et al. Paroxetine treatment in children and adolescents with major depressive disorder: a randomized, double-blind, placebo-controlled trial. *J Am Acad Child Adolesc Psychiatry*. 2006;45:709-719.
17. Berard R, Fong R, Carpenter DJ, Thomason C, Wilkinson C. An international, multicenter, placebo-controlled trial of paroxetine in adolescents with major depressive disorder. *J Child Adolesc Psychopharmacol*. 2006;16:59-75.
18. Wagner KD, Jonas J, Findling RL, Ventura D, Saikali K. A double-blind, randomized, placebo-controlled trial of escitalopram in the treatment of pediatric depression. *J Am Acad Child Adolesc Psychiatry*. 2006;45:280-288.
19. Wagner KD, Robb AS, Findling RL, Jin J, Gutierrez MM, Heydorn WE. A randomized, placebo-controlled trial of citalopram for the treatment of major depression in children and adolescents. *Am J Psychiatry*. 2004;161:1079-1083.
20. Whittington CJ, Kendall T, Fonagy P, Cottrell D, Cotgrove A, Boddington E. Selective serotonin reuptake inhibitors in childhood depression: systematic review of published versus unpublished data. *Lancet*. 2004;363:1341-1345.
21. MHRA Committee on Safety of Medicines Report of the CSM Expert Working Group on the safety of selective serotonin reuptake inhibitor antidepressants. http://www.mhra.gov.uk/home/groups/pl-p/documents/drugsafetymessage/con019472.pdf. Accessed June 15, 2005.
22. MHRA Committee on Safety of Medicines Selective serotonin reuptake inhibitors (SSRIs): overview of regulatory status and CSM advice relating to major depressive disorder (MDD) in children and adolescents including a summary of available safety and efficacy data. http://www.mhra.gov.uk/home/idcplg?IdcService=SS_GET_PAGE&ssTargetNodeId=221&useSecondary=true&ssDocName=CON019494&showpage=1. Accessed February 27, 2006.
23. Simeon JG, Dinicola VF, Ferguson HB, Copping W. Adolescent depression: a placebo-controlled fluoxetine treatment study and follow-up. *Prog Neuropsychopharmacol Biol Psychiatry*. 1990;14:791-795.
24. Emslie GJ, Heiligenstein JH, Wagner KD, et al. Fluoxetine for acute treatment of depression in children and adolescents: a placebo-controlled, randomized clinical trial. *J Am Acad Child Adolesc Psychiatry*. 2002;41:1205-1215.
25. von Knorring AL, Olsson GI, Thomsen PH, Lemming OM, Hulten A. A randomized, double-blind, placebo-controlled study of citalopram in adolescents with major depressive disorder. *J Clin Psychopharmacol*. 2006;26:311-315.
26. Emslie GJ, Findling RL, Rynn MA, Marcus RN. Efficacy and safety of nefazodone in the treatment of adolescents with major depressive disorder [abstract]. *J Child Adolesc Psychopharmacol*. 2002;12:299.
27. Dubitsky GM. Review and evaluation of clinical data: placebo-controlled antidepressant studies in pediatric patients. http://www.fda.gov/OHRMS/DOCKETS/ac/04/briefing/2004-4065b1-08-TAB06-Dubitsky-Review.pdf. Accessed January 10, 2005.
28. Cheung AH, Emslie GJ, Mayes TL. Review of the efficacy and safety of antidepressants in youth depression. *J Child Psychol Psychiatry*. 2005;46:735-754.
29. Emslie GJ, Findling RL, Yeung PP, Kunz NR, Li Y. Venlafaxine ER for the treatment of pediatric subjects with depression: results of 2 placebo-controlled trials. *J Am Acad Child Adolesc Psychiatry*. In press.
30. Liebowitz MR, Turner SM, Piacentini J, et al. Fluoxetine in children and adolescents with OCD: a placebo-controlled trial. *J Am Acad Child Adolesc Psychiatry*. 2002;41:1431-1438.
31. Rynn MA, Siqueland L, Rickels K. Placebo-controlled trial of sertraline in the treatment of children with generalized anxiety disorder. *Am J Psychiatry*. 2001;158:2008-2014.
32. Rynn MA, Riddle MA, Yeung PP, Kunz NR. Efficacy and safety of extended-release venlafaxine in the treatment of generalized anxiety disorder in children and adolescents: two placebo-controlled trials. *Am J Psychiatry*. 2007;164:290-300.
33. Tourian KA, March JS, Mangano RM. Venlafaxine ER in children and adolescents with SAD. Paper presented at: 157th Annual Meeting of the American Psychiatric Association; May 1-6, 2004; New York, NY.
34. March JS, Entsuah AR, Rynn M, Albano AM, Tourian KA. A randomized controlled trial of venlafaxine ER versus placebo in pediatric social anxiety disorder. *Biol Psychiatry*. In press.
35. Riddle MA, Scahill L, King RA, et al. Double-blind, crossover trial of fluoxetine and placebo in children and adolescents with obsessive-compulsive disorder. *J Am Acad Child Adolesc Psychiatry*. 1992;31:1062-1069.
36. Braconnier A, Le Coent R, Cohen D, Group DS. Paroxetine versus clomipramine in adolescents with severe major depression: a double-blind, randomized, multicenter trial. *J Am Acad Child Adolesc Psychiatry*. 2003;42:22-29.
37. Paroxetine Study 453 A 38-week, two phase, multicenter study to investigate the safety and effectiveness of paroxetine (10-60 mg/day) in the treatment of children and adolescent outpatients with obsessive-compulsive disorder. http://www.gsk.com/media/paroxetine/ocd_453_full.pdf. Accessed November 6, 2005.
38. Mandoki MW, Tapia MR, Tapia MA, Sumner GS, Parker JL. Venlafaxine in the treatment of children and adolescents with major depression. *Psychopharmacol Bull*. 1997;33:149-154.
39. Black B, Uhde TW. Treatment of elective mutism with fluoxetine: a double-blind, placebo-controlled study. *J Am Acad Child Adolesc Psychiatry*. 1994;33:1000-1006.
40. Meyer WJ III, Robert RWT, Rosenberg L, et al. Double blind placebo controlled study of acute stress disorder (ASD). Paper presented at: American Academy of Child and Adolescent Psychiatry; October 19-24, 2004; Washington, DC.
41. Glod CA, Lynch A, Berkowitz C, Hennen J, Baldessarini RJ. Bupropion versus citalopram versus placebo in adolescents with major depression. Paper presented at: 157th Annual Meeting of the American Psychiatric Association; May 1-6, 2004; New York, NY.
42. Detsky AS, Naylor CD, O'Rourke K, McGeer AJ, L'Abbe KA. Incorporating variations in the quality of individual randomized trials into meta-analysis. *J Clin Epidemiol*. 1992;45:255-265.
43. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials*. 1986;7:177-188.
44. Hedges LV. Estimation of effect size from a series of independent experiments. *Psychol Bull*. 1982;92:490-499.
45. Sackett DL, Straus SE, Richardson WS, Rosenberg W, Haynes RB. *Evidence-Based Medicine: How to Practice and Teach EBM*. 2nd ed. New York, NY: Churchill Livingstone; 2000.
46. Altman DG. Confidence intervals for the number needed to treat. *BMJ*. 1998;317:1309-1312.
47. Rosenthal R. Parametric measures of effect size. In: Cooper H, Hedges LV, eds. *The Handbook of Research Synthesis*. New York, NY: Russell Sage Foundation; 1994:231-244.
48. Higgins JPT, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med*. 2002;21:1539-1558.
49. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. *Biometrics*. 1994;50:1088-1101.

©2007 American Medical Association. All rights reserved.

Downloaded from www.jama.com at Ohio State University on May 5, 2009

50. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ*. 1997;315:629-634.
51. US Food and Drug Administration. Review and Evaluation of Clinical Data—NDA: 20-152 S-032, nefazodone hydrochloride (Serzone). http://www.fda.gov/cder/foi/esum/2004/20152s032_Serzone_clinical_BPCA_FIN.pdf. Accessed March 9, 2006.
52. Guy W. *ECDEU Assessment Manual for Psychopharmacology*. 2nd ed. Washington, DC: US Government Printing Office; 1976. DHEW publication 76-388.
53. Poznanski E, Mokros H. *Children's Depression Rating Scale-Revised (CDRS-R).* Los Angeles, Calif: Western Psychological Services; 1995.
54. Goodman WK, Price LH, Rasmussen SA, et al. The Yale-Brown Obsessive Compulsive Scale, II: validity. *Arch Gen Psychiatry*. 1989;46:1012-1016.
55. Goodman WK, Price LH, Rasmussen SA, et al. The Yale-Brown Obsessive Compulsive Scale, I: development, use, and reliability. *Arch Gen Psychiatry*. 1989;46:1006-1011.
56. Walkup J, Davies M. The Pediatric Anxiety Rating Scale (PARS): a reliability study. Paper presented at: 46th Annual Meeting of the American Academy of Child and Adolescent Psychiatry; October 19-24, 1999; Chicago, Ill.
57. Eli Lilly and Co. Summary ID#236: clinical study summary: study B1Y-MC-HCCJ. http://www.lillytrials.com/results_files/prozac/prozac_summary_236.pdf. Accessed December 20, 2005.
58. US Food and Drug Administration. NDA 20-415 SE5-011: Mirtazapine pediatric supplement. http://www.fda.gov/CDER/foi/esum/2004/20415SE5_011_Mirtazapine%20MO%20ReviewFIN.pdf. Accessibility verified March 9, 2007.
59. Safer DJ, Zito JM. Treatment-emergent adverse events from selective serotonin reuptake inhibitors by age group: children versus adolescents. *J Child Adolesc Psychopharmacol*. 2006;16:159-169.
60. Martin A, Young C, Leckman JF, Mukonoweshuro C, Rosenheck R, Leslie D. Age effects on antidepressant-induced manic conversion. *Arch Pediatr Adolesc Med*. 2004;158:773-780.
61. Curry J, Rohde P, Simons A, et al. Predictors and moderators of acute outcome in the Treatment for Adolescents with Depression Study (TADS). *J Am Acad Child Adolesc Psychiatry*. 2006;45:1427-1439.
62. Donnelly CL, Wagner KD, Rynn M, et al. Sertraline in children and adolescents with major depressive disorder. *J Am Acad Child Adolesc Psychiatry*. 2006;45:1162-1170.
63. March JS, Klee BJ, Kremer CM. Treatment benefit and the risk of suicidality in multicenter, randomized, controlled trials of sertraline in children and adolescents. *J Child Adolesc Psychopharmacol*. 2006;16:91-102.
64. Mayes TL, Tao R, Rintelmann JW, et al. Do children and adolescents have differential response rates in placebo-controlled trials of fluoxetine? *CNS Spectr*. 2007;12:147-157.
65. Pine DS, Cohen P, Gurley D, Brook J, Ma Y. The risk for early-adulthood anxiety and depressive disorders in adolescents with anxiety and depressive disorders. *Arch Gen Psychiatry*. 1998;55:56-64.
66. Weissman MM, Wolk S, Goldstein RB, et al. Depressed adolescents grown up. *JAMA*. 1999;281:1707-1713.
67. Rush AJ, Trivedi MH, Wisniewski SR, et al. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: A STAR*D report. *Am J Psychiatry*. 2006;163:1905-1917.
68. Kraemer HC, Robinson TN. Are certain multicenter randomized clinical trial structures misleading clinical and policy decisions? *Contemp Clin Trials*. 2005;26:518-529.
69. Kaizar EE, Greenhouse JB, Seltman H, Kelleher K. Do antidepressants cause suicidality in children? a Bayesian meta-analysis. *Clin Trials*. 2006;3:73-98.
70. DeAngelis CD, Drazen JM, Frizelle FA, et al. Clinical trial registration: a statement from the International Committee of Medical Journal Editors. *JAMA*. 2004;292:1363-1364.
71. Bridge JA, Barbe RP, Birmaher B, Kolko DJ, Brent DA. Emergent suicidality in a clinical psychotherapy trial for adolescent depression. *Am J Psychiatry*. 2005;162:2173-2175.
72. Apter A, Lipschitz A, Fong R, et al. Evaluation of suicidal thoughts and behaviors in children and adolescents taking paroxetine. *J Child Adolesc Psychopharmacol*. 2006;16:77-90.
73. Mavissakalian MR, Perel JM. Imipramine treatment of panic disorder with agoraphobia: dose ranging and plasma level-response relationships. *Am J Psychiatry*. 1995;152:673-682.
74. McMahon FJ, Buervenich S, Charney D, et al. Variation in the gene encoding the serotonin 2A receptor is associated with outcome of antidepressant treatment. *Am J Hum Genet*. 2006;78:804-814.
75. Weisz JR, McCarty CA, Valeri SM. Effects of psychotherapy for depression in children and adolescents: a meta-analysis. *Psychol Bull*. 2006;132:132-149.
76. James A, Soler A, Weatherall R. Cognitive behavioural therapy for anxiety disorders in children and adolescents. *Cochrane Database Syst Rev*. 2005;(4):CD004690. doi:10.1002/14651858.CD004690.pub2.

 ©2007 American Medical Association. All rights reserved.

Downloaded from www.jama.com at Ohio State University on May 5, 2009

eTable 1. Differences in Efficacy Outcomes for Antidepressant-Treated and Placebo-Treated Groups, by Indication

Drug	Source	Response Criterion	Response Rate, No. Response/Total (%)		Risk Difference,% (95% CI)	NNT (95% CI)[a]	Primary Scalar Measure of Efficacy	Scalar Measure of Efficacy, Hedges *g* (95% CI)
			Treatment	Placebo				
			Major Depressive Disorder					
Fluoxetine	Simeon et al,[23,57] 1990	CGI-I ≤2	NA	NA	NA	NA	HAM-D total score	0.21 (–0.40 to 0.82)
	Emslie et al,[4] 1997	CGI-I ≤2	27/48 (56)	16/48 (33)	23 (4 to 42)	5 (3 to 28)	CDRS-R total score	0.60 (0.19 to 1.00)
	Emslie et al,[24] 2002	≥30% decrease in CDRS-R	71/109 (65)	54/101 (54)	12 (–2 to 25)	. . .	CDRS-R total score	0.50 (0.23 to 0.77)
	TADS Study Team,[5] 2004	CGI-I ≤2	66/109 (61)	39/112 (35)	26 (13 to 39)	4 (3 to 8)	CDRS-R total score	0.40 (0.13 to 0.66)
	Pooled estimates		164/266 (62)	109/261 (42)	20 (11 to 29)	6 (4 to 10)		0.46 (0.29 to 0.62)
Paroxetine	Keller et al,[14] 2001	HAM-D ≤8 or ≥50% reduction from baseline	60/90 (67)	48/87 (55)	12 (–3 to 26)	. . .	HAM-D total score	0.22 (–0.08 to 0.51)
	Berard et al,[17] 2006	≥50% decrease in MADRS	107/177 (61)	53/91 (58)	2 (–10 to 15)	. . .	K-SADS-L depression subscale	0.07 (–0.19 to 0.32)
	Emslie et al,[16] 2006	CGI-I ≤2	49/101 (49)	46/100 (46)	3 (–11 to 16)	. . .	CDRS-R total score	–0.06 (–0.33 to 0.22)
	Pooled estimates		216/368 (59)	147/278 (53)	5 (–3 to 13)	. . .		0.07 (–0.09 to 0.23)
Sertraline	Wagner et al,[15] 2003[b]	≥40% decrease in adjusted CDRS-R	127/185 (69)	105/179 (59)	10 (0 to 20)	10 (6 to 500)	CDRS-R total score	0.28 (0.08 to 0.49)
Citalopram	Wagner et al,[19] 2004	CDRS-R score ≤28	32/89 (36)	20/85 (24)	12 (–1 to 26)	. . .	CDRS-R total score	0.32 (0.02 to 0.61)
	von Knorring et al,[25] 2006[c]	K-SADS-P depression and anhedonia items ≤2[d]	50/83 (60)	47/77 (61)	–1 (–16 to 14)	. . .	K-SADS-P total score	–0.01 (–0.32 to 0.30)
Escitalopram	Wagner et al,[18] 2006	CGI-I ≤2[e]	81/129 (63)	69/132 (52)	11 (–1 to 22)	. . .	CDRS-R total score	0.13 (–0.12 to 0.37)
Citalopram/ escitalopram	Pooled estimates		163/301 (54)	136/294 (46)	8 (1 to 16)	13 (7 to 200)		0.15 (–0.02 to 0.31)
Venlafaxine	Emslie et al[29,b]	≥35% decrease in adjusted CDRS-R[f]	120/169 (71)	99/165 (60)	11 (1 to 21)[g]	10 (5 to 112)	CDRS-R total score	0.14 (–0.07 to 0.35)
Nefazodone	CN104-141[26]	CGI-I ≤2	61/99 (62)	40/96 (42)	20 (6 to 34)	6 (3 to 17)	CDRS-R total score	0.28 (–0.01 to 0.56)
	CN104-187[51]	CGI-I ≤2	NA	NA	NA	NA	CDRS-R total score	0.03 (–0.18 to 0.23)
	Pooled estimates		61/99 (62)	40/96 (42)	20 (6 to 34)	6 (3 to 17)		0.13 (–0.11 to 0.37)
Mirtazapine	003-045[22,58,28,b]	CGI-I ≤2	93/164 (57)	42/85 (49)	7 (–6 to 20)	. . .	CDRS-R total score	0.20 (–0.07 to 0.46)
			Obsessive-Compulsive Disorder					
Fluoxetine	Geller et al,[8] 2001	≥40% reduction in CY-BOCS	35/71 (49)	8/32 (25)	24 (5 to 43)	5 (3 to 19)	CY-BOCS total score	0.49 (0.07 to 0.91)
	Liebowitz et al,[30] 2002	CGI-I ≤2	12/21 (57)	7/22 (32)	25 (–3 to 54)	. . .	CY-BOCS total score	0.24 (–0.35 to 0.83)
	Pooled estimates		47/92 (51)	15/54 (28)	25 (9 to 40)	5 (3 to 12)		0.41 (0.07 to 0.75)
Fluvoxamine	Riddle et al,[9] 2001	≥25% reduction in CY-BOCS	24/57 (42)	17/63 (27)	15 (–2 to 32)	. . .	CY-BOCS total score	0.31 (–0.04 to 0.67)
Paroxetine	Geller et al,[6] 2004	≥25% reduction in CY-BOCS	61/94 (65)	42/102 (41)	24 (10 to 37)	5 (3 to 10)	CY-BOCS total score	0.45 (0.17 to 0.73)
Sertraline	March et al,[7] 1998	≥25% reduction in CY-BOCS[h]	49/92 (53)	35/95 (37)	16 (2 to 31)	7 (4 to 44)	CY-BOCS total score[i]	0.43 (0.14 to 0.71)
	POTS Study Team,[10] 2004	CY-BOCS total score ≤10	6/28 (21)	1/28 (4)	18 (1 to 35)	6 (3 to 84)	CY-BOCS total score	0.44 (–0.09 to 0.96)
	Pooled estimates		55/120 (46)	36/123 (29)	17 (6 to 28)	6 (4 to 16)		0.43 (0.17 to 0.68)

(continued)

©2007 American Medical Association. All rights reserved.

Downloaded from www.jama.com at Ohio State University on May 5, 2009

eTable 1. Differences in Efficacy Outcomes for Antidepressant-Treated and Placebo-Treated Groups, by Indication (cont)

Drug	Source	Response Criterion	Response Rate, No. Response/Total (%)		Risk Difference,% (95% CI)	NNT (95% CI)[a]	Primary Scalar Measure of Efficacy	Scalar Measure of Efficacy, Hedges *g* (95% CI)
			Treatment	Placebo				
Non–Obsessive-Compulsive Anxiety Disorders[j]								
Fluoxetine	Birmaher et al,[12] 2003	CGI-I ≤2	22/36 (61)	13/37 (35)	26 (4 to 48)	4 (3 to 27)	PARS total score	0.53 (0.08 to 0.99)
Fluvoxamine	RUPP Anxiety Study Group,[11] 2001	CGI-I ≤3[k]	48/63 (76)	19/65 (29)	47 (32 to 62)	3 (2 to 4)	PARS total score	1.06 (0.69 to 1.43)
Paroxetine	Wagner et al,[13] 2004	CGI-I ≤2	125/161 (78)	59/154 (38)	39 (29 to 49)	3 (3 to 4)	LSAS-CA total score	0.88 (0.65 to 1.12)
Sertraline	Rynn et al,[31] 2001	CGI-I ≤2	10/11 (91)	1/11 (9)	82 (58 to 106)	2 (1 to 2)	HAM-A total score[l]	1.48 (0.56 to 2.39)
Venlafaxine	Rynn et al,[32] 2007[b]	CGI-I ≤2[m]	106/154 (69)	77/159 (48)	20 (10 to 31)	5 (4 to 11)	K-SADS-GAD total score	0.45 (0.22 to 0.67)
	March et al[33,34]	CGI-I ≤2	76/137 (56)	54/148 (37)	19 (8 to 30)	6 (4 to 14)	SAS-CA total score	0.57 (0.33 to 0.81)
	Pooled estimates		182/291 (63)	131/307 (43)	20 (12 to 28)	6 (4 to 9)		0.51 (0.34 to 0.67)

Abbreviations: CDRS-R, Children's Depression Rating Scale-Revised; CGI-I, Clinical Global Impressions-Improvement scale; CY-BOCS, Children's Yale-Brown Obsessive Compulsive Scale; ellipses, significant treatment effect not observed; GAD, generalized anxiety disorder; HAM-A, Hamilton Anxiety Scale; HAM-D, Hamilton Rating Scale for Depression; K-SADS, Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children; L, lifetime; LSAS-CA, Liebowitz Social Anxiety Scale for Children and Adolescents; MADRS, Montgomery-Asberg Depression Rating Scale; NA, response data not available; NNT, number needed to treat to benefit; P, present; PARS, Pediatric Anxiety Rating Scale; SAS-CA, Social Anxiety Scale for Children and Adolescents.

[a] Values are given only when a significant treatment effect was observed.
[b] Trial comprised 2 studies pooled for analysis.
[c] Efficacy outcomes based on observed-case analyses.
[d] Fifty percent or greater reduction on MADRS total score was also defined as a measure of response.
[e] CDRS score ≤28 was also defined as a primary measure of response.
[f] CGI-I score ≤2 or ≥50% decrease in MADRS or HAM-D21 scores were also defined as measures of response.
[g] Individual venlafaxine trials did not reveal significant treatment effect ($P>.10$ for each study).
[h] CGI-I score ≤2 was also defined as a primary measure of response.
[i] The National Institute for Mental Health (NIMH) Global Obsessive Compulsive Scale (GOCS) and the NIMH CGI-I and CGI-S (severity) rating scales were also used as primary scalar measures of efficacy.
[j] Social phobia, separation anxiety disorder, or generalized anxiety disorder.
[k] Indicated by a score of 3 (improved), 2 (much improved), or 1 (free of symptoms).
[l] The HAM-A psychic and somatic factor scores and the CGI-I and CGI-S scores were also used as primary scalar measures of efficacy.
[m] A 50% reduction in composite score on the 9 delineated items of the Columbia K-SADS or in the PARS score was also defined as a measure of response.

©2007 American Medical Association. All rights reserved.

Downloaded from www.jama.com at Ohio State University on May 5, 2009

eTable 2. Overall and Age-Grouped Effects of Antidepressant Medication on Pooled Measures of Efficacy, by Indication[a]

	Within Group						Effect of Age		
				Heterogeneity					
Age Grouping	No. of Trials	Scalar Measure of Efficacy (95% CI)[b]	*P* Value	Q_{df} Within	*P* Value	Variance Explained, %	Q_{df} Between	*P* Value	Variance Explained, %
Major Depressive Disorder									
All participants	15	0.20 (0.12 to 0.29)	<.001	21.6_{14}	.09	35	NT	NT	NT
Children	7	0.21 (–0.11 to 0.53)	.19	27.9_{6}	<.001	78	0.06	.82	0
Adolescents	13	0.25 (0.16 to 0.34)	<.001	8.0_{12}	.78	0			
Obsessive-Compulsive Disorder									
All participants	6	0.41 (0.26 to 0.56)	<.001	0.8_{5}	.98	0	NT	NT	NT
Children	3	0.41 (0.12 to 0.71)	.01	0.4_{2}	.80	0	0.01	.94	1
Adolescents	3	0.43 (0.11 to 0.75)	.01	0.1_{2}	.96	0			
Non–Obsessive-Compulsive Anxiety Disorders									
All participants	6	0.73 (0.50 to 0.96)	<.001	15.2_{5}	.01	67	NT	NT	NT
Children	3	0.76 (0.11 to 1.41)	.02	8.8_{2}	.01	77	0.15	.70	1
Adolescents	3	0.62 (0.43 to 0.81)	<.001	2.1_{2}	.36	3			

Abbreviations: CI, confidence interval; NT, not tested.
[a] Depending on study criteria, children were defined as being younger than 12 years or younger than 13 years; adolescents, as 12 years or older or 13 years or older.
[b] Overall risk difference estimated using the DerSimonian and Laird method,[43] which may vary from the difference in the pooled response rates.

©2007 American Medical Association. All rights reserved.

Downloaded from www.jama.com at Ohio State University on May 5, 2009

eTable 3. Moderators of Effect of Antidepressant Medications on Pooled Measures of Efficacy and Suicidal Ideation and Suicide Attempt/Preparatory Actions Toward Imminent Suicidal Behavior, by Indication

	Risk Difference in Response			Scalar Measure of Efficacy			Risk Difference in Suicidal Ideation/Suicide Attempt/Preparatory Actions		
Moderator	Difference, % (95% CI)	*P* Value[a]	Variance Explained, %[b]	Hedges *g* (95% CI)	*P* Value[a]	Variance Explained, %[b]	Difference, % (95% CI)	*P* Value[a]	Variance Explained, %[b]
Major Depressive Disorder									
Trial features, publication status		.67	1		.39	3		.16	10
Published or in press	11 (6 to 15)			0.22 (0.12 to 0.33)			1.4 (0.1 to 2.8)		
Not published	13 (10 to 26)			0.14 (–0.01 to 0.29)			0.2 (–0.9 to 1.2)		
No. of trial sites		.008	49		.001	54		.89	0
<25	17 (11 to 23)			0.36 (0.25 to 0.48)			0.8 (–1.3 to 3.0)		
≥25	7 (3 to 12)			0.11 (0.03 to 0.20)			1.0 (–0.2 to 2.2)		
Study location		.02	36		.13	10		.45	3
US only	15 (9 to 20)			0.25 (0.14 to 0.36)			0.7 (–0.7 to 2.2)[c]		
Not US only	6 (0 to 12)			0.12 (–0.02 to 0.25)			1.6 (–0.1 to 3.2)		
Placebo run-in		.89	0		.36	4		.69	1
No	11 (5 to 18)			0.17 (0.06 to 0.28)			1.1 (–0.3 to 2.6)		
Yes	11 (5 to 16)			0.26 (0.11 to 0.40)			0.6 (–1.3 to 2.6)		
Medication		.70	1		.27	6		.92	0
SSRI	11 (6 to 15)			0.23 (0.12 to 0.35)			0.9 (–0.4 to 2.1)		
Non-SSRI	12 (5 to 19)			0.14 (0.02 to 0.26)			1.0 (–1.0 to 3.0)[d]		
Episode duration, mo		.18	21		.008	50		.20	11
<16.2	18 (10 to 25)			0.41 (0.26 to 0.56)			2.9 (–0.0 to 5.8)		
≥16.2	11 (6 to 17)			0.15 (0.03 to 0.27)			0.6 (–1.3 to 2.5)		
Obsessive-Compulsive Disorder									
Trial features, placebo run-in		.36	67		.74	14		.92	0
No	22 (14 to 31)			0.43 (0.23 to 0.63)			0.9 (–1.3 to 3.2)		
Yes	16 (5 to 27)			0.38 (0.16 to 0.61)			0.7 (–4.1 to 5.4)		
Non–Obsessive-Compulsive Anxiety Disorders									
Trial features, primary funding source		.35	6		.53	3		.56	16
NIMH	38 (18 to 59)			0.81 (0.30 to 1.33)			0.0 (–2.6 to 2.6)		
Industry	26 (13 to 40)[e]			0.63 (0.38 to 0.89)[f]			0.9 (–0.3 to 2.1)		
Medication		.001	72		.02	46		.68	8
SSRI	40 (31 to 48)			0.86 (0.62 to 1.10)			1.0 (–0.7 to 2.7)		
Non-SSRI[g]	20 (12 to 28)			0.51 (0.34 to 0.67)			0.5 (–0.9 to 1.9)		

Abbreviations: CI, confidence interval; NIMH, National Institute of Mental Health; SSRI, selective serotonin reuptake inhibitor.
[a] Derived from tests of the effect of each moderator variable on outcome.
[b] Percentage of variance explained by the moderator.
[c] Test of heterogeneity: $Q_8 = 16.3$, $P = .04$, $I^2 = 51\%$.
[d] Test of heterogeneity: $Q_3 = 10.5$, $P = .02$, $I^2 = 71\%$.
[e] Test of heterogeneity: $Q_2 = 9.2$, $P = .01$, $I^2 = 78\%$.
[f] Test of heterogeneity: $Q_2 = 7.3$, $P = .03$, $I^2 = 73\%$.
[g] Venlafaxine (extended release).

©2007 American Medical Association. All rights reserved.

Downloaded from www.jama.com at Ohio State University on May 5, 2009