Remission Rates Following Antidepressant Therapy With Bupropion or Selective Serotonin Reuptake Inhibitors: A Meta-Analysis of Original Data From 7 Randomized Controlled Trials

Michael E. Thase, M.D.; Barbara R. Haight, Pharm.D.; Nathalie Richard, M.S.; Carol B. Rockett, Pharm.D.; Melinda Mitton, Pharm.D.; Jack G. Modell, M.D.; Susan VanMeter, M.D.; April E. Harriett, M.A.; and Younghua Wang, Ph.D.

Background: Although it is widely believed that the various classes of antidepressants are equally effective, clinically meaningful differences may be obscured in individual studies because of a lack of statistical power. The present report describes a meta-analysis of original data from a complete set of studies comparing the norepinephrine/dopamine reuptake inhibitor (NDRI) bupropion with selective serotonin reuptake inhibitors (SSRIs; sertraline, fluoxetine, or paroxetine).

Method: Individual patient data were pooled from a complete set of 7 randomized, double-blind studies comparing bupropion (N = 732) with SSRIs (fluoxetine, N = 339; sertraline, N = 343; paroxetine, N = 49) in outpatients with major depressive disorder (DSM-III-R or DSM-IV); 4 studies included placebo (N = 512). Response and remission rates were compared at week 8 or endpoint in both the intent-to-treat sample, using the last-observation-carried-forward (LOCF) method to account for attrition, and the observed cases. Tolerability data, including incidence of sexual side effects, were also compared.

Results: The LOCF response and remission rates for the bupropion (62% and 47%) and SSRI (63% and 47%) groups were similar; both active therapies were superior to placebo (51% and 36%; all comparisons, $p < .001$). The same pattern of results was demonstrated on the observed cases analyses. Although bupropion and SSRIs were generally well tolerated, SSRI therapy resulted in significantly higher rates of sexual side effects as compared to both bupropion and placebo. SSRIs were also associated with more somnolence and diarrhea, and bupropion was associated with more dry mouth.

Conclusion: Bupropion and the SSRIs were equivalently effective and, overall, both treatments were well tolerated. The principal difference between these treatments was that sexual dysfunction commonly complicated SSRI therapy, whereas treatment with bupropion caused no more sexual dysfunction than placebo.

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Received April 13, 2004; accepted Jan. 20, 2005. From the Department of Psychiatry, University of Pittsburgh Medical Center, Pittsburgh, Pa. (Dr. Thase); and GlaxoSmithKline, Research Triangle Park, N.C. (Drs. Haight, Rockett, Mitton, Modell, VanMeter, and Wang and Mss. Richard and Harriett).

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Corresponding author and reprints: Michael E. Thase, M.D., Department of Psychiatry, University of Pittsburgh Medical Center, Western Psychiatric Institute and Clinic, 3811 O'Hara Street, Pittsburgh, PA 15213-2593 (e-mail: thaseme@upmc.edu).

Bupropion hydrochloride is a norepinephrine and dopamine reuptake inhibitor (NDRI) and has no clinically significant effects on serotonin neurotransmission or muscarinic, histaminergic, dopaminergic, or α-adrenergic receptors.[1] Efficacy of bupropion was initially established in randomized controlled trials (RCTs) of placebo and tricyclic antidepressants[2–5] and related compounds[6] and subsequently in additional RCTs with selective serotonin reuptake inhibitors (SSRIs).[7–12] None of these studies, however, had adequate statistical power to detect differences in efficacy of the magnitude likely to be observed in contemporary studies of antidepressants (i.e., at least 80% power to detect ≥ 10% between-group differences in remission rates).[13] In the absence of large, adequately powered trials, meta-analytic approaches can be used to assess relative efficacy by combining information from the individual studies.[14] We therefore conducted a meta-analysis of original patient data from a complete set of 7 RCTs that compared bupropion to SSRIs (sertraline, fluoxetine, and paroxetine). In addition to response and remission rates, rates of attrition and common adverse

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Table 1. Study Designs of the 7 Pooled Randomized Controlled Trials

Study Treatment	Daily Dose, mg/d Mean	Daily Dose, mg/d Range	Safety/ ITT, N/N	Patients Discontinued, N (%)	Protocol Duration, wk
Feighner et al[7]					6
Bupropion IR	338	103–415	60/60	15 (25)	
Fluoxetine	26	10–41	60/60	16 (27)	
Kavoussi et al[8]					16
Bupropion SR	224	50–285	119/118	32 (27)	
Sertraline	104	36–175	125/118	42 (34)	
Coleman et al[10]					8
Bupropion SR	290	100–365	119/118	24 (20)	
Sertraline	107	42–167	115/109	40 (35)	
Placebo	…	…	121/117	37 (31)	
Croft et al[9]					8
Bupropion SR	293	127–361	118/116	34 (29)	
Sertraline	121	6–166	118/116	38 (32)	
Placebo	…	…	119/116	39 (33)	
Coleman et al[12]					8
Bupropion SR	289	100–351	143/135	49 (34)	
Fluoxetine	30	17–40	151/146	55 (36)	
Placebo	…	…	148/145	46 (31)	
Weihs et al[11]					6
Bupropion SR	199	100–254	48/47	8 (17)	
Paroxetine	22	10–31	52/49	8 (15)	
Unpublished[a]					8
Bupropion SR	282	90–352	141/138	56 (40)	
Fluoxetine	28	16–39	137/133	52 (38)	
Placebo	…	…	136/134	43 (32)	

[a]Data on file, GlaxoSmithKline, Research Triangle Park, N.C.
Abbreviations: IR = immediate release, ITT = intent to treat, SR = sustained release.

events, including treatment-emergent sexual dysfunction, are compared.

METHOD

This report includes original individual patient data from 7 RCTs comparing bupropion to sertraline,[8–10] paroxetine,[11] or fluoxetine (references 7 and 12 and data on file, GlaxoSmithKline, Research Triangle Park, N.C.). These were the only completed studies comparing these medications for treatment of major depressive disorder sponsored by any division of GlaxoSmithKline and its affiliates at the time this analysis was undertaken (i.e., January 2003) and, to our knowledge, represented every known RCT completed worldwide. The study designs are summarized in Table 1. All studies included a 1-week screening phase followed by either 6 weeks (2 studies[7,11]), 8 weeks (4 studies; references 9, 10, and 12 and data on file, GlaxoSmithKline, Research Triangle Park, N.C.) or 16 weeks (1 study[8]) of double-blind therapy. Four studies included a placebo group (references 9, 10, and 12 and data on file, GlaxoSmithKline, Research Triangle Park, N.C.). All but one[7] of the trials evaluated the sustained release (SR) formulation of bupropion. Studies were conducted in accordance with International Conference on Harmonisation guidelines[15] for conduct of efficacy and safety studies of pharmaceuticals (including written informed consent) and were approved by the institutional review board of each investigational site.

Patients

In 6 studies (references 7–10 and 12 and data on file, GlaxoSmithKline, Research Triangle Park, N.C.), eligible patients were at least 18 years of age; the seventh study[11] enrolled patients aged 60 and older. All patients met criteria for a current episode of moderate to severe recurrent major depressive disorder of at least 1 month's duration as defined in the *Diagnostic and Statistical Manual of Mental Disorders*, Third Edition, Revised (DSM-III-R) or Fourth Edition (DSM-IV). Prior to receiving study medication, patients were required to score a minimum of either 18 or 20 on the 21-item Hamilton Rating Scale for Depression (HAM-D-21).[16] All studies excluded patients with chronic major depression (i.e., current episode greater than 2 years' duration). Patients who were predisposed to seizures or were receiving medications that lowered the seizure threshold also were excluded from all studies. Five studies[7–11] excluded patients with any previous exposure to bupropion or the comparator SSRI; the remaining 2 studies (references 12 and data on file, GlaxoSmithKline, Research Triangle Park, N.C.) excluded patients with exposure to either study medication during the previous year. Two studies[11,12] also excluded patients who had previously not responded to any form of antidepressant treatment.

In 5 studies (references 8–10 and 12 and data on file, GlaxoSmithKline, Research Triangle Park, N.C.), eligibility depended on patients' reports of normal sexual functioning (i.e., not currently experiencing orgasm dysfunction, premature ejaculation, dyspareunia, vaginismus, or a sexual arousal disorder). Participants of these studies also had to report a history of engaging in sexual activity that could lead to orgasm at least once every 2 weeks.

Study Medication

A total of 2030 patients were randomly assigned to receive bupropion (N = 748), an SSRI (N = 758), or (in 4 trials) placebo (N = 524). All studies used double-dummy, escalating, flexible-dose designs in which doses were titrated for each patient to optimize therapeutic response. Doses of active study medications were bupropion SR 150 to 400 mg/day (N = 521), bupropion SR 100 to 300 mg/day (N = 167), bupropion immediate release (IR) 225 to 450 mg/day (N = 60), sertraline 50 to 200 mg/day (N = 358), fluoxetine 20 to 60 mg/day (N = 288), fluoxetine 20 to 80 mg/day (N = 60), and paroxetine 10 to 40 mg/day (N = 52).

Efficacy and Safety Assessments

The primary analyses were performed on the intent-to-treat (ITT) study group (N = 1975), which included all patients who had at least 1 evaluation on double-blind

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Table 2. Pretreatment Characteristics of the Treatment Groups (safety population, N = 2030)[a]

Characteristic	Bupropion (N = 748)	SSRI (N = 758)	Placebo (N = 524)
Age, y			
Mean (SD)	40 (13.0)	41 (13.6)	38 (10.9)
Range	18–85	18–88	18–65
Sex, %			
Female	56	56	58
Male	44	44	42
Race, %			
White	86	88	84
Black	8	6	10
Other	6	6	6
Modal dose, mean, mg/day	313	NA[b]	NA
Daily dose, mean, mg/day	276.1	NA[c]	NA
HAM-D-17 total score, mean (SE)[d]	22.5 (0.1)	22.4 (0.1)	22.0 (0.2)

[a]Data from Feighner et al.[7]; Kavoussi et al.[8]; Croft et al.[9]; Coleman et al.[10,12]; Weihs et al.[11]; and data on file, GlaxoSmithKline, Research Triangle Park, N.C.
[b]Mean modal doses: sertraline (N = 358) = 128 mg/day, fluoxetine (N = 348) = 25 mg/day, and paroxetine (N = 52) = 25 mg/day.
[c]Mean daily doses: sertraline = 110.5 mg/day, fluoxetine = 28.4 mg/day, and paroxetine = 221 mg/day.
[d]Mean HAM-D-17 scores are based on the ITT population (N = 1975).
Abbreviations: HAM-D = Hamilton Rating Scale for Depression, ITT = intent to treat, NA = not applicable, SSRI = selective serotonin reuptake inhibitor.

therapy. The last-observation-carried-forward (LOCF) method was used to estimate the outcomes of patients who did not complete the treatment protocols. The HAM-D was completed to assess symptom severity at week 0 and at either weekly or every other week intervals thereafter. The outcome of primary interest was remission, which was defined as a score of ≤ 7 on the first 17 items of the HAM-D at study endpoint.[13]

Tolerability indices of study medications were compared, including attrition rates and the incidence of common adverse events. In 5 trials (references 8–10 and 12 and data on file, GlaxoSmithKline, Research Triangle Park, N.C.), the presence of sexual dysfunction (i.e., orgasmic dysfunction, sexual arousal disorder, and sexual desire disorder, as defined by DSM-IV criteria) was evaluated at each visit via an investigator-conducted (blinded to study medication) interview.

Statistical Analyses

The analyses of response and remission rates were conducted using a logistic regression model that contained the following terms: study, week 0 HAM-D-17 score, and treatment. Given the likelihood of similar outcomes, therapeutic equivalence (i.e., noninferiority) within 5% of remission rates between the bupropion and pooled SSRI group was established by a 95% confidence interval (CI). Incidence of sexual dysfunction (orgasmic dysfunction, sexual arousal disorder, and sexual desire disorder) was compared as a dichotomous value (present/absent) by using a logistic regression model that contained the following terms: study, sex, and treatment. The equivalence within 5% between bupropion and placebo was also established by a 95% CI. Pairwise comparisons of other common adverse events were performed with Fisher exact probability tests. Statistical analyses were considered significant when $p \leq .05$.

RESULTS

Background

Pretreatment patient characteristics are presented in Table 2. The bupropion, SSRI, and placebo groups were similar on all variables. Figure 1 summarizes remission rates in the 7 individual studies. In no case did the difference between active therapies approach conventional statistical significance. Bupropion was significantly more effective than placebo in 2 of the 4 comparisons. The comparator SSRI was significantly more effective than placebo in 1 of the 4 comparisons.

Primary Efficacy Analysis

Depression remission rates for the ITT study group (bupropion, N = 732; SSRIs, N = 731; and placebo, N = 512) are summarized in Figure 2. Remission rates on active therapy were identical at 47% and statistically equivalent within 5%; the 95% CI for the difference was –0.05 to 0.05. The odds ratio of remission rates was 1.00, with 95% CI = 0.81 to 1.23.

Both bupropion (Wald $\chi^2 = 9.18$, df = 1, $p < .01$) and the SSRIs (Wald $\chi^2 = 9.35$, df = 1, $p < .01$) were significantly more effective than placebo (36%). The odds ratio for remission with bupropion versus placebo was 1.46, with 95% CI of 1.14 to 1.86, while the odds ratio of SSRI versus placebo was 1.46, with 95% CI of 1.15 to 1.87. Similarly, when the analysis was limited to the 4 placebo-controlled studies, remission rates on both active therapies were identical at 45%, and both bupropion (Wald $\chi^2 = 9.10$, df = 1, $p < .01$) and SSRI (Wald $\chi^2 = 8.37$, df = 1, $p < .01$) therapies were significantly more effective than placebo. Among the placebo-controlled studies, the remission rate odds ratio of bupropion versus placebo was 1.48, with 95% CI of 1.15 to 1.91, while the odds ratio of SSRI versus placebo was 1.46, with 95% CI of 1.13 to 1.88.

Secondary Efficacy Analysis

Additional comparisons included remission rates for the observed cases sample at the study endpoint (either week 6 or 8) and response rates (i.e., ≥ 50% reduction in HAM-D-21 scores) for both the ITT (LOCF) and observed cases (completers) samples. Results of these comparisons are summarized in Table 3. Regardless of the study group or definition of favorable outcome, the same pattern of results was observed: both active treatments

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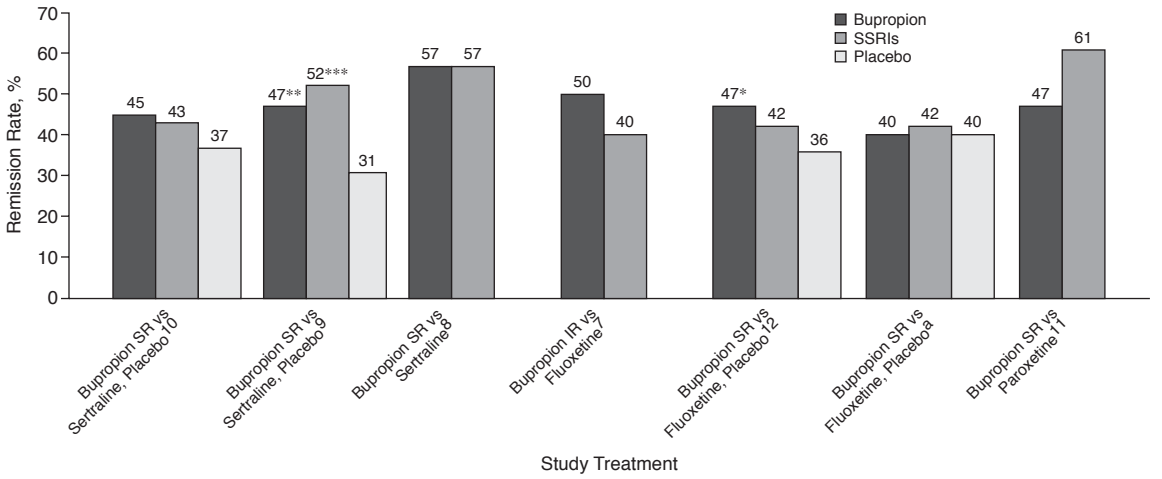
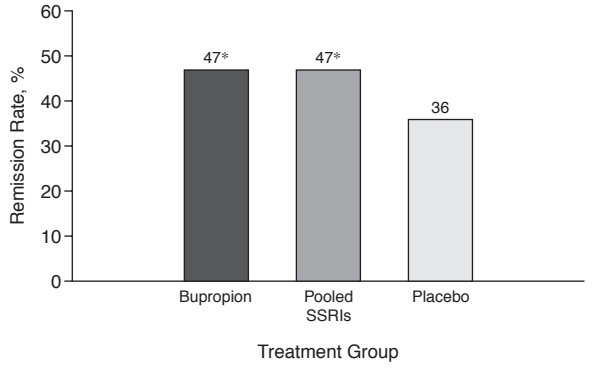
Figure 1. Remission Rates at Week 8 or Endpoint for 7 Individual Studies (ITT/LOCF)



[a]Data on file, GlaxoSmithKline, Research Triangle Park, N.C.
*p < .05, bupropion versus placebo.
**p < .01, bupropion versus placebo.
***p < .001, SSRI versus placebo.
Abbreviations: IR = immediate release, ITT = intent to treat, LOCF = last observation carried forward, SR = sustained release, SSRI = selective serotonin reuptake inhibitor.

Figure 2. Remission Rates at Week 8 or Endpoint for Bupropion, SSRI, and Placebo Treatment Groups[a,b]



[a]Data from Feighner et al.[7]; Kavoussi et al.[8]; Croft et al.[9]; Coleman et al.[10,12]; Weihs et al.[11]; and data on file, GlaxoSmithKline, Research Triangle Park, N.C.
[b]Remission was defined as HAM-D-17 total score of ≤ 7 at week 8 or endpoint (ITT/LOCF). Bupropion (N = 732), pooled SSRIs (N = 731), and placebo (N = 512).
*p < .01, bupropion and pooled SSRIs versus placebo.
Abbreviations: HAM-D-17 = 17-item Hamilton Rating Scale for Depression, ITT = intent to treat, LOCF = last observation carried forward, SSRI = selective serotonin reuptake inhibitor.

were significantly more effective than placebo, and bupropion and the SSRIs were comparably effective.

Tolerability

Overall, 59% of patients completed double-blind treatment, with comparable percentages of patients completing treatment in each arm (bupropion, 59%; SSRI, 55%; placebo, 65%). The most common reason for not completing treatment was "consent withdrawn" (12.6%), affecting similar percentages of patients treated with bupropion (12%), SSRI (13%), and placebo (13%). Identical percentages of bupropion- and SSRI-treated patients (7%) withdrew due to adverse events. Attrition due to adverse events was significantly greater in both active therapy groups when compared to the placebo group (2%) (Fisher exact probability tests, p < .01).

Figure 3 illustrates the incidence of sexual dysfunction in the 1759 patients (bupropion SR, N = 625; sertraline and fluoxetine, N = 622; and placebo, N = 512; ITT) who participated in the 5 RCTs in which sexual dysfunction was formally assessed (references 8–12 and data on file, GlaxoSmithKline, Research Triangle Park, N.C.) (sexual dysfunction was not formally assessed in the studies of paroxetine[11] and bupropion IR/fluoxetine[7]). SSRI treatment resulted in significantly higher rates of orgasmic dysfunction and sexual arousal disorder compared to both bupropion SR and placebo (see Table 4). In addition, the orgasmic dysfunction (95% CI = –2.7 to 4.7) and sexual arousal disorder rates (95% CI = –3.7 to 1.7) for bupropion SR and placebo were statistically equivalent within 5%.

The incidence of sexual desire disorder at week 8 was significantly higher among the SSRI group (27%) compared to both the bupropion SR (18%, Wald $\chi^2 = 15.26$, df = 1, p < .001) and placebo (19%, Wald $\chi^2 = 4.76$, df = 1, p < .05) treatment groups. However, as these comparisons included patients who met criteria for sexual desire disorder at the start of double-blind therapy, analyses were

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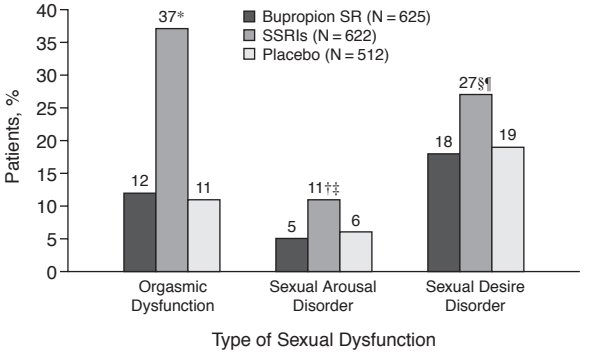
Table 3. Secondary Efficacy Analyses Comparing Bupropion, SSRIs, and Placebo[a]

Study Group	Outcome[b]	Rate of Response/Remission, % (N/N)			Significance (χ^2)[d]			
		Bupropion	SSRIs[c]	Placebo	Overall	Bupropion vs Placebo	SSRI vs Placebo	Bupropion vs SSRI
ITT (LOCF)	Response	62 (456/732)	63 (463/731)	51 (260/512)	23.0	16.3	19.5	0.17
Observed cases (completers)	Response	77 (341/441)	77 (316/410)	64 (219/341)	21.1	16.2	15.0	0.01
Observed cases (completers)	Remission	60 (265/441)	62 (253/410)	47 (160/341)	19.5	13.4	16.4	0.23

[a]Data from Feighner et al.[7]; Kavoussi et al.[8]; Croft et al.[9]; Coleman et al.[10,12]; Weihs et al.[11]; and data on file, GlaxoSmithKline, Research Triangle Park, N.C.
[b]Response defined as ≥ 50% reduction in HAM-D-21 scores; remission defined as a final HAM-D-17 score of ≥ 7.
[c]Sertraline, fluoxetine, and paroxetine.
[d]χ^2 tests have either 2 (overall) or 1 (pairwise) degree(s) of freedom. Reported χ^2 values are statistically significant (all values, $p < .001$).
Abbreviations: ITT = intent to treat, LOCF = last observation carried forward, SSRI = selective serotonin reuptake inhibitor.

Figure 3. Incidence of Sexual Dysfunction in Bupropion SR, SSRI (fluoxetine and sertraline), and Placebo Treatment Groups[a]



[a]Data from Kavoussi et al.[8]; Croft et al.[9]; Coleman et al.[10,12]; and data on file, GlaxoSmithKline, Research Triangle Park, N.C.
*$p < .001$, SSRI vs. bupropion and placebo (orgasmic dysfunction).
†$p < .01$, SSRI vs. placebo (sexual arousal disorder).
‡$p < .001$, SSRI vs. bupropion (sexual arousal disorder).
§$p < .05$, SSRI vs. placebo (sexual desire disorder).
¶$p < .001$, SSRI vs. bupropion (sexual desire disorder).
Abbreviations: SR = sustained release, SSRI = selective serotonin reuptake inhibitor.

repeated for the subgroup of 1228 patients (bupropion SR, N = 427; pooled sertraline and fluoxetine, N = 428; and placebo, N = 373) that did not meet criteria for a sexual desire disorder at pretreatment. Rates of sexual desire disorder were again significantly higher among the SSRI group compared to both the bupropion SR and placebo treatment groups (see Table 4). By contrast, the treatment-emergent sexual desire disorder rates for bupropion SR and placebo were statistically equivalent within 5% (95% CI = –3.3 to 3.3).

To ensure that the apparent differences in rates of sexual dysfunction were not the result of an unanticipated drug-by-response interaction, rates of orgasmic dysfunction were recomputed for only the remitted patients. In this more advantaged subset, the same pattern of rates of orgasmic dysfunction were observed: bupropion, 11% (42/386); SSRI, 40% (156/387); and placebo, 13% (34/260).

Other common treatment-emergent adverse events were compared in the 2030 patients (bupropion, N = 748; SSRI, N = 758; and placebo, N = 524) who took at least 1 dose of study medication. The most common adverse events reported during treatment (i.e., those reported by ≥ 10% patients in at least 1 of the groups) are presented in Table 5. The proportions of patients who reported these adverse events were generally similar between the bupropion and SSRI treatment groups, except that the bupropion group experienced more dry mouth (21% vs. 16%, $p = .007$) and the SSRI group experienced more diarrhea (8% vs. 18%, $p < .001$) and somnolence (3% vs. 12%, $p < .001$). The number of serious adverse events reported was low (< 1% of all patients), and similar rates were reported in the bupropion, SSRI, and placebo treatment groups.

DISCUSSION

The results of individual RCTs usually suggest that there is little difference in efficacy between various classes of antidepressants. With respect to bupropion and the SSRIs, there have been 7 head-to-head studies, and none found significant differences in efficacy. Nevertheless, because these trials did not have the statistical power to reliably detect even 15% differences in remission rates, the possibility that type II error systematically obscured detection of more modest differences in efficacy (i.e., false negative findings) could not be excluded. This interpretive dilemma is precisely the reason that meta-analytic methods are increasingly used to fill the vacuum created by the absence of large, adequately powered studies comparing various types of modern antidepressants.[14]

There are 2 basic types of meta-analyses used to summarize and synthesize results from individual studies. The original data from individual patients are not typically available and, consequently, the meta-analysis must use the summary data from the individual studies. While

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Table 4. Incidence of Sexual Dysfunction During Double-Blind Treatment[a]

Test of Sexual Dysfunction	Incidence of Sexual Dysfunction, N (%)			Statistical Comparisons									
				SSRI vs Bupropion				SSRI vs Placebo			Equivalence Testing, Bupropion vs Placebo		
	Bupropion (N = 625)	SSRI (N = 622)	Placebo (N = 512)	Wald χ^{2b}	p	OR	95% CI	Wald χ^{2b}	p	OR	95% CI	Difference	95% CI	OR	95% CI
Orgasmic dysfunction	73 (12)	233 (37)	58 (11)	102.96	< .001	4.6	3.43 to 6.18	86.30	< .001	4.7	3.39 to 6.5	1%	–2.7 to 4.7	1.00	0.70 to 1.48
Sexual arousal disorder	33 (5)	70 (11)	32 (6)	14.26	< .001	2.3	1.49 to 3.56	8.52	< .01	1.95	1.25 to 3.06	–1%	–3.7 to 1.7	0.85	0.51 to 1.41
Treatment-emergent sexual desire disorder[c]	26 (6)	73 (17)	22 (6)	19.73	< .001	3.0	1.84 to 4.84	12.92	< .001	2.5	1.53 to 4.23	0%	–3.3 to 3.3	0.85	0.47 to 1.55

[a]Data from Kavoussi et al.[8]; Croft et al.[9]; Coleman et al.[10,12]; and data on file, GlaxoSmithKline, Research Triangle Park, N.C.
[b]df = 1.
[c]Patients with sexual desire disorders prior to treatment excluded from this analysis. Revised Ns are as follows: bupropion, N = 427; SSRI, N = 428; placebo, N = 373.
Abbreviations: OR = odds ratio, SSRI = selective serotonin reuptake inhibitor.

useful, this approach (1) requires a relatively large number of RCTs (because statistical power is dependent on the number of comparisons), (2) is susceptible to the "file drawer" effect (i.e., a large proportion of studies with negative findings go unpublished), and (3) can be biased by arbitrary selection of studies that are included in or excluded from the analysis.[14]

The second approach, a meta-analysis of individual patient data, is feasible when complete data sets are available. This approach provides a more powerful alternative when the number of RCTs is finite, because the analysis retains the outcomes of individual patients.[14] Thus, in the current pooled analysis, there were 1975 patients in the ITT study group, rather than 7 pairs of observations with about 730 patients in each active treatment group, and there was approximately 80% power to detect between-group differences in remission rates of 7% (i.e., 45% vs. 38%; χ^2 test, $p < .05$).

A meta-analysis of original patient data is not without problems, and, similar to a meta-analysis of studies, the file drawer effect and other study selection factors can bias results. Moreover, design differences among the studies (i.e., inpatient vs. outpatient, with or without placebo control, or fixed vs. flexible dosing) may compromise the validity of the pooling of results. These potential sources of bias are minimized in the present analysis, because we examined a complete set of ambulatory studies (i.e., no study comparing bupropion to an SSRI was omitted), all 7 studies used flexible dosing, and similar efficacy and safety endpoints were employed across studies.

Arguably the greatest strength of this report is that there was sufficient statistical power to conclude that "not statistically different" actually meant equivalently effective. Said another way, with more than 700 patients per treatment arm, it was possible to conclude with 99% certainty that bupropion and SSRI remission rates could not differ by 5% or more. In the case of therapeutic equivalence, it must be ensured that the standard of comparison (in this case, the SSRIs) was indeed effective. Otherwise, one is left with the unsatisfying conclusion that the medication being compared worked as well as a treatment of uncertain efficacy.

The efficacy of SSRI therapy in the current meta-analysis, as established versus double-blind placebo, was similar to the findings reported in other meta-analyses.[17,18] As summarized in Table 6, not only were the absolute drug–placebo differences similar across these different data sets (i.e., ranging from 5%–10% across meta-analyses), the likelihood of remission on SSRI therapy (as quantified by odds ratios) was comparable across data sets. Moreover, the results of these meta-analyses are similar to the effect sizes observed in the studies conducted by the manufacturers of the SSRIs, as submitted to the U.S. Food and Drug Administration for regulatory review.[19] Therefore, the conclusion of therapeutic equivalence in the current meta-analysis is based on a reliable estimate of SSRI efficacy.

The second strength is that the large study group permitted a more powerful comparison of tolerability indices than ever before possible. With the important exception of sexual side effects, bupropion and the SSRIs were similarly well tolerated, and the attrition rates of the 2 antidepressants due to adverse events were identical. The observed differences in rates of sexual dysfunction were not surprising and, in fact, were large enough to have been detected in all 5 of the individual trials that included these assessments (references 8–10 and 12 and data on file, GlaxoSmithKline, Research Triangle Park, N.C.). The statistical power of this meta-analysis did permit an extension of the earlier findings by demonstrating that the incidence of sexual side effects during bupropion therapy was *equivalent* to placebo within 5%. In contrast, the incidence of orgasm dysfunction alone during treatment with fluoxetine or sertraline was more than 3-fold greater. As sexual side effects are an important cause of nonadherence,

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Table 5. Common Adverse Events Reported During Double-Blind Treatment[a,b]

Adverse Event	Incidence of Adverse Events, %			Pair-Wise Comparisons (p values)		
	Bupropion (N = 748)	Pooled SSRIs (N = 758)	Placebo (N = 524)	Bupropion vs Placebo	SSRI vs Placebo	SSRI vs Bupropion
Any event	81	83	77	.066	.018	.592
Headache	31	29	27	.169	.488	.464
Dry mouth	21	16	15	.002	.529	.007
Nausea	17	21	14	.161	.002	.057
Insomnia	17	16	7	< .001	< .001	.623
Agitation	10	7	9	.497	.291	.053
Diarrhea	8	18	12	.018	.004	< .001
Somnolence	3	12	5	.232	< .001	< .001

[a]Data from Feighner et al.[7]; Kavoussi et al.[8]; Croft et al.[9]; Coleman et al.[10,12]; Weihs et al.[11]; and data on file, GlaxoSmithKline, Research Triangle Park, N.C.
[b]Safety population, N = 2030.
Abbreviation: SSRI = selective serotonin reuptake inhibitor.

Table 6. Efficacy of SSRI Therapy in 4 Recent Meta-Analyses

Study	Remission Rate, %[a]		Odds Ratio	95% CI
	SSRI	Placebo		
Current study	45	36	1.46	1.13 to 1.88
Thase et al[13]	30	25	1.34	1.00 to 1.80
Nemeroff et al[17]	29	24	1.33	1.10 to 1.61
Thase et al[18]	38	28	1.56	1.19 to 2.06

[a]Remission defined as LOCF HAM-D-17 score ≤ 7 at week 8 or study endpoint.
Abbreviations: HAM-D-17 = 17-item Hamilton Rating Scale for Depression, LOCF = last observation carried forward, SSRI = selective serotonin reuptake inhibitor.

minimizing sexual dysfunction could significantly improve overall satisfaction with treatment and the ultimate success of therapy.[20]

Perhaps the greatest shortcoming of this meta-analysis is that, like the individual RCTs, there is limited generalizability to everyday clinical practice. This is largely because only a fraction of patients seeking treatment for depression are eligible or willing to participate in controlled studies. Large simple trials, utilizing broader inclusion criteria and a minimum of exclusion criteria, are needed to ascertain if effectiveness is comparable in more representative populations.

Another limitation of the individual RCTs is that the efficacy comparisons ended after 6 to 8 weeks of therapy. Thus, we cannot rule out that significant differences may have emerged across 3 or 4 months of additional therapy.

A third limitation is that the patients enrolled in these studies were relatively responsive to placebo, with pooled placebo response and remission rates of 51% and 36% in the ITT/LOCF sample. High placebo response rates significantly reduce the design sensitivity of RCTs,[19] and the meta-analysis of Walsh et al.[21] documents that the likelihood of placebo response in antidepressant RCTs has virtually doubled over the past 30 years. That average drug–placebo differences are smaller than anticipated in contemporary studies is reflected in this data set by the fact that 3 of the 4 placebo-controlled studies failed to detect a significant effect for the SSRI comparator.

A fourth limitation of the current meta-analysis is that there were no studies of citalopram, escitalopram, or fluvoxamine. Further, there was only a single study using paroxetine as the active comparator, and this late-life depression study was the smallest of the 7. It therefore must be noted that our results basically reflect the comparisons of bupropion with fluoxetine and sertraline. We believe that it is appropriate to group the individual SSRIs together as a class, as has been done for other comparisons of SSRIs versus tricyclic antidepressants,[22,23] venlafaxine,[13,15,24] mirtazapine,[25] or duloxetine.[18] Confidence in grouping together the SSRIs is strengthened by a lack of consistent evidence favoring one member of the class over the others.[26] Nevertheless, the various SSRIs are not fully interchangeable, and it is possible that subtle differences in efficacy or tolerability might affect the results of a pooled analysis.

A final limitation of the current report is that the manufacturer of bupropion funded all of the studies included in this pooled analysis. Although independent replication is desirable, this issue is largely moot, because, at the time these data were collected, these were the *only* double-blind studies that compared bupropion and an SSRI. Moreover, 2 potential sources of proprietary bias (suppression of negative findings and unfair dosing)[14] were not factors. With respect to fair dosing, we consider comparisons of the average doses of bupropion and the SSRIs in relation to the minimum indicated doses to provide the best index. We note, however, that in none of the trials did the average dose of SSRI approach the maximum indicated dose. There are at least 3 other relevant RCTs conducted by independent sponsors: 2 studies of bipolar depression (1 is completed but the results are not yet known[27] and the other[28] is still under way) and 1 still ongoing study of treatment-resistant major depressive disorder.[29] It will be of interest to see if results in those special populations are consistent with these reported herein.

The finding that distinctly different classes of antidepressants can result in similar response and remission rates raises interesting theoretical questions. For example,

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are there common intracellular pathways that can be activated by medication effects on different serotoninergic, noradrenergic, or dopaminergic transporters or receptors? If so, the current findings indicate that the "dual reuptake inhibitor" effects of bupropion on norepinephrine and dopamine neurotransmission do not convey additional therapeutic efficacy. Alternatively, bupropion and the SSRIs may have only partly overlapping efficacy profiles, with specific efficacy for relatively small, similarly sized subsets of patients. In support of the latter position, we note that the placebo effect may account for up to 75% of activity of the antidepressants,[30] leaving only about 10% to 15% (i.e., 25% × 51%) true drug responders in each group.

CONCLUSION

The results of the current meta-analysis confirm that bupropion is as effective as the current standard of first-line therapy, the SSRIs,[31,32] with comparable overall tolerability and a significantly lower incidence of sexual dysfunction.

Drug names: bupropion (Wellbutrin and others), citalopram (Celexa and others), duloxetine (Cymbalta), escitalopram (Lexapro), fluoxetine (Prozac and others), mirtazapine (Remeron and others), paroxetine (Paxil and others), sertraline (Zoloft), venlafaxine (Effexor).

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