Safety Results

Patient Deaths and Serious Adverse Experiences

Thirteen SAEs, five in the Treatment and Taper Phases, and eight in the Follow-up Phase, have been reported to date. Four were classified in the cardiovascular body system, three in the skin body system, and six were in various other body systems. Three of the SAEs were fatalities, all of which occurred in the Follow-up Phase and were judged to be not reasonably attributable to study medication by the investigators and the reviewer. There were no seizures in this study. These SAEs are discussed below.

Deaths

Patient (HAB), a 67-year-old white female, experienced a fatal myocardial infarction approximately three months after completing the Treatment and Taper Phases. No prior history of cardiovascular disease had been reported. The patient had a recent history of an upper respiratory infection. An autopsy revealed an acute, focally transmural myocardial infarction with a rupture of the lateral left ventricle. Atherosclerotic coronary artery and aortic disease were also noted.

Patient (HAB), a 68-year-old white female, died of a pulmonary embolism approximately 4½ months after discontinuing study medication. The patient choked on some food and developed pneumonia for which she was admitted to the hospital two days before her death. The cause of death was listed as pulmonary thromboembolus due to right middle lobe pneumonia due to aspiration pneumonia due to choking on food.

Patient (HAB), a 52-year-old white male, fell while working on his house and experienced a fatal head injury. His last dose of study drug was approximately 6 months prior to the event.

Skin

Three patients (WB SR), (WB SR) and (WB SR/HAB)] experienced an SAE which was dermatologic in nature. All three patients were on treatment at the time of the event and all three events were rated as reasonably attributable to study medication.

Patient (WB SR), a 46-year-old white female, was seen in the ER on Day 20 of the study for treatment of an allergic reaction characterized by rash, pruritus, and dyspnea. At the time of the ER visit, the symptoms had been present for 1 to 2 days. Her vital signs were reportedly normal and no wheezing was noted on lung examination. The patient was noted to have matted areas of erythema with associated pruritus and was administered subcutaneous epinephrine and BENADRYL. She responded to the ER

interventions and was discharged the same morning on oral antihistamines. Study medication was discontinued at that time. Full resolution of symptoms occurred on Day 34. The patient's history was significant for a similar reaction 15 years prior attributed to minocycline. The prior reaction was characterized by erythema, dyspnea, edema and associated pruritus and had been treated with epinephrine and oral antihistamines.

Patient (WB SR), a 36-year-old white female, experienced a disseminated rash which began on Day 19 of the study with the onset of pruritus and hives. She contacted the investigator and was instructed to discontinue study medication; the next day she visited her primary care physician, who prescribed a prednisone taper. On Day 21, the patient presented at the ER complaining of diffuse rash, pruritus, and lower chest tightness on deep inspiration. The patient was noted to have raised erythematous lesions with associated pruritus ranging from 1-12 cm; lungs were noted to be clear. The patient was treated with subcutaneous epinephrine, and intravenous saline and SOLU-MEDROL. The ER diagnosis was erythema multiforme. She was discharged later that day on oral prednisone. Full resolution of symptoms occurred on Day 41.

Patient (WB SR/HAB), a 34-year-old white female, experienced a hypersensitivity drug reaction beginning on Day 14 of the study. On the evening of Day 14, the patient noticed pruritus on her chest and removed the nicotine patch. The next morning she noted hives and was seen at an urgent care facility. She was prescribed prednisone, cimetidine, and BENADRYL. Study medication was discontinued at that time. On Day 16, the patient noted swelling in her hands and knees and went to the ER, where she was diagnosed with an acute drug hypersensitivity reaction. She was treated with SOLU-MEDROL, SUSPHRINE, BENADRYL, and albuterol. The patient experienced symptom relief following these treatments and was discharged on a prednisone taper, cimetidine, and BENADRYL. Clinical laboratory assessments done at this time were within normal limits. On the evening of Day 16, she experienced pruritus and contacted her physician the morning of Day 17. At that time the patient had no respiratory symptoms or joint swelling, but presented with pruritus and extensive urticaria. She was prescribed ATARAX, which alleviated her symptoms. Full resolution of her symptoms was achieved on Day 33.

Cardiovascular

Four SAEs were cardiovascular in nature. All four occurred in the Follow-up Phase. Patient (WB SR) experienced chest pain, Patient (HAB) experienced a fatal myocardial infarction (see above), Patient (PBO) experienced a blocked iliac artery, and Patient (HAB) experienced a fatal pulmonary embolism (see above).

All four of these SAEs were considered by the investigator and the reviewer to be not reasonably attributable to study medication.

Patient (WB SR), a 45-year-old white female, experienced chest pain two days after completing the Treatment and Taper Phases. She was evaluated in the ER and hospitalized for evaluation. Cardiac catheterization, ECGs and blood tests for cardiac enzymes indicated no myocardial infarction or blockage. It was determined that the chest pain was likely secondary to cardiac artery spasms. The patient had smoked one pack of cigarettes per day for 25 years and stopped smoking during the study. Her family history was significant for cardiovascular disease.

Patient PBO), a 56-year-old white female, experienced leg pains that made it difficult for her to walk, beginning several weeks after completing the Treatment and Taper Phases. She underwent an angiogram and was diagnosed as having a blockage of the iliac artery. She underwent angioplasty as an outpatient on Day 146, but was hospitalized overnight as a precaution after she experienced frequent premature ventricular contractions (PVCs) during the procedure. The patient had a history of exertional dyspnea and dyspnea at rest for at least 4-6 months, admitted to being a very heavy coffee drinker, smoked very strong cigarettes, and had a history of PVCs both prior to and during the Treatment Phase of the study. In addition, the patient was taking NORVASC and hydrochlorothiazide for hypertension, PREMARIN and PROVERA for hormone replacement, and melatonin.

Other

Other five serious AE cases are listed below. The investigator judged that the events were not reasonably attributable to study medications. The reviewer agrees that the events were unlikely due to the study medications.

Patient (HAB), a 34-year-old white male, experienced asthma exacerbation secondary to a viral upper respiratory infection, which began on Day 65, the day after the patient completed the Treatment and Taper Phases. He was prescribed clarithromycin. Most of his symptoms resolved the next day, but he returned to his physician on Day 67 with congestion, increased shortness of breath and wheezing. He was treated with oxygen, intravenous steroids and nebulized inhalers and diagnosed with asthmatic exacerbation secondary to a viral upper respiratory infection. The patient was discharged on Day 74; symptoms resolved fully by Day 77.

Patient (HAB), a 38-year-old white female, was diagnosed with viral spinal meningitis during the study. Symptoms began on Day 60 of the study. She was admitted to the hospital on Day 64, where she was diagnosed with meningitis and treated with PERCOCET, DARVOCET-N, and intravenous morphine. She was discharged on Day 67 with prescriptions for PERCOCET and DARVOCET. Symptoms were fully resolved by Day 77.

Patient (WB SR/HAB) a 58-year-old white female, experienced leg pain approximately 4½ months after discontinuation of study medication. According to the history from the patient, her personal physician diagnosed "borderline lupus." Additional blood tests and a bone scan were scheduled. The patient also reported a concurrent non-serious kidney infection. She had no previous history of musculoskeletal or other related problems. Further information is unavailable as the patient has refused to sign a release-of-information form.

Patient (WB SR/HAB), a 59-year-old white female, was hospitalized overnight for rheumatoid arthritis approximately seven months after her last dose of study medication. She was treated with antibiotics and steroids and had fluid aspirated from the left elbow. Approximately three to four years previously, the patient was diagnosed with bone chips in the left elbow. She had reported a sore elbow joint during the Treatment Phase.

Patient (WB SR), a 46-year-old white male, experienced chest pain on Day 4 of the study. At Screening, the patient had reported a history of episodes of chest tightness which occurred about once a week and were not brought on or worsened by exertion; these episodes could be relieved with antacids or aspirin. He denied a history of chest pain or pressure. On Day 4, he presented at the ER with complaints of chest pain and was admitted for observation. The pain lasted approximately two hours. The pain was not relieved by nitroglycerin and according to the patient did not go away until his wife left the room. At the time of discharge on Day 5, ECGs and blood tests for cardiac enzymes revealed no heart problems. A stress echocardiogram was performed on Day 6; results were negative. It was determined that the chest pain was likely due to gastric reflux for which he was prescribed PRILOSEC. The last dose of study medication was taken on the morning of Day 7.

AEs Leading to Premature Discontinuation of Study Medication

Of the 893 patients randomized to treatment, 311 (34.8%) discontinued study medication(s) prematurely: 78 (48.8%) in the PBO group, 76 (31.1%) in the WB SR group, 87 (35.7%) in the HAB group, and 70 (28.6%) in the WB SR/HAB group. A total of 134 of the 311 patients who prematurely discontinued study medication agreed to enter the Follow-up Phase of the study. The reasons for discontinuation are summarized by treatment group in the table below.

Summary of Reasons for Premature Discontinuation of Tablet and/or Patch Medication

Reason for Discontinuation	PBO		WB SR		HAB		WB SR/HAB		TOTAL	
	N = 160		N = 244		N = 244		N = 245		N = 893	
	N	%	N	%	N	%	N	%	N	%
Adverse Experience	6	3.8	29	11.9	16	6.6	28	11.4	79	8.8
Consent Withdrawn	56	35.0	35	14.3	56	23.0	35	14.3	182	20.4
Lost to Follow-Up	3	1.9	3	1.2	2	0.8	0	0.0	8	0.9
Protocol Violation	4	2.5	1	0.4	6	2.5	1	0.4	12	1.3
Scheduling Difficulties	9	5.6	8	3.3	7	2.9	6	2.4	30	3.4
Total	78	48.8	76	31.1	87	35.7	70	28.6	311	34.8

A total of 79 (8.8%) patients 6 (3.8%) PBO, 29 (11.9%) WB SR, 16 (6.6%) HAB, 28 (11.4%) WB SR/HAB prematurely discontinued tablet and/or patch study medication during the Treatment and Taper Phases for an adverse experience. Forty-three of these 79 patients discontinued only one treatment (24 discontinued tablets only, 19 discontinued patches only). Twenty-four completed the study on the second medication and 19 prematurely discontinued the second medication.

If patients who prematurely discontinued only patch medication are excluded, then 26 (10.7%) patients in the WB SR group prematurely discontinued tablet medication compared to 3 (1.9%) patients in the PBO group. Similarly, if patients who prematurely discontinued only tablet medication are excluded, then 12 (4.9%) HAB patients prematurely discontinued patch medication compared to 4 (2.5%) PBO patients.

A total of 30 patients (1 PBO, 14 WB SR, 8 HAB, 7 WB SR/HAB) discontinued study medication(s) due to an AE judged to be severe in intensity and 5 patients (3 WB SR, 1

HAB, 1 WB SR/HAB) discontinued study medication(s) due to an AE judged to be serious (see Section Patient Deaths and Serious Adverse Experiences). Application site reaction and rash were the most commonly cited AEs leading to premature discontinuation of study medication. Application site reaction was reported in 9 patients (2 WB SR, 2 HAB, and 5 WB SR/HAB). Rash was reported in 9 patients (4 WB SR, 1 HAB, and 4 WB SR/HAB). Urticaria was the third most common reason for premature discontinuation, 7 patients (4 WB SR, 1 HAB, and 2 WB SR/HAB).

Other Adverse Experiences

All reported adverse experiences (AEs) were listed, but only treatment-emergent AEs were summarized. A treatment-emergent AE is one that was not present during Screen and emerged during treatment or one that was present during Screen and worsened in seriousness and/or intensity with treatment. Reported adverse experience terms were grouped using COSTART body systems. The number and percent of patients who reported a treatment-emergent AE while on study medication were tabulated by treatment group and by phase of the study (i.e., Treatment, Taper, and Follow-up Phases).

Of the 889 patients in the safety database, 776 (87%) reported at least one treatment-emergent AE during the 7-week Treatment Phase. The incidence of AEs, in general, was slightly higher in both the WB SR group and the WB SR/HAB group. The percentages of patients who reported at least one AE across treatment groups were 80%, 90%, 86%, and 90% for PBO, WB SR, HAB and WB SR/HAB groups, respectively. About two-thirds of AEs across all four treatment groups were rated as mild.

A summary of treatment-emergent AEs reported by 5% of patients in any of the active treatment groups is provided in the table below. Cardiovascular AEs were also listed in the table.

For the WB SR group, the most common AEs (10% incidence and more frequent than PBO) were insomnia, rhinitis and application site reaction. For two AEs (insomnia and pharyngitis), were the differences from PBO statistically significant. Other increased common AEs were nausea, constipation, disturbed concentration, and dizziness.

For the HAB group, the most common AEs were insomnia, dream abnormality, rhinitis and application site reaction. Eight AEs were reported more frequently in the WB SR group than in the HAB group: palpitation, dry mouth, disturbed concentration, dizziness, insomnia, nervousness, urticaria, and menstrual disorder. The adverse experience profile of HAB is slightly better than those seen with WB SR and WB SR/HAB. This same conclusion is reached when the incidence of premature discontinuation of study

medication(s) is compared, 7% for HAB compared to 12% for WB SR and 11% for WB SR/HAB.

For the WB SR/HAB group, the most common AEs were insomnia, nausea, dream abnormality, and application site reaction. For two AEs (dry mouth and insomnia), was the difference in incidence of occurrence between WB SR and PBO ≥5%. In addition, the incidence for anorexia, pharyngitis and pruritus was statistically significantly different from PBO.

For application site reaction, the incidence was highest for those on the active patches: 7%, PBO; 11% WB SR; 17% HAB; 15% WB SR/HAB. The majority (64% to 78%) of patients who had an application site reaction had an intensity rating of mild. Six patients (3 WB SR, 3 HAB) had an intensity rating of severe. Nine patients (2 WB SR, 2 HAB, 5 WB SR/HAB) had study medication(s) prematurely discontinued due to application site reaction. The data suggest that patients on WB SR might sensitize to application site reaction.

Mean blood pressure and pulse were either decreased or remained unchanged in all four treatment groups. PBO exhibited the greatest change with consistent decreases for both vital signs. Statistical analyses revealed differences at several timepoints between active groups and PBO. For SBP, there were six timepoints for WB SR (Weeks 2-6 and 8) and four timepoints for WB SR/HAB (Weeks 3, 5, 8 and 9), where statistically significant differences from PBO were noted. For all of these comparisons, change values were decreased for PBO (-2.4 to -5.2 mmHg) whereas values were relatively unchanged for WB SR (-0.1 to 0.8 mmHg) and WB SR/HAB (-0.7 to 0.4 mmHg). There were no statistically significant differences between HAB and PBO. These results reinforce the importance of monitoring blood pressure in patients with pre-existing hypertension in accordance with good clinical practice.

More WB SR/HAB patients met criteria for or had an adverse experience of hypertension. A total of 30 (3.4%) patients (5 (3.2%) PBO, 9 (3.7%) WB SR, 3 (1.2%) HAB, and 13 (5.3%) WB SR/HAB met the criteria for an increase in SBP or DBP or had hypertension reported as an AE while on study medication. Twenty-six (87%) of the 30 patients had evidence of pre-treatment hypertension (elevated Screen or Baseline blood pressure and/or a clinical history of hypertension). Four patients (1 HAB, 3 WB SR/HAB) had study medication(s) prematurely discontinued due to hypertension.

Weight gain occurred across all groups and was greatest in the PBO group, and least in the WB SR/HAB group.

A total of 176 patients reported a Taper Phase treatment-emergent AE with similar percentages across groups (19% to 21%). The incidence of individual AEs was low and differences in percent incidence between active groups and PBO were small with the largest difference (active treatment incidence higher than PBO) being 2%.

Common Treatment-Emergent Adverse Experiences (>= 5%) and Cardiovascular Aes By Treatments: WB SR, HAB, and WB SR/HAB Groups, While In the Treatment Phase

Body System	Adverse Experience (Costart Term)	PBO Number of Patients N	PBO (%)	WB SR Number of Patients N	WB SR (%)	HAB Number of Patients N	HAB (%)	WB SR/HAB Number of Patients N	WB SR/HAB (%)	Total Number of Patients N	Total (%)
Number of patients who took >=1 dose of the study drug		159		243		243		244		889	
Body	HEADACHE	44	(27.7)	55	(22.6)	63	(25.9)	62	(25.4)	224	(25.2)
	INFECT	22	(13.8)	26	(10.7)	29	(11.9)	26	(10.7)	103	(11.6)
	FLU SYND	13	(8.2)	15	(6.2)	18	(7.4)	15	(6.1)	61	(6.9)
	PAIN BACK	12	(7.5)	12	(4.9)	14	(5.8)	10	(4.1)	48	(5.4)
Digestive	NAUSEA	7	(4.4)	22	(9.1)	17	(7.0)	27	(11.1)	73	(8.2)
	DRY MOUTH	7	(4.4)	23	(9.5)	9	(3.7)	22	(9.0)	61	(6.9)
	DYSPEPSIA	12	(7.5)	16	(6.6)	16	(6.6)	12	(4.9)	56	(6.3)
	CONSTIP	5	(3.1)	19	(7.8)	10	(4.1)	21	(8.6)	55	(6.2)
Nervous	INSOMNIA	29	(18.2)	98	(40.3)	69	(28.4)	110	(45.1)	306	(34.4)
	DREAM ABNORM	4	(2.5)	11	(4.5)	43	(17.7)	32	(13.1)	90	(10.1)
	ANXIETY	9	(5.7)	19	(7.8)	15	(6.2)	23	(9.4)	66	(7.4)
	DISTURBED CONCENTRAT	7	(4.4)	21	(8.6)	8	(3.3)	21	(8.6)	57	(6.4)
	DIZZINESS	10	(6.3)	23	(9.5)	5	(2.1)	19	(7.8)	57	(6.4)
	NERVOUSNESS	14	(8.8)	16	(6.6)	14	(5.8)	13	(5.3)	57	(6.4)
	IRRITABILITY										
Respiratory	RHINITIS	13	(8.2)	30	(12.3)	26	(10.7)	21	(8.6)	90	(10.1)
Skin	APPLICAT SITE REACT	11	(6.9)	27	(11.1)	42	(17.3)	37	(15.2)	117	(13.2)
	PRURITUS	1	(0.6)	8	(3.3)	2	(0.8)	13	(5.3)	24	(2.7)
Cardiovascular	HYPERTENS	0		2	(0.8)	1	(0.4)	5	(2.0)	8	(0.9)
	PALPITAT	0		4	(1.6)	0		3	(1.2)	7	(0.8)
	TACHYCARDIA	2	(1.3)	1	(0.4)	2	(0.8)	1	(0.4)	6	(0.7)
	HOT FLASHES	1	(0.6)	2	(0.8)	1	(0.4)	2	(0.8)	6	(0.7)
	MIGRAINE	0		2	(0.8)	1	(0.4)	0		3	(0.4)
	VASODILAT	0		0		1	(0.4)	1	(0.4)	2	(0.2)

CONCLUSIONS

The study provided substantial evidence of efficacy of WELLBUTRIN SR 300 mg/day as an aid to smoking cessation in conjunction with brief individual smoking cessation and relapse prevention counseling.

The study also provided supportive evidence of efficacy of the combination WELLBUTRIN SR 300 mg/day and HABITROL 21 mg/day as an aid to smoking cessation when administered as part of a treatment program. The conclusion was made base upon the fact that the efficacy was only demonstrated in a single study, and optimal combination of the WB SR and HABITROL was not studied.

In this study, the WB SR reduced six of the eight DSM-IV symptoms of nicotine withdrawal compared to PBO, which may explain its efficacy in smoking cessation, especially in preventing early smoking relapse.

WELLBUTRIN SR was associated with insomnia, rhinitis, nausea, constipation, disturbed concentration, and dizziness.

Unusual risks of WELLBUTRIN SR appear to be dermatologic hypersensitivity drug reaction (1%), and the combination WELLBUTRIN SR and HABITROL might be associated with hypertension in a small group of people (1%).

Chang Q Li 11/15/96

Chang Q. Li, MD, DrPH
Medical Review Officer

NDA 20-711

CC: Original
HFD-170 Division File
HFD-170 Chang Q Li

11/15/96

Celia Winchell
Medical Peer Review

REVIEW AND EVALUATION OF CLINICAL DATA
Consultative Review

NDA:	20-711 Zyban (20-358-Wellbutrin SR [bupropion sustained release for the treatment of depression])
Sponsor:	GlaxoWellcome
Drug:	Zyban (bupropion sustained release)
Indication:	Smoking Cessation Aid
Dates of Submission:	April 2, 1997
Materials Reviewed:	Draft Labeling
Consult requested by:	Celia Winchell HFD-170

Background
Wellbutrin SR is the trade name for bupropion HCl sustained release formulation (BSR) made by Glaxo-Wellcome Co. marketed for the treatment of depression. Wellbutrin immediate release tablets are currently marketed for the same indication.

The sponsor now wishes to market BSR under another name as an aid to cessation of smoking. HFD-170 requested that HFD-120 review the draft labeling most recently negotiated with the sponsor to ensure that it does not conflict importantly with the labeling for Wellbutrin SR.

Review of Labeling
The description and clinical pharmacology section differ in that they do not discuss BIR; however, this is appropriate and does not withhold any information that is necessary regarding safe prescribing. The clinical trials section is clear and makes no claims beyond the scope of the data presented. The indications and contraindications sections are clear and include all of the contraindications noted in the BSR/BIR labeling for depression.

The warnings section allows safety information regarding 300 mg/day dose that was emphasized less in the BSR for depression labeling; however, this is appropriate in this case because the sponsor has shown efficacy in at least two well controlled studies at this maximum dose. The safety information for the higher doses is appropriately included even though the labeling is clear that Zyban should not be used at doses greater than 300

mg/day.

The adverse event section contains a table of events occurring at least one percent of the time and greater than placebo but does not include any comparisons to adverse events occurring in the depressed population. The 461 Zyban exposed patients and 150 placebo patients present a large enough group of patients for this table and adverse events in the two populations are similar enough not to include data from the depressed population.

The section on the use of Zyban in pregnancy suggests that pregnant patients first try smoking cessation using behavioral and supportive techniques before the use of pharmacologic intervention (lines 321-323). This strongly implies that pharmacologic intervention using Zyban and/or transdermal nicotine is at some clearly definable point appropriate in pregnant patients and therefore implies that the risk of using Zyban and/or transdermal nicotine patches during pregnancy outweighs the risk of smoking to the fetus. Is there data to support this?

The Zyban labeling is otherwise harmonious with the Wellbutrin SR labeling.

4/21/97

Paul J. Andreason, M.D., M.S.
Medical Reviewer, CDER, DNDP, HFD-120

cc: P Andreason
P David
G Dubitsky
T Laughren

4-22-97
I have no objection to the Zyban labeling as proposed.
T. Laughren, MD
TL, PDP

Review and Evaluation of Clinical Data

NDA 20-711
Sponsor: Glaxo Wellcome
Product: Bupropion SR
Reviewer: Celia Jaffe Winchell, M.D.
Protocol Reviewed: A Single Center Evaluation of Wellbutrin (bupropion hydrochloride) Versus Placebo as an Aid to Smoking Cessation (Study 401)

Abstract: This was a pilot study conducted without IND by the Principal Investigator of Study 402. Although the results were encouraging, flaws in randomization render this study supportive, but not substantial evidence of efficacy.

Design:

This was a small, pilot study similar in design to Study 402, conducted by Dr. Linda Hyder Ferry at the Jerry L. Pettis VAMC in Loma Linda, California. It was a single-center, parallel, randomized, double-blind, placebo-controlled trial involving 52 male outpatients who were heavily-dependent, chronic cigarette smokers. The study consisted of 4 phases: a Screen/Baseline Phase, a 12-week Treatment Phase, a 4-week Post-treatment Phase, and a 36-week Follow-up Phase. Clinic visits were scheduled at 2-week intervals during the Treatment and Post-treatment Phases. Follow-up evaluations were performed at 6 and 12 months.

Patients were included who were 21 to 75 years old, smoked on average at least 20 cigarettes per day, smoked before leaving the house in the morning, had made at least 2 previous attempts to stop smoking, and experienced withdrawal symptoms during cessation attempts. All patients signed an informed consent form and stated that they would set a target quit date during the first 4 weeks of the Treatment Phase. Patients were excluded who had uncontrolled chronic diseases, any predisposition to seizures, a history of psychiatric disorders, or a current history of chemical dependency, including alcohol.

Eligible patients entered the Treatment Phase and were randomized to received Wellbutrin, 100 mg t.i.d., or placebo as a component of a treatment program which included one hour group smoking cessation and relapse prevention counseling sessions on Study Days 4-8 and at each subsequent clinic visit through the end of the Post-treatment Phase.

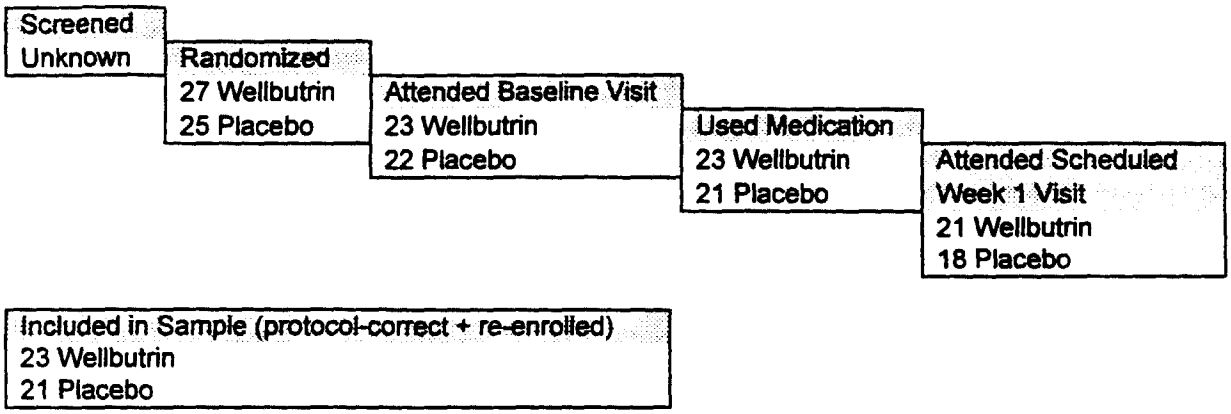
The study was not conducted under IND, and no primary efficacy measure was prospectively identified. The efficacy measures included abstinence from smoking during any consecutive 4-week period in the Treatment Phase; continuous abstinence from Day 29 to end-of-treatment; continuous abstinence from first successful quit week to end-of-treatment, 6 and 12 months; and weekly point prevalence abstinence rates. Smoking abstinence was ascertained by patient report and biochemical confirmation was determined by salivary cotinine ($\leq$ 15 ng/ml). Additional efficacy measures included the daily number of cigarettes smoked by nonquitters; nicotine craving, and nicotine withdrawal symptoms.

Results: Efficacy

Twelve Wellbutrin patients and 1 Placebo patient successfully quit for a period of 4 weeks during the treatment phase. All but one of the abstinent Wellbutrin patients maintained abstinence

through 12 months of follow-up. This finding is statistically significant whether an intent-to-treat denominator (all randomized patients) or a denominator including only those who used the medication is employed.

Randomization to medication conditions occurred prior to the no-treatment run-in. A total of 52 patients were randomized, but seven (4 Wellbutrin, 3 placebo) did not return to receive study medication. A fourth placebo patient dropped out of the study before receiving medication. Five patients (2 Wellbutrin, group A and 3 placebo, group B) attended the Baseline visit and received medication, but were unable to attend the scheduled Week 1 clinic visit and counseling session. These subjects were re-assigned to the therapy groups which had not yet convened (Wellbutrin group B and placebo group D).



There was not a differential rate of drop-out between the treatment conditions, a potential source of bias in studies in which randomization does not immediately precede initiation of treatment.

However, more importantly, because of the unavailability of a matching placebo, the investigator elected to separate placebo-treated and Wellbutrin-treated subjects by creating therapy groups that consisted of subjects who were all assigned to the same medication condition, in the hope that subjects would thereby be prevented from learning that there were two different colors of tablets. It seems that this was a relatively successful maneuver, as at the 12-month visit, the investigator asked subjects if they had been aware of the discrepancy in the color of the tablets, and if they had an idea of what treatment they were assigned to. No subjects reported awareness of the discrepancy during the treatment phase. Unfortunately, this effort to protect the blinding seriously damaged the randomization of treatment. Differences in group leaders, the presence of a particularly inspiring or discouraging colleague, or other group factors can influence the outcome of group psychotherapy even in the absence of any differences among groups with respect to medications used. The only way to control for these factors is to randomly distribute subjects from the various medication conditions among the groups. Furthermore, assuming that the medication had a beneficial effect on smoking cessation, one could expect the effect to be magnified as abstinent members of a group encourage the abstinence of others. In the placebo group, one would then expect the higher failure rate to produce a higher rate of discouragement among group members, and a lower rate of abstinence. In fact, although specific group assignment (A, B, C, D) is not reported, one can assume that the climate in the placebo groups differed from that in the Wellbutrin groups, since only two placebo subjects reported abstinence of at least a week in the first *six weeks* of the study, and one of these relapsed after a week. Conversely, 10 subjects in the two Wellbutrin groups quit within the first week and maintained abstinence for at least a week.

Because of the serious compromise of randomization in this study, the findings can be considered useful, hypothesis-generating results, but should not be included in the assessment of efficacy of Wellbutrin for smoking cessation or in the labeling regarding efficacy.

Results: Safety

Vital Signs/Weight

No statistically significant differences in treatment groups were seen with respect to systolic blood pressure changes from baseline. Diastolic blood pressure change from baseline showed a statistically significant difference at one year, where the mean change was -1.1 mmHg for the Wellbutrin group versus 6.2 mmHg for the Placebo group; this is unlikely to be related to drug administered over 6 months previously and has little clinical relevance. No statistically significant differences were noted with respect to pulse rates. Mean change in weight was greater for the Wellbutrin group than for the placebo group (2.4 kg vs 1.8 kg at end of treatment) and reached statistical significance at some time points (Weeks 8 and 10 of Treatment Phase and Weeks 14 and 16 of post-treatment phase). This may reflect the higher number of abstinent subjects in the Wellbutrin group.

Adverse Events

No patient deaths occurred during the Treatment Phase of the study.

One patient, assigned to Wellbutrin treatment, who had a history of coronary disease and angina underwent elective angioplasty during the last week of the Post-Treatment phase. The procedure was unsuccessful, and the patient required emergency CABG, after which he developed hypotension and died. He was stable at the time of the elective procedure and the unfortunate outcome was assessed by the investigator as being unrelated to study medication. This conclusion seems reasonable.

Another patient (placebo group) died during the follow-up phase from diabetic complications of a leg amputation. This was not attributed to study medication; this conclusion also seems reasonable.

There were no seizures; none would be expected in a sample this size. According to the study report, no other serious adverse events were reported during the conduct of the study. However, as noted below, two subjects required surgery for events which one would assume would require hospitalization, and therefore meet the criteria for seriousness. No other information on these subjects is provided.

Adverse events leading to premature discontinuation included:

Treatment	Pt #	Adverse Event
Placebo		Discontinued prior to surgery for small bowel obstruction
Wellbutrin		Nausea Nervousness Shakiness of the Hands Discontinued prior to surgery for septic arthritis Discontinued after sustaining head injury in MVA

Of the 44 subjects included in the safety sample, forty reported at least one adverse event, and some reported several (as many as 18). The small sample size makes it difficult to make comparisons between treatment groups, but insomnia/sleep disturbance, dry mouth,

anxiety/nervousness, and tremor appear to be drug-related. Chest pain was also reported more frequently by the Wellbutrin group, with verbatim terms vague enough (i.e. "chest pain," "chest tightness") that cardiovascular origin cannot be ruled out. The single report of angina was in the Wellbutrin group as well. However, chest pain (and cardiovascular events in general, apart from dizziness) has not generally been associated with Wellbutrin in previous placebo-controlled trials. Dyspepsia was also reported more frequently by the Wellbutrin group (5 subjects vs 1 placebo subject), but examination of Costart coding reveals that inconsistent coding of similar verbatim terms divided the reports between "Dyspepsia" and "Pain Abdomen." When these like terms are combined, the rates (5 Placebo vs 6 Wellbutrin) are similar. More frequently reported by the placebo group were back pain and changes in stool color (most frequent verbatim term: "dark stool," Costart term: "Stool Abnorm"). This latter AE was the most frequently reported event in the placebo group, with 10 subjects reporting (vs only 1 in Wellbutrin group). The clinical significance of this finding is unclear. All events reported in the study are listed below.

ADVERSE EVENTS REPORTED BY ONE OR MORE SUBJECTS

BODY SYSTEM	COSTART	PLACEBO (N = 21)		WELLBUTRIN (N = 23)	
BODY AS A WHOLE		N	%	N	%
	ANOREXIA	0	0%	1	4%
	APPETITE CHANGE	1	5%	0	0%
	ASTHENIA	0	0%	2	9%
	CHILLS	0	0%	1	4%
	FLU SYND	4	19%	2	9%
	HEADACHE	3	14%	2	9%
	INFECT	4	19%	2	9%
	INJURY ACCID	0	0%	1	4%
	MALAISE	0	0%	1	4%
	PAIN	1	5%	1	4%
	PAIN ABDO	4	19%	2	9%
	PAIN BACK	4	19%	0	0%
	PAIN CHEST	0	0%	5	22%
	REACT AGGRAV	0	0%	1	4%
CARDIOVASCULAR					
	ANGINA PECTORIS	0	0%	1	4%
	FLUSHING	0	0%	1	4%
	HYPERTENS	1	5%	0	0%
	HYPOTENS POSTURAL	0	0%	1	4%
	PALPITAT	0	0%	1	4%
	TACHYCARDIA	0	0%	1	4%
DIGESTIVE					
	CONSTIP	5	24%	7	30%
	DIARRHEA	2	10%	2	9%
	DRY MOUTH	4	19%	7	30%
	DYSPEPSIA	1	5%	5	22%
	FLATUL	2	10%	4	17%
	HEMORR RECTAL	1	5%	0	0%
	MELENA	1	5%	0	0%
	NAUSEA	3	14%	5	22%
	OBSTRUCT INTESTINE	1	5%	0	0%
	STOOL ABNORM	10	48%	1	4%
	VOMIT	0	0%	1	4%

BODY SYSTEM	COSTART	PLACEBO	(N = 21)	WELLBUTRIN	(N = 23)
METABOLIC AND	NUTRITIONAL	N	%	N	%
	EDEMA PERIPH	0	0%	1	4%
	HYPERGLYCEM	1	5%	1	4%
	THIRST	0	0%	1	4%
	WEIGHT DEC	1	5%	0	0%
	WEIGHT INC	0	0%	1	4%
MUSCULOSKELETAL					
	ARTHRITIS	1	5%	0	0%
	ARTHRITIS PYOGEN	0	0%	1	4%
	CRAMPS LEG	0	0%	1	4%
NERVOUS					
	ANXIETY	1	5%	3	13%
	DEPRESSION	1	5%	0	0%
	DIZZINESS	0	0%	4	17%
	EMOTION LABIL	1	5%	1	4%
	INSOMNIA	2	10%	6	26%
	IRRITABILITY	2	10%	4	17%
	MEMORY DECREASED	0	0%	1	4%
	NERVOUSNESS	1	5%	4	17%
	SLEEP DISORDER	2	10%	3	13%
	SOMNOLENCE	2	10%	1	4%
	THINKING ABNORM	0	0%	1	4%
	TREMOR	0	0%	4	17%
RESPIRATORY					
	BRONCHITIS	1	5%	0	0%
	COUGH INC	0	0%	2	9%
	DYSPNEA	0	0%	1	4%
	EPISTAXIS	1	5%	1	4%
	PHARYNGITIS	0	0%	1	4%
	RHINITIS	1	5%	2	9%
	SINUSITIS	1	5%	0	0%
SKIN					
	PRURITUS	2	10%	1	4%
	RASH	0	0%	1	4%
	SWEAT	0	0%	1	4%
	URTICARIA	0	0%	1	4%
SPECIAL SENSES					
	AMBLYOPIA	0	0%	1	4%
	BLEPHARITIS	0	0%	1	4%
	DIPLOPIA	0	0%	1	4%
	PAIN EAR	1	5%	0	0%
	TASTE PERVERS	0	0%	1	4%
UROGENITAL					
	DYSURIA	0	0%	1	4%
	IMPOTENCE	0	0%	1	4%
	URIN FREQUENCY	0	0%	1	4%

Reviewer's Comments/Conclusions

The design flaws in this study render it unsuitable as a pivotal trial. However, it is a helpful pilot study, with findings indicating that Wellbutrin 300 mg/day is effective as an aid to smoking cessation when used in conjunction with group counseling sessions, and that it is relatively well-tolerated, with few serious adverse events and few premature discontinuations related to non-serious events. Drug-related events appear to include sleep disturbance, dry mouth, tremor, and anxiety.

11/8/96

Celia Jaffe Winchell, M.D.
Medical Officer

11/14/96

Monte L. Scheinbaum, Ph.D., M.D.
Peer Reviewer

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Archival: NDA 20-711
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HFD-170/J. Ma
HFD-170/Division File

MEDICAL REVIEW

NDA#:	20711	
Drug:	bupropion SR	
Proposed Indication:	Smoking Cessation	
Sponsor:	Glaxo-Welcome	
Submitted:		
Reviewer:	E Douglas Kramer	
Peer Reviewer:	Celia Winchell	
CSO:		
Dates:	November 5, 1996	Review Assigned
	November 13, 1996	Review Completed

Nicotine replacement products (gum, patches) had been prescribed about times by the end of 1995. Other nicotine products have been approved (nicotine nasal spray). Still others are under review (nicotine inhaler). The safety experience with these products experience with these products has been remarkable. Adverse event reports are predominantly related to local irritant effects of the dosage form and symptoms consistent with nicotine withdrawal. Few serious adverse events have been reported, and many of these appear to be related to the long-term effects of smoking rather than to the effects of these products themselves. The adverse event profile is described below. Special attention is paid to the risk of seizure, since this is a new potentially serious adverse experience for smoking cessation products.

Nonserious Adverse Events

The adverse events associated with nicotine replacement products are of 5 types:

- Local irritant effects. These are usually application site reactions. Itching, redness, or myalgia are common with the nicotine patches. Mouth, tooth and jaw problems can be seen with the gum. Nicotine nasal spray can be quite irritating to the nasal passages and throat.

- Events consistent with nicotine withdrawal. Classic nicotine withdrawal symptoms (irritability, restlessness, impaired concentration, craving etc.) are common in smoking cessation studies. Dizziness is also commonly reported and may reflect an (expected) lowering of nicotine tolerance during quitting. In general, these symptoms are <u>less</u> on active treatment than on placebo.

- Events consistent with the pharmacologic effects of nicotine. Possible nicotinic effects associated with use of nicotine replacement products include minor gastrointestinal symptoms such as dyspepsia, nausea and abdominal pain and cardiac symptoms such as palpitations. These symptoms may be more common in persons with underlying GI or cardiac disease but they are not always more common on active medication in controlled trials. They are not associated with serious adverse effects.

- Events most likely attributable to the deleterious effects of smoking on health. Cough, bronchitis, shortness of breath and other respiratory complaints are common

among users of smoking cessation products. While the irritant effects of some nicotine delivery systems may contribute to these complaints (e.g. cough in the case of nicotine nasal spray), many instances would not appear to be attributable to the nicotine replacement per se.

- Events that are most likely unrelated to smoking, nicotine, or nicotine withdrawal. Intercurrent diseases (flu, infections, minor surgery etc.) are prominent in trials of smoking cessation products. While some of these events (e.g. lung cancer) would be attributable to the long term effects of smoking, most are not.

Serious adverse events

Serious adverse events occurring in association with nicotine replacement therapy are unusual. They are generally smoking-related diseases (e.g. lung cancer, bronchitis) or other pre-existing conditions that lead to hosptialization.

Myocardial Infarction

Although concern has been expressed about a possible relationship between myocardial infarction and the use of nicotine replacement products, studies from the OTC switch of these products involving thousands of subjects do not suggest that the rate of first myocardial infarction or cardiac death is greater than would be expected for a demographically similar population of smokers not on nicotine replacement therapy.

Seizures

Approximately 48 reports (including duplicates) of patients who may have experienced seizures while under treatment with nicotine replacement products are filed with the SRS. After removing obvious duplicates, illegible reports, reports with sufficient medical follow-up to point to an alternative diagnosis (e.g. heart attack), and reports with no information 27 remained. The breakdown of these is given in the following table:

Spontaneous Reports of Possible Seizures on Nicotine Replacement

Description	Number of Cases
History of seizures denied, no possible predisposing conditions reported	8
Seizure following cessation of use	1
On psychiatric medication	2
On anticonvulsant medication or history of predisposing factors (e.g. febrile childhood seizures, Hx of trauma, alcoholism, migraine).	6
Other known or suspected cause for possible neurological disorder (e.g. CJD, suicide attempt)	4
Possibly related to nicotine overdose	2
Insufficient information to classify. Possible non-epileptic event or minimal information about Dx and Rx.	6

These data do not suggest that nicotine replacement is likely to be associated with seizures. Many of these events may represent non-epileptic neuropsychiatric

disorders, or seizures occurring in susceptible individuals for unrelated reasons (e.g. history of seizures or predisposing conditions).

Assessment

Nicotine containing smoking cessation products have a remarkable safety record. Many of the adverse effects reported for these products likely to be the effects of nicotine withdrawal or local irritant effects related to the route of administration. Minor effects (mostly GI) possibly related to the pharmacologic actions nicotine are fairly common. Serious adverse effects are very rare and where they occur they are most likely to be related to a pre-existing medical condition or to the consequences of tobacco abuse.

E Douglas Kramer, MD
Medical Officer

11/13/96

Celia Winchell, MD
Medical Officer

11/13/96

CC: Orig. NDA 20-711
Div. File
HFD-170/B.McNeal
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HFD-170/T.Permutt
HFD-170/J.Ma
HFD-170/P.Lockwood
HFD-170/B.Hayes
HFD-170/P.Maturu
HFD-170/Q.Li

MEDICAL OFFICER REVIEW

NDA: 20-711
SPONSOR: Glaxo Wellcome
DRUG: Bupropion Hydrochloride Sustained Release
TYPE OF SUBMISSION: Safety Update
PROPOSED INDICATION: Smoking Cessation
MEDICAL OFFICER: Celia Jaffe Winchell, M.D.
PEER MEDICAL OFFICER: Curtis Wright, M.D.
LETTER DATE BY SPONSOR: 3/17/97
DATE RECEIVED BY CDER: 3/18/97
DATE RECEIVED BY REVIEWER: 3/25/97
REVIEW DATE: 4/7/97
CSO: Bonnie McNeal

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1. Abstract: Glaxo-Wellcome has submitted a final safety update for NDA 20-711, Bupropion Hydrochloride Sustained Release for Smoking Cessation. A previous update was submitted on October 11, 1996, but the material in that submission was incorporated into the original review of the NDA. In the present submission, the sponsor was asked to submit narratives of all deaths, serious adverse events, seizures, and anaphylactoid allergic reactions occurring since the October submission. This update includes events occurring in Study 405 (only the treatment phase had been completed at the time of the October submission), and two previously unidentified events occurring in the follow-up phase of Study 403. No new safety problems were identified in the review of these events. The summaries below incorporate information submitted in the original NDA submission, the 10/11/96 safety update, and the 3/17/97 safety update.

2. Dates of data collection: Serious adverse event data reported in Studies 403, 405 between 10/7/96 and 3/12/97 are included in this submission.

3. Serious Adverse Events
3.1 Study 403
A total of 615 patients were enrolled in the study. No patients died during the treatment phase of the study. However, one subject died of pulmonary edema two weeks after completing the 49-day treatment phase on WB SR 300. The patient had severe, pre-existing medical problems, and it seems plausible to classify this event as unrelated to study drug.

There were no seizures during the study.

The following two non-fatal serious adverse events occurred during the treatment phase of the study, **and were included in the original review of the NDA**. One subject experienced an episode of uncharacteristic "**uncontrollable rage**" during a traffic incident. The event is judged to be possibly attributable to study drug

One subject experienced an **anaphylactic reaction** (dyspnea, swelling, and petechiae) during the treatment phase of the study which can be considered possibly related to study drug.

There were also two SAE's during follow-up involving subjects randomized to placebo, **which were discussed in the original NDA review**: A 47 year-old male subject experienced a myocardial infarction and a 71 year-old white female subject contracted pneumonia.

Two previously unreported SAE's occurring during the follow-up phase were reported in the 3/17/97 safety update. Neither is considered related to study medication. A 45 year-old female subject randomized to receive bupropion SR 100 mg/day was hospitalized due to dehydration secondary to vomiting related to a migraine headache. The patient's last dose of study medication had been 4 months prior to the event. A 37 year-old male subject randomized to receive bupropion SR 150 mg/day was hospitalized for heparin treatment of deep vein thrombosis. The subject has a history of DVT's and had been off study medication for seven weeks.

3.2 Study 405
A total of 893 patients were enrolled in the trial.

There were three deaths during the study **which were discussed in the original NDA review**. All three occurred during the follow-up phase, involved patients who had been randomized to receive Habitrol only, and were considered not reasonably attributable to study drug. These included a 67 year-old white female who experienced a fatal myocardial infarction approximately three months after completing the Treatment and Taper phases; a 68 year-old white female who died of a pulmonary embolus approximately 4.5 months after discontinuing study medication; and a 52 year-old white male who sustained a fatal head injury in an accidental fall approximately 6 months after his last dose of study medication.

There were no seizures during the study.

There were sixteen non-fatal serious adverse events, five of which occurred during the Treatment and Taper Phases and eleven during Follow-up. Three events were judged to be reasonably attributable to study drug, and all involved anaphylactoid reactions in patients receiving active bupropion SR. **These events were also discussed in the original NDA review:**

A 46-year-old white female, randomized to receive WB SR, required emergency room treatment of an **allergic reaction** characterized by rash, pruritus, and dyspnea. She received subcutaneous epinephrine and Benadryl and was discharged the same morning on oral antihistamines. Study medication was discontinued at that time. The reaction was judged to be reasonably attributable to study drug.

A 36-year-old white female, randomized to receive WB SR, experienced **pruritus, hives, diffuse rash**, and lower **chest tightness on deep inspiration** requiring emergency room treatment with subcutaneous epinephrine, and intravenous saline and Solu-Medrol. The ER diagnosis was **erythema multiforme**. She was discharged later that day on oral prednisone. The event was judged to be reasonably attributable to study drug.

A 34-year-old white female, randomized to receive WB SR/HAB, developed pruritis and hives requiring treatment with prednisone, cimetidine, and Benadryl at an urgent care facility. Subsequently she noted swelling in her hands and knees and was treated in an emergency room with with Solu-Medrol, Susphrine, Benadryl, and albuterol, receiving a diagnosis of **acute drug hypersensitivity reaction**. She subsequently presented to her physician with pruritus and extensive urticaria. She was prescribed Atarax, which alleviated her symptoms. These events were judged to be reasonably attributable to study drug.

Seven other serious adverse events occurring in patients treated with bupropion SR were not reasonably attributable to study medication. **Four of these were discussed in the original NDA review.** Events included the following: A 45 year-old white female (WB SR) who was hospitalized for evaluation of chest pain two days after completing the Taper Phase. A 46 year-old white male (WB SR) was hospitalized for evaluation of chest pain on day 4 of the study and was diagnosed

with gastric reflux. A 46 year-old white male (WB SR) with a history of coronary artery disease experienced a myocardial infarction seven months after his last dose of study medication. A 56 year-old white male required hospitalization and CABG for chest pain eight months after his last dose of study medication. A 58 year-old white female (WB SR/HAB) experienced leg pain approximately 4.5 months after discontinuing study medication and received a diagnosis of "borderline lupus" from her personal MD. A 59 year-old white female (WB SR/ HAB) was hospitalized overnight for rheumatoid arthritis approximately 7 months after her last dose of study medication. A 57 year-old white female (WB SR) with a history of non-Hodgkins lymphoma developed a recurrence of lymphoma two months after her last dose of study medication.

The remainder of the serious events occurred in subjects randomized to receive either placebo or Habitrol alone and were not reasonably attributable to study medication.

These twenty-four events are summarized in the table below

Pt Description	Event (verbatim)	Event (Costart)	Phase of Study	Tx Group	On medication at onset?	Medication discontinued?
57 yo WF	Chest pain secondary to esophageal reflux	GI disorder	DB	unk	yes x 322 days	no
32 yo WM	Accidental death--airplane crash	Death	DB	unk	yes x 276 days	N/A
53 yo WF	Arachnoid cyst--Sylvian fissure	Cyst	DB	unk	yes x 337 days	yes
43 yo WF	Dehydration	Dehydration	DB	unk	no	N/A
70 yo WM	Paroxysmal atrial fibrillation with 2:1 AV block Loss of consciousness 2° to atrial fibrillation	Atrial fibrillation Atrial fibrillation	DB DB	unk unk	yes x 285 days yes x 333 days	no no
63 yo WF	Hole in retina in both eyes	Retinal disorder	DB	unk	yes x 324 days	no
53 yo WM	Gallstone	Cholelithiasis	DB	unk	yes x 360 days	no
45 yo WM	Gallbladder obstruction	Cholecystitis	DB	unk	yes x 316 days	no
63 yo WM	Sinus tachycardia	Tachycardia	FU	unk	no	N/A
52 yo WF	Sternal fracture due to accidental injury Traumatic pericarditis	Accidental injury Pericarditis	DB DB	unk unk	yes x 223 days yes x 223 days	no no
69 yo WM	Inferior posterior myocardial infarctions	Myocardial infarction	DB	unk	yes x 175 days	no
54 yo WM	Myocardial infarction	Myocardial infarction	DB	unk	yes x 94 days	no
48 yo WF	Chest pain	Chest pain	OL	300 mg/day	yes x 20 days	no
58 yo WF	Basal cell carcinoma	Carcinoma skin	DB	unk	yes x 74 days	no
60 yo WF	Adjustment disorder with mixed emotional features	Emotional lability	OL	300 mg/day	yes x 21 days	yes
63 yo WM	Prostate cancer	Carcinoma prostate	DB	unk	yes x 210 days	no
61 yo WM	Inguinal hernia	Hernia	OL	300 mg/day	yes x 40 days	no
50 yo WM	Angina	Angina	DB	unk	yes x 225 days	no
57 yo WM	Kidney stones	Kidney calculus	DB	unk	yes x 82 days	no
53 yo WM	Abnormal stress test with shortness of breath	Dyspnea	DB	unk	yes x 242 days	no
57 yo WM	Abdominal pressure	Abdominal pain	DB	unk	yes x 132 days	no
63 yo WM	Pulmonary edema	Edema lung	DB	unk	yes x 176 days	no

DB = double-blind OL = open-label FU = follow-up
Dose unknown for double-blind phase because blind has not been broken; all in DB phase completed open-label phase.

Additionally, two patients experienced allergic reactions requiring emergency room treatment during the open-label phase of the study. A 30 year-old white male developed a **rash, itching, and swelling of the lips and eyes** after 18 days of open-label treatment. He self-medicated with Benadryl and visited an emergency room where he received treatment with prednisone and Atarax and was discharged after a brief visit. The reaction resolved after four days and the patient was discontinued from the study. The event was rated as moderate, and possibly attributable to study drug.

A 43 year-old white female developed **hot flashes, a rash, and itching** after a month of open-label treatment. She was treated in an emergency room with Benadryl and epinephrine. She discontinued study medication and took a four day course of hydroxyzine. The reaction resolved within three days and the patient resumed study medication without recurrence of the rash. The event was rated as severe but not serious, and not reasonably attributable to study drug by the investigator.

4.0 Conclusions

This update reports that there have been no seizures reported to date in the 1732 patients who have been exposed to bupropion SR during these clinical trials. It also confirms the importance of warning patients regarding the possibility of allergic reactions which may warrant medical intervention, as there were two such events in the 781-patient Study This number is not unexpected, based on previous experience. This safety update reports few additional serious adverse events attributable to bupropion SR, and raises no new safety issues.

Celia Jaffe Winchell, M.D.
Medical Officer

Curtis Wright, M.D.
Acting Division Director

4/18/97

CC:
Orig NDA 20-711
HFD-170/Div File
HFD-170/CWinchell
HFD-170/BMcNeal
HFD-344
R/D Init. by: CWright/4-18-97
F/T by: sl/4-21-97

Medical and Statistical Review and Evaluation of Clinical Data

NDA 20-711
Sponsor: Glaxo Wellcome
Product: Bupropion SR
Reviewers: Celia Jaffe Winchell, M.D.
Z. Jonathan Ma, Ph.D.
Protocol Reviewed: A Multicenter Dose Response Evaluation of Wellbutrin (bupropion hydrochloride) Sustained Release Versus Placebo as an Aid to Smoking Cessation (Study 403)

1. Objective/Rationale

The objective of this trial was to compare the safety and efficacy of three doses of sustained-release bupropion and placebo as aids to smoking cessation in chronic cigarette smokers when used in conjunction with brief, individual counseling.

2. Investigators and Locations

Three sites participated in this trial. The investigators were Elbert D. Glover, Ph.D., at the West Virginia University Health Sciences Center, Richard D. Hurt, M.D., at the Mayo Clinic, and David P.L. Sachs, M.D., at the Palo Alto Center for Pulmonary Disease Prevention.

3. Design

This was a parallel, randomized, multicenter, double-blind, placebo-controlled trial involving 615 male and female chronic cigarette smokers. The study consisted of 3 phases: a Screen/Baseline Phase (minimum of 7 days), a 7-week Treatment Phase, and a 45 week Follow-up Phase. Eligible patients entered the Treatment Phase and were randomized to receive either WB SR 100 mg/day (50 mg b.i.d.), WB SR 150 mg/day (150 mg q.d.), WB SR 300 mg/day (150 mg b.i.d.) or placebo (PBO). Treatment was provided in conjunction with brief individual smoking cessation and relapse prevention counseling standardized across centers.

3.1 Protocol

3.1.1 Population

Patients were included who:

- were at least 18 years of age
- were in general good health
- smoked an average of at least 15 cigarettes/day during the past year, with no period of abstinence greater than three months in the past year
- were motivated to quit smoking
- were available for participation in the study for one year.

Patients were excluded who:

- had uncontrolled chronic diseases
- had any predisposition to seizures
- had a history or current diagnosis of anorexia nervosa or bulimia
- had a history of alcohol or substance abuse within the past year
- had used any psychoactive drug within one week of the Treatment Phase.
- were using nicotine replacement or other treatment(s) for smoking cessation
- used tobacco products other than cigarettes
- had a history of prior treatment with Wellbutrin or bupropion sustained-release
- were pregnant, nursing, or (female) not using contraception
- had another household member who wished to participate.

All patients signed an informed consent form.

3.1.2 Procedures

Interested subjects who responded to advertisements and news releases were evaluated by phone, and if appropriate, were invited to an information session. Attendees who remained motivated to participate were scheduled for a screening visit at which medical history, lab tests, electrocardiogram (EKG), chest x-ray (CXR), serum cotinine, smoking history, Fagerstrom Tolerance Questionnaire, Structured Clinical Interview for DSM Diagnosis (SCID), and Beck Depression Inventory (BDI) were completed.

Patients who satisfied criteria at the initial screening visit were asked to select a target quit date (TQD). The second screening visit was scheduled 8 days prior to the TQD (but no less than seven days after the first visit) to allow for a minimum of 7 days of treatment before the quit attempt. Patients were instructed not to try to quit smoking prior to their TQD. They were given a diary including questions on number of cigarettes smoked, severity of nicotine craving, and withdrawal symptoms.

At the second screening visit, assessments included physical exam, vital signs, weight, exhaled carbon monoxide (CO), medication record, adverse experiences, and concomitant medications. Subjects were not enrolled if safety assessments were unsatisfactory, if they had not completed the daily diary or seemed otherwise insufficiently motivated, or if they had quit smoking. Thus, enrolled subjects were those who had demonstrated commitment to participation through a multiple-visit screening phase and compliance with the daily diary task, yielding a sample enriched for committed, compliant subjects.

Subjects entered into the treatment phase were randomized in blocks of 8 to receive placebo, bupropion SR 100 mg/day (50 mg b.i.d.), bupropion SR 150 mg/day(150 mg q.d.), or bupropion SR 300 mg/day (150 mg b.i.d). Patients received blister cards containing bupropion SR 50 mg and/or 150 mg and/or matching placebo tablets, providing the amount of medication needed for the seven days between appointments plus 3 extra days in case of missed appointments. The investigator provided a new blister card at the baseline visit and at each of the weekly (weeks 1-6) visits. Subjects were instructed to take two tablets b.i.d. and to return the blister cards and all unused medication at the next visit. Compliance was assessed by weekly review of unused medication.

Subjects randomized to the bupropion SR 300 mg/day (WB SR 300) titrated to full dose over 3 days, beginning with 150 mg/day for 3 days and then increasing to 150 mg b.i.d. on day 4. Those in the other treatment groups began at the full dose assigned. Subjects unable to tolerate the assigned dose discontinued the study drug but were encouraged to continue with the scheduled assessments through the remainder of the study.

The dosing schedule employed for the four groups is shown in the following table:

Treatment	AM Dose		PM Dose*	
	150 mg	50 mg	150 mg	50 mg
WB SR 100	Placebo	Active	Placebo	Active
WB SR 150	Active	Placebo	Placebo	Placebo
WB SR 300	Active	Placebo	Active*	Placebo
Placebo	Placebo	Placebo	Placebo	Placebo

* placebo for days 1-3

All subjects who were randomized to treatment also received brief individual counseling to encourage abstinence, provided by a trained clinician at each clinic visit. These were based on information presented in the National Cancer Institute's (NCI) manual, "How to Help Your Patients Stop Smoking." Each subject also received a copy of the NCI's self-help manual, which they were asked to read prior to their TQD. Telephone contact for counseling was also provided at several time points throughout the follow-up phase.

Clinic visits occurred weekly during the treatment phase. At each visit, assessments included vital signs, weight, adverse experiences, concomitant medications, daily diary records (includes craving/withdrawal ratings, and number of cigarettes smoked), and exhaled CO. During the 45-week follow-up phase,

subjects were seen at weeks 8 and 12, and at 6 months and 1 year. They were also contacted by phone at weeks 9, 10, and 11, and monthly between week 12 and one year. Efficacy data were collected during the follow-up phase, including abstinence survival, craving, and withdrawal. Only serious adverse events were collected during the follow-up phase. The BDI was repeated at weeks 3, 7, 8, 12, and at 6 and 12 months.

3.2 Endpoints

3.2.1 Efficacy

The *a priori* primary efficacy measure was abstinence from smoking during a specified 4-week period of the Treatment Phase (Weeks 4 through 7). Abstinence was defined as a patient's report of no smoking (0 cigarettes/day), confirmed by exhaled air carbon monoxide (CO) levels less than or equal to 10 ppm.

Secondary efficacy measures included: continuous quit from Day 22, weekly point prevalence abstinence rates, daily craving scores, daily withdrawal symptom scores, and number of cigarettes smoked per day by nonquitters. Depression, quality of life and resource utilization were also assessed.

3.2.2 Safety

Safety assessments included vital signs, weight, and an adverse experience probe.

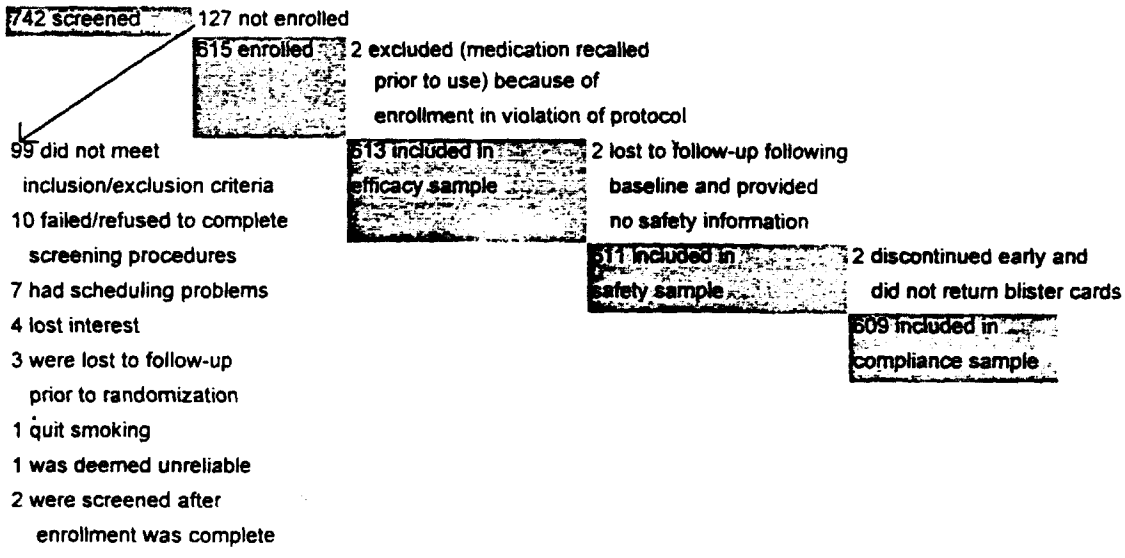
3.3 Statistical Considerations

Two-sided tests and confidence intervals with a 0.05 α level of significance were used for treatment comparisons. For analysis of demographic data and baseline characteristics, between-treatment group comparisons were made using ANOVA for continuous variables and chi-square for categorical variables. Between-treatment group statistical comparisons for quit rates were made using the chi-square test. An initial test to determine the effects of treatment, center, and treatment-by-center interaction on quit rate was performed using logistical regression. Chi square tests were performed comparing each of the active treatment groups to placebo. Additional analyses were performed to explore the potential effects of gender, age, race, and history of depression.

4. Results

4.1 Patient Disposition, Comparability

Patient disposition is illustrated in the diagram below.



A total of 742 subjects entered the screen/baseline phase. Of these, 127 were not randomized to treatment. The investigator classified the reasons for non-entry for each subject, but the following data

were derived from reviewer examination of the line listings with verbatim descriptions of the reasons subjects were not enrolled. There were several who were assigned to different categories by the reviewer and the investigator. The 127 non-randomized subjects include 99 who were not entered into treatment due to inclusion/exclusion criteria. Ten subjects failed or refused to complete the screening procedures. Seven had scheduling difficulties that precluded study participation. Four lost interest. One subject quit smoking prior to randomization, one was deemed by the investigator to be unreliable, and three were lost to follow-up prior to randomization. Two subjects were screened but not randomized because the study enrollment was complete.

Thus, 615 subjects entered the treatment phase and were randomized to treatment or placebo. Two of these subjects (both assigned to placebo) returned all of their study medication before taking any tablets (on request of the investigator after realizing they had been enrolled in violation of criteria). They are not included in the safety or efficacy analyses. Two subjects (one in the placebo group and one assigned to WB SR 100) were lost to follow-up following the baseline visit and did not return their study medication blister cards. They are included as non-quitters in the efficacy analysis but excluded from the denominator of the safety analysis because no data was obtained. Finally, two additional patients who discontinued early did not return their blister cards. Because there was at least one safety assessment, they are included in the safety analysis. They are included as non-quitters in the efficacy analysis. Because there is no data on their compliance, they are excluded from the denominator in the compliance analysis. The resultant sample sizes are 613 for efficacy, 611 for safety, and 609 for compliance.

4.1.1 Demographic and baseline characteristic data

Demographic and baseline characteristic data are summarized in the following table.

Summary of Demographics, Baseline Characteristics, Smoking History, and Fagerstrom Tolerance (FTS) Data

Variable	Statistic or Category	Treatment Group PBO (N=151[a])		WB SR 100 (N=153[a])		WB SR 150 (N=153[a])		WB SR 300 (N=156[a])		All Patients (N=613[a])		Between Treatment Difference
Sex	Male	61	40%	64	42%	76	50%	77	49%	278	45%	NS
	Female	90	60%	89	58%	77	50%	79	51%	335	55%	
Race	White	146	97%	148	97%	148	97%	147	94%	589	96%	
	Black	3	2%	4	3%	3	2%	5	3%	15	2%	NS
	Other	2	1%	1	<1%	2	1%	4	3%	9	2%	
Age	Mean	43.0		44.1		42.3		45.0		43.6		
	Std. Dev.	10.76		10.47		11.26		11.84		11.12		NS
	Range	22.0-71.0		20.0-76.0		21.0-77.0		20.0-79.0		20.0-79.0		
Cigarettes per Day	Mean	26.4		26.2		27.5		27.2		26.8		
	Std. Dev.	8.95		8.55		9.60		10.85		9.52		NS
	Range	12.0-60.0		15.0-50.0		15.0-80.0		10.0-60.0		10.0-80.0		
Years Smoked	Mean	25		27		25		27		26		
	Std. Dev.	10.8		10.3		11.3		11.5		11.0		NS
	Range	2-52		4-55		2-53		3-61		2-61		
# of Stop Smoking Attempts	n	151		153		153		154		611		
	Mean	4		4		4		4		4		
	Std. Dev.	5.0		3.4		6.5		5.4		5.2		NS
	Range	0-50		0-24		0-66		0-50		0-66		
Cotinine (ng/ml)	n	149		152		152		156		609		
	Mean	328		337		339		327		333		
	Std. Dev.	159.7		137.0		152.6		139.4		147.1		NS
	Range	66-812		20-1011		76-863		41-710		20-1011		
FTS	Mean	6.3		6.4		6.3		6.3		6.3		
	Std. Dev.	1.45		1.32		1.27		1.31		1.34		NS
	Range	2.0-10.0		3.0-9.0		3.0-9.0		2.0-10.0		2.0-10.0		

[a] Unless otherwise specified

As illustrated above, the four treatment groups were comparable at baseline with respect to sex, race, age, smoking history, and degree of nicotine dependence (as measured by FTS).

4.2 Premature discontinuation

A total of 197 (32%) of the 615 subjects discontinued the study medication prematurely. As summarized in the table below, the most common reason in all dose groups was "consent withdrawn." The reason for discontinuation in each case was determined by the investigator. In some cases, the subject may have reported an adverse experience, lack of efficacy, or other reason but the investigator was asked to assess the underlying nature of the discontinuation. Half (98/197) of the premature terminations fall into this loosely-defined category; thus it is difficult to draw conclusions from this data.

	PBO N (%)	WB 100 N (%)	WB 150 N (%)	WB 300 N (%)	Total N (%)
Reason for Discontinuation					
Adverse Experience	8 (5.2)	9 (5.9)	7 (4.6)	13 (8.3)	37 (6.0)
Consent Withdrawn	26 (17.0)	26 (17.0)	22 (14.4)	24 (15.4)	98 (15.9)
Lost to Follow-up	10 (6.5)	10 (6.5)	7 (4.6)	6 (3.8)	33 (5.4)
Protocol Deviation	2 (1.3)	5 (3.3)	1 (0.7)	3 (1.9)	11 (1.8)
Scheduling Difficulties	5 (3.3)	4 (2.6)	9 (5.9)	0 (0.0)	18 (2.9)
Total	51 (33.3)	54 (35.3)	46 (30.1)	46 (29. 5)	197 (32.0)

Denominator Sample Sizes: PBO=153, WB 100=153, WB 150=153, WB 300=156

4.3 Efficacy endpoint outcomes

The primary efficacy endpoint was the four-week quit rate, representing abstinence from day 22 through the end of week 7 (a variation on the week 2-6 abstinence used in most nicotine replacement trials, to allow for one week of acclimating to the medication prior to making the quit attempt). The majority of abstinent subjects chose day 8 as their quit day. The sponsor defined abstinence as *self-report of smoking zero cigarettes **plus** confirmatory breath CO at each clinic visit*. However, if a subject missed a clinic visit but had been abstinent at the clinic visits prior to and following the missing visit, and claimed abstinence throughout, that subject was classified by the sponsor as abstinent. Dropouts and subjects lost to follow-up were classified as non-abstinent. The resulting quit rates are presented in the following table:

Treatment	Number (%) abstinent	p-value vs. placebo
Placebo (N=151)	26 (17.22)	
WB SR 100 (N=153)	33 (21.57)	0.338
WB SR 150 (N=153)	42 (27.45)	0.032
WB SR 300 (N=156)	56 (35.90)	<0.001

While the sponsor's classification of subjects with missing values as abstinent seems reasonable, one might wish to apply stricter criteria to evaluate the robustness of the findings. Thus, an exploratory analysis was performed reclassifying as smokers all subjects with missing CO samples. The number of subjects involved was:

Placebo	3
WB SR 100	2
WB SR 150	5
WB SR 300	6

Furthermore, in retrospect it was determined that several subjects had used psychotropics in violation of protocol. Most of these were ultimately classified as smokers, but six subjects listed among the four-week quitters used various medications prohibited by the protocol. These included:

Placebo	none
WB SR 100	one subject used Valium
WB SR 150	one subject used Nytol one subject used Elavil
WB SR 300	one subject used Versed one subject used Vistaril one subject used Nicorette gum

The most conservative approach to analysis would reclassify all of these individuals as smokers due to protocol violation. One could argue that the various non-nicotine medications used might have had an effect on the subjects' withdrawal symptoms, such as anxiety or insomnia, and therefore these individuals would have been unable to maintain abstinence with bupropion SR alone. However, it may be more reasonable to re-classify only the subject who used Nicorette. Performing the most conservative possible analysis, one finds the quit rates below (all with missing CO's and all who used psychotropics reclassified):

Treatment	Number (%) abstinent	p value vs placebo
Placebo (N=151)	23 (15.23)	
WB 100 (N=153)	30 (19.61)	0.315
WB 150 (N=153)	36* (23.93)	0.067
WB 300 (N=156)	47 (30.13)	0.002

*one subject both missed a CO sample and used a psychotropic

Thus, even in a worst-case scenario analysis, the active drug shows improvements over the placebo quit-rate in a dose-dependent fashion.

For purposes of other exploratory analyses, the sponsor's definition of abstinence was adopted. This is because it seems reasonable to assume, as they did, that individuals who reported abstinence over the period of a missing clinic visit, who had demonstrated low CO's as verification of their other claims of abstinence, very probably were, in fact, abstinent. Additionally, it seems unlikely that the various drugs used by the protocol-violators noted above would have a significant impact on abstinence, with the exception of Nicorette. Since this one mis-classified individual is unlikely to change the statistical outcomes in any important way, the sponsor's classifications were used for convenience of review.

The sponsor also calculated rates of abstinence from Day 22 through the ends of weeks 8, 12, 26, and 52. Continuous quit rates (CQR'S) at six and twelve months (weeks 26 and 52) are displayed in the table below.

In the follow-up phase, eight subjects (two WB SR 100, two WB SR 150, and four WB SR 300) were classified as abstinent despite missing confirmatory CO measurements (i.e. missed clinic visits or failed to provide a sample at the clinic visit). These individuals all made subsequent visits at which continuous abstinence was reported and confirmed with CO; the classification of these individuals as abstinent seems reasonable. One subject (assigned to WB SR 150) who was abstinent through week 52 used Nicorette gum. If a worst-case scenario analysis is performed, re-classifying the eight subjects with missing CO values and the subject who used Nicorette, the resultant continuous quit rates are still higher for the drug-treated groups than for the placebo group.

	Comparison of CQR at Three Time Points Using Sponsor's vs Strictest Definition of Abstinence															
	PBO (N=151)				WB SR 100 (N=153)				WB SR 150 (N=153)				WB SR 300 (N=156)			
Time Point	sponsor		"worst-case"		sponsor		"worst-case"		sponsor		"worst-case"		sponsor		"worst-case"	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
4 weeks	26	17.22	23	15.23	33	21.57	30	19.61	42	27.45	36	23.53	56	35.90	47	30.13
6 months	17	11.26	17	11.26	25	16.34	24	15.69	28	18.30	28	18.30	30	19.23	28	17.95
12 months	15	9.93	15	9.93	20	13.07	18	11.76	23	15.03	21	13.73	21	13.46	19	12.18

The quit rates for the medication-treated groups remain superior to placebo in an essentially dose-dependent fashion throughout the follow-up period.

Analysis by center reveals that WB SR 300 was significantly superior to placebo at two centers, WB SR 150 at one center, and WB SR 100 at none. There were no apparent gender differences, and small sample sizes preclude meaningful analysis by race.

	Treatment Group											
	PBO			WB SR 100			WB SR 150			WB SR 300		
	Subgroup	Quitters		Subgroup	Quitters		Subgroup	Quitters		Subgroup	Quitters	
Center	N	N	%	N	N	%	N	N	%	N	N	%
1	50	9	18.0%	51	10	19.6%	50	10	20.0%	51	11	21.6%
2	51	5	9.8%	51	11	21.6%	51	14	27.5%	52	18	34.6%
3	50	12	24.0%	51	12	23.5%	52	18	34.6%	53	27	50.9%

Having established that the overall quit rate for the WB SR 300 group is over twice the placebo rate for the *a priori* primary outcome variable, several additional analyses seem potentially useful. It is appealing to attempt to explain the results through some logical mechanism: does the drug, an antidepressant, affect smoking in some way by treating subclinical depression? Does the drug, in some way unexplained, reduce craving or withdrawal symptoms?

4.3.1 Role of Depressive Symptoms:

It is useful to note that Wellbutrin SR has *not* been demonstrated to be effective for the treatment of major depression at the doses used in this study; however, although clinically depressed individuals may have been screened out of the study via exclusion criteria which included use of psychotropics, the possibility of sub-clinical depression which could theoretically respond to an antidepressant remains. Baseline BDI scores were obtained for each subject, and the BDI was repeated at clinic visits at weeks 3, 7, 8, 12, 26, and 52. In the practice of psychiatry, a BDI score of 10-17 is considered to be evidence of depression. Out of a total of 615 subjects entering the study, there were 9 subjects with baseline BDI scores over 17. They were evenly divided among the 4 treatment groups and 2 of them were quitters at the end of the 8th week.

The sponsor performed a subgroup analysis to determine whether subjects with a history of depression had different quit rates from those without. The following table shows the distribution among treatment groups of subjects with and without history of major depression.

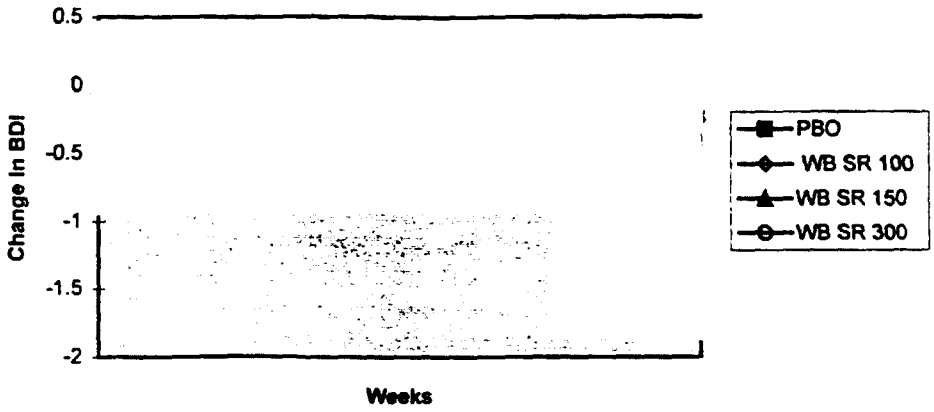
Four-week Quit Rates for Subjects With and Without Depression History								
	Treatment Group							
	PBO (N=151)		WB SR 100 (N=153)		WB SR 150 (N=153)		WB SR 300 (N=156)	
	N	4wk QR	N	4wk QR	N	4wk QR	N	4wk QR
History of Depression	30	16.7	35	20	26	34.6	22	27.3
No History of Depression	121	17.4	118	22	127	26	134	37.3

4wk QR = % of subjects meeting criteria for 4 -week abstinence

No consistent pattern was identified to suggest that depression history had an effect on the outcome for individual subjects.

The treatment groups were also compared by the sponsor to determine whether they differed with respect to BDI scores at baseline, or if the change in BDI scores over time varied among groups. The groups were similar at baseline and had similar overall change scores.

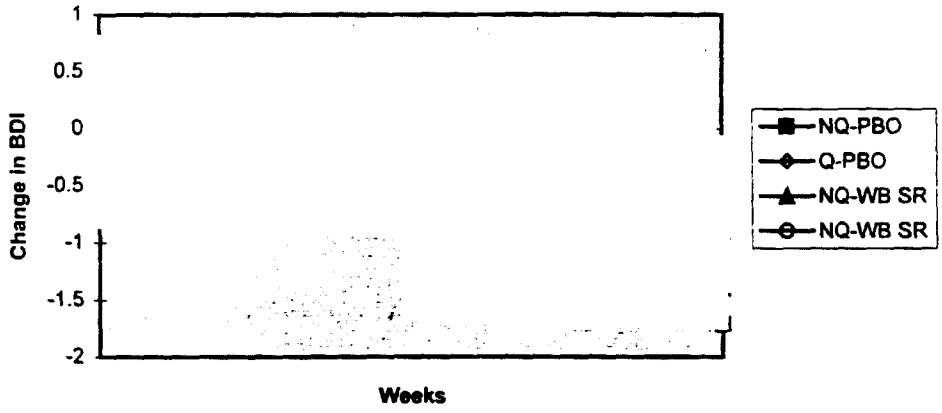
Change in BDI for all 4 treatment groups



BDI scores appeared to be slightly improved over time from baseline to the 7th week across all four groups. The average improvement in BDI was around 1.0-1.5, which is not clinically significant. The three active treatment groups did not show greater improvement in BDI scores than the placebo group. This may not be very surprising because the doses used in this trial were lower than those for treating major depression, and, furthermore most subjects had low baseline BDI scores, leaving very small room for improvement. It appears that Wellbutrin SR did not work through improving depressive symptomatology (as measured by BDI) in individuals without a clinical diagnosis of depression.

As shown in the figure below, quitters in general appeared to have lower BDI scores across time than the non-quitters in both placebo group and the combined treatment group.

Change in BDI score for quitters and non-quitters



A logistic regression analysis was done by the reviewer to investigate the association between successful quitting and the change of BDI at the 7th week. In the logistic model, both the change of BDI score and the treatment turned out to be significant (p=0.03 for BDI; p=0.02 for overall treatment vs. Placebo, p=0.2 for WB100, p=0.05 for WB150 and p=0.01 for WB300). It then appeared that adjusting for the BDI score would alter little about the significance of the treatment effect. However, it is difficult to interpret the significant association between quitting and the change of BDI score: the direction of causality is unclear, if it exists at all, and the actual differences among scores are so small as to be clinically insignificant.

Thus, the differences in quitting rates in the four treatment groups could not be explained by the change of BDI scores over time.

4.3.2 Role of Nicotine Withdrawal Symptoms:
Scores were collected individually each week for:

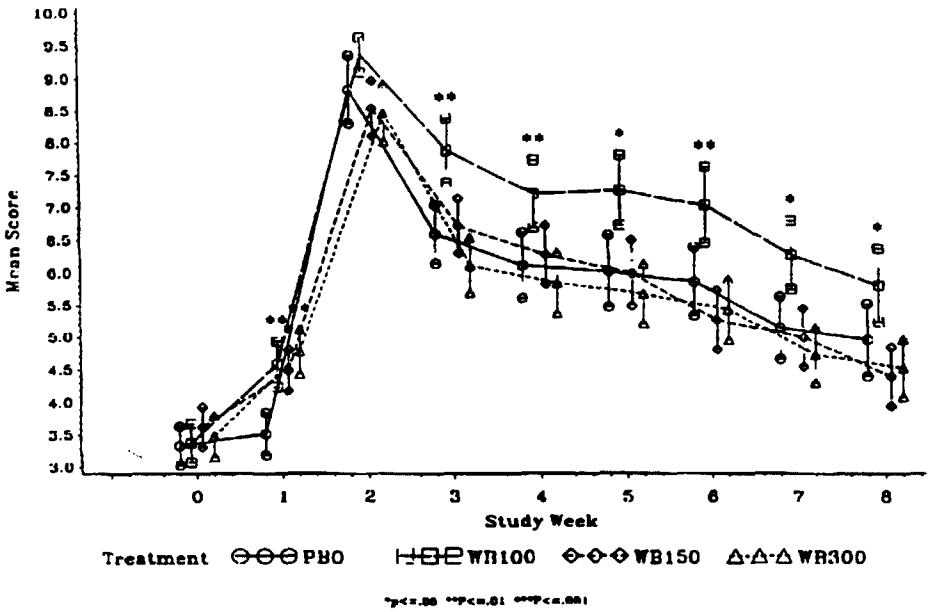
- depressed mood
- difficulty falling asleep
- awakening at night
- irritability, frustration, or anger
- anxiety
- difficulty concentrating
- restlessness
- increased appetite

A composite score was also calculated.

Overall, the mean scores for the individual withdrawal symptoms were low, with not mean scores for any treatment group extending above 2 (severity=mild). Change scores for the eight individual symptoms were calculated and statistical comparisons were performed for each individual symptom, comparing treatment groups to placebo in pair-wise comparisons. For six of the symptoms, statistically significant differences between one or more of the drug treatment groups (usually WB SR 100) and placebo were identified and most often favored the placebo.

Composite withdrawal symptom scores were similar at baseline across treatment groups. As illustrated below, scores peaked at week 2 and decreased steadily thereafter. Although the WB SR 150 and WB SR 300 groups had composite scores similar to placebo, the WB SR 100 group demonstrated higher composite scores compared to the other three groups throughout the treatment and follow-up phases. The significance of this finding is unclear.

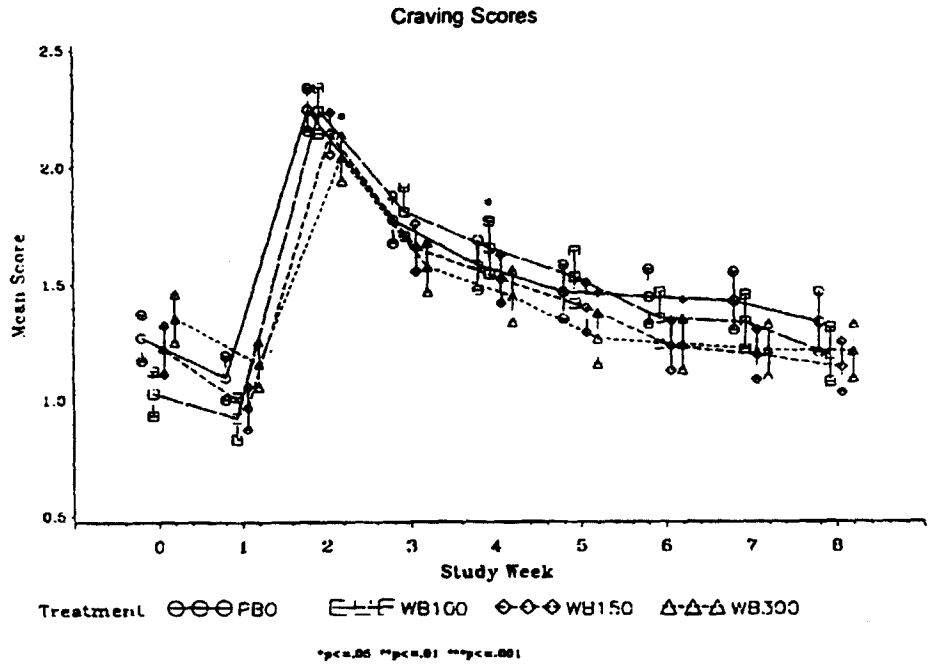
Composite Withdrawal Scores, Mean ±SEM



No other systematic differences in withdrawal symptoms among the treatment groups are apparent; it would appear that effects on withdrawal do not account for the efficacy of the drug in improving abstinence rates.

4.3.3 Role of Nicotine Craving:

No systematic differences in craving scores among treatment groups are apparent, either during treatment or during follow-up. This is illustrated in the diagram below.



Thus, the data from this study do not indicate an effect of WB SR on craving, in contrast to the findings in Studies 402 and 405, which used different measures of craving.

4.4 Safety comparisons

4.4.1 Exposure to Study Drug

4.4.1.1 Mean dose

The mean daily doses and compliance rates for the three drug treatment groups are listed below. Because of the three-day titration period employed in the 300 mg group, the mean daily dose for a fully compliant patient would be 291 mg.

	Treatment Group			
	PBO	WB SR 100	WB SR 150	WB SR 300
Mean Daily Dose	0	96	145	273
% Compliance	95	96	95	96

Thus, compliance in all groups was high and was comparable across groups.

4.4.1.2 Duration of Exposure

In the table below, four patients randomized to receive WB SR are omitted. One (WB SR 100) was lost to follow-up; two patients (one WB SR 100 and one WB SR 300) did not return their week 1 blister cards.

The fourth subject (WB SR 300) did not receive medication beyond the escalation period (first four days). Because this table shows a mean daily dose calculated for day 4 onward for the WB SR 300 group (the other groups did not have an escalation period), that subject is not included.

Duration of Treatment (Days)	WB SR Mean Daily Dose Groups								All Groups Combined	
	#125 mg		126-175 mg		176-250 mg		251-350 mg			
	N	%	N	%	N	%	N	%	N	%
1-6	5	3	5	3	1	20	0	0	11	2
7-13	13	8	6	4	1	20	9	6	29	6
14-20	8	5	10	7	0	0	12	8	30	7
21-27	6	4	6	4	0	0	5	3	17	4
28-34	8	5	9	6	0	0	2	1	19	4
35-41	12	8	2	1	1	20	6	4	21	5
42-48[a]	9	6	6	4	1	20	7	5	23	5
49-55	96	60	102	70	1	20	107	72	306	67
≥56	2	1	0	0	0	0	0	0	2	<1
Total	159	100	146	100	5[b]	100	148	100	458	100

[a] Includes some patients who were normal completers; in case of scheduling conflicts, subjects were permitted to have Treatment Phase Discontinuation Assessments within ±3 days of Day 49.
[b] These five patients were randomized to the WB SR 300 group.

4.4.2 Deaths

No patients died during the treatment phase of the study. However, four days after completing the 49-day treatment phase on WB SR 300, a 63 year-old black female subject experienced cardiopulmonary arrest and was hospitalized in coma. She had chronic, pre-existing cardiomyopathy and was taking multiple medications, including hydrochlorothiazide, lisinopril, propranolol, aspirin, potassium, calcium, niacin, and vitamin E. The investigator reported that the coma was attributable to hypoxic encephalopathy, secondary to cardiac and pulmonary arrest, secondary to pulmonary edema, secondary to chronic, pre-existing cardiomyopathy. Upon her death, ten days later, the investigator judged that the event most directly leading to the patient's death was pulmonary edema; the investigator judged the death as not reasonably attributable to study drug. Bupropion (immediate release) is not known to be associated with any particular cardiac or respiratory side effects. The safety database for the development of Bupropion SR now includes over 4000 patients, and there is no suggestion of events of this nature being related to study drug. Given this patient's severe, pre-existing medical problems, it seems plausible to classify this event as unrelated to study drug.

4.4.3 Serious Adverse Events

Two non-fatal serious adverse events occurred during the treatment phase of the study. A 25 year-old white male subject who had been taking WB SR 300 for 16 days and had been abstinent from smoking for 8 days reported that he had been feeling increasingly anxious and restless since quitting smoking, and ultimately experienced and episode of uncharacteristic "**uncontrollable rage**" during a traffic incident. The investigator judged the event to be possibly attributable to study drug, and the medication was discontinued. Although irritability might be expected of an individual attempting to quit smoking, reports of hostility have also been associated with Wellbutrin during its development as an antidepressant (reported by 5.6% of drug-treated patients in clinical trials reported in Wellbutrin labeling, vs. 3.8% of placebo patients, although not seen in bupropion SR depression trials).

A 66 year-old white female experienced an **anaphylactic reaction** (dyspnea, swelling, and petechiae) during the treatment phase of the study. She had been taking WB SR 300 for six days when she began taking Augmentin for bronchitis. The following day she experienced itching, then urticaria progressing over several days. The Augmentin was discontinued after 10 days and Benadryl was initiated. Eight days later, the patient elected to discontinue study medication. The following day, after taking her usual dose of verapamil for hypertension and eating a peanut butter sandwich, the patient developed dyspnea, blue lips, hand and foot swelling, periorbital and perioral edema, and petechiae on the extremities. She was treated

Medical and Statistical Review and Evaluation of Clinical Data

NDA 20-711
Sponsor: Glaxo Wellcome
Product: Bupropion SR
Reviewers: Celia Jaffe Winchell, M.D.
Z. Jonathan Ma, Ph.D.
Protocol Reviewed: A Single Center Evaluation of Wellbutrin (bupropion hydrochloride) Versus Placebo as an Aid to Smoking Cessation (Study 402)

1. Objective/Rationale

The objective of this trial was to compare the safety and efficacy of bupropion (100 mg t.i.d.) and placebo as aids to smoking cessation in heavily-dependent chronic cigarette smokers when used in conjunction with group smoking cessation and relapse prevention counseling sessions.

2. Investigators and Locations

This was a two center trial, conducted at the Jerry L. Pettis Memorial Veterans Affairs Medical Center in Loma Linda, California, by Linda Hyder Ferry, M.D., M.P.H., and at the Department of Veteran's Affairs Outpatient Clinic in Las Vegas, Nevada, by the same investigator.

3. Design

This was a two center, parallel, randomized, double-blind, placebo-controlled trial involving 190 male and female chronic, heavy (≥20 cigarettes/day) cigarette smokers. The study consisted of four phases: a Screen/Baseline Phase, a 12-week Treatment Phase, a 4-week Post-Treatment Phase, and a 36 week Follow-up Phase. Eligible patients entered the Treatment Phase and were randomized to receive either Wellbutrin 100 mg t.i.d. or placebo (PBO). During the Treatment and Post-Treatment Phases, subjects were seen every two weeks and received group smoking cessation and relapse prevention counseling. The follow-up phase included clinic visits at 6 and 12 months, but no counseling or medication was provided.

3.1 Protocol

3.1.1 Population

Patients were included who:

- were at least 21-75 years of age
- smoked an average of at least 20 cigarettes/day
- smoked before leaving the house in the morning
- had made at least two previous attempts to quit smoking
- experienced withdrawal symptoms during cessation attempts
- stated intention to attempt to stop smoking during the first four weeks of the Treatment Phase.

Patients were excluded who:

- had uncontrolled chronic diseases
- had any predisposition to seizures
- had mental retardation, dementia, or organic brain syndrome
- had severe anxiety and/or panic disorder
- had schizophrenia, psychotic disorders, bulimia, anorexia nervosa, or a recent depressive episode
- were currently depressed (HAM-D≥12)
- had been treated with an antidepressant within the previous four weeks
- were treated with AZT
- had used any nonprescibed mood-altering drug within 30 days (besides ethanol)
- consumed ≥5 drinks/day (average) or >5 drinks/day on two or more days per week
- had a history of alcohol or substance abuse within the past 3 months
- had a history of prior treatment with Wellbutrin

- were pregnant (females).

3.1.2 Procedures

Patients were referred by the staff physicians or recruited through posted notices at the VAMC in Loma Linda, California, and, after several groups were enrolled at that site, patients were similarly recruited at the VA outpatient clinic in Las Vegas, Nevada. A telephone questionnaire was used to screen patients who expressed interest in the study. Patients who satisfied the preliminary study entry criteria were scheduled for a clinic visit. At the initial screening visit, patients were given information about the study, and completed an intake questionnaire including demographic data, smoking history, and Fagerstrom Tolerance Questionnaire (FTQ). Depressive symptoms were assessed using the Center for Epidemiological Studies-Depression (CES-D) questionnaire. Attendees who remained eligible to participate were scheduled for a second screening visit at which medical history, physical exam, lab tests, electrocardiogram (EKG), Schedule for Affective Disorders and Schizophrenia-Lifetime (SADS-L) and Hamilton Rating Scale for Depression (HAM-D) were completed.

The Baseline (Day 1) Clinic visit was scheduled once a group of 20-25 eligible patients had been identified. Subjects completed daily diaries while awaiting the baseline visit. At the baseline visit, subjects were not enrolled if safety assessments were unsatisfactory, if they seemed insufficiently motivated, or if they no longer met inclusion/exclusion criteria. Thus, enrolled subjects were those who had demonstrated commitment to participation through a multiple-visit screening phase and compliance with the daily diary task, yielding a sample enriched for committed, compliant subjects. Baseline weight, vital signs, adverse experiences, and withdrawal symptoms were recorded and saliva was collected for a cotinine level.

Subjects entered into the treatment phase were randomized to receive placebo or bupropion. Patients received study medication bottles containing 51 bupropion 100 mg or matching placebo tablets, providing the amount of medication needed for the two weeks between appointments plus 3 extra days in case of missed appointments. Study personnel provided a new bottle at the baseline visit and at each of the subsequent visits. Medication was begun at one tablet b.i.d. for the first three days, and then increased to t.i.d. for the remainder of the Treatment Phase. Subjects were instructed to return the bottles and all unused medication at the next visit. Compliance was assessed by review of unused medication.

Subjects also participated in a behavioral treatment component consisting of a four-week behavior-modification "stop smoking class," which met in hourly sessions on days 5-9 and at each bi-weekly clinic visit. After seven "stop smoking classes," the sessions utilized a supportive format described as being similar to Smokers Anonymous and offered educational material focused on relapse prevention. Patients who missed a scheduled clinic visit were required to view a videotape of the session missed.

Clinic visits occurred every two weeks during the treatment phase. At each visit, assessments included vital signs, weight, pill count, daily diary records (includes craving scales and number of cigarettes smoked) adverse experience (using a checklist) and a patient-completed "smoking clinic record" including an open-ended AE probe and questions about smoking, craving, and withdrawal. Subjects who reported $\geq$5 days of abstinence provided a saliva sample for cotinine determination. Those who reported smoking were asked to set a new target quit date.

During the Post-Treatment Phase (weeks 13-16), subjects continued to complete daily diaries. Clinic visits were scheduled for weeks 14 and 16, with assessments as above (except medication compliance). Counseling sessions at those visits focused on relapse prevention.

During the follow-up phase, subjects were seen at approximately 6 and 12 months following randomization to treatment. Efficacy data were collected during the follow-up phase, including abstinence survival and craving. Salivary cotinine was collected from patients who reported $\geq$5 days of abstinence prior to the clinic visit.

3.2 Endpoints

3.2.1 Efficacy

The *a priori* primary efficacy measure was abstinence from smoking during any 4-week period of the Treatment Phase (Day 1 through Day 56) Abstinence was defined as a patient's daily diary report having smoked zero cigarettes for the specified period of time. Cotinine confirmation of abstinence was considered to be present if there were at least two confirmatory ($\leq$15 ng/ml) during the period of abstinence. Quit rates were defined as the ratio of the number of patients meeting the quit criterion to the number of patients initially treated (i.e. intent-to-treat analysis). Drop-outs were defined as non-abstinent. If diary data was missing for patients who had been abstinent prior to and after the time of the missing entries, patients were considered abstinent if data in the "Smoking Clinic Record" was available to confirm continuous abstinence.

Secondary efficacy measures included: continuous quit from Day 29, continuous quit rates from first successful quit week to end of treatment (week 12), 6 months and 12 months, weekly point prevalence abstinence rates, daily craving scores, daily withdrawal symptom scores, and number of cigarettes smoked per day by nonquitters.

3.2.2 Safety

Safety assessments included vital signs, weight, and an adverse experience probe.

3.3 Statistical Considerations

Two-sided tests with a 0.05 α level of significance were used for treatment comparisons. For analysis of demographic data and baseline characteristics, between-treatment group comparisons were made using the 2-sample, 2-sided t-test for continuous variables and the chi-square test for categorical variables. Between-treatment group statistical comparisons for quit rates were made using the chi-square test.

4. Results

4.1 Patient Disposition, Comparability

190 subjects entered the treatment phase and were randomized to treatment or placebo. No information is available on subjects who were screened and not entered.

Demographic and baseline characteristic data are summarized in the following table prepared by the sponsor.

		Treatment						
Variable	Statistic or Category	PBO (N=95)		WB (N=95)		Total		Between Treatment Difference
Sex	Male	82	(86%)	78	(82%)	160	(84%)	NS[c]
	Female	13	(14%)	17	(18%)	30	(16%)	
Race	White	79	(83%)	81	(85%)	160	(84%)	NS
	Black	9	(9%)	10	(11%)	19	(10%)	
	Hispanic	5	(5%)	4	(4%)	9	(5%)	
	Asian	1	(1%)	0	(0%)	1	(1%)	
	Amer. Indian	1	(1%)	0	(0%)	1	(1%)	
Age (years)	Mean	54		51		52		0.05
	Std. Dev.	11.3		11.8		11.6		
	Range	27-74		22-73		22-74		
Height (inches)	Mean	69.6		69.0		69.3		NS
	Std. Dev	3.31		3.30		3.31		
	Range	61.0-76.0		60.0-76.0		60.0-76.0		
Weight (kg)	Mean	86.4		82.7		84.6		NS
	Std. Dev.	18.31		17.08		17.76		
	Range	46.5-160.0		50.8-147.4		46.5-160.0		
Cigarettes/ Per Day	1 pack	30	(33%)	37	(40%)	67	(36%)	NS
	1.5 packs	36	(39%)	27	(29%)	63	(34%)	
	2 packs	11	(12%)	18	(19%)	29	(16%)	
	2.5 packs	8	(9%)	8	(9%)	16	(9%)	
	> = 3 packs	7	(8%)	3	(3%)	10	(5%)	
Number of Stop Smoking Attempts	0	0	(0%)	2	(2%)	2	(1%)	NS
	1	9	(9%)	4	(4%)	13	(7%)	
	2	17	(18%)	19	(20%)	36	(19%)	
	3	27	(28%)	20	(21%)	47	(25%)	
	4	11	(12%)	12	(13%)	23	(12%)	
	> = 5	31	(33%)	38	(40%)	69	(36%)	
FTQ[b] Score	Mean	6.9		7.2		7.0		NS
	Std. Dev.	1.78		1.89		1.84		
	Range	2.0-11.0		2.0-11.0		2.0-11.0		
HAMD Score	Mean	1.9		1.8		1.9		NS
	Std. Dev.	2.26		2.42		2.34		
	Range	0.0-11.0		0.0-11.0		0.0-11.0		

[a] HAMD: Hamilton Rating Scale for Depression
[b] FTQ: Fagerstrom Nicotine Tolerance Questionnaire Score
[c] NS: Difference is not significant (p > 0.05)

Groups were significantly different (p=0.05) with only respect to age: the mean age of the placebo (PBO) group was 54 years and the mean age of the Wellbutrin (WB) group was 51 years. Although this small difference was statistically significant, it would not be expected to have an impact on the clinical outcome of the two groups. The majority of patients were white (84%) and male (84%), consistent with the VAMC

population. Treatment groups did not differ with respect to other demographic variables, smoking history, or measures of depression.

4.2 Premature discontinuation

A total of 64 (34%) of the 190 subjects (39% of placebo group and 28% of treatment group) discontinued the study medication prematurely. At the time of discontinuation, the patient was asked to indicate his reason for withdrawing, from a checklist offering as options: side effects, illness, work problems, program not helping me, transportation, and other. A reason for discontinuation in each case then assigned by the investigator, using the categories: adverse experience, withdrew consent, protocol violation, ineffectiveness, condition deteriorating, adminstrative, other, and lost to follow up. Verbatim listings of reasons for discontinuation are not available, so it is difficult to determine the nature of discontinuations classified as "other" by the patient, or the many discontinuations classified as "withdrew consent" by the investigator. Some subjects reporting, for example, transportation problems were classified as "withdrew consent," while others were classified as "protocol violation." There were three subjects (two WB and one PBO) who gave "side effects" as their reason for discontinuation, but were classified as "withdrew consent" by the investigator. These patients were re-classified as "adverse experience" by the reviewer. Conversely, two patients who "did not want to take study medication for the prescribed period of time" (per final study report) were classified as "protocol violation." These patients were re-classified by the reviewer as "withdrew consent." As summarized in the table below, the most common reason in both groups was "withdrew consent." Two thirds (42/64) of the premature terminations fall into this loosely-defined category; thus it is difficult to draw conclusions from this data.

Reason for Discontinuation	Treatment			
	PBO (N=95)		WB (N=95)	
	N	(%)	N	(%)
Withdrew Consent	23	(24)	17	(18)
Protocol Violation	4	(6)	3	(3)
Condition Deteriorating	1	(1)	0	(0)
Lost to Follow-Up	0	(0)	1	(1)
Administrative	0	(0)	0	(0)
Ineffectiveness	6	(6)	1	(1)
Adverse Experience	3	(3)	3	(3)
Other	0	(0)	2	(2)
TOTAL	37	(39)	27	(28)

(Table prepared by reviewer from sponsor's data)

4.3 Efficacy endpoint outcomes

The primary efficacy endpoint was the four-week quit rate, representing abstinence during any consecutive 28-day period during the treatment phase (a variation on the week 2-6 abstinence used in most nicotine replacement trials). The majority of abstinent subjects quit smoking during week 2. The sponsor defined abstinence prospectively as *self-report (in diary) of smoking zero cigarettes plus at least two confirmatory cotinine samples.* However, in the analysis reported by the sponsor, a quit rate based on self-report alone was also calculated. The resulting quit rates are presented in the following table:

Four-Week Quit Rates Based on Sponsor's Classification of Patients							
	Placebo		Wellbutrin				
	N	%	N	%	p-value	Odds Ratio	95% C.I.
Self-report	25	26.3	41	43.2	0.02	2.13	1.16 - 3.91
Cotinine Confirmed	22	23.2	35	36.8	0.04	1.94	1.03 - 3.64

There were a variety of protocol violations in this study, including subjects who were allowed to re-enroll in the study after discontinuing; subjects who did not meet inclusion criteria with respect to number of attempts to quit smoking, readiness to quit, and minimum number of cigarettes smoked per day; subjects whose post-treatment phase visits were late, subjects whose diary data was missing, and subjects who reported use of nicotine-containing products other than cigarettes at the intake visit. Some of these subjects, if abstinent, were excluded by the sponsor from the efficacy numerator . As mentioned above,

those with missing diary data were included as abstinent if their clinic visit records confirmed a self-report of abstinence. Subjects who reported used of nicotine gum, patches, snuff, or pipes were not excluded because "all of these patients had either used these products some time in the past or were asked to discontinue use of these products following review of the intake questionnaire by study staff." During the study, no patients reported use of non-cigarette nicotine-containing products. However, the clinic visit record did not include an inquiry about concomitant medications at all, or an inquiry about nicotine replacement in particular. Admittedly, use of any nicotine replacement therapy should result in an elevated cotinine level; thus any subject using these products would be classified as abstinent when using the standard of cotinine confirmation.

One might wish to explore the robustness of the sponsor's findings using stricter definitions of abstinence. In the table below, the patients involved in the various protocol violations who were also among the four-week quitters are listed, along with the specific violation. Patients who were not qualified for the study because of insufficient numbers of previous quit attempts or insufficient readiness to quit are not included, because these would not be expected to introduce a bias toward the medication. Many protocol violators are not listed below because they were not also four-week quitters.

GROUP	PT #	VIOLATION
PLACEBO		UNCONFIRMED
		MISSING DIARY DATA
		REENROLLED
		NICOTINE PATCH
		MISSING DIARY DATA
		NICOTINE PATCH
		REENROLLED
		UNCONFIRMED
		MISSING DIARY DATA
		UNCONFIRMED
		NICOTINE PATCH
WELLBUTRIN		UNCONFIRMED
		NICOTINE GUM
		UNCONFIRMED
		SNUFF
		UNCONFIRMED
		MISSING DIARY DATA
		NICOTINE PATCH
		UNCONFIRMED
		UNCONFIRMED
		UNCONFIRMED
		MISSING DIARY DATA
		MISSING DIARY DATA
		MISSING DIARY DATA
		MISSING DIARY DATA

(Table prepared by reviewer from sponsor's data)

The most conservative approach to analysis would reclassify all of these individuals as smokers due to protocol violation. Performing the most conservative possible analysis, one finds the "worst case" quit rate below (all without cotinine confirmation and all those with protocol violations reclassified):

Four-Week Quit Rates Based on Various Classifications of Patients							
	Placebo		Wellbutrin				
	N	%	N	%	p-value	Odds Ratio	95% C.I.
Self-report	25	26.3	41	43.2	0.02	2.13	1.16 - 3.91
Cotinine Confirmed	22	23.2	35	36.8	0.04	1.94	1.03 - 3.64
"Worst Case"	15	15.8	27	28.4	0.04	2.12	1.04-4.31

(Table prepared by reviewer from sponsor's data)

Thus, even in a worst-case scenario analysis, the active drug shows improvements over the placebo quit-rate.

It seems reasonable to assume, as the sponsor did, that individuals with missing diary data but abstinence reported on clinic visit forms and confirmed by cotinine very probably were, in fact, abstinent. Additionally, by requiring the standard of cotinine confirmation, subjects who used nicotine replacement products during the course of the study would be detected and excluded from the abstinence group. Therefore, the sponsor's "confirmed" group differs from the reviewer's group of abstinent subjects only by the sponsor's inclusion of the two re-enrolled placebo patients who achieved abstinence. Since these two subjects bias the study toward placebo, for ease of review, the sponsor's definition of (confirmed) abstinence was therefore adopted in the exploratory analyses.

The sponsor also calculated continuous quit rates from Day 29 to various time points. Many smoking cessation trials have used a definition of abstinence involving a *particular* four-week period. Day 29 was chosen as the starting point for this period because the protocol specified that all patients would set a target quit date within the first four weeks of the study. Patients reporting abstinence at Day 29 were required to have a confirmatory cotinine sample at Week 2, 4, or 6 to be included in the Day 29 quit rate, and patients with a cotinine level >15 ng/ml at any time after Day 29 were considered smokers for each week subsequent to the time of the patients previous cotinine of ≤15 ng/ml. Confirmatory cotinine samples at 6 months and 12 months were required for patients to be included in the quit rates at those time points. The Continuous Quit Rates (CQR) at 4 weeks, 6 months, and 12 months from Day 29 are shown below.

CQR from Day 29 to Three Time Points					
	Placebo		Wellbutrin		p-values
Abstinence	N	%	N	%	
On Day 29	21	22.11	40	42.11	0.003
To week 8 (4 weeks)	19	20.00	27	28.42	0.18
To 6 months	8	8.42	17	17.89	0.05
To 12 months	6	6.32	13	13.68	0.09

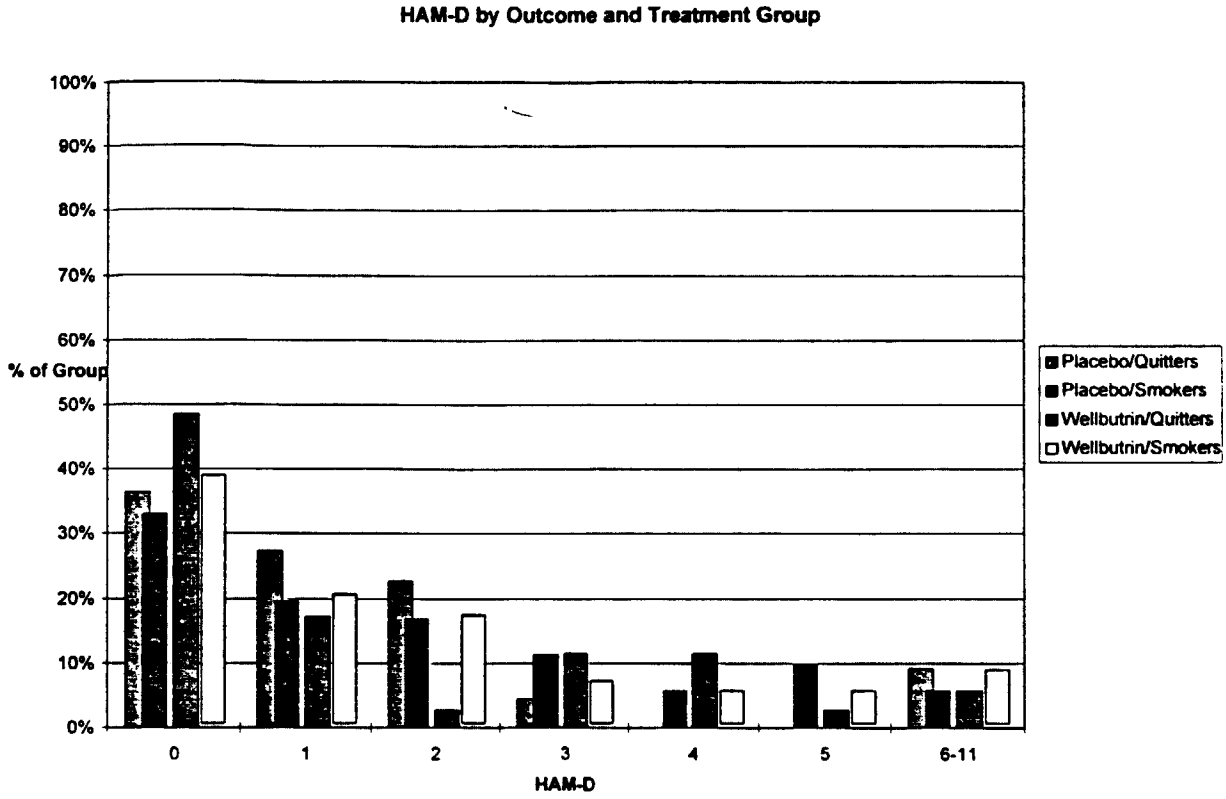
(Table prepared by reviewer from sponsor's data)

Interestingly, the "floating" 4 week quit rate (any 28 days during treatment phase) shows statistically significant differences between treatment and placebo, while the fixed (Day 29 through Week 8) does not. However, statistical significance in the *a priori* primary outcome variable is supported by significance in the CQR at 6 months and a trend toward significance at one year. Having established this, several additional analyses seem potentially useful. It is appealing to attempt to explain the results through some logical mechanism: does the drug, an antidepressant, affect smoking in some way by treating subclinical depression? Does the drug, in some way unexplained, reduce craving or withdrawal symptoms?

4.3.1 Role of Depressive Symptoms:

Although clinically depressed individuals were screened out of the study, the possibility of sub-clinical depression which could theoretically respond to an antidepressant remains. Depression history was obtained at baseline, and an assessment of current depressive symptomatology, the 17-item Hamilton Rating Scale for Depression (HAM-D) was performed. Subjects were excluded if HAM-D score exceeded 12. At baseline, the HAM-D scores of the treatment and placebo groups did not differ. The scale was not

repeated after treatment, so it is not possible to determine if changes in HAM-D were observed or were correlated with abstinence. However, the distribution of initial HAM-D scores was similar among groups of placebo-treated quitters, placebo-treated smokers, Wellbutrin-treated quitters, and Wellbutrin-treated smokers, and all were quite low, as shown below in a diagram prepared by the reviewer from the sponsor's data.



Additionally, a subgroup analysis of the outcome of treatment in subjects with and without depression history is possible. One might think that subjects with affective illness would be responsive to this medication, an antidepressant, in a way different from those without. As shown in the table below, there is no difference in quit rates between the groups as a whole; however, there is a marked difference in drug effect between the two groups. Subjects without a history of depression were far more successful on Wellbutrin than on placebo, while the opposite was true for subjects with a history of depression.

Four-week Quit Rates for Subjects With and Without Depression History

	Treatment Group				All Subjects (N=190)	
	PBO (N=95)		WB (N=95)			
	N	4wk QR	N	4wk QR	N	4wk QR
History of Depression	24	37.5	22	22.7	46	30.4
No History of Depression	71	18.3	73	41.1	144	29.9

4wk QR = % of subjects meeting criteria for 4-week abstinence (confirmed)

(Table by reviewer from sponsor's data)

This finding is difficult to explain. The data from this study would appear to suggest that non-depressed individuals with a history of depression are actually impeded in smoking cessation efforts by the use of Wellbutrin. Importantly, the finding was not replicated in Study 403, where the overall quit rate was lower for subjects with a history of depression than for those without (19% vs 26%), but Wellbutrin SR treatment had a beneficial effect on quit rates in subjects both with and without depression history.

4.3.2 Role of Nicotine Withdrawal Symptoms:
Scores were collected via written questionnaire at each clinic visit for nicotine withdrawal symptoms, which included:

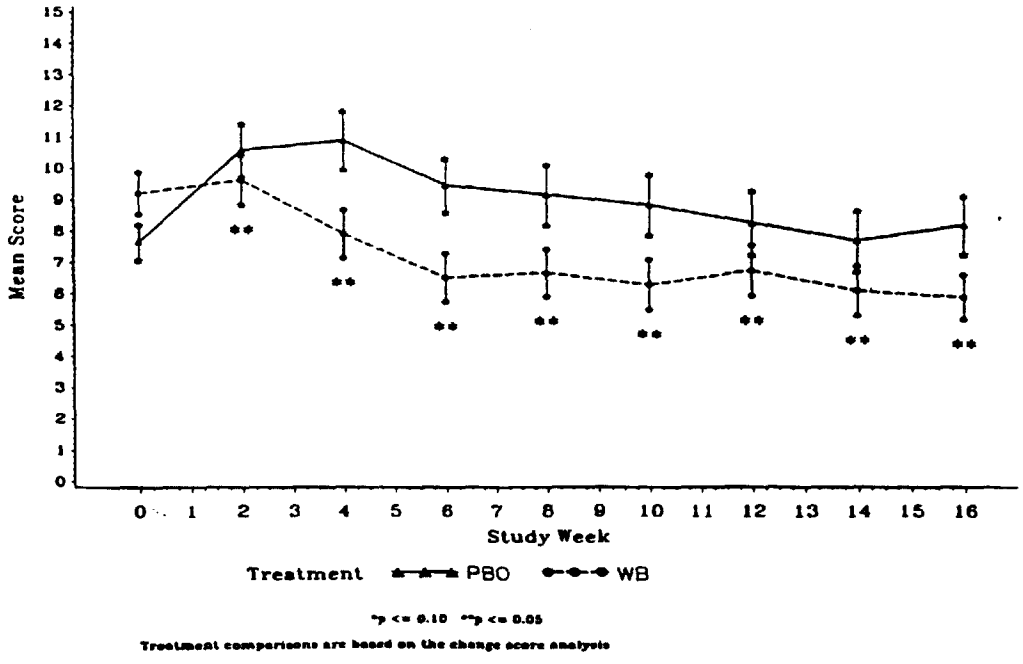
- nicotine craving
- irritability
- frustration
- anger
- anxiety
- difficulty concentrating
- restlessness

A composite score was also calculated.

Overall, the mean scores for the individual withdrawal symptoms were low, with no mean scores for any treatment group extending above 2 (severity=mild), except on the measure of "nicotine craving," which peaked at 2.51 on a scale of 0 - 4. Change scores for the eight individual symptoms were calculated and statistical comparisons were performed for each individual symptom, comparing the Wellbutrin group to placebo. For two of the symptoms, nicotine craving and anger, statistically significant differences favoring the drug treatment over placebo were identified at each treatment phase assessment. Four symptoms: anxiety, frustration, irritability, and difficulty concentrating, also showed statistically significant differences favoring Wellbutrin at weeks 4-10.

Composite withdrawal symptom scores (sum of component scores) were higher at baseline for the Wellbutrin group than the placebo group. As shown below in a diagram prepared by the sponsor, scores for the Wellbutrin group peaked at week 2 and decreased thereafter, while the placebo group scores did not peak until week 4.

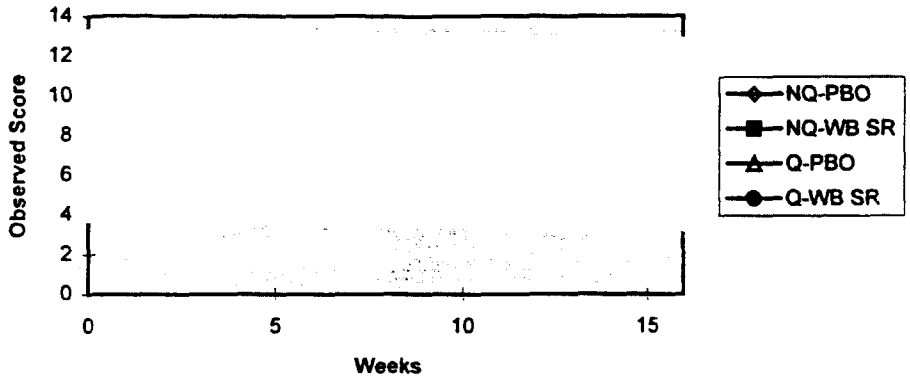
Nicotine Withdrawal Symptoms: Composite Score



Statistical comparisons of the two groups were performed on the change scores, and showed significant differences favoring Wellbutrin throughout the treatment and post-treatment phase and at 6-month follow-up. However, no analysis was performed by the sponsor to determine whether quitters and non-quitters differed in their reported withdrawal symptoms.

Analysis by the statistical reviewer reveals that, in general, quitters reported lower levels of withdrawal than non-quitters (composite withdrawal score), as illustrated below.

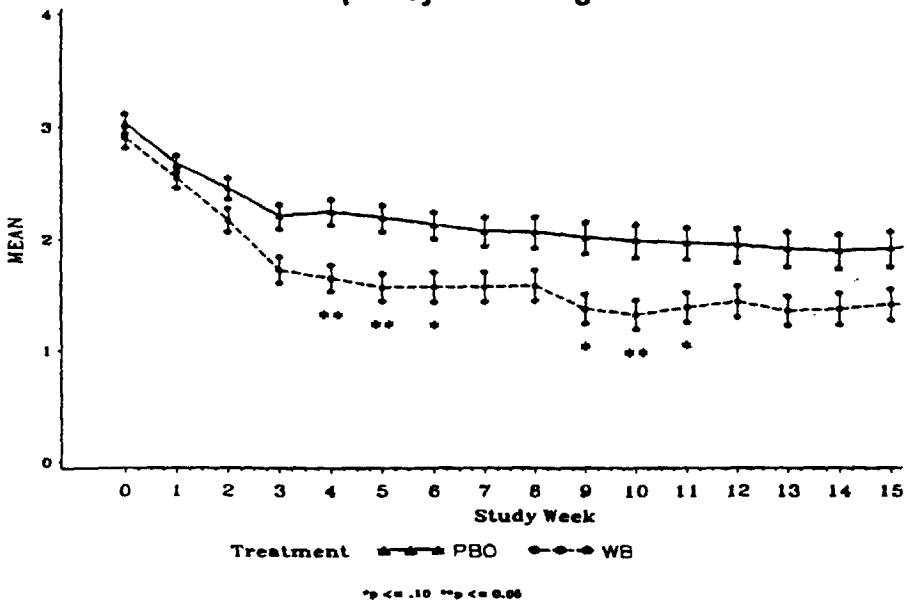
Nicotine Withdrawal Symptoms: Composite Score, for Quitters and Non-Quitters



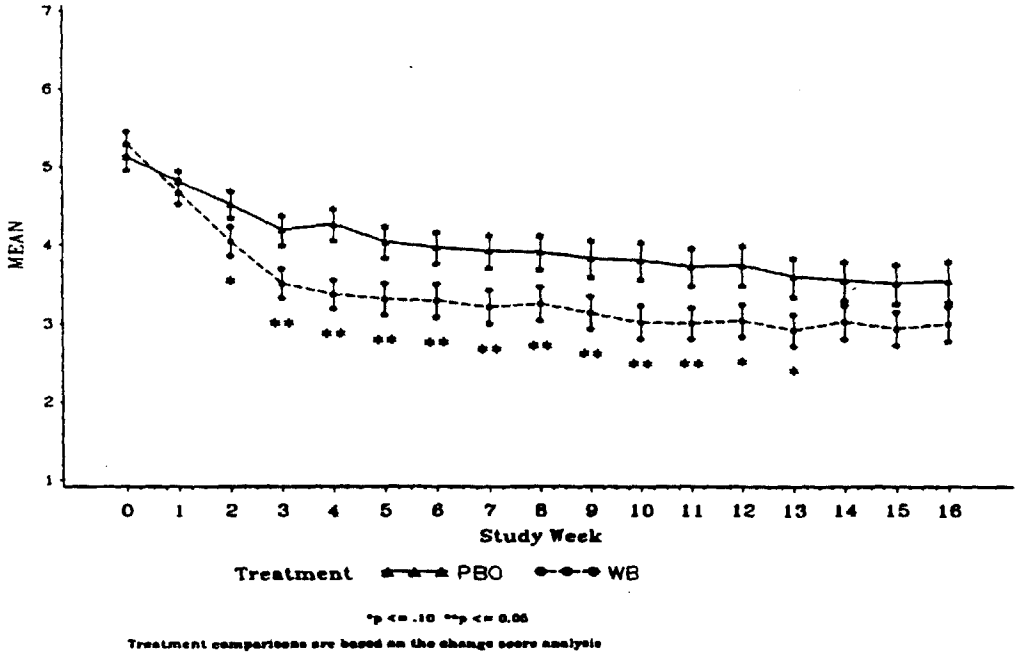
4.3.3 Role of Nicotine Craving:

Craving was assessed through several measures: mean daily scores from diary entries, and scores on the craving subscale of the withdrawal assessment obtained at clinic visits. The patient daily diary included a question, "Do you have an urge to smoke a cigarette right now?" Subjects responded using a 7-point scale ranging from 1 = "very definitely not" to 7 = "very definitely." Weekly means were calculated from the daily scores; the mean score is referred to by the sponsor as the "Craving Now" measure. The diary also included an item labeled "Craving Scale (how often you really feel the need to smoke)." Subjects responded using a 5 point scale ranging from A = "none at all" to E = "I am conscious of my need to smoke continuously." The weekly mean values for this measure (using A = 0 through E = 4) are referred to as the "Craving Scores" or "frequency of craving." The craving subscale of the withdrawal assessment is referred to as "Nicotine Craving Score." Not surprisingly, these three scales yielded similar findings. Statistical comparisons were performed comparing the treatment groups on each of the measures. For the "Craving Now" measure, statistically significant differences favoring Wellbutrin over placebo were observed at Weeks 3-11 and at 6-month follow-up. For the frequency of craving measure, statistically significant differences favoring Wellbutrin were observed at some time points during the treatment phase (Weeks 4, 5 and 10) but not others, and at the 6-month follow-up. For the nicotine craving subscale of the withdrawal assessment, statistically significant differences favoring Wellbutrin over placebo were noted at each treatment phase assessment. These findings are presented graphically below in diagrams prepared by the sponsor.

"Frequency of Craving" Scores

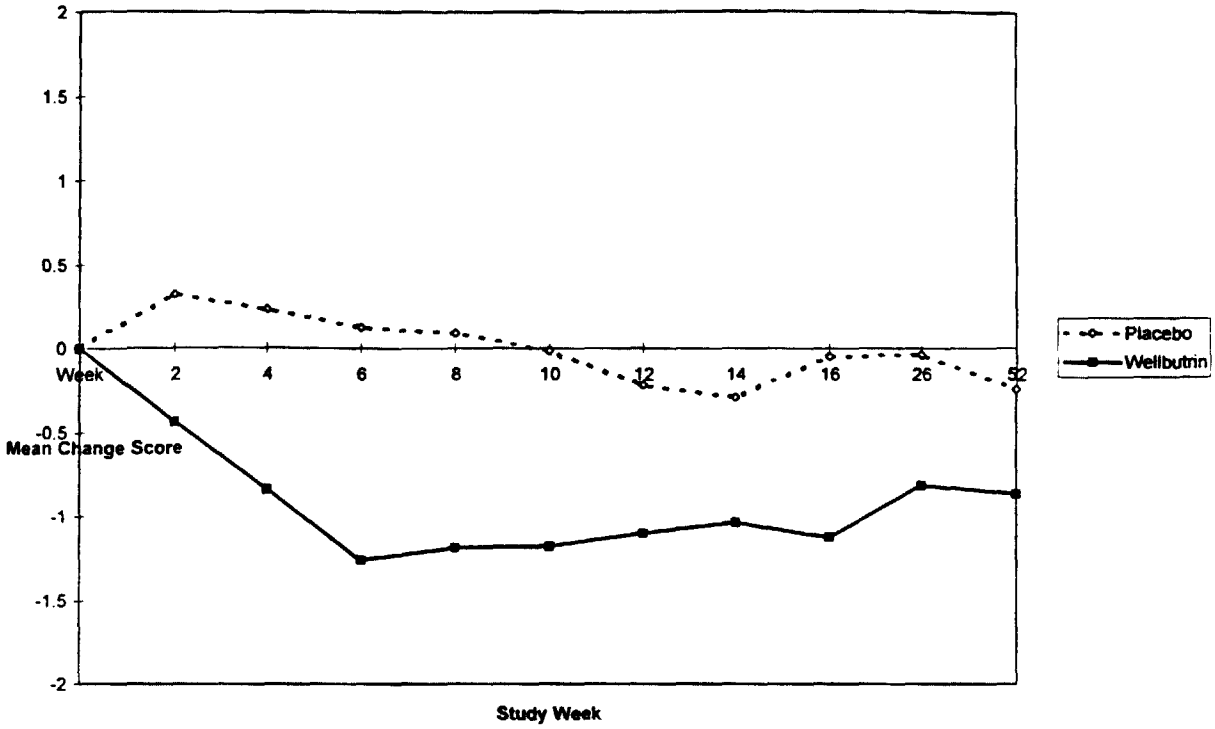


"Craving Now" Scores



Treatment comparisons are based on the change score analysis

Nicotine Craving Change Scores (Withdrawal Scale)



4.4 Safety comparisons

4.4.1 Exposure to Study Drug

4.4.1.1 Compliance Rates

The compliance rates for the two treatment groups were calculated by estimating the number of days on study drug by examination of the daily diaries and determining the latest date for which data were reported. The number of tablets a protocol-compliant patient should have taken in that number of days was compared to the number of tablets not returned at the bi-weekly visits. Subjects non-compliant with diary use, or who failed to return for a final visit at discontinuation and retained pills that should have been returned, generated spuriously high ratios (some as high as 5-10). A fully compliant patient would have taken 246 tablets (using one b.i.d. for the first three days and one t.i.d for days 4 - 84). Over 12 weeks it is reasonable to expect a certain number to be lost, dropped, or left at home instead of returned; ratios between 1.00 and 1.20 may well represent this type of mis-count, and were re-coded to 1.00 for the purposes of the calculation below. Ratios above 1.20 probably represent a more significant violation of protocol affecting either the numerator (didn't come back for a visit/kept an entire bottle of pills but didn't use them) or the denominator (didn't record use in the diary). It is difficult to determine the degree of compliance of these patients; they have been re-defined as "missing", but it is reasonable to imagine that overall, they were *less* compliant than the rest of the group. As shown below, the overall compliance rates were similar between treatment groups, suggesting that Wellbutrin was well-tolerated. If anything, missing values and extreme values presumed to represent non-compliance, as well as calculated compliances of less than 50% were more common in the placebo group.

Estimated Compliance by Treatment Group

	Placebo (N = 95)	Wellbutrin (N = 95)
Average Compliance	91%	89%
Missing values	7	4
Number Redefined as "missing"	10	7
Compliance 50% or less	5	3

(Table prepared by reviewer from sponsor's data)

4.4.1.2 Duration of Exposure

As shown below, nearly 70% of the patients were exposed to drug for the full twelve weeks of treatment. This represents the upper limit of the duration of treatment recommended in the labeling.

Estimated Duration of Treatment*

	Placebo		Wellbutrin		Total	
Days	N	%	N	%	N	%
1-6	7	7%	3	3%	10	5%
7-13	3	3%	2	2%	5	3%
14-20	6	6%	7	7%	13	7%
21-27	1	1%	1	1%	2	1%
28-35	3	3%	3	3%	6	3%
36-41	0	0%	2	2%	2	1%
42-48	2	2%	2	2%	4	2%
49-55	1	1%	0	0%	1	1%
56-62	5	5%	2	2%	7	4%
63-69	1	1%	1	1%	2	1%
70-76	2	2%	2	2%	4	2%
77-84	57	60%	66	69%	123	65%
missing	7	7%	4	4%	11	6%
Total	95	100%	95	100%	190	100%

*Estimate is based on examination of daily diary, and represents last day during the 12-week treatment phase for which data was reported

(Table prepared by reviewer from sponsor's data)

4.4.2 Deaths

No patients died during the treatment phase of the study. One patient randomized to placebo died after the completion of the treatment phase, and two placebo-group patients died following discontinuation from the study.

Patient completed the treatment and post-treatment phases of the study, using placebo. He died on approximately Day 130, and the investigator reported the probable cause of death was myocardial infarction. Patient withdrew from the study after 8 weeks of placebo treatment, because of lack of effect. He subsequently died of emphysema on Day 129. Patient also using placebo, discontinued the study after two weeks because of nausea and vomiting. He died on Day 316 in his sleep; the cause of death was felt to be myocardial infarction.

4.4.3 Serious Adverse Events

There were no other serious adverse events reported during the conduct of the study.

4.4.4 Adverse Events Associated with Premature Discontinuation

A total of 6 subjects (two in the Wellbutrin-treated group and three in the placebo-treated group) prematurely discontinued study medication because of adverse events.

4.4.4.1 Non-serious Events

Of the 190 patients randomized to treatment, 64 (34%) discontinued study medication prematurely. Only 3 patients (1.6%) are listed as having discontinued due to adverse events. As noted above, the reason for discontinuation was classified by the investigator, and there were also two others who stated that "side effects" led to discontinuation, but were assigned another reason by the investigator. All reasons for discontinuation by treatment group are displayed in the table above (Sect. 4.2).

Those who reported discontinuing due to a (non-serious) adverse event are listed in the table below.

Non-Serious AE's Leading to Early Termination of Study Drug

Treatment	Patient	Costart	Maximum Severity	Drug Related? (Investigator's Assessment)
Placebo	1	AMBLYOPIA	Moderate	Yes
	75	CONSTIPATION	Severe	Yes
	178	NAUSEA	Moderate	Yes
		VOMITING	Moderate	Yes
Wellbutrin	7	ANOREXIA	Mild	Yes
		SWEAT	Moderate	Unknown
		DIARRHEA	Severe	Unknown
	107	PALPITATIONS	Moderate	Unknown
		REACTION UNEVALUABLE*		
	186	VASODILATION	Moderate	No
		PALPITATIONS	Moderate	No
		HEADACHE	Moderate	Yes
		SWEAT	Moderate	Unknown
		SLEEP DISORDER	Moderate	Yes

*Verbatim Term = "Pulsating Sensation in Esophagus"

(Table prepared by reviewer from sponsor's data)

4.4.5 Other Non-Serious Adverse Events

Subjects were queried at each visit regarding adverse events, using both a subject-completed form that asked "Have you had any problems since the last visit two weeks ago? If yes, describe all adverse experiences, whether or not related to study drug," and a checklist completed by a study site physician. The checklist included headache, dizziness, dry mouth, agitation, sleepiness, tremor, rash, blurred vision, constipation, diarrhea, nausea/vomiting, fast heart rate, and sleep disturbance. A number of subjects also

are listed with the verbatim term "blood pressure increased," and the verbatim term "hypertension." It appears that the finding of increased pressure when vital signs were obtained may also have been coded as an AE. Of the 190 subjects, 116 (61%) reported one or more adverse experiences. The percentages of subjects experiencing at least one event were similar in the two treatment groups, with 58% of the placebo group and 64% of the Wellbutrin group reporting at least one event.

The tables below list all (unique) events reported by study subjects. The safety database was examined by the primary reviewer and the Costart coding of the verbatim terms was corrected in a few instances (i.e. all events for a single subject erroneously coded as "diarrhea," including verbatim terms of sleep disturbance, blurred vision,and agitation). Duplicate reports of events were deleted so that each subject had no more than one event per Costart code.

Among patients receiving Wellbutrin, the most commonly reported AE's (≥10% of the group) were dry mouth, headache, sleep disorder (Costart term for checklist item "sleep disturbance"), and constipation. For the placebo group, there were no AE's reported by more than 7% of the group. There were six AE's for which the rate of occurrence in any of the WB SR treatment groups differed from placebo by more than 5%. These included dry mouth, sleep disorder, headache, constipation, diarrhea, and hypertension (includes increases in blood pressure).

In contrast to studies of Wellbutrin SR for both depression and smoking cessation, where allergic phenomenon such as allergic reaction, rash, pruritis, and urticaria were found to be drug-related, in this study there were no reports of allergic reaction, urticaria, or pruritis, and reports of rash were equal in the Wellbutrin and placebo groups. Anxiety symptoms (anxiety, nervousness, and panic) have also been noted in other studies, but there were no events coded as nervousness or panic in this study, and anxiety was reported by 7% in each group.

ADVERSE EVENTS DURING TREATMENT AND POST-TREATMENT PHASES

COSTART	TREATMENT			
BODY SYSTEM	PLACEBO		WELLBUTRIN	
	N	%	N	%
BODY AS A WHOLE				
ASTHENIA	1	1%	2	2%
FLU SYNDROME	0	0%	2	2%
HEADACHE	4	4%	13	14%
INFECTION	3	3%	5	5%
PAIN	0	0%	1	1%
PAIN ABDOMEN	1	1%	1	1%
PAIN BACK	1	1%	4	4%
PAIN CHEST	2	2%	5	5%
REACTION AGGRAVATED*	0	0%	2	2%
REACTION UNEVALUABLE**	0	0%	2	2%
CARDIOVASCULAR				
ANGINA PECTORIS	1	1%	2	2%
CARDIOVASCULAR DISORDER	0	0%	1	1%
HYPERTENSION	4	4%	9	9%
HYPOTENSION	1	1%	0	0%
INFARCTION MYOCARDIAL	1	1%	0	0%
PALPITATION	0	0%	2	2%
SYNCOPE	1	1%	1	1%
TACHYCARDIA	4	4%	0	0%
VASODILATION	0	0%	1	1%
DIGESTIVE				
ANOREXIA	1	1%	1	1%
APPETITE INCREASED	0	0%	1	1%
CONSTIPATION	5	5%	11	12%
DIARRHEA	3	3%	9	9%
DRY MOUTH	6	6%	14	15%
DYSPEPSIA	0	0%	2	2%
DYSPHAGIA	1	1%	0	0%
ERUCTATION	1	1%	0	0%
FLATULENCE	1	1%	3	3%
GI DISORDER	1	1%	0	0%
HEMORRHAGE GUM	0	0%	1	1%
MELENA	1	1%	0	0%
MONILIA ORAL	0	0%	1	1%
NAUSEA	5	5%	5	5%
PANCREATITIS	0	0%	1	1%
RECTAL DISORDER	1	1%	0	0%
STOMATITIS APHTHOUS	0	0%	2	2%
ULCER DUODENAL	1	1%	0	0%
VOMITING	5	5%	5	5%
METABOLIC/NUTRITIONAL				
DIABETES MELLITUS	0	0%	1	1%
EDEMA GENITAL	0	0%	1	1%
EDEMA PERIPHAL	1	1%	2	2%
HYPERGLYCEMIA	1	1%	0	0%
HYPOGLYCEMIA	1	1%	0	0%
WEIGHT INCREASED	3	3%	3	3%

*Verbatim terms refer to nicotine craving

**Verbatim terms = "pulsating sensation in esophagus," "marital problems"

ADVERSE EVENTS DURING TREATMENT AND POST-TREATMENT PHASES, continued				
COSTART	TREATMENT			
BODY SYSTEM	PLACEBO		WELLBUTRIN	
	N	%	N	%
MUSCULOSKELETAL				
ARTHRALGIA	1	1%	0	0%
ARTHRITIS	1	1%	1	1%
PAIN BONE	1	1%	0	0%
TENOSYNOVITIS	0	0%	1	1%
NERVOUS				
AGITATION	7	7%	7	7%
DEPRESSION	5	5%	4	4%
DIZZINESS	3	3%	3	3%
DREAM ABNORMALITY	1	1%	0	0%
DYSPHORIA	0	0%	1	1%
EMOTIONAL LABILITY	2	2%	0	0%
HYPERKINESIA	0	0%	2	2%
HYPESTHESIA	1	1%	0	0%
IRRITABILITY	0	0%	2	2%
NEURITIS PERIPHAL	1	1%	0	0%
PARALYSIS FACIAL	1	1%	0	0%
PARESTHESIA	2	2%	2	2%
SLEEP DISORDER	6	6%	13	14%
SOMNOLENCE	1	1%	2	2%
THINKING ABNORMALITY	1	1%	0	0%
TREMOR	0	0%	2	2%
RESPIRATORY				
BRONCHITIS	0	0%	1	1%
COUGH INCREASED	4	4%	5	5%
DYSPNEA	2	2%	2	2%
EPISTAXIS	0	0%	2	2%
PHARYNGITIS	3	3%	1	1%
PNEUMONIA	1	1%	0	0%
RHINITIS	2	2%	3	3%
SINUSITIS	1	1%	2	2%
VOICE ALTERATION	1	1%	0	0%
SKIN				
RASH	3	3%	3	3%
SWEAT	0	0%	3	3%
SPECIAL SENSES				
AMBLYOPIA	1	1%	1	1%
OTITIS EXTERNA	1	1%	0	0%
OTITIS MEDIA	1	1%	0	0%
PAIN EAR	1	1%	1	1%
TASTE LOSS	1	1%	0	0%
TASTE PERVERSION	2	2%	0	0%
UROGENITAL				
DYSURIA	0	0%	2	2%
NOCTURIA	1	1%	0	0%
POLYURIA	1	1%	1	1%
PROSTATE DISORDER	0	0%	2	3%
TESTIS DISORDER	1	1%	0	0%
URINARY TRACT DISORDER	0	0%	1	1%

Denominators for male-specific AE's: Placebo = 82, Wellbutrin = 78
(Table prepared by reviewer from sponsor's data)