Development of Depression During Placebo-Controlled Trials of Bupropion for Smoking Cessation: Case Reports

Christi A. Patten, Ph.D.; Teresa A. Rummans, M.D.; Ivana T. Croghan, Ph.D.; Richard D. Hurt, M.D.; and J. Taylor Hays, M.D.

Received April 27, 1998; accepted Dec. 9, 1998. *From the Nicotine Research Center (Drs. Patten, Croghan, and Hurt), the Department of Psychiatry (Dr. Rummans), and the Division of General Internal Medicine (Dr. Hays), Mayo Clinic, Rochester, Minn.*

Supported by a grant from Glaxo Wellcome, Inc., Research Triangle Park, N.C.

Reprint requests to: Christi A. Patten, Ph.D., Mayo Clinic, Nicotine Research Center, Colonial B-23, 200 First Street S.W., Rochester, MN 55905 (e-mail: patten.christi@mayo.edu).

Background: Recent attention has focused on the relationship between depression and smoking cessation. This article describes 5 cases of severe depression that occurred during 2 multicenter trials using bupropion for smoking cessation.

Method: Subjects were participants in 2 randomized, double-blind, placebo-controlled studies investigating the efficacy of bupropion for smoking cessation. Data from both trials were restricted to subjects at the Rochester, Minn., site in order to have access to the medical records for information on depression diagnosis, treatment, and follow-up. The first trial involved 205 smokers who received active bupropion or placebo for 7 weeks. In the second trial, 252 smokers received open-label bupropion therapy for 7 weeks. Those abstinent from smoking at the end of week 7 (N = 148) were randomly assigned to a 45-week, double-blind, relapse-prevention phase.

Results: In the first trial, 1 of the 205 participants (0.49%) experienced major depression during the 7-week treatment phase. In the second trial, none of the 252 subjects developed major depression during the 7-week, open-label phase. When results of both trials across the 7-week treatment phase (study 1, N = 205; study 2, N = 252) are combined, the rate of developing major depression was 0.22% (1 of 457). Of the 457 subjects, none of the 51 who received placebo and 1 (0.25%) of the 406 who received active bupropion developed major depression. In the second trial, 4 (2.7%) of the 148 subjects randomly assigned to the 45-week, relapse-prevention phase developed depression. Overall, 4 of the 5 cases from the 2 trials had a past history of major depression prior to study entry, but none had current major depression.

Conclusion: Major depression may occur in some individuals during smoking cessation treatment with bupropion.

(J Clin Psychiatry 1999;60:436–441)

Recent attention has focused on the relationship between depression and smoking cessation.[1,2] The nicotine withdrawal syndrome as defined by the DSM-IV criteria[3] includes symptoms such as irritability, dysphoria, and sleep disturbance that parallel some symptoms of a depressive episode. These symptoms may interfere with successful attempts at initiating smoking abstinence and contribute to relapse.[4] The onset of major depression during smoking abstinence has also been observed.[5–8] However, most studies have not reported the proportion of smokers experiencing major depression relative to the total sample enrolled for smoking cessation. In 2 studies that reported such data, the occurrence of major depression during smoking cessation treatment was approximately 7%.[9,10]

Additional research indicates that a former history of major depression may be a risk factor for developing a major depressive episode during smoking abstinence.[10] In a trial of clonidine for smoking cessation, Glassman et al.[11] observed that 6 (5.3%) of 113 smokers with a past history of major depression developed depression during smoking treatment compared with 1 (0.6%) of 153 without such a history. When considering only those subjects abstinent from smoking at the end of treatment, these authors found the proportion who developed major depressive disorder was higher: 18% of those with a past history of major depression versus 2% of those with no such history.[12] Covey et al.[10] also found that 20.6% of 34 nondepressed subjects with a past history of major depression experienced an episode of major depression within 3 months of smoking cessation compared with 2% of 91 without a history of major depression.

In this report, we describe 5 cases of severe major depression that occurred during bupropion trials for smok-

ing cessation conducted at the Mayo Clinic, Rochester, Minn.

METHOD

Subjects were participants in 2 studies investigating the efficacy of bupropion for smoking cessation. In the 2 bupropion trials conducted, inclusionary criteria required that subjects be at least 18 years of age and smoke at least an average of ≥ 15 cigarettes per day for the previous year. Exclusion criteria included an unstable medical or psychiatric illness including a current major depressive episode, history of alcohol or nonnicotine substance dependence within the past year, prior use of bupropion, current use of psychotropic medications, and current use of nicotine replacement therapy or other medications for smoking cessation (e.g., clonidine). After complete description of the study to the subjects, written informed consent was obtained. Baseline assessments were made prior to start of medication and attempt to stop smoking. The Fagerström Tolerance Questionnaire (FTQ)[13] was used to assess the level of nicotine dependence at baseline. At baseline, subjects were interviewed using the Structured Clinical Interview (SCID) to assess for a lifetime history of major depression according to the DSM-IV criteria.[14] Severity of depressive symptoms was assessed at baseline and following the target quit date using the Beck Depression Inventory (BDI).[15] The BDI scores were not used as part of the screening criteria for study entry.

The first trial was a randomized, double-blind, placebo-controlled study of bupropion for smoking cessation performed at 3 sites.[16] Subjects were randomly assigned to receive a sustained-release form of bupropion at dosages of 100 mg/day, 150 mg/day, or 300 mg/day or placebo. Subjects had a target quit date 1 week after beginning medication. They returned weekly during the 7-week treatment phase, and brief counseling was provided by a study assistant. The second study was a randomized, double-blind, relapse-prevention trial of bupropion that was performed at 5 sites (R.D.H., unpublished data). Subjects received open-label sustained-release bupropion (300 mg/day) for 7 weeks. Similar to the first study, subjects had a target quit date 1 week after beginning medication. Those abstinent from smoking at week 7 were randomly assigned to active bupropion (300 mg/day) or placebo for a total of 45 weeks.

At each visit, subjects were considered nonsmoking if they reported no smoking during the past 7 days with confirmation by an expired-air carbon monoxide value of ≤ 10 ppm. Subjects with missing data were classified as smoking. Use of concomitant medications for smoking cessation, including nicotine replacement therapies, was assessed at baseline and at each visit. With the exception of 1 subject in the first trial who reported using only 1 piece of nicotine gum, participants who reported use of these medications during the treatment phase were discontinued from the study. Data from both trials were restricted to subjects at the Rochester, Minn., site in order to have access to the medical records for information on depression diagnosis, treatment, and follow-up.

Depressive symptoms were first reported by the subject to a study assistant, and, if necessary, the physician investigator evaluated the subject. Referral for psychiatric evaluation was made by the physician investigator when appropriate. The diagnosis of major depression was established by a board-certified psychiatrist using the DSM-IV criteria.[14]

CASE REPORTS

Case 1 was from the first trial of bupropion for smoking cessation. Of the 205 subjects enrolled at the Rochester, Minn., site, 36 (17.6%) had a past history of major depression while 169 had no prior history of depression. The subjects were assigned to placebo (N = 51) or active bupropion at dosages of 100 mg/day (N = 51), 150 mg/day (N = 51), or 300 mg/day (N = 52) for 7 weeks. Of the 205 participants entering the trial, only 1 (0.49%) experienced an episode of major depression during the 7-week study medication phase. This individual was receiving active bupropion, 150 mg/day.

When considering the rates of development of major depression by biochemically confirmed smoking status at the end of week 7, the proportion was 0% among the 70 subjects who were confirmed nonsmokers at the end of treatment compared with 1 (0.74%) of the 135 subjects who continued to smoke. When considering the proportion of subjects who developed major depression during the 7-week treatment phase by past history of major depression, 1 (2.8%) of the 36 with a history of major depression developed depression compared with none of the 169 without a history of major depression. Among the 70 subjects who were abstinent from smoking at the end of treatment, the rate of development of major depression was 0% (0 of 14) and 1.8% (1 of 56) for those with and without a past history of major depression, respectively.

The 1 case of major depression that occurred in the first trial is described below.

Case 1

Ms. A, a 45-year-old divorced, employed white woman, had smoked an average of 25 cigarettes per day for 27 years. Her baseline FTQ score was 8. She had 3 previous attempts at smoking cessation, with her last attempt 20 months prior to baseline. Her baseline BDI score was 4. She had a history of 1 major depressive episode at age 38, when she had attempted to stop smoking. At that time, she was hospitalized briefly and was treated with imipramine for 1.5 years.

Within 1 week following her target quit date, Ms. A complained of trouble sleeping, but had not smoked. At

week 3, her BDI score was 17, and she complained of sleep disturbance, decreased appetite, emotional lability with crying spells, and increased irritability. At week 4, she was abstinent from smoking but reported depression, decreased concentration, and insomnia, and she was tearful. Five days later during a telephone follow-up, she reported that she had begun smoking 3 to 5 cigarettes per day and was feeling worse. Psychiatric evaluation revealed moderate major depressive symptoms, and she was removed from the study. It was determined that the patient had been assigned to bupropion, 150 mg/day, and she was switched to sertraline, 100 mg/day. Unfortunately, she developed psychotic symptoms, and the antipsychotic risperidone was added. Subsequent follow-up visits revealed progressively severe depression with BDI scores of 35 and 33 at weeks 7 and 8, respectively. During this time, she continued to smoke < 5 cigarettes per day. She received electroconvulsive therapy (ECT) with initial resolution of depression. However, her depression relapsed within 4 weeks and she received a second course of ECT with resolution of depression. She was maintained on divalproex and venlafaxine. At monthly follow-up visits 5 through 12, Ms. A's depression was in remission, and she was abstinent from smoking. She reported that the depression was an incentive for her not to smoke again.

Cases 2 Through 4

Cases 2 through 4 were from the second trial of bupropion for smoking cessation. In this trial, 252 smokers received open-label bupropion, 300 mg/day, for 7 weeks. Of these, 67 (26.6%) had a past history of major depression, while 185 had no history of major depression. None of the 252 subjects developed major depression during the 7-week, open-label phase.

Of the 252 subjects, 148 were abstinent from smoking at week 7 and were randomly assigned to the double-blind phase. Seventy-four subjects were assigned to active bupropion, and 74 received placebo. Of the 148, 38 (25.7%) had a past history of major depression while 110 had no such history. Four (2.7%) of the 148 participants developed an episode of major depression after random assignment to the double-blind phase. One of the 4 was assigned to active bupropion, while 3 cases were assigned to placebo. Thus, the rates of development of depression for the active and placebo groups were 1.4% and 4.1%, respectively (Fisher exact test, p = .620).

All 4 subjects who developed major depression self-reported not smoking at the end of the relapse-prevention phase as determined by notations in the medical record by the psychiatrist treating the subject's depression. This approach to classifying smoking status is less conservative than the intent-to-treat analysis where the cases were classified as smoking at the end of treatment because of missed study visits and lack of biochemical confirmation of smoking status after the onset of their depression. At the end of the relapse-prevention phase, 69 of the 148 randomized subjects were confirmed nonsmokers in the intent-to-treat analysis. The rate of developing major depression would therefore be 0% if we included as the denominator only abstinent smokers. However, if we were to use a less conservative approach and classify the 4 cases of major depression as nonsmoking, the rate of development of major depression during the relapse-prevention phase among abstinent smokers was 5.5% (4 of 73) compared with 0% of the 75 who continued to smoke (Fisher exact test, p = .057).

Three of the 4 cases had a past history of major depression. The rate of developing an episode of major depression during the 45-week double-blind phase among those with a past history of major depression (7.8%; 3 of 38) was higher than the proportion among those without a past history of major depression (0.9%; 1 of 110), although this difference was not statistically significant (Fisher exact test, p = .052). If we consider as the denominator only confirmed nonsmokers at the end of the relapse-prevention phase and classified the 4 cases as nonsmoking, the rate of developing major depression among those nonsmokers with a past history of major depression (14.3%; 3 of 21) was higher than among those without a history of major depression (1.9%; 1 of 52; Fisher exact test, p = .069).

The 4 cases of depression that occurred during the relapse-prevention trial are described below.

Case 2. Ms. B, a 54-year-old divorced, employed white woman, had smoked an average of 20 cigarettes per day for 41 years. Her baseline FTQ score was 9. She had made 1 previous attempt at smoking cessation 7 months prior to baseline. Her baseline BDI score was 12. She had a history of 1 episode of major depression at the age of 46 and was treated with imipramine, 100 mg/day, and perphenazine; her depression resolved within 7 weeks.

Ms. B was abstinent from smoking throughout the open-label and double-blind treatment phase. One week after her target quit date, she reported onset of "the blues" and that she had been crying easily. However, during weekly visits 3 through 10, she had no complaints of depression. At weeks 7 and 8, she had a BDI score of 5. At week 12, her BDI score was also 5, but she reported increased stress due to family problems. Four days prior to her scheduled visit at week 16, she developed symptoms including overwhelming sadness and crying and was diagnosed with major depression by a psychiatrist. Ms. B was removed from the study, and it was determined that she had been assigned to placebo. She was placed on paroxetine treatment, 40 mg/day, in conjunction with psychotherapy. Her depression resolved within 2 months. At her last follow-up with the psychiatrist, 1.5 years after she began treatment for her depression, Ms. B continued on paroxetine treatment and reported that she was abstinent from smoking.

Case 3. Ms. C, a 35-year-old married, employed white woman, had smoked an average of 20 cigarettes per day for 18 years. Her baseline FTQ score was 9. She had made 2 previous stop attempts, with her last attempt 10 months prior to baseline. Her baseline BDI score was 15. She had no previous history of major depression.

Ms. C was abstinent from smoking throughout the open-label and double-blind treatment phases. Prior to her target quit date, she complained of sleeplessness, ringing in her ears, "spaced-out" feelings, and "the jitters." At week 7, she reported cravings for nicotine. At weeks 7, 8, and 12, her BDI scores were 6, 3, and 2, respectively. At week 20, she reported having depressed mood. Approximately 19 days later, a psychiatrist reported to the research staff that Ms. C had been evaluated for depression. The psychiatrist had elicited a 2-year history of depressive symptoms that had worsened, including tearfulness, decreased energy, decreased interest and enjoyment in activities, and irritability, and the patient was diagnosed with a dysthymic disorder. Ms. C was removed from the study, and it was determined that she had been assigned to placebo. She was treated for depression with bupropion sustained-release, 150 mg/t.i.d., for 1 week, but was switched to sertraline, 100 mg/day, secondary to side effects (irritability and "the jitters") while taking the bupropion. At the 3-month follow-up with the psychiatrist, she reported that she was abstinent from smoking and there was improvement in her depressive symptoms while remaining on sertraline treatment.

Case 4. Ms. D, a 55-year-old married, unemployed white woman, had smoked an average of 30 cigarettes per day for 30 years. Her baseline FTQ score was 8. She had made 2 previous attempts at stopping smoking, with her last attempt 1 year prior to baseline. Her baseline BDI score was 17. She had a history of 2 previous episodes of major depression. Her first episode was at age 25, when she was treated with an unknown type of antidepressant. Her second episode of depression was 1 year prior to baseline when she had tried to stop smoking; information on the type of depression medication was not available.

One day prior to her target quit date, Ms. D complained of mild tension, which continued for the duration of the study. On the target quit date, she smoked 6 cigarettes, but was abstinent from smoking at all subsequent visits during the open-label and double-blind phases. At week 3, she was tearful and reported that she was dealing with stressful situations in her life. At week 8, she reported that others had observed her to be restless. Her BDI scores ranged from 9 at week 7 to 6 at week 12. At week 16, she complained of a rapid heart beat and frequent urges to smoke. At week 24, she reported weight gain and depressed mood, which she attributed to her smoking abstinence. However, at week 28, Ms. D was in good spirits, had lost 4 lb (1.8 kg), and was engaging in physical exercise. At weeks 36, 40, and 44, she complained of mild depressed mood, but no longer reported problems with restlessness. During week 45, she developed marked depressive symptoms, including initial and terminal insomnia and decreased energy, and was diagnosed with major depression by a psychiatrist. Ms. D was removed from the study and found to have been assigned to active bupropion. This was switched to sertraline, 75 mg/day, and trazodone, 50 mg/h.s. At the 9-month follow-up with the psychiatrist, she was abstinent from smoking, and her depression resolved while remaining on treatment with both medications.

Case 5

Mr. E, a 44-year-old married, employed white man, had smoked an average of 20 cigarettes per day for 24 years. His baseline FTQ score was 8. He had made 1 serious attempt to stop $5^1/_2$ years prior to baseline. His baseline BDI score was 10. He had a history of 1 previous episode of major depression at age 40 and was treated with fluoxetine for 2 years.

Mr. E reported smoking from the target quit date through the week 3 visit and indicated that he was having a difficult time dealing with anger without smoking. However, he was abstinent from smoking at all subsequent visits during the open-label and double-blind treatment phases. At weeks 7 and 8, his BDI scores were 7 and 8, respectively. At week 8, he complained of fatigue. At week 9, he complained of depression and was evaluated by the physician investigator. He reported 2 weeks of emotional lability, increased appetite, 10- to 15-lb (4.5- to 6.8-kg) weight gain, decreased energy, difficulty sleeping, and loss of interest in daily activities. At the week 10 visit, he was tearful and reported that the depressive symptoms had worsened. He was diagnosed with major depression by a psychiatrist. Mr. E was removed from the study, and it was determined that the patient had been assigned to placebo. He was placed on bupropion treatment, 150 mg t.i.d. Four months later, his depressive symptoms had improved except for a further increase in weight and memory problems. He was switched to fluoxetine, 20 mg/day. At 8-month follow-up with the psychiatrist, he was switched to nefazodone, 100 mg b.i.d., because of side effects of the fluoxetine, and he began psychotherapy. The nefazodone dosage was increased to 150 mg b.i.d. at 10-month follow-up. The depression resolved by the 12-month follow-up. At the 19-month follow-up with the psychiatrist, Mr. E was abstinent from smoking and was asymptomatic with respect to depression while remaining on nefazodone treatment.

DISCUSSION

This case series builds on previous studies which indicate that a major depressive episode may occur in some patients during smoking cessation treatment.[5–11] No previ-

ous work has examined the development of major depression during trials of bupropion for smoking cessation. The proportion of subjects who developed depression for both studies combined was 1.1% (5 of 457), which is lower than the rate of 7% previously reported in the literature. [9,10] The 2 bupropion trials were very different in that the first study was an acute-treatment trial and the second, a long-term relapse-prevention trial. Thus, the period of risk for development of depression was 7 weeks in one and 45 weeks in the other. When combining results of both trials across the 7-week treatment phase (study 1, N = 205; study 2, N = 252), the rate of developing major depression was 0.22% (1 of 457). During the 45-week relapse-prevention phase, the proportion of subjects developing depression was 2.7% (4 of 148).

An important issue in establishing the rate of development of depression is whether to include all randomized subjects or all subjects abstinent from smoking as the denominator on which these calculations are based. Those who continue to smoke may not be at the same risk for emergence of depression as those who abstain from smoking. However, it is plausible that even attempts to stop smoking or reductions in nicotine blood levels associated with reduced cigarette consumption may trigger depression.[9] The work of Glassman and colleagues[10,11] indicates that the proportion of subjects who develop major depression is lower when all randomized subjects are considered (2.6%)[11] than when the analyses include only those subjects who achieve abstinence from smoking (7%).[10] Similarly, if we consider only the 143 subjects abstinent at the end of treatment (study 1, N = 70; study 2 relapse-prevention phase, N = 73), the rate of development of major depression for both studies combined is slightly higher (3.5%), but still lower than the rates observed in previous trials. However, these results should be interpreted in light of our approach to classifying smoking status among the 4 cases in the relapse-prevention trial, which is different than the intent-to-treat analysis where these individuals were classified as smoking. The subjects in our study developed depression at varying timepoints, ranging from 3 to 44 weeks after their target quit date. Although it would be informative to examine the rate of emergent depression among abstinent subjects using a survival-type analysis, such an analysis is beyond the scope of this case series.

One issue that could influence the reported rate of development of major depression is the definition of cases. The clinical procedure used to ascertain cases of depression during the smoking cessation trials may have been less sensitive than needed to detect all cases of depression that did not necessitate treatment. Additionally, some individuals may have experienced subthreshold levels of depression and returned to smoking or began treatment for depression to ameliorate their symptoms. Smokers with a history of major depression may have been particularly sensitive to the emergence of depressive symptoms and averted the recurrence of a major depressive episode by restarting an antidepressant medication or other therapy for depression and/or resuming smoking. Our method of ascertaining cases also may not have captured episodes of depression among subjects who missed study visits or were discontinued from the study. Thus, it is likely that the proportion of subjects who developed major depression is underestimated, since undocumented episodes of depression undoubtedly occurred. Furthermore, although subjects with current major depression at baseline were ineligible for the study, the BDI score was not used as part of the screening criteria. Thus, the rate of development of depression was likely not affected by the screening criteria used to assess depression.

A prior history of major depression has been implicated as a risk factor for development of a major depressive episode during smoking cessation.[10] Thus, the percentage of smokers with a history of major depression should influence the occurrence of new depressive episodes following cessation. For the 2 bupropion trials combined, 22.5% of the subjects had a former history of major depression, which is lower than previous estimates of between 30% and 61% among smokers entering clinical trials for smoking cessation.[17,18] However, similar to the rate that we observed, a recent trial[19] found the proportion of subjects with a past history of major depression to be 22%. It is possible that the relatively lower rate of past history of major depression as well as the rate of development of major depression in our clinical trials is reflective of the sociodemographic characteristics of smokers attending the Mayo Clinic in Rochester, Minn. Higher rates may have been obtained in the various study site locations.

Four of the 5 cases who developed major depression had a former history of major depression. Moreover, the 1 case without a past history of major depression did have a 2-year history of dysthymia. None of the 4 cases with a history of major depression were depressed at the time they initiated smoking treatment and had not been for an average of 5 years (range, 1 to 7 years). In the second trial, there was a trend for those with a past history of major depression to be more likely to develop major depression during the relapse-prevention phase than those without such a history (8% vs. 1% among all randomized subjects; 14.3% vs. 1.9% among all subjects abstinent from smoking). The small number of subjects included in these comparisons limits our ability to detect statistically significant differences. These observations are consistent with the findings of Glassman et al.,[11] who observed that 5.3% of those with a past history of major depression developed depression during a trial of clonidine for smoking cessation compared with 0.6% of those with no such history, even though the period of risk for development of depression was different from our study (10 weeks vs. 45 weeks). When considering only those subjects abstinent from smoking at the end of treatment, those investigators found the proportion of

subjects with a past history of major depression who developed major depression to be even higher (18%) compared with those with no history of major depression (2%).[12] Thus, a former history of depression may be associated with a higher likelihood of developing major depression during smoking cessation.[10] Additional treatment is likely needed to assist individuals with comorbid psychopathology in maximizing their chances at successful abstinence from smoking.[20] It is noteworthy that all 5 of the present cases, including those with a past history of major depression, achieved long-term abstinence from smoking, which may have been due in part to early recognition and treatment of their major depression.

While inferences cannot be drawn from this case series, it is possible that bupropion treatment prevents development of depression during smoking cessation. Three of the 5 cases who developed major depression were receiving placebo instead of bupropion. The remaining 2 cases were receiving 150 mg/day and 300 mg/day of bupropion, respectively, and neither is considered the optimal dose for treatment of depression. When combining results of both trials across the 7-week treatment phase, the rate of developing major depression was 0% among the 51 subjects who received placebo and 0.25% (1 of 406) among those who received active bupropion. In the second trial, during the relapse-prevention phase, the rate of development of major depression was higher, though not statistically significant, among placebo-treated subjects (4.1%; 3 of 74) than those treated with active bupropion (1.4%; 1 of 74). In a previous report,[21] we examined changes in BDI scores from baseline to end of treatment among abstinent smokers enrolled in the first trial of bupropion for smoking cessation. There was no evidence that increases in BDI score were related to bupropion dose. Prospective trials with larger numbers of subjects will be needed to address the potential effect of bupropion in development of major depression and/or elevated levels of depressive symptoms.

Further research is needed to determine the period of vulnerability to major depression during abstinence from smoking. Previous studies have also used varying time periods to assess emergence of depression following smoking cessation. The diagnostic criteria for depression has also varied across studies. Some reports have simply used severe depressive symptoms while others have applied standard DSM diagnostic criteria. The systematic assessment of depressive symptoms at various points during smoking cessation treatment may shed light on the time course of depression during smoking abstinence.

Drug names: bupropion (Zyban, Wellbutrin), clonidine (Catapres and others), divalproex sodium (Depakote), fluoxetine (Prozac), nefazodone (Serzone), paroxetine (Paxil), perphenazine (Trilafon and others), risperidone (Risperdal), sertraline (Zoloft), trazodone (Desyrel and others), venlafaxine (Effexor).

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