Annals of Internal Medicine | ORIGINAL RESEARCH

# Action to Stop Smoking in Suspected Tuberculosis (ASSIST) in Pakistan

## A Cluster Randomized, Controlled Trial

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**Background:** Tobacco use is responsible for a large proportion of the total disease burden from tuberculosis. Pakistan is one of the 10 high-burden countries for both tuberculosis and tobacco use.

**Objective:** To assess the effectiveness of a behavioral support intervention and bupropion in achieving 6-month continuous abstinence in adult smokers with suspected pulmonary tuberculosis.

**Design:** Cluster randomized, controlled trial. (Current Controlled Trials: ISRCTN08829879)

**Setting:** Health centers in the Jhang and Sargodha districts in Pakistan.

**Patients:** 1955 adult smokers with suspected tuberculosis.

**Intervention:** Health centers were randomly assigned to provide 2 brief behavioral support sessions (BSS), BSS plus 7 weeks of bupropion therapy (BSS+), or usual care.

**Measurements:** The primary end point was continuous abstinence at 6 months after the quit date and was determined by carbon monoxide levels in patients. Secondary end points were point abstinence at 1 and 6 months.

**Results:** Both treatments led to statistically significant relative risks (RRs) for abstinence compared with usual care (RR for BSS+, 8.2 [95% CI, 3.7 to 18.2]; RR for BSS, 7.4 [CI, 3.4 to 16.4]). Equivalence between the treatments could not be established. In the BSS+ group, 275 of 606 patients (45.4% [CI, 41.4% to 49.4%]) achieved continuous abstinence compared with 254 of 620 (41.0% [CI, 37.1% to 45.0%]) in the BSS group and 52 of 615 (8.5% [CI, 6.4% to 10.9%]) in the usual care group. There was substantial heterogeneity of program effects across clusters.

**Limitations:** Imbalances in the urban and rural proportions and smoking habits among treatment groups, and inability to confirm adherence to bupropion treatment and validate longer-term abstinence or the effect of smoking cessation on tuberculosis outcomes.

**Conclusion:** Behavioral support alone or in combination with bupropion is effective in promoting cessation in smokers with suspected tuberculosis.

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Tuberculosis and tobacco use are considered to be 2 "colliding epidemics" that lead to 1.4 million and 6 million deaths per year, respectively (1). Tobacco smoking increases the risk for tuberculosis infection and disease (2, 3). Patients with the disease who smoke deteriorate more rapidly and have a higher risk for death than those who do not smoke (2). In addition, tobacco smoking is associated with higher rates of treatment noncompletion, treatment failure, and relapse (4, 5), and tuberculosis transmission is higher in smoking households than in those with smoking restrictions (6). As much as 20% of the total disease burden from tuberculosis is attributable to tobacco use (2). On the basis of current smoking trends, it is estimated that tobacco use will lead to an extra 18 million tuberculosis cases and 40 million tuberculosis deaths between 2010 and 2050 (7). Moreover, tuberculosis predominantly occurs in low- and middle-income countries, where smoking prevalence is highest (8–10).

The World Health Organization has proposed addressing tobacco use in tuberculosis control programs (11). Exploratory studies in Sudan, Malaysia, and Indonesia suggest that such integration is feasible and potentially beneficial (12–14). However, the effectiveness of smoking cessation interventions for patients in tuberculosis control programs has not been established (15). Although such interventions as behavioral support, nicotine replacement therapy, and bupropion therapy have been shown to be effective for smoking cessation (16, 17), their use in patients with suspected tuberculosis has not been evaluated.

Pakistan has one of the highest tuberculosis burdens worldwide, with approximately 400 000 incident cases and 58 000 deaths annually (1). Tobacco use is also prevalent in Pakistan. We aimed to establish the effectiveness of interventions for smoking cessation in patients with suspected tuberculosis attending a control program. Because pharmacotherapy may be prohibitively expensive for most people in Pakistan, we investigated behavioral support sessions (BSS) with and without pharmacotherapy compared with usual care.

## METHODS

### Design Overview

ASSIST (Action to Stop Smoking In Suspected Tuberculosis) is a balanced, pragmatic, cluster randomized

*See also:*

**Web-Only**
Supplements

***Context***

Tobacco use increases the risk for tuberculosis, active disease, and poor outcomes. Targeting tobacco cessation efforts to smokers with suspected tuberculosis might be an effective use of limited resources in low- and middle-income countries.

***Contribution***

In this trial of smokers with suspected tuberculosis in Pakistan, behavioral support with or without bupropion was more effective than usual care at achieving abstinence at 6 months.

***Caution***

The study could not establish whether the addition of bupropion provided additional benefit over behavioral support alone.

***Implication***

Inexpensive behavioral interventions should be evaluated together with other means of promoting smoking cessation among smokers suspected of having tuberculosis in resource-poor areas.

*—The Editors*

trial with 3 groups. Patients in one group received 2 brief BSS (BSS group), patients in the second group received 2 brief BSS plus 7 weeks of bupropion therapy (BSS+ group), and patients in the control group received usual care. Given the lack of any routine advice or educational materials in Pakistan, we provided a self-help leaflet on smoking cessation to all participants (for details, see the **Appendix**, available at www.annals.org). The trial protocol has been published elsewhere (18). This study received approval from the research ethics committees of Pakistan Medical Research Council, Islamabad, Pakistan, and University of Leeds, Leeds, United Kingdom.

## Setting and Participants

All 38 health centers registered as diagnostic centers by the tuberculosis program in the Jhang and Sargodha districts were eligible; 33 agreed to participate.

Consenting patients aged 18 years or older with suspected pulmonary tuberculosis (cough for ≥3 weeks without any other cause) who were also regular tobacco smokers (≥1 cigarette/d) were enrolled in the trial between June 2010 and February 2011. We excluded patients requiring hospitalization or urgent medical attention. Physicians at the health center referred eligible patients to facilitators for directly observed therapy (DOT). The facilitators were paramedics who were responsible for registering new patients, providing education, and supervising treatment.

## Randomization and Interventions

We randomly allocated health centers by using a simple stratified randomization procedure to achieve a balance of Tehsil headquarter health centers (THQs) and rural health centers across trial groups. This was important because THQs are situated in urban settings, where cigarette smoking is more common, whereas hookah smoking is more prevalent in rural settings (19). A researcher who was blinded to center identity used computer-generated random-number lists to generate the allocation sequence.

### *BSS Group*

The behavioral support intervention (**Appendix Table 1**, available at www.annals.org) was based on the World Health Organization's "5 A's" approach (11) and included behavior change techniques (20). It was adapted through focus group interviews with physicians, DOT facilitators, and smokers and was reviewed by an expert panel that included a smoking cessation specialist, a behavioral scientist, policymakers, and practitioners. The intervention comprised 2 structured sessions delivered by DOT facilitators using an educational flipbook (for details, see **Supplements 1** and **2**, available at www.annals.org). A 30-minute session was offered at the first visit to encourage patients to envision themselves as nonsmokers and to plan for a quit day 1 week later. The second session, which lasted 10 minutes, was arranged to coincide with the quit day to review progress. All DOT facilitators from health centers in the intervention groups attended a 1-day training program delivered by the research team. Other health professionals at these centers were also briefed about BSS.

### *BSS+ Group*

Participants at BSS+ centers received a free 7-week course of bupropion in addition to BSS. Physicians at these centers received training and written guidance on prescribing bupropion, including its contraindications. Participants received sustained-release bupropion, 75 mg/d for the first week and 150 mg/d thereafter. They were asked about any adverse effects and treatment adherence, the latter of which was based on self-reports at follow-up. Adherence was considered "complete" if the participant reported adherence for the full 7 weeks and "partial" if the participant reported partial or irregular adherence.

### *Control Group*

At control centers, participants received usual care and the self-help leaflet on smoking cessation (**Supplements 1** and **2**). The DOT facilitators at these centers received information on trial procedures only.

## Outcomes and Follow-up

The DOT facilitators followed participants in the BSS+ and BSS groups at 1, 5, and 25 weeks after first contact and control participants at 5 and 25 weeks.

The primary outcome was continuous smoking abstinence, defined as an expired carbon monoxide (CO) mea-

surement (piCO+ Smokerlyzer, Bedfont Scientific, Maidstone, United Kingdom) of 9 ppm or less (Russell standard) (21) at the 1- and 6-month follow-up visits. This cutoff has high sensitivity (88% for cigarettes and 84% for all types of smoking) and specificity (84%) (22). Secondary outcomes were point abstinence at 1 and 6 months. The DOT facilitators recorded and reported any adverse events, serious or otherwise, in all centers.

Trial monitoring procedures included telephone calls to randomly selected participants (≥2 per center each month) to confirm whether CO tests had been done, verify data collected, and check for protocol violations (for example, participants not receiving interventions as per allocation).

### Statistical Analysis

We estimated that a sample size of 1320 participants would be required to provide 80% power (2-sided $P < 0.05$) to detect a difference of at least 10% in continuous abstinence, assuming a 10% continuous smoking abstinence rate among control participants (16, 23) and adjusting for cluster effect using an intraclass correlation coefficient of 0.036 (24). With 33 clusters (11 in each group) and assuming a 20% attrition rate, we needed 50 participants per cluster.

We set a noninferiority margin of difference of 5% between the intervention groups, which was based on a recent smoking cessation noninferiority trial and has also been recognized as an acceptable effect size for any new smoking cessation intervention (25–27).

Analyses were done in general accordance with the CONSORT (Consolidated Standards of Reporting Trials) statement and its extension to cluster and pragmatic trials (28, 29). All analyses were performed using SAS, version 9.3 (SAS Institute, Cary, North Carolina).

Univariate distributions and frequencies were examined to identify covariates and categorize continuous variables (such as age and income) and recategorize categorical variables. Smoking type varied, with some participants smoking cigarettes only, some smoking hookah only, and some smoking both. To quantify smoking, each hookah "session" was considered equivalent to smoking 2 cigarettes (30).

Outcomes were primarily analyzed in a missing-at-random architecture by fitting generalized linear mixed models using a log link and assuming an underlying Poisson distribution with clusters treated as a random effect. We performed 2 sensitivity analyses. In the first, missing data on the primary outcome in all 3 groups were imputed as failures or smokers (informative censoring 1). In the second, we imputed missing data in the intervention groups as failures or smokers and analyzed the control group as observed (informative censoring 2). We also repeated the primary analysis with men only (95% of the total sample). All analyses accounted for clustering through the random intercept model. The crude and adjusted (for age, sex, income, smoking duration, and quantity smoked per day) relative risks (RRs) and corresponding 95% CIs were estimated. We used estimates of the adjusted model to construct a forest plot showing empirical Bayes estimates and corresponding 95% CIs within and across treatment groups. Coefficients of intraclass correlation were calculated for all analyses using the following formula: [between-group variance/(between-group variance + $\pi^{2/3}$)]. We compared outcomes between participants with and those without tuberculosis by using a 2 × 2 frequency table. We estimated recruitment and abstinence rates for individual clusters, and we explored associations between cluster characteristics and outcomes by using multilevel modeling.

### Role of the Funding Source

The International Development Research Centre (Ottawa, Ontario, Canada) provided funding for the study. The funding source approved the protocol and provided feedback on progress reports but had no influence on the progress or reporting of the study.

## RESULTS

### Participant Flow and Trial Execution

We enrolled 1955 participants in 33 health centers (**Figure 1**). Eight participants died (1 in the BSS group, 5 in the BSS+ group, and 2 in the control group). All of the 659 participants in the BSS+ group received the first session. Seventy-three did not complete the full intervention: 37 received both sessions but not bupropion (8 declined, 20 were partially adherent, and 9 did not receive it), 2 received bupropion but not the second session, and the remaining 34 received only the first session and did not receive bupropion. In the BSS group, 8 participants did not receive the second session. Primary outcome data were missing for 5.5% of participants.

### Baseline Data

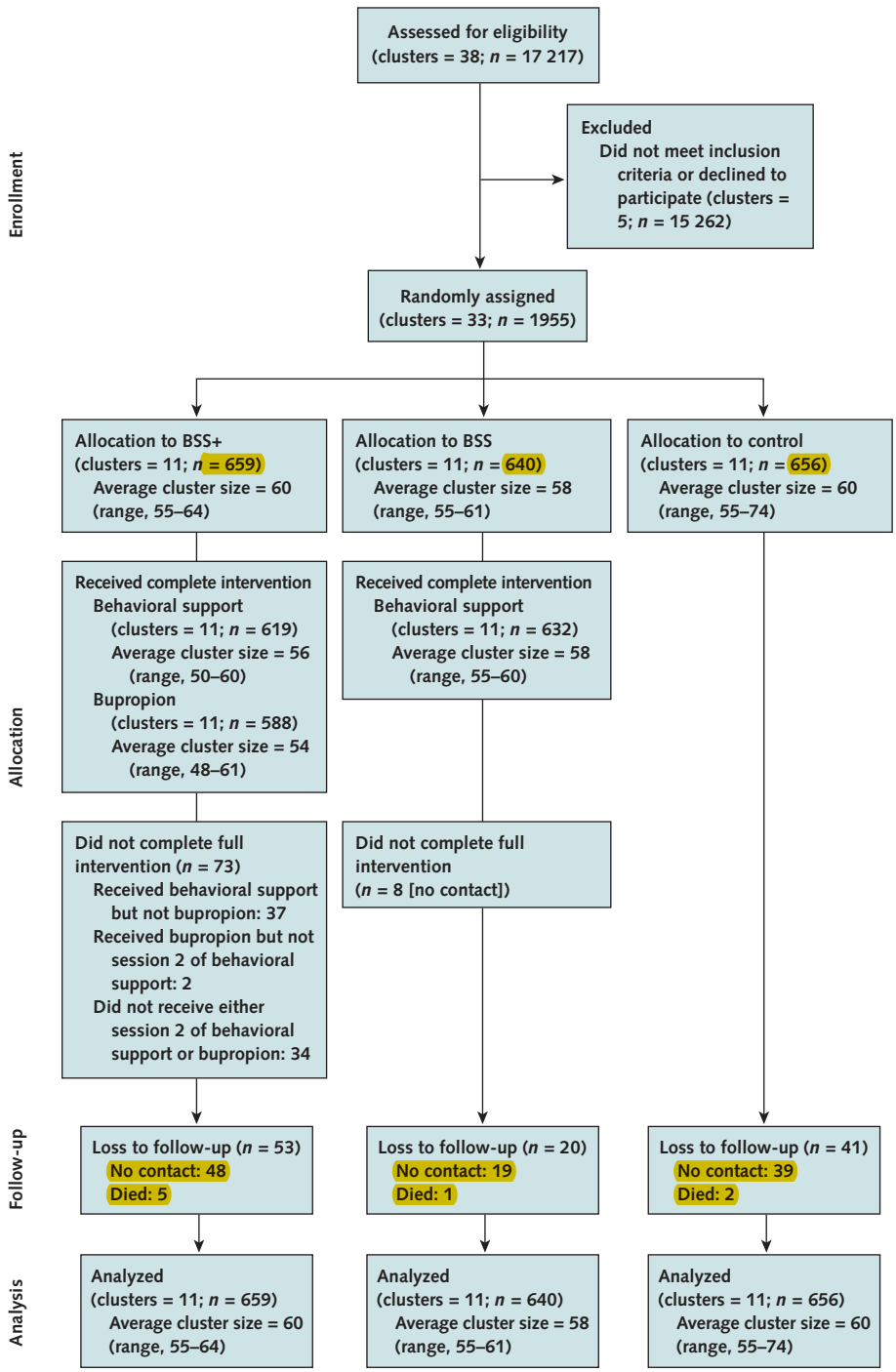
The 3 groups were generally similar with respect to the baseline characteristics (**Table 1**), although mean age, sex, and smoking type differed slightly.

### Outcomes

#### *Primary Outcome*

Behavioral support, alone or in combination with bupropion, was effective in achieving continuous smoking abstinence at 6 months compared with usual care (RR for BSS+, 8.2 [95% CI, 3.7 to 18.2]; RR for BSS, 7.4 [CI, 3.4 to 16.4]) (**Table 2**). The association became stronger after adjustment for potential confounders, such as age, sex, income, smoking duration, and quantity smoked per day (RR for BSS+, 9.3 [CI, 4.0 to 21.6]; RR for BSS, 8.5 [CI, 3.7 to 19.6]). However, the equivalence of effect between the BSS+ and BSS groups (RR, 1.1 [CI, 0.5 to 2.3]) could not be established. Confidence intervals were wider than the predefined noninferiority margin.

*Figure 1.* **Study flow diagram.**




BSS = behavioral support sessions; BSS+ = behavioral support sessions plus 7 wk of bupropion therapy.

### *Secondary Outcomes*

Behavioral support alone or in combination with bupropion was effective in achieving point abstinence at 1 and 6 months (**Table 2**); however, more participants in the control group reported abstinence at 6 months than at 1 month. Of 1955 participants recruited with suspected tuberculosis, 109 were diagnosed with the disease. Continuous abstinence rates were higher in patients with tuberculosis than in those who were suspected to have but were not subsequently diagnosed with it (RR, 1.8 [CI, 1.5 to 2.2]) (**Table 3**).

Recruitment and abstinence rates for individual clusters are shown in **Appendix Table 2** (available at www

*Table 1.* **Baseline Characteristics**

| Characteristic | BSS+ Group | BSS Group | Control Group |
|---|---|---|---|
| **Clusters** | | | |
| Total, *n* | 11 | 11 | 11 |
| DOT facilitators, *n* | 11 | 11 | 11 |
| DOT facilitators who were regular smokers, *n* | 0 | 1 | 0 |
| Male DOT facilitators, *n* | 9 | 9 | 8 |
| THQ health centers, *n* | 3 | 2 | 2 |
| **Participants** | | | |
| Total, *n* | 659 | 640 | 656 |
| Mean age (SD), *y* | 38.3 (12.4) | 42.8 (13.5) | 41.7 (13.4) |
| Men, *n/N (%)* | 619/649 (95) | 598/635 (94) | 632/655 (97) |
| Mean age when started smoking (SD), *y* | 20.2 (6.9) | 20.5 (6.4) | 20.7 (7.2) |
| Mean duration of smoking (SD), *y* | 18.2 (11.4) | 22.3 (13.2) | 21.0 (12.3) |
| Median cigarettes smoked per day (IQR), *n* | 20 (12.0) | 15 (10.0) | 15 (10.0) |
| Median cigarettes and hookah smoked per day (IQR), *n** | 20 (14.5) | 20 (18.0) | 19 (13.0) |
| Age group, *n/N (%)* | | | |
| 18–29 y | 169/657 (26) | 103/640 (16) | 133/656 (20) |
| 30–39 y | 180/657 (27) | 134/640 (21) | 146/656 (22) |
| 40–49 y | 182/657 (28) | 207/640 (32) | 176/656 (27) |
| 50–59 y | 82/657 (12) | 99/640 (15) | 105/656 (16) |
| ≥60 y | 44/657 (7) | 97/640 (15) | 96/656 (15) |
| Smoking type, *n/N (%)* | | | |
| Cigarette | 632/659 (96) | 521/640 (81) | 585/656 (89) |
| Hookah-only | 27/659 (4) | 119/640 (19) | 71/656 (11) |
| Monthly household income, *n/N (%)*† | | | |
| ≤$37.5 (below poverty line) | 62/649 (10) | 67/634 (11) | 98/648 (15) |
| $37.6–$80 | 179/649 (28) | 205/634 (32) | 242/648 (37) |
| $81–$115 | 147/649 (23) | 117/634 (19) | 127/648 (20) |
| ≥$116 | 261/649 (40) | 245/634 (39) | 181/648 (28) |

BSS = behavioral support sessions; BSS+ = behavioral support sessions plus 7 wk of bupropion therapy; DOT = directly observed therapy; IQR = interquartile range; THQ = Tehsil headquarter health center.
* 1 hookah session = 2 cigarettes.
† $1 = 86 Pakistani rupees.

.annals.org). Although heterogeneity in program effects was substantial across clusters (**Figure 2**), we did not find cluster characteristics to be associated with the primary outcome (**Appendix Table 3**, available at www.annals.org).

### Sensitivity Analyses

Results of sensitivity analyses did not differ substantially from those of the primary analysis (**Appendix Table 4**, available at www.annals.org). Findings from the analysis

*Table 2.* **Primary and Secondary Outcomes***

| Outcome | Trial Group | Patients | | Relative Risk (95% CI) | *P* Value | ICC |
|---|---|---|---|---|---|---|
| | | Total, *n/N*† | Proportion (95% CI) | | | |
| Continuous abstinence at 6 mo (primary) | BSS+ | 275/606 | 45.4 (41.4–49.4) | 8.2 (3.7–18.2) | <0.001 | 0.28 |
| | BSS | 254/620 | 41.0 (37.1–45.0) | 7.4 (3.4–16.4) | <0.001 | |
| | Control | 52/615 | 8.5 (6.4–10.9) | 1.0 | – | |
| | BSS+ vs. BSS | – | – | 1.1 (0.6–2.2) | 0.76 | |
| Adjusted estimates for continuous abstinence at 6 mo (primary)‡ | BSS+ vs. control | – | – | 9.3 (4.0–21.6) | <0.001 | 0.32 |
| | BSS vs. control | – | – | 8.5 (3.7–19.6) | <0.001 | |
| | BSS+ vs. BSS | – | – | 1.1 (0.5–2.3) | 0.79 | |
| Point abstinence at 1 mo (secondary)‡ | BSS+ | 320/612 | 52.3 (48.3–56.3) | 8.8 (4.1–18.5) | <0.001 | 0.35 |
| | BSS | 361/622 | 58.0 (54.1–62.0) | 9.9 (4.7–20.9) | <0.001 | |
| | Control | 59/631 | 9.4 (7.2–11.9) | 1.0 | – | |
| | BSS+ vs. BSS | – | – | 0.9 (0.5–1.7) | 0.71 | |
| Point abstinence at 6 mo (secondary)‡ | BSS+ | 395/608 | 65.0 (61.0–68.8) | 4.1 (2.1–7.9) | <0.001 | 0.43 |
| | BSS | 318/623 | 51.0 (47.0–55.0) | 3.2 (1.7–6.3) | <0.001 | |
| | Control | 142/626 | 22.7 (19.5–26.2) | 1.0 | – | |
| | BSS+ vs. BSS | – | – | 1.3 (0.7–2.3) | 0.45 | |

BSS = behavioral support sessions; BSS+ = behavioral support sessions plus 7 wk of bupropion therapy; ICC = intraclass correlation coefficient.
* All analyses accounted for clustering.
† Number abstaining among the total number in the group.
‡ Adjusted for age, sex, income, smoking duration, and quantity smoked per day.

*Table 3.* **Abstinence Outcomes in Participants With and Without Tuberculosis**

| Outcome | Patients | BSS+ Group | BSS Group | Control Group | Total |
|---|---|---|---|---|---|
| Continuous abstinence (6 mo) | Tuberculosis, *n/N (%)** | 6/10 (60.0) | 47/67 (70.2) | 4/29 (13.8) | 57/106 (53.8) |
| | No tuberculosis, *n/N (%)** | 269/596 (45.1) | 207/553 (37.4) | 48/586 (8.2) | 524/1735 (30.2) |
| | RR (95% CI)† | 1.3 (0.8–2.2) | 1.9 (1.6–2.3) | 1.7 (0.7–4.4) | 1.8 (1.5–2.2) |
| Point abstinence (1 mo) | Tuberculosis, *n/N (%)** | 6/10 (60.0) | 51/68 (75.0) | 5/29 (17.2) | 62/107 (57.9) |
| | No tuberculosis, *n/N (%)** | 314/602 (52.2) | 310/554 (56.0) | 54/602 (9.0) | 678/1758 (38.6) |
| | RR (95% CI)† | 1.2 (0.7–1.9) | 1.3 (1.1–1.6) | 1.9 (0.8–4.4) | 1.5 (1.3–1.8) |
| Point abstinence (6 mo) | Tuberculosis, *n/N (%)** | 9/10 (90.0) | 57/67 (85.1) | 10/29 (34.5) | 76/106 (71.7) |
| | No tuberculosis, *n/N (%)** | 386/598 (64.6) | 261/556 (46.9) | 132/597 (22.1) | 779/1751 (44.5) |
| | RR (95% CI)† | 1.4 (1.1–1.7) | 1.8 (1.6–2.1) | 1.6 (0.9–2.6) | 1.6 (1.4–1.8) |

BSS = behavioral support sessions; BSS+ = behavioral support sessions plus 7 wk of bupropion therapy; RR = relative risk.
* Number abstaining among the total number in the group.
† Relative risk and 95% CI of abstinence for participants diagnosed with tuberculosis compared with those not diagnosed.

that included men only were also consistent with those from the primary analysis (**Appendix Table 5**, available at www.annals.org).

### Adverse Events

The 8 reported deaths were not considered to be related to the intervention or trial procedures. Other serious adverse events, such as seizures, suicidal ideation, or cardiovascular events, were not reported. In the BSS+ group, 214 participants reported adverse events secondary to bupropion, most commonly headache, constipation, and nausea (**Appendix Table 6**, available at www.annals.org). No other adverse events were reported.

## DISCUSSION

Our findings suggest that, compared with usual care, behavioral support alone or in combination with bupropion is effective in achieving smoking abstinence at 6 months and that it is feasible to offer it in a tuberculosis control program in a low-income country. We were not able to confirm the noninferiority of behavioral support alone compared with behavioral support with bupropion.

We found substantial heterogeneity across clusters, with some intervention centers showing a smaller effect than control centers. However, none of the cluster characteristics that we investigated showed an association with continuous abstinence. Variation in the methods used by DOT facilitators may have influenced outcomes, which could explain some of the observed heterogeneity in the intervention and control groups. This warrants further investigation.

Our results support offering help to quit tobacco use by means of the methods advocated by the World Health Organization (31) and for recommending smoking cessation as one of the "best buys" in the fight against noncommunicable diseases. Our findings are particularly relevant to low- and middle-income countries, where 80% of smokers live. Smoking cessation, erroneously perceived to be expensive, often receives lower priority than other legislative and fiscal policy initiatives in low- and middle-income countries. Although we recognize the importance of these other measures, we argue for prioritizing smoking cessation, particularly where health care staff can be trained to deliver behavioral support inexpensively and relatively easily. Integrating smoking cessation into tuberculosis programs can be viewed as "low-hanging fruit" because of the high prevalence of smoking in patients with tuberculosis, the ability to reach a much larger cohort of those suspected to have the disease, and the potential to improve outcomes for patients with tuberculosis or other noncommunicable diseases.

The estimated cost of behavioral support ($2.50 per participant) was approximately one tenth that of behavioral support plus bupropion ($20.90 per participant). Low- and middle-income countries, where access to and affordability of medicine is constrained, might favor an inexpensive nonpharmacologic intervention that can be delivered by existing staff. However, we could not confirm the noninferiority of BSS compared with BSS+.

The effect sizes seen in this trial, although higher than those in high-income countries (16), are similar to those in some quasi-experimental studies of smoking cessation in patients with tuberculosis in low- and middle-income countries (12–14). A change of this magnitude is possible in a low- or middle-income country, such as Pakistan, where the baseline public awareness of the harms of smoking is limited (32). This is also consistent with the shifts in smoking trends observed in the 1970s in high-income countries (33) and with the steep change in behavior that occurs because of early adopters. Moreover, DOT facilitators in this study may have been more determined to persuade participants with suspected tuberculosis to quit than in other studies. Similarly, participants with suspected tuberculosis who had heightened anxiety due to their symptoms, knew their likelihood of having the disease and its consequences, and had recently acquired knowledge of the association between tuberculosis and smoking might have felt more motivated to quit than those in the general smoking population.

Key limitations of our study include imbalances in the urban and rural proportions and smoking habits among

treatment groups, the inability to confirm adherence to bupropion treatment, and the inability to validate longer-term abstinence or the effect of smoking cessation on tuberculosis outcomes.

Hookah smoking is more common in rural settings. Because the study involved 7 THQs, it was not possible to achieve a balance in the urban and rural proportions and smoking habits across the 3 groups. Moreover, 2 THQs in the BSS group were recently upgraded from rural health centers, and their catchment population was still primarily rural. As a result, we saw an imbalance in smoking type across treatment groups (19% of participants in the BSS group were hookah smokers compared with 3% in the BSS+ group). However, the risk of bias was probably minimal because cigarettes were still the predominant smoking type across all groups.

ASSIST was a pragmatic trial and, as such, the intervention was loosely applied, as is commonly required in such trials. We therefore assessed adherence to bupropion therapy on the basis of self-reports. This included a record of patients who declined bupropion, did not collect more after the first week, or reported partial use.

Cotinine, which has a longer half-life than CO, is generally the preferred biomarker for smoking detection (34). However, collection, transport, and analysis of cotinine samples were challenging in Pakistan. Therefore, CO breath tests were used, which is consistent with the international standards for assessing outcomes in such studies (21). Some participants may have quit smoking only a day or 2 before follow-up, thus giving a negative CO reading. The lack of blinding also meant that a degree of observer bias was possible.

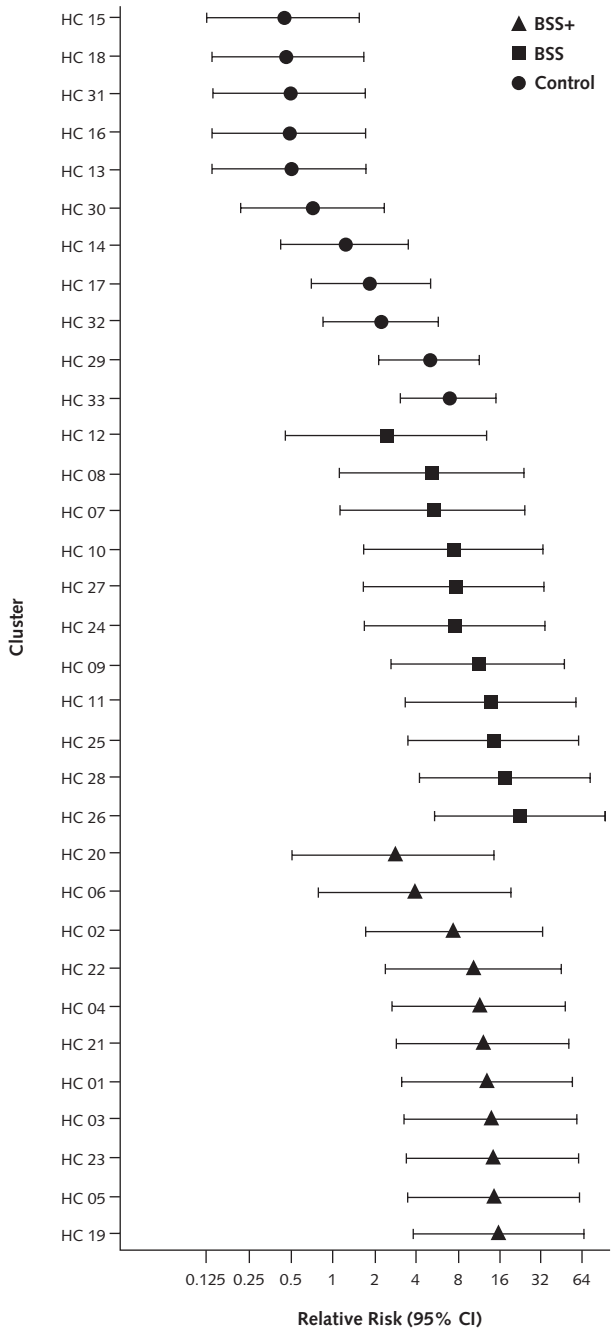
A higher effect was seen in the 5% of participants with tuberculosis than in those without tuberculosis, possibly because of additional ongoing care by the DOT facilitators. Participants with tuberculosis might have received more encouragement to quit than those without tuberculosis, resulting in an overall inflated effect size in all groups.

Although our results can be generalized to a large population of persons with suspected tuberculosis, our choice of inclusion criteria and outcomes restricted our ability to assess the effect of quitting on tuberculosis outcomes.

In Pakistan, smokeless tobacco use is also common (35). However, we excluded patients who used only smokeless tobacco because evidence linking it with tuberculosis is lacking. Some participants may have replaced smoking with smokeless tobacco, but this is less likely because the latter is not commonly used in the trial districts. Another study found no increase in smokeless tobacco use among patients with tuberculosis despite high quit rates for smoking (10).

Measuring continuous abstinence at 12 months would have been a closer approximation of lifelong abstinence. However, because of resource limitations, we opted for abstinence at 6 months, which is consistent with the international recommendations for measuring abstinence (36).

***Figure 2.*** **Empirical Bayes estimates (random-effects) for health centers.**




Substantial heterogeneity was seen across centers in their relative rates (empirical Bayes estimates) of achieving the primary outcome. In general, centers assigned to the control group had lower-than-average success rates (relative risk 1). However, some control centers (HC 29 and HC 33) were able to achieve abstinence rates similar to those of the best BSS and BSS+ centers. Furthermore, some BSS (HC 12, HC 08, and HC 07) and BSS+ (HC 20 and HC 06) centers were not statistically better than the 5 worst control centers. BSS = behavioral support sessions; BSS+ = behavioral support sessions plus 7 wk of bupropion therapy; HC = health center.

This provided a reasonable balance between the need for validation and efficiency.

Further investigation is required to examine the effect of smoking cessation on tuberculosis outcomes and transmission. Smoking cessation may also need to include household smoking restrictions to provide comprehensive protection. Researchers should develop and evaluate such approaches.

This trial suggests that behavioral support alone or in combination with bupropion is effective in achieving continuous abstinence at 6 months in patients with suspected tuberculosis in Pakistan. We also found a large cluster-level effect indicating a strong influence from the health care facility in determining the success of the intervention. This should be considered when implementing such programs in the future. We recommend scaling up smoking cessation interventions in tuberculosis programs in countries with similar contexts. Future research should examine the effect of smoking cessation on tuberculosis outcomes.

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**Reproducible Research Statement:** *Study protocol:* Available at www.biomedcentral.com/1471-2458/10/160. *Statistical code:* Available from Dr. Siddiqi (e-mail, kamran.siddiqi@york.ac.uk). *Data set:* Available from Dr. Siddiqi (e-mail, kamran.siddiqi@york.ac.uk) after written agreements.

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**2012 *ANNALS* POETRY PRIZE**

Congratulations to Daniela Matei, MD, winner of the 2012 *Annals* Poetry Prize. Her poem "Bloom" was published in the 21 August 2012 issue (vol. 157, no. 4, page 297). Dr. Matei is Associate Professor in Medicine/Oncology at the Simon Cancer Center of Indiana University.

*Annals* extends thanks to the contest judges: David Elpern, humanist and editor of Cell2Soul; and Abigail Zuger, who writes for *The New York Times*. She is Associate Clinical Professor of Medicine at Einstein and an infectious disease expert. *Her Strong Shadows: Scenes from an Inner City AIDS Clinic* was published by WH Freeman in 1995.

For information on the Poetry Prize contest, visit www.annals.org/public/poetryprize.aspx.

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## Appendix

### Flipbook (BSS)

The flipbook contains 25 slides, each of which has a set of images on one side and a description of the images and a group of instructions for the DOT facilitator on the other. For each slide, the facilitator first asked patients to make relevant observations about the images. Patients were then guided to understand and reiterate the implied message in each slide. Slides were grouped to address the following objectives:

Slide 1: to learn about types of tobacco smoking and the settings in which they occur.

Slides 2 to 5: to understand the harms of tobacco smoking on one's own health and the effect of secondhand smoke on the health of children and other nonsmoking family members.

Slide 6: to set a goal of quitting smoking by a specific date and to be able to carry out the required tasks beforehand.

Slide 7: to visualize the health and financial benefits for the entire family of giving up tobacco smoking.

Slide 8: to be able to plan before quitting, including identifying people who can help.

Slides 9 to 16: to know about the various triggers for smoking and to be able to act on various approaches addressing them.

Slide 17: to be able to use bupropion (only in the BSS+ group).

Slides 18 to 25: to learn about withdrawal symptoms and be able to implement coping strategies.

### Self-Help Leaflet (Control Group)

The leaflet offered in the control group highlights the harm caused by tobacco smoking on one's own health, the effect of secondhand smoke on the health of children and other nonsmoking family members, the advantages of quitting, and some useful tips for quitting. It also contains a table listing possible withdrawal symptoms of smoking cessation and some potentially useful coping strategies.

*Appendix Table 1.* **Behavioral Support Intervention**

| Component* | Activity | Purpose |
|---|---|---|
| **Consultation 1 (before quit day): confirmation, planning, and preparation** | | |
| Ask and advise | Confirm that smokers are aware of tobacco-related harm and would like to stop smoking | To confirm awareness of the health and financial consequences of smoking and to ensure that smokers are quitting because they wish to and are willing to commit to a quit day |
| Assess | Smoking assessment | To ascertain how dependent smokers are and to recognize their normal smoking pattern |
| Assist | Preparing and planning to stop smoking | To help smokers identify the times and situations that are likely to be more difficult during the quit attempt and to develop coping strategies |
| Arrange | Conclusion | To summarize the information provided and reaffirm the quit day |
| **Consultation 2 (on quit day): reflection** | | |
| Assist | Review tasks and coping strategies from previous week | To confirm that smokers have completed the preparation to quit and understand the strategies being prepared |
| Assist | Discuss withdrawal symptoms | To prepare smokers for possible withdrawal symptoms that may jeopardize the quit attempt |

* Based on the World Health Organization's "5 As" approach (11).

*Appendix Table 2.* **Cluster-Specific Recruitment and Abstinence Rates**

| Cluster | Recruitment Rate, *n/N (%)** | Abstinent Patients at 1-mo Follow-up, *n/N (%)*† | Abstinent Patients at 6-mo Follow-up, *n/N (%)*† |
|---|---|---|---|
| 1 | 61/350 (17.4) | 38/61 (62.3) | 46/59 (78.0) |
| 2 | 60/314 (19.1) | 21/60 (35.0) | 30/60 (50.0) |
| 3 | 60/202 (29.7) | 45/57 (79.0) | 43/58 (74.1) |
| 4 | 64/564 (11.3) | 42/53 (79.3) | 26/53 (49.1) |
| 5 | 60/1530 (3.9) | 36/49 (73.5) | 37/48 (77.1) |
| 6 | 60/179 (33.5) | 13/59 (22.0) | 9/59 (15.3) |
| 7 | 60/390 (15.4) | 43/60 (71.7) | 17/60 (28.3) |
| 8 | 59/117 (50.4) | 28/59 (47.5) | 14/58 (24.1) |
| 9 | 59/71 (83.1) | 54/58 (93.1) | 28/58 (48.2) |
| 10 | 60/167 (35.9) | 24/52 (46.2) | 21/55 (38.2) |
| 11 | 60/171 (35.1) | 45/60 (75.0) | 36/59 (61.0) |
| 12 | 60/628 (9.6) | 7/57 (12.3) | 17/57 (29.8) |
| 13 | 61/194 (31.4) | 0/57 (0.0) | 1/55 (1.8) |
| 14 | 60/86 (69.8) | 6/59 (10.2) | 8/60 (13.3) |
| 15 | 60/1420 (4.2) | 2/59 (3.4) | 0/59 (0.0) |
| 16 | 59/533 (11.1) | 0/59 (0.0) | 1/59 (1.7) |
| 17 | 74/306 (24.2) | 5/58 (8.6) | 16/61 (26.2) |
| 18 | 60/564 (10.6) | 0/58 (0.0) | 0/54 (0.0) |
| 19 | 62/719 (8.6) | 35/53 (66.0) | 42/52 (80.8) |
| 20 | 60/199 (30.2) | 4/54 (7.4) | 17/54 (31.5) |
| 21 | 60/157 (38.2) | 33/60 (55.0) | 57/60 (95.0) |
| 22 | 55/707 (7.8) | 22/52 (42.3) | 35/51 (68.6) |
| 23 | 57/661 (8.6) | 31/54 (57.4) | 53/54 (98.2) |
| 24 | 61/827 (7.4) | 18/55 (32.7) | 21/55 (38.2) |
| 25 | 55/531 (10.4) | 34/55 (61.8) | 54/55 (98.2) |
| 26 | 57/331 (17.2) | 42/57 (73.7) | 52/57 (91.2) |
| 27 | 54/827 (6.5) | 25/54 (46.3) | 19/54 (35.2) |
| 28 | 55/614 (9.0) | 41/55 (74.6) | 39/55 (70.9) |
| 29 | 55/1527 (3.6) | 16/55 (29.1) | 24/55 (43.6) |
| 30 | 60/552 (10.9) | 1/60 (1.7) | 19/57 (33.3) |
| 31 | 55/540 (10.2) | 1/55 (1.8) | 28/54 (51.9) |
| 32 | 55/444 (12.4) | 6/55 (10.9) | 13/55 (23.6) |
| 33 | 57/795 (7.2) | 22/57 (38.6) | 32/57 (56.1) |

* Number recruited among the total number suspected of having tuberculosis.
† Number abstaining among the total number recruited per cluster.

*Appendix Table 3.* **Cluster Characteristics and Associated Relative Risks**

| Cluster | Location Type | Mean Age (SD), *y* | Men, *n (%)* | Mean Smoking Duration (SD), *y* | Median Quantity Smoked (IQR), *d* | Median Monthly Household Income (IQR), *$** |
|---|---|---|---|---|---|---|
| 1 | Rural | 32 (11) | 61/61 (100) | 16 (10) | 20 (10) | 116 (81) |
| 2 | Rural | 44 (12) | 54/60 (90) | 19 (9) | 20 (13) | 116 (105) |
| 3 | Rural | 37 (12) | 58/60 (97) | 19 (12) | 20 (18) | 96 (67) |
| 4 | Rural | 38 (13) | 62/64 (97) | 19 (11) | 20 (14) | 70 (47) |
| 5 | Urban | 43 (14) | 54/60 (90) | 21 (11) | 17 (12) | 116 (116) |
| 6 | Rural | 36 (10) | 59/60 (98) | 16 (9) | 27 (23) | 105 (47) |
| 7 | Rural | 39 (10) | 56/60 (93) | 21 (10) | 20 (13) | 58 (58) |
| 8 | Rural | 39 (11) | 59/59 (100) | 20 (10) | 20 (30) | 116 (81) |
| 9 | Rural | 40 (12) | 57/59 (97) | 21 (11) | 20 (25) | 128 (116) |
| 10 | Rural | 44 (16) | 58/60 (97) | 21 (17) | 17 (14) | 105 (105) |
| 11 | Urban | 44 (12) | 59/60 (98) | 23 (14) | 20 (23) | 105 (110) |
| 12 | Rural | 40 (6) | 56/60 (93) | 17 (6) | 10 (6) | 174 (70) |
| 13 | Rural | 41 (13) | 59/61 (97) | 22 (12) | 20 (10) | 64 (47) |
| 14 | Rural | 40 (12) | 59/60 (93) | 20 (12) | 21 (11) | 47 (41) |
| 15 | Rural | 38 (15) | 60/60 (100) | 19 (14) | 10 (7) | 93 (38) |
| 16 | Rural | 38 (12) | 59/59 (100) | 22 (12) | 20 (7) | 70 (47) |
| 17 | Urban | 45 (13) | 73/74 (99) | 24 (13) | 20 (18) | 58 (70) |
| 18 | Urban | 43 (14) | 60/60 (100) | 23 (14) | 18 (15) | 81 (86) |
| 19 | Rural | 41 (14) | 57/61 (93) | 24 (12) | 20 (12) | 70 (47) |
| 20 | Rural | 38 (11) | 60/60 (100) | 21 (11) | 20 (10) | 116 (105) |
| 21 | Rural | 33 (9) | 57/57 (100) | 12 (10) | 17 (10) | 93 (47) |
| 22 | Urban | 44 (14) | 47/55 (86) | 18 (11) | 20 (8) | 93 (47) |
| 23 | Urban | 37 (12) | 50/51 (98) | 16 (11) | 20 (22) | 81 (58) |
| 24 | Rural | 44 (17) | 54/61 (89) | 26 (17) | 20 (30) | 58 (23) |
| 25 | Rural | 42 (12) | 53/55 (96) | 23 (12) | 20 (14) | 58 (41) |
| 26 | Rural | 50 (15) | 47/53 (89) | 28 (12) | 39 (10) | 116 (58) |
| 27 | Urban | 45 (16) | 52/53 (98) | 24 (16) | 20 (5) | 70 (67) |
| 28 | Rural | 43 (15) | 47/55 (86) | 24 (14) | 24 (18) | 64 (47) |
| 29 | Rural | 45 (16) | 55/55 (100) | 25 (15) | 12 (12) | 58 (47) |
| 30 | Rural | 41 (12) | 59/60 (98) | 21 (10) | 25 (15) | 93 (41) |
| 31 | Rural | 38 (12) | 52/55 (95) | 16 (9) | 20 (5) | 47 (29) |
| 32 | Rural | 45 (12) | 48/55 (87) | 21 (10) | 20 (9) | 140 (81) |
| 33 | Rural | 44 (14) | 48/56 (86) | 21 (13) | 12 (7) | 81 (58) |
| Relative risk (95% CI)† | 0.88 (0.44–1.73) | 1.05 (0.91–1.21) | 0.96 (0.91–1.02) | 1.06 (0.92–1.22) | 0.97 (0.92–1.01) | 0.99 (0.98–1.00) |

IQR = interquartile range.
* $1 = 86 Pakistani rupees.
† Multilevel modeling for level-2 (cluster) predictors.

## *Appendix Table 4.* Sensitivity Analysis*

| Analysis and Outcome | Trial Group | Patients | | Relative Risk (95% CI) | *P* Value | ICC |
|---|---|---|---|---|---|---|
| | | Total, *n/N*† | Proportion (95% CI) | | | |
| **Informative censoring 1 (all failures)** | | | | | | |
| Continuous abstinence at 6 mo (primary) | BSS+ | 275/659 | 41.7 (37.9–45.6) | 9.2 (3.9–21.4) | <0.001 | 0.32 |
| | BSS | 254/640 | 39.7 (35.9–43.6) | 8.8 (3.8–20.5) | <0.001 | |
| | Control | 52/656 | 7.9 (6.0–10.3) | 1.0 | – | |
| | BSS+ vs. BSS | – | – | 1.0 (0.5–2.2) | 0.91 | |
| Point abstinence at 1 mo (secondary) | BSS+ | 320/659 | 48.6 (44.7–52.5) | 8.5 (4.0–18.0) | <0.001 | 0.34 |
| | BSS | 361/640 | 56.4 (52.5–60.3) | 10.1 (4.7–21.4) | <0.001 | |
| | Control | 59/656 | 9.0 (6.9–11.5) | 1.0 | – | |
| | BSS+ vs. BSS | – | – | 0.8 (0.4–1.6) | 0.61 | |
| Point abstinence at 6 mo (secondary) | BSS+ | 395/659 | 59.9 (56.1–63.7) | 4.0 (2.0–7.7) | <0.001 | 0.41 |
| | BSS | 318/640 | 49.7 (45.7–53.6) | 3.3 (1.7–6.5) | 0.004 | |
| | Control | 142/656 | 21.7 (18.6–25.0) | 1.0 | – | |
| | BSS+ vs. BSS | – | – | 1.2 (0.6–2.2) | 0.57 | |
| **Informative censoring 2 (intervention failures; control as observed)** | | | | | | |
| Continuous abstinence at 6 mo (primary) | BSS+ | 275/659 | 41.7 (37.9–45.6) | 8.6 (3.7–19.9) | <0.001 | 0.27 |
| | BSS | 254/640 | 39.7 (35.9–43.6) | 8.3 (3.6–19.1) | <0.001 | |
| | Control | 52/615 | 8.5 (6.4–10.9) | 1.0 | – | |
| | BSS+ vs. BSS | – | – | 1.0 (0.5–2.1) | 0.91 | |
| Point abstinence at 1 mo (secondary) | BSS+ | 320/659 | 48.6 (44.7–52.5) | 8.2 (3.8–17.3) | <0.001 | 0.29 |
| | BSS | 361/640 | 56.4 (52.5–60.3) | 9.7 (4.6–20.6) | <0.001 | |
| | Control | 59/631 | 9.4 (7.2–11.9) | 1.0 | – | |
| | BSS+ vs. BSS | – | – | 0.8 (0.4–1.6) | 0.60 | |
| Point abstinence at 6 mo (secondary) | BSS+ | 395/659 | 59.9 (56.1–63.7) | 3.8 (2.0–7.4) | <0.001 | 0.40 |
| | BSS | 318/640 | 49.7 (45.7–53.6) | 3.2 (1.6–6.1) | 0.006 | |
| | Control | 142/626 | 22.7 (19.5–26.2) | 1.0 | – | |
| | BSS+ vs. BSS | – | – | 1.2 (0.6–2.2) | 0.57 | |

BSS = behavioral support sessions; BSS+ = behavioral support sessions plus 7 wk of bupropion therapy; ICC = intraclass correlation coefficient.
*All analyses account for clustering and were adjusted for age, sex, income, smoking duration, and quantity smoked per day.
† Number abstaining among the total number in the group.

## *Appendix Table 5.* Ancillary Analysis*

| Outcome | Trial Group | Patients | | Relative Risk (95% CI) | *P* Value | ICC |
|---|---|---|---|---|---|---|
| | | Total, *n/N*† | Proportion (95% CI) | | | |
| Continuous abstinence at 6 mo (primary) | BSS+ | 264/579 | 45.6 (41.5–49.8) | 8.2 (3.7–18.0) | <0.001 | 0.28 |
| | BSS | 238/583 | 40.8 (36.8–44.9) | 7.4 (3.4–16.3) | <0.001 | |
| | Control | 50/593 | 8.4 (6.3–11.0) | 1.0 | – | |
| | BSS+ vs. BSS | – | – | 1.1 (0.6–2.2) | 0.78 | |
| Adjusted estimates for continuous abstinence at 6 mo (primary)‡ | BSS+ vs. control | – | – | 9.2 (4.0–21.1) | <0.001 | 0.32 |
| | BSS vs. control | – | – | 8.4 (3.7–19.4) | <0.001 | |
| | BSS+ vs. BSS | – | – | 1.1 (0.5–2.2) | 0.81 | |
| Point abstinence at 1 mo (secondary)‡ | BSS+ | 306/585 | 52.3 (48.2–56.4) | 8.7 (4.1–18.2) | <0.001 | 0.35 |
| | BSS | 339/585 | 58.0 (53.8–62.0) | 9.8 (4.7–20.7) | <0.001 | |
| | Control | 56/609 | 9.2 (7.0–11.8) | 1.0 | – | |
| | BSS+ vs. BSS | – | – | 0.9 (0.5–1.7) | 0.69 | |
| Point abstinence at 6 mo (secondary)‡ | BSS+ | 381/581 | 65.6 (61.6–69.4) | 4.2 (2.2–8.0) | <0.001 | 0.43 |
| | BSS | 298/586 | 50.9 (46.7–55.7) | 3.3 (1.7–6.3) | 0.004 | |
| | Control | 134/604 | 22.2 (18.9–25.7) | 1.0 | – | |
| | BSS+ vs. BSS | – | – | 1.3 (0.7–2.3) | 0.45 | |

BSS = behavioral support sessions; BSS+ = behavioral support sessions plus 7 wk of bupropion therapy; ICC = intraclass correlation coefficient.
* All analyses account for clustering ($n$ = 1865, excluding 90 women).
† Number abstaining among the total number in the group.
‡ Adjusted for age, sex, income, smoking duration, and quantity smoked per day.

*Appendix Table 6.* **Adverse Events in the BSS+ Group***

| Adverse Event | Events, *n* |
|---|---|
| Headache | 130 |
| Constipation | 79 |
| Nausea | 50 |
| Dry mouth | 42 |
| Insomnia | 28 |
| Vomiting | 23 |
| Allergic skin reactions | 3 |
| Reduced appetite | 3 |
| Tinnitus | 2 |
| Tremor | 1 |
| Feeling "spaced out" | 1 |
| Elevated blood pressure | 1 |
| Visual disturbance | 0 |
| Other | 5 |
| Serious adverse events | |
| Confusion | 0 |
| Seizure | 0 |
| Cardiovascular event | 0 |
| Suicidal ideation | 0 |
| Total | 368 |

BSS+ = behavioral support sessions plus 7 wk of bupropion therapy.
* Adverse events secondary to therapy were reported by 214 of the 590 participants who received bupropion.