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# A multicentre, randomized, double-blind, placebo-controlled, 1-year study of bupropion SR for smoking cessation

P. TØNNESEN[1], S. TONSTAD[2], A. HJALMARSON[3], F. LEBARGY[4], P. I. VAN SPIEGEL[5], A. HIDER[6], R. SWEET[6] & J. TOWNSEND[6]

*From the [1]Department of Pulmonary Medicine, Gentofte University Hospital, Gentofte, Denmark; [2]Clinic for Preventive Medicine, Ullevål University Hospital, Oslo, Norway; [3]Smoking Cessation Clinic, Sahlgrenska University Hospital, Gothenburg, Sweden; [4]Department of Pulmonary Medicine, Hospital Maison Blanche, Reims Cedex, France; [5]Department of Pulmonary Medicine, Slotervaart Hospital, Amsterdam, The Netherlands; and [6]GlaxoSmithKline Research and Development, Greenford, Middlesex, UK*

**Abstract.** Tønnesen P, Tonstad S, Hjalmarson A, Lebargy F, van Spiegel PI, Hider A, Sweet R, Townsend J (Gentofte University Hospital, Gentofte, Denmark; Clinic for Preventive Medicine, Ullevål University Hospital, Oslo, Norway; Smoking Cessation Clinic, Sahlgrenska University Hospital, Gothenburg, Sweden; Hospital Maison Blanche, Reims Cedex, France; Slotervaart Hospital, Amsterdam, The Netherlands; and GlaxoSmithKline Research and Development, Greenford, Middlesex, UK). A multicentre, randomized, double-blind, placebo-controlled, 1-year study of bupropion SR for smoking cessation. *J Intern Med* 2003; **254:** 184–192.

**Background.** Bupropion sustained release (bupropion SR) has been shown to increase smoking cessation success rates in the US studies.

**Objective.** To determine whether bupropion SR, in combination with counselling, is effective for smoking cessation in a multi-country study.

**Methods.** This randomized, double-blind, placebo-controlled trial enrolled 707 smokers. A total of 527 received bupropion SR 300 mg daily for 7 weeks and 180 received placebo. A total of 11 clinic visits and 10 telephone contacts were scheduled, during the course of 1 year. Seven-week and 12-month abstinence rates were the study outcomes.

**Results.** Both continuous and weekly point prevalence smoking abstinence rates were significantly higher in the bupropion SR group compared with placebo. The continuous abstinence rate from weeks 4 to 7 was 46% in the bupropion SR group compared with 23% in the placebo group [odds ratio (OR) = 2.82; 95% confidence interval (CI) 1.89–4.28; $P < 0.001$). At month 12, the continuous abstinence rates were 21% for the bupropion SR group and 11% for the placebo group (OR = 2.19; 95% CI 1.29–3.86, $P = 0.002$). For most nicotine-withdrawal symptoms small changes were measured. Adverse events were higher for the bupropion SR group compared with placebo (insomnia 24% vs. 15%; dry mouth 13% vs. 5%).

**Conclusion.** Bupropion SR in combination with counselling increased the abstinence rate compared with placebo, and was well tolerated.

**Keywords:** bupropion sustained release, randomized controlled trials, smoking cessation, weight gain, withdrawal symptoms.

## Introduction

Bupropion sustained release (bupropion SR), an antidepressant of the amino-ketone class, has been shown to be effective and well tolerated for use in smoking cessation [1–4]. Its effect in smoking cessation is thought to be via inhibition of the presynaptic uptake of dopamine and noradrenaline in specific areas in the brain, although other mechanisms might be involved [5].

In two randomized controlled trials (RCT) in smoking cessation in specialist settings in the USA, bupropion SR doubled 1-year success rate compared with placebo in a general smoking population [1, 2].

In addition, bupropion SR doubled absolute smoking abstinence rates in patients with chronic obstructive pulmonary disease, although the absolute success rates were somewhat lower in this heavily addicted population [3].

We found it of value to try to replicate the US studies in a multi-country population using a similar design.

The study objectives were to evaluate the efficacy of bupropion SR when compared with placebo as an aid to smoking cessation, and to evaluate the tolerability of bupropion SR and its effect on body weight and withdrawal symptoms.

## Methods

*Participants*

Smokers aged $\geq$18 years of age who had smoked an average of $\geq$10 cigarettes per day on average during the previous 12 months, and who had not made a serious attempt to quit smoking during the previous 3 months, were recruited to the study. All subjects were motivated to quit smoking and were free of significant cardiac, gastrointestinal, hepatic, renal, haematological, neurological and psychiatric disease.

Subjects were not included if they were predisposed to a lowered seizure threshold, were currently depressed, or had a history or current diagnosis of bulimia, anorexia nervosa, panic disorder, psychosis or bipolar disorder. Subjects were also excluded if they had uncontrolled hypertension, had used nicotine replacement therapy (NRT) during the previous 3 months, had previously used bupropion SR for smoking cessation or if they were currently using other smoking cessation treatments.

*Study design and assessments*

This was a multicentre, randomized, parallel-group, double-blind, placebo-controlled study conducted at 26 centres in Norway, Sweden, Denmark, the Netherlands, France, South Africa, Australia and New Zealand. Investigational centre ethics committees or the Institutional Review Board of participating centres approved the study. Written informed consent was obtained from all subjects.

The study comprised a 1–2-week screening/baseline phase, a 7-week drug treatment phase and follow-up at 3, 6 and 12 months. A total of 11 clinic visits and 10 telephone contacts were scheduled. Recruitment was conducted through advertisements.

*Screening/baseline phase*

At the screening visit, subjects were assessed against the selection criteria and provided informed consent. Subjects who satisfied the selection criteria were scheduled a baseline visit and also set a date on which they intended to stop smoking. This target quit date (TQD) was scheduled between 8 and 14 days following the baseline visit. At the baseline visit, subjects were weighed and completed the Fagerström Tolerance Questionnaire [6] and the DSM-IV Criteria for Nicotine Withdrawal 292.0 [7]. Subjects' smoking status was also recorded and their expiratory carbon monoxide (CO) levels measured. Daily diary cards were provided to subjects on which to record their cigarette consumption and subjects were instructed not to attempt to quit or reduce their smoking prior to their TQD. Subjects eligible for enrolment were randomized in a 3 : 1 ratio to receive bupropion SR 150 mg twice daily or placebo throughout the 7-week treatment phase.

*Treatment phase*

During the treatment phase, subjects were contacted by telephone 1 day prior to their TQD and reminded that they were due to stop smoking the following day and were provided with motivational support. Each subject was also contacted 3 days after the TQD to provide further motivational support to encourage a successful quit, and given helpful hints to tackle the initial withdrawal symptoms. Subjects visited the clinic each week throughout the treatment phase, where the daily diary cards recording cigarette consumption were collected. Questionnaires about withdrawal symptoms were completed. Subjects were also weighed and their vital signs (blood pressure and pulse rate) and expiratory CO levels recorded. Expired CO levels were measured using a CO analyser (Bedfont Smokelyzer, Sittingbourne, UK). Any subject with a CO level >9 p.p.m. was categorized as a smoker [8].

*Follow-up*

During the follow-up phase, subjects were contacted at monthly intervals by phone to encourage abstinence from smoking and prevent relapse. During the

clinic visits at months 3, 6 and 12 daily diary cards recording cigarette consumption were collected, subjects were weighed, and vital signs and expiratory CO levels were measured.

*Nicotine-withdrawal symptoms*

The Wisconsin Smoking Withdrawal Scale (WSWS) was completed at each clinic visit [9]. This 28-item scale is divided into seven subscales associated with smoking cessation: anger, anxiety, concentration, craving, hunger, sadness and sleep. The score for each subscale and the composite score is from 0 to 4. For all symptoms a higher score indicates a worse intensity of withdrawal. Composite scores were calculated for these subscales by taking the average of the observed scores. Summary statistics were computed for each subscale for each treatment group every time the scale was collected. Daily diary card assessments of cigarette satisfaction, taste, craving and the individual DSM-IV assessments of withdrawal were averaged for each week and summarized by treatment group. The eight questions comprising the DSM-IV assessments (dysphoric or depressed mood; insomnia; irritability, frustration or anger; anxiety; difficulty concentrating; restlessness; increased appetite; weight increase) were totalled for each day and then averaged for each study week.

*Study drug and dosage*

GlaxoSmithKline supplied bupropion SR 150 mg and placebo-to-match tablets for oral administration as white, film-coated tablets. The tablets were manufactured and packed in bottles by GlaxoWellcome, Zebulon, North Carolina, USA. Bupropion SR 150 mg or placebo were administered once daily during days 1–3 of the 7-week treatment phase and then twice daily for the remainder of the treatment phase. Medication and all visits were free of charge. GlaxoSmithKline created a randomization schedule in a 3 : 1 bupropion: placebo ratio. Each centre received a list with treatment numbers and subjects were consecutively assigned a treatment number at the baseline visit.

*Counselling*

At each visit (10–15 min in duration) and telephone contact (5–10 min) an individual counselling session was given to encourage smoking cessation and prevent relapse. All centres used a counselling manual (developed by Professor P. Hajek at St Bartholomew's and the Royal London School of Medicine, London, UK). Subjects were also given take-home written material with advice and tips on smoking cessation.

*Adverse events*

At each clinic visit, once the subject had the opportunity spontaneously to report any changes since the last visit, the investigator inquired about adverse events by asking the following standard questions: 'Have you had any (other) medical problems since your last clinic visit?' and 'Have you taken any new medicines, other than those given to you in this study, since your last clinic visit?'

*Definition of success for smoking cessation*

Continuous abstinence (i.e. subjects not smoking from week 4 and continuing through to the end of week 7 of the treatment phase or during the follow-up phase at 12, 26 and 52 weeks) was confirmed by investigator's assessment of the individual's smoking status based on a report of not smoking (0 cigarettes/day) and an expiratory CO level <10 p.p.m.

Weekly point prevalence abstinence for the previous week was determined at each visit during the treatment phase and follow-up phase. Abstinence was confirmed by investigator's assessment of the individual's smoking status based on a report of not smoking (0 cigarettes/day) and an expiratory CO level <10 p.p.m.

*Statistical analysis*

Based on previous studies conducted in the USA, it was estimated that the 4-week continuous abstinence rate for subjects receiving placebo in this study would be 20%. A 13% increase in the continuous abstinence rate for subjects receiving bupropion SR is considered clinically relevant. Therefore, it was assumed that 20% of subjects receiving placebo and 33% of subjects receiving bupropion SR would remain continuously abstinent during weeks 4–7 of the current study. With 688 individual participants randomized 3 : 1 (516 bupropion SR vs. 172 placebo) this study would have at least 90% power

to detect this difference at the two-sided 5% level of significance.

Data were analysed using SAS® (v.6.12) statistical software. For the primary end-point, continuous abstinence from weeks 4–7, comparison of the treatment groups was performed using an exact test according to Gart and Cox stratified by country [10, 11]. Continuous abstinence from weeks 4–26 and 4–52 was also compared using this method. For point prevalence abstinence, the treatment groups were compared using the exact test at weeks 3, 7, 26 and 52 only. Changes in weight, relative to baseline, were compared between groups using analysis of covariance (ANCOVA) including terms for treatment, centre, gender and abstention status with baseline weight as a covariate.

## Results

*Number of subjects included*

A total of 710 subjects were randomized into the study at 26 centres: 180 in the placebo group and 530 in the bupropion SR group. Of this population, 707 subjects received treatment (i.e. at least one dose of study medication) and were included in the intent to treat population (527 bupropion SR vs. 180 placebo).

The subject demographics and baseline characteristics were similar in both treatment arms (Table 1).

*Premature discontinuations*

Premature discontinuation from the study (treatment and follow-up phases) was greater for placebo (43%) than for bupropion SR (33%). Primary reasons for discontinuation were adverse events (8% bupropion SR vs. 6% placebo), consent withdrawn (10% bupropion SR vs. 16% placebo) and lost to follow-up (9% bupropion SR vs. 12% placebo). A total of 457 subjects (65%) – 355 in bupropion SR group and 102 in placebo group – attended the 1-year visit.

*Success rates*

Both continuous and weekly point prevalence smoking abstinence rates (Figs 1 and 2) were significantly higher in the bupropion SR group compared with the placebo group. Continuous abstinence from weeks 4–7 was 46% in the bupropion SR group and 23% in the placebo group (OR = 2.82, 95% CI 1.89–4.28; $P < 0.001$). At month 12, these rates were 21% for the bupropion SR group and 11% for the placebo group (OR = 2.19, 95% CI 1.29–3.86; $P = 0.002$). During the first 7 weeks, the weekly point prevalence abstinence was very high for the bupropion SR group versus the placebo group (57–60% vs. 32–37%; $P < 0.001$). The weekly point prevalence after 12 months was 28% vs. 14% for bupropion SR versus placebo, respectively (OR = 2.34, 95% CI 1.47–3.86; $P < 0.001$). The quit rate seen in females tended to be lower than in males for both bupropion and placebo groups i.e. overall continuous abstinence at week 52 for females 36% and for males 44% ($P = 0.06$).

*Weight gain*

Initial weight gain was lower for the bupropion SR group compared with placebo up to 7 weeks, when

**Table 1** Subject demographics and baseline characteristics [mean (SD)]

| | Bupropion SR ($n = 527$) | Placebo ($n = 180$) |
|---|---|---|
| Age (years)[a] | 42.4 (9.8) | 41.9 (9.5) |
| Gender, males (%) | 48 | 50 |
| Weight (kg)[a] | 73.5 (14.2) | 74.0 (14.4) |
| Cigarettes/day[b] (range) | 22.4 (8.2) (5–60) | 23.5 (9.8) (10–80) |
| Age started smoking[c] (range) | 16.9 (3.5) (9–40) | 17.1 (3.5) (6–32) |
| Pack years (range) | 30.0 (16.2) (3.6–106.3) | 31.1 (19.8) (4–164) |
| FTND score[d] | 5.5 (1.9) | 5.4 (2.0) |
| CO (p.p.m.)[a] | 21.6 (9.9) | 22.8 (9.6) |
| Salivary-cotinine (ng $mL^{-1}$) | 105 (58) | 112 (63) |

[a]Bupropion sustained release (SR) $n = 527$, placebo $n = 180$.
[b]Bupropion SR $n = 527$, placebo $n = 178$.
[c]Bupropion SR $n = 526$, placebo $n = 178$.
[d]Bupropion SR $n = 514$, placebo $n = 177$.
FTND = Fagerström Test for nicotine dependence; CO = carbon monoxide.

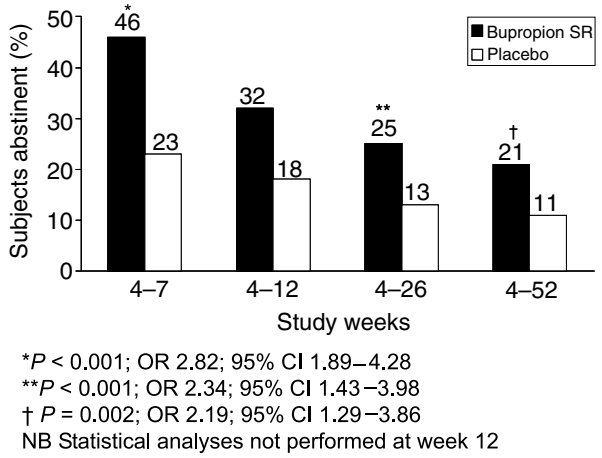


**Fig. 1** Continuous smoking abstinence [intent to treat (ITT) population].

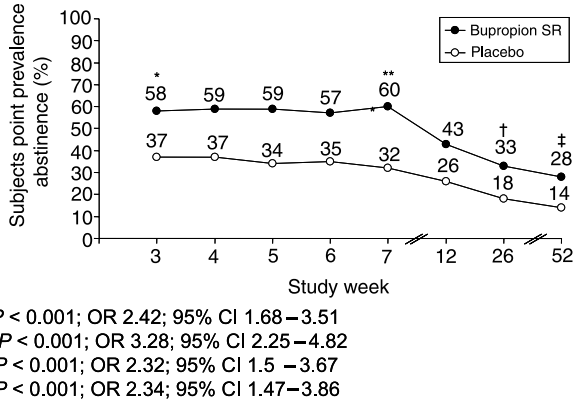


**Fig. 2** Weekly point prevalence [intent to treat (ITT) population].

drug treatment was terminated. On average, abstainers at 4 weeks on bupropion SR gained 1.21 kg (95% CI 0.56–1.85 kg) less than those on placebo (Fig. 3). During the follow-up phase this statistically significant difference in weight gain was lost, with a total weight gain of 5.5 kg for bupropion SR and 6.1 kg for placebo, a difference of 0.61 kg (95% CI −2.56–1.34).

### *Nicotine-withdrawal symptoms*

For withdrawal symptoms – measured by DSM-IV – small changes were observed during the treatment phase for both bupropion SR and placebo groups. For all symptoms, a higher score indicates worse withdrawal intensity. For 'depressed mood', 'anxiety', 'difficulty concentrating' and 'restlessness'

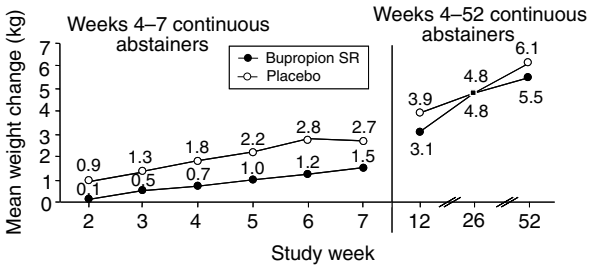


**Fig. 3** Mean weight gain from baseline in the bupropion sustained release (SR) group compared with the placebo group for the continuously abstinent population.

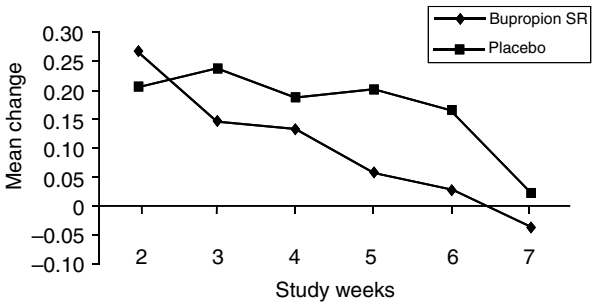


**Fig. 4** Mean change from baseline for Wisconsin Smoking Withdrawal Scale as mean composite score for continuous abstainers treated with bupropion sustained release (SR) or placebo for 7 weeks. $n = 241$ (bupropion SR); $n = 42$ (placebo).

small changes and differences between groups were found. For 'increase in appetite' an increase was found for both groups. 'Irritability, frustration or anger' and 'urge to smoke right now' had a higher score amongst the placebo group. For the composite score bupropion SR scored lower than the placebo group for weeks 3–7.

For the WSWS, the mean composite score and the mean craving score were lower (i.e. better or improved) in the bupropion SR group compared with placebo for continuous abstainers during weeks 2–7 (Figs 4 and 5). Analyses of covariance for change in composite WSWS score and craving at week 2 showed that whether or not a subject manages to abstain continuously from week 4 to 7 had a significant effect on the change in composite WSWS score from baseline to week 2. Treatment did not have a significant effect. For the craving subscale, both treatment and 4–7-week continuous abstinence had a significant effect on change in

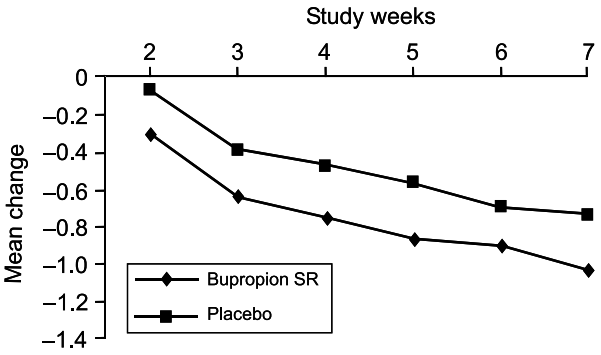


**Fig. 5** Mean change from baseline for Wisconsin Smoking Withdrawal Scale as mean craving score for continuous abstainers treated with bupropion sustained release (SR) or placebo for 7 weeks. $n = 241$ (bupropion SR); $n = 42$ (placebo).

the craving score from baseline to week 2 (Table 2).

At the end of the 7-week treatment phase, subjects were asked whether or not withdrawal symptoms whilst on study medication were a problem. For 'urge to smoke' 27% on bupropion SR and 56% on placebo answered that this was a problem. For 'mood swings' the answers were 21% vs. 32% for bupropion and placebo, respectively, whilst there were only minimal differences between the bupropion SR and placebo groups for 'weight gain' (22% vs. 22%) and for 'appetite' (21% vs. 25%).

### *Adverse events*

Overall, 75% of the bupropion SR group and 65% of the placebo group reported at least one adverse event. For several adverse events the incidences were higher for the bupropion SR group versus placebo (Table 3). At the end of the 7-week treatment phase subjects were asked whether or not adverse events experienced whilst on study medication had become a problem. Twenty-nine per cent of subjects receiving bupropion SR and 12% receiving placebo answered that side-effects had become a problem and for disruption to sleeping patterns the answer was 42% vs. 18%, respectively. Adverse events leading to discontinuation of study medication were 8% for bupropion SR and 6% for placebo (Table 4).

Serious adverse events were reported for seven subjects receiving bupropion SR and one receiving placebo. For the bupropion SR group the serious adverse events were as follows: fainting after 1 week of treatment (diagnosed as insomnia) (one subject), acute bowel obstruction after 1 week of treatment (one subject), asthma attack 1 day after completing treatment (one subject), urticaria and angioedema of lips and throat after 3 weeks of treatment (two subjects), cholecystitis after 1 month of treatment (one subject) and pregnancy (two subjects) [one normal birth at 40 weeks of a male infant with no birth defects and one (noted 4 weeks after treatment termination) birth at 7 months of twin girls, one healthy (2230 g) and one stillborn]. The serious adverse event for the placebo-treated subject occurred after 4 weeks of treatment where the subject had a fall and developed a right inguinal hernia.

One subject in the placebo group died during follow-up. The details of this case are not available

**Table 2** Analyses of covariance in relation to mean changes[a] on the Wisconsin Smoking Withdrawal Scale (WSWS) after 2 weeks for total score and craving in 4–7 week abstainers and smokers, and for treatment

| | *N* | Mean change from baseline | Difference in mean[b] | Confidence interval (CI) | *P*-value |
|---|---|---|---|---|---|
| Change in composite score from baseline to week 2 | | | | | |
| Bupropion sustained release (SR)[a] | 487 | 0.276 | −0.050 | −0.145, 0.046 | 0.306 for treatment |
| Placebo[a] | 162 | 0.325 | | | |
| 4–7-week abstainers[a] | 280 | 0.217 | −0.167 | −0.255, 0.079 | <0.001 for abstinence |
| 4–7-week smokers[a] | 369 | 0.384 | | | |
| Change in craving score from baseline to week 2 | | | | | |
| Bupropion SR[a] | 493 | −0.174 | −0.328 | −0.505, −0.151 | <0.001 for treatment |
| Placebo[a] | 164 | 0.154 | | | |
| 4–7-week abstainers[a] | 282 | −0.233 | −0.448 | −0.611, −0.284 | <0.001 for abstinence |
| 4–7-week smokers[a] | 375 | 0.213 | | | |

[a]Adjusted mean: the variables included in the models were WSWS score (total and craving) baseline, centre, treatment group and continuous abstinence (weeks 4–7).
[b]Differences are expressed as bupropion SR versus placebo or abstainers versus smokers.

**Table 3** Adverse events (%) during the treatment phase (i.e. up to 2 weeks after drug treatment ended) for bupropion sustained release (SR) and placebo groups for events with an incidence greater than 5%

| | Bupropion SR ($n = 527$) | Placebo ($n = 180$) |
|---|---|---|
| Insomnia | 24 | 15 |
| Sleep disorder | 10 | 7 |
| Dizziness | 7 | 4 |
| Dry mouth | 13 | 5 |
| Nausea | 9 | 6 |
| Constipation | 6 | 1 |
| Headache | 13 | 10 |
| Flu syndrome | 4 | 6 |
| Taste perversion | 6 | 5 |

**Table 4** Percentage of subjects discontinuing study medication due to adverse events

| | Buproprion sustained release (%) | Placebo (%) |
|---|---|---|
| Overall discontinuation rate | 8 | 6 |
| Primary reasons for discontinuation (% of the overall discontinuation rate) | | |
| Insomnia | 2 | 2 |
| Headache | 2 | 0 |
| Depression | <1 | 2 |
| Nausea | 1 | 1 |

as the investigator did not consider the event that led to the subject's death to be treatment-related.

No clinically significant changes were observed for blood pressure or pulse rate during the study.

Three subjects in the bupropion group and two subjects in the placebo group used NRT during the treatment phase (protocol violation).

## Discussion

This study showed that 7 weeks of treatment with bupropion SR almost doubled the long-term continuous and weekly point prevalence abstinence rates (both for absolute rates and for OR) in smoking cessation when used in combination with moderately intensive counselling.

Several of the centres were specialist centres experienced in smoking cessation. The 1-year continuous success rate of 21% is in accordance with the findings in two studies in the USA with bupropion SR using a similar design [1, 2]. The smokers were self-referred and thus probably high in motivation to quit, although we did not measure motivation. For these two reasons we cannot generalize results from the present study to general practice. However, from results with NRT in general practice one would expect lower success rates than those seen in clinical trials and specialist settings [12, 13].

The optimal treatment duration for bupropion SR from this study can only be theorized. However, an almost constant point prevalence success of approximately 60% during the first 7 weeks in the bupropion SR arm with a decrease to 43% at 12 weeks suggests that a longer duration of treatment might be more efficacious. However, in one recently published RCT bupropion SR was used as relapse prevention therapy in 461 of 784 participants who were abstainers after 7-week open-label treatment with bupropion SR [14]. Subjects were randomized to bupropion SR or placebo for 45 weeks and followed up to the 2-year time-point. Weekly point prevalence abstinence and continuous abstinence were consistently greater in the bupropion SR treatment group compared with placebo from randomization through follow-up. Even so, the differences in continuous abstinence rates between the bupropion SR group and the placebo group did not reach statistical significance from week 36 to month 24. Thus, 7 weeks of treatment with bupropion SR seems adequate treatment duration for smoking cessation, although longer treatment prolongs time to relapse. Nevertheless, repeated treatment with bupropion SR in smokers treated previously with bupropion SR should be tried as this was shown to increase outcome in a recently published RCT with 450 smokers that showed a 6-month continuous abstinence rate of 12% for the bupropion SR and 2% for the placebo [15].

The supportive counselling in the present study was moderately intensive and the weekly sessions during the first 7 weeks were especially important as the majority of relapses usually occur in this period. The placebo success rate of 11% in the present study is higher than in studies where a lower intensity of support has been used but lower compared with studies employing group therapy [16–20].

Only one study has been published comparing NRT with bupropion SR [2]. In this study, placebo, nicotine patches, bupropion SR and a combination of bupropion SR and nicotine patches were used for 9 weeks in 893 smokers. The 1-year continuous

abstinence rates were 5.6% for placebo, 9.8% for nicotine patches, 18.4% for bupropion SR and 22.5% for the combination. Bupropion SR and the combination were more effective than nicotine patches alone, although the effect of combination was not statistically significant. We have to await ongoing studies comparing bupropion SR, NRT and their combination to confirm these promising findings.

Weight gain was reduced during the treatment phase with bupropion SR, and this may be another way in which bupropion SR increases abstinence compared with placebo (i.e. by preventing relapse in those subjects who would not accept an increase in body weight). Longer treatment duration to prevent weight gain could be considered. However, as the effect of bupropion SR on body weight was not significant after 1 year, a combination with counselling in lowering daily caloric intake and increase in exercise might be important for a more permanent effect on body weight.

As in other smoking cessation studies only relatively small changes were observed in withdrawal symptoms [21, 22]. This emphasizes the possibility that instruments may not be sensitive enough for the accurate measurement of withdrawal symptoms. A general problem in analysing withdrawal symptoms is missing data as a consequence of subject dropout. In this study, greater withdrawal discomfort may explain relapses and dropouts. Analyses of composite nicotine withdrawal scores during weeks 4–7 did reveal higher scores and higher increase in nicotine-withdrawal symptoms for initial nonabstainers compared with abstainers. However, because this analysis was not adjusted for informative dropouts, differences between abstainers and nonabstainers may be slightly underestimated.

Composite withdrawal scores, craving and 'urge to smoke right now' were lower in the bupropion SR group, explaining one of the ways in which bupropion SR might increase success in smoking cessation. In a 3-day study with bupropion SR, depression, difficulty concentrating and irritability were reduced compared with placebo [23]. Although the weight gain was less with bupropion SR compared with placebo no difference was found in withdrawal scores for hunger and increase in appetite. This could be due to insensitive withdrawal scales or another mechanism of weight suppression.

Overall, bupropion SR was well tolerated. Side-effects of bupropion SR were observed in the same range as in other studies with insomnia, dry mouth and dizziness being the most common. The participants perceived most of the side-effects as mild. Due to a higher percentage of abstinent subjects in the bupropion SR group, over reporting of adverse events might have occurred as some might be difficult to differentiate from accepted withdrawal symptoms such as constipation, sleep disorders, anxiety and depression. We did not observe any cases of seizure. Postmarketing reports have been published with several cases of seizure even in subjects with no known disposition to seizures or intentional overdose [24–26]. An incidence of seizures of 0.1% should be suspected.

In summary, bupropion SR treatment, in combination with counselling, has been found to be an effective smoking cessation therapy with 21% of subjects continuously abstinent at 1 year compared with 11% on placebo. Bupropion SR was well tolerated and experienced similar rates of discontinuation due to adverse events when compared with placebo.

## Conflict of interest statement

GlaxoSmithKline has provided a grant for this study.

S. Tonstad has received honoraria from GlaxoSmithKline for lectures on smoking cessation. R. Sweet is a former employee of GlaxoSmithKline. A. Hider and J. Townsend are currently employees of GlaxoSmithKline. For A. Hjalmarsson, P.I. Van Spiegel, P. Tonnesen: no conflict of interest was declared.

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*Correspondence:* Dr Philip Tønnesen, Department of Pulmonary Medicine Y, Opgang 3 A, 2nd Floor, Gentofte University Hospital, Niels Andersensvej 65, DK-2900 Hellerup, Denmark (fax: +45 39 77 76 93; e-mail: Philipt@dadlnet.dk).