Changes in health-related quality of life with smoking cessation treatment

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Background: Cigarette smoking causes reduced health-related quality of life (QoL) and smoking abstinence improves health-related QoL. We assessed the effects of treatment for tobacco dependence on the health-related QoL in a 52-week randomized controlled trial of varenicline and bupropion sustained release (SR).

Methods: Subjects who smoked ≥10 cigarettes per day for the past year were randomly assigned to receive varenicline 1 mg twice daily (n=696), bupropion SR 150 mg twice daily (n=671) or placebo (n=685) for 12 weeks and followed post-therapy for an additional 40 weeks. Health-related QoL was assessed using the Smoking Cessation Quality of Life questionnaire at baseline and Weeks 12, 24 and 52.

Results: Health transition (perceived health compared with baseline) and self-control were both significantly improved among subjects receiving varenicline and bupropion SR compared with placebo at Weeks 12, 24 and 52. Similarly, varenicline-treated subjects had significantly improved health transition and self-control compared with subjects who received bupropion SR at Weeks 12 and 24, and at Week 52 for health transition. A significant positive association existed between length of continuous abstinence and improved health transition, vitality, self-control, anxiety and overall mental profile. In most instances both a direct and an indirect effect (through continuous smoking abstinence) of each active treatment (vs. placebo) contributed to improved self-control and health transition.

Conclusion: Treatment with varenicline and bupropion SR for smoking cessation resulted in improved self-control and health transition that was mediated in large part by continuous smoking abstinence.

Introduction

The chronic use of tobacco via cigarette smoking remains the most important cause of preventable morbidity and premature mortality in the world. Projected annual tobacco-attributable deaths worldwide will reach nearly 6.5 million by 2015. Staggering as this statistic is, it does not account for the substantial negative impact that smoking has on quality of life (QoL) due to the myriad adverse health effects caused by cigarette smoking. It is clear that health-related QoL decreases in those who smoke more heavily and for a longer duration. Importantly, we know that health-related QoL improves following smoking cessation with a greater improvement measured among those who formerly smoked heavily. Because cigarette smoking remains prevalent in developed countries, with growing prevalence in developing countries, the negative impacts on health-related QoL due to smoking will continue to increase globally. Evidence-based smoking cessation treatment should include effective behavioural intervention and first-line pharmacotherapy. These treatment approaches should be employed in all smokers to aid in smoking cessation and positively impact health-related QoL.

Varenicline, an α4β2 nicotinic acetylcholine receptor partial agonist, is the most recently approved medication for tobacco dependence treatment. In two pivotal clinical trials varenicline had greater efficacy for smoking cessation than did sustained release (SR) bupropion and placebo. All participants had data collected at various time points regarding their perceptions on health-related QoL using validated self-administered instruments. The aim of this study was to analyse the effect of smoking cessation pharmacotherapies (12-week treatment with varenicline, bupropion SR or placebo) and smoking abstinence on perceived health-related QoL using data pooled from these two smoking cessation trials.

Methods

For the current analysis, we used data from two identically designed double-blind, randomized, placebo-controlled trials that consisted of 12 weeks of treatment with varenicline 1 mg twice daily (BID), bupropion SR 150 mg BID or placebo, with non-treatment follow-up for 40 weeks (to Week 52).

Study interventions

Medication

All subjects were randomly assigned to one of three drug treatments: varenicline 1 mg BID, bupropion SR 150 mg BID or placebo. All treatment assignments were blinded and random assignment was concealed from the investigators.
Counselling

Brief office counselling (≥10 min) in accord with recommended clinical practice guidelines4 was provided at Weeks 1 through 12 during the double-blind treatment phase, and at Weeks 13, 24, 36, 44 and 52 during non-treatment follow-up.

Data measures collected

Abstinence from smoking was assessed at each clinic visit by self-report and confirmed by measurement of expired carbon monoxide (CO) levels ≤10 parts per million (ppm). The health-related QoL was assessed at baseline and Weeks 12, 24 and 52 using the Smoking Cessation Quality of Life (SCQoL) questionnaire, a validated instrument composed of the SF-36 (version 1) as the generic core and five additional smoking-related domains.13

The five cessation-targeted domains include social interactions (two items), self-control (five items), sleep (three items), cognitive functioning (three items) and anxiety (two items). The SF-36 includes an item on health change in the past year (health transition item) and 35 items on eight domains: physical functioning (10 items), role functioning limitations due to physical problems (four items), bodily pain (two items), general health perceptions (five items), vitality (four items), social functioning (two items), role functioning due to emotional problems (three items) and mental health (five items).13 In addition, the SF-36 contains two summary scores: the physical component summary and the mental component summary.14

Except for the single-item health transition item on the SF-36, which contains five response options (from 1 = much better now than 1 year ago to 5 = much worse now than 1 year ago), higher scores on each SCQoL domain were more favourable (more of a desirable attribute or less of an undesirable attribute). The Physical Component Summary and the Mental Component Summary scores were aggregated to conform to a mean of 50 and standard deviation (SD) of 10 in the US general population. Each of the remaining SCQoL domains, including the five cessation-targeted domains and the eight SF-36 domains, had a possible range of 0–100, with higher scores being more favourable (e.g. better functioning or well-being, more self-control, less anxiety). Subjects completed the SCQoL questionnaire based on how they have been feeling over the past 4 weeks. Subjects were assessed at four occasions: baseline, Week 12 (end of double-blind phase), Week 24 and Week 52.

Study subjects

Subjects participated in two randomized, double-blind, placebo-controlled clinical trials that were conducted between June 2003 and March 2005 consisting of a 12-week treatment period with a 40-week post-treatment follow-up of smoking status to Week 52. Written informed consent was obtained from all participants, with consent forms and procedures approved by the institutional review board at each of 33 study sites. The study was conducted in compliance with the ethical principles of the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practices Guidelines.

Generally healthy smokers between 18 and 75 years of age, who smoked ≥10 cigarettes per day and were willing to quit by participating in a research study were eligible for enrolment. Study exclusions were: serious or unstable medical condition within the previous 6 months; treatment for depression within previous 12 months; history of panic disorder, psychosis or bipolar disorder; a history of any varenicline exposure and/or bupropion use; and use of nicotine replacement therapy, nortriptyline, clonidine or tobacco products other than cigarettes within the previous month.

Statistical analysis

Analyses were based on all available data, requiring a baseline SCQoL score and at least one follow-up score. Longitudinal repeated measures models15,16 were applied with change from baseline as the outcome, and the following categorical predictors: a time-varying treatment term (defined as a variable whose value changed over time for the same subject—varenicline at Week 12 and non-treatment at Weeks 24 and 52; bupropion at Week 12 and non-treatment at Weeks 24 and 52; or placebo at Week 12 and non-treatment at Weeks 24 and 52); a fixed treatment term based on randomized assignment (varenicline, bupropion SR or placebo); a time term (Week 12, 24, 52); time-by-randomized treatment interaction term and a centre within-study term.

Relevant treatment differences were defined as having met three criteria: (i) difference in means between treatment groups of ≤5 points, which is deemed clinically relevant, except those not based on a 100-point scale (SF-36 health transition item and two component summaries);13 (ii) standardized effect size of ≤0.20 SD units (difference in mean changes from baseline between a pair of treatments, divided by pooled baseline SD), which is indicative of at least a small but noteworthy effect;17 and (iii) 95% confidence interval (CI) did not include zero.

The relationship between continuous abstinence and health-related QoL was also investigated across treatment groups using a longitudinal repeated measures model with change from baseline as the outcome, levels of continuous abstinence as categorical predictors and with all treatment groups combined. Noteworthy differences between a pair of continuous abstinence levels (≤4 weeks, 4–15 weeks, 16–43 weeks, ≥44 weeks) were based on the same standards as those for treatment differences, with a pair of continuous abstinence levels replacing a pair of treatments. For purposes of data presentation we considered that 4 weeks of continuous abstinence represented >4 weeks but ≤16 weeks; 16 weeks of continuous abstinence represented ≥16 weeks but <44 weeks; and 44 weeks of continuous abstinence represented ≥44 weeks.

Statistical mediation models18,19 were applied to determine the relationship between continuous abstinence from smoking, QoL (measured by SF-36 domains and the five cessation-targeted domains of the SCQoL), and treatment assignment (varenicline vs. placebo and bupropion SR vs. placebo). The mediator variable was continuous smoking abstinence and the explanatory variable was treatment. The QoL variables for each subject were assessed by calculating the change from baseline to Weeks 12, 24 and 52 for each of the SF-36 and cessation-targeted domains of the SCQoL. Calculations were performed separately for every time point. The effects at Week 12 (end of treatment) may be thought of as representing the direct effects of drug treatment; and effects at Weeks 24 and 52 can be considered as residual effects of prior pharmacologic intervention.

All computations were performed in SAS.20

Results

Subject characteristics

This analysis is based on 2052 participants who were randomized to receive treatment with varenicline, bupropion SR or placebo (696, 671 and 685, respectively). Baseline demographic and smoking characteristics were similar between treatment groups (table 1), as were baseline SCQoL scores (data not shown). Supplementary figure 1 displays the disposition of study subjects, and the percent for which we had complete data for the two SCQoL domains showing the most significant change (health transition and self-control) by treatment group and by length of smoking abstinence.

Treatment differences on QoL

The SCQoL domains that met our criteria for clinically relevant treatment differences from baseline to Week 12, 24 or 52 between treatment groups were health transition (lower scores indicate health improvement) and self-control (higher scores indicate improvement in smoking-related self-control) (table 2). Relative to placebo, both active drug comparisons were significantly and meaningfully improved for both SCQoL domains at all time points. Compared with bupropion SR, varenicline did not show a clinically meaningful difference (effect size <0.20) on health transition from baseline to Week 52, and on self-control from baseline to Weeks 24 and 52.
Table 1 Baseline demographic and smoking characteristics

<table>
<thead>
<tr>
<th></th>
<th>Varenicline (n=696)</th>
<th>Bupropion SR (n=671)</th>
<th>Placebo (n=685)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), mean (SD)</td>
<td>43.5 (11.3)</td>
<td>42.5 (11.8)</td>
<td>42.5 (11.7)</td>
</tr>
<tr>
<td>Gender, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>366 (52.6)</td>
<td>398 (59.3)</td>
<td>384 (56.1)</td>
</tr>
<tr>
<td>Women</td>
<td>330 (47.4)</td>
<td>273 (40.7)</td>
<td>301 (43.9)</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>574 (82.5)</td>
<td>547 (81.5)</td>
<td>552 (80.6)</td>
</tr>
<tr>
<td>Black</td>
<td>67 (9.6)</td>
<td>64 (9.5)</td>
<td>75 (10.9)</td>
</tr>
<tr>
<td>Asian</td>
<td>12 (1.7)</td>
<td>9 (1.3)</td>
<td>15 (2.2)</td>
</tr>
<tr>
<td>Other</td>
<td>43 (6.2)</td>
<td>51 (7.6)</td>
<td>43 (6.3)</td>
</tr>
<tr>
<td>Number of years smoked</td>
<td>25.7 (2–59)</td>
<td>24.8 (2–61)</td>
<td>24.5 (0–61)</td>
</tr>
<tr>
<td>Number of cigarettes/day in past month</td>
<td>21.8 (10–70)</td>
<td>21.4 (10–65)</td>
<td>21.5 (10–80)</td>
</tr>
<tr>
<td>Fagerstrom test score</td>
<td>5.28 (2.19)</td>
<td>5.29 (2.14)</td>
<td>5.27 (2.09)</td>
</tr>
</tbody>
</table>

a: Based on data provided (respectively, n=695, 670, 685)
b: Based on data provided (respectively, n=693, 670, 681)

All other comparisons failed to meet our a priori criteria for meaningful and significant differences when comparing baseline values with values obtained at Weeks 12, 24 and 52 (Supplementary tables 1, 2 and 3, respectively). In addition, very few differences, when comparing baseline scores with follow-up scores of a measure at Weeks 12, 24 or 52, reached statistical significance alone (P<0.05) and there were virtually no consistent findings. For example, baseline to Week 12 results for the varenicline and bupropion treatment groups compared with placebo for the ‘general health perception’ domain showed a statistically significant difference that persisted for the baseline to Week 24 comparison only for varenicline compared with placebo. Similarly, the cessation-targeted ‘sleep’ domain was statistically different (in the negative direction) for varenicline and bupropion compared with placebo for the baseline to Week 12 comparison only.

Relationship between abstinence and QoL

Subjects who abstained from smoking for longer periods rated their health more favourably compared with their baseline, as measured by significantly and meaningfully improved health transition (figure 1). For health transition each of the six pair-wise comparisons between the four levels of continuous abstinence was relevant: for <4 vs. 4 weeks the difference between their mean changes from baseline was 0.74 (P<0.01, effect size = 0.22); and for 16 vs. 44 weeks the difference between their mean changes from baseline was 5.46 (P<0.01, effect size = 0.30).

In addition, smoking cessation was associated with improved vitality, reduced smoking-related anxiety and improvement in the mental component summary score. Specifically, subjects who stopped smoking for ≥44 weeks had improved vitality compared with subjects with <4 weeks of continuous abstinence (difference = 6.15, P<0.01, effect size = 0.34). Additionally, subjects who abstained from smoking for ≥16 weeks (but <44 weeks) and for ≥44 weeks had less anxiety than subjects with <4 weeks of cessation (<4 vs. ≥16 weeks: difference = 5.14, P<0.01, effect size = 0.26; <4 vs. ≥44 weeks: difference = 5.90, P<0.01, effect size = 0.29). Finally, subjects who abstained from smoking for ≥16 weeks but <44 weeks and ≥44 weeks had better standardized mental component profiles than subjects with <4 weeks of cessation (<4 vs. ≥16 weeks: difference = 2.02, P<0.01, effect size = 0.25; <4 vs. ≥44 weeks: difference = 2.35, P<0.01, effect size = 0.29).

Direct and indirect effects of treatment on QoL

Direct effects of active treatment (vs. placebo) and indirect or mediated effects of active treatment (through continuous smoking abstinence) on health-related QoL are reported only for those domains with a statistically significant and meaningful treatment difference (table 3). A substantial direct effect existed for both varenicline and bupropion SR, each relative to placebo, on health transition and self-control at Week 12, as did a significant indirect effect of each active treatment (vs. placebo) on health transition and self-control through continuous smoking abstinence. For varenicline the direct effects of drug treatment on health transition and self-control were not significant (P>0.05) at Week 52; direct effects were also not significant for self-control at Week 24. The direct effects of bupropion SR were significant for health transition and self-control at all times, with the exception of Week 52 for health transition. The indirect effects of both active agents on health transition and self-control via continuous smoking abstinence remained significant at each assessed week.

Discussion

Our results show a significant effect for smoking cessation on health-related QoL, particularly for general health perception compared with general health 1 year ago (health transition). There is a rapid effect for smoking cessation on improvements in health transition, with the greatest separation between groups noted when comparing participants who were abstinent less than 4 weeks with those who were continuously abstinent for ≥44 weeks. Other researchers have noted similar health-related QoL improvements positively associated with length of smoking abstinence when comparing continuing smokers to those who were abstinent for 1 year.7,21 Our results confirm continued improvement
Table 2 Differences in mean change for selected SCQoL domains from baseline to Weeks 12, 24 and 52 between treatment groups.

<table>
<thead>
<tr>
<th></th>
<th>Baseline to Week 12</th>
<th>Baseline to Week 24</th>
<th>Baseline to Week 52</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>P-value of difference</td>
<td>Effect size&lt;sup&gt;b&lt;/sup&gt;</td>
<td>P-value of difference</td>
</tr>
<tr>
<td>Health transition</td>
<td>-0.83</td>
<td>-0.18</td>
<td>-0.54</td>
</tr>
<tr>
<td>Varenicline to Placebo</td>
<td>&lt;0.01</td>
<td>0.10</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Bupropion SR to Placebo</td>
<td>&lt;0.01</td>
<td>0.59</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Varenicline to Bupropion</td>
<td>&lt;0.01</td>
<td>0.52</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

<sup>a</sup> Only results for clinically meaningful and statistically significant differences in SCQoL domains are displayed in the table. All other SCQoL domain differences did not meet one or both of these criteria.

<sup>b</sup> Effect size = difference in mean changes from baseline between a pair of treatments, divided by pooled baseline SD.

C: General health improvement (health transition) compared with 1-year ago is measured on a scale from 1 (‘Much better now than 1 year ago’) to 5 (‘Much worse now than 1 year ago’). Subjects who indicated their general health perception changed more than 1 category were considered to have a positive change in health transition.

Figure 1 Abstinence, smoking-related self-control and perception of health (health transition): mean changes from baseline by levels of continuous abstinence. Self-control (SC) is measured on a scale from 0 (poor) to 100 (excellent). Health transition (HT) is measured on a scale from 1 (much better now than 1 year ago) to 5 (much worse now than 1 year ago); a negative change indicates an improvement in general health perception compared with 1 year ago.

In health transition with longer continuous abstinence through 1 year of follow-up. Consistent with this, significant and meaningful treatment differences were observed when comparing varenicline and bupropion with placebo, and when comparing varenicline with bupropion for health transition from baseline through Week 24 (Supplementary tables 1 and 2). These treatment differences are in part related to the positive effects of the medications on smoking abstinence.

Among all health-related QoL domains, we found the largest positive effect for smoking abstinence on cessation-targeted self-control. Similar to health transition, the greatest positive change in self-control was noted comparing participants who were abstinent for less than 4 weeks with participants who were continuously abstinent for ≥44 weeks. In a study of the performance of the SCQoL (same smoking cessation QoL instrument used in our study), Shaw et al. also found a rapid and robust improvement in self-control even with short-term smoking abstinence. The ‘resource depletion’ model of self-control suggests that self-control will be reduced after a recent period of temptation resistance. However, among people trying to stop smoking a recent study found the opposite—recently resisted temptation reduces the risk of smoking lapses. Our results showing continued improvement in self-control with longer smoking abstinence (and presumably cumulatively more temptations resisted) are consistent with these recently published findings as well. Also in keeping with our findings of treatment effects on health transition, we found significant treatment effects for varenicline and bupropion compared with placebo for self-control comparing change from baseline to Weeks 12 and 24. Again, these effects are related to the positive effect medication treatment has on smoking abstinence, although there may be additional mechanisms at work as discussed below.

Given the well-known adverse health effects caused by cigarette smoking, it is not surprising that some key aspects of health-related QoL improve with smoking abstinence. However, we also found in a mediation analysis that there were important effects for medication on both health transition and self-control. The effects for treatment (‘direct effect’ column in Supplementary table 1) were greatest at Week 12 (end of...
In this prospective clinical trial, we have shown that health-related QoL improves rapidly and substantially with successful smoking cessation. The positive impact on health-related QoL is mediated primarily by smoking abstinence, but there also appear to be direct effects of pharmacological treatment (e.g. amelioration of withdrawal symptoms) that directly contributed to improved self-control and health transition. Effective therapy for tobacco use and dependence includes both pharmacological and behavioural treatment. Providing effective treatment for tobacco use and dependence will not only help smokers successfully to stop using tobacco and add years of life expectancy, but will also improve health-related QoL for those additional years.27

Supplementary data

Supplementary data are available at EURPUB online.

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Conflict of interest: J.C.C., C.L.B. and A.G.B. are employees and shareholders of Pfizer.

Key points

- Health-related QoL is improved with treatment for tobacco use and dependence using the non-nicotine medications varenicline and SR bupropion compared with placebo.
- Although smoking abstinence mediates most of the improvement in health-related QoL, early in treatment, there are direct
treatment effects (apart from smoking abstinence) of varenicline and SR bupropion that also mediate the improvement.
- The improvement in health-related QoL occurs rapidly after achieving smoking abstinence and improves steadily with longer duration of abstinence up to 1 year.

References


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Smoking during pregnancy and associated risk factors in a sample of Romanian women

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Background: Smoking during pregnancy is one of the most modifiable risk factor for poor birth outcomes. This study assesses the prevalence and correlates of smoking during pregnancy. Methods: A questionnaire was applied to pregnant women in two urban clinics in Romania to assess smoking prevalence, attitudes and knowledge about smoking, and other risks poorly documented in Romania, such as depressive symptoms, stress and social support. The response rate was >80% and the valid sample comprised of 916 women. Descriptive statistics and logistic regressions were used to estimate the prevalence of smoking and other risk factors and to identify correlates of smoking during pregnancy. Results: Approximately 15% of the women continued smoking during pregnancy, and 26% of all women said they smoked prior to pregnancy, but quit upon finding out they were pregnant. Depressive symptoms and stress were not associated with smoking during pregnancy. Women with no social support had higher odds of continued smoking vs. non-smoking (OR = 2.3, P < 0.01), and vs. quitting (OR = 2.3, P < 0.05). Roma women had 5.2 times the odds (P < 0.01) of continued smoking vs. non-smoking. Lack of awareness about the benefits of quitting smoking and about the risks of smoking light cigarettes were associated with continued smoking during pregnancy.