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Cost-effectiveness of varenicline and three different behavioral treatment formats for smoking cessation

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Abstract

There is a lack of evidence of the relative cost-effectiveness of proactive telephone counseling (PTC) and Web-based delivery of smoking cessation services in conjunction with pharmacotherapy. We calculated the differential cost-effectiveness of three behavioral smoking cessation modalities with varenicline treatment in a randomized trial of current smokers from a large health system. Eligible participants were randomized to one of three smoking cessation interventions: Web-based counseling (n=401), PTC (n=402), or combined PTC-Web counseling (n=399). All participants received a standard 12-week course of varenicline. The primary outcome was a 7-day point prevalent nonsmoking at the 6month follow-up. The Web intervention was the least expensive followed by the PTC and PTC-Web groups. Costs per additional 6-month nonsmoker and per additional lifetime quitter were $1,278 and $2,601 for Web, $1,472 and $2,995 for PTC, and $1,617 and $3,291 for PTC-Web. Cost per life-year (LY) and quality-adjusted life-year (QALY) saved were $1,148 and $1,136 for Web, $1,320 and $1,308 for PTC, and $1,450 and $1,437 for PTC-Web. Based on the cost per LY and QALY saved, these interventions are among the most cost-effective life-saving medical treatments. Web, PTC, and combined PTC-Web treatments were all highly cost-effective, with the Web treatment being marginally more cost-effective than the PTC or combined PTC-Web treatments.

Keywords

Smoking cessation, Varenicline, Cost-effectiveness, Quality-adjusted life-years saved, Behavioral intervention

Implications

Practice: The results highlight that (1) clinicians have three evidence-based options to support the prescription of varenicline for cessation; if the first choice determined jointly with the patient does not work well, then two other drug-counseling options are available, increasing flexibility and patient acceptance.

Policy: The evidence herein shows that smoking cessation counseling in conjunction with first-line medications such as varenicline are highly cost-effective in comparison to other life-saving medical procedures and should be supported through mechanisms such as increased insurance coverage.

Research: The results highlight the need: (1) to determine the conditions (environmental or personal characteristics) that maximize the cost-effectiveness of these interventions; (2) to determine the extent to which these results generalize to other populations, and (3) to determine the effectiveness if these materials are translated into different languages for use in other cultures.

INTRODUCTION

Proactive telephone counseling (PTC) is a popular mode of delivery of behavioral counseling for which meta-analyses report odds ratios (OR) for smoking cessation ranging from 1.2 [1] to 1.6 [2]. Web-based delivery of health information and cessation behavioral counseling is widely available and has been the focus of several assessments [3–5] and randomized trials [6–10]. Although the combination of PTC and Web-based delivery could result in higher cessation rates than either delivery method alone, there is a lack of an evidence base for these combined treatments in conjunction with pharmacotherapy [1].

Varenicline is a first-line medication for the treatment of tobacco dependence that has substantial evidence for efficacy, with a relative "risk" for abstinence of 2.3 in one review [11] and an OR of 3.1 in another [1] relative to placebo. These efficacy estimates are derived from phase 2 [12–14] and phase 3 [15–19] randomized placebo-controlled trials that provided up to 240 min of face-to-face clinic-based and PTC-based counseling. The effectiveness of varenicline with less intensive real-world adjunctive counseling approaches such as those available through the Web or quitlines has not been assessed.

The objective of the Comprehensive Medication Program and Support Services (COMPASS) randomized, real-world clinical trial was to determine the relative effectiveness of three forms of behavioral counseling offered in conjunction with varenicline

pharmacotherapy: standard PTC, a newly developed Web-based program modeled after the principles of the standard PTC program, and a combined PTC and Web-based program. Herein, we compare the cost-effectiveness of these three treatments from a societal perspective. Although these three treatments had similar clinical effectiveness, given the recent national concern with health care cost containment, it is important from a policy perspective to quantify their cost-effectiveness.

METHODS

Setting and participants–Participants were recruited from Group Health in Seattle, WA, a consumer-governed non-profit health care organization. Participants were eligible if they: were at least 18 years old; smoked at least ten cigarettes per day over the past year and five cigarettes per day within the past week; had dependable telephone and Internet access and self-reported comfort using the Internet; were eligible for smoking cessation services under current health plan coverage; and were medically appropriate for varenicline use.

Group Health members were recruited from October 2006 to October 2007 through health plan magazine advertisements, clinician referrals, and through Free & Clear's Quit For Life® Program. The 2,093 screened volunteers were, on average, aged 47.5 (±11.5) years, smoked 20.6 (±8.9) cigarettes per day in the past year, and were 64.6% female. Overall, 804 (31.2%) volunteers were excluded from participation in the current study, with the most common reasons being computer-related (lack of Internet or e-mail access), too few cigarettes smoked per day, and excessive daily alcohol use or binge drinking. Eligible volunteers were similar to those who were excluded with respect to number of cigarettes smoked per day at screening and were significantly younger and more likely to be female. Complete details can be found in Swan et al. 2010 [26].

The 1,202 study participants were, on average, 47.3 years old, 66.9% female, 89.7% white, had 14.0 years of formal schooling, had a BMI of 27.8 kg/m^2, smoked 19.7 cigarettes per day, and 56.2% self-report having have ever suffered from depression.

Eligible volunteers participated in a 20-min telephone intake survey to assess smoking history, quitting history, motivation to quit, psychosocial characteristics, and demographics. At the end of the intake survey, participants were randomly assigned to one of the three treatment groups. A telephone follow-up survey was conducted by non-intervention study staff approximately 6 months after the target quit date to collect information on quit attempts, smoking, and medication use. All participants were asked to contact Free & Clear with questions about varenicline and to report side effects. Side effects and adverse events were also addressed during each intervention call.

Behavioral intervention–The three behavioral interventions were provided by Free & Clear, Inc. (Free & Clear). The PTC condition was the standard Free & Clear Quit For Life® program, which has been validated in a number of empirical studies [20–24]. The Web and PTC-Web components were developed to replicate the principles and components of the PTC-based Quit For Life program. Once randomized to treatment, all participants received a 5–10-min orientation call, printed Quit Guides, and access to a 1-800 inbound support line. Other services varied by intervention group. PTC participants received up to five one-on-one proactive (Free & Clear initiated) phone counseling sessions with a specialist. Web participants had access to the online program which contained standardized content as well as targeted and tailored components and interactive tools. They could call in for phone support at any time, but only received one proactive 5–10 min orientation call. PTC-Web participants received access to both programs. For those participants in the PTC-Web group that used the Web, the specialists had real-time access to information regarding number and duration of logins and areas of the website visited. They could also update the participants' target quit date as necessary based on their conversation and interact with participants through online discussion forums.

Medication–Participants in all three treatment groups received a 12-week supply of varenicline (provided to the study by Pfizer, Inc.), to be taken according to recommended guidelines [1] starting 1 week prior to the target quit date. Medication was shipped from the pharmacy to the participant. At each follow-up, we asked participants if they used nicotine patch, nicotine gum, nicotine spray or inhaler, or bupropion. At the 21st-day follow-up, less than 2% of respondents used any of these supplemental treatments. At the 12th-week follow-up, 3.6% had used one of these supplemental treatments. At the sixth-month follow-up, 9.1% had used one of these supplemental treatments.

Outcome measure–For the cost-effectiveness study, nonsmoking was defined as the self-report of no smoking, not even a puff, within the past 7 days. Individuals who were not reached for follow-up were considered to be smoking.

Details concerning trial methodology and trial outcomes are presented elsewhere [25, 26].

Web development and administration costs–The Web module was developed by Free & Clear in 2005 and 2006 and went online in late 2006. Costs were incurred for outsourced contracts, and Free & Clear personnel in the following areas: (1) product development (responsible for designing product features and functions, and developing program content, materials, and protocols), (2) Web development (responsible for the architecture, design, and implementation of Web applications), (3) infrastructure (to manage server configurations and databases), and (4) quality assurance (to develop test cases, conduct

tests, and work with developers to resolve defects). Costs for Free & Clear personnel were estimated within each category by multiplying the number of full time equivalents by the midpoint of the range of salary and benefits for personnel in that category (as of Nov 2008). Outsourced contracts (during 2005 and 2006) were valued at the invoiced amount. Per person costs for Web development and administration were obtained by dividing the total personnel and outsourced contract costs by the number of registered users of the company website ending Oct 2008.

Costs for telephone-based contact–For the Web group, a single brief orientation call was scheduled. For the other two groups, five proactive calls were scheduled which included the study orientation and counseling calls. The average cumulative minutes per enrollee for all scheduled calls was 8.3 for the Web group, 61.7 for the PTC group, and 64.3 for the PTC-Web group. The average cumulative minutes per enrollee for calls initiated by the participant were 5.6, 6.3, and 8.1 min, respectively. Average cost per telephone minute was estimated as the average salary plus benefits per minute for registration staff and quit coaches (the two personnel categories who were involved on the telephone calls) to which was added the costs for trainers, supervisors, and schedulers, and direct telephone costs.

Non-medication material and supply cost–Non-medication materials and supplies included a quit kit consisting of an introduction letter, a notice of privacy practices, three printed booklets (a smoking cessation guide, a secondhand smoke guide, and an ally guide), and chronic conditions fact sheets (asthma, diabetes, COPD, CHD, etc.) if pertinent. In addition, letters were sent to patients when there was a failure to successfully complete a scheduled call or occasionally for some other reason when contact was required. Costs for these non-medication materials and supplies included the cost of production, mailing, and personnel time involved in assembling and mailing these materials.

Medication cost–Varenicline drug costs per enrollee were estimated as the average price from Costco mail order, Bartell pharmacy, CanadaDrugs.com, and Drugstore.com in July 2008 for a 12-week standard course of treatment.

Adverse events and other support-line interactions–For adverse events, staff time averaged 1 min per enrollee and MD time averaged 1.1 min per enrollee. Support-line staff time for other events (medication access, Web help, etc.) averaged 0.7 min per enrollee. Costs per minute were estimated using the same approach as for telephone counseling.

Overhead costs–Overhead costs were estimated based on the cost to employers for the Quit for Life program, which includes both the Web component and Nicotine Replacement Therapy (NRT). (Costs for non-employers were considered to be proprietary.) NRT costs were obtained from Costco mail order, Candadrugs.com, drugstore.com, and the CVS pharmacy website. These costs were subtracted from the employer cost for the Quit for Life program. The result was divided by the estimated cost for the phone plus Web intervention calculated as described earlier. The costs for the phone only, Web only, and phone plus Web programs as derived above were multiplied by this ratio to obtain an approximate cost including overhead.

Excluded costs–Participant time and telephone or other expenses associated with telephone counseling or time on the website were unavailable and not included. Costs for the development of the telephone intervention were unavailable; the telephone program has undergone continual development over a period of many years and has been administered to hundreds of thousands of enrollees. Since the Web component was modeled after the phone component, if costs for the phone component had been available, a substantial portion of those costs would also have been added to the Web component. Exclusion of the costs of web development would have reduced total costs for the Web group by 7.7% and the PTC-Web group by 5.5%.

There were no severe adverse events (SAEs) that could be attributed directly to treatment. Thus, no costs associated with these SAEs were included in the analysis. Nine non-fatal SAEs that occurred during the trial were not considered to be causally related to treatment except for a moderate allergic event that did not require medical attention. Two fatal SAEs occurred in participants with pre-existing cardiac disease and risk factors and were considered unlikely to be associated with treatment.

Baseline cost-effectiveness calculations–Six-month abstinence rates were not biochemically confirmed. Estimates from three reviews of the validation of self-reported smoking status [27–29] suggest a nonvalidation rate for self-reported abstinence between 3.2% and 5.5% for studies that also report cotinine in blood or saliva using appropriate cutoff levels. We have applied a 5% nonvalidation rate to self-reported abstinence.To extrapolate results to lifetime quitters, this rate was further reduced by a relapse rate of 22% [30, 31] to reflect the expected reduction in abstinence from 6 to 12 months. Previous research [32–34] estimates a 30–40% lifetime probability of relapse from smoking cessation after 1 year of abstinence. Lifetime nonsmoking rates in the present analysis were calculated assuming a 37% relapse rate. The cost per additional lifetime nonsmoker was derived by dividing the cost per enrollee by the lifetime placebo-adjusted quit rate.

The number of life-years (LYs) and quality-adjusted life-years (QALYs) saved per lifetime quitter by age and gender were obtained via Monte Carlo simulation following the method described in Javitz et al. [35]. The lifetimes of current smokers of a given age, gender, and smoking status (heavy or

light) were simulated 10,000 times taking into account a 1.5% probability each year that the smoker would quit without assistance [32, 33, 36–38]. The lifetimes of current quitters were simulated assuming that their mortality rates transitioned over a 17-year period to those of never smokers. The life-years saved for a current quitter was calculated as the difference between the lifetimes. Mortality rates were obtained from Croghan et al. [39] (which take into account the age, gender, and smoking status–heavy, light, or never–of the individual and the number of years since the successful quit attempt. We extrapolated these rates down to age 18 and up to 100 years using piecewise linear extrapolation. Each year of life was multiplied by the Healthy People 2000 quality of life measure for smokers and nonsmokers [32, 40], to obtain quality-adjusted life-years. Our simulations specified half of the smokers being light and half being heavy (>20 cigarettes/day). Average life-years and QALYs saved were obtained using the age and gender distribution of study participants.

The cost per LY and QALY saved was calculated as the cost per lifetime quitter divided by the discounted number of LYs or QALYs saved per lifetime quitter. Both calculations used a 3% discount rate for future LYs and QALYs.

Sensitivity analyses–We examined the sensitivity of our results to parameter values by developing two scenarios that modified parameters so as to minimize or maximize cost-effectiveness (denoted as the pessimistic and optimistic scenarios).

RESULTS

The response rates at 6 months were 74.3%, 73.4%, and 74.9% for Web, PTC, and PTC-Web, respectively. Cessation rates among 6 month respondents were 41.4%, 46.9%, and 45.2%, respectively. On an intent-to-treat basis, with nonrespondents classified as smokers, the cessation rates were 30.7%, 34.3%, and 33.8%, respectively.

Intent-to-treat estimates (which involve use of all randomized study participants) commonly also assume all nonrespondents are smokers. To provide an estimate the cessation rate of nonrespondents, we imputed the probability of being a nonsmoker at 6 months for those individuals based on separate logistic regressions for each group. The dependent variables included smoking status at 21 days after planned quit date, smoking status at 12 weeks after planned quit date, cigarettes per day at baseline, motivation to quit, years of education, any previous quit of 6 months or longer duration, gender, age (and age squared), whether there was another smoker at home, whether the respondent was married, a depression index score, the Fagerstrom Test for Nicotine Dependence score, and body mass index. Including imputed probabilities of being a nonsmoker in the computation, the average 6 month cessation rates were 40.7%, 46.5%, and 45.2% for the Web, PTC, and PTC-Web groups, respectively. (These estimates are the expected values that would be obtained using multiple imputation [41].) Thus, if imputed 6 month smoking status had been used instead of assuming individuals with missing data to be smokers, cost-effectiveness would have been 21.7%, 22.7%, and 22.1% greater, respectively. Prior research suggests that missing data imputation methods for inferring smoking cessation status are still subject to biases [42].

Participants in the PTC and PTC-Web groups completed an average of 4.1 and 4.2 calls, respectively, while participants in the Web group completed 1.6 calls on average (including calls for additional support beyond the orientation call). Average call durations (in minutes) were: 14.4 Web, 67.8 PTC, and 72.4 PTC-Web. Logins averaged 5.7 and 3.4 for the Web and PTC-Web groups, respectively. Web use duration averaged 110.5 and 42.7 min for the Web and PTC-Web groups, respectively. However, the distribution of minutes on the Website was extremely skewed. Truncating at 250 min (the 95th percentile), Web use duration averaged 53.9, and 28.5 min for the Web and PTC-Web groups, respectively.

The LYs and QALYs saved following smoking cessation are shown Table 1, using the baseline scenario discount rate of 3%, as well as under discount rates of 0% and 5% (later used in the optimistic and pessimistic scenarios, respectively). The LYs saved varies by age, gender, and discount rate. At discount rates of 3% and 5%, there are generally fewer years saved at younger ages (mortality rates are low for both smokers and nonsmokers and future LYs saved are discounted) and at older ages (fewer LYs remain). With no discounting, LYs and QALYs are comparable for participants from 20 to 60 years old and decrease at older ages. Using the age and gender distribution of 6 month abstainers in our study and a 0% discount rate, the average LYs and QALYs are 6.17 and 5.51, respectively. Discounting by 3% reduces the average LYs and QALYs saved to 2.27 and 2.29, respectively. Discounting by 5% reduces the average LYs and QALYs saved to 1.22 and 1.35, respectively.

The average number of LYs saved with a 0% discount rate that we calculated is similar to the 5.65 LY saved reported by Solberg et al. [43], using data from the National Health Interview Survey and the National Mortality Feedback Survey for never, current, and former smokers (as compiled by Rogers and Powell-Griner [44], a 14-year prospective study of 1.2 million US residents by Taylor et al. [45], and the 2003 Behavioral Risk Factor Surveillance Study (BRFSS) [46]).

The cessation rates observed in this trial are comparable to those seen in phase 3 clinical trials of varenicline. The 6-month point prevalence rates for all treatment groups (30.7–34.3% before adjustment for biochemical validation) fall within the 95%

Table 1 | Life-years (LYs) and quality-adjusted life-years (QALYs) saved per lifetime quitter by gender and age of smoking cessation

LY or QALY[a]		LY	LY	LY	QALY	QALY	QALY
Discount rate (%)		0.0	3.0	5.0	0.0	3.0	5.0
Males	% Pop[b]						
20–29 years old	1.8	6.41	1.43	0.56	7.33	2.22	1.12
30–39 years old	8.6	6.60	1.90	0.86	7.14	2.60	1.42
40–49 years old	8.6	6.65	2.45	1.28	6.60	2.82	1.67
50–59 years old	11.9	6.11	2.81	1.69	5.52	2.77	1.77
60–69 years old	5.6	4.65	2.61	1.77	3.86	2.27	1.59
70–79 years old	0.3	2.87	1.93	1.47	2.19	1.51	1.16
Females							
20–29 years old	4.8	6.03	1.19	0.43	6.02	1.68	0.83
30–39 years old	9.3	6.37	1.62	0.68	5.96	1.96	1.03
40–49 years old	19.7	6.51	2.10	1.01	5.62	2.14	1.19
50–59 years old	22.2	6.26	2.56	1.42	4.97	2.22	1.33
60–69 years old	5.8	5.37	2.74	1.74	3.96	2.11	1.39
70–79 years old	1.5	3.66	2.28	1.64	2.53	1.61	1.17
Average across age and gender		6.17	2.27	1.22	5.51	2.29	1.35

[a] All calculations assume a 1.5% yearly probability that an unaided smoker will quit for 12 months and a lifetime relapse rate of 37% for smokers who are abstinent for 1 year
[b] The distribution of ages and genders of 6 month abstainers in the study population

CI for the abstinence rate estimated from currently available varenicline trials (28.9–37.8%) [1].

Costs per nonsmoker in the baseline scenario are presented in Table 2. Cost per additional 6-month and additional lifetime quitter are similar across the three groups with the cost for the Web group being slightly lower. The cost per enrollee for the Web group ($373) was lower than the other two groups ($480 and $519), nevertheless the Web group was only modestly more cost effective ($2,601 per additional lifetime quitter versus $2,995 and $3,291 for the Web and PTC-Web groups, respectively), due to a marginally lower 6 month nonsmoking rate.

Table 2 also contains study results with respect to cost per LY and QALY saved under baseline assumptions. The cost per LY saved varied

Table 2 | Cost-effectiveness with respect to 6 month and lifetime nonsmoking rates

	Combined varenicline and behavioral therapy		
	Web	PTC	PTC-Web
Number in treatment group	401	402	399
6-month nonsmoking rate (%)	30.7	34.3	33.8
Adjusted for biochemical validation	29.2	32.6	32.1
95% confidence interval	24.7–33.6	28.0–37.2	27.5–36.7
Estimated 12-month nonsmoking rate (%)[a]	22.7	25.4	25.0
Estimated lifetime nonsmoking rate (%)[b]	14.3	16.0	15.8
Cost of interventions per enrollee ($)			
Behavioral intervention ($)	120.10	226.95	266.62
Varenicline costs ($)	252.68	252.68	252.68
Total cost per enrollee ($)	372.78	479.63	519.30
Cost per additional nonsmoker at 6 months ($)	1,278	1,472	1,617
Cost per additional lifetime quitter ($)	2,601	2,995	3,291
Cost per LY saved ($)[c]	1,148	1,320	1,450
Cost per QALY saved ($)[c]	1,136	1,308	1,437
95% CI for cost per QALY saved($)[d]			
Lower Limit	917	1,069	1,171
Upper Limit	1,493	1,685	1,858

PTC proactive telephone calls; *Web* Web plus one proactive telephone call; *PTC-Web* Combination of PTC and Web behavioral treatment
[a] Calculated by multiplying the biochemically adjusted 6 month nonsmoking rate by the complement of the relapse rate from 6 to 12 months
[b] Calculated by multiplying the estimated 12-month nonsmoking rate by the complement of the lifetime relapse rate
[c] Cost per lifetime quitter divided by LYs (or QALYs) saved per lifetime quitter, averaged over the age and gender distribution of 6 month self-reported abstainers
[d] Confidence interval based on corresponding upper and lower limits on biochemically adjusted 6 month abstinence rate

Table 3 | Parameters used in sensitivity analysis

Parameter	Cost-effectiveness scenario		
	Baseline	Pessimistic	Optimistic
Spontaneous unaided yearly quit rate (%)	1.5	2.5	0.5
Six-month nonsmoking rates (%)[a]			
Web with varenicline	29.2	24.7	33.6
PTC with varenicline	32.6	28.0	37.2
PTC-Web with varenicline	32.1	27.5	36.7
Relapse rate from 6 months to 12 months (%)	22.0	26.4	17.6
Relapse rate for 12-month quitters (%)	37.0	44.4	29.6
Cost of Web ($)	120.10	144.12	96.08
Cost of PTC ($)	226.95	272.34	181.56
Cost of PTC-Web ($)	266.62	319.94	213.30
Cost of varenicline ($)	252.68	303.22	202.14
Discount rate for LYs and QALYs (%)	3.0	5.0	0.0

PTC proactive telephone calls, *Web* Web plus one proactive telephone call, *PTC-Web* Combination of PTC and Web behavioral treatment
[a] Six-month nonsmoking rates reduced by 5% to reflect estimated percentage of respondents whose self-reports would not be biochemically verified

narrowly from $1,148 to $1,450 and the cost per QALY saved varied between $1,136 and $1,437. Upper and lower confidence limits on cost per QALY (based on corresponding confidence limits for the 6 month abstinence rate) vary from the point estimates by −20% to 31%.

The parameters used in developing pessimistic and optimistic scenarios for sensitivity analysis are shown in Table 3. The 6 month nonsmoking rates were set at the limits for the 95% confidence intervals; the spontaneous unaided yearly quit rates at 0.5% and 2.5% (relatively low and high values in the literature); the discount rates at 0% and 5% (two common values for sensitivity analyses); and other parameters at plus or minus 20% of the baseline values.

The results for the pessimistic and optimistic scenarios are shown in Table 4. Under the pessimistic scenario (see upper half of Table 4), the cost for each additional 6-month nonsmoker ranged from $1,810 to $2,264. The cost per additional lifetime quitter ranged from $4,423 to $5,532. The cost per LY saved ranged from $3,623 to $4,531 and the cost per QALY saved ranged from $3,274 to $4,095. Under the optimistic scenario (see lower half of Table 3), the cost for each additional 6-month nonsmoker ranged from $887 to $1,132, and the cost per lifetime quitter ranged from $1,529 to $1,952. Cost per LY and

Table 4 | Cost-effectiveness using pessimistic and optimistic scenarios

	Varenicline–counseling combined therapy		
	Web	PTC	PTC-Web
PESSIMISTIC SCENARIO			
LY saved per lifetime quitter[b]	1.22	1.22	1.22
QALYs saved per lifetime quitter[b]	1.35	1.35	1.35
6 months nonsmoking rate (%)[a]	24.7	28.0	27.5
Lifetime nonsmoking rate (%)	10.1	11.5	11.3
Cost per additional nonsmoker at 6 mo ($)	1,810	2,055	2,264
Cost per additional lifetime quitter ($)	4,423	5,023	5,532
Cost per LY saved ($)[b]	3,623	4,114	4,531
Cost per QALY saved ($)[b]	3,274	3,718	4,095
OPTIMISTIC SCENARIO			
LYs saved per lifetime quitter[b]	6.17	6.17	6.17
QALYs saved per lifetime quitter[b]	5.51	5.51	5.51
6 months nonsmoking rate (%)[a]	33.6	37.2	36.7
Lifetime nonsmoking rate (%)	19.5	21.6	21.3
Cost per additional nonsmoker at 6 mo ($)	887	1,032	1,132
Cost per additional lifetime quitter ($)	1,529	1,780	1,952
Cost per LY saved ($)[b]	248	289	317
Cost per QALY saved ($)[b]	278	323	354

PTC proactive telephone calls, *Web* Web plus one proactive telephone call, *PTC-Web* Combination of PTC and Web behavioral treatment
[a] Adjusted by multiplying the 95% confidence bound limits for the self-reported 6 month nonsmoking rate by 95% to adjust for an estimated 5% of responses that would not have been verified by biochemical testing
[b] Cost per lifetime quitter divided by the LYs (or QALYs) saved per lifetime quitter, averaged across the age and gender distribution of the study population

QALY saved range from $278 to $354. There are only modest differences between groups in either the pessimistic or optimistic scenarios.

DISCUSSION

A meta-analysis of three phase 3 clinical trials found varenicline to be substantially more effective than bupropion [47] (OR=1.56, 95% CI 1.10–2.21, P=0.01). Although those clinical trials used 300 mg of bupropion, in a previous study of bupropion [22], we found that the Free & Clear PTC behavioral therapy combined with 150 and 300 mg yielded very comparable 12-month quit rates (31.4% and 33.2%, respectively), suggesting that the OR from clinical trials would also hold for varenicline versus 150 mg bupropion. With varenicline, the cost per enrollee in this study was $373 for the Web group and $519 for the PTC-Web group. If 150 mg generic bupropion ($95 per enrollee using the same pharmacies as for varenicline) had been substituted for varenicline, the cost would have been $215 and $361, respectively. Thus, the cost ratio varies between 1.44 and 1.73, leading to the conclusion that cost-effectiveness for bupropion and varenicline may be roughly equivalent. We note that the observed 6-month nonsmoking rate in this study for the PTC and PTC-Web group in this study (34.3% and 33.8%, before adjustment for biochemical validation) are approximately equal to the observed 12-month rates seen for varenicline [22], suggesting that, in a real-world situation, the abstinence rates for varenicline and bupropion may be more similar than suggested from the clinical trials and that cost-effectiveness may favor generic bupropion.

Prior cost-effectiveness analyses for varenicline differed from the current analysis in that they have (1) relied on efficacy results from clinical trials that compare varenicline with bupropion, nicotine replacement therapy, or placebo; (2) have utilized the Benefits of Smoking Cessation on Outcomes (BENESCO) simulation model (which reduces intervention costs by expected cost reductions from reduced incidence of smoking-related diseases); and (3) have calculated incremental cost-effectiveness (i.e., the net cost per additional quit) [48–50]. The current analysis is not directly comparable to those estimates since it uses real-world quit rates; all groups receive varenicline and consequently the comparison group is continuing smokers, and costs are exclusive of changes in medical costs (including both costs of smoking-related diseases and costs for medical services used as a result of additional years of life).

Solberg et al. [43] identified 13 economic evaluations of smoking cessation in the USA that excluded cost-offsets from smoking-related illness with costs per quit ranging from $1,000 to $4,000. This range is comparable to the cost per lifetime quitter in our study which ranged from $2,601 to $3,291.

The smoking cessation interventions in our study compare favorably with other generally accepted preventive health strategies with respect to cost per LY saved [32, 51–55]. Tengs et al. [52] reviewed 500 life-saving interventions and after adjusting for inflation (to 1993 dollars), discount rate (5%), and excluding indirect costs, the median intervention cost was $42,000 per LY saved. Warner [56] states "a life-year saved at a cost of less than $20,000 (the highest cost estimate in the smoking cessation treatment literature) constitutes a very worthwhile investment." In addition, as noted by Oster et al. [37], the relative cost-effectiveness of smoking cessation treatments may be underestimated because they are relatively brief and incur only relatively minor adverse effects. Under the optimistic scenario the cost per LY and QALY saved range from $278 to $354, making these treatments similar to vaccines in terms of cost-effectiveness.

Discounting has a substantial effect on the benefit of smoking cessation in terms of LYs saved as well as having differential effects for different age groups. As the discount rate changes from 0% to 5%, the average number of discounted life-years saved is reduced a factor of 5.1. Furthermore, the effect of discounting on younger adults is greater than on older adults. Without discounting, the expected LY savings for a 25-year-old male lifetime quitter is 6.52 LYs, whereas the comparable savings for a 75-year-old male is only 2.77 LYs. However, with a discount rate of 3.0%, the savings advantage is reversed (i.e., 1.43 and 1.90, respectively) since the life-years saved for the younger quitter occur many years into the future and consequently have a relatively small present value. These two factors makes it difficult to compare cost-effectiveness estimates in the literature unless discount rates are equal and the population age (and gender) distributions are comparable.

Website content was purposefully developed to be duplicative of the content in the calls from the telephone counselors. As a result, the PTC-Web participants may not have felt the need to study the information on the Website as thoroughly as participants in the Web group. This may explain the finding that the number of minutes spent on the Website by PTC-Web participants was approximately half of the number of minutes spent by the Web participants.

The findings of this study should be interpreted cautiously because of limitations inherent in the methodology and assumptions. The data used to derive mortality rates for quitters was obtained from the Cancer Prevention Study (CPS) II database, and the participants in that study are generally acknowledged to be healthier than the general US population. This will tend to result in an overestimation of LYs saved for the general population (although not necessarily for managed care populations of generally healthy individuals). However, no adequate method for adjusting for the better health status of the CPS II population (relative to the general US population) is apparent. Estimates of mortality rates were extrapo-

lated to ages younger than 45 years and older than 79 years and quality of life was extrapolated to ages younger than 25 years and older than 69 years. Extrapolation involves assumptions concerning the applicability of relationships observed in some age groups to other age groups and may not be accurate.

The study sample used in these analyses was predominantly Caucasian and middle-class, and consisted of volunteers who knew that they would receive varenicline. Smoking cessation rates achieved in this population may not be reflective of smoking cessation rates in the general population. The study also was not blinded and did not include a medication placebo group. The study did not include biochemical verification of smoking cessation, although requiring verification can result in a response bias unrelated to abstinence. Also, we adjusted the 6-month nonsmoking rate by the expected prevalence of nonvalidation. For the trial, nonrespondents at 6 months were classified as smokers. This may have decreased the 6-month cessation rates and the estimates of cost-effectiveness.

Our baseline scenario assumed a constant spontaneous unaided yearly quit rate of 1.5%. Other research [57] suggests that quit rates increase with age. However, some of these increases may be due to poorer health status with increasing age, increased interventions by physicians to encourage their patients to stop smoking, or greater use of smoking cessation aids. More research is necessary to quantify the relationship between the spontaneous unaided quit rate and age.

In summary, smoking cessation treatment consisting of varenicline combined with a telephone-based or Web-based counseling program (with one proactive telephone call) had similar cost-effectiveness, with a slight advantage for the Web intervention over PTC or PTC-Web, and were as cost-effective as many other smoking cessation interventions discussed in the literature, quite likely including generic bupropion SR combined with a PTC program. The cost per LY and QALY saved were sufficiently low for all modalities to rate any of these smoking cessation interventions as among the most cost-effective of life-saving medical treatment.

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Future studies: These results suggest avenues for future work, including the following: (1) studying the role of adherence and its impact on cost-effectiveness; (2) studying the cost-effectiveness of these treatments delivered via other means such as cell phone, Twitter, and Facebook, especially for teenage and young adult smokers, and (3) identifying subgroups of individuals for whom the cost-effectiveness is especially high or low.

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