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Cost-Effectiveness of Real World Administration of Tobacco Pharmacotherapy in the United States Veterans Health Administration

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None. The authors have no competing interests to declare. Authors have had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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ABSTRACT

Background and aims. Cost-effectiveness studies in randomized clinical trials have shown that tobacco cessation pharmacotherapy is among the most cost-effective of health care interventions. Clinical trial eligibility criteria and treatment protocols may not be followed in actual practice. This study aimed to determine whether tobacco cessation pharmacotherapy is cost-effective in real-world settings.

Design. A retrospective analysis of costs and outcomes

Setting. Hospitals and clinics of the US Veterans Health Administration, USA.

Participants: A total of 589,862 US veterans who screened positive for tobacco use in 2011.

Intervention and comparator. Tobacco users who initiated smoking cessation pharmacotherapy in the 6 months after screening were compared with those who did not use pharmacotherapy in this period. Pharmacotherapy included nicotine replacement theapy, bupropion (if prescribed at 300 mg per day or specifically for tobacco cessation), or varenicline.

Measures. Effectiveness was determined from responses to a subsequent tobacco screening conducted between 7 and 18 months after the treatment observation period. Cost of medications and prescribing health care encounters was determined for the period between initial and follow-up tobacco use screening. Multivariate fixed -effects regression was used to assess the effect of initial treatment status on cost and outcome while controlling for differences in case-mix with propensity weighting to adjust for confounding by indication.

Findings. 13.0% of participants received tobacco cessation pharmacotherapy within 6 months of initial screening. After an average of an additional 218 days follow-up, those who initially received pharmacotherapy incurred $144 in additional treatment cost and had a 3.1% absolute increase in tobacco quit rates compared with those who were not initially treated. This represents an incremental cost-effectiveness ratio of $4,705 per quit. The upper limit of the 99.9% confidence region was $5,600 per quit. Without propensity adjustment, the cost-effectiveness ratio was $7,144 per quit, with the upper limit of the 99.9% confidence region $9,500/quit.

Conclusions. Tobacco cessation pharmacotherapy provided by the US Veterans Health Administration in 2011/12 was cost-effective in this real-world setting, with an incremental cost-effectiveness ratio of $4,705 per quit.

INTRODUCTION

Randomized clinical trials (RCTs) indicate that tobacco use can be successfully treated using tobacco cessation pharmacotherapy, including nicotine replacement therapy (NRT), bupropion, and varenicline (1). However, the efficacy demonstrated in trials does not necessarily translate to equivalent effectiveness in actual practice (2) because treatment is extended to patients who may not meet strict eligibility criteria, including those with co-occurring substance use disorders and serious mental illness. Furthermore, treatment may not follow the protocol used in trials, including adjuvant counseling (3).

While some studies in real-world settings have found tobacco pharmacotherapies to be effective (4, 5), especially when accompanied by behavioral support or brief advice (6), others studies have found that increased use of NRT has not improved long-term quit (7) or relapse rates (8). Such observational studies have been limited by small sample sizes, lack of covariates and concerns over study design, including the non-random nature of treatment assignment, which may result in selection bias (9-11).

Cost-effectiveness studies based on cost and outcomes observed in clinical trials have determined that tobacco cessation pharmacotherapy is among the most cost-effective health care interventions (12-14). Real-world cost-effectiveness may differ. As treatment is expanded to reach smokers who are harder to treat, more resources are required to achieve a successful quit, and cost-effectiveness can be expected to decline (15).

The United States Veterans Health Administration (VHA) expanded its tobacco cessation program in 2004, increasing the percentage of tobacco using patients who received a pharmacotherapy from 13.8% in 2004 to 26.8% in 2008 (16). In a recent study published in *Tobacco Control*, we studied 589,862 Veterans who screened positive for tobacco use at VHA in 2011 and found that (controlling for case-mix and confounding by indication) quit rates for those who received pharmacotherapy were significantly higher than that in those who were not treated, 19.8% versus 16.7% ($p<0.001$) (17). In the current paper, we test the hypothesis that tobacco cessation pharmacotherapy is cost-effective in the real world setting of VHA.

METHODS

This retrospective cohort study was assembled using data extracted from Electronic Medical Record (EMR) of VHA, including information on tobacco status recorded in response to clinical reminders (18), dispensed prescriptions for tobacco cessation pharmacotherapy, patient demographics, and diagnoses assigned in inpatient stays and outpatient visits. The study protocol was approved by the Institutional Review Boards (IRBs) at the Ann Arbor and VA Palo Alto VHAs. Approval was granted for retrospective use of data from the date of the IRB submission, September 30, 2013.

Sample

The participants included VHA outpatients identified as using tobacco in routine screening conducted in the year that ended on September 30, 2011. The treatment observation

period was the 6 months after initial screening. Outcomes were as assessed in the last tobacco use screening that occurred within 7 and 18 months after the end of this treatment observation period.

To focus the evaluation on the initiation of new episodes of tobacco cessation pharmacotherapy, patients were excluded if they had used pharmacotherapy in the 12 months prior to the index date (19). Also excluded were those whose EMR had missing data on race, follow- up tobacco use, or other covariates needed to adjust for the propensity to receive pharmacotherapy. Of 838,309 tobacco users without pharmacotherapy in the prior year, 53,218 (6.3%) were excluded because of missing data (chiefly race or ethnicity) and 195,229 (23.3%) were excluded because there was no follow-up tobacco use assessment. Complete details on the cohort are reported in an earlier paper on pharmacotherapy effectiveness (17).

Measures

Treatment. Participants were deemed treated if NRT, bupropion, or varenicline was released to the Veteran either in person or by mail during the 6-month period following the initial screening. Since bupropion can be prescribed for purposes other than tobacco cessation, bupropion was regarded as tobacco cessation pharmacotherapy only if the prescription was labeled as being for tobacco cessation or if it was prescribed at a dose of 300 mg per day, the dosage approved by the Food and Drug Administration for tobacco cessation. Lower dosages of bupropion, typically used for depression, but not for tobacco treatment, were not considered cessation pharmacotherapy.

Outcomes. Outcomes were based on the results of tobacco use screening that was approximately 12-months after the initial assessment. A 12 month follow-up period is recommended for the evaluation of tobacco cessation interventions (20-22). Screenings are not scheduled, but provided during routine visits according to VHA policy to provide tobacco users with annual screening. Outcomes were determined using the results of the last tobacco use screening that occurred between 7 and 18 months after the index date. Since preference rated health related quality of life, the information needed to express outcomes in terms of Quality Adjusted Life Years (the standard outcome used for cost-effectiveness analysis) is not routinely gathered and was not available in the electronic medical record, cost-effectiveness was determined as the cost per quit, a measure reported by most economic evaluations of randomized trials.

Case-Mix. Case-mix measures were patient characteristics available in the EMR that are known to affect quit rates, including age, sex, race, and ethnicity, as well as psychiatric, substance abuse, and medical comorbidities (23-28) assigned in encounters in the 12 months prior to the initial tobacco use screening. Medical comorbidities were defined using the most recent update of the method developed by Elixhauser (23).

Cost. Cost and quantity of tobacco cessation pharmacotherapy were determined for the treatment period (from initial screening until 6 months later) and for the follow-up period (from the beginning of the seventh month until the date of the follow-up tobacco use assessment). Cost was assessed from the perspective of VHA, which is both the health care provider and the

health care sponsor. The direct cost of medication was the VHA acquisition cost as recorded in prescription records. Implausibly extreme values for the unit cost of a dispensed prescription of pharmacotherapy were corrected by using the median unit cost of the medication for records with costs below the 10th or above the 90th percentile (or for NRT nasal spray, because of the increased variability in this small number of records, below the 25th or above the 75th percentile). Pharmacy costs other than medication (including supplies, labor costs, and overhead) were determined by analysis of the VHA Managerial Cost Accounting system. These non-medication costs were included by adding 66% to the direct medication cost of NRT, 56% to the medication cost of bupropion, and 48% to the medication cost of varenicline.

Because VHA provides tobacco cessation pharmacotherapy only by prescription, the cost of patient evaluation and pharmacotherapy prescription was included. A cost of $27 was assigned for new prescriptions. This was the 2013 Medicare reimbursement for intensive tobacco use cessation counseling during an office-based visit (CPT code 99407). Additional cost was added for each new prescription. No additional evaluation cost was assigned for a second prescription filled on the same day, or for prescription refills. Since both treated and untreated individuals had an initial and follow-up tobacco use assessment, a cost for these assessments was not included as it would not affect estimates of the incremental cost of treatment. Tobacco cessation counseling was not consistently identifiable in VA utilization data and its cost was not included.

Current evidence is contradictory on whether tobacco use cessation is associated with increased or decreased subsequent health care utilization and cost (29-31). Moreover, human studies only allowed retrospective data collection from the date of approval. For these reasons, a short-term horizon was adopted with the assumption that neither cessation nor continuation effects health care cost. Costs were adjusted to 2013 U.S. Dollars using the Consumer Price Index for urban consumers for all items.

Statistical analysis

The effect of pharmacotherapy treatment was estimated using generalized linear regression models with the independent variable an indicator representing receipt of treatment in the initial 6 months of observation. A logistic regression was used for discrete dependent variables (quit, use of pharmacotherapy), negative binomial regression for count dependent variables (quantity of pharmacotherapy received), and gamma regression for cost dependent variables.

Fixed effects regression models were estimated. These fixed effects were indicator variables for the facility where the initial tobacco use assessment took place. They were included to control for unmeasured facility-level differences in the use of pharmacotherapy and location-specific differences affecting tobacco use, such as tobacco tax rates and smoking regulations.

Propensity Weighting. Since participants were not randomly assigned to treatment, propensity weighting was used to adjust for selection bias. Observations were weighted by the

inverse of the probability of receiving the treatment the subject actually received during the 6 month treatment period (32). The inverse probability of treatment weight (IPTW) increases the influence of observations with an unlikely assignment (e.g., Veterans with characteristics suggesting they would receive treatment who were not treated) and decreases the influence of observations with a likely assignment (e.g., Veterans with characteristics suggesting they would receive treatment who were treated). This correction is designed to approximate the randomized assignment of treatment in a RCT. It is comparable to the weights that are used adjust surveys so that they represent the population being sampled.

IPTWs were estimated from a multivariable logistic regression model that used pharmacotherapy initiation as the dependent variable and patient demographics and diagnoses as independent variables (33). To provide the best possible predicted propensity, the model included diagnosis indicator variables, polynomial terms for age, counts of psychiatric and medical conditions, and interaction terms of age by each psychiatric and medical diagnosis. The propensity model also included facilities as fixed effects.

Plots of propensity to receive treatment by treatment groups were evaluated and it was determined that overlap was sufficient to justify adjustment by IPTW. Standardized mean difference in covariates between treatment groups of less than 0.10, a frequently used criterion for adequacy of covariate balancing, was used as the threshold to evaluate if adjustment for baseline differences was adequate (34, 35). Unadjusted analysis was contrasted to the IPTW adjusted findings to provide information on the effect of adjustment.

Cost-effectiveness analysis. The incremental cost-effectiveness ratio (ICER) was estimated as the incremental cost (difference in propensity weighted mean cost) per additional quit (difference in propensity weighted proportion that quit) over the short-term, the interval between screenings (the 6 months of the medication observation period plus an additional 7 to 18 months until the follow-up screening).

Bootstrap sampling was used to estimate the uncertainty of the ICER. Each replicate included 589,862 observations obtained by selecting randomly with replacement from study data. The probability of selection was proportional to the observation's IPTW. The criterion for statistical significance was a probability of less than 0.001 for a Type I statistical error. The upper limit of the 99.9% confidence region of the ICER was found in 1,000 bootstrap replicates.

RESULTS

There were 589,862 individuals who met study inclusion criteria. Table 1 compares the 76,739 (13.0%) initially treated (those who received pharmacotherapy within 6 months of the initial screening for tobacco use) to the 513,123 (87.0%) tobacco users who were not initially treated. Those initially treated had more psychiatric comorbidities, except for schizophrenia, which was more common among those not initially treated. Those initially treated had fewer medical comorbidities but more chronic obstructive pulmonary disease and cirrhosis than those not initially treated.

Table 1 also shows the standardized differences in the mean values of covariates between groups defined by initial treatment status. Unweighted differences exceeded 0.10 standard

deviations for 5 of the 44 baseline characteristics, suggesting some important difference between the groups. After IPTW adjustment, the standardized difference of all covariates had an absolute value of less than 0.10. The use of propensity adjustment was supported by the substantial overlap in predicted probabilities between treatment groups: range 0.0047-0.7734 for those initially treated and 0.0010-0.7584 for those not initially treated. Because of this overlap, and because standardized differences were reduced by adjustment, trimming of observations with extreme probability values was deemed unnecessary.

Table 2 describes the use of tobacco cessation pharmacotherapy during the initial 6-month treatment observation period in those initially treated. NRT was received by 77.7%, bupropion was received by 26.7%, and only 5.6% received varenicline. Some participants had more than one treatment, and the total exceeds 100%. On average, the cost of treatment during the initial period was $120.51, including $81.58 medication cost and $38.93 prescribing cost.

Use and cost of tobacco cessation pharmacotherapy in the follow-up period is presented by treatment group in Table 3. During the follow-up period, 28.2% of those initially treated received pharmacotherapy, however (as might also occur in an RCT) some (8.2%) of those not initially treated received pharmacotherapy in the follow-up period ($p < 0.001$). Tobacco pharmacotherapy cost during the follow-up period was greater in those initially treated versus those not initially treated ($32.70 versus $9.42, $p < 0.001$). The average length of the follow-up period was slightly longer among those initially treated (220.6 days versus 218.1 days, $p<0.001$).

Table 4 compares the cost and outcomes by treatment group and reports the ICER. The average cost among those initially treated was $143.79 greater than those not initially treated ($153.21 versus $9.42, p <0.001). The absolute difference in percentage quit was 3.06% more in the initially treated group (19.73% versus 16.67%, p < 0.001). The ICER was $4,705 per quit ($4705=$143.79/0.0306). Bootstrap evaluation of study data found a standard error of $233/quit. Uncertainty of the estimate of cost per quit was also plotted on a cost-effectiveness acceptability curve (Figure 1). The upper limit of the 99.9% confidence region of the ICER was $5,600/quit (that is, 99.9% of 1,000 bootstrap replicates had an ICER below this threshold).

Cost effectiveness was also determined without propensity adjustment (also shown in Table 4). Bootstrap sampling with equal probability and with replacement found increment cost of pharmacotherapy was $147.98 ($157.24 in initially treated versus $9.26 in not initially treated) and the incremental effectiveness was 2.07% additional quits (18.80% quit in initially treated vs. 16.73% quit in not initially treated). The ICER was $7,144 per quit, (7,144 =147.98/.0207) with a standard error of $514/quit. The upper limit of the 99.9% confidence region of the unadjusted ICER was $9,500/quit.

DISCUSSION

This study of real-world practice found that Veterans who use tobacco and initiated a new episode of cessation pharmacotherapy incurred $143.79 in additional cost, with a 3.1% greater absolute rate of quitting tobacco. The resulting incremental cost-effectiveness ratio of $4,705 per quit was similar to that found by RCTs (36, 37). For example, Ronckers

standardized the cost-effectiveness ratios found by 23 economic evaluations of cessation studies and found the interquartile range of these estimates was $2,160-$5,180 per quit (all cost-effectiveness estimates from the literature in this discussion were converted to 2013 U.S. dollars to be comparable to the findings of this study). Moreover, the interquartile range of 15 studies reviewed by Shearer was $2,080-$4,030 per quit. This suggests that tobacco cessation pharmacotherapy in a real-world setting delivers similar value as has been demonstrated in RCTs.

Previous estimates of the cost-effectiveness of tobacco cessation pharmacotherapy have relied on data from RCTs, many of which excluded potential participants with substance use disorders or serious mental illness. Since these conditions are associated with lower treatment success and higher relapse rates (38, 39), it is possible that existing cost-effectiveness estimates are overly optimistic. This is an especially important concern because those with these conditions are more likely to use tobacco (38, 40, 41). This study included many tobacco users with substance use disorders and serious mental illness and found the ICER to be comparable to other RCTs, suggesting that this concern may not be warranted. Further study of cost-effectiveness of specific pharmacotherapies in different patient sub-groups is needed.

This study did not express outcomes in terms of Life Years or Quality Adjusted Life Years or consider long-term relapse or quit rates. Models of cost-effectiveness of tobacco cessation pharmacotherapy have found that over the long-run, successful quitters gain about two years of life relative to those who did not quit (42). If those who initially received

pharmacotherapy in this study realized a similar benefit, cessation pharmacotherapy as practiced by VHA would be estimated to have an ICER of about $2,350 per life year. This is consistent the cost-effectiveness of tobacco cessation treatments found in other studies, which report ICERs that range from $1,210-$4,546 per life year gained (42). These values are quite low compared to other health care interventions, making tobacco cessation among the most cost effective of health services (15).

The size of the effect of pharmacotherapy was small, in part because the quit rate in the group not initially treated was 16.7%, higher than the 5%–6% annual quit rates observed in other populations (43, 44). This is consistent with some clinical trials that have noted high quit rates in their control groups (8, 45). Although the effect size found it this study was small, it was sufficiently large relative to the cost of the intervention to be considered cost-effective.

The study did not include the cost of behavioral counseling beyond that provided by the provider during the visit in which a new tobacco cessation pharmacotherapy was prescribed. Other tobacco cessation counseling cannot be easily identified in the EMR, as it is often provided as part of a visit in which other services are provided. This study did not include the cost of this additional counseling, possibly understating the cost of pharmacotherapy. Participants who did not receive pharmacotherapy were also screened for tobacco use and were likely to have received at least brief advice to quit. Such brief advice and the receipt of pharmacotherapy in the follow-up period may explain the high quit rate in the group that was not initially treated.

It was assumed that higher doses of bupropion were prescribed for smoking cessation, but these higher doses may have been prescribed for depression. About 6% of the potential cohort was excluded because data for race were missing. Sensitivity analyses involving alternative criteria for defining bupropion for tobacco cessation, and including observations with missing data on race (and excluding race from the covariates) showed little effect on the estimate of treatment effectiveness (17). These sensitivity analyses were not repeated for this cost-effectiveness study.

Cost-effectiveness analysis without adjustment by IPTW weights results in a cost-effectiveness ratio that is higher than when propensity adjustment is used. This difference suggests that tobacco users with a lower chance of quitting are more likely to get pharmacotherapy; adjustment for this imbalance improves cost-effectiveness, reducing the incremental cost effectiveness ratio from $7,144/quit to $4,407/quit. Even without propensity adjustment, pharmacotherapy cost less than $9,500 per quit in 99.9% of the bootstrap replications .

This evaluation of treatment as actually practiced comes with the risk of bias from non-random assignment. Even though we used best practices for adjusting for confounding by indication, re-weighting observations to approximate the result of random assignment, this method relies on the untestable assumption that the observed covariates fully account for propensity to receive treatment. However, the strength of real world observational studies such as this one is the generalizability that is not realized in RCTs.

CONCLUSION

This observational study used propensity adjustment to control for non-random treatment assignment and found that tobacco cessation pharmacotherapy as currently provided by VHA has an incremental cost-effectiveness ratio of $4,705 per quit. This finding adds to the evidence that these medications deliver sufficient value to justify their cost.

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Table 1. Percent baseline patient characteristics by tobacco cessation pharmacotherapy treatment group and standardized weighted and unweighted differences (n=589,862)

Characteristics	Initially Treated (N=76,739)	Not Initially Treated (N=513,123)	p-Value*	Standardized Difference, Unweighted**	Standardized Difference, Weighted***
Psychiatric Diagnosis					
Depression	32.8	25.2	<.001	0.168	0.028
Bipolar Disorder	5.3	3.8	<.001	0.072	0.003
Schizophrenia	3.2	4.0	<.001	-0.044	-0.037
Post-Traumatic Stress Disorder	18.7	15.1	<.001	0.095	0.005
Alcohol	18.6	15.8	<.001	0.076	-0.005
Other Substance Use Disorders	13.3	10.2	<.001	0.097	0.001
Other Anxiety	13.0	10.5	<.001	0.079	0.002
Other Psychosis	1.6	1.6	0.884	-0.001	-0.014
Medical Comorbidity					
Congestive Heart Failure	2.9	3.5	<.001	-0.035	0.003
Cardiac Arrhythmia	5.5	6.9	<.001	-0.060	-0.004
Valvular Disease	1.2	1.6	<.001	-0.032	0.000
Pulmonary Circulation Disorders	0.6	0.6	0.251	-0.004	0.002
Peripheral Vascular Disorders	6.7	7.1	0.001	-0.013	0.014
Hypertension Uncomplicated	48.7	55.7	<.001	-0.139	-0.016
Hypertension Complicated	0.7	1.2	<.001	-0.045	-0.005
Paralysis	0.6	0.7	<.001	-0.014	-0.004
Other Neurological Disorders	2.8	3.4	<.001	-0.033	-0.018
Chronic Obstructive Pulmonary Disease	20.6	18.7	<.001	0.047	0.045

Diabetes Uncomplicated	18.1	21.9	<.001	-0.096	-0.012
Diabetes Complicated	4.2	5.2	<.001	-0.045	-0.002
Hypothyroidism	4.0	4.8	<.001	-0.037	-0.010
Renal Failure	2.4	3.7	<.001	-0.079	-0.010
Liver Disease	4.4	4.1	<.001	0.015	-0.001
Peptic Ulcer Disease excluding bleeding	0.9	1.0	0.001	-0.013	-0.001
AIDS/HIV	0.7	0.7	0.993	0.000	-0.002
Lymphoma	0.4	0.4	0.016	-0.010	0.001
Metastatic Cancer	0.2	0.3	0.018	-0.009	-0.001
Solid Tumor without Metastasis	5.5	6.4	<.001	-0.040	0.004
Rheumatoid Arthritis	1.5	1.6	0.134	-0.006	-0.001
Coagulopathy	0.8	1.0	<.001	-0.027	-0.006
Obesity	14.7	14.8	0.492	-0.003	-0.005
Weight Loss	2.2	2.2	0.941	0.000	0.008
Fluid and Electrolyte Disorders	2.6	3.2	<.001	-0.031	-0.006
Blood Loss Anemia	0.1	0.1	0.949	0.000	0.002
Deficiency Anemia	1.3	1.7	<.001	-0.035	-0.007
Age Group			<.001		
18-44	20.3	14.9		0.142	0.003
45-54	22.6	18.1		0.112	-0.002
54-64	41.7	41.0		0.014	0.003
65 & over	15.4	25.9		-0.263	-0.005
Male	92.2	94.2	<.001	-0.081	-0.002
Race			0.002		
White	76.8	77.4		-0.014	-0.006
Black	19.5	19.0		0.012	0.005
Other	3.7	3.6		0.006	0.003
Hispanic	3.5	3.5	0.754	0.001	0.002

*From standard chi-square test comparing treated and not treated group of the unweighted cohort (prior to propensity weighting)

**Standardized difference is the difference in means divided by the square root of the pooled variance.

***Weighted standardized differences are based on inverse probability of treatment from a multivariable logistic regression of pharmacotherapy initiation with independent variables age, gender, race, Hispanic ethnicity, 8 psychiatric/substance use disorder diagnoses, 27 medical diagnoses, facility fixed effects, count of psychiatric/substance use diagnoses, count of medical conditions, age-squared, age-cubed, interactions of age with each psychiatric and medical diagnosis.

Table 2. Propensity-adjusted tobacco cessation pharmacotherapy utilization & cost in initial treatment period among those treated for tobacco use (N=76,739)

Type of pharmacotherapy	Percent receiving different types of pharmacotherapy	Unit	Mean quantity of pharmacotherapy	Mean cost of pharmacotherapy (US 2013 dollars)
NRT patch	58.7	days' supply	28.6	44.37
NRT gum	18.4	pieces	39.7	9.79
NRT lozenge	11.7	pieces	21.4	10.69
NRT inhaler	0.08	cartridges	0.22	0.23
NRT nasal spray	0.017	10 ml bottles	0.0011	0.05
Any type of NRT	77.7	N/A	N/A	65.13
Bupropion	26.7	days' supply	19.7	6.98
Varenicline	5.6	days' supply	2.5	9.47
Any type of pharmacotherapy	100.0			81.58
Prescription visits				38.93
Total cost, initial period				120.51

N/A=Not applicable NRT=Nicotine Replacement Therapy

Table 3. Propensity-adjusted tobacco cessation pharmacotherapy utilization and cost in follow-up period, by treatment group

	Percent of individuals receiving pharmacotherapy		Mean quantity of pharmacotherapy		Mean cost of pharmacotherapy (US 2011 dollars)	
	Initially Treated	Not Initially Treated	Initially Treated	Not Initially Treated	Initially Treated	Not Initially Treated
NRT patch (days' supply)	11.4%	4.8% *	5.45	2.29 *	7.82	3.29 *
NRT gum (pieces)	4.9%	1.6% *	12.08	3.25 *	2.91	0.78 *
NRT lozenge (pieces)	3.7%	1.1% *	7.86	1.84 *	3.86	0.90 *
NRT inhaler (cartridges)	0.038%	0.009% *	0.11	0.03 +	0.11	0.03 *
NRT nasal spray (10 ml bottles)	0.012%	0.002% *	0.0017	0.0001 *	0.09	0.005 *
Any type of NRT	17.3%	6.4% *			14.78	5.01 *
Bupropion (days' supply)	12.3%	2.2% *	13.41	1.76 *	4.48	0.56 *
Varenicline (days' supply)	1.7%	0.3% *	0.83	0.15 *	3.19	0.59 *
Any type of pharmacotherapy	28.2%	8.2% *			22.45	6.16 *
Prescription visits					10.25	3.26 *
Total					32.70	9.42 *

Initially treated with pharmacotherapy (N=76,739) versus not initially treated with pharmacotherapy (N=513,123)

* $p < .001$; + $p < .05$

Mean follow-up period 220.6 days initially treated versus 218.1 days not initially treated, $p<0.001$
NRT=Nicotine Replacement Therapy

Table 4. Tobacco cessation pharmacotherapy cost, outcomes, and cost-effectiveness by treatment group (propensity-adjusted and unadjusted results)

	Initially treated with pharmacotherapy	Not initially treated with pharmacotherapy	Difference	p-value
Estimates with Propensity Weighting Adjustment for Selection Bias				
Initial period cost	120.51	0.00	120.51	-
Follow-up period cost	32.70	9.42	23.28	<.001
Total cost	153.21	9.42	143.79	<.001
Percent quit tobacco use at follow-up	19.73%	16.67%	3.06%	<.001
Incremental cost effectiveness ratio (cost per quit)		Mean	$4,705/quit	
		Standard Error	± $232.91/quit	<.001
		Upper limit of 99% confidence region	$5,600/quit	
Raw Estimates (No Propensity Adjustment)				
Initial period cost	122.58	0.00	122.58	-
Follow-up period cost	34.66	9.26	25.39	<.001
Total cost	157.24	9.26	147.98	<.001
Percent quit tobacco use at follow-up	18.80%	16.73%	2.07%	<.001
Incremental cost effectiveness ratio (cost per quit)		Mean	$7,144/quit	<.001
		Standard Error	± $513.89/quit	
		Upper limit of 99% confidence region	$9,500/quit	

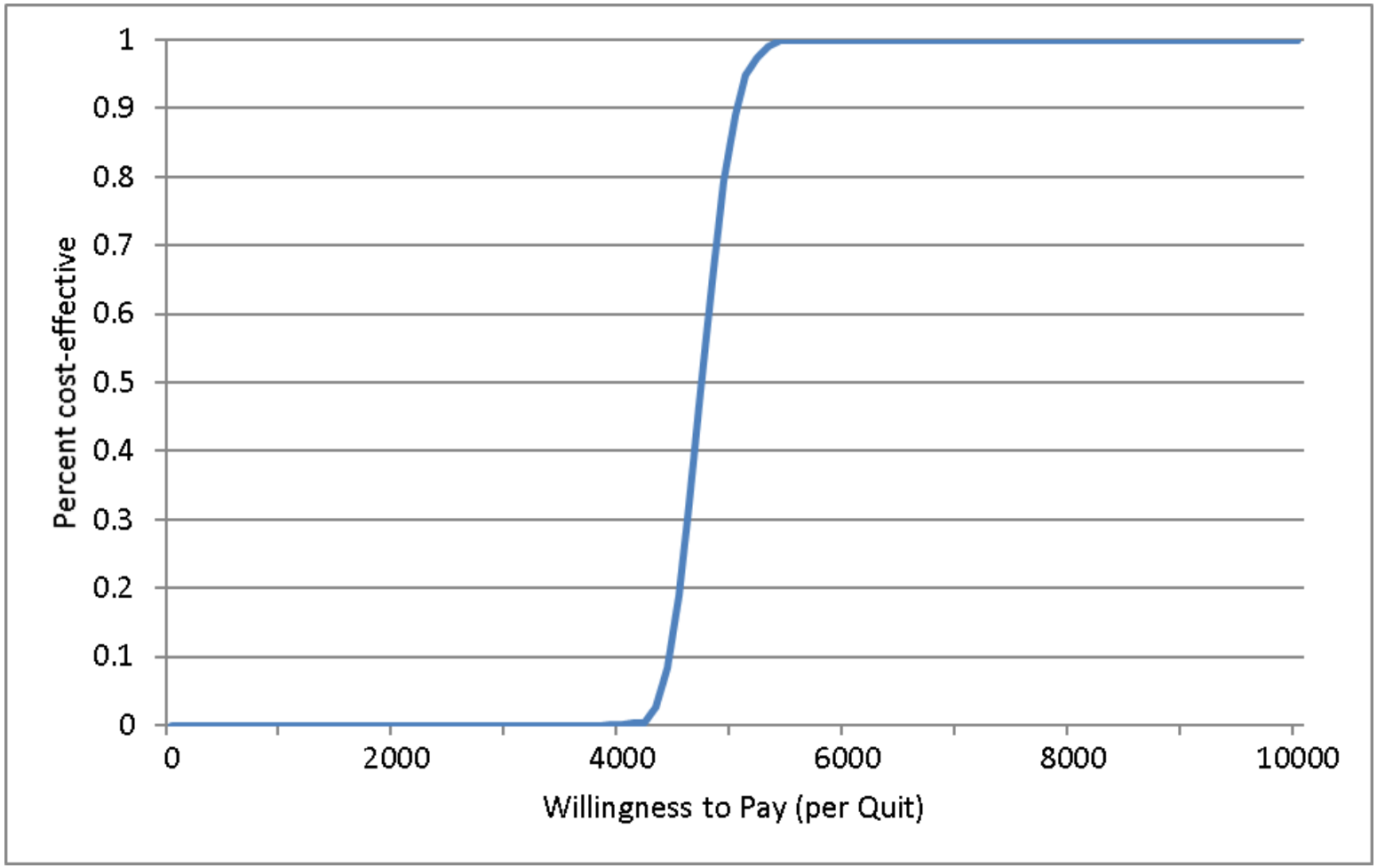

Figure 1. Cost-Effectiveness Acceptability Curve. The upper limit of the 99.9% confidence region of the ICER was $5,600/quit (that is, 99.9% of 1,000 bootstrap replicates had an ICER below this threshold).