

Impact of Medications on Smoking Cessation

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OVERVIEW The proven pharmacotherapies for smoking cessation are nicotine gum, inhaler, nasal spray, and patch (Hughes, 1996; Hughes *et al.*, 1999) and the non-nicotine therapies bupropion (Hughes *et al.*, 1999), and perhaps nortriptyline (Prochazka *et al.*, 1998). All of these methods have been shown to double quit rates compared to placebo in several randomized controlled trials (Hughes, 1996). Because the nicotine nasal spray has had limited sales, the inhaler has just been marketed, and nortriptyline has not been marketed for cessation, the current analyses will focus on nicotine gum, the nicotine patch, and bupropion. Nicotine gum was originally approved in the United States as prescription only (Rx) medication in 1984 as a 2 mg form, and 4 mg nicotine patches were approved as Rx only in 1993. In April 1996, the nicotine gum became available for over-the-counter (OTC) sales. Nicotine transdermal patches, which became available as a prescription device in 1992, were approved for OTC sale in 1996. In May of 1997, bupropion became available as an Rx-only medication.

This paper will present two sets of data that estimate the population-based extent of medication use for smoking cessation. The first data are from the 1996 California Tobacco Survey (CTS), a large population-based survey of California adults (see Chapter 2). This survey asked all smokers over the age of 25 whether they had tried to stop smoking in the last year and, if so, whether they had used nicotine gum or patch. The survey was conducted from September 1996 through January 1997. Thus, depending on when a smoker was surveyed, the gum would have been available OTC for 5-10 months prior to the survey, the patches would still have been Rx-only, and bupropion would not have been available yet.

The second data set is from nationally representative prescription and OTC sales data and physician prescribing data obtained in the last 6 months of 1997 from audits done by, or for, the pharmaceutical companies. In this data set, the gum would have been available OTC for 14-20 months, two patches would have been available OTC for 10-17 months, and bupropion would have been available Rx-only for 5-10 months. Both sales and physician audit allow one to estimate the number of new purchases.

To examine population-based efficacy of these medications, this chapter will use cessation data among users in the 1996 CTS. In addition, since sales data for 1997 do not provide cessation data, we will review Current Population Survey (CPS) data (see Chapter 2), meta-analyses (Fiore, 2000) and recent scientific studies in prescription (Rx) and over-the-counter (OTC) settings (Hughes *et al.*, 1999).

USE OF MEDICATIONS

**Nicotine Gum
and Patch**

Table 5-1 presents the 1996 CTS data on the use of patch, gum, and counseling in various combinations among different groups. In the 1996 CTS, 45 percent of those over age 25 who were daily smokers 1 year prior to the survey reported making a quit attempt that lasted more than 24 hours during the prior year. Of those who made a quit attempt, 21 percent reported using either patch or gum. Patch and gum use was more common in older, white, more educated, and higher income smokers. The 1996 estimates for patch and gum use represent a substantial increase from those recorded in a prior CTS in 1993, when patch and gum were available only as Rx products. In that survey, 47 percent of smokers reported quitting in the prior year, but only 10 percent used a patch, and 3 percent used gum (Pierce *et al.*, 1995).

A different estimate can be derived using national pharmaceutical company sales data. A recent article estimated that in 1997, 5.8 million quit attempts were made with OTC gum and patch and 0.5 million were made with Rx gum and patch (Gilpin and Pierce, 1994). The number of smokers over age 18 nationally was estimated at 47 million in 1995 by the CDC and 44 million by the CPS (see Chapter 2). If one uses the CDC definition of a quit attempt, requiring 24 hours of abstinence, then about 17 million of those smokers made a quit attempt in 1995 (see Chapter 2). Assuming that the number of smokers and the incidence of quitting have not changed between 1995 and 1997 (see Chapter 2), and that smokers do not make more than one quit attempt using patch or gum per year, then 36 percent of all quits in 1997 involved gum or patch. Since it is likely that smokers who are trying to quit may make more than one attempt per year and may use patch or gum on one or more of those attempts, it is likely that the 36 percent figure represents an overestimate of the fraction of quit attempts in which patch or gum was utilized. In the 1990 California Tobacco Survey, approximately 36 percent of those smokers who made a quit attempt in the prior 12 months made more than 1 quit attempt in that 12-month period, and some had made as many as 15 attempts each (Gilpin and Pierce, 1994). A minimum of 57 percent of the quit attempts occurred among those who made more than one attempt. These data would suggest that the ratio between the total number of quit attempts and the number of individuals who have made a quit attempt in the last year may be approximately 1.5. Dividing the number of quit attempts estimated from sales data by this ratio would reduce the 36 percent presented above to 24 percent of all quit attempts that are accompanied by nicotine patch and gum—a number closely matching the estimate from population-based survey data (21 percent; Table 5-1).

Table 5-1
Cessation Methods Reported by Daily Smokers 1 Year prior to the Survey Who Made a Quit Attempt in the Last 12 Months, 1996 CTS*

	Single Aid Only												Combination of Aids**						Pop Samp Size (n)			
	None			Self-Help Materials			Nicotine Patch			Nicotine Gum			Self-Help Materials			Nic Patch or Gum				Unknown		
	%	± CI		%	± CI		%	± CI		%	± CI		%	± CI		%	± CI			%	± CI	
Total	72.3	2.0	1.7	0.7	2.5	0.7	4.6	0.8	3.3	0.8	7.1	1.1	9.3	1.3	21.0	1.8	0.7	0.3	1,266,663	2,680		
Gender																						
Male	75.2	2.7	1.3	0.8	2.4	1.0	4.7	1.1	2.7	1.0	5.6	1.4	8.0	1.7	19.2	2.3	0.6	0.5	707,535	1,377		
Female	68.5	3.4	2.2	1.1	2.7	1.1	4.4	1.2	3.9	1.4	8.9	1.6	11.0	1.9	23.4	2.9	0.7	0.5	559,127	1,303		
Age (Years)																						
25-44	74.6	2.1	1.9	0.9	2.9	0.9	3.9	0.8	2.7	0.9	6.0	1.2	9.0	1.7	18.2	2.0	0.9	0.5	797,986	1,661		
45-64	69.3	4.2	1.7	1.4	2.0	1.0	5.7	1.8	3.6	1.5	9.2	2.6	10.0	2.6	24.1	3.5	0.3	0.4	365,166	803		
65+	64.3	7.7	0.4	0.8	1.3	1.8	6.3	2.8	6.6	5.1	7.7	3.8	9.1	4.8	32.5	7.5	.	.	103,509	216		
Race/Ethnicity																						
NH White	68.4	2.2	1.2	0.6	2.6	0.7	6.1	1.1	3.5	1.1	6.8	1.1	9.7	1.4	25.1	2.1	0.7	0.4	806,518	1,930		
Hispanic	80.6	4.6	2.7	2.1	2.0	1.6	2.0	1.6	2.5	1.8	6.5	3.0	7.6	2.9	13.2	4.0	0.4	0.7	224,058	332		
Afric-Am	79.5	6.2	1.8	2.9	3.6	2.6	.	.	2.4	2.2	9.5	4.9	10.7	4.1	11.4	4.9	2.1	2.3	111,550	185		
Asian/PI	77.9	7.7	2.6	4.1	2.2	2.4	5.7	4.1	2.9	2.9	8.0	6.4	5.9	3.9	15.5	6.1	.	.	70,309	135		
Nativ Am	72.5	13.7	2.9	4.2	1.3	2.5	1.8	2.1	4.6	8.3	7.4	4.7	12.0	6.5	20.7	11.1	.	.	54,227	98		
Other	0	0	
Education (Years)																						
<12	77.2	5.6	3.8	2.5	1.5	1.2	2.1	1.4	3.3	2.0	8.3	3.1	7.2	3.0	15.8	4.8	1.0	0.8	299,599	312		
12	72.0	3.1	1.1	0.6	2.7	1.0	6.1	1.5	2.1	1.0	6.0	1.9	9.2	2.2	22.3	2.9	0.5	0.5	364,834	903		
13-15	71.9	3.7	1.0	0.7	2.6	1.2	5.2	1.6	2.8	1.0	6.7	1.8	9.8	2.1	20.4	3.2	1.1	0.9	359,691	887		
16+	67.1	4.8	1.0	0.8	3.4	1.5	4.6	1.6	5.5	2.4	7.7	2.5	11.3	2.7	26.5	4.2	.	.	242,537	578		
Household Income (Dollars)																						
≤10K	78.2	5.3	3.0	2.7	1.9	1.5	1.8	1.9	3.2	2.5	8.3	4.0	6.9	3.3	14.8	4.7	1.2	1.3	156,924	264		
10-20K	76.3	4.9	2.5	2.1	1.9	1.3	3.7	1.8	2.6	1.8	6.8	3.2	6.4	2.7	18.2	4.5	0.7	1.0	187,040	354		
20-30K	78.5	4.4	0.6	0.7	3.1	1.7	3.6	1.8	1.8	1.1	4.5	2.0	9.7	2.9	14.9	4.3	0.8	1.1	190,339	398		
30-50K	69.7	4.4	1.5	1.4	2.5	1.3	6.0	2.2	2.9	1.5	7.6	2.6	10.4	2.9	23.8	4.1	0.6	0.7	271,517	605		
50-75K	66.9	5.7	1.6	1.5	3.6	2.0	5.4	2.1	3.3	1.7	8.6	3.1	13.5	4.1	23.9	5.0	0.7	0.9	200,708	452		
>75K	64.9	5.6	2.3	2.4	1.2	1.2	6.6	2.5	5.4	3.6	7.7	3.2	6.9	2.8	29.9	5.5	0.4	0.7	148,285	377		
Unknown	71.9	6.4	0.4	0.7	3.4	2.3	4.4	2.9	4.8	3.9	5.2	2.5	9.7	4.0	21.5	5.7	0.4	0.7	111,848	230		

*Those 25+ years of age who have made a quit attempt in the past year and were daily smokers 1 year ago.

**Combination includes use of the method alone or with any other method.

The difference in usage rates (14 percent in the 1993 CTS versus 21 percent in the 1996 CTS, versus 24 percent in the 1997 U.S. sales data) could be due to several reasons. There is good evidence that the historical trend is due to increased recognition of the efficacy of patch and gum and due to their increased availability as an OTC item (Shiffman *et al.*, 1997a & b). Some smokers may have purchased gum or patch but never actually made a quit attempt; however, recent work indicates that 94 percent of OTC nicotine replacement therapy (NRT) use is for cessation purposes (Pillitteri *et al.*, 1998).

In summary, it is reasonable to estimate that between one-fifth and one-quarter of all quit attempts are accompanied by the use of nicotine gum or patch.

Bupropion Bupropion was not yet available for smoking cessation when the 1996 CTS was conducted. When the pharmacy sales data were collected in 1997, Zyban® (the trade name of bupropion when used for smoking) had only been available for smoking cessation for between 1 and 6 months. Use of Zyban® appeared to stabilize the last 3 months of these data. Projections for a full year based on these last 3 months of pharmacy audits indicate that 2.4 million quit attempts/year may involve Zyban®. In addition, it is estimated that 15 percent of Wellbutrin® use (the trade name of bupropion for depression) is actually for smoking cessation (Glaxo-Wellcome, personal communication). Adding these usage measures together results in an estimate of 3.7 million quits/year with bupropion. Using the same value of 1.5 for the ratio between quit attempts and number of individuals who have attempted to quit in the last 12 months would yield an estimate of 14 percent of all quit attempts that involve bupropion.

Any medication Although no data are available, it is thought that in 1997 there was little concomitant use of gum with patch or of bupropion with gum or patch. Recent publications suggest that combined use may improve quit rates (Hughes *et al.*, 1999; Jorenby *et al.*, 1999). But if we assume that combined use is minimal, then based on pharmacy sales data, the use of any medication would be projected to occur in 35-38 percent of all quit attempts in 1998, based on assumptions about the number of quit attempts stated above.

**EFFICACY/
EFFECTIVENESS**

**Nicotine Gum
and Patch:**

The 1996 CTS asked those who were daily smokers 1 year prior to the survey whether they had made a quit attempt lasting more than 24 hours. Those who had made a quit attempt were asked what method or methods they had used (Table 5-1).

Table 5-2 presents the current smoking status of those who had made a quit attempt in the last 12 months by the method of cessation assistance they reported using. Of those who reported using no cessation assistance, 17 ± 2 percent were former smokers at the time of the survey. Of those who reported using patch or gum, either alone or in combination with other methods, 32 ± 5 percent were former smokers at the time of the survey. When the data were analyzed for those who had been quit for 3+ months at the time of the survey, results were less impressive (11.2 ± 2.6

Table 5-2

Current Smoking and Cessation Status by Method of Cessation Reported by Those who were Daily Smokers 1 Year prior to the Survey and who Made a Quit Attempt in the Last 12 Months: 1996 CTS*

	Current Smoker w/Quit Attempt				Former Smoker of		Pop Size (N)	Samp Size (n)
	Daily		Occasional		Any Quit Length			
	%	CI	%	CI	%	CI		
Total	71.79	2.09	7.56	1.21	20.65	1.90	1,266,663	2,680
Single Aid Only								
None	74.59	2.30	8.35	1.60	17.06	2.20	915,186	1,886
Counseling Only	.	.	3.79	5.39	.	.	21,538	38
Self-Help Only	73.04	9.63	6.48	5.66	20.48	8.88	32,124	74
Patch Only	67.11	8.17	6.49	4.06	26.40	8.04	58,422	142
Gum Only	57.49	14.99	8.00	6.32	34.52	14.16	41,251	92
Aids in Combination								
Counseling**	71.81	7.11	3.32	2.55	24.87	7.16	89,356	189
Self-Help**	69.06	6.22	4.34	3.07	26.60	6.08	117,871	260
Patch/Gum**	62.62	4.87	5.68	1.76	31.71	4.51	266,595	612
Unknown	8,549	16

*Those 25+ years of age who have made a quit attempt in the past year and were daily smokers 1 year ago.

**Combination includes use of the method alone or with any other method.

percent for any use of patch or gum versus 9.7 ± 0.7 percent for no methods used). The results for 3+ month cessation were not statistically different, possibly due to the small number of observations.

In intervention studies, the one community practice Rx study found a long-term (6-12 months) quit rate with nicotine gum of 18 percent (Smith Kline Beecham, 1995). Across five studies of Rx nicotine patch (Table 5-3), quit rates ranged from 5 percent to 11 percent. In OTC settings, two gum studies reported long-term quit rates of 13 percent and 15 percent. Six studies of OTC patch reported quit rates from 5 percent to 17 percent with a median of 10 percent. Most studies that directly compared patch in Rx and OTC settings found similar quit rates (Hughes *et al.*, 1999).

In summary, a reasonable estimate for a real-world quit rate for OTC and Rx gum and patch is 10 percent. Thus, with 6.3 million uses, 630,000 successful quits/year are estimated to be associated with gum or patch use (see Table 5-4). Given that those who choose to use gum or patch are more heavily dependent than those who choose to quit on their own (Hughes *et al.*, 1997), this estimate may be biased to show smaller gum/patch effects. The difference in percentage of quit rates in which patch or gum are used between 1993 and 1996 could be because of the Rx barrier to obtaining patch or gum that existed in 1993 but did not exist in 1996.

Table 5-3

Six-Month Quit Rates in Minimal-Contact Studies of Nicotine Gum and Patches^a

	OTC		Rx NRT	Risk Ratio of OTC NRT vs. Placebo
	NRT	Placebo		
Nicotine Gum				
Smith Kline Beecham, 1995	15	—	18 ^b	—
Schneider <i>et al.</i> , 1983	13	8	30	1.6
Nicotine Patch				
Hays <i>et al.</i> , 1997	9	4	—	2.5
Alza Corporation, 1996	9	—	7 ^b	—
McNeil Pharmaceuticals, 1996	11	—	12	—
Leischow <i>et al.</i> , 1997	5	—	5	—
Sonderskov <i>et al.</i> , 1997	11	4	—	2.8

^aDue to differences in study design and in data collection, quit rates can be compared within rows but not across rows

^bSurveys, not experimental trials. Because so few returned for CO verification, these are self-reported quit rates. With CO verification they are likely to be somewhat lower.

Bupropion There are no community practice Rx studies with bupropion. There is one head-to-head comparison of nicotine therapy versus bupropion (Jorenby *et al.*, 1999). In this study, bupropion had higher quit rates than a nicotine patch (30 percent versus 16 percent). On the other hand, long-term quit rates for bupropion in other studies were similar to those found with gum and patch studies. In summary, because there is but one study, this paper will assume that the quit rates for real-world bupropion are similar to that for real-world gum and patch—*i.e.*, 10 percent. Thus with 3.7 million users, 370,000 quits/year are estimated to be associated with bupropion.

Any medication As discussed above, bupropion and NRT are probably rarely used together. Thus, the total number of medication-associated quits projected is $630,000 + 370,000 = 1.0$ million quits for 1998.

Quits with medications from the CTS To calculate the proportion of additional successful quits (not quit attempts) associated with medication, one has to make assumptions about the quit rate in those who do not use medications to quit. We assume that the 1-year quit rate for those who do not use medication is similar to the self-quit rate. This rate has been estimated at 5 percent (Hughes *et al.*, 1992), and the 1996 CTS data (See Chapter 2) reports an 11.5 percent quit rate for 3+ months among those who were daily smokers one year prior to the survey, which, if converted to a 1-year quit rate, would approximate the 5 percent estimated rate. With this assumption of a doubling of the success rate with medication, 50 percent of all quits in which medications are used during 1998 are projected to be additional quits associated with medication use.

Table 5-4
Use of, and Cessation with, Most Commonly Used Smoking Cessation Medications*

Basis	Nicotine Gum and Patch			Total	National Estimates
	Nicotine Gum	Patch	Bupropion		
Use from Sales Data (millions)	6.3		3.7	10.0	Number of smokers over age 18 (1996 CPS Data)
Use (% of all quit attempts)	21–24%		14%	34–38%	Quit attempts in the last year that are currently successful for 3 or more months (% of all daily smokers age 25+) (See Table 2-2)
Successful Quits Associated with Use (millions)	0.63		0.37	1.00	Quit attempts successful for 3+ months (millions)
Excess Quits Attributable to Medication (% of successful quits where medication is used)	15–50%		15–50%	15–50%	Number of quit attempts attributable to medication
Excess Quits Attributable to Medication (millions)	0.10–0.32		0.06–0.18	0.15–0.50	Fraction of all successful quit attempts attributable to medication

* See text for basis of calculations.

AHRQ Analyses

A recent meta-analysis of treatment patch or gum performed as part of the U.S. Public Health Service Agency for Healthcare Research and Quality (AHRQ) *Clinical Practice Guideline* suggested that there was a doubling of the cessation rate for nicotine patch therapy and a 30 to 80 percent increase in cessation with nicotine gum (Fiore, 2000). Data from the 1996 CTS suggest that patch or gum use was associated with an increased likelihood of being quit at the time of the survey—approximately twice that of no therapy (31.7 percent compared to 17.1 percent; Table 5-2)—but the likelihood of being quit for 3 or more months was increased by only 15 percent. This population estimate of a 15 percent increase is based on a small number of observations and is substantially lower than estimates of larger populations studied as part of cessation evaluations. In addition, it is based on self-selected groups and, for the reasons discussed above, it probably represents an underestimate of the effect of those medications and is included as a lower bound of the likely magnitude of the effect.

INTERPRETATION

Before discussing the significance of the above projections, some cautions are needed. First, the projections may actually be underestimates, as they do not include quits from medications other than nicotine patch, nicotine gum, and bupropion. On the other hand, the numbers may be overestimates, as they assume smokers do not use more than one medication at a time and do not use more than one medication per year. As stated above, we do not have any actual data on these two issues. Third, the calculations assume that all medication use is for cessation. A recent survey found that 94 percent of OTC gum use is, in fact, for cessation (Pillitteri *et al.*, 1998). Fourth, these estimates assume that utilization will continue at the same rate. Often, medications have an initial period of popularity followed by a decline in use. OTC gum and patch have been available for a sufficient period to indicate that sales are now stable. Bupropion has been available for less than a year; thus, whether its sales will decline (or alternately, they might still increase) is difficult to know.

The term “quits *associated with medication*” has been used to avoid the often implicit assumption that the effects of medication are entirely due to traditional pharmacological effects.

Of course, some of these effects are due to placebo effects and other non-pharmacological effects, including telephone-based counseling offered to smokers trying to quit. The one randomized study of such counseling showed that it improved quit rates on its own by a factor of 1.7 (Shiffman *et al.*, 1997a & b). However, probably less than 5 percent of medication users take advantage of such a program (Smith Kline Beecham, personal communication). Thus the contribution of telephone counseling to medication-associated quits is probably small. Another non-pharmacological effect is that medication availability may prompt quit attempts. OTC availability has made it easier to access medications among smokers who do not have to see a physician for such medication. Finally, the pharmaceutical companies have engaged in a large amount of direct-to-consumer advertising, the majority of which includes a stop-smoking message and encourages cessation, and the impact of this advertising on cessation activity has not yet been examined (Shiffman *et al.*, 1997a & b).

Neither did the analyses address whether any medication-associated quits are from “stealing” quitters who would have quit via behavior therapy. There are no data on whether this is the case; however, even if it were, the effect would be very small given the miniscule utilization of behavior therapy (<2 percent of all quits; Smith Kline Beecham, 1995).

With these caveats in mind, Table 5-4 presents a number of summary estimates for the effects of medication. With 44 million smokers and 17 million making quit attempts each year, and with 11.5 percent of those quit attempts lasting at least 3 months, approximately 2 million successful quits (for at least a 3-month period) would occur. Drug-use data would suggest that 6.3 million uses of patch and gum would occur (some individuals would use medications in more than one cessation attempt per year), and 3.7 million uses of bupropion would occur. Of the total population of daily smokers, 21-24 percent of those who make a quit attempt are estimated to use patch and gum, and an additional 14 percent are estimated to use bupropion. If 10-percent success rates are estimated for use of either medication, then approximately 1 million successful quits would be associated with medication. If the attributable fraction for medication use is between 0.15 and 0.5, then the number of excess quits produced by medication would be 150,000 to 500,000, or 7.5 to 25 percent of all successful quits.

CONCLUSION The major conclusions of these analyses are that medications are widely utilized for smoking cessation and make a substantial contribution to cessation success in the smoking population. Up to 1 million successful quits/year may be accompanied by medication use, and there may be an additional 150,000 to 500,000 successful quitters associated with medication use in the United States each year.

The development of truly effective medications, the decreased professional time necessary with OTC medications, the large increase in availability with OTC access, and the direct-to-consumer advertising for both Rx and OTC drugs by the pharmaceutical companies have led to a situation in which medications make an important contribution to smoking cessation in the United States.

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