TABLE 2. OTHER MODEL PARAMETERS*

Parameter type	Input	Source for default
Smoking parameters	Age at smoking cessation	NHANES III 1988-94
Disease rates	US population size by age and gender	NHIS, 1993
	Population distribution by smoking status	NHIS, 1993
	Disease risks by age and gender for CAD, COPD, and CVD	NHIS, 1993
	Disease risks by age and gender for lung cancer	NCI, 1993
	Likelihood of pregnancy by age	NHIS, 1994
	Disease risks for pregnancy complications	DiFranza and Lew, 1995 and Marks et al, 1990
	Relative risk values by smoking status	SAMMEC 3.0
Mortality	Mortality relative risk by smoking status	American Cancer Society, CPS II
	Life tables data from Vital Statistics of United States	NCHS, 1993

*Full references for published literature are available in the Reference List attached. If the reference is a government database, it is described briefly in the assumptions section which follows.

IMPORTANT SAFETY INFORMATION

Important Safety Information

- There is a risk of seizure associated with Zyban® (bupropion hydrochloride). To reduce this risk, don't take Zyban if:
  - You have or have had an eating or seizure disorder
  - You are already taking Wellbutrin®, Wellbutrin SR®, or any other medication that contains bupropion
- Also, do not take Zyban if you are currently taking or have recently taken an MAO Inhibitor
- Do not take Zyban if you are pregnant or breast-feeding

Please see accompanying complete Prescribing Information for Zyban.

MODEL ASSUMPTIONS

Assumptions for ROSCO Model

1. Population distribution by age, gender, and smoking status

The information for this parameter was abstracted from the 1993 National Health Interview Survey database. The data reflects specific groups/categories for each of the four regions of the country and industry/health plan type.

2. Population distribution by occupation type

This information was obtained from the 1997 Current Population Survey, specific for each of the four regions of the country and industry type.

3. Adult dependents

The model assumes that there are 0.6 adult dependents for each employee/health plan member (based on values supplied by Towers Perrin). Adult dependents are assumed to be the same age and opposite gender of the employee/health plan member. The smoking status distribution for the adult dependents is the same as specified in #1 (above) for employees/health plan members of the specified age cohort and gender. Adult dependents do not incur any indirect costs and may change smoking status independent of the employee/health plan member.

4. Mean hourly salary by occupation type

This information was obtained from the 1997 Current Population Survey, specific for each of the four regions of the country or the state (if specified).

5. Workforce or health plan turnover

For the model with replacement, the turnover rate has a default value of 10% annually; this value incorporates job termination and retirement. For the cohort model, a schedule for turnover rate with years of continuous employment is used. Values for both the model with replacement and the cohort model were supplied by Towers Perrin. The rate schedule for turnover in the cohort model is as follows:

Model Year(s)	1	2	3-5	6-10	11+
Annual Turnover Rate	0.10	0.07	0.04	0.03	0.02

In the model with replacement, the program assumes that employees/health plan members who leave prior to age 65 will be replaced by new employees/health plan members with the same age and gender. The smoking status of the replacement employee/health plan member will be determined based on the distribution from the original model population (i.e., the smoking status distribution in the overall population, based on age, gender, occupation mix, and region of country), not the current distribution in the workforce or health plan when the employee/health plan member leaves. When an employee/health plan member leaves, a proportional number of adult dependents also leave (based on the proportion of employees/health plan members to adult dependents). The departing adult dependents will have the same age and opposite gender of the departing employees/health plan members. The smoking status of departing adult dependents will be based on the proportion of never/former/current smokers currently in the workforce/health plan for that gender and age cohort. Employees dying prior to age 65 will be replaced in a similar fashion.

6. Probability of using smoking cessation aids

Based on data from Towers Perrin, if smoking cessation aids are covered by an employer or health plan, 14% of smokers attempting to quit will use Zyban (alone or with nicotine patches) while the remaining 86% will use other aids (such as nicotine replacement therapy only) or no aids. If smoking cessation aids are covered and Zyban is promoted, 17% will use Zyban while the remaining 83% will use other aids or no aids. If smoking cessation aids are not covered, only 7% of smokers attempting to quit will use Zyban, while the remaining 93% will use other aids or no aid.

Among smokers using Zyban (with or without coverage), 97% will use Zyban alone while 3% will use Zyban plus nicotine patches. Among smokers not using Zyban (again, with or without coverage), 30% will use other aids and 70% will use no aids.

7. Effectiveness of smoking cessation interventions by level of counseling

Cessation rates for Zyban alone and Zyban plus nicotine patches were based on data from a Glaxo Wellcome clinical trial with 5 minutes of brief counseling for Zyban and Zyban plus patch. The efficacy of other aids was based on rates from Tonnesen et al. Efficacy rates of the no aids option were based on Cromwell et al. The change in effectiveness of each of these cessation aids in conjunction with low or no/minimal levels of counseling was estimated using data from Cromwell et al (1997). For example, Cromwell et al report that comparing cessation using nicotine patch therapy with full counseling (equivalent to the high counseling level in the ROSCO model) to brief counseling (equivalent to the low counseling level in the ROSCO model), decreases effectiveness by 7.6%. Therefore, the model assumes that going from the clinical trial data with full counseling to a low level of counseling, effectiveness for Zyban alone, Zyban plus nicotine patch, or other aids will decrease by 7.6%. Similarly, comparing use of nicotine patch therapy with full counseling versus minimal counseling (equivalent to the no counseling level in the ROSCO model), Cromwell et al report that cessation effectiveness decreases by 9.3%. For smokers attempting to quit using no aids, Cromwell et al report that the success rate decreases by 4.34% going from full counseling to brief counseling (with no aids) and by 6.2% going from full counseling to no counseling (with no aids).

8. Cost of smoking cessation interventions by level of counseling

Individuals using any aids for smoking cessation were assumed to have at least minimal counseling associated with the aids. Therefore, the cost for cessation using any aid(s) in the ROSCO model with no counseling includes the cost reported by Cromwell et al (1997) for minimal counseling. Costs in the ROSCO model associated with a low level of counseling include the Cromwell et al cost for brief counseling, and model costs for a high level of counseling include the Cromwell et al cost for full counseling. Smokers in the model using no aids incur no cessation cost when no counseling is present, and incur brief or full counseling costs for the low and high levels, respectively.

9. Physician costs for smoking cessation with Zyban

For the individuals attempting smoking cessation using Zyban when cessation aids are covered, 9% will have a physician visit solely to receive the prescription for Zyban. The other 91% of individuals attempting to quit using Zyban will receive their prescription at a physician visit primarily involving other reasons. The cost of the physician for this 9% and the time off of work to go to the physician (4 hours) will be included in the cost of the covered cessation attempt. The 9% and 4-hour values were supplied by Towers Perrin.

10. Length of therapy and dosing for Zyban

Patients receive 9 weeks of 150 mg BID Zyban in the clinical trial utilized for this model.

11. Pricing for Zyban

The starting price for Zyban is based on average wholesale price (AWP) for 7 weeks of therapy. This model assumes that the pharmacy is reimbursed by the third-party payor at 13% off of AWP plus a dispensing fee of $2.50. Smokers attempting to quit using Zyban (alone or with nicotine patches) receive the medication in two prescriptions, each having a copayment of $8.00.

This model assumes for Medicaid plans that the pharmacy is reimbursed by the third-party payor at a 10% discount and 12.3% rebate from AWP. There are two prescription copayments of $1.00 each and two dispensing fees of $4.00 each. There is then a federal match of 50% of the total cost, resulting in states being responsible for the remaining 50%.

12. Smoking cessation promotion

Employers and health plans that cover cessation aids may optionally choose to promote cessation. No promotion is associated with no additional costs and a rate of attempting smoking cessation of 34.0%, equal to the participation rate with no coverage of cessation aids. Low promotion costs $200 and increases participation in cessation attempts by 1.5% (i.e., 35.5% of smokers attempt cessation). Medium promotion costs $500 and

increases participation in cessation attempts by 3%, while high promotion costs $1000 and increases participation in cessation attempts by 4.5% (costs and effects of promotion from data supplied by Towers Perrin and Glaxo Wellcome).

13. Disease and mortality risk by age, gender, and smoking status

The impact of smoking status on disease risks and overall mortality was assessed using relative risk values from two sources: SAMMEC II for CAD (ICD-9 codes 410-414), CVD (430-438), COPD (496), and lung cancer (162); and the American Cancer Society Cancer Prevention Study-2 (CPS-2) for overall mortality. Although the SAMMEC relative risk values are for mortality, not morbidity, other age/gender/smoking status disease rates or relative risk values could not be identified. Following consultation with a number of experts in this field, we elected to use the SAMMEC values for disease rates.

Separate relative risk values for current versus former smokers (both compared to never smokers) and males versus females within each smoking status group were used. In addition, separate relative risk values for CAD and CVD for current and former smokers ages 35-64 versus age greater than 65 were also used. For individuals less than age 35, the relative risk value from the 35-64 age-group was also used.

To determine the annual rates of CAD, CVD, and COPD by age, gender, and smoking status, the overall population size and population disease rate were determined using the 1993 National Health Interview Survey for males and females in six age cohorts: 18-24, 25-34, 35-44, 45-54, 55-64, and 65+. The proportion of never, current, and former smokers in each of these age/gender stratum was determined using the Year 2000 supplement from the 1993 NHIS. The disease rate among never smokers in a given age/gender stratum, R, was then determined as:

$$R = \frac{NUM}{NS + (CS*RRcs) + (FS*RRfs)}$$

where

NUM = the total number of individuals in the age/gender stratum developing the specified disease
= the rate of disease in the age/gender stratum times the total population of the stratum

NS = the number of never smokers in the age/gender stratum

CS = the number of current smokers in the age/gender stratum

RRcs = the relative risk for the disease condition among current smokers

FS = the number of former smokers in the age/gender stratum

RRfs = the relative risk for the disease condition among former smokers

To determine the disease rate among former or current smokers, the rate among never smokers was multiplied by the appropriate relative risk value. For lung cancer, a similar calculation was performed; however, lung cancer rates among males and females by age-group were obtained from the National Cancer Institute's Cancer Statistics Review. A similar calculation was also performed for overall mortality, using annual mortality rates by age and gender from the 1993 National Center for Health Statistic's Vital Statistics of the United States.

For evaluating pregnancy complications, the rate of spontaneous abortions among smokers versus non-smokers (former plus never) was derived from DiFranza and Lew, 1995, while the rate of low birth weight infants was obtained from Marks et al, 1990. It was assumed that former and never smokers experienced the same rate of pregnancy complications. Annual pregnancy rates by age were determined using the 1993 NHIS, and an assumption was made that no pregnancies occurred after age 44. Based on Marks et al, 1990, we also assumed that 20% of female smokers temporarily stop smoking when pregnant and thus experience the same rate of pregnancy complications as non-smokers;

these women resumed smoking following conclusion of the pregnancy. Age-specific rates of induced (elective) abortion were also included to determine the actual number of live births and the proportion of live births (by smoking status) of low birth weight.

14. Length of time after quitting before smoker presents medically as a non-smoker

Based on data from Towers Perrin, former smokers' overall healthcare costs equal those of never smokers at 16 years following cessation. However, former smokers risks for specific conditions evaluated in the model (COPD, CAD, CVD, and lung cancer) as well as excess mortality risk remains elevated to that of never smokers throughout the model, as the relative risks for these conditions and for overall mortality are based on data comparing all former smokers to never smokers.

15. Annual medical care costs for current and never smokers

Annual medical care costs were derived from values reported by Hodgson (1992). Hodgson presented costs over a period of several years, and presented separate costs for smokers/non-smokers who survived for the specified time period or died during the period. We determined weighted average annual costs for current and never smokers by evaluating the proportion in each age/gender/smoking status cohort who survived vs. died in each period and the number of years of survival among the population dying in each period. These costs were then inflated to 1997 values using the medical care component of the consumer price index (CPI). Overall annual medical care costs for male current smokers, male never smokers, female current smokers, and female never smokers are determined by weighting the annual costs in each age/gender/smoking status cohort by the proportion of individuals in each age-group (e.g., the annual medical care costs for male smokers is determined by summing the proportion of male smokers in each age cohort multiplied by the annual medical care costs for males smokers in that age cohort).

16. Annual medical care costs for former smokers

Values were supplied by Towers Perrin determining the proportion of excess medical costs incurred by current smokers which former smokers experience annually, based on years since cessation. After 16 years of cessation, former smokers have the same costs as never smokers. However, the data supplied by Towers Perrin were a step function (discrete annual values), which led to costing abnormalities (e.g., costs for individuals who quit 10.99 years ago were substantially different from costs for individuals who quit 11 years ago). To smooth these values and avoid such abnormalities, we used curve-fitting software to determine a function fitting the Towers Perrin data. The function was created using quadratic curve fitting, where the percent of incremental smokers' total healthcare costs applicable to former smokers after X years of cessation equals (0.87075-0.09084804*X+0.00247549*X^2) for X<18 and equals zero for X= >18. The R-squared value for the quadratic curve fitting of the Towers Perrin data is 0.9933143. The years since cessation used in the regression equation is a weighted average of all former smokers in each age/gender cohort. Years since cessation for individuals who are former smokers at the start of the model (i.e., quit smoking prior to the start of the model) was determined for each age/gender cohort using data from the NHANES, 1988-1994.

17. Recidivism Rate

Schedule of annual recidivism rates:

Years since cessation	2	3	4	5	6-11	12+
No cessation aid coverage	14.30%	10.50%	3.40%	3.00%	1.50%	0.00%
Cessation aid coverage	14.30%	10.50%	3.40%	3.00%	1.50%	0.00%

18. Productivity

Average lost productivity cost in employer charts was calculated only for the employee-covered lives (not dependents). It is assumed that smokers have an additional cost of 1.4% of payroll due to greater time off and workplace breaks for smoking.

19. Smoking Cessation Success Rates

Success rates with Zyban are based on clinical trial results after 1 year. Towers Perrin assumes medical and productivity savings do not accrue to the plan or the employer unless a smoker has been abstinent for a full year. Other than therapy with Zyban, success rates are the weighted average success rates of nicotine replacement therapy and cold turkey. Fifty-two-week continuous abstinence data were used. Continuous abstinence is defined as the percent of patients who were continuously smoke free from their quit day to the day of follow-up.

Treatment	Efficacy rates (%)	Source
Zyban	23.0%	Glaxo Wellcome data
Zyban + Habitrol®* (nicotine transdermal system)	28.2%	Glaxo Wellcome data
Other	17.0%	Tonnesen et al, 1998
No Aids	7.5%	Cromwell et al, 1997

* Habitrol® is a registered trademark of Ciba-Geigy Corp.

MODEL OUTPUTS

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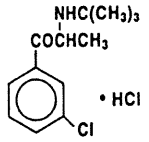
ZYBAN®
(bupropion hydrochloride)
Sustained-Release Tablets

DESCRIPTION: ZYBAN (bupropion hydrochloride) Sustained-Release Tablets are a non-nicotine aid to smoking cessation. Initially developed and marketed as an antidepressant (WELLBUTRIN® [bupropion hydrochloride] Tablets and WELLBUTRIN SR® [bupropion hydrochloride] Sustained-Release Tablets), ZYBAN is chemically unrelated to tricyclic, tetracyclic, selective serotonin re-uptake inhibitor, or other known antidepressant agents. Its structure closely resembles that of diethylpropion; it is related to phenylethylamines. It is (±)-1-(3-chlorophenyl)-2-[(1,1-dimethylethyl)amino]-1-propanone hydrochloride. The molecular weight is 276.2. The molecular formula is $C_{13}H_{18}ClNO \cdot HCl$. Bupropion hydrochloride powder is white, crystalline, and highly soluble in water. It has a bitter taste and produces the sensation of local anesthesia on the oral mucosa. The structural formula is:



ZYBAN is supplied for oral administration as 150-mg (purple), film-coated, sustained-release tablets. Each tablet contains the labeled amount of bupropion hydrochloride and the inactive ingredients carnauba wax, cysteine hydrochloride, hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polysorbate 80 and titanium dioxide and is printed with edible black ink. In addition, the 150-mg tablet contains FD&C Blue No. 2 Lake and FD&C Red No. 40 Lake.

CLINICAL PHARMACOLOGY:

Pharmacodynamics: Bupropion is a relatively weak inhibitor of the neuronal uptake of norepinephrine, serotonin, and dopamine, and does not inhibit monoamine oxidase. The mechanism by which ZYBAN enhances the ability of patients to abstain from smoking is unknown. However, it is presumed that this action is mediated by noradrenergic and/or dopaminergic mechanisms.

Pharmacokinetics: Bupropion is a racemic mixture. The pharmacologic activity and pharmacokinetics of the individual enantiomers have not been studied. Bupropion follows biphasic pharmacokinetics best described by a two-compartment model. The terminal phase has a mean half-life (±% CV) of about 21 hours (±20%), while the distribution phase has a mean half-life of 3 to 4 hours.

Absorption: Bupropion has not been administered intravenously to humans; therefore, the absolute bioavailability of ZYBAN Sustained-Release Tablets in humans has not been determined. In rat and dog studies, the bioavailability of bupropion ranged from 5% to 20%.

Following oral administration of ZYBAN to healthy volunteers, peak plasma concentrations of bupropion are achieved within 3 hours. The mean peak concentration (C_{max}) values were 91 and 143 ng/mL from two single-dose (150-mg) studies. At steady state, the mean C_{max} following a 150-mg dose every 12 hours is 136 ng/mL.

In a single-dose study, food increased the C_{max} of bupropion by 11% and the extent of absorption as defined by area under the plasma concentration-time curve (AUC) by 17%. The mean time to peak concentration (t_{max}) was prolonged by 1 hour. This effect was of no clinical significance.

Distribution: In vitro tests show that bupropion is 84% bound to human plasma proteins at concentrations up to 200 mcg/mL. The extent of protein binding of the hydroxybupropion metabolite is similar to that for bupropion, whereas the extent of protein binding of the threohydrobupropion metabolite is about half that seen with bupropion. The volume of distribution (V_d/F) estimated from a single 150-mg dose given to 17 subjects is 1950 L (20% CV).

Metabolism: Bupropion is extensively metabolized in humans. There are three active metabolites: hydroxybupropion and the amino-alcohol isomers threohydrobupropion and erythrohydrobupropion, which are formed via hydroxylation of the *tert*-butyl group of bupropion and/or reduction of the carbonyl group. Oxidation of the bupropion side chain results in the formation of a glycine conjugate of meta-chlorobenzoic acid, which is then excreted as the major urinary metabolite. The potency and toxicity of the metabolites relative to bupropion have not been fully characterized; however, it has been demonstrated in mice that hydroxybupropion is comparable in potency to bupropion, while the other metabolites are one tenth to one half as potent. This may be of clinical importance because the plasma concentrations of the metabolites are higher than those of bupropion. In vitro findings suggest that cytochrome P450 2B6 (CYP2B6) is the principal isoenzyme involved in the formation of hydroxybupropion, while cytochrome P450 isoenzymes are not involved in the formation of threohydrobupropion.

Following a single dose in humans, peak plasma concentrations of hydroxybupropion occur approximately 6 hours after administration. Peak plasma concentrations of hydroxybupropion are approximately 10 times the peak level of the parent drug at steady state. The AUC at steady state is about 17 times that of bupropion. The times to peak concentrations for the erythrohydrobupropion and threohydrobupropion metabolites are similar to that of the hydroxybupropion metabolite, and steady-state AUCs are 1.5 and 7 times that of bupropion, respectively.

Elimination: The mean (±% CV) apparent clearance (Cl/F) estimated from two single-dose (150-mg) studies are 135 (±20%) and 209 L/hr (±21%). Following chronic dosing of 150 mg of ZYBAN every 12 hours for 14 days (n = 34), the mean Cl/F at steady state was 160 L/hr (±23%). The mean elimination half-life of bupropion estimated from a series of studies is approximately 21 hours. Estimates of the half-lives of the metabolites determined from a multiple-dose study were 20 hours (±25%) for hydroxybupropion, 37 hours (±35%) for threohydrobupropion, and 33 hours (±30%) for erythrohydrobupropion. Steady-state plasma concentrations of bupropion and metabolites are reached within 5 and 8 days, respectively.

Following oral administration of 200 mg of ^{14}C-bupropion in humans, 87% and 10% of the radioactive dose were recovered in the urine and feces, respectively. The fraction of the oral dose of bupropion excreted unchanged was only 0.5%.

The effects of cigarette smoking on the pharmacokinetics of bupropion were studied in 34 healthy male and female volunteers; 17 were chronic cigarette smokers and 17 were nonsmokers. Following oral administration of a single 150-mg dose of ZYBAN, there was no statistically significant difference in C_{max}, half-life, t_{max}, AUC, or clearance of bupropion or its major metabolites between smokers and nonsmokers.

Bupropion and its metabolites exhibit linear kinetics following chronic administration of 150 to 300 mg/day.

Population Subgroups: Factors or conditions altering metabolic capacity (e.g., liver disease, congestive heart failure, age, concomitant medications, etc.) or elimination may be expected to influence the degree and extent of accumulation of the active metabolites of bupropion. The elimination of the major metabolites of bupropion may be affected by reduced renal or hepatic function because they are moderately polar compounds and are likely to undergo further metabolism or conjugation in the liver prior to urinary excretion.

Hepatic: The disposition of bupropion following a single 200-mg oral dose was compared in eight healthy volunteers and eight weight- and age-matched volunteers with alcoholic liver disease. The half-life of hydroxybupropion was significantly prolonged in subjects with alcoholic liver disease (32 hours [±41%] versus 21 hours [±23%]). The differences in half-life for bupropion and the other metabolites in the two patient groups were minimal.

Renal: The effect of renal disease on the pharmacokinetics of bupropion has not been studied. The elimination of the major metabolites of bupropion may be affected by reduced renal function.

Left Ventricular Dysfunction: During a chronic dosing study with bupropion in 14 depressed patients with left ventricular dysfunction (history of congestive heart failure [CHF] or an enlarged heart on x-ray), no apparent effect on the pharmacokinetics of bupropion or its metabolites, compared to healthy normal volunteers, was revealed.

Age: The effects of age on the pharmacokinetics of bupropion and its metabolites have not been fully characterized, but an exploration of steady-state bupropion concentrations from several depression efficacy studies involving patients dosed in a range of 300 to 750 mg/day, on a three times a day schedule, revealed no relationship between age (18 to 83 years) and plasma concentration of bupropion. A single-dose pharmacokinetic study demonstrated that the disposition of bupropion and its metabolites in elderly subjects was similar to that of younger subjects. These data suggest there is no prominent effect of age on bupropion concentration (see PRECAUTIONS: Geriatric Use).

Gender: A single-dose study involving 12 healthy male and 12 healthy female volunteers revealed no sex-related differences in the pharmacokinetic parameters of bupropion.

CLINICAL TRIALS: The efficacy of ZYBAN as an aid to smoking cessation was demonstrated in two placebo-controlled, double-blind trials in nondepressed chronic cigarette smokers (n = 1508, ≥15 cigarettes per day). In these studies, ZYBAN was used in conjunction with individual smoking cessation counseling.

The first study was a dose-response trial conducted at three clinical centers. Patients in this study were treated for 7 weeks with one of three doses of ZYBAN (100, 150, or 300 mg/day) or placebo; quitting was defined as total abstinence during the last 4 weeks of treatment (weeks 4 through 7). Abstinence was determined by patient daily diaries and verified by carbon monoxide levels in expired air.

Results of this dose-response trial with ZYBAN demonstrated a dose-dependent increase in the percentage of patients able to achieve 4-week abstinence (weeks 4 through 7). Treatment with ZYBAN at both 150 and 300 mg/day was significantly more effective than placebo in this study.

Table 1 presents quit rates over time in the multicenter trial by treatment group. The quit rates are the proportions of all persons initially enrolled (i.e., intent to treat analysis) who abstained from week 4 of the study through the specified week. Treatment with ZYBAN (150 or 300 mg/day) was more effective than placebo in helping patients achieve 4-week abstinence. In addition, treatment with ZYBAN (7 weeks at 300 mg/day) was more effective than placebo in helping patients maintain continuous abstinence through week 26 (6 months) of the study.

Table 1: Dose-Response Trial: Quit Rates by Treatment Group

	Treatment Groups			
Abstinence From Week 4 Through Specified Week	Placebo (n = 151) % (95% CI)	ZYBAN 100 mg/day (n = 153) % (95% CI)	ZYBAN 150 mg/day (n = 153) % (95% CI)	ZYBAN 300 mg/day (n = 156) % (95% CI)
Week 7 (4-week quit)	17% (11-23)	22% (15-28)	27%* (20-35)	36%* (28-43)
Week 12	14% (8-19)	20% (13-26)	20% (14-27)	25%* (18-32)
Week 26	11% (6-16)	16% (11-22)	18% (12-24)	19%* (13-25)

* Significantly different from placebo ($P \leq 0.05$).

The second study was a comparative trial conducted at four clinical centers. Four treatments were evaluated: ZYBAN 300 mg/day, HABITROL® (nicotine transdermal system) (NTS) 21 mg/day, combination of ZYBAN 300 mg/day plus NTS 21 mg/day, and placebo. Patients were treated for 9 weeks. Treatment with ZYBAN was initiated at 150 mg/day while the patient was still smoking and was increased after 3 days to 300 mg/day given as 150 mg twice daily. NTS 21 mg/day was added to treatment with ZYBAN after approximately 1 week when the patient reached the target quit date. During weeks 8 and 9 of the study, NTS was tapered to 14 and 7 mg/day, respectively. Quitting, defined as total abstinence during weeks 4 through 7, was determined by patient daily diaries and verified by expired air carbon monoxide levels.

In this study, patients treated with either ZYBAN or NTS achieved greater 4-week abstinence rates than patients treated with placebo. In addition, patients treated with the combination of ZYBAN and NTS achieved higher abstinence rates than patients treated with either of the individual active treatments alone, although only the comparison with NTS achieved statistical significance.

Table 2 presents quit rates over time by treatment group for the comparative trial. Both ZYBAN and NTS were more effective than placebo in helping patients maintain abstinence through week 10 of the study. The treatment combination of ZYBAN and NTS displayed the highest rates of continuous abstinence throughout the study.

Table 2: Comparative Trial: Quit Rates by Treatment Group

	Treatment Groups			
Abstinence From Week 4 Through Specified Week	Placebo (n = 160) % (95% CI)	Nicotine Transdermal System (NTS) 21 mg/day (n = 244) % (95% CI)	ZYBAN 300 mg/day (n = 244) % (95% CI)	ZYBAN 300 mg/day and NTS 21 mg/day (n = 245) % (95% CI)
Week 7 (4-week quit)	23% (17-30)	36%* (30-42)	49%*† (43-56)	58%*†‡ (51-64)
Week 10	20% (14-26)	32%* (26-37)	46%*† (39-52)	51%*† (45-58)

* $P < 0.01$ versus placebo.
† $P < 0.01$ versus NTS.
‡ $P = 0.06$ versus ZYBAN.

Quit rates in clinical trials are influenced by the population selected. Quit rates in an unselected population may be lower than the above rates.

Treatment with ZYBAN reduced withdrawal symptoms compared to placebo. Reductions on the following withdrawal symptoms were most pronounced: irritability, frustration, or anger; anxiety; difficulty concentrating; restlessness; and depressed mood or negative affect. Depending on the study and the measure used, treatment with ZYBAN showed evidence of reduction in craving for cigarettes or urge to smoke compared to placebo.

INDICATIONS AND USAGE: ZYBAN is indicated as an aid to smoking cessation treatment.

CONTRAINDICATIONS: ZYBAN is contraindicated in patients with a seizure disorder.

ZYBAN is contraindicated in patients treated with WELLBUTRIN, WELLBUTRIN SR, or any other medications that contain bupropion because the incidence of seizure is dose dependent.

ZYBAN is contraindicated in patients with a current or prior diagnosis of bulimia or anorexia nervosa because of a higher incidence of seizures noted in patients treated for bulimia with the immediate-release formulation of bupropion.

The concurrent administration of ZYBAN and a monoamine oxidase (MAO) inhibitor is contraindicated. At least 14 days should elapse between discontinuation of an MAO inhibitor and initiation of treatment with ZYBAN.

ZYBAN is contraindicated in patients who have shown an allergic response to bupropion or the other ingredients that make up ZYBAN.

WARNINGS: Patients should be made aware that ZYBAN contains the same active ingredient found in WELLBUTRIN and WELLBUTRIN SR used to treat depression, and that ZYBAN should not be used in combination with WELLBUTRIN, WELLBUTRIN SR, or any other medications that contain bupropion.

Because the use of bupropion is associated with a dose-dependent risk of seizures, *clinicians should not prescribe doses over 300 mg/day for smoking cessation.* The risk of seizures is also related to patient factors, clinical situation, and concurrent medications, which must be considered in selection of patients for therapy with ZYBAN.

- **Dose: *For smoking cessation, doses above 300 mg/day should not be used.* The seizure rate associated with doses of sustained-release bupropion up to 300 mg/day is approximately 0.1% (1/1,000). This incidence was prospectively determined during an 8-week treatment exposure in approximately 3100 depressed patients. Data for the immediate-release formulation of bupropion revealed a seizure incidence of approximately 0.4% (4/1000) in depressed patients treated at doses in a range of 300 to 450 mg/day. In addition, the estimated seizure incidence increases almost tenfold between 450 and 600 mg/day.**
- **Patient factors: Predisposing factors that may increase the risk of seizure with bupropion use include history of head trauma or prior seizure, central nervous system (CNS) tumor, and concomitant medications that lower seizure threshold.**
- **Clinical situations: Circumstances associated with an increased seizure risk include, among others, excessive use of alcohol; abrupt withdrawal from alcohol or other sedatives; addiction to opiates, cocaine, or stimulants; use of over-the-counter stimulants and anorectics; and diabetes treated with oral hypoglycemics or insulin.**
- **Concomitant medications: Many medications (e.g., antipsychotics, antidepressants, theophylline, systemic steroids) and treatment regimens (e.g., abrupt discontinuation of benzodiazepines) are known to lower seizure threshold.**

Recommendations for Reducing the Risk of Seizure: Retrospective analysis of clinical experience gained during the development of bupropion suggests that the risk of seizure may be minimized if

- the total daily dose of ZYBAN does *not* exceed 300 mg (the maximum recommended dose for smoking cessation), and
- the recommended daily dose for most patients (300 mg/day) is administered in divided doses (150 mg twice daily).
- No single dose should exceed 150 mg to avoid high peak concentrations of bupropion and/or its metabolites.
- ZYBAN should be administered with extreme caution to patients with a history of seizure, cranial trauma, or other predisposition(s) toward seizure, or patients treated with other agents (e.g., antipsychotics, antidepressants, theophylline, systemic steroids, etc.) or treatment regimens (e.g., abrupt discontinuation of a benzodiazepine) that lower seizure threshold.

Potential for Hepatotoxicity: In rats receiving large doses of bupropion chronically, there was an increase in incidence of hepatic hyperplastic nodules and hepatocellular hypertrophy. In dogs receiving large doses of bupropion chronically, various histologic changes were seen in the liver, and laboratory tests suggesting mild hepatocellular injury were noted.

PRECAUTIONS:

General: ***Allergic Reactions:*** Anaphylactoid reactions characterized by symptoms such as pruritus, urticaria, angioedema, and dyspnea requiring medical treatment have been reported at a rate of about 1-3 per thousand in clinical trials of ZYBAN. In addition, there have been rare spontaneous postmarketing reports of erythema multiforme, Stevens-Johnson syndrome, and anaphylactic shock associated with bupropion.

Insomnia: In the dose-response smoking cessation trial, 29% of patients treated with 150 mg/day of ZYBAN and 35% of patients treated with 300 mg/day of ZYBAN experienced insomnia, compared to 21% of placebo-treated patients. Symptoms were sufficiently severe to require discontinuation of treatment in 0.6% of patients treated with ZYBAN and none of the patients treated with placebo.

In the comparative trial, 40% of the patients treated with 300 mg/day of ZYBAN, 28% of the patients treated with 21 mg/day of NTS, and 45% of the patients treated with the combination of ZYBAN and NTS experienced insomnia compared to 18% of placebo-treated patients. Symptoms were sufficiently severe to require discontinuation of treatment in 0.8% of patients treated with ZYBAN and none of the patients in the other three treatment groups.

Insomnia may be minimized by avoiding bedtime doses and, if necessary, reduction in dose.

Psychosis, Confusion, and Other Neuropsychiatric Phenomena: In clinical trials with ZYBAN conducted in nondepressed smokers, the incidence of neuropsychiatric side effects was generally comparable to placebo. Depressed patients treated with bupropion in depression trials have been reported to show a variety of neuropsychiatric signs and symptoms including delusions, hallucinations, psychosis, concentration disturbance, paranoia, and confusion. In some cases, these symptoms abated upon dose reduction and/or withdrawal of treatment.

Activation of Psychosis and/or Mania: Antidepressants can precipitate manic episodes in bipolar disorder patients during the depressed phase of their illness and may activate latent psychosis in other susceptible individuals. The sustained-release formulation of bupropion is expected to pose similar risks. There were no reports of activation of psychosis or mania in clinical trials with ZYBAN conducted in nondepressed smokers.

Use in Patients With Systemic Illness: There is no clinical experience establishing the safety of ZYBAN in patients with a recent history of myocardial infarction or unstable heart disease. Therefore, care should be exercised if it is used in these groups. Bupropion was well tolerated in depressed patients who had previously developed orthostatic hypotension while receiving tricyclic antidepressants, and was generally well tolerated in a group of 36 depressed inpatients with stable CHF. However, bupropion was associated with a rise in supine blood pressure in the study of patients with CHF, resulting in discontinuation of treatment in two patients for exacerbation of baseline hypertension.

In the comparative trial, 6.1% of patients treated with the combination of ZYBAN and NTS had treatment-emergent hypertension compared to 2.5%, 1.6%, and 3.1% of patients treated with ZYBAN, NTS, and placebo, respectively. The majority of these patients had evidence of preexisting hypertension. Three patients (1.2%) treated with the combination of ZYBAN and NTS and one patient (0.4%) treated with NTS had study medication discontinued due to hypertension compared to none of the patients treated with ZYBAN or placebo. Monitoring for treatment-emergent hypertension is recommended in patients receiving the combination of ZYBAN and NTS.

Because bupropion hydrochloride and its metabolites are almost completely excreted through the kidney and metabolites are likely to undergo conjugation in the liver prior to urinary excretion, treatment of patients with renal or hepatic impairment should be initiated at reduced dosage as bupropion and its metabolites may accumulate in such patients to a greater extent than usual. The patient should be closely monitored for possible toxic effects of elevated blood and tissue levels of drug and metabolites.

Information for Patients: See PATIENT INFORMATION at the end of this labeling for the text of the separate leaflet provided for patients. Physicians are advised to review the leaflet with their patients and to emphasize that ZYBAN contains the same active ingredient found in WELLBUTRIN and WELLBUTRIN SR used to treat depression and that ZYBAN should not be used in conjunction with WELLBUTRIN, WELLBUTRIN SR, or any other medications that contain bupropion hydrochloride.

Laboratory Tests: There are no specific laboratory tests recommended.

Drug Interactions: In vitro studies indicate that bupropion is primarily metabolized to hydroxybupropion by the CYP2B6 isoenzyme. Therefore, the potential exists for a drug interaction between ZYBAN and drugs that affect the CYP2B6 isoenzyme metabolism (e.g., orphenadrine and cyclophosphamide). The threohydrobupropion metabolite of bupropion does not appear to be produced by the cytochrome P450 isoenzymes. No systemic data have been collected on the metabolism of ZYBAN following concomitant administration with other drugs or, alternatively, the effect of concomitant administration of ZYBAN on the metabolism of other drugs.

Animal data indicated that bupropion may be an inducer of drug-metabolizing enzymes in humans. However, following chronic administration of bupropion, 100 mg t.i.d. to 8 healthy male volunteers for 14 days, there was no evidence of induction of its own metabolism. Because bupropion is extensively metabolized, the coadministration of other drugs may affect its clinical activity. In particular, certain drugs may induce the metabolism of bupropion (e.g., carbamazepine, phenobarbital, phenytoin), while other drugs may inhibit the metabolism of bupropion (e.g., cimetidine).

Studies in animals demonstrate that the acute toxicity of bupropion is enhanced by the MAO inhibitor phenelzine (see CONTRAINDICATIONS).

Limited clinical data suggest a higher incidence of adverse experiences in patients receiving concurrent administration of bupropion and levodopa. Administration of ZYBAN to patients receiving levodopa concurrently should be undertaken with caution, using small initial doses and gradual dose increases.

Concurrent administration of ZYBAN and agents (e.g., antipsychotics, antidepressants, theophylline, systemic steroids, etc.) or treatment regimens (e.g., abrupt discontinuation of benzodiazepines) that lower seizure threshold should be undertaken only with extreme caution (see WARNINGS).

Physiological changes resulting from smoking cessation itself, with or without treatment with ZYBAN, may alter the pharmacokinetics of some concomitant medications, which may require dosage adjustment.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Lifetime carcinogenicity studies were performed in rats and mice at doses up to 300 and 150 mg/kg per day, respectively. These doses are approximately ten and two times the maximum recommended human dose (MRHD), respectively, on a mg/m² basis. In the rat study, there was an increase in nodular proliferative lesions of the liver at doses of 100 to 300 mg/kg per day (approximately three to ten times the MRHD on a mg/m² basis); lower doses were not tested. The question of whether or not such lesions may be precursors of neoplasms of the liver is currently unresolved. Similar liver lesions were not seen in the mouse study, and no increase in malignant tumors of the liver and other organs was seen in either study.

Bupropion produced a positive response (two to three times control mutation rate) in two of five strains in the Ames bacterial mutagenicity test and an increase in chromosomal aberrations in one of three in vivo rat bone marrow cytogenic studies.

A fertility study in rats at doses up to 300 mg/kg revealed no evidence of impaired fertility.

Pregnancy: ***Teratogenic Effects: Pregnancy Category B:*** Teratology studies have been performed at doses up to 450 mg/kg in rats (approximately 14 times the MRHD on a mg/m² basis), and at doses up to 150 mg/kg in rabbits (approximately 10 times the MRHD on a mg/m² basis). There is no evidence of impaired fertility or harm to the fetus due to bupropion. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed. Pregnant smokers should be encouraged to attempt cessation using educational and behavioral interventions before pharmacological approaches are used.

To monitor fetal outcomes of pregnant women exposed to ZYBAN, Glaxo Wellcome Inc. maintains a Bupropion Pregnan Registry. Health care providers are encouraged to register patients by calling (800) 722-9292, ext. 39441.

Labor and Delivery: The effect of ZYBAN on labor and delivery in humans is unknown.

Nursing Mothers: Bupropion and its metabolites are secreted in human milk. Because of the potential for serious adver reactions in nursing infants from ZYBAN, a decision should be made whether to discontinue nursing or to discontinue t drug, taking into account the importance of the drug to the mother.

Pediatric Use: Clinical trials with ZYBAN did not include individuals under the age of 18. Therefore, the safety and effica in a pediatric smoking population have not been established. The immediate-release formulation of bupropion was studi in 104 pediatric patients (age range, 6 to 16) in clinical trials of the drug for other indications. Although generally well tol ated, the limited exposure is insufficient to assess the safety of bupropion in pediatric patients.

Geriatric Use: Of the approximately 6000 patients who participated in clinical trials with bupropion sustained-release tabl (depression and smoking cessation studies), 275 were 65 and over and 47 were 75 and over. In addition, several hund patients 65 and over participated in clinical trials using the immediate-release formulation of bupropion (depression studie No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and ot reported clinical experience has not identified differences in responses between the elderly and younger patients, but grea sensitivity of some older individuals cannot be ruled out.

A single-dose pharmacokinetic study demonstrated that the disposition of bupropion and its metabolites in elderly subje was similar to that of younger subjects (see CLINICAL PHARMACOLOGY).

Bupropion hydrochloride and its metabolites are almost completely excreted through the kidney and metabolites are lik to undergo conjugation in the liver prior to urinary excretion. The risk of toxic reaction to this drug may be greater in patie with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be tak in dose selection, and it may be useful to monitor renal function (see Use in Patients with Systemic Illness).

ADVERSE REACTIONS: (see also WARNINGS and PRECAUTIONS)

The information included under ADVERSE REACTIONS is based primarily on data from the dose-response trial and comparative trial that evaluated ZYBAN for smoking cessation (see CLINICAL TRIALS). Information on additional adve events associated with the sustained-release formulation of bupropion in depression trials, as well as the immediate-relea formulation of bupropion, is included in a separate section (see Other Events Observed During the Clinical Development a Postmarketing Experience of Bupropion).

Adverse Events Associated With the Discontinuation of Treatment: Adverse events were sufficiently troublesome cause discontinuation of treatment in 8% of the 706 patients treated with ZYBAN and 5% of the 313 patients treated w placebo. The more common events leading to discontinuation of treatment with ZYBAN included nervous system dist bances (3.4%), primarily tremors, and skin disorders (2.4%), primarily rashes.

Incidence of Commonly Observed Adverse Events: The most commonly observed adverse events consistently ass ated with the use of ZYBAN were dry mouth and insomnia. The most commonly observed adverse events were definec those that consistently occurred at a rate of five percentage points greater than that for placebo across clinical studies.

Dose Dependency of Adverse Events: The incidence of dry mouth and insomnia may be related to the dose of ZYB The occurrence of these adverse events may be minimized by reducing the dose of ZYBAN. In addition, insomnia may minimized by avoiding bedtime doses.

Adverse Events Occurring at an Incidence of 1% or More Among Patients Treated With ZYBAN: Table 3 enumera selected treatment-emergent adverse events from the dose-response trial that occurred at an incidence of 1% or more were more common in patients treated with ZYBAN compared to those treated with placebo. Table 4 enumerates selec treatment-emergent adverse events from the comparative trial that occurred at an incidence of 1% or more and were m common in patients treated with ZYBAN, NTS, or the combination of ZYBAN and NTS compared to those treated with pla bo. Reported adverse events were classified using a COSTART-based dictionary.

Table 3: Treatment-Emergent Adverse Event Incidence in the Dose-Response Trial*

Body System/ Adverse Experience	ZYBAN 100 to 300 mg/day (n = 461) %	Placebo (n = 150) %
Body (General)		
Neck pain	2	<1
Allergic reaction	1	0
Cardiovascular		
Hot flashes	1	0
Hypertension	1	<1
Digestive		
Dry mouth	11	5
Increased appetite	2	<1
Anorexia	1	<1
Musculoskeletal		
Arthralgia	4	3
Myalgia	2	1
Nervous system		
Insomnia	31	21
Dizziness	8	7
Tremor	2	1
Somnolence	2	1
Thinking abnormality	1	0
Respiratory		
Bronchitis	2	0
Skin		
Pruritus	3	<1
Rash	3	<1
Dry skin	2	0
Urticaria	1	0
Special Senses		
Taste perversion	2	<1

* Selected adverse events with an incidence of at least 1% of patients treated with ZYBAN and more frequent than in placebo group.

Table 4: Treatment-Emergent Adverse Event Incidence in the Comparative Trial*

Adverse Experience (COSTART Term)	ZYBAN 300 mg/day (n = 243) %	Nicotine Transdermal System (NTS) 21 mg/day (n = 243) %	ZYBAN and NTS (n = 244) %	Placebo (n = 159) %
Body				
Abdominal pain	3	4	1	1
Accidental injury	2	2	1	1
Chest pain	<1	1	3	1
Neck pain	2	1	<1	0
Facial edema	<1	0	1	0
Cardiovascular				
Hypertension	1	<1	2	0
Palpitations	2	0	1	0

Table 4: Treatment-Emergent Adverse Event Incidence in the Comparative Trial* *(cont.)*

Adverse Experience (COSTART Term)	ZYBAN™ 300 mg/day (n = 243) %	Nicotine Transdermal System (NTS) 21 mg/day (n = 243) %	ZYBAN and NTS (n = 244) %	Placebo (n = 159) %
Digestive				
Nausea	9	7	11	4
Dry mouth	10	4	9	4
Constipation	8	4	9	3
Diarrhea	4	4	3	1
Anorexia	3	1	5	1
Mouth ulcer	2	1	1	1
Thirst	<1	<1	2	0
Musculoskeletal				
Myalgia	4	3	5	3
Arthralgia	5	3	3	2
Nervous system				
Insomnia	40	26	45	18
Dream abnormality	5	18	13	3
Anxiety	8	6	9	6
Disturbed concentration	9	3	9	4
Dizziness	10	2	8	6
Nervousness	4	<1	2	2
Tremor	1	<1	2	0
Dysphoria	<1	1	2	1
Respiratory				
Rhinitis	12	11	9	8
Increased cough	3	5	<1	1
Pharyngitis	3	2	3	0
Sinusitis	2	2	2	1
Dyspnea	1	0	2	1
Epistaxis	2	1	1	0
Skin				
Application site reaction†	11	17	15	7
Rash	4	3	3	2
Pruritus	3	1	5	1
Urticaria	2	0	2	0
Special Senses				
Taste perversion	3	1	3	2
Tinnitus	1	0	<1	0

* Selected adverse events with an incidence of at least 1% of patients treated with either ZYBAN, NTS, or the combination of ZYBAN and NTS and more frequent than in the placebo group.
† Patients randomized to ZYBAN or placebo received placebo patches.

Other Events Observed During the Clinical Development and Postmarketing Experience of Bupropion: In addition to the adverse events noted above, the following events have been reported in clinical trials with the sustained-release formulation of bupropion in depressed patients and in nondepressed smokers, as well as in clinical trials and postmarketing clinical experience with the immediate-release formulation of bupropion.

Adverse events for which frequencies are provided below occurred in clinical trials with bupropion sustained-release. The frequencies represent the proportion of patients who experienced a treatment-emergent adverse event on at least one occasion in placebo-controlled studies for depression (n = 987) or smoking cessation (n = 1013), or patients who experienced an adverse event requiring discontinuation of treatment in an open-label surveillance study with bupropion sustained-release tablets (n = 3100). All treatment-emergent adverse events are included except those listed in Tables 3 and 4, those events listed in other safety-related sections of the insert, those adverse events subsumed under COSTART terms that are either overly general or excessively specified so as to be uninformative, those events not reasonably associated with the use of the drug, and those events that were not serious and occurred in fewer than two patients.

Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions of frequency: Frequent adverse events are defined as those occurring in at least 1/100 patients. Infrequent adverse events are those occurring in 1/100 to 1/1000 patients, while rare events are those occurring in less than 1/1000 patients.

Adverse events for which frequencies are not provided occurred in clinical trials or postmarketing experience with the immediate-release formulation of bupropion. Only those adverse events not previously listed for sustained-release bupropion are included. The extent to which these events may be associated with ZYBAN is unknown.

Body (General): Frequent were asthenia, fever, and headache. Infrequent were back pain, chills, inguinal hernia, musculoskeletal chest pain, pain, and photosensitivity. Rare was malaise.

Cardiovascular: Infrequent were flushing, migraine, postural hypotension, stroke, tachycardia, and vasodilation. Rare was syncope. Also observed were cardiovascular disorder, complete AV block, extrasystoles, hypotension, myocardial infarction, phlebitis, and pulmonary embolism.

Digestive: Frequent were dyspepsia, flatulence, and vomiting. Infrequent were abnormal liver function, bruxism, dysphagia, gastric reflux, gingivitis, glossitis, jaundice, and stomatitis. Rare was edema of tongue. Also observed were colitis, esophagitis, gastrointestinal hemorrhage, gum hemorrhage, hepatitis, increased salivation, intestinal perforation, liver damage, pancreatitis, stomach ulcer, and stool abnormality.

Endocrine: Also observed was syndrome of inappropriate antidiuretic hormone.

Hemic and Lymphatic: Infrequent was ecchymosis. Also observed were anemia, leukocytosis, leukopenia, lymphadenopathy, and pancytopenia.

Metabolic and Nutritional: Infrequent were edema, increased weight, and peripheral edema. Also observed was glycosuria.

Musculoskeletal: Infrequent were leg cramps and twitching. Also observed were arthritis and muscle rigidity/fever/rhabdomyolysis.

Nervous System: Frequent were agitation, depression, and irritability. Infrequent were abnormal coordination, CNS stimulation, confusion, decreased libido, decreased memory, depersonalization, emotional lability, hostility, hyperkinesia, hypertonia, hypesthesia, paresthesia, suicidal ideation, and vertigo. Rare were amnesia, ataxia, derealization, and hypomania. Also observed were abnormal electroencephalogram (EEG), akinesia, aphasia, coma, delirium, delusions, dysarthria, dyskinesia, dystonia, euphoria, extrapyramidal syndrome, hypokinesia, increased libido, manic reaction, neuralgia, neuropathy, paranoid reaction, and unmasking tardive dyskinesia.

Respiratory: Rare was bronchospasm. Also observed was pneumonia.

Skin: Frequent was sweating. Infrequent was acne and dry skin. Rare was maculopapular rash. Also observed were angioedema, exfoliative dermatitis, and hirsutism.

Special Senses: Frequent was amblyopia. Infrequent were accommodation abnormality and dry eye. Also observed were deafness, diplopia, and mydriasis.

Urogenital: Frequent was urinary frequency. Infrequent were impotence, polyuria, and urinary urgency. Also observed were abnormal ejaculation, cystitis, dyspareunia, dysuria, gynecomastia, menopause, painful erection, prostate disorder, salpingitis, urinary incontinence, urinary retention, urinary tract disorder, and vaginitis.

DRUG ABUSE AND DEPENDENCE: ZYBAN is likely to have a low abuse potential.

Humans: There have been few reported cases of drug dependence and withdrawal symptoms associated with the immediate-release formulation of bupropion. In human studies of abuse liability, individuals experienced with drugs of abuse reported that bupropion produced a feeling of euphoria and desirability. In these subjects, a single dose of 400 mg (1.33 times the recommended daily dose) of bupropion produced mild amphetamine-like effects compared to placebo on the Morphine-Benzedrine Subscale of the Addiction Research Center Inventories (ARCI), which is indicative of euphoriagenic properties and a score intermediate between placebo and amphetamine on the Liking Scale of the ARCI.

Animals: Studies in rodents and primates have shown that bupropion exhibits some pharmacologic actions common to psychostimulants. In rodents, it has been shown to increase locomotor activity, elicit a mild stereotyped behavioral response and increase rates of responding in several schedule-controlled behavior paradigms. In primate models to assess the positive reinforcing effects of psychoactive drugs, bupropion was self-administered intravenously. In rats, bupropion produced amphetamine- and cocaine-like discriminative stimulus effects in drug discrimination paradigms used to characterize the subjective effects of psychoactive drugs.

The possibility that bupropion may induce dependence should be kept in mind when evaluating the desirability of including the drug in smoking cessation programs of individual patients.

OVERDOSAGE:

Human Overdose Experience: There has been very limited experience with overdosage of the sustained-release formulation of bupropion; three such cases were reported during clinical trials in depressed patients. One patient ingested 3000 mg of bupropion sustained-release tablets and vomited quickly after the overdose; the patient experienced blurred vision and lightheadedness. A second patient ingested a "handful" of bupropion sustained-release tablets and experienced confusion, lethargy, nausea, jitteriness, and seizure. A third patient ingested 3600 mg of bupropion sustained-release tablets and a bottle of wine; the patient experienced nausea, visual hallucinations, and "grogginess." None of the patients experienced further sequelae.

There has been extensive experience with overdosages of the immediate-release formulation of bupropion. Thirteen overdoses occurred during clinical trials in depressed patients. Twelve patients ingested 850 to 4200 mg and recovered without significant sequelae. Another patient who ingested 9000 mg of the immediate-release formulation of bupropion and 300 mg of tranylcypromine experienced a grand mal seizure and recovered without further sequelae.

Since introduction, overdoses of up to 17,500 mg of the immediate-release formulation of bupropion have been reported. Seizure was reported in approximately one third of all cases. Other serious reactions reported with overdoses of the immediate-release formulation of bupropion alone included hallucinations, loss of consciousness, and sinus tachycardia. Fever, muscle rigidity, rhabdomyolysis, hypotension, stupor, coma, and respiratory failure have been reported when the immediate-release formulation of bupropion was part of multiple drug overdoses.

Although most patients recovered without sequelae, deaths associated with overdoses of the immediate-release formulation of bupropion alone have been reported rarely in patients ingesting massive doses of the drug. Multiple uncontrolled seizures, bradycardia, cardiac failure, and cardiac arrest prior to death were reported in these patients.

Management of Overdose: Following suspected overdose, hospitalization is advised. If the patient is conscious, vomiting should be induced by syrup of ipecac. Activated charcoal also may be administered every 6 hours during the first 12 hours after ingestion. Baseline laboratory values should be obtained. Electrocardiogram and EEG monitoring also are recommended for the next 48 hours. Adequate fluid intake should be provided.

If the patient is stuporous, comatose, or convulsing, airway intubation is recommended prior to undertaking gastric lavage. Although there is little clinical experience with lavage following an overdose of bupropion, it is likely to be of benefit within the first 12 hours after ingestion since absorption of the drug may not yet be complete.

While diuresis, dialysis, or hemoperfusion are sometimes used to treat drug overdosage, there is no experience with their use in the management of overdoses of bupropion. Because diffusion of bupropion and its metabolites from tissue to plasma may be slow, dialysis may be of minimal benefit.

Based on studies in animals, it is recommended that seizures be treated with an intravenous benzodiazepine preparation and other supportive measures, as appropriate.

Further information about the treatment of overdoses may be available from a poison control center.

DOSAGE AND ADMINISTRATION:

ZYBAN: *Usual Dosage for Adults:* The recommended and maximum dose of ZYBAN is 300 mg/day, given as 150 mg twice daily. Dosing should begin at 150 mg/day given every day for the first 3 days, followed by a dose increase for most patients to the recommended usual dose of 300 mg/day. There should be an interval of at least 8 hours between successive doses. Doses above 300 mg/day should not be used (see WARNINGS). Treatment with ZYBAN should be initiated while the patient is still smoking, since approximately 1 week of treatment is required to achieve steady-state blood levels of bupropion. Patients should set a "target quit date" within the first 2 weeks of treatment with ZYBAN, generally in the second week. Treatment with ZYBAN should be continued for 7 to 12 weeks; duration of treatment should be based on the relative benefits and risks for individual patients. If a patient has not made significant progress towards abstinence by the seventh week of therapy with ZYBAN, it is unlikely that he or she will quit during that attempt, and treatment should probably be discontinued. Dose tapering of ZYBAN is not required when discontinuing treatment. It is important that patients continue to receive counseling and support throughout treatment with ZYBAN, and for a period of time thereafter.

Individualization of Therapy: Patients are more likely to quit smoking and remain abstinent if they are seen frequently and receive support from their physicians or other health care professionals. It is important to ensure that patients read the instructions provided to them and have their questions answered. Physicians should review the patient's overall smoking cessation program that includes treatment with ZYBAN. Patients should be advised of the importance of participating in the behavioral interventions, counseling, and/or support services to be used in conjunction with ZYBAN. See information for patients at the end of the package insert.

The goal of therapy with ZYBAN is complete abstinence. If a patient has not made significant progress towards abstinence by the seventh week of therapy with ZYBAN, it is unlikely that he or she will quit during that attempt, and treatment should be discontinued.

Patients who fail to quit smoking during an attempt may benefit from interventions to improve their chances for success on subsequent attempts. Patients who are unsuccessful should be evaluated to determine why they failed. A new quit attempt should be encouraged when factors that contributed to failure can be eliminated or reduced, and conditions are more favorable.

Maintenance: Although clinical data are not available regarding the long-term use (>12 weeks) of bupropion for smoking cessation, bupropion has been used for longer periods of time in the treatment of depression. Whether to continue treatment with ZYBAN for periods longer than 12 weeks for smoking cessation must be determined for individual patients.

Combination Treatment With ZYBAN and a Nicotine Transdermal System (NTS): Combination treatment with ZYBAN and NTS may be prescribed for smoking cessation. The prescriber should review the complete prescribing information for both ZYBAN and NTS before using combination treatment. See also CLINICAL TRIALS for methods and dosing used in the ZYBAN and NTS combination trial. Monitoring for treatment-emergent hypertension in patients treated with the combination of ZYBAN and NTS is recommended.

HOW SUPPLIED: ZYBAN Sustained-Release Tablets, 150 mg of bupropion hydrochloride, are purple, round, biconvex film-coated tablets printed with "ZYBAN 150" in bottles of 60 (NDC 0173-0556-02) tablets and the ZYBAN Advantage Pack containing 1 bottle of 60 (NDC 0173-0556-01) tablets.

Store at controlled room temperature, 20° to 25° C (68° to 77°F) (see USP). Dispense in tight, light-resistant containers as defined in the USP.

PATIENT INFORMATION: The following wording is contained in a separate leaflet provided for patients.

Information for the Patient
ZYBAN® (bupropion hydrochloride) Sustained-Release Tablets

Please read this information before you start taking ZYBAN. Also read this leaflet each time you renew your prescription in case anything has changed. This information is not intended to take the place of discussions between you and your doctor. You and your doctor should discuss ZYBAN as part of your plan to stop smoking. Your doctor has prescribed ZYBAN for your use only. Do not let anyone else use your ZYBAN.

IMPORTANT WARNING:

There is a chance that approximately 1 out of every 1000 people taking bupropion hydrochloride, the active ingredient in ZYBAN, will have a seizure. The chance of this happening increases if you:

- have a seizure disorder (for example, epilepsy);
- have or have had an eating disorder (for example, bulimia or anorexia nervosa);
- take more than the recommended amount of ZYBAN; or

- take other medicines with the same active ingredient that is in ZYBAN, such as WELLBUTRIN® (bupropion hydrochloride) Tablets and WELLBUTRIN SR® (bupropion hydrochloride) Sustained-Release Tablets. (Both of these medicines are used to treat depression.)

You can reduce the chance of experiencing a seizure by following your doctor's directions on how to take ZYBAN. You should also discuss with your doctor whether ZYBAN is right for you.

1. What is ZYBAN?

ZYBAN is a prescription medicine to help people quit smoking. Studies have shown that more than one third of people quit smoking for at least 1 month while taking ZYBAN and participating in a patient support program. For many patients, ZYBAN reduces withdrawal symptoms and the urge to smoke. ZYBAN should be used with a patient support program. It is important to participate in the behavioral program, counseling, or other support program your health care professional recommends.

2. Who should not take ZYBAN?

You should not take ZYBAN if you:

- have a seizure disorder (for example, epilepsy).
- are already taking WELLBUTRIN, WELLBUTRIN SR, or any other medicines that contain bupropion hydrochloride.
- have or have had an eating disorder (for example, bulimia or anorexia nervosa).
- are currently taking or have recently taken a monoamine oxidase inhibitor (MAOI).
- are allergic to bupropion.

3. Are there special concerns for women?

ZYBAN is not recommended for women who are pregnant or breast-feeding. Women should notify their doctor if they become pregnant or intend to become pregnant while taking ZYBAN.

4. How should I take ZYBAN?

- You should take ZYBAN as directed by your doctor. The usual recommended dosing is to take one 150-mg tablet in the morning for the first 3 days. On the fourth day, begin taking one 150-mg tablet in the morning and one 150-mg tablet in the early evening. Doses should be taken at least 8 hours apart.
- **Never take an "extra" dose of ZYBAN.** If you forget to take a dose, do not take an extra tablet to "catch up" for the dose you forgot. Wait and take your next tablet at the regular time. Do not take more tablets than your doctor prescribed. This is important so you do not increase your chance of having a seizure.
- It is important to swallow ZYBAN Tablets whole. Do not chew, divide, or crush tablets.

5. How long should I take ZYBAN?

Most people should take ZYBAN for 7 to 12 weeks. Follow your doctor's instructions.

6. When should I stop smoking?

It takes about 1 week for ZYBAN to reach the right levels in your body to be effective. So, to maximize your chance of quitting, you should not stop smoking until you have been taking ZYBAN for 1 week. You should set a date to stop smoking during the second week you're taking ZYBAN.

7. Can I smoke while taking ZYBAN?

It is not physically dangerous to smoke and use ZYBAN at the same time. However, continuing to smoke after the date you set to stop smoking will seriously reduce your chance of breaking your smoking habit.

8. Can ZYBAN be used at the same time as nicotine patches?

Yes, ZYBAN and nicotine patches can be used at the same time but should only be used together under the supervision of your doctor. Using ZYBAN and nicotine patches together may raise your blood pressure. Your doctor will probably want to check your blood pressure regularly to make sure that it stays within acceptable levels.

DO NOT SMOKE AT ANY TIME if you are using a nicotine patch or any other nicotine product along with ZYBAN. It possible to get too much nicotine and have serious side effects.

9. What are possible side effects of ZYBAN?

Like all medicines, ZYBAN may cause side effects.

- The most common side effects include dry mouth and difficulty sleeping. These side effects are generally mild and oft disappear after a few weeks. If you have difficulty sleeping, avoid taking your medicine too close to bedtime.
- The most common side effects that caused people to stop taking ZYBAN during clinical studies were shakiness and sk rash.
- Contact your doctor or health care professional if you have a rash or other troublesome side effects.
- Use caution before driving a car or operating complex, hazardous machinery until you know if ZYBAN affects your abil to perform these tasks.

10. Can I drink alcohol while I am taking ZYBAN?

It is best to not drink alcohol at all or to drink very little while taking ZYBAN. If you drink a lot of alcohol and suddenly sto you may increase your chance of having a seizure. Therefore, it is important to discuss your use of alcohol with your do tor before you begin taking ZYBAN.

11. Will ZYBAN affect other medicines I am taking?

ZYBAN may affect other medicines you're taking. It is important not to take medicines that may increase the chance for y to have a seizure. Therefore, you should make sure that your doctor knows about all medicines—prescription or over-th counter—you are taking or plan to take.

12. Do ZYBAN Tablets have a characteristic odor?

ZYBAN Tablets may have a characteristic odor. If present, this odor is normal.

13. How should I store ZYBAN?

- Store ZYBAN at room temperature, out of direct sunlight.
- Keep ZYBAN in a tightly closed container.
- Keep ZYBAN out of the reach of children.

This summary provides important information about ZYBAN. This summary cannot replace the more detailed informatio that you need from your doctor. If you have any questions or concerns about either ZYBAN or smoking cessation, talk your doctor or other health care professional.

GlaxoWellcome

Manufactured by Catalytica Pharmaceuticals, Inc.
Greenville, NC 27834
for Glaxo Wellcome Inc.
Research Triangle Park, NC 27709

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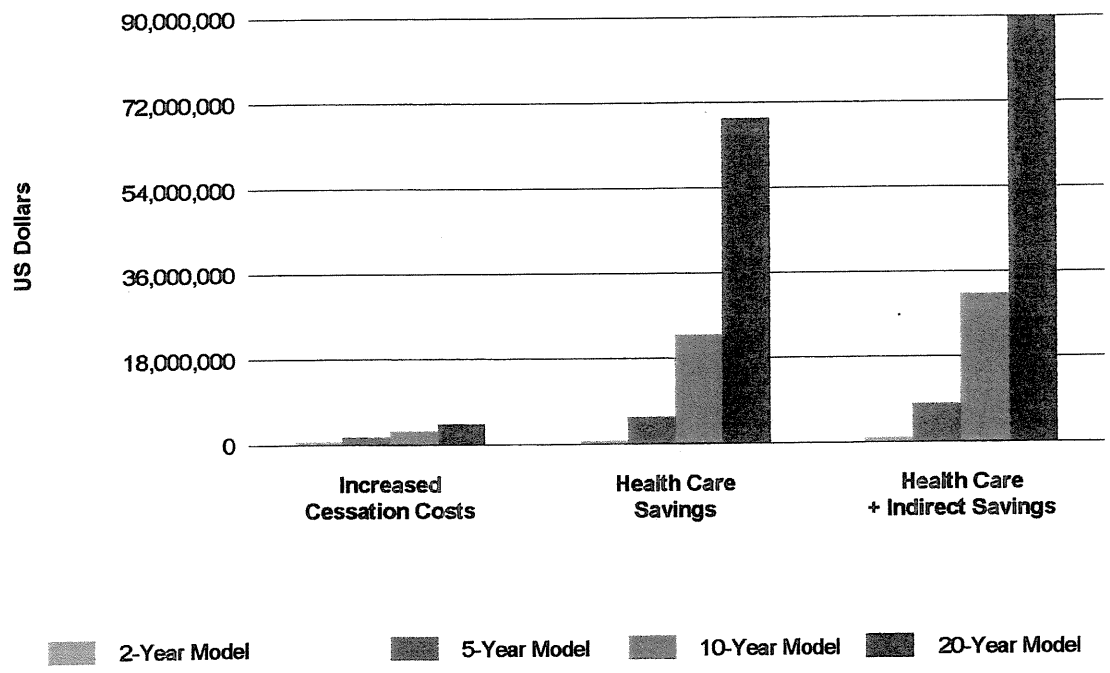
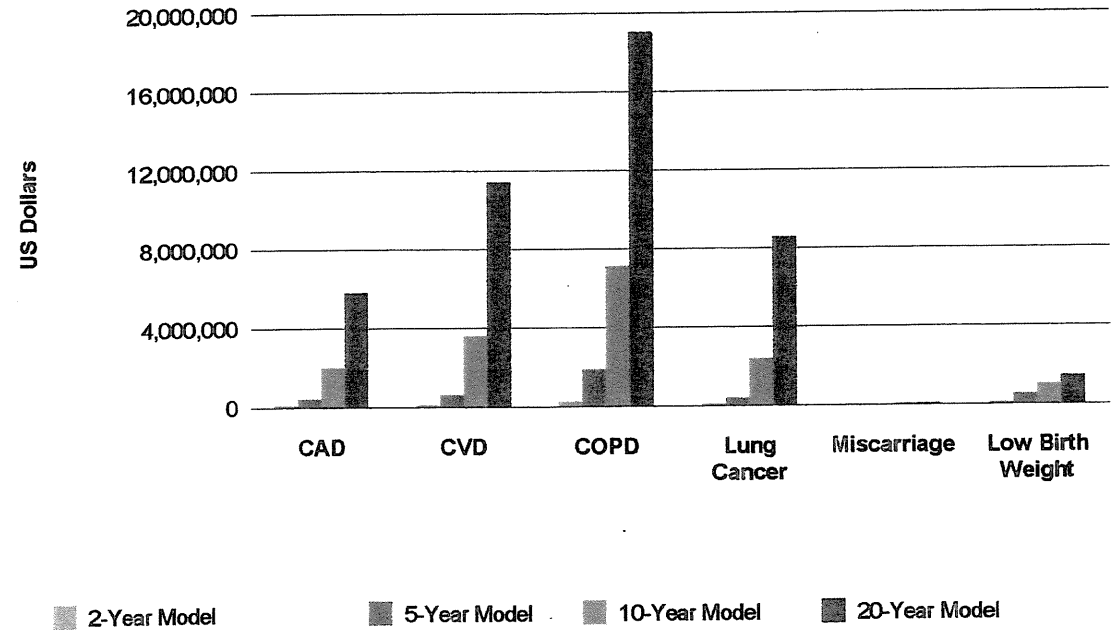
Change in Costs with Cessation Aid Coverage



Disease Cost Savings with Cessation Aid Coverage



Improved Outcomes Using Zyban

	Model Year			
	2	5	10	20
Increased Smoking Cessations	2057.522	4812.004	8658.077	14304.157
CAD Cases Avoided	3.025	26.719	143.351	508.080
CVD Cases Avoided	2.038	18.013	117.543	459.843
COPD Cases Avoided	33.447	296.240	1221.959	3899.415
Lung Cancer Cases Avoided	0.789	6.865	48.745	211.610
Miscarriages Avoided	0.697	6.098	12.591	19.569
Low Birth Weight Infants Avoided	1.033	9.066	18.804	29.334
Deaths Postponed	2.049	20.622	98.269	427.222

Outcomes expressed as the number of cases.

Benefit-Cost Analysis

	Health Costs	Indirect Costs	Cessation Costs
Costs without Cessation Aids Coverage			
To Age 65	$7,102,596,919	$231,270,520	$3,195,325
To Age 85	$8,809,278,414	$274,027,282	$3,788,314
Costs with Cessation Aids Coverage			
To Age 65	$7,012,806,778	$204,818,452	$7,894,324
To Age 85	$8,681,983,467	$236,386,168	$9,116,425
Savings with Cessation Aids Coverage			
To Age 65	$89,790,141	$26,452,068	-$4,698,999
To Age 85	$127,294,947	$37,641,114	-$5,328,111

Benefit-Cost Ratios

	Health Care Costs Only	Health Care + Indirect Costs
To Age 65	19.11	24.74
To Age 85	23.89	30.96

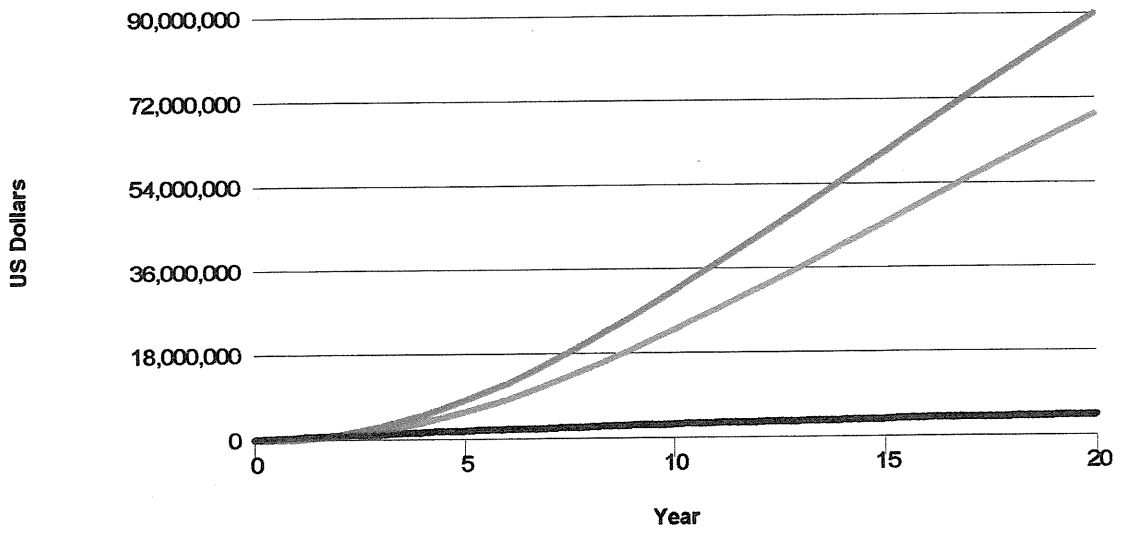
Zyban incremental cost of pharmaceutical coverage, Per Employee Per Year (First year only) $4.76

Internal Rate of Return

Health Care Costs Only	159.42%
Health Care + Indirect Costs	233.57%

IRR costs and savings are calculated for a 20 year period.

Break-Even Graph



Break-Even Table

Model Year	Annual Cess. Costs w Coverage	Incr. Cess. Costs With Coverage (1)	Health Care Savings (1)	ROI, Health Care Costs Only	Health + Indirect Savings (1)	ROI, Health Care + Indirect Costs
1	384,329	384,329	0	-100.0%	0	-100.0%
2	357,774	742,103	611,088	-17.7%	909,403	22.5%
3	333,114	1,075,217	1,831,041	70.3%	2,675,119	148.8%
4	311,094	1,386,311	3,487,883	151.6%	5,044,513	263.9%
5	290,040	1,676,351	5,682,964	239.0%	8,124,107	384.6%
6	271,434	1,947,785	8,175,932	319.8%	11,622,609	496.7%
7	253,617	2,201,402	11,367,021	416.4%	15,934,824	623.8%
8	234,892	2,436,294	14,935,573	513.0%	20,714,036	750.2%
9	218,167	2,654,461	18,783,309	607.6%	25,838,478	873.4%
10	203,385	2,857,846	22,876,977	700.5%	31,239,958	993.1%
11	190,274	3,048,120	27,173,524	791.5%	36,852,845	1109.0%
12	177,935	3,226,055	31,571,749	878.6%	42,581,462	1219.9%
13	166,437	3,392,492	36,086,909	963.7%	48,438,446	1327.8%
14	156,113	3,548,605	40,801,848	1049.8%	54,495,850	1435.7%
15	146,848	3,695,453	45,555,434	1132.7%	60,581,413	1539.4%
16	138,501	3,833,954	50,307,372	1212.2%	66,646,854	1638.3%
17	130,768	3,964,722	55,059,144	1288.7%	72,683,914	1733.3%
18	119,745	4,084,467	59,724,570	1362.2%	78,608,561	1824.6%
19	109,944	4,194,411	64,265,042	1432.2%	84,376,249	1911.6%
20	101,295	4,295,706	68,675,338	1498.7%	89,976,297	1994.6%

(1) These costs are cumulative.

Organization Parameters

Type of organization:	Public administration
Region:	Midwest
State:	Wisconsin
Employee population:	80769
Adult dependent population:	129231
Total population:	210000

General Model Parameters

Model mode:	Model with Replacement
Level of counseling:	Low
Intervention availablility:	Continuous

Medical Expense Parameters

	Males			Females		
	Current Smokers	Former Smokers	Never Smoked	Current Smokers	Former Smokers	Never Smoked
Additional absenteeism days/yr	3.9	0	NA	2.1	0	NA
Decreased productivity	1.40%	0.00%	NA	1.40%	0.00%	NA
Additional annual direct costs	$0	$0	$0	$0	$0	$0
Additional annual indirect costs	$0	$0	$0	$0	$0	$0

Medical expense allocation: By Smoker Status

	Males			Females		
	Current Smokers	Former Smokers	Never Smoked	Current Smokers	Former Smokers	Never Smoked
Mean annual medical expenses	$2,772	See Note	$1,476	$3,198	See Note	$2,154

Note. Annual cost for former smokers calculated by time since cessation.

Intervention Parameters

Level of Promotion

Cost level	None ($ 0)
Time off work for physician visit (hours)	4.00
Zyban physician visits (smoking cessation only)	9.00%
Zyban promotion	Yes

Participation Rates

Without coverage	10.00%
With coverage	20.00%

Zyban Cost (9-week course)

AWP	$18.04
Copayment	$8.00
Number of presecriptons	2.00
Discount	13.00%
Dispensing Fee	$2.50
Total	$98.85

Intervention Costs and Success Rates

Type of Cessation Aid	Success Rate	Non-Zyban Cost	Total Cost Per Quit Attempt
Zyban alone	30.30%	$37.79	$146.57
Zyban plus Nicotine patch	35.50%	$179.68	$288.46
Other aids	16.40%	$162.59	$162.59
No aids	15.60%	$37.79	$37.79

Summary of Success Rates and Costs

	Success Rate	Covered Cost Per Quit Attempt	Total Cost Per Quit Attempt
Cessation aids covered	18.32%	$56.28	$88.08
Cessation aids not covered	16.86%	$40.35	$80.52

Schedule of Recidivism Rates

Years since cessation	2	3	4	5	6-11	12+
Without cessation aid coverage	14.30%	10.50%	3.40%	3.00%	1.50%	0.00%
With cessation aid coverage	14.30%	10.50%	3.40%	3.00%	1.50%	0.00%

Employee Demographics

Employee Population

Age Group	Male	Female
18-24	2596	1370
25-34	8853	8432
35-44	12448	11380
45-54	11808	9363
55-64	7264	4288
65+	1315	1651
Totals	44284	36484

Average family size	2.60
Annual turnover rate	5.00%

Adult Dependent Population

Age Group	Male	Female
18-24	2192	4154
25-34	13491	14165
35-44	18208	19917
45-54	14981	18893
55-64	6861	11622
65+	2642	2104
Totals	58375	70855

Occupation Distribution

Occupation	Percent Workforce	Hrly Salary
Executive, administrative, and managerial	21.03%	$21.16
Professional specialty	15.24%	$18.25
Technicians and related support	4.48%	$15.68
Sales	0.59%	$10.68
Administrative support including clerical	25.78%	$9.85
Protective services	25.16%	$11.60
Service and household	2.50%	$7.27
Farming, forestry, and fishing	0.25%	$9.67
Precision production, craft, and repair	3.54%	$14.12
Machine operators, assemblers and inspectors	0.40%	$10.42
Transportation and material moving	0.81%	$11.66
Handlers, equipment cleaners, helpers, and labor	0.23%	$8.91
Mean Hourly Salary		$14.32

Disease Costs

Chronic Obstructive Pulmonary Disease (annual)	$6,979
Lung Cancer (lifetime)	$60,234

Coronary Heart Disease (lifetime)

Age Group	Males	Females
35-39	$19,629	$19,183
40-44	$19,002	$18,639
45-49	$18,290	$18,015
50-54	$17,497	$17,305
55-59	$16,241	$16,500
60-64	$15,332	$15,596
65-69	$13,517	$16,510
70-74	$12,335	$14,877
75-79	$11,193	$13,218

Cerebrovascular Disease (lifetime)

Age Group	Males	Females
18-35	$44,000	$45,000
36-55	$43,000	$45,000
56-75	$34,000	$35,000
76-85	$18,000	$18,000

Physician Visit	$53

Pregnancy Complications (one time)

Spontaneous Abortion	$1,672
Low Birth Weight	$61,010

Smoking Characteristics

	Males			Females		
	Current Smokers	Former Smokers	Never Smoked	Current Smokers	Former Smokers	Never Smoked
All	26.12%	28.97%	45.10%	24.68%	21.49%	54.05%
18-24	26.43%	8.73%	64.84%	21.97%	5.68%	72.35%
25-34	27.54%	16.33%	56.13%	24.26%	11.25%	64.49%
35-44	28.34%	26.21%	45.45%	26.58%	19.24%	54.18%
45-54	26.49%	36.26%	37.25%	26.20%	28.07%	45.73%
55-64	22.21%	41.60%	36.19%	22.48%	32.93%	44.59%
65+	11.40%	43.41%	45.19%	11.58%	34.50%	53.92%

AHCPR

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The Cost Effectiveness of AHCPR's Smoking Cessation Guideline

U.S Department of Health and Human Services
Public Health Service
Agency for Health Care Policy and Research

The Cost-Effectiveness of AHCPR's Smoking Cessation Guideline

Final Report

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1.0 Introduction and Review of Findings

1.1 Purpose and Brief Summary of *Guideline*

Tobacco use has been cited as the chief avoidable cause of death in the United States, responsible for more than 420,000 deaths annually from an assortment of attributable diseases, including lung cancer, heart disease, stroke, and pulmonary disease (CDC, 1990). Despite its adverse health consequences, physicians and other practitioners fail to assess and counsel smokers consistently and effectively (AHCPR, 1996). Recognizing these facts, AHCPR commissioned a panel of smoking cessation experts to develop a *Guideline* for clinicians and behavioralists encouraging smokers to quit.

Over the course of several meetings and extensive quantitative analysis of published smoking cessation interventions, the AHCPR panel developed a thorough *Guideline* that made many recommendations in terms of screening for tobacco use, advising patients to quit and assessing their smoking status, and the kinds of interventions that appeared most efficacious. The recommendations were based on rigorous logistic regression meta-analyses of various cessation interventions, ranging from self-help materials to multi-session group counseling lasting several hours or more. Recommendations were targeted specifically to primary care clinicians, cessation specialists, and insurers and purchasers of health care services.

The *Guideline* describes a sequential process beginning with initial screening in a clinician's office or during a hospital admission. Patients are recommended to be screened each time they see a physician or other practitioner concerning their smoking status. If they continue to smoke, they should be advised to quit. If they are not ready at the time, the physician is to provide a motivational talk. If they would like to try and quit, the patient is recommended to undertake one of four counseling interventions:

1. Minimal counseling with the clinician for less than 3 minutes with one follow-up visit within 2 weeks;
2. Brief counseling with the clinician for 3-10 minutes with one follow-up 10-minute visit within 2 weeks;
3. Full counseling for over 10 minutes with the clinician with two 10-minute follow-up visits; or
4. Referral to intensive counseling with smoking cessation specialists for 5-7 sessions of individual or group therapy.

For all interventions, the patient would be encouraged to use nicotine replacement in the form of the transdermal patch or nicotine gum.

1.2 Cost-Effectiveness Analysis of the *Guideline*

It is valuable to policymakers to assess the costs of each of the AHCPR guidelines relative to their clinical effectiveness. This is especially true of the *Smoking Cessation Guideline*. Many of the other guidelines are procedure-oriented, treating a focused population with a given condition. Hence, it is possible through the use of claims to accurately measure current costs of treating the illness under a small set of alternative interventions. Each guideline is designed to reflect best practice. Costing the guidelines informs the policymaker whether best practice will cost more or less.

Evaluating the *Smoking Cessation Guideline* is more challenging in some important respects. First, no claims data exist to quantify current practice. Most counseling services are an integral part of physician-patient contacts with no separate billing. Other services, such as nicotine replacement and intensive counseling, are generally not covered by insurance and, hence, do not produce a claims trail. Moreover, many different approaches to stopping smoking exist. Variation within approach, e.g., length of physician counseling session, also complicates the definition of "current practice." Then there is hypnotism, acupuncture, and other nontraditional forms of care that add to the costing efforts.

Finally, and most telling, smoking cessation programs are more closely related to prevention than procedure-oriented interventions. Acute interventions usually result in immediate relief and measurable improvements in health status. Smoking cessation programs, by contrast, focus on quit rates, which may be analogous to a patient's "surviving the operation." The latter is only meaningful if the operation substantially improves health status. Similarly, quitting smoking is of little interest by itself. More relevant is the long-run quit rate and the expected gains in health status. This raises another difference between prevention and procedure-oriented guidelines. Smoking cessation interventions

will have quite delayed benefits in terms of extra years of life of higher quality. Health status improvements to quitting smoking, while noticeable in the short-run, are only a small part of the long-run gains. Quit rates must be translated into long-run gains in health status, then discounted to account for the delayed benefit stream.

1.3 Brief Description of Cost-Effectiveness Methods

Neither the costs nor the effectiveness measures used in this study were based on individual patients undergoing a prospective clinical trial. Rather, the various recommended interventions were costed based on estimated resource inputs found in the *Guideline* report. Similarly, estimates of effectiveness were also taken from the *Guideline*.

Costing was done, first, by estimating the per minute cost of counselors, both physicians and specialists, then multiplying by the panel's estimated time involvements in each intervention component, i.e., screening, advice, motivation, counseling. Nicotine replacement costs were based on wholesale prices per unit times the number of units recommended in the *Guideline*. Surveys of local pharmacies found no significant net mark-up in patch or gum costs over wholesale prices. Because of the significant costs patients incur in traveling to the counseling site, some scenarios impute a cost of patient travel time based on median earnings of U.S. workers. When such costs are included, a broader societal perspective is taken, versus a slightly narrower one involving cessation providers alone. Excluding patient travel costs would also be more relevant to insurers if they covered the costs of the program.

Three measures of effectiveness were evaluated:

1. Marginal quit rates;
2. Years of life (discounted) saved; and
3. Quality-adjusted years of life (discounted) saved.

Marginal quit rates were derived by taking the odds ratios published in the *Guideline* for the various interventions and applying them to the underlying quit rate among smokers nationally. Years of life saved were based on a recent study of survival probabilities for various age and gender groups (Fiscella and Franks, 1996). These authors also made quality adjustment to years of life based on the *Healthy People 2000* years of life measure.

Two general methodological approaches were taken. Under one approach, all smokers were assumed to undertake a particular intervention. This answers the "what if?" question: What would be the cost-effectiveness if all smokers could be encouraged to undertake one of the interventions recommended by the *Guideline* panel? When the resulting cost-effectiveness ratios are compared across cessation interventions, this informs policymakers which interventions appear to be the most cost effective given universal implementation.

Under the second scenario, panel experts were queried regarding the likelihood of patients choosing one of the four counseling interventions with or without nicotine replacement. These probabilities were used to weight the costs and quit rates of the interventions. The result was a combined global cost-effectiveness ratio for the *Guideline* as a whole. It answers the question: How much would the *Guideline* cost per life-year saved if adopted by practitioners, given the expected preferences of smokers for different interventions?

The *Guideline* recognizes two loci of patient intake: the office and the hospital. Interventions in each of these sites were analyzed separately. Then, the results of the two sites were integrated into a single combined cost-effectiveness ratio, assuming that the counseling intervention is undertaken only once during the year. All the screening, advice, and motivation costs incurred repetitively during several annual office visits were included. In addition, the screening costs of the hospitalized population were added, plus the direct intervention costs of counseling and nicotine replacement for hospitalized patients. Direct intervention costs of hospitalized patients were debited from those incurred by ambulatory patients. This avoids double counting such costs.

Sensitivity analysis was performed on many of the key assumptions, including the marginal quit rates, the discount rate to years of life saved, the time involved in counseling, and the likelihood that patients would undertake a particular intervention.

1.4 Summary of Principal Findings

Table 1-1 shows cost-effectiveness ratios for 15 smoking cessation interventions that are described in the *Guideline*. These results were derived by assuming that *all* smokers would make at least one quit attempt during the year using a particular intervention. Cost per quitter among the counseling interventions without pharmacotherapy ranged from a low of $1,689 for group intensive counseling to a high of $5,572 for minimal counseling. Cost per quality-adjusted life-year was slightly lower, ranging from $1,433 for group intensive counseling to $4,726 for minimal counseling.

Table 1-1. Cost-Effectiveness of Smoking Cessation, by Intervention

Intervention	Cost per Quitter	Cost per Quality-Adjusted Life-Year (5% Discount)
Without Nicotine Replacement		
Minimal Counseling	$5,572	$4,726
Brief Counseling	4,739	4,019
Full Counseling	2,357	1,999
Individual Intensive Counseling	2,881	2,444
Group Intensive Counseling	1,689	1,433
With Transdermal Nicotine		
Minimal Counseling	3,856	3,271
Brief Counseling	3,413	2,895
Full Counseling	2,231	1,892
Individual Intensive Counseling	2,365	2,006
Group Intensive Counseling	1,891	1,604
With Nicotine Gum		
Minimal Counseling	7,292	6,185
Brief Counseling	6,004	5,093
Full Counseling	3,487	2,958
Individual Intensive Counseling	3,636	3,084
Group Intensive Counseling	2,950	2,502

Notes: Assumes that all patients who smoke attempt to quit at least once during the year. Quitters discounted by 35 percent to account for relapse.

As the amount of clinician time increases, intervention costs and the number of quitters both increase, while the cost per quitter *decreases* (except for individual intensive counseling). Group intensive counseling is a particularly low-cost intervention even though it involves the greatest amount of patient-clinician time (seven 1-hour sessions). This is because it not only generates a large number of new quitters because of its intensity of contact, but intervention costs are also shared across groups of 10 patients, lowering the cost per quitter even further.

Adding pharmacotherapy increases the costs of each intervention but also increases their marginal effectiveness substantially. When using transdermal nicotine (the patch) as adjunct therapy to each of the counseling interventions, the cost per quitter ranged from $1,891 for group intensive counseling to $3,856 for minimal counseling. This translated to $1,604 and $3,271 per quality-adjusted life-year. Nicotine gum with counseling is also more effective than counseling alone, although it does not generate as many new quitters as the patch. The cost per quitter for counseling with nicotine gum ranged from $2,950 for group intensive counseling to $7,292 for minimal counseling. The cost per quality-adjusted life-year ranged from $2,502 to $6,185.

In actual practice, patients and providers vary in their intervention preferences, and it is highly unlikely that all smokers would choose the same intervention. While group intensive counseling costs less per quitter than any of the other interventions, very few patients would actually choose this treatment option. Table 1-2 shows the cost-effectiveness of the combined *Smoking Cessation Guideline*, derived by weighing each of the individual interventions by the likelihood of a smoker choosing it. Based on the *Guideline* and the likely cessation intervention preferences of patients, it would cost $8.1 billion annually to provide all smokers with the intervention of their choice. This would result in 2.63 million new quitters at an average cost of $3,069 per quitter. The cost per life-year saved (discounted at 5 percent) would be $2,875. Adjusting for quality decreases the cost per life-year saved to $2,603.

Smoking cessation is cost effective relative to other medical interventions. Annual mammographies for women aged 40-49 are estimated to be $61,744 while hypertension screening for men age 40 is

Table 1-2. Cost-Effectiveness of Combined Guideline Smoking Cessation Interventions

Intervention	Cost	Number of Quitters[a]	Life-Years Saved[b]	Quality Life-Years Saved[c]
		(thousands)		
Without Nicotine Replacement				
Minimal Counseling	$103,715	19	20	22
Brief Counseling	279,282	59	63	69
Full Counseling	347,299	147	157	174
Intensive Counseling	37,772	13	14	15
Group Counseling	22,143	13	14	15
With Transdermal Nicotine				
Minimal Counseling	1,279,074	332	354	391
Brief Counseling	2,271,158	665	710	785
Full Counseling	2,120,791	951	1,015	1,121
Intensive Counseling	194,835	82	88	97
Group Counseling	155,761	82	88	97
With Nicotine Gum				
Minimal Counseling	263,540	36	39	43
Brief Counseling	470,864	78	84	92
Full Counseling	451,644	130	138	153
Intensive Counseling	41,404	11	12	13
Group Counseling	33,589	11	12	13
Combined Interventions[d]	8,072, 870	2,630	2,808	3,101
Cost Per Quitter		$3,069		
Cost Per Life-Year Saved			$2,875	
Cost Per Quality-Adjusted Life-Years Saved				$2,603

[a]Number of quitters discounted by 35 percent to account for relapse.
[b]Life-years saved (discounted 5%) derived by using 1.07 adjustment factor to the number of quitters.
[c]Quality-adjusted life-years saved (discounted 5%) derived by using 1.18 adjustment factor to the number of quitters.
[d]Derived by weighing the individual interventions by the likelihood of smokers choosing each intervention.

reported to be $23,335. A few medical interventions (e.g., one-time cervical screening for women over 64, $2,053; polio immunization for children <$0); exhibit lower cost-effectiveness ratios, but most acute interventions (e.g., coronary artery bypass surgery, $12,350; angioplasty for men aged 55 with severe angina, $7,395) are considerably more costly than the *Smoking Cessation Guideline*.

1.5 Organization of Report

The report is presented below in five chapters. Chapter 2 reviews three relevant literatures: cost-of-illness due to smoking; costs and effectiveness of cessation programs; and the cost-effectiveness of alternative medical interventions. It is not enough to compare cost-effectiveness ratios among the various cessation interventions. Policymakers need to know how effective each of the interventions might be relative to interventions in treating other diseases. Chapter 3 then provides a stylized description of the *Smoking Cessation Guideline*. It is stylized in the sense that minor recommendations having little impact on the cost-effectiveness analysis are not modeled. Also, decisions had to be made regarding issues such as lengths of counseling and sequencing of patients, and the like that are not fully described in the *Guideline* itself. This chapter also discusses special populations and exclusions, such as smokeless tobacco and alternative therapies (e.g., hypnosis). Chapter 4 provides an extensive discussion of the cost-effectiveness methods employed. It presents the challenges to costing the *Guideline*, the interventions actually analyzed, and how all of the key parameters were calibrated.

Chapter 5 contains all of the findings. It begins with a summary of the key simulation parameters. Then, the number of quitters and years of life saved for each intervention are given, followed by a decomposition of the costs associated with each intervention. Cost-effectiveness ratios are presented by intervention and globally using each of the three effectiveness measures, and results of sensitivity analyses are summarized. Chapter 6 concludes with a comparison of the major cost-effectiveness ratios under the *Guideline* with a selected number of cost-effectiveness ratios from other medical interventions.

2.0 Review of Cost-of-Smoking Literature

2.1 Scope of Review

This chapter examines the literature related to smoking cost-of-illness and smoking cost-of-cessation. The review is structured in three parts. We begin with a brief description of the identification of relevant literature. Next, we summarize the articles collected, classified by intervention type, population, study design, and results. Then, we critique the methodological issues in costing an intervention, exploring how a study's perspective is determined, how costs should be defined and measured, and how discounting affects long-term health outcomes. Finally, we consider the cost-effectiveness of other medical interventions and present a limited set of possible benchmarks against which smoking cessation ratios might be compared.

2.2 Identification of Relevant Literature

We searched the HEALTH and CBA/CEA CDC WONDER bibliographic databases for relevant literature. HEALTH, the Health Planning and Administration database, covers the international literature on health care planning and facilities, health insurance, financial management, manpower planning, and personnel administration. Information in HEALTH is derived from MEDLINE, the Hospital Literature Index, and selected journals. The database is produced by the National Library of Medicine. The CDC Wonder cost-benefit/cost-effectiveness analysis bibliography contains 3,206 articles, collected between 1979 and 1990, and classified into more than 250 topics. Information in the database was collected from MEDLARS, CATLINE, and other health policy, planning, and administration literature. The CBA/CEA CDC WONDER bibliography listings are also printed in a special edition of the journal *Medical Care* (Elixhauser *et al.*, 1993).

Using Medical Subject Headings (MeSH), we performed two searches on the HEALTH database between the years of 1975-1995. Both searches included citations where smoking was the primary focus of the article, but the first search identified articles relating to "cost" while the second identified those relating to "economics." The first search elicited 103 citations of those relating to "cost" and the second search elicited 45 citations relating to "economics." There was occasional duplication of citations among the two searches. Next, we identified nine relevant articles from the CBA/CEA CDC WONDER bibliography that contained the subject heading of tobacco and smoking. These articles were compiled along with the HEALTH database citations to form a list of 56 articles relating to smoking costs and are listed in the Appendix.

We next searched for articles relevant to smoking cessation programs more narrowly. Nine articles met our criteria of reporting costs per unit of benefit or effectiveness for a specific intervention program. The collection of articles make up a heterogeneous group. The articles, spanning the period 1984-1993, illustrate the range of intervention programs, and include such varied approaches as a smoking cessation class, contest, self-help kit (leaflets, manuals, pamphlets), counseling session (nurse, physician, and health educator managed), and nicotine gum therapy.

2.3 Cost-of-Illness Literature

2.3.1 General Methodological Issues

Literature examining the cost-of-illness of smoking can be classified in two broad categories: prevalence-based costs and incidence-based costs. Prevalence-based costs estimate the current direct and indirect costs of smoking during a specific period of time (usually 1 year). Therefore, it accounts for the impact of past smoking on the current occurrence of smoking-related illnesses, mortality, and other economic costs. Incidence-based costs represent the direct and indirect costs expected to occur over the lifetime of a group of new smokers. They take into account the impact of smoking behavior on the life expectancy and the future occurrence of disease.

Attributable Risk. Conducting a cost-of-illness analysis requires knowledge about each smoking-related disease's duration, the medical care needed to treat it, and the cost of providing health care services. Based on epidemiological evidence, the analyst must determine the degree to which smoking puts an individual at risk for these diseases and the excess mortality that can be attributed to smoking for each disease. The medical costs of smokers must be calculated taking into consideration the fact that some of the costs of smoking-related diseases also occur among nonsmokers as well. Therefore, the attributable risk to smokers must be determined. For example, in the literature, the attributable risk of

smoking among men ranges from 81 percent for cancer of the trachea, bronchus, and lungs to 18 percent for stomach cancer, while among the female population the attributable risk ranges from 56 percent for cancer of the esophagus to 14 percent for kidney cancer (Rice *et al.*, 1986).

Attributable risk further assumes that other factors influencing the occurrence of smoking-related illness are distributed evenly among smokers and nonsmokers. However, on average, smokers vary from nonsmokers in several ways, including increased alcohol consumption (Bradstock *et al.*, 1985; Pearson *et al.*, 1987). Schoenborn and Benson (1988) found that smokers are more likely to drink heavily, refrain for exercising actively, and sleep fewer hours; they also have poorer nutritional habits than people who never smoked. Smoking is more prevalent among blacks than whites, people with low levels of education, and blue collar workers (Elixhauser, 1990). Some researchers (Leu and Schaub, 1983; Manning *et al.*, 1989) have dealt with this issue by comparing smokers to nonsmoking smoker-types, i.e., individuals who do not smoke but who are like smokers in every other respect (e.g., similar education, income, race, drinking patterns). Other analysts (Hodgson, 1992) have assumed that the difference in medical expenditures between smokers and nonsmoking smoker-types is small, and, therefore, draw comparisons between smokers and individuals who never smoked.

Extent of Dependency. Studying the lifetime medical expenditures of smokers versus quitters is complicated by differences among individuals who quit. The attributable risk of smoking-related illnesses varies among quitters based on the number of years and how heavily they smoked as well as the age at which they quit. There are also variations across diseases in the degree to which someone who quits can return to a relative risk of someone who never smoked. For example, light smokers' risk of lung cancer returns to that of nonsmokers around 5 years after quitting (Hammond, 1966). However, quitters never regain lost lung functioning. So while quitting may return the rate of decline of respiratory functioning to that of a nonsmoker, emphysema may still occur in an individual who quits (Fletcher *et al.*, 1976). This complicates the estimation of medical expenditures incurred by quitters and may explain why literature in this area is lacking.

Discounting. Discounting expenditures accounts for the time preference of money and assigns current spending a higher value than future spending. In particular, discounting costs can have a profound effect on preventive health measures that seek to avoid future costs and realize future benefits. This means that any future medical expenditures occurring during additional years of life saved, either by not smoking or quitting, are adjusted to account for the general preference to postpone costs until later years. Therefore, many of the costs associated with smoking-related illnesses, which occur earlier in a person's lifetime, are valued at a relatively higher level than those occurring during added years of life. While the exact rate at which costs are discounted varies (and in some instances, discounting is completely ignored) in the literature, normally rates are set at approximately 3 or 5 percent. These rates are below secular inflation rates and most likely are well below individuals' time preferences for additional years of life. Indeed, part of the reason smokers don't quit is that they are willing to give up an extra year or two at the end of their life to continue to enjoy the pleasures of smoking.

Neonatal Medical Costs. A smaller number of cost-of-illness studies have focused specifically on maternal smoking during pregnancy and the resulting medical expenditures for neonatal care. Oster *et al.* (1988) used estimates of the relative risk of low birth weight birth according to maternal smoking status combined with data on the prevalence of smoking among pregnant women. They estimated that maternal smoking during pregnancy resulted in 35,816 low-birth-weight infants and 14,977 neonatal intensive care unit admissions. The additional costs of care due to smoking, in 1982 dollars, were estimated at $267 million. They calculated that the average cost of neonatal care for infants born to smokers was $288 more than the cost of care for the infants of nonsmokers spread across all births. These results were confirmed by study by Li *et al.* (1994), who found that the incremental costs of neonatal care due to pregnant smokers relative to never smokers was between $238 and $482 (in 1992 dollars) with low-birth-weight infants born to heavy smoking mothers costing more than those born to light smokers.

2.3.2 Prevalence-Based COI Literature

Most cost-of-illness studies in the area of smoking are prevalence-based. Early estimates varied between $4.3 billion (1970 dollars) and $11.5 billion (1974) dollars (Luce and Schweitzer, 1977). Later figures estimated that the annual cost of smoking in the U.S. (in 1993 dollars) ranged from $39 billion to $55 billion (Shultz, 1985). Rice *et al.* (1986) reported that a number of studies (Simon (1986), Hedrich (1971), Williams and Justus (1974),

Freeman *et al.* (1976), Kristein (1977), Luce and Schweitzer (1978), Forbes and Thompson (1983), Office of Technology Assessment (1985), and Vogt and Schweitzer (1985)) have examined the societal costs of smoking, but their results cannot be compared because they consider different costs, diseases, and categories of smokers. Rice's group estimated the economic costs of smoking by applying attributable risk to the direct and indirect costs of malignant neoplasms and diseases of the circulatory and respiratory systems. They calculated that the total cost of smoking in 1984 was $53.7 billion. The authors then compared their results to those of Luce and Schweitzer (1978) and OTA (1985). The costs of smoking estimated by Luce and Schweitzer was $52.8 billion (in 1984 dollars) while OTA arrived at $62.2 billion.

More recent medical care cost estimates were performed by Rice, other researchers at the University of California Berkeley, and CDC (1994). Using data from the 1987 National Medical Expenditures Survey (NMES-2), a longitudinal survey of the civilian, noninstitutionalized population, researchers determined smoking-attributable health care expenditures for conditions including heart disease, emphysema, arteriosclerosis, stroke, and cancer. Costs were adjusted for 1992 by applying attributable percentages to national health care expenditures reported by HCFA. The total smoking-attributed medical expenditures were $21.9 billion, accounting for 7.1 percent of total NMES-2 reported expenditures. The authors recognized these were conservative estimates because they did not include all of the direct medical costs attributable to smoking such as burns resulting from fire, perinatal care for low-birth-weight infants, and costs attributable to treating illnesses caused by environmental tobacco smoke. In addition, the indirect costs of morbidity and mortality were not included.

2.3.3 Incidence-Based COI Literature

Oster *et al.* (1984) performed an incidence-based study of the economic costs of smoking and benefits of quitting for individual smokers examining the direct and indirect costs associated with three major smoking-related diseases: lung cancer, coronary heart disease, and emphysema. Costs varied with disease, age, and smoking intensity (light, moderate, or heavy). The total expected lifetime costs for the three illnesses ranged from $1,758 among 75-79 year-old men who were light smokers to $61,304 among 35-39 year-old men who were heavy smokers. The economic costs for women ranged from $1,046 among 75-79 year-old light smokers to $20,901 among 35-39 year-old heavy smokers. Using estimates of excess mortality due to smoking for the three diseases, the authors calculated the economic benefits of quitting. Their findings demonstrated that benefits vary according to age, gender, and disease. They reported that the economic benefits resulting for reduced risk of lung cancer, coronary heart disease, and emphysema ranged from $582 among 75-79 year-old light smokers to $40,829 among 35-39 year-old heavy smokers. The economic benefits to women ranged from $404 among 75-79 year-old light smokers to $13,594 among 35-59 year-old heavy smokers. So as individuals grow older, the economic benefits of quitting diminish because fewer smoking-related medical costs are incurred by the elderly—especially after discounting. And heavy smokers, who typically have higher lifetime medical expenditures, can realize greater economic benefits from quitting than light or moderate smokers.

While Oster *et al.* clearly established that there are significant costs associated with smoking and benefits that can be realized from quitting, the authors did not explore all of the health care costs associated with extending an individual's life through smoking cessation. It is clear that refraining from smoking prevents smoking-related illnesses and increases life expectancy. However, whether the medical expenditures incurred by smokers over their lifetimes are greater than those of nonsmokers is a more complex issue. This is because nonsmokers not only live longer, but they also incur medical expenses during these additional years of life. Whether the medical costs associated with treating smoking-related illnesses over a smoker's relatively shorter lifetime outweigh the medical costs associated with providing a nonsmoker with medical care over a longer lifetime has been debated in a handful of studies found in the literature. The conclusions of these analyses vary considerably according to their estimates of smoking versus non-smoking-related medical costs and their use of discounting.

One such analysis was performed by Leu and Schaub (1983), who studied the cost-of-illness of smoking for Swiss men over the age of 35. They found that the lifetime medical expenditures of nonsmokers exceeded those of smokers due to the costs associated with caring for nonsmokers during their elderly years. The authors assumed that the average smoker had 8 percent more physician visits and 10 percent more hospital visits per year than nonsmokers. They found that the expected lifetime

medical expenditures for the average male smoker at age 35 was 67,900 Swiss francs while the cost for a nonsmoker was 72,700 Swiss francs, indicating that the lifetime medical expenditures of nonsmokers actually exceed those of smokers.

A similar conclusion was drawn by Lippiatt (1990), who used estimates of the cost of smoking and benefits of quitting calculated by Oster *et al.* to calculate the lifetime medical expenditures of smokers versus quitters. To determine the cost of smoking, Lippiatt deducted the average annual per capita medical costs for nonsmokers over the age of 65 for every reduced year of life. This accounts for the fact that smokers, who die prematurely, would have otherwise incurred non-smoking-related medical expenditures in their later years of life. Conversely, average annual per capita medical costs were deducted for every added year of life among people who quit. This adjustment recognized that smoking-related medical expenditures are offset by non-smoking-related health costs incurred during additional years of life saved. Annual per capita medical expenditures for nonsmokers were estimated using per capita expenditures for the total population, the proportion of nonsmokers in the population, and the difference in average medical expenditures of smokers versus nonsmokers as estimated by Leu and Schaub. Lippiatt estimated that, for each additional year of life that it saves, smoking cessation *increased* medical costs by $280.

Hodgson's (1992) study of the lifetime medical expenditures of smoking disputed these earlier findings, claiming that the lifetime medical expenditures of nonsmokers exceed those of smokers. He noted that Leu and Schaub (1983) failed to discount lifetime medical expenditures, thus overstating the expenditures of nonsmokers that are incurred later in life. Furthermore, he argued that Leu and Schaub based their costs on low estimates of the rates of excess medical care use. He cited findings of 2.6-fold excess utilization of physicians' services by smokers compared to nonsmokers and excess use of hospital care over 7.7 times higher. Hodgson also pointed out that Lippiatt's study used underestimates of the cost of smoking and overestimates of the lifetime medical expenditures of nonsmokers. The Oster *et al.* estimates upon which Lippiatt's study were based only consider the costs and benefits associated with lung cancer, coronary heart disease, and emphysema. However, these illnesses are only a portion of all smoking-related diseases and account for less than half of the total short-term hospital days required for all diseases associated with smoking (Graham, 1988). Smoking is also a major agent for chronic bronchitis, cerebrovascular disease, peripheral artery occlusive disease, cancers of the oral cavity, larynx, and esophagus, and bladder. It is also a contributing factor in cancers of the pancreas and kidney, and is associated with stomach and cervical cancers. In addition, Lippiatt relied on Leu and Schaub's (1993) estimate of the average medical expenditures of smokers versus nonsmokers, which underestimates the difference in lifetime medical expenditures between smokers and nonsmokers.

Hodgson's own estimates were markedly different from these earlier findings. Using a life-cycle model, he calculated excess medical expenditures due to smoking totaling $185 billion ($2,324 per smoker) in the first 5 years from his baseline. Hodgson calculated average lifetime medical expenditures using several data sources including: the National Nursing Home Survey for hospital and physician utilization, National Health and Nutrition Examination Survey Epidemiological Follow-up Study for nursing-home care, the American Cancer Society's Cancer Prevention Study II for mortality, the National Medical Care Utilization and Expenditure Survey, and Medicare data files for medical care charges. Medical care expenditures of smokers were compared to individuals who never smoked, broken down by gender and age. Lifetime medical expenditures of moderate male smokers were estimated at $32,891, which was 21 percent higher than never smokers. And heavy smokers were estimated to cost $40,187, which was 47 percent higher than never smokers.

Hodgson's estimates of lifetime medical expenditures employed a discount rate of 3 percent. This adjustment served to place a higher value on the excess medical expenditures incurred by smokers earlier in life than on those health care costs incurred by never smokers because they live longer than never smokers. He determined that the expected medical expenditures of smokers exceed those of never smokers at all ages between 17 and 74. After age 75, the expected medical expenditures of never smokers is greater than those of smokers. This is because, while smokers above the age of 75 have higher medical expenditures than nonsmokers, few actually survive that long. Therefore the *expected* expenditures that would be incurred are less per smoker than nonsmoker. For both men and women, the cumulative excess medical expenditures of smokers rise steadily from between ages 35 and 75. After age 75, these excess cumulative expenditures begin to fall but remain positive through the smoker's lifetime (calculated through age 95).

The fact that smokers have a shorter life expectancy than nonsmokers yet incur greater lifetime medical expenditures leads to variations in the sources of health care financing between smokers and nonsmokers. Hodgson estimated that 50 percent of smokers' lifetime medical expenditures are supported with private insurance, while only 43.7 percent of medical expenditures of never smokers are supported through private insurance. However, because nonsmokers have a longer life expectancy than smokers, a greater proportion of their medical expenses are covered by Medicare, 25.1 percent, while smokers only depend on Medicare for 20.7 percent of their health care costs.

Similarly, one may speculate as to the impact of smoking on the Social Security system. If large number of smokers quit, would there be a corresponding increase in pressure on Social Security as former smokers live longer (primarily, nonproductive years) and qualify for additional years of Social Security benefits? Schelling (1986) recognizes such a possibility and considers that, in the long run, institutions may adapt to account for a healthy population that is living longer, allowing them to be capable and willing to work at older ages than had previously been possible. This would increase society's productive base, offsetting the social costs of the growing elderly population. In the absence of such a transition, however, a population's increased life expectancy should be a welcome trend regardless of the burden that it places on the young, working population.

2.4 Cost-of-Cessation Literature

Table 2-1 lists the significant cost-effectiveness studies in the literature. Differences in intervention, population of interest, study design, and results are identified.

2.4.1 General Methodological Issues

Perspective of Costing. Perspective shapes any study by deciding which costs are important for the potential decision or policymaker. A study's perspective is significant because it often results in excluding some costs while including others. There are four common perspectives for health related studies. A *societal* perspective broadly includes all resources used and considers the welfare of society regardless of when the costs are incurred or who must pay for them. A *payer's* perspective, such as an insurer or government, includes the charges for which the third party is responsible. The *provider's* perspective examines the costs to the particular institution providing health care. Lastly, a *patient's,* or individual's, perspective includes both out-of-pocket costs (i.e., co-payments or deductibles) and time.

We analyzed each of the cost categories defined in the studies to see which costs were consistently included for a particular perspective (Table 2-2). Four cost categories are most relevant for determining perspective: personnel, materials, overhead, and patient time. Personnel includes the wages of physicians, nurses, health educators, and administrative assistants. Materials include both the costs of printed materials and pharmaceuticals. Overhead refers to the overhead costs regardless of a clinical or nonclinical treatment setting. Patient time were the only measure of patient costs identified in the studies.

The societal perspective is best illustrated by Altman *et al.* (1987). The authors provide a thorough analysis of costs, including personnel, materials, overhead, and patient time. Other studies are more vague about perspective. In a study by Marks *et al.* (1990) of a smoking cessation program for pregnant women, patient time is not considered a cost, but personnel, materials, and practice overhead are. The inclusion of these costs implies that the perspective is that of a hospital or organization where the decisionmaker would be responsible not only for personnel and materials, but also overhead. Moreover, in their concluding remarks, they comment that, "based on this analysis and those documenting the health benefits and effectiveness of cessation programs, we conclude that physician third-party payers, managed-care organizations, and public health programs should offer this preventive service to all pregnant women who smoke." This study clearly took the organizational, payer, and hospital perspective.

A problem arises when a study includes a cost that conflicts with the stated, or implied, perspective of the study. Hughes *et al.* (1991) test whether patients who must pay for the cost of nicotine gum have better outcomes. By concluding that it is cost-effective for "prepaid or health insurance plans to reimburse patients for nicotine gum prescriptions," he implies that his perspective is that of a payer, hospital, or organization. In his inventory of costs, however, he includes patient time as a cost at $10/hr. and comments that he did not include the costs for evaluation and promotion because "the typical medical practice would not likely spend money for these activities." While excluding these costs would not alter the authors' conclusion, patients' costs are not incurred by the payer and

Table 2-1. Smoking Cessation Programs

Author	Year	Intervention	Population	Study Design	Result
Davis, et al.	1984	Four alternatives: 1. ALA leaflet 2. leaflet and maintenance manual 3. cessation manual 4. cessation and maintenance manual	Community (n=1237)	CEA/ randomized experiment	Cost per quitter: 1. $921 2. $497 3. $669 4. $396
Oster, et al.	1986	Counseling and nicotine gum	Routine office visit by patient (n=250)	CEA/ meta-analysis	Cost per life-year saved: Men: $4,113 - $6,465 Women: $6,880 - $9,473
Altman, et al.	1987	Three alternatives: 1. class 2. contest 3. self-help kit	Community (n=1140)	CEA/ quasi-experimental	Cost per quitter: 1. $235-$399 2. $129-$235 3. $ 22-$144
Windsor, et al.	1988	Three alternatives: 1. information and advice 2. advice plus smoking cessation manual 3. advice, manual, and manual for smoking women	Pregnant women (n=309)	CEA/ randomized experiment	Cost per quitter: 1. $104 2. $119 3. $51
Cummings, et al.	1989	Physician counseling (includes self-help booklet)	routine office visit (n=3290)	CEA/ meta-analysis	Cost per life-year saved: Men: $705 - $988 Women: $1,204 - $2,058
Ershoff, et al.	1990	Self-help printed materials	Pregnant women in large HMO (n=323)	CBA/ randomized clinical trial	Benefit cost ratio: 3.17:1
Marks, et al.	1990	Health educator or nurse managed counseling program (includes self-help materials)	Pregnant women (n=783,510)	CEA using published effectiveness research	Cost per neonatal year of life saved: $2,934
Hughes, et al.	1991	Physician counseling and nicotine gum (includes self-help book) Three costs to patient for gum: 1. free 2. $6 3. $20	Routine office visit in rural family practice (n=106)	CBA/CEA randomized experiment	Cost per quitter: 1. $725 2. $1,656 3. $735
Krumholz, et al.	1993	Nurse-managed smoking cessation program (includes self-help materials)	Post-acute myocardial infarction (AMI) patient (n=2426)	CEA using published effectiveness research	Cost per life-year saved: $220
Fiscella and Franks	1996	Physician counseling and nicotine patch and gum	Brief office visit	CEA simulation using published effectiveness research Developed own QALY adjustment to life-years saved	Cost per QALY-adjusted life-year saved from use of patch: male, age 45 = $4,671 Cost per quitter = $7,332 Cost per QALY-adjusted life-year saved from use of gum: male, age 45 = $10,000

Table 2-2. Comparison of Cost Factors

Study	Personnel	Materials	Overhead	Patient Time
Davis, et al.	♦	♦		
Oster, et al.	♦	♦		
Altman, et al.	♦	♦	♦	♦
Windsor, et al.	♦	♦		
Cummings, et al.	♦	♦		
Ershoff, et al.	♦	♦	♦	
Marks, et al.	♦	♦	♦	
Hughes, et al.	♦	♦		♦
Krumholz, et al.	♦	♦		

would be excluded from studies using a payer perspective.

In addition to including costs that do not belong to a perspective, a study can also exclude costs as well. Cummings *et al.* (1989) investigated the cost-effectiveness of counseling smokers to quit during a routine office visit, stating early on that "we assumed a societal perspective in our analysis." In the cost analysis, however, patient costs are ignored. The authors reconcile this omission by stating that the patient counseling session occurs within the context of a routine office visit. Even so, physician time is calculated as a percentage of time in the routine office visit and the patient time can be done similarly. Moreover, during sensitivity analysis, a follow-up visit dedicated solely to smoking cessation counseling is considered, and yet, patient time is again not included. One explanation for the exclusion of these costs may be that they are considered incidental, and therefore unlikely to affect the cost-effectiveness ratios. This may or may not be true.

One study included costs more relevant to the development and evaluation of the intervention than the cost of the intervention alone. Davis *et al.* (1984) report on self-help smoking cessation materials offered through the American Lung Association. Because the study solely evaluates self-administered smoking cessation programs, costs should be minimal, including the cost of materials and patient time. Instead, the study includes the costs of patient recruitment, interviewer wages, staff wages for training interviewers (though not telephone utility bills). Interviewers "were specifically advised that their task was to collect data and not to encourage the participant in their efforts to quit smoking." Unfortunately, patient time, which seems important in this self-help study, is not included, and there is no reference to the amount of time necessary to read the printed materials.

In some studies, it is reasonable to exclude certain costs. Ershoff *et al.* (1990) studied an intervention in an HMO for pregnant women, partially funded by the HMO. The study included the costs of personnel, materials, and overhead, but excluded the cost of patient time, which is consistent for a study taking the organizational perspective. Oster *et al.* (1986), in evaluating the cost-effectiveness of a nicotine gum therapy in a routine office visit, includes only personnel and materials as a cost. From a payer, hospital, or organizational perspective, it might appear inappropriate to exclude overhead costs. One explanation is that overhead charges would have been included in the physician's charge for a routine office visit. Similarly, Krumholz *et al.* (1993) in their evaluation of a nurse-managed smoking cessation program for treating smokers with acute myocardial infarction, exclude both overhead and patient time. These are legitimate exclusions because the patients are hospitalized so they presumably cannot work and do not utilize resources in excess of the those that place them in hospitalization.

Defining and Measuring Costs. Commonly the most expensive cost factor in the studies was personnel (Table 2-3). The hourly wage assigned to personnel, on the average, increased according to education level, ranging from $9.62/hr. to $150/hr. Physicians had the highest hourly wage, nurses had the next highest, health educators and individuals with bachelor degrees less, and administrative support the lowest.

The wage for each education level, however, was not uniform across studies. Physicians' imputed hourly wages ranged from $150/hr. (Hughes *et al.*, 1991) to $50 (Oster *et al.*, 1986). Moreover, because

Table 2-3. Variation in Hourly Personnel Costs by Degree

Study	Personnel Degree	Hourly Rate
Krumholz	R.N.	$30
Davis	B.A.	$9.62
Cummings	M.D.	$30
Windsor	B.A.	$12
Oster	M.D.	$50
Ershoff	B.A. or R.N.	$33.00
Hughes	M.D.	$150
Marks	B.A./M.A./R.N.	$15
Altman	N/A	N/A
Mean		$37

N/A = Not Applicable

physicians do not usually charge by the hour, but by the type of office visit, Cummings reported an office visit charge to be $30, but reasoned that only one-third of the time would be devoted to the smoking cessation advice.

Nurses' hourly wage rates were more similar. Krumholz *et al.* (1993) and Ershoff *et al.* (1990) both report hourly wages at approximately $30/hr. The duties assigned to the Ershoff wage rate of $30/hr. can also be performed by a B.A. trained individual. Marks *et al.* (1990) also averages the personnel wage for B.A., M.A., and R.N. trained personnel, but comes to a lower figure of $15/hr.

Length of Interactions. Personnel costs account for the greatest share of intervention costs. Another variable factor is the length of the interaction between personnel and program participants. Table 2-4 describes the nature of the interaction between personnel and participants. It lists the intervention type, personnel type, and length of interaction (initial, follow-up, and total) incorporated into each analysis.

Physicians spent less time with patients than other personnel types. The physician time in the Oster and Cummings studies was 5 and 4 minutes, respectively, and 10 minutes in Hughes *et al.* (1991). Cummings allotted an additional 12 minutes for a follow-up visit and Hughes an additional 5-10 minutes. Overall, the amount of time for physician counseling was between 5 and 20 minutes.

The counseling time by physicians is dwarfed by the counseling offered in nurse-managed smoking cessation programs. Marks *et al.* reported 75 minutes and Krumholz *et al.* reported 180 minutes. Moreover, Windsor *et al.* (1989), a study that relied primarily on printed materials and advice provided by nurses or bachelor-degreed health educators, involved minimal counseling and follow-up support for between 10-15 minutes varying with the intervention type.

Table 2-4. Comparison of Intervention Length and Personnel

Study	Intervention Type	Personnel	Length of Time (Minutes)		
			Initial	Follow-up	Total
Marks	counseling	R.N., H.E.*	15	2x30 min.	75
Ershoff	printed materials	H.E.	45	n/a	45
		H.E.	48	n/a	48
Oster	counseling/nicotine gum	M.D.	5	n/a	5
Cummings	counseling	M.D.	4	12	16
Windsor	advice, printed materials	B.A. or R.N.	5	2,3	10
		B.A. or R.N.	10	2,3	15
		B.A. or R.N.	10	2,3	15
Altman	class	H.E.	60	7x60+	540
Davis	printed materials	n/a	n/a	n/a	n/a
Krumholz	counseling/materials	R.N.	unspecified	7x??	180
Hughes	counseling/nicotine gum	M.D.	10	5,10	15-20

* = health educator
n/a = not applicable

Studies with the greatest interaction between personnel and participants employed health educators, which might include both bachelor and masters' trained health professionals. These professionals were involved in explaining the use of printed materials (Ershoff *et al.*) and teaching a health care class (Altman *et al.*). Depending on whether the participant received the additional 3 minutes of time hearing about the self-help materials, participants received either 45 or 48 minutes of personnel time. Participants enrolled in the smoking cessation class in Altman *et al.* received about 9 hours of time.

The intensive smoking cessation option outlined in the *Guideline* (see Chapter 3) recommends more patient-provider interaction than the less intensive physician interventions. However, these intensive inventions may involve less costly professionals or counseling in a group setting, which may offset (in whole or in part) the marginal increase in patient-provider interaction. The challenge of our cost-effectiveness analysis was to understand the dynamics of these varying costs relative to any marginal changes in effectiveness that they may encourage.

Discounting. Because most of the costs associated with providing smoking cessation interventions are direct medical costs that occur over a short period of time, these costs are largely unaffected by discounting. However, smoking cessation outcomes, which are normally measured in years-of-life-saved, occur over an extended period of time. Weinstein and Stason (1976) argued that if years-of-life-saved are not discounted, then there is no incentive to save lives in the present and health care spending is deferred. In other words, in the absence of discounting, it makes sense to invest money elsewhere to increase per capita incomes that could be used to support greater health care spending in the future. Discounting current years-of-life-saved recognizes that *effects*, like costs, are more valuable in the present than at some future time.

Only four of the cost-effectiveness studies reviewed employed discounting: Cummings *et al.* (1989), Krumholz (1993), Fiscella and Franks (1996), and Oster *et al.* (1986). The study by Cumming *et al.* drew from discounted life expectancy estimates calculated by Oster *et al.* Both Krumholz *et al.* and Oster *et al.* employed a discount rate of 5 percent to estimate life expectancy and tested their results using sensitivity analysis. For example, Oster *et al.* estimated that the average man between 40 and 44 years of age who quits smoking saves 4.6 years of life. The 5 percent discounted effect, however, is only 1.07 years saved. Men between 65 and 69 years of age save an undiscounted 1.32 years of life due to quitting. Discounted, this figure becomes .66 years.

Oster *et al.* tested the sensitivity of their 5 percent discount rate by applying rates of 3 and 7 percent. Table 2-5 shows these cost-effectiveness results using nicotine gum. It is not surprising that at the lower discount rates, the cost per year of life saved is substantially lower. Thus, discounting both costs and life-years saved can greatly effect the final results of a cost-effectiveness analysis.

Table 2-5. Cost of Nicotine Gum per Life-Year Saved Evaluated at Different Discount Rates

Discount Rate	Range of Cost per Year of Life Saved	
	Men	Women
3%	$2,516 - $4,995	$4,249 - $7,114
5%	$4,748 - $6,465	$8,996 - $9,473
7%	$6,141 - $8,214	$10,299 - $16,317

Source: Oster, G; Huse, D.; Delea, T; and Colditz, G.: "Cost-Effectiveness of Nicotine Gum as an Adjunct to Physician's Advice Against Cigarette Smoking." *Journal of the American Medical Association.* 256(10):1986, p. 1316.

Fiscella and Franks (1996) cite a recent panel of experts who recommend that 3 percent be used to discount life-years saved.

2.5 Cost-Effectiveness Literature of Comparable Medical Interventions

To assess the cost-effectiveness (CE) of the *Smoking Cessation Guideline*, other benchmark CE ratios are needed. Given methodological variations across cost-effectiveness analyses, comparisons among different studies are difficult to make. Inconsistency in perspectives, cost categories identified, the reliability of effectiveness findings, the populations studied, and the discount rate employed frequently occur among studies making resulting cost-effectiveness ratios impossible to compare without adjustments to the original methodology. Some analysts, however, have attempted to compare disparate interventions by calculating a series of cost-effectiveness ratios using a methodologically consistent approach.

Table 2-6 presents the results of three literature reviews. The first review by Eddy (1992) includes the cost-effectiveness results of a series of screening

Table 2-6. Comparisons of Cost-Effectiveness Ratios

Author	Intervention	Cost per Year of Life Saved
Eddy (1992)	Cervical cancer screening	$1,429 - $667
	Colorectal cancer screening	$1,429 - $667
	Mammography	$3,333 - $1,429
	Hypertension screening	$3,333- $1,429
	Cholesterol screening	$3,333 - $10,000
	Anti-tobacco education program	$143
Russell (1984)		
OTA (1981)	Influenza vaccine (all ages)	$2,700
Cretin (1977)	Cholesterol screening for boys screened at age 10	5,700-11,200
Willems et al. (1980)	Pneumococcal vaccine (all ages)	$6,700
Weinstein and Stason (1976)	Hypertension screening and treatment	$11,800
Tengs et al. (1994)	**Smoking Cessation**	
Marks et al. (1990)	Advice for pregnant smokers	≤$0
Cumming et al. (1989)	Advice for men age 35-54	$989 - $1,050
Cumming et al. (1989)	Advice for women age 35-54	$1,386 - $2,888
Oster et al. (1986)	Nicotine gum and advice for men 35-69	$7,460
Kristein (1977)	Advice for heavy smokers	$9,799
Oster et al. (1986)	Nicotine gum and advice for women 35-69	$11,473
	Other Selected Interventions	
White et al. (1985)	Measles, mumps, and rubella immunization for children	≤$0
Knox (1988)	Mammography every 3 years for women 50-65	$2,706
England et al. (1989)	Colorectal cancer screening for people age 40+	$4,524
Bryers et al. (1978)	Hypertension screening for men 45-54	$5,153
Moskowitz and Fox (1979)	Annual mammography and breast exam for women 35-49	$10,477

Notes: Costs calculated by Tengs et al. are expressed in 1993 dollars. Costs that are calculated by Russell are in 1981 dollars. Tengs et al. and Russell employed a discount rate of 5 percent. OTA (1981), Willems et al., (1980), and Weinstein and Stason (1976) results represent life-years adjusted for health status. Tengs' estimates were calculated by dividing the net marginal costs of the intervention by the net margin years of life saved. Therefore, some results are less than zero.
Sources: Eddy, D.M. David Eddy ranks the test. Harvard Health Letter. July 1992, pp. 10-11. Russell, L.B. The economics of prevention. Health Policy. 4(1984), p. 93. Tengs, T.; Adams, M; Pliskin, J.; Safran, D.; Siegel, J. Weinstein, M.; and Graham, J. Five-Hundred Life Saving Interventions and Their Cost-Effectiveness. An unpublished report developed by the Harvard Center for Risk Analysis supported by research grant SES-9110225 from the National Science Foundation.

tests. He assumed that the tests were performed using the methods and intervals that were most cost-effective and that the individuals targeted for the intervention did not have any risk factors. Cervical cancer and colorectal screening were found to be the most cost-effective screening tests ($667-$1,429 per year of life saved) while mammography and hypertension screening (both between $1,429 and $3,333) were placed in a slightly less, but still excellent, cost-effective tier of screening tests. Cholesterol screening ($3,333-$10,000) was deemed more costly than the other screening tests for each year of life that it saves. Eddy then attempted to put the cost-effectiveness of these screening tests into perspective by considering a smoking education program that costs $1,000 to get a single smoker to quit. He determined that this program would cost $143 for each year of life that it saves, making it a far more cost effective intervention than any of the screening tests that he examined.

Russell (1984) compared cost-effectiveness ratios from four different studies. These studies were chosen because they used similar methods, each examining only medical care costs. Results were adjusted to 1981 dollars. She found that influenza vaccination was relatively more cost effective than pneumococcal vaccination ($2,700 versus $6,700 per year of life saved). Hypertension screening was more costly than both of these interventions per year of life saved ($11,200). Cholesterol screening cost

from $5,700-$11,200 per year of life. However, this result was based on *healthy* years of life saved, making it difficult to compare to the other interventions.

Tengs *et al.* (1994) recalculated a series of cost-effective ratios, expressed in cost per life-year saved, for 587 interventions. A few selected interventions are listed in Table 2-6. Note the variation in smoking cessation studies. Differences in gender, age, smoking intensity, and cessation method led to varying cost-effectiveness ratios. The results ranged from less than $0 per year of life saved (i.e., it generated savings due to lower net medical costs over one's lifetime) for advice to pregnant women to $11,473 per year of life saved for nicotine gum and advice to women between ages 35 and 69. Other interventions that Tengs *et al.* reviewed exhibited similar variations. While measles, mumps, and rubella immunization for children all exhibited negative net costs per life-year saved, annual mammographies and breast exams for women ages 35 to 49 cost $10,477 per year of life saved. The latter interventions proved to be more costly than most smoking cessation interventions.

3.0 Description of AHCPR's *Smoking Cessation Guideline*

The *Guideline* presents recommendations based on a series of meta-analyses that draw from published literature in the area of smoking cessation and identify variations in effectiveness among different interventions for selected populations. Recommendations are directed at three target audiences: (1) primary care clinicians, (2) tobacco cessation specialists/programs, and (3) health care administrators, insurers, and purchasers. Our analysis addresses the first two sets of recommendations.

Following the presentation of the model smoking cessation interventions, the *Guideline* presents research evidence pertaining to individual interventions and special issues (e.g. gender, pregnancy, hospitalized smoker). Based on the results of the meta-analyses in these areas, the *Guideline* Panel rated the strength of the research evidence and used these assessments to develop their sets of recommendations.

3.1 Overview of Stylized Approach

The *Smoking Cessation Guideline* is different from practically all the other AHCPR guidelines. Many previous guidelines have been procedure oriented with a focused population faced with a given condition, e.g., poor vision, ischemic heart disease. The *Smoking Cessation Guideline* does focus on smokers, but they are an addicted group that must be treated primarily using psychological and pharmacotherapy interventions. Hence, unlike, say, cataract surgery where the eye responds fairly uniformly to treatment, smoking cessation interventions have a wide variety of outcomes with relatively modest success rates.

Another difference is the rather vague notion of "current practice." In other guidelines, researchers have had a wealth of claims data available in order to track the services and procedures currently performed on patients. No such claims trail exists for smoking cessation. This makes costing the *Guideline* against "current practice" almost impossible. Further complicating the definition is the multidimensional aspect of "current practice." Counseling is a key intervention performed by a variety of physicians and other clinical professionals. Who conducts the counseling may change the intervention in material ways. The duration of counseling has been found to be important in achieving better outcomes; yet, the length of treatment varies widely across patients and providers in unknown ways.

Smoking cessation is more closely related to disease prevention than procedure-oriented interventions. Acute interventions usually result in immediate relief and measurable improvements in health status. Smoking cessation programs focus on quit rates, which may be analogous to a patient's "surviving the operation." The latter is only meaningful if the operation substantially improves health status. Similarly, quitting smoking is of little interest by itself. More relevant is the long-run quit rate and the expected gains in health status. Significantly delayed health benefits raise several issues to greater prominence than in other guidelines. What discount rate to use? If benefits are postponed 20-30 years, the choice makes a big difference. What changes in health status are associated with quitting? With most other interventions, causality is more demonstrable, although the cessation literature is fairly comprehensive on this point.

3.2 Major Intervention Strategies

The primary care clinician recommendations are designed to "change clinical culture and practice patterns so as to ensure that every patient who smokes is offered cessation treatment." The *Guideline* suggests that this should be accomplished by providing a brief smoking cessation message for all smokers at an initial clinical visit. The following five steps are recommended.

1) Screen every patient to determine smoking-status;
2) Advise all smokers to quit;
3) Determine those smokers willing to quit;
4) Assist smokers to successfully quit by setting a quit date, offering nicotine replacement (when appropriate), providing self-help materials, and giving advice on successful quitting; as well as
5) Scheduling a follow-up counseling visit (either in person or via telephone).

Smoking cessation specialists/programs offer more intensive interventions. However, the *Guideline* recognizes that only a minority of smokers will wish to participate in these programs and that resources may not be available for all willing smokers. Intensive interventions begin with screening and advice from a primary care clinician. However, rather than assisting the smoker with his/her quit

attempt, the primary care clinician refers the patient to a smoking cessation specialist for a series of individual or group counseling sessions. The *Guideline* recommends that patients be provided the option of intensive counseling pending the availability of resources. The following suggestions were made for smoking cessation specialists:

- Assess whether smokers are motivated to quit via an intensive cessation program;
- Use multiple types of providers;
- Provide sessions that are at least 20-30 minutes in length;
- Provide 4-7 sessions over a period of 2-8 weeks;
- Provide individual or group counseling that includes problems-solving and/or skill training as well as in-treatment support; and
- Offer transdermal nicotine replacement (except in special circumstances).

3.2.1 Decision Flow Chart

Figure 3-1 depicts the recommendations in the *Guideline* outlining the different smoking interventions delivered by primary care clinicians and smoking cessation specialists. Patients enter the flow chart via an office visit to their primary care clinician or admission to a hospital. All patients are screened to determine their smoking status. Patients who do not smoke are either provided with relapse prevention or primary prevention to ensure that they maintain their nonsmoking status. Every patient that smokes is advised to quit. Those who are unwilling to make a quit attempt after receiving this initial advice are provided with a brief motivational message further encouraging them to undergo an intervention. Smokers who are still unwilling to quit after receiving a motivational message exit the flow chart and do not re-enter until their next visit their primary care clinician or hospital admission.

For those patients who are willing to quit after being advised by their primary care clinician, there are four different intervention options. The *Guideline* has determined that all of these interventions are effective: (1) clinician minimal visit, (2) clinician brief visit (3) clinician full counseling, and (4) behavioralist intervention. The first three of these interventions are provided by the primary care clinician in an office setting. They only differ in the length of time that the patient is counseled: less than 3 minutes, 3-10 minutes, or greater than 10 minutes. Each of these interventions involves follow-up time with the clinician. Minimal and brief counseling involve one follow-up visit within 2 weeks of the intervention. Minimal follow-up is only 3 minutes long, whereas brief follow-up involves 10 minutes of clinician time. The full counseling intervention involves the greatest amount of clinician time and includes two follow-up visits each 10 minutes long. The first follow-up visit is provided in the second week after the intervention, and the second follow-up visit provided in the fourth week after the initial intervention. Patients who choose the fourth intervention, behavioralist intensive counseling, are referred to a smoking cessation specialist for a series of individual or group intensive counseling sessions. Smokers receiving individual intensive counseling are provided with five 30-minute sessions, and smokers receiving group intensive counseling attend seven 1-hour sessions along with nine other smokers.

All smokers[1] willing to make a quit attempt are provided the option of using pharmacotherapy. Patients willing to use pharmacotherapy, may choose either transdermal nicotine (the patch) or nicotine gum. For light smokers, those who smoke 10-15 cigarettes per day or less, the *Guideline* recommends that the clinician consider lowering the starting dosage of the preferred treatment.

After completing their intervention, smokers making a quit attempt re-enter the *Guideline* during their next visit to their primary care clinicians or period of hospitalization. Their smoking status is determined, and those that have successfully quit are provided relapse prevention. Unsuccessful quitters are encouraged to make another quit attempt.

3.2.2 Detailed Description of Interventions

The *Guideline* addresses seven intervention dimensions: 1) provider, 2) format, 3) intensity of person-to-person contact, 4) content of intervention, 5) self-help, 6) duration of intervention, and 7) pharmacological aides. Meta-analyses were performed in each of these areas, and recommendations were made based on the results. Within most dimensions, several variations of the intervention were deemed effective. The panel, however, chose not to focus on comparing interventions, but instead identified all of the interventions that were considered effective and recognized that "the selection or use of a particular intervention technique or strategy is usually a function of practical influences: time available,

[1]The *Guideline* recommends the pregnant women receive pharmacotherapy only if the increased likelihood of smoking cessation, with its potential benefits, outweigh the risk of nicotine replacement and potential concomitant smoking.