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SMOKLER CENTER FOR HEALTH POLICY RESEARCH

Cost-Utility Analyses of Interventions to Reduce the Smoking-Related Burden of Disease in Israel

Gary Ginsberg

in collaboration with

Bruce Rosen ♦ Elliot Rosenberg



RESEARCH REPORT

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Gary Ginsberg

Israeli Ministry of Health, Medical Technology Assessment Sector

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Bruce Rosen

*Smokler Center for Health Policy Research
Meyers-JDC-Brookdale Institute*

Elliot Rosenberg

*Israeli Ministry of Health
Healthy Israel 2020 Initiative*

Myers-JDC-Brookdale Institute
Smokler Center for Health Policy Research
P.O.B. 3886
Jerusalem 91037, Israel
Tel: (02) 655-7400
Fax: (02) 561-2391
Web site: www.jdc.org.il/brookdale

Executive Summary

Introduction

Smoking is a serious and expensive risk factor for many chronic diseases. In 2008, the smoking-related burden of disease in Israel was approximately 96,000 QALYs (Quality Adjusted Life Years). Included in that figure are around 9,000 deaths. In economic terms, in 2008, the direct cost to Israel's health services was roughly NIS 1.75 billion, the equivalent of 0.25% of the country's Gross National Product (GNP).

Multiple effective tobacco control interventions exist. No one single intervention can totally reduce the considerable burden of disease from smoking. Therefore, a multi-faceted approach is required, combining public health interventions such as smoke-free legislation, counter-advertising, and increased taxation with a variety of clinical and community-level prevention and cessation interventions. As public resources are limited and do not suffice to fund all the possible interventions, it is necessary for policymakers to prioritize them.

Objectives

The objective of the study was to assist Israeli policymakers in their efforts to prioritize interventions and develop a national tobacco-control program by calculating cost-effectiveness ratios of interventional modalities known to reduce the smoking-related burden of disease.

Methods

Internationally-derived, evidence-based intervention effectiveness were modeled to Israeli epidemiologic, economic and demographic conditions. A twenty-five year horizon and only direct costs were included in the model. The analysis covered fiscal and clinical interventions. Public health interventions such as those delivered at schools, worksites and other community settings were not covered as the literature does not provide sufficient information to calculate generalizable cost-utility analyses.

For all interventions involving medications and prescription nicotine substitutes, the calculations took into account the investment of physician time required for initial assessment, smoking-cessation counseling, pharmacotherapy assessment (including screening for possible contraindications), communication of the steps to be taken if side effects emerge, and follow-up to both provide encouragement and monitor for side effects.

Results

Eight cost-saving and 13 very cost-effective interventions were identified. Cost-saving interventions are those where the treatment costs averted by the decrease in morbidity exceed the cost of the intervention. Very cost-effective interventions are those that achieve an increase in QALYs at a relatively low cost (the cost per QALY is less than the per capita GNP, in keeping with the accepted WHO criteria).

Cost-Saving Interventions (ranked by descending order of QALYS saved)

- 1) Raising the tax on tobacco products from the current rate of 62% of the base price to at least 150%
- 2) Varenicline (2mg/day)*
- 3) Raising the tax on tobacco products from the current rate of 62% of the base price to 100%
- 4) Medication and quitline counseling
- 5) Clonidine**
- 6) Nortriptyline**
- 7) Raising the tax on tobacco products from the current rate of 62% of the base price to 75%
- 8) A national tobacco cessation quit-line, in which at least part of the calls are initiated by the counselor

Very Cost-Effective Interventions (ranked from lowest to highest cost per QALY saved)

- 9) Nicotine Lozenges
- 10) Varenicline (1mg/day)*
- 11) Nicotine patch, alone and in combination with second generation anti-depressants
- 12) Bupropion SR (Slow Release)
- 13) Nicotine Gum (6-14 week course)
- 14) High dose nicotine patch (>25mg)
- 15) Medication and counseling.
- 16) Group Counseling
- 17) Nicotine Nasal Spray
- 18) Long-term Nicotine Patch (>14 weeks)
- 19) Long Term Nicotine Gum (>14 weeks)
- 20) Individual counseling
- 21) Nicotine Inhaler

Policy Implications

To provide a wide selection of interventions likely to assist a variety of smokers, a combination of the five non fiscal cost-saving and the top eight very cost-effective interventions listed above could be chosen for implementation. Assuming, each intervention would be aimed at approximately 8% of smokers, the NIS 539-million initial intervention cost could be covered by earmarking most of the increased revenues from a tobacco tax increase from 62% to 100%. Approximately NIS 790 million would be saved as a result of decreases in treatment costs due to the programs and the tax increase. Consequently, this package would save about NIS 261 million and 50,796 QALYs.

Caveat: *The FDA, EMEA and other organizations have raised concerns about the safety of some of the medications. Policy-makers should continue to monitor the information that will be emerging on these issues.*

* Pending determination of ultimate relative risk on the basis of additional studies

** Considered a second-line intervention due to its side-effect profile

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1. Introduction

Cost-utility analysis (CUA) combines the disciplines of epidemiology, medicine and economics in order to rank projects according to the Cost per QALY (Quality Adjusted Life Years) saved. CUA is now used by many countries throughout the world as a necessary (but not sufficient) tool in deciding health-service priorities. Other factors such as equity and political pressure may need to be taken into account.

In addition, the use of CUA enables preventive and curative projects to compete for limited societal resources on a "level playing field", thus making it possible to avoid the universal domination of preventive medicine by curative/therapeutic medicine.

In 2005, the Ministry of Health launched the Healthy Israel 2020 initiative. Under its auspices, roughly 300 professionals have been involved in developing Year 2020 health objectives, targets and interventions within the context of 20 different committees. The work of three subcommittees of the Health Behaviors committee focused on the areas of obesity control, smoking control, and enhancement of physical activity. Subcommittee members have recommended a variety of interventions in their respective areas. To implement them in a resource-limited environment, they need to be prioritized, first within subcommittees, and then between them.

This study is the first comprehensive CUA assessing interventions to reduce the burden of disease from smoking within the Israeli healthcare system. It is the second in a three-part series assessing the CUA of key health behaviors. A forthcoming report in this series will address interventions to prevent and treat obesity.

2. Methods

All the interventions in this review were costed in an Israeli context. Estimates were made of the averted treatment costs and the increases in QALYs due to decreased smoking-related morbidity and mortality. These provide an objective method of prioritizing potential interventions according to their cost-utility ratios (i.e., the net cost of providing one extra QALY).

2.1 Estimation of Smoking-Attributable Mortality (SAM)

Smoking is the biggest single preventable risk factor for mortality in developed countries (WHO, 2002). Globally, tobacco-attributable deaths are projected to rise from 5.4 million in 2005 to 6.4 million in 2015 and to 8.3 million in 2030 (Mathers, 2006). As a result of decreasing trends in prevalence in high-income countries, tobacco-attributable deaths are projected to decline by 9% between 2002 and 2030, but to double from 3.4 million to 6.8 million in low- and middle-income countries due to the impact of increasing tobacco consumption over past decades (Mathers, 2006).

In Israel, evidence submitted to the national Gillon Commission (Gillon, 2000), convened during 2000 and 2001 with the mandate to recommend strategies to help reduce the national health and economic burden due to smoking, estimated the burden in 1999 to be 9,527 deaths from active smoking and a further 1,385 deaths from passive smoking by fetuses, children, spouses and workmates. These estimates were based on an assumed nine-year lag period for each of the diagnoses but did not consider elevated risks in former smokers and were not based on age-specific categories.

The U.S. Centers for Disease Control (CDC – Centers, 2008) provides a widely-used, on-line, user-friendly calculator called SAMMEC (Smoking Attributable Mortality, Morbidity, and Economic Costs) to produce estimates of tobacco-related mortality. However, SAMMEC has several weaknesses: it does not include some diseases such as diabetes which have subsequently been proven to be smoking-related (Fox, 2005), some cancer-related relative risks are based on studies (Centers-Data, 2008) carried out as long ago as the 1980s, it limits its calculations to adults over the age of 35 and most importantly, the standard SAMMEC approach does not take into account the latency period that occurs between exposure to the risk factor (tobacco) and tobacco-induced morbidity.

A recent estimate (Ginsberg, 2008) of mortality from active smoking in Israel was adjusted for some of the deficiencies of the SAMMEC calculator by utilizing an expanded list of diseases derived from an updated assessment of the scientific literature, by making allowances for lag-times and by including deaths in persons aged 20 and above. The calculations (Table 1) estimated SAM to be 8,932 persons in 2007, including 185 deaths averted due to the protective effect of smoking on Parkinson's Disease. Cardiovascular causes account for 43% of SAM, malignant neoplasms for 29%, and respiratory diseases 14%. Six specific diagnoses accounted for 72% of SAM: coronary artery disease (25%), lung cancer (14%), chronic obstructive pulmonary disease (including emphysema) (11%), diabetes (10%), cerebrovascular disease (5.5%) and acute myocardial infarction (5.1%).

These 8,932 deaths account for 21.4% of the total mortality in Israel in 2007. This parallels the 19.5% figure estimated by the CDC for the United States and reported in the 2004 Surgeon General's Report (U.S. Surgeon, 2004). The higher Israeli estimate presumably reflects the slightly higher smoking rates in Israel.

Thus, despite the decline in smoking rates from the 1970s and 1980s when the prevalence of male and female smoking was 40-50% and 26%-31%, respectively, smoking still constitutes a major (if not the major) preventable public health risk in Israel.

Table 1: Active Smoking-Attributable Mortality - Israel 2007

	Males	Females	Total	
Malignant Neoplasms				
Bladder	130	37	167	
Unspecified	94	83	177	
Cervical	0	11	11	
Esophageal	38	26	64	
Laryngeal	40	11	52	
Leukemia	93	110	203	
Lung	949	338	1287	
Lip, Buccal, Pharynx	42	17	59	
Pancreatic	137	110	247	
Renal	55	23	77	
Stomach	141	77	218	
Ureter	1	44	44	
Other Cancers	1	9	10	
Sub-Total	1721	895	2616	29.3%
Respiratory Diseases				
Tuberculosis	4	1	5	
Bronchitis	1	1	2	
COPD including emphysema	565	457	1022	
Pneumonia	7	6	13	
Asthma adults	21	29	50	
Other Respiratory	75	78	154	
Sub-Total	674	572	1246	13.9%
Cardiovascular Diseases				
Rheumatic heart disease	6	9	15	
Hypertension	78	95	173	
Coronary artery disease	1230	1029	2259	
Coronary heart disease	350	332	682	
Cardiac dysrhythmias	25	10	35	
Myocardial infarction	154	305	458	
Peripheral vascular disease	76	102	178	
Other heart disease	5	5	10	
Sub-Total	1924	1886	3810	42.7%
Cerebrovascular Diseases				
Cerebrovascular disease	294	196	490	5.5%
Digestive System Diseases				
Crohn's disease	4	2	6	
Peptic ulcers	0	6	6	
Stomach ulcers	3	1	3	
Other ulcers	14	13	27	
Inguinal hernias	2	1	2	
Ulcerative colitis	2	1	3	
Sub-Total	25	23	48	0.5%
Endocrine-Metabolic				
Diabetes	449	456	905	10.1%
Other Disorders				
Burns	1	1	1	
Parkinson's Disease	-95	-90	-185	
Viral disease	0	0	1	
Sub-Total	-94	-89	-183	-2.1%
Total	4993	3939	8932	100%

2.2 Calculating Cost-Utility

The basic formula used for calculating the cost per QALY is

$$\text{Cost per QALY} = \frac{\text{Net Cost of Intervention}}{\text{QALYs gained}}$$

where:

Net Cost of Intervention = Costs of (intervention) program less the savings achieved in treatment costs as a result of decreased morbidity due to implementation of the program.

QALYs gained = Gain in QALYs as a result of decreases in disease incidence and mortality due to the intervention.

The Average Cost Effectiveness Ratio (ACER) and The Incremental Cost Effectiveness Ratio (ICER) are the two types of cost-effectiveness ratios that are widely reported in the literature:

This analysis primarily provides estimates of the ACER of each intervention. The ACER relates the net costs of the intervention (compared with a do-nothing scenario) to the gain in QALYS as a result of the intervention. Using the ACER answers the question of whether the intervention is worthwhile per se.

The ICER relates the incremental net costs of the intervention (compared with an alternative intervention) to the incremental gain in QALYs (compared with an alternative intervention) as a result of the intervention. The ICER provides decision-makers with information comparing a typically new intervention, A, versus remaining with an existing intervention, B.

Except for the specific case of Physician Advice to Quit (see Appendix II), the ACER was used. The net efficacy of the intervention was calculated by deducting the 10% annual background quit rate, derived from the weighted average from the various placebo groups listed in the meta-analyses in Fiore et al. (Fiore, 2008). The 10% background rate was identical to the rate used by cigarette manufacturers in their marketing projections (Unknown, 2001). This efficacy data was used to provide estimates of the RR (relative risk) of persons abstinent from smoking at least 26 weeks after quitting.

2.2.1 Cost of Interventions

Included are the direct costs viewed from a "narrow" health services perspective as there are no readily available data in Israel on costs that fall outside the health system, such as work absences, transportation to receive treatment and out-of-pocket expenses. Our estimates as to the cost-utility of interventions may thus be viewed as conservative since the inclusion of savings in work absences and transport would have reduced the costs per QALY of the interventions.

All calculations were based on a mid-year population in 2008 of 7,302,100 persons (Unknown, 2001). Costs were presented in new Israeli shekels (NIS) at 2008 price levels. Future costs and utilities were discounted at a rate of 3% per annum. Data on employment costs of health service

staff were provided by the Budgeting Department of the Ministry of Health, with physician costs increased by 24.4% to reflect the latest pay increase in November 2008.

Pharmaceutical costs were obtained from the website of the Pharmaceutical Department of the Ministry of Health and from a local retail pharmacist. Value added tax (VAT) at 15.5% was deducted from the retail prices as this constitutes a transfer payment. Dosing levels and duration were based on the average of the studies included in the meta-analyses to calculate the intervention efficacies (Fiore, 2008).

Building costs were based on NIS 5,405 (\$1,500) per square meter amortized over 40 years at 3%. Maintenance costs, including heating and utilities, amounted annually to 8% of building costs, resulting in an annual cost of NIS 671 per square meter.

The calculation of annual intervention costs was based on the unit costs of treating the targeted number of smokers. All interventions involving medications and prescription nicotine substitutes were assumed to require:

1. An initial 15 minute visit for initial assessment, smoking-cessation counseling, pharmacotherapy assessment (including screening for possible contraindications) and communication of the steps to be taken if side effects emerge
2. A series of 10 minute follow up visits to provide encouragement and monitor for side effects
 - a. First follow-up visit: within two weeks after the initial visit
 - b. Monthly visits throughout the duration of the treatment (in conjunction with prescription renewals)
3. Two minutes per month for secretarial overheads

These assumptions are based on consultations with leading smoking-cessation experts in Israel (Shani Efek and The Israeli College of Physicians of Smoking Prevention and Cessation) and the U.S. (Nancy Rigotti from the Harvard Medical School and the Massachusetts General Hospital, and Adam Goldstein from the University of North Carolina Medical School).

The analysis also assumed the average duration of pharmacological treatment to be the drug-specific duration as shown in Fiore's data on the efficacy of each specific intervention.

Based on current media costs and estimates as to what resources are ideally required to promote a new intervention nationally, a NIS 10 allocation per targeted smoker was made for a budget to advertise all interventions except those relying solely on an MD or on pharmaceuticals (as retail drug costs include provision for company advertising of their product). Finally, provision was made for the training costs of staff needed to implement these programs, which included organizational, room, material and refreshment costs, as well as trainer's wages and the opportunity cost (i.e., the next best choice in a trade-off situation) of time spent by those attending the training sessions during their work-day.

2.2.2 Cost of Treating Smoking-Attributable Morbidity

Our morbidity estimates were based on the estimated 496,000 smoking-attributable hospitalization days in 1999 (from the Gillon Committee calculations). These data were adjusted by the change in population from 1999 to 2008 (CBS, 2008), the projected change in hospital utilization rates (Ministry of Health, 2007) and the decrease in lagged prevalence rates.

This resulted in an estimate of 456,374 hospitalization days in 2008 attributable to smoking in general hospitals. Using the average cost of NIS 1,855 per hospitalization day (Ministry of Health, 2008), in 2008, smoking-attributable illnesses cost approximately NIS 847 million in in-patient general hospital care, 74% of which is attributable to active smoking.

A literature search showed that for every \$100 spent on *smoking*-related inpatient costs, the following sums were spent on smoking-related *non-inpatient* care costs (including ambulatory, home care, medications, rehabilitation and nursing care):

\$167 in Hong-Kong (McGhee, 2006), \$161 in China (Sung, 2006), \$135 in Taiwan (Yang, 2005), \$110.30 in Germany (Neubauer, 2006), and \$102.50 in the U.S. (Miller, 1998).

We used a conservative approach based on the average of the least expensive countries, the U.S. and Germany, to estimate a cost of NIS 900 million attributable to non-inpatient health care costs (i.e., \$106.40 for every \$100 spent on in-patient care listed above). Thus, in 2008, the total smoking-related medical care costs reached NIS 1,747 million, or NIS 1,687 per smoker in Israel. These costs are influenced by smoking habits of previous decades, which develop into diseases after a latency period.

Due to the downward trend in smoking prevalence (between 1996 and 2008) and to decreases in the average length of hospital stay, estimated smoking-related costs for the 2008 cohort of smokers (i.e., excluding persons who start smoking after 2008) in 2020 (after a 12-year lag-time) are estimated at NIS 1,578 million.

We carried out a meta-analysis of smoking-cessation interventions recidivism rates in the literature (Bancej 2007, Becona 1997, Becona 1998, Carlson 2000, Carlson 2002, Kanzler 1976, Kopel 1975, Lichtenstein 1973, Miguez 2008, Murray 2000, Olsen 1991, Sachs 1993, Schmahl 1972, Serraino 1993, Stapleton 1995, Weinrobe 1974, Wetterqvist 1973). This analysis estimated recidivism rates of persons who had stopped smoking after six months to be 21% (at 12 months), 57% (at 24 months), 61% (at 36 months), 62% (at 48 months) and 63% (at 60 months)]. We assumed rates would remain constant between five and 13 years after the intervention. We conservatively assumed that a successful program would not have an impact on health care costs until 12 years into the future (Mackay, 2002), due to the lagged response of disease-related risks to smoking cessation. Thus, the time horizon of our studies was 25 years (13 years of response to quitting plus 12 years lag). Using a 3% per annum discount rate meant that a “theoretical” program that could cause an initial 100% quit rate would save NIS 5,630 million over the next 25 years. Hence, for every 1% who quit, a savings of NIS 56.3 million would accrue.

2.2.3 Coverage and Adherence

Since Israel is a small country with national health insurance, we assumed that the coverage (or access) rates of all the interventions would be 100%. We assumed (based on a small-scale local survey) that 40% of all written medical prescriptions would not be filled and that 12% (i.e., 20% of the remaining 60%) would be used to purchase pharmaceuticals that would not be used. Therefore, full adherence would be attained only by 48% of the target population. This 48% adherence rate was applied to all other interventions listed by Fiore et al. (Fiore, 2008) with the exception of a telephone counseling line where we assumed a 24% adherence rate was appropriate for smokers who initiated calls. The actual quit rate achieved is the product of the program's quit rate, multiplied by the coverage rate (100%) and the adherence rate (48% or 24%).

2.2.4 Quality Adjusted Life Years (QALYs) Lost due to Mortality

The spreadsheet that formed the basis of the SAM estimates in Israel (Ginsberg, 2008) contained information on age of death and gender. Potential years of life lost (PYLL) from SAM were calculated from estimates of the age and gender-specific life expectancy (CBS 2006). Using data from the WHO (WHO 2002), the PYLL were converted into gender-specific health-adjusted life expectancies (HALE) in order to take into account the increase in dysfunction due to the aging process. For example, in 2002, the life expectancy of 60 year-old Israeli males and females was 21.25 and 23.80 years, respectively, but due to the aging process, the HALE was only 15.8 and 16.9 years, respectively (WHO 2002).

Losses due to SAM in 2008 are estimated to have reached 72,092 QALYs, based on the smoking prevalence in 1996 (i.e., incorporating a 12-year lag). However, since the increase in population slightly overcompensates for the downward trend in smoking prevalence (based on 2008 prevalence rates), estimated smoking losses will be around 74,193 QALYs in 2020. After adjusting for the recidivism rate, there is a potential for 269,172 QALYs to be saved from SAM during the 25-year time horizon of this study. Thus a program initiated in 2008 that causes a 1% decrease in smoking prevalence will save a total of 2,692 QALYs from decreased mortality.

2.2.5 Quality Adjusted Life Years (QALYs) Lost due to Morbidity

QALY losses also occur because of morbidity. Due to time and data constraints it was unfeasible to carry out the task of calculating the QALY losses due to morbidity for each of the disease categories listed in Table 1. Therefore, based on WHO world-wide estimates (Lopez, 2006), we assumed morbidity losses from smoking to be around one-third of the mortality losses, accounting for 25% of total QALY losses.

Thus, losses due to Smoking-Attributable Morbidity in 2008 are estimated to have reached 24,031 QALYs ($=72,092/3$), based on the smoking prevalence in 1996. These losses have been estimated as rising to 24,731 QALYs in 2020 (i.e., $74,193/3$). After adjusting for the recidivism rate, there is a potential reduction of 89,724 QALYs (i.e., $269,172/3$) from smoking attributable morbidity during the 25-year horizon of this study. Thus a program initiated in 2008 that causes a 1% decrease in smoking prevalence will save 897 QALYs as a result of reduced morbidity. Together with the 2,693 from mortality reductions, this totals 3,590 QALYs.

2.2.6 Decision Rules/Definitions

By combining data relating to costs and effectiveness, the cost per QALY was calculated for each intervention. Taking into account the resources available in Israel, an intervention is defined as being very cost-effective and cost-effective if the cost per QALY is less than the per capita GNP (estimated to be NIS 97,621 in 2008, based on a 6.1% growth rate of the economy and a 1.7% population growth rate) or between 1-3 times the per capita GNP (NIS 97,621-NIS 292,863) respectively. If the cost per QALY is more than three times the per capita GNP (> NIS 292,863) then the intervention is regarded as not being cost-effective (WHO 2001). If the savings from the reduction in treatment costs are larger than the intervention costs, then the program is said to be cost-saving.

2.3 Assessing Tobacco Control Interventions

There are a myriad of potential interventions and combinations of interventions purported to reduce the burden of disease from smoking. These include public health interventions such as legislative and regulatory actions, governmental fiscal policy, use of mass and other media strategies, and broad educational initiatives, as well as smaller-scale community, workplace, family and individual-clinical preventive and cessation interventions. The direct estimation of efficacy in an Israeli context, and the costing of interventions which take place outside of the medical system were beyond the scope of the resources made available for this study and should be addressed within the context of future studies. The current study focused on two important types of interventions: fiscal interventions to increase tobacco taxes and clinical cessation interventions.

The former assesses efficacy in terms of its potential to reduce cigarette consumption. We assumed that 50% of the consumption loss would manifest as complete cessation (or persons not starting to smoke) and 50% would manifest as persons cutting down their consumption (Ding, 2003). In addition, we conservatively assumed that decreases in individual consumption (as opposed to quitting or never starting) would have no impact on mortality or morbidity from smoking (Tverdal, 2006).

It should be noted that while these interventions do not directly reduce second-hand smoke (as opposed to, say, legislation against smoking in public places, one may generally assume that by implementing them, the ensuing decrease in active smoking will induce a similar decrease in the effects of involuntary smoking.

3. Results

3.1. Main Findings

A wide selection of interventions proved to be either cost-saving or very cost-effective. Cost-saving interventions are those where the treatments costs averted by the decrease in morbidity as a result of the intervention exceed the cost of the intervention. Due to large-scale decreases in morbidity, treatment savings exceeded the intervention costs for many interventions. These cost-saving interventions have been ranked by their absolute level of QALY savings (Table 2) and by

the net savings they induce (Table 2a). They are win-win situations whose implementation would provide QALYs to the citizens of Israel at no additional net cost over the 25-year horizon of the analysis.

Table 3 exhibits those interventions found to be very cost-effective. Very cost-effective interventions are those that supply QALYs at a relatively low cost (the cost per QALY is less than the per capita GNP). Background data supporting all interventions may be found in Appendix I.

Table 2: Cost-Saving Interventions Ranked by QALYs Saved (in descending order)

Interventions	Net Cost (a)	QALYs saved (b)
Tobacco tax (up from 62% to 200%)	-2,075,236,820	133,641
Tobacco tax (up from 62% to 150%)	-1,323,339,421	85,220
Varenicline (2mg/day)	-61,067,278	39,961
Tobacco tax (up from 62% to 100%)	-571,442,023	36,800
Medication & quitline counseling (c,d)	-45,989,604	35,108
Clonidine (e)	-284,249,204	25,835
Nortriptyline (e)	-175,455,949	21,529
Tobacco tax (up from 62% to 75%)	-195,493,324	12,589
Quitline counseling (d)	-49,162,698	8,515

Notes:

- (a) Intervention cost less savings in treatment costs
- (b) Consisting of 75% savings in mortality QALYs and 25% in morbidity QALYs.
- (c) Based on equal percentages of varenicline (2mg & 1mg), clonidine, bupropion and nortriptyline.
- (d) Quitline calls usually initiated by counselor
- (e) Considered a second-line option by FDA due to concerns about potential side effects.

Table 2a : Cost Saving Interventions Ranked by Net Cost Saved (in descending order)

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Varenicline (2mg/day)	- 61,067,278	39,961
Quitline Counselling (e)	-49,162,698	8,515
Medication & quitline counseling (d,e)	- 45,989,604	35,108

Notes:

- (a) Intervention cost less savings in treatment costs
- (b) Consisting of 75% savings in mortality QALYs and 25% in morbidity QALYs.
- (c) Considered a second-line option by FDA due to concerns about potential side effects.
- (d) Based on equal percentages of Varenicline (2mg & 1mg), Clonidine, Bupropion and Nortriptyline.
- (e) Quitline calls usually initiated by counselor

**Table 3: Very Cost-Effective Interventions (a) by Cost (NIS) per QALY
(ranked in ascending order)**

Interventions	Net Cost NIS (b)	QALYs saved (c)	Cost (NIS) per QALY
Nicotine Lozenge (2mg)	20,665,844	24,457	845
Varenicline (1mg/day)	135,615,447	26,524	5,113
Nicotine Patch (6-14 weeks)	163,551,502	23,079	7,087
Nicotine Patch + Nortriptyline	298,617,606	29,798	10,022
Bupropion SR	317,229,935	24,457	12,971
Nicotine Gum (6-14 weeks)	282,292,873	15,499	18,213
High Dose Nicotine Patch (>25 mg)	540,570,898	28,419	19,021
Medication & counseling	632,044,448	27,946	22,617
Nicotine Patch + Bupropion SR	926,066,101	32,554	28,447
Group counseling (f)	178,571,294	4,946	36,102
Nicotine Nasal Spray	1,098,581,794	28,764	38,193
Long-Term Nicotine Patch (>14 weeks)	1,024,095,934	23,596	43,402
Long-Term Nicotine Gum (>14 weeks)	1,263,581,819	27,730	45,567
Individual counseling (f)	499,902,724	9,573	52,218
Nicotine Inhaler	1,821,454,892	25,491	71,455

Notes:

(a) Defined as cost per QALY < 97,621 NIS (per capita GNP)

(b) Intervention cost less savings in treatment costs

(c) Consisting of 75% savings in mortality QALYs and 25% in morbidity QALYs.

(d) SSRIs and SNRIs.

(e) Smoker contacts the quitline and is referred to group counseling

(f) Counseling can be generally divided into individual and group counseling. These can be further subdivided into the following sub-categories:

Practical counseling (problem solving/skills training) (Table 3).

Intra-treatment social support (Table 4)

Extra-treatment social support. (found to be ineffective)

Telephone counseling (Table 3)

Quitline counseling (Table 2)

(g) The following interventions were excluded since their efficacy did not reach statistical significance:
Selective Serotonin re-uptake inhibitors,
self-help materials, rapid and other adverse smoking measures, extra-treatment social support.

3.2. Broad Categories of Interventions

3.2.1. Fiscal Interventions: Raising Taxes

Every intervention assessed in this category proved to be cost-saving (Table 2, 2a).

Raising taxes on cigarettes (currently set at 62% of the base price in Israel) is another instrument that can be used to reduce SAM. Intervention costs were valued at zero, since imposition of an increased tax is essentially imposing a transfer payment from individuals to the government, affecting no real change in real use of resources.

Lobbying and legislation costs to changed taxation are miniscule compared with the huge increase in revenues from increased taxation. Notwithstanding the gain to the government's budget, there are real resource savings due to the decrease in treatment costs resulting from the expected absolute 2% decline in quit rates¹ that a 10% increase in cigarette prices would generate ([Townsend 1998, Abedian 1998]; equivalent to a price elasticity² of demand of 0.4). Raising the tax from the current 62% of the base price to 75%, 100%, 150% or 200% would therefore generate 3.2% (i.e. $\{[175\%-162\%]/162\} \times 0.4$), 9.4%, 21.7% and 34.1% changes in net consumption, respectively. Recidivism rates are set at zero as they are already factored into the net declines in consumption.

An 8% increase in cigarette prices (arising from an increase in tobacco tax from 62% of the base price to 75%) would add 12,589 QALYs and save NIS 195 million. A much more substantial price increase of 85.2% (arising from an increase in tobacco tax from 62% of the base price to 200%) would have a larger impact, adding 133,600 QALYs, and saving around NIS 2.07 billion over the 25-year horizon of this analysis. If due to increases in income levels (Tverdal, 2006), the price elasticity of demand were to fall from -0.4 to -0.2, then increasing tobacco tax from 62% of the base price to 200% would still save substantial amounts of money (NIS 1.03 billion) and QALYs (66,800).

3.2.2. Clinic-Based Interventions

These interventions included tobacco cessation medications, counseling of various kinds, and a variety of other interventional formats.

Five interventions appear to be cost saving. Use of varenicline (2mg/day) would provide 40,000 QALYs and save NIS 61 million. Clonidine, and nortriptyline would also generate substantial QALYs and would be cost saving. As noted in the footnotes to Tables 2 and 2a, these two drugs are considered second-line therapeutic options due to their side-effect profiles.

Fifteen interventions are estimated to be very cost-effective (i.e., their cost per QALY is less than the per capita GNP of NIS 97,621 [See Table 3]).

In contrast to its higher dose usage (2mg/day), use of varenicline (1mg/day) would not be cost-saving, but still ranks second (to Nicotine Lozenges at NIS 845 per QALY) in the list of the very cost-effective therapies as it would provide 26,500 QALYs at a cost of NIS 136 million, with a cost per QALY ratio of NIS 5,113.

¹ The further 2% decline in consumption predicted by the price elasticity was assumed not to lead to complete cessation of smoking, but only to a decrease in consumption and hence have no long-term health benefits (42).

² Price elasticity is the measure of responsiveness in the quantity demanded for a commodity as a result of the change in price of the same commodity.

Combination therapies that would be very cost-effective include use of the nicotine patch with the following therapies: second-generation anti-depressants such as paroxetine or venlaflexine (NIS 8,452 per QALY), nortriptyline (NIS 10,022 per QALY), and bupropion³ (at NIS 12,971 per QALY). It should be noted that none of these are significantly more cost-effective than the nicotine patch alone.

A good example of synergism obtained by combining therapies is seen in the fourfold greater QALY savings that would be generated by combining medications with support from a quitline counselor, in contrast to using the quitline intervention alone, and the 2.5-fold increase in cost-utility when medication and counseling are combined rather than using individual counseling alone.

Use of a regular duration nicotine patch (6-14 weeks) provides 23,079 QALYs at a cost of NIS 164 million (i.e., NIS 7,087 per QALY). Long-term patch usage (>14 weeks) provides somewhat more (23,596) QALYs, but this comes at a cost of NIS 1,024 million (i.e., NIS 43,402 per QALY). Put another way, the Incremental Cost Effectiveness Ratio (ICER) of moving from regular to long-term nicotine patch use, provides a small gain of 517 QALYs, but comes at a huge additional cost (NIS 731 million), giving an ICER of over NIS 1.66 million per QALY, which is clearly not cost-effective. On the other hand, moving from regular duration (6-14 weeks) nicotine gum use to long-term use (>14 weeks) is recommended, as it will provide 12,231 additional QALYs at a very cost-effective incremental cost of only NIS 80,230 per QALY. Cost per QALY of using a nicotine inhaler was NIS 71,455.

Group counseling is less effective than individual counseling in that it provides fewer QALYs (4,946 vs. 9,573 QALYs) due to its lower quit rate (2.9% vs. 5.6%). But due to economies of scale, it is more cost-effective than individual counseling (NIS 36,102 vs. NIS 52,218 per QALY). Here too, synergy can be seen: adding medications to counseling increases QALY gains fivefold and reduces the cost per QALY from NIS 36,102 to NIS 22,617.

The use of the cost-saving and very cost-effective pharmaceuticals is complemented by Physician Advice to Quit (PAQ). Our calculations included an overhead of around 55, 75 and 135 minutes for pharmaceutical interventions lasting 4, 6 and 12 months respectively for PAQ per patient. We therefore examined the PAQ data of Fiore et al. to see if this overhead was worthwhile from a CUA standpoint. By examining the Average Cost Effectiveness Ratios (ACER) listed in Appendix II, we see that the ACER of providing 1-3 minutes of PAQ, with its relative quit rate of 3.1%, is cost-saving. Increasing PAQ times to 4-30 or 31-90 minutes has a very cost-effective ACER of 7,617 and NIS 25,607 per QALY respectively.

³ Note that the patent for Bupropion recently expired. If this results in a drop in price, then the cost per QALY will fall accordingly.

However expansion to the 90-300 minutes PAQ only provides a cost-effective ACER of 103,703 per QALY. PAQ time over 300 minutes has ACERs that are just cost-effective at NIS 248,763 per QALY.

The largest QALY gains using pharmacotherapy (46,000 QALYs) would be obtained by combining long-term nicotine patches with the nicotine gum or spray. However, these gains have a relatively higher cost of NIS 103,000 per QALY, which makes them merely cost-effective interventions (Table 4). Counseling based on intra-treatment social support or the use of a combination of nicotine patch with inhaler provide a per QALY cost of NIS 116,351 and NIS 158,718, respectively, which also make them merely cost-effective (Table 4).

Table 4: Cost-Effective Interventions (a) Ranked by Cost (NIS) per QALY

Interventions	Net Cost NIS (b)	QALYs saved (c)	Cost (NIS) per QALY
Patch (>14 wk) + ad lib NRT (gum/spray)	4,707,846,875	45,646	103,137
Intra-treatment social support	572,850,370	4,923	116,351
Nicotine Patch + Inhaler	4,319,255,855	27,213	158,718

Notes:

- (a) Defined as NIS 292,863 >cost per QALY > NIS 97,621
- (b) Intervention cost less savings in treatment costs
- (c) Consisting of 75% savings in mortality QALYs and 25% in morbidity QALYs.
- (d) Negative effects not included as effectiveness is not statistically significant.

Appendix III has been added for the sake of completeness. It contains a list of the interventions that were not shown to be effective and hence not considered in this CUA (e.g., acupuncture, cigarette fading, or relaxation/breathing).

4. Discussion

Smoking is a serious and expensive risk factor for many chronic diseases. The human burden in 2008 was a loss of 96,123 QALYs due to morbidity and mortality losses, resulting in 8,932 annual deaths. In economic terms, in 2008, the total direct cost to Israel's health services was approximately NIS 1.75 billion, equivalent to approximately 0.25% of Israel's Gross National Product.

Our findings suggest that policy-makers have a wide variety of cost-saving and very cost-effective interventions from which to choose. They are listed below in decreasing order of QALYs saved:

4.1 Cost-Saving Interventions (ranked by descending order of QALYS saved)

- 1) Raising the tax on tobacco products from the current rate of 62% to at least 150%
- 2) Varenicline (2mg/day)*
- 3) Raising the tax on tobacco products from the current rate of 62% to 100%
- 4) Medication and quitline counseling
- 5) Clonidine**
- 6) Nortriptyline**
- 7) Raising the tax on tobacco products from the current rate of 62% to 75%
- 8) A national tobacco cessation quit-line in which at least part of the calls are initiated by a counselor

4.2. Very Cost-Effective Interventions (ranked from lowest to highest cost per QALY saved)

- 9) Nicotine Lozenges
- 10) Varenicline (1mg/day)*
- 11) Nicotine patch, alone and in combination with second generation anti-depressants
- 12) Bupropion SR (Slow Release)
- 13) Nicotine Gum (6-14 week course)
- 14) High dose nicotine patch (>25mg)
- 15) Medication and counseling.
- 16) Group Counseling
- 17) Nicotine Nasal Spray
- 18) Long-term Nicotine Patch (>14 weeks)
- 19) Long Term Nicotine Gum (>14 weeks)
- 20) Individual counseling
- 21) Nicotine Inhaler

** Pending determination of ultimate relative risk on the basis of additional studies*

*** Considered a second-line intervention due to its side-effect profile*

The identification of many potential programs as cost-saving need not be viewed with surprise or skepticism. From 1989-2004, the Californian tobacco control program (costing \$1.8 billion) was associated not only with reduced smoking, but also with an \$86 million reduction in health expenditures (Lightwood, 2008). It was based on a different strategy than the fiscal or clinical strategy described in this paper, focusing instead on changing social norms among adult smokers and aiming to create a social milieu and legal climate in which tobacco became less desirable, less acceptable and less accessible (Lightwood, 2008). The program was premised on the fact that youth smoking will decline when more adults stop smoking (Tobacco, 1998).

Our estimates of health benefits from reduced consumption because of tobacco taxation were based on an assumed 50% drop due to quitters (or persons not starting to smoke), while the other

50% would be due to cuts in individual consumption (Ding, 2003). In addition, the estimates may be viewed as conservative since we assumed that decreases in individual consumption (as opposed to quitting) would have no significant impact on mortality or morbidity from smoking (Tverdal, 2006). Another conservative assumption was the price elasticity of smoking consumption. We used data reported for adult smokers (Ding, 2003). Youth smoker quit rates have been reported to be between 1.75 (Tobacco, 1998) and 7 times higher than for adult smokers (Ding, 2003).

The above estimates, referring to PAQ, are predicated upon recommended practices where primary-care practitioners (PCPs) devote 55, 85 and 135 minutes for pharmaceutical interventions lasting 4, 7 and 12 months, respectively. Our PAQ overhead appears to be very cost-effective or cost-effective (Appendix II). However it should be noted that due to the small increase in quit rates from 14.1% to 15.8% obtained by increasing PAQ time from 31-90 to 91-300 minutes per year, the ICER is not cost-effective (NIS 740,897 per QALY). Therefore, when medications are provided for longer than 7 months, consideration could be given to cutting down the duration of contact time per patient.

4.3 Assumptions and Limitations

Our use of government and retail price lists for pharmaceuticals and nicotine replacement therapies may overestimate costs (and hence cost-utility ratios) to the extent that Israeli health service funds negotiate discounts with suppliers.

We were unable to obtain efficacy and cost data on the provision of maintenance therapy at regular intervals. Such maintenance therapy has the potential to decrease recidivism rates (Lando, 1982) and to increase cost utility.

Our QALY estimates were calculated using relative risks from the literature. These were primarily based on U.S. populations since Israeli-based relative risks generated from large-scale studies are not yet available. Mortality and morbidity loss estimates will be upwardly or downwardly biased to the extent that these relative risks overestimate or underestimate the risk in the Israeli population.

On the one hand, our estimates of QALYs gained were *underestimated* since our study was limited to a twenty-five year horizon. On the other, they could be considered an *overestimation* since we did not consider the background mortality (deaths in the cohort from other causes).

Our calculated recidivism rate was based on meta-analyses of the few studies available that reported such rates. We assumed uniform recidivism rates across interventions. It is conceivable that recidivism rates may differ across interventions.

Due to lack of information, our calculated CUAs did not take into account cost and QALY losses due to side effects. As side effects are more likely with pharmaceutical than with counseling or fiscal interventions, the Cost-Utility ratio of the former is likely to be somewhat underestimated.

As with all CUA analyses, our analysis did not incorporate all factors of interest to policy-makers, such as feasibility, equity and public acceptability.

Since universal healthcare coverage is available in Israel, we assumed that the interventions were accessible to 100% of the Israeli population. However, the assumption of 48% adherence was only based on a small-scale survey and served to standardize comparisons across all interventions except for telephone counseling calls, for which we chose a 24% rate. Until the interventions are actually offered, any estimates of adherence are likely to be inaccurate since trial adherence is apt to be higher than that encountered in the real world. In any case, changing the adherence figure would not significantly impact the cost-utility calculation as both the numerator (cost) and the denominator (QALYs saved) would be changed by similar proportions (with the exception of the costs related to setting-up, training, non-compliance to medication, and advertising).

Recent meta-analyses of varenicline have calculated odds-ratios of 2.33 (Cahill) at 12 months (dosage not noted) and 2.41 (50, 51) for abstinence lasting 6-12 months (dosage not noted). These are lower than the odds-ratio of 3.32 calculated (Fiore) for a dose of 2mg, but similar to the 2.54 relative risk quoted for 1mg. Using these other recent meta-analyses would reclassify varenicline (2mg) as solely very cost effective rather than as a cost-saving intervention, as it appears in Tables 2 and 2a of this paper. Additionally, since varenicline is a relatively new cessation drug, its effectiveness and safety profile may change over time. The FDA (Varenicline, 2008) and the EMEA (53 Varenicline Europe, 2009) have issued warnings about potentially severe neuropsychiatric side effects in the varenicline medication guide for patients and have alerted health professionals to assess and monitor patients accordingly. Indeed, since its release and based on reports of neurological side effects, U.S. air and land transportation authorities have decided to prohibit its use in people engaged in sensitive operations such as airline pilots and professional drivers (Institute, 2008).

4.4 Funding Tobacco Prevention and Cessation

As stated above, tobacco pricing is a very useful tool for controlling the smoking epidemic. Our estimate of -0.4 (Townsend 1998, Abedian 1998) is situated at the lower end of a range of estimates of price elasticity (-0.2 to -0.9 (WHO 2001) and -0.3 to -0.7 (Lightwood, 2008). Use of a larger elasticity value would only increase both QALY and cost savings. Thus, increasing tobacco taxes is clearly cost-saving in addition to adding revenues to the country's treasury. Agreement by the Finance Ministry to earmark some or all of these funds for further smoking-cessation activities would generate an even greater impact in terms of decreasing the burden of disease attributable to smoking.

To provide a wide selection of interventions likely to assist a variety of smokers, an equally-weighted combination of the non-fiscal cost-saving and the top eight very cost-effective interventions listed above could be chosen. The NIS 539-million initial intervention cost could be adequately covered by earmarking most of the increased revenues from a tobacco tax increase from 62% to 100%. Approximately NIS 790 million would be saved as a result of decreases in treatment costs due to the programs and the tax increase. Consequently, this package would save about NIS 261 million and 50,796 QALYS.

It is clearly in the interest of the four (quasi-HMO) Health Funds to provide interventions that are cost saving. However, for historical and economic reasons, Health Funds expect the government to finance such interventions from the national Basket of Health Services or from Ministry of Health budgets. They claim that the treatment savings they would accrue from reduced morbidity secondary to tobacco control interventions should not be recognized as future revenue. Because the savings from today's interventions only accrue far into the future, perhaps a low or zero interest loan mechanism could be set up whereby the Finance Ministry funds these essential programs now in return for payments from the Health Funds in the future.

Such an approach was recommended by the U.S. DHHS CDC in 2006. They recommended allocating from (a minimal) \$6.47 to (an optimal) \$17.14 per capita to fund comprehensive tobacco control programs (54 Institute). This translates into a range of funding between NIS 34 and NIS 88 per capita in Israel in 2008, after adjusting for Purchasing Power Parity and percentage of program costs attributable to tradable pharmaceuticals including Nicotine Replacement Therapies (NRT). The elasticity of demand for expenditures on smoking with respect to tobacco control expenditures is 0.017 (Farrelly, 2008); i.e., a 100% increase (or doubling) in tobacco control expenditures will cause a 1.7% decrease in smoking expenditures. This translates into decreased smoking consumption of 2.9%, 5.2% and 7.5% (e.g., NIS 88/NIS 10 = 4.4 doublings of tobacco control expenditures x 1.7%) for minimal, medium (i.e., midway between minimum and optimum) and optimal –funding of tobacco control programs, respectively.

Formal cost-utility analysis was not done for each component of the above strategy. Indeed, the CUA of many components (e.g., increased taxation, counseling with and without quitlines, and cessation medications) has already been calculated in this paper. Hence, a comparison of the complete "black box" strategy with the specific interventions listed in Tables 2-4 was not deemed appropriate. Yet, the impact of the entire suite of interventions does have benefit and was therefore calculated. The methodology used was similar to that described above regarding changes in treatment costs and QALYS, with recidivism rates set at zero (as they are implicitly incorporated into the consumption rates that form the basis of measuring the efficacy of this type of intervention).

Funding prevention and cessation programs together as part of a comprehensive tobacco control expenditure package would save NIS 104-269 million and provide 23,000-59,000 extra QALYS.

However, these results are sensitive to the initial assumption regarding the estimated low level of current funding for the smoking prevention effort: NIS 10 per capita. If the true current funding level is NIS 20 per capita (meaning that about NIS 146 million is spent annually on smoking prevention), then a minimal and an optimal program would provide relative gains of only 1.45% and 3.74% respectively, saving 11,000 and 29,000 QALYS at a cost of NIS 6,375 per QALY.

Our results showed all kinds of counseling to be either cost-effective or very cost-effective (with the exception of quitline counseling, with and without medication, which was found to be cost-saving). The CUA was based on delivery of initial interventions with quit rates adjusted for recidivism. The provision of maintenance therapy (repeated interventions over the years) would increase both intervention costs and treatment savings. A U.S. study (Solberg, 2006) found that cost-effective counseling interventions became cost-saving if repeated over the lifetime of smokers.

4.5 Conclusions

Our analysis expanded Fiore's primarily efficacy-based analysis to a full cost-utility analysis, based on efficacy, costs, treatment, morbidity and mortality savings, in an Israeli context. Fiore reported many of the clinical interventions cited in our study to be highly cost-effective relative to other reimbursed treatments, and recommended providing them to all smokers. Future research should explore the unique circumstances underlying the results of each of these studies.

No one single intervention can totally reduce the considerable burden of disease from smoking. A multi-faceted approach is required, combining legislation, counter-advertising, taxation, prevention and cessation interventions (Farrelly, 2008). Many examples of the latter are detailed in this paper. Ideally, resources would be made available to carry out this strategy. Such an approach could be coordinated by a national authority along the lines of the currently-funded authority which aims to reduce traffic accidents, especially since the latter cause only around 5% of the burden of mortality attributable to tobacco. But, it is more likely that real-world budget constraints will necessitate hard choices. It will, therefore, be necessary to prioritize among the many effective interventions known to reduce the burden of disease from smoking. The cost-utility ratios reported in this study provide important objective evidence to aid policy-makers reach such decisions in a rigorous and transparent fashion.

5. Policy Implications

To provide a wide selection of interventions likely to assist a variety of smokers, an equally-weighted combination of the non-fiscal, cost-saving and top eight very cost-effective interventions listed above could be chosen. The NIS 539-million initial intervention cost could be adequately covered by earmarking most of the increase in revenues from a tobacco tax increase from 62% to 100%. Approximately NIS 790 million would be saved as a result of decreases in treatment costs due to the programs and the tax increase. Consequently, this package would save about NIS 261 million and 50,796 QALYS.

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Appendix I: Efficacy and Costs (NIS) of Intervention

	Six-month quit rate (a)	Intervention Cost	Treatment savings	Net cost (NIS)
Public Health and Non-Pharmaceutical Clinical Interventions				
Tobacco tax (up from 62% to 75%)	1.6%	0 (b)	195,493,324	-195,493,324
Tobacco tax (up from 62% to 100%)	4.7%	0 (b)	571,442,023	-571,442,023
Tobacco tax (up from 62% to 150%)	10.9%	0 (b)	1,323,339,421	-1,323,339,421
Tobacco tax (up from 62% to 200%)	17.0%	0 (b)	2,075,236,820	-2,075,236,820
PAQ Total Time (1-3 minutes)	3.1%	35,198,233	83,558,213	-48,359,979
PAQ Total Time (4-30 minutes)	7.1%	285,414,721	191,692,370	93,722,351
PAQ Total Time (31-90 minutes)	14.1%	1,002,701,987	380,927,145	621,774,841
PAQ Total Time (91-300 minutes)	15.8%	3,254,650,377	427,621,440	2,827,028,937
PAQ Total Time (>300 minutes)	13.2%	6,007,031,744	356,351,200	5,650,680,544
Telephone counseling, followed by referral to group counseling	2.1%	24,884,906	2,158,950	22,725,956
Group counseling	2.9%	256,167,564	77,596,270	178,571,294
Individual counseling	5.6%	650,089,054	150,186,330	499,902,724
Quitline counseling	4.9%	84,414,791	133,577,488	-49,162,698
Intra-treatment social support	2.9%	650,089,054	77,238,684	572,850,370
Practical counseling (Problem solving/Skills training)	4.5%	650,089,054	120,685,443	529,403,611
Monotherapies				
Varenicline (2mg/day)	23.2%	565,841,661	626,908,939	-61,067,278
Nicotine nasal spray	16.7%	1,549,825,427	451,243,633	1,098,581,794
High dose nicotine patch (>25 mg)	16.5%	986,409,445	445,838,547	540,570,794
Long-term nicotine gum (>14 weeks)	16.1%	1,698,610,193	435,028,374	1,203,581,819
Varenicline (1mg/day)	15.4%	551,726,019	416,110,572	135,615,447
Nicotine inhaler	14.8%	2,221,350,205	399,895,313	1,821,454,892
Clonidine	15.0%	121,051,195	405,300,399	-284,249,204
Bupropion SR	14.2%	700,909,989	383,680,054	317,229,935
Nicotine patch (6-14 weeks)	13.4%	526,611,211	362,059,709	163,551,502
Long-term nicotine patch (>14 weeks)	13.7%	1,394,263,272	370,167,338	1,024,095,934
Nortriptyline	12.5%	162,280,871	337,736,820	-175,455,949
Nicotine gum (6-14 weeks)	9.0%	525,440,683	243,147,809	282,292,873
Combination Therapies				
Nicotine Patch (>14 wk) + ad lib NRT gum/spray)	26.5%	5,423,939,739	716,092,864	4,707,845,875
Nicotine Patch + Bupropion SR	18.9%	1,436,765,684	510,699,583	926,066,101
Nicotine Patch + Nortriptyline	17.3%	766,076,498	467,458,892	298,617,606
Nicotine Patch + Inhaler	15.8%	4,746,176,600	426,920,745	4,319,255,855
Nicotine Patch + Second generation anti- depressants	14.3%	594,545,930	386,382,597	208,163,333
Nicotine lozenge (2mg)	14.2%	404,345,898	383,680,054	20,665,844
Medication & quitline counseling	20.4%	504,776,738	550,766,542	-45,989,804
Medication & counseling	16.2%	1,070,451,001	438,406,553	632,044,448

Notes:

(a) based on quit rate from meta-analyses less 10% background rate

(b) government receives tax revenues, but these are transfer payments, so real resource cost is zero

n.s. indicates non-significant effectiveness

Appendix II: Physicians Advice to Quit (PAQ) by Intervention Time (a)

	Six-month quit rate (b)	Net cost NIS (c)	QALYs saved (d)	Cost (NIS) per QALY ACER	Cost (NIS) per QALY ICER
PAQ total time (1-3 minutes)	3.1%	-48,359,979	5,326	cost-saving	cost-saving
PAQ total time (4-30 minutes)	7.1%	93,722,351	12,219	7,670	20,613
PAQ total time (31-90 minutes)	14.1%	621,774,841	24,282	25,607	43,776
PAQ total time (91-300 minutes)	15.8%	2,827,028,937	27,258	103,713	740,897
PAQ total time (>300 minutes)	13.2%	5,650,680,544	22,715	248,763	dominated

Notes:

(a) based on an average of NIS 1,714 spent on medications or NRT per smoker and 48% adherence rate

(b) based on quit rate from meta-analyses less 10.0% background rate

(c) intervention cost less savings in treatment costs

(d) consisting of 75% savings in mortality QALYs and 25% morbidity QALYs

Appendix III: Interventions that are not Effective

Acupuncture, Cigarette fading, Contingency contracting, Weight/diet, Relaxation/Breathing, Naltrexone, Negative Effect, Other Adverse Smoking, Rapid Smoking, SSRI's