Cigarette Smoking

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Internal Medicine Grand Rounds

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October 19, 2007

Disclosure: The above is not an actual picture of Jonathan C. Weissler M.D.

This is to acknowledge that Dr. Weissler has not disclosed any financial interests or other relationships with commercial concerns related directly to this program. Dr. Weissler will not be discussing off-label uses in his presentation.

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Introduction

In 1962 the United States Surgeon General, Dr. Luther L. Terry convened a panel comprised of 10 experts in medicine, statistics, pharmacology, and surgery to review the data regarding the impact of smoking on health. Over the next 14 months the committee reviewed the available literature and finally issued a report linking cigarettes with a 70% increase in overall mortality in smokers, a ten-fold increase in the risk of lung cancer, and a strong correlation with the development of chronic lung disease. The information contained in the report had an immediate impact on the American psyche. While a Gallup survey in 1958 had found that only 44% of Americans thought there was an association between cigarettes and cancer, 78% of the population believed this to be the case by 1968. When the report was released on January 11, 1964 it garnered headlines in every major newspaper published the following day. As detailed in a review by the National Library of Medicine the decision to release the report on a Saturday was not only made to maximize exposure in the Sunday papers but also to minimize any impact on the stock market. (http://profiles.nlm.nih.gov/NN/Views/Exhibit/narrative/smoking.html)

An updated version of the Surgeon Generals report on the effect of smoking on health (http://www.cdc.gov/tobacco/data_statistics/sgr/sgr_2004/chapters.htm) was released in 2004. This report found evidence "sufficient to infer a causal relationship between smoking and" 29 separate diseases including 10 different malignancies. In an analysis performed by the CDC in 1994, 6-8% of all direct medical expenses in the United States were related to cigarette smoking.

Expense category	Smoking attributable fraction (%)	Expense ($ in billions)
Hospitals	7.5	26.9
Ambulatory care	7.7	15.5
Nursing home care	6.6	4.9
Prescription drugs	2.6	1.8
Home health care	7.0	0.9
Total	**7.1**	**$50.0**

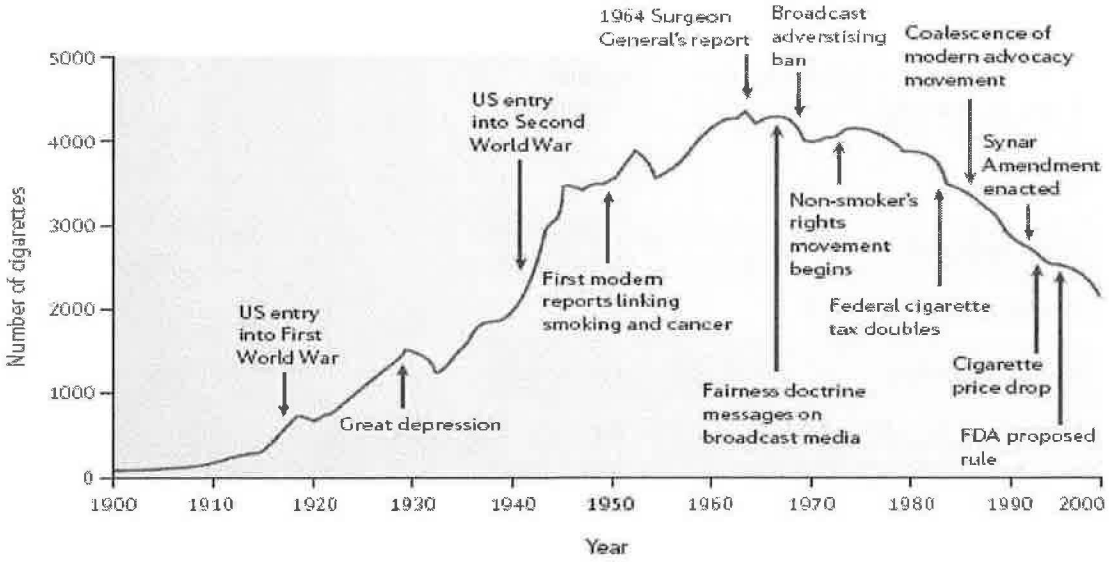
Source: Centers for Disease Control and Prevention 1994.

Indirect costs in the United States were estimated to range from 35 to 80 billion dollars per year, depending on whether models accounting for a reduction in Social Security, disability, or Medicare payments owing to a diminished life expectancy were utilized. Estimates from Hong Kong have suggested that approximately 25% of the total cost of smoking may be due to the effects of passive smoking[1].
Overall the CDC estimated that the average time lived without disability in a 30 year old smoker would be reduced by 2.5 years for men and 1.9 years for women.

Perhaps in no other aspect of American society has the intersection of health, economics, the judicial system, public policy, and human suffering played out on a more sustained basis than in the area of cigarette use. Similar interactions are now taking place around the globe and may have particular pertinence in developing countries. This review will attempt to summarize recent trends in the epidemiology of cigarette smoking, new data relating to the mechanisms of addiction to tobacco, efforts both societal and medical to decrease the consumption of cigarettes, and finally address the issue of routine screening for bronchogenic carcinoma in smokers utilizing CT imaging.

Who Smokes?

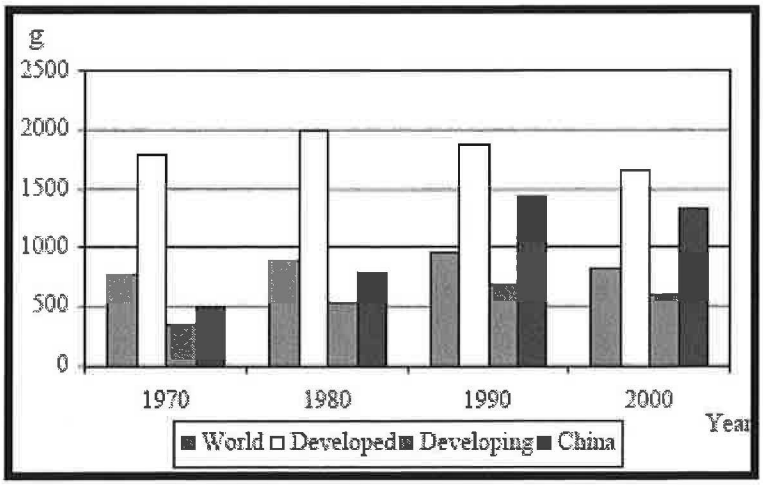
In 2004 approximately 46 million Americans smoked cigarettes, the same absolute number of smokers as existed in 1964 [2]. Per capita cigarette consumption in the U.S. has declined markedly over the past 4 decades.



Per capita consumption of cigarettes per the Food and Drug Adminstration[3].

In 2001 roughly 25% of American men and 22% of American women smoked, a drop from peak levels of 57% (men) in the mid 1950s and 34%(women) in 1965. Smoking rates amongst American men rank in the lowest 20% worldwide, however rates in American women rank in the highest 30% globally. Kentucky had the highest smoking rate (31%) while Utah the lowest (13%). Overall smoking rates have largely plateaued since 1990, although some data suggested that smoking rose in adults aged 18-24 (from 23 to 27%) during this period[2]. Since 2003 smoking amongst youths in grades 9-12 appears to be stable, with 23% having consumed at least 1 cigarette in the preceding 30 days while 9% are regular smokers.
(http://www.cdc.gov/HealthyYouth/yrbs/pdf/trends/2005_YRBS_Tobacco_Use.pdf)

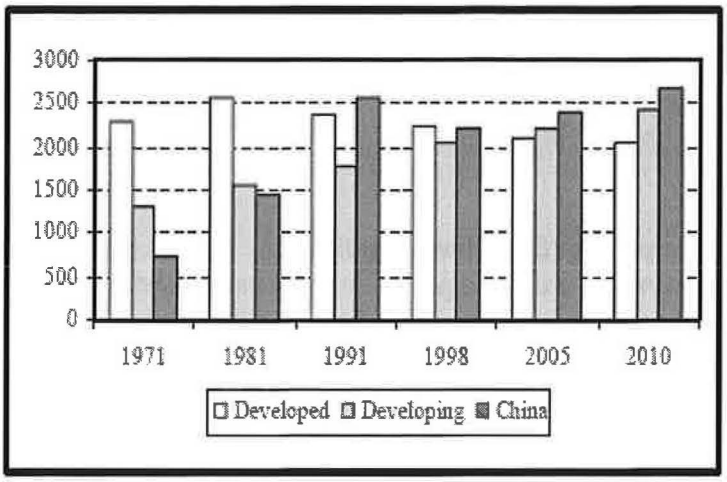
Worldwide trends in cigarette use parallel the situation in the U.S., though the fall in per capita consumption has been delayed by a decade particularly in nations with developing economies and China. In virtually all countries the rate of smoking in men dwarfs that seen in women.



Per capita tobacco consumption (grams) from 1970-2000 according to the Food and Agriculture Organization of the United Nations.
www.fao.org/DOCREP/006/Y4956E/y4956e04.htm

Many nations in Asia continue to have smoking rates amongst men which are in excess of 60%; similar data exist for the former Soviet Union and many Eastern European countries. The socioeconomic factors influencing cigarette consumption in the U.S. appear to be altered or at least delayed in developing countries. While smoking is more prevalent in lower socioeconomic groups in the U.S. initial economic development is associated with a sharp rise in smoking amongst women.

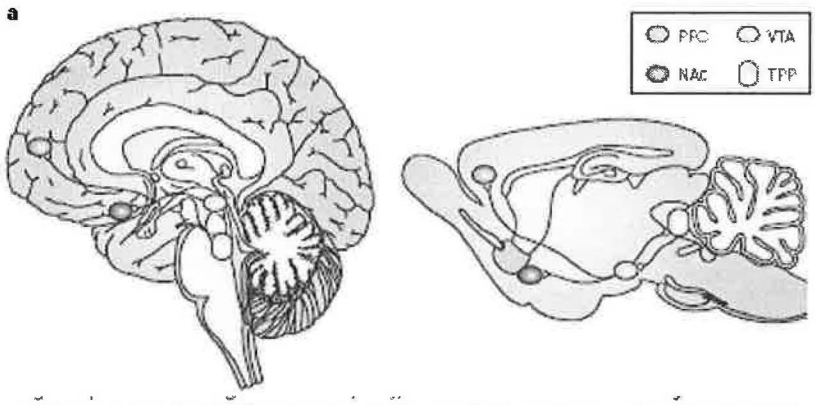
Overall per capita consumption is predicted to decline, though the absolute amount of tobacco consumed will rise. In countries such as China the expected rise in consumption may predict a looming public health catastrophe.



Tobacco consumption patterns –actual and predicted.
www.fao.org/DOCREP/006/Y4956E/y4956e04.htm

Why is Smoking Addictive?

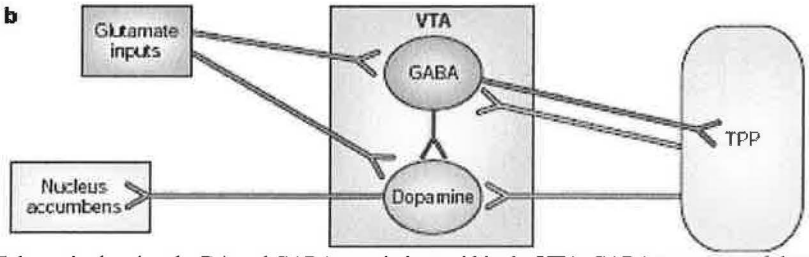
Surveys suggest that 70 % of American smokers would like to quit yet each year less than 5% are able to do so (http://www.surgeongeneral.gov/tobacco/treating_tobacco_use.pdf). Cigarette smoking is a complex behavior that is under multiple levels of regulation. Most evidence suggests that nicotine is the component most responsible for the reward, reinforcement, and withdrawal effects of tobacco [4-6]. Nicotine interacts with nicotinic acetylcholine receptors (nAcR) located throughout the brain resulting in a release of dopamine and other neurotransmitters. Several different areas of the brain are thought to be involved in regulating the response to nicotine. The ventral tegmental area (VTA) plays a central role in the reward properties of many different addicting substances including cocaine, alcohol, opiates, and nicotine. Interactions between the VTA and other areas such as the nucleus accumbens, which was previously thought to be the central site of nAcR activation, are complex[7].



a | Human (left) and rat (right) brains, showing the mesolimbic and mesocortical dopamine (DA) pathways, which originate in the VTA and send ascending projections to the nucleus accumbens (NAc) and prefrontal cortex (PFC), respectively. These pathways are strongly activated by nicotine and are implicated in its rewarding and aversive psychological properties. The VTA also sends a descending projection to the tegmental pedunculopontine nucleus (TPP), a brain region that is involved in non DA mediated signal reward[7]

Dopaminergic (DA) neurons within the VTA provide input through ascending projections to the prefrontal cortex and nucleus accumbens. A population of GABA neurons located within the VTA provide inhibitory signals to the DA neurons. Following acute exposure to nicotine DA neurons likely provide the initial "reward" sensation. However this is rapidly followed by desensitization of the nAcR for these neurons. At the same time GABA neurons are also stimulated through the nAcR and provide an inhibitory signal to the DA neurons. The nAcR associated with these neurons also rapidly desensitize with repetitive exposure to nicotine. The net effect of these interactions appears to be that the inhibitory signals of the GABA neurons are lost to a greater degree than are the stimulating properties through the DA neurons. In addition glutaminergic neurons in the VTA have nAcR and provide a stimulatory input to the DA neurons. The glutaminergic nAcR appear to be less susceptible to downregulation with repetitive exposure to nicotine.

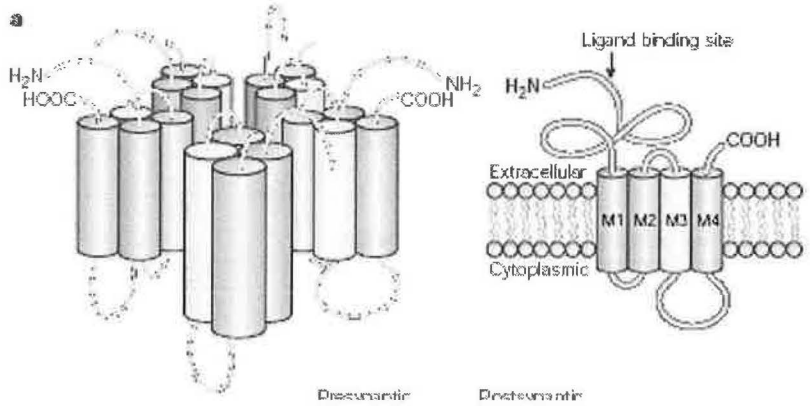
The VTA also receives cholinergic input from a brainstem nucleus the tegmental pedunculopontine nucleus (TPP); these neurons synapse with both DA and GABA neurons in the VTA. Behavioral effects of the ascending cholinergic neurons depend predominantly on signaling through muscarinic AcR in the VTA. Blockade of these receptors is more effective at blunting the reward stimulus mediated through the TPP than is blockade of nAcR.



b) Schematic showing the DA and GABA populations within the VTA. GABA neurons send descending projections to the TPP and provide inhibitory input to DA neurons. Both neuronal populations are activated by nicotine and also receive excitatory glutaminergic inputs which can regulate activity of DA and GABA activity in the VTA[7].

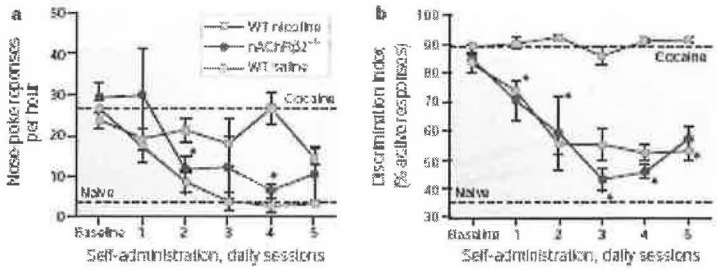
The Nicotinic AcR

Although other types of signaling in response to tobacco smoke inhalation occur, the major therapeutic focus has been on the interaction between nicotine and the nAcR.



a | Although the precise molecular structure of nAChRs is not known, they are believed to be pentameric ion channels. Each nAChR is composed of five subunits arranged in either homomeric or heteromeric complexes of α- or β-subunit arrangements (left). Different subunit combinations confer unique functional properties to the ubiquitously distributed nAChRs throughout the brain. The schematic on the right shows the transmembrane topology of a single nAChR subunit. The transmembrane domains are labelled M1–M4. The larger amino-terminal domain contains the acetylcholine-binding site, whereas the M2 domain determines the ionic selectivity of the receptor [7]

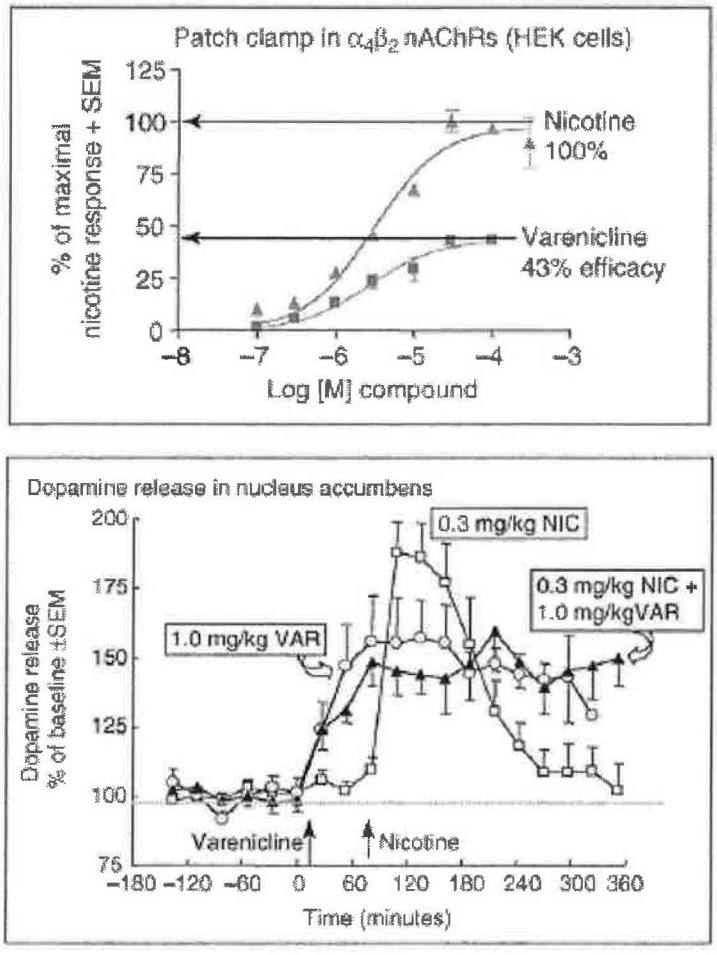
Nicotinic AcRs are pentameric receptor complexes composed of distinct alpha and beta subunits; most receptors are heterodimers of alpha and beta subunits but the alpha 7-alpha9 subunits can form homodimeric nAcR. The functional diversity of nAcR is primarily due to to the variation in subunit types. DA neurons in the VTA express the alpha2-alpha 7 and beta2-beta4 subunits; one prominent subtype appears to be homomeric alpha7 receptor which has been shown to be involved in the pathway of immediate nicotine reward mediated through the TPP. The beta2 receptor chain in turn appears to be particularly important for the reinforcing effect of nicotine[8]. Transgenic mice which lack the beta2 subunit do not exhibit the reinforcing behavior seen in wild type mice; this effect is specific for nicotine as the reinforcing properties of cocaine exposure are maintained.



nicotine exposure. a | Nicotine self-administration is significantly attenuated in mice lacking the nicotinic acetylcholine receptor (nAChR) subunit β2 (nAChRβ2$^{-/-}$), relative to wild-type (WT) animals. b | This attenuation is specific to nicotine, as the reinforcing effects of cocaine are unaffected in these mutant animals.[8]

GABA neurons in the VTA primarily contain the alpha4 and beta2 subunits. The central role that GABA neurons play in the pathogenesis of nicotine addiction has been underscored by the recent use of the partial nicotine agonist varenicline, which is marketed under the trade name of ***Chantix***. The property of a partial agonist appears to be particularly important; the ion channel flow following stimulation with a partial agonist is considerably less than with nicotine [9]. Weak agonists might not be able to compete with nicotine for binding to this subunit. Conversely strong agonists (such as nicotine replacement) would be unlikely to provide long term release of DA by the nAcR owing to their short half life and rapid rise and fall in serum. Theoretical models suggested that 30-70% efficacy relative to nicotine would be optimal. Varenicline has a high binding affinity for the alpha4/beta2 nAcR and approximately 40-60% efficacy relative to nicotine.

Cells transfected with the alpha4/beta2 subunits have a blunted nicotine induced ion flow following exposure to varenicline. However DA release may continue for a prolonged period, implying either sustained levels of varenicline relative to nicotine or altered desensitization of the receptor.



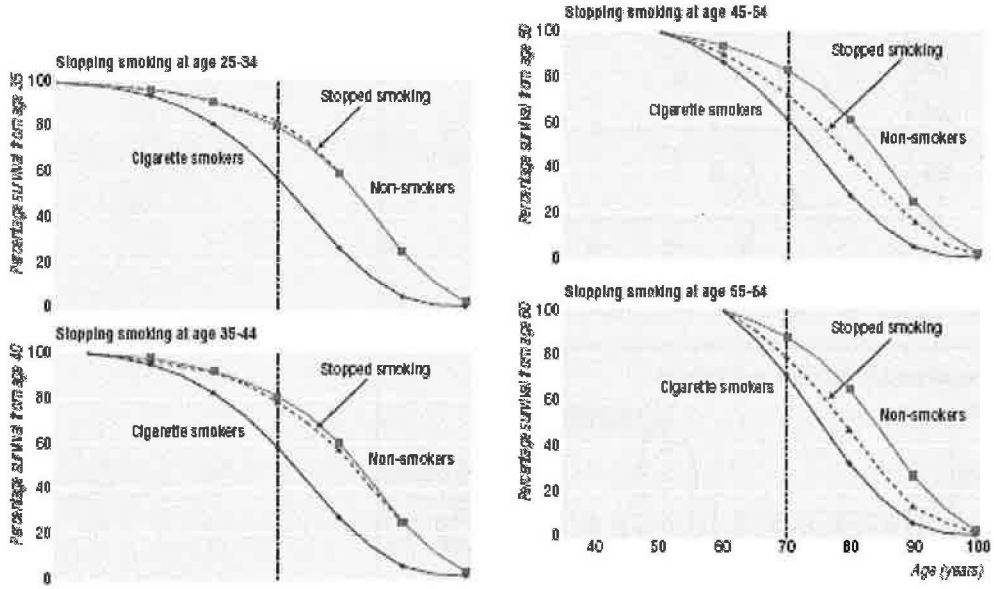
Functional nAcR efficacy (top) in transfected HEK cells expressing the alpha4/beta2 subunit assessed by patch clamping; radiolabelled DA release (bottom) in nucleus accumbens isolated brain slices. DA release over time was preserved [9].

Why stimulation of GABA neurons, which are thought to be inhibitory of DA release in the VGA would be effective in maintaining prolonged DA levels in the nucleus accumbens is not well understood. One hypothesis is that the chronic exposure to nicotine results in desensitization of the inhibitory GABA neurons and an up-regulation of pro-DA glutaminergic input in the VGA.

Several other agents used in smoking cessation also have effects on the alpha4/beta2 subunit. Bupropioin, an accepted first line therapy for smoking cessation has recently been shown to be an antagonist of this receptor and a drug marketed in Eastern Europe cytisine (***Tabex***) is also a weak partial agonist.

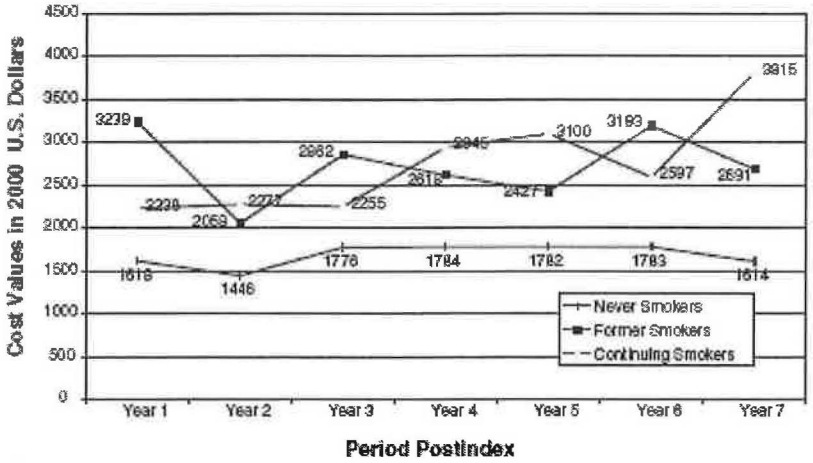
Smoking Cessation and Prevention

The benefits of smoking cessation have been shown in a number of studies. Data from a longitudinal study of British physicians[10] demonstrated that regardless of the age at which smoking cessation occurred a significant survival benefit was evident.

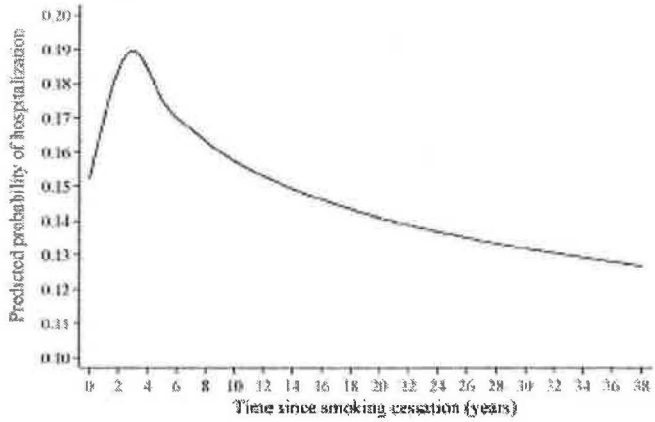


The effect on survival following smoking cessation at different ages. Survival is shown from ages 35, 40, 50, and 60 in the various groups [10].

While long term healthcare utilization falls in smokers who have quit, there is significant data to suggest that paradoxically short term health care utilization and hospitalization is actually increased in the first 1-3 years following smoking cessation [11-13].



Health care utilization costs were significantly higher in the first year after smoking cessation compared to a cohort of patients who continued to smoke [13].



Probability of hospitalization increased over the first three years following smoking cessation [11].

The explanations offered for this data are multiple but include selection bias for those who are urged to stop smoking by their physician because of serious health issues, patients with systemic diseases who have lost their appetite for cigarettes, and smoking cessation following a prolonged hospitalization. However it is not possible to exclude a physiologic contribution of nicotine withdrawal to an acute decline in health status.

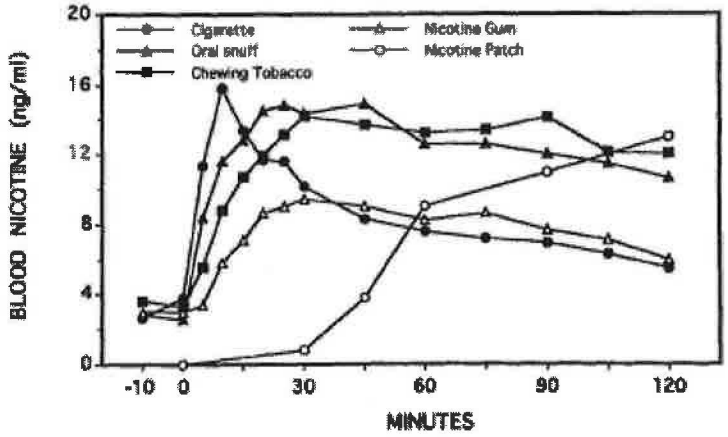
Strategies to Decrease the Use of Cigarettes

Attention has focused on various therapies to assist smokers wishing to cease the use of cigarettes[5]. It is also clear that support mechanisms (family, friends, healthcare providers) are important in the success of any smoking cessation program[14]. Full exploration of these interventions is outside the scope of this review yet their existence is readily acknowledged to be instrumental in ultimate outcome. The major current aids are discussed below. The Parkland smoking cessation clinic headed by Dr. David Balis can be accessed by patients at 214-590-5603.

Pharmacotherapy

Nicotine replacement

Nicotine replacement therapy (NRT) remains a first line pharmaceutical strategy to assist in smoking cessation[15]. Multiple delivery systems for nicotine replacement exist though the kinetics of nicotine delivery vary greatly[4, 16].



Venous blood nicotine levels are shown over 2 hours for 5 different delivery systems. Levels with a nicotine patch Were significantly higher than with chewing gum [4].

The primary mechanism by which NRT exerts its effect is the reduction of abstinence symptoms. As such not only the peak level of nicotine but also the duration of these levels is of theoretical importance. The most commonly used delivery system at present is the nicotine sustained release patch, which usually gives peak levels between 2-4 hours for *Nicoderm* and 6-12 hours for *Habitrol* or *Nicotrol*. Therapy is continued utilizing tapering doses over 12-20 weeks. In placebo controlled trials NRT delivered by a patch increased quit rate by a factor of 2.8 compared to placebo[17]. Overall sustained quit rates are less than 20% using NRT. Patients utilizing nicotine replacement must stop smoking or face the possibility of nicotine toxicity, characterized by nausea, vomiting, and diarrhea. Use of nicotine patches is thought to be safe in individuals with coronary

artery disease though it should not be started in a peri-MI period as accelerated hypertension has been reported in this setting [18].

Non-nicotine therapies

Nicotine vaccines

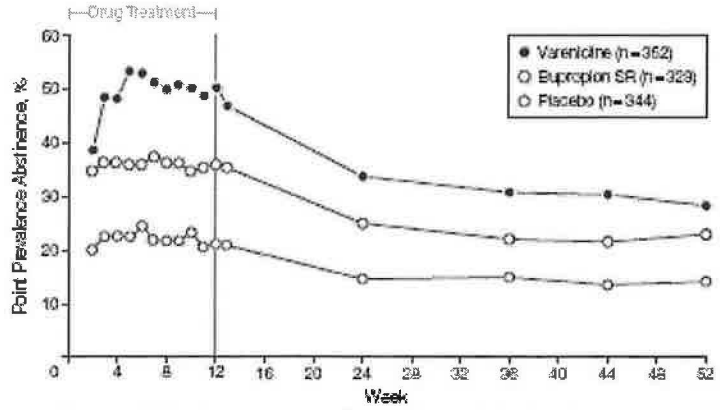
The strategy behind nicotine vaccines is to prevent nicotine from crossing the blood brain barrier. A number of companies are developing these vaccines; roughly 65% of nicotine following exposure to 2 cigarettes is bound to antibodies. In theory small amounts of nicotine which cross into the brain in this setting might actually increase the desire for nicotine. Passive immunization has also been utilized in animal models to overcome this limitation. Nicotine is nonimmunogenic and must be conjugated to larger carrier proteins. One clinical trial of nicotine vaccination reported by its commercial sponsor claimed that individuals producing high antibody titers had a 12 month quit rate of 42% compared to 21% in non-vaccinated subjects[5]. Use of nicotine vaccines may be particularly helpful in individuals who have already stopped as an aid to prevent recidivism.

Anti-depressants

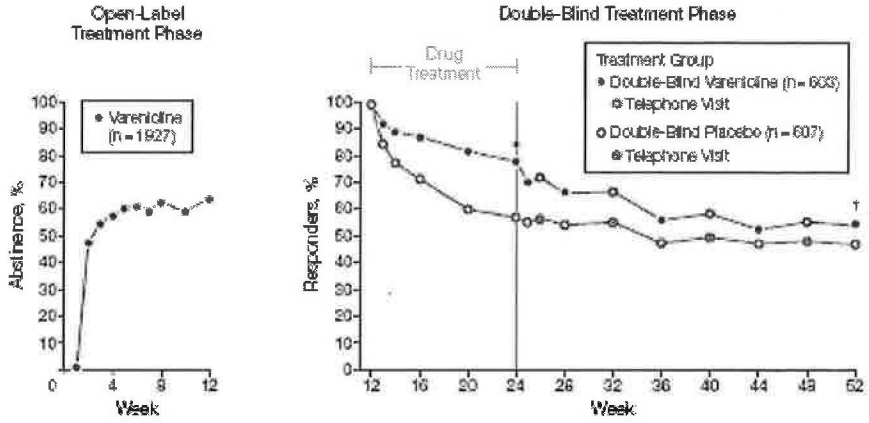
Bupropion (***Wellbutrin/Zyban***) is approved by the FDA for smoking cessation. The mechanisms by which Bupropion exerts its effects are unclear but likely relate to increasing the amount of DA in the mesolimbic system. Bupropion can bind to striatal dopamine transporters and prevent DA reuptake [19, 20]. Bupropion can also act as a noncompetitive antagonist of nAcR suggesting that it may lessen the rewarding properties of exposure to nicotine[21]. Bupropion can reduce cravings in recently abstinent smokers and alleviates other symptoms associated with nicotine withdrawal. A Cochrane review of 40 trials using Bupropion demonstrated a 2 fold increase in the rate of cessation compared to placebo (CI 1.72 – 2.19)[22]. Preliminary data with other antidepressants suggests that nortiptyline may have similar efficacy; the SSRI type of antidepressants however appear to be ineffective.

Varenicline

Varenicline is a partial agonist of the alpha4/beta2 nAcR as discussed above. Patients continue to smoke for the first week of therapy while starting half the maintenance dose of varenicline, with the full dose being given upon cessation in the second week. Nausea frequently occurs on this medication. The efficacy of varenicline has been evaluated in several trials. A Cochrane analysis of 5 separate trials found a pooled odds ratio abstinence rate of 3.22 (CI 2.43 – 4.27) favoring varenicline to placebo and 1.66 (CI 1.28 – 2.16) compared to bupropion[23]. Separate individual trials have demonstrated the efficacy of this therapy [24, 25]. The optimal duration of therapy appears to be greater than the usual 3 month program. Significantly higher rates of abstinence were maintained on a total of 6 months therapy though following discontinuation there was a significant decay in abstinence rates[26]. The effects of longer term use of varenicline are unknown.



Point prevalence of abstinence as confirmed by exhaled carbon monoxide during and following a 12 week course of varenicline, bupropion, or placebo [24]



Abstinence during an initial 12 week course of varenicline (left). Abstainers were then randomized to receive either another 12 weeks of varenicline or placebo (right). Significantly higher abstinence rates were seen with continued therapy [26].

A major barrier to successful smoking cessation is the effect of cigarette use on weight. Daily smoking men and women had a significantly lower body mass index (3% for men, 5% for women) than never smokers and reported significantly lower concern about their weight[27]. Successful smoking cessation is often accompanied by a 5-7 kg weight gain[28]. The weight gain stems from both an increased caloric intake and the removal of a higher basal metabolic rate associated with nicotine use[29]. Concern about weight gain has been demonstrated to be a particular impediment to smoking cessation among women[30], a group now recognized to be at increased risk of COPD related to smoking[31].

Societal Initiatives to Combat Smoking

Given the enormous health and economic burden that cigarettes impose on society a variety of initiatives have been undertaken to combat smoking. These have run the gamut

from making cigarette consumption expensive enough to drive down demand to developing programs aimed at promoting education about the risks of smoking. Over the past decade the legal system has also played a prominent role in efforts to fund initiatives against smoking. In particular the Master Settlement Agreement (MSA), reached in 1998 between the attorneys general of 46 states and the four major tobacco companies, has had a significant impact on the relationship between government and cigarette consumption.

The Master Settlement Agreement

The mid 1990s saw a wave of government initiated legal proceedings to recapture Medicaid costs linked to smoking. These efforts were largely spurred on by the leaking of confidential documents demonstrating that tobacco companies were aware of the dangers of smoking as early as the late 1950s and sought to manipulate nicotine levels to make their product more addictive. In 1996 leaders of state and federal government, tobacco company representatives, and private attorneys began work on a "global settlement" to handle all pending litigation against corporate tobacco[2]. At the same time 4 states, Texas amongst them, reached a separate agreement with the tobacco industry to pay in excess of $34 billion over 25 years. By 1998 legislation, which would have provided immunity from future lawsuits based on past practices of the tobacco companies in return for funding of public health initiatives, was ready for submission. Although the legislation was approved by the Senate Commerce Committee by a 19-1 vote, it was never brought up for consideration by the full Senate.

In November 1998 the remaining 46 states reached an agreement with the tobacco industry which was promoted as providing funding for public health efforts to reduce smoking, restore the fiscal health of the Medicaid system, and punish the tobacco companies for deceptive practices. The outline of the MSA provided for a total of 206 billion dollars to be paid out of tobacco company sales over the next 25 years (http://www.ncsl.org/statefed/tmsasumm.htm). The monetary settlement, which had been largely justified by the states attorneys general on the basis of the medical costs associated with smoking, was to be paid into the general funds of each state. Because expenditure of state funds is under the control of the legislative branch of government, the MSA could not guarantee how the settlement would be ultimately used. The MSA also established the American Legacy Foundation, to be funded over 5 years at a cost of 1.7 billion dollars, to promote tobacco education and smoking cessation efforts. The MSA prohibited pro-tobacco advertising aimed at young people, dissolved a number of pro-tobacco/industry funded lobbying groups, and finally established a repository of confidential tobacco company documents[32, 33] at the University of California.

Impact of the MSA

The MSA payment structure made damages from the tobacco companies dependent directly on the future number of packs sold[34] rather than a lump sum settlement. Given the "shock" of the settlement, the MSA may have actually facilitated price collusion as all major tobacco companies were forced to pass the cost forward to consumers similar to an excise tax. The calculated impact of the MSA on price per pack in 1999 was $0.40,

the reduction of a $12 billion bond placed on Phillip Morris by an Illinois judge in a private lawsuit that was awaiting appeal.

The distribution of legal fees for attorneys involved in negotiating the settlement also contributed to a poor public perception of the MSA. A total of $13 billion was distributed to participating attorneys by 2002. For the attorneys responsible for preparing Michigan's case the compensation involved worked out to $22,500 per hour. In defending this rate to the panel responsible for allotting fees a successful comparison was made to the hourly compensation rates of professional baseball players who earned $30-50,000 per hour [44]. The lure of cash proved too difficult for some public officials to resist. Dan Morales, the former Attorney General of Texas who obtained a $17 billion settlement from the tobacco companies in 1998, plead guilty to backdating documents in an effort to steer over $1 million in unearned fees to a Houston law firm. He served almost 3 years in prison before his release in March 2007.

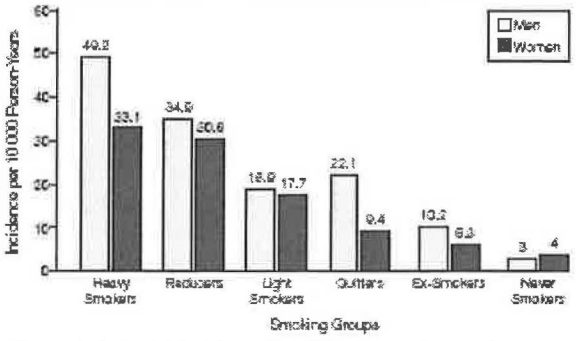
Litigation against tobacco companies remains an evolving process and it must be remembered that although the states have an agreement with the tobacco industry, the federal government does not[33]. In 2006 a federal judge ruled that the tobacco industry had substantially violated the RICO (Racketeer Influenced and Corrupt Organizations) act. Further developments from this case have been slowly winding their way through the legal system[33].

Screening for Lung Cancer in Smokers or ex-Smokers

One of the greatest fears amongst cigarette smokers is the risk of developing bronchogenic carcinoma, which annually accounts for 25% of cancer deaths and 6% of all deaths in the United States [45]. It is now widely appreciated that conventional screening measures such as a plain CXR and sputum cytology are ineffective in reducing death from lung cancer [46], (http://www.cancer.gov/cancertopics/pdq/screening/lung/healthprofessional). Recent attention has largely focused on using yearly low dose CT scans in at risk populations[45-49].

Data suggests that there is an overall relationship between the number of cigarettes smoked and the risk of lung cancer[50]. While the risk of lung cancer declines with successful cessation it remains markedly elevated, particularly in men, over a prolonged period of follow-up.

Figure. Age-Standardized Incidence Rates of Lung Cancer



Incidence rates are based on the second examination in 11 151 men and 8563 women from Copenhagen, Denmark.

Early reports of screening CT scans in high risk populations were enthusiastic. The Early Lung Cancer Action Project began to enroll 1000 smokers over the age of 60 in 1993. Initial results, published in 1999, demonstrated both the complexity and potential of this screening strategy[51]. Noncalcified lung nodules were detected in 23% of patients at baseline by CT compared with only 7% by plain CXR. However, only a small fraction of the patients with nodules were ultimately shown to have malignancies (12% of the

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