SESSION III IMPLICATIONS OF ALTERNATIVE TREATMENT GOALS

Introduction

John R Hughes

Our next presenters will be discussing several of the implications of the different kinds of harm reduction. Then we shall have the reactions of our panelists. Let me introduce our presenters and panelists.

Our first presenter is Neal L Benowitz who is going to talk about medical implications of harm reduction. Dr Benowitz is professor of medicine, psychiatry, and pharmacology and chief of the division of clinical pharmacology and experimental therapeutics at the University of California–San Francisco. His research has focused primarily on human pharmacology and toxicology of nicotine.

Our next speaker is Judith K Ockene who is going to review the public health implications. Dr Ockene is a professor and director of the division of preventive and behavioral medicine in the department of medicine, University of Massachusetts Medical School. Her major research has been in the area of physician education and developing counselling skills for interventions.

Our third speaker is Kenneth E Warner. He will address the financial implications of harm reduction. Dr Warner is the Richard D Remington Collegiate Professor of Public Health and chair of the department of public health policy and administration at the University of Michigan School of Public Health. His research has focused on the economic and policy aspects of disease prevention and health promotion, with a special emphasis on smoking and health.

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Next is Charles W Gorodetzky. Dr Gorodetzky is therapeutic area vice president for CNS in the clinical research department at Marion Merrell Dow, Inc. He worked at the National Institute on Drug Abuse Addiction Research Center in Lexington, Kentucky, and was Director of that laboratory from 1979 to 1984. One of his first efforts at Marion Merrell Dow was – and this shows you what we are battling with – to convince them that nicotine actually was a central nervous system drug and should be moved from general medicine to the CNS.

Our panel has three members. The first is John C Ball, who is a professor in the department of psychiatry at the University of Maryland School of Medicine. I know Dr Ball mostly for his pioneering work in showing that methadone decreases HIV positivity, and he has battled for looking at harm reduction with opioid dependents.

Next we have Carl C Peck, who is director of the Center for Drug Development Science at the department of pharmacology at Georgetown University. He was director of FDA's Center for Drugs where he took an active role in nicotine replacement therapies.

Our last panelist is Stephen I Rennard. He is Larson professor of medicine and chief of the pulmonary and critical medicine section at the University of Nebraska Medical Center. He was also one of the authors on the slides I showed you looking at reduction strategies. He did some of the first research where the goal was reduction instead of cessation.

Medical implications

Neal L Benowitz

In relation to the medical aspects of harm reduction, two medical issues are of concern: (1) Do harm reduction strategies reduce the medical complications of tobacco use? (2) Are the treatments used to promote harm reduction in themselves harmful; which is analogous to the question – does the harm reduction policy cause harm?

I shall deal with these two general issues in the context of four treatment scenarios: (1) nicotine replacement or any other treatment with the goal of reducing cigarette consumption; (2) nicotine maintenance to support tobacco abstinence; (3) over-the-counter nicotine availability; and (4) physical modification of cigarettes to reduce the adverse health consequences of smoking. I shall discuss efficacy and safety for each strategy.

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Cigarette consumption and disease risk

The first general area is nicotine replacement, with a goal of smoking fewer cigarettes. The first question is, does smoking fewer cigarettes

substantially reduce the risk of smoking related disease? Most probably this is the case, with a couple of caveats.

Let us look at the three major diseases that are associated with smoking. Dose-response data on chronic obstructive lung disease are found in the British Physician Study.[1] This very large study showed clearly that mortality from chronic lung disease increased as a function of smoking more cigarettes.

Lung cancer data, such as those from a study published by Rosengren, showed a clear dose related increase in lung cancer with a greater number of cigarettes smoked per day.[2] The heart disease data are less clear. Different studies have reported different types of results. Some studies have reported roughly linear dose-responses, that is, greater mortality with more cigarettes smoked per day.

In the Wilhelmsen study, there was a relatively flat dose-response for cigarettes per day versus heart disease mortality or odds ratio for heart disease.[3] In support of this flat dose-response curve are case-control studies in the USA showing that even smoking one to four cigarettes per day produces a very substantial increase in heart disease risk, much more than you would expect if there were a linear dose-response.[4]

Thus at present the nature of the dose-response relation for heart disease versus cigarette consumption is unclear. But we can probably say that dose-response relations are likely to differ for different diseases, and for some diseases, such as heart disease, there may not be as much benefit from reduced smoking as there would be for cancer. In sum, the strategy of reducing cigarette consumption (rather than total cessation), while not directly harmful to health and possibly beneficial in reducing some smoking related diseases, may not be as beneficial in reducing all smoking related diseases as we might suppose.

A caveat regarding interpretation of the dose-response data is that these data are based on self selected number of cigarettes smoked per day. The risks associated with a particular self selected consumption level does not necessarily reflect the impact of smoking that number of cigarettes for someone who has reduced their consumption. Studies from my laboratory and others have shown that if a smoker reduces the number of cigarettes smoked daily, at least in the short term (and no one has studied the long term) people smoke each cigarette more intensely.[5] In our study, people increased their nicotine intake (and hence smoke exposure) threefold when the number of cigarettes was restricted. Instead of taking in 1 mg of nicotine per cigarette and, say, 12 mg of tar, the smoker would be taking in an equivalent of 3 mg of nicotine and 36 mg of tar per cigarette. Thus we do not know whether someone who is addicted to a particular level of nicotine and reduces their cigarette consumption has the same disease rates as someone who is spontaneously smoking at that particular consumption level.

Safety of nicotine maintenance therapy

The next issue is nicotine maintenance to support tobacco abstinence. The question here is whether long term nicotine exposure is harmful, and if so, what are the relative risks of continued smoking versus nicotine maintenance.

Let us consider the safety of nicotine per se. Others have suggested that nicotine is important as a cause of heart disease. That may or may not be so. Various medical problems have been identified as possibly associated with nicotine. These include nicotine intoxication, coronary and peripheral vascular disease, stroke, complications of hypertension (not hypertension per se), delayed wound healing after plastic surgery, reproductive disorders (which may be related to cardiovascular effects), peptic ulcer disease, and oesophageal reflux. Reproductive toxicity may be obstetric in nature, including premature delivery, low birthweight, placenta previa, and placental abruption, or it may be fetopathic. The latter could include abnormal maturation of the fetal nervous system owing to effects of nicotine on fetal neurones during critical stages of development. Nicotine is not itself carcinogenic, but theoretically could be converted in the gastrointestinal tract to nicotine derived nitrosamines, which are carcinogenic. To date, this conversion has not been shown in humans.

At present these are still theoretical concerns. There are no data showing for sure that nicotine causes any of these problems (other than nicotine intoxication, of course). The main concern is about nicotine and cardiovascular disease.[6] It is useful to consider atherosclerotic vascular disease and acute ischaemic events separately.

The figure summarises my view on the strength of the evidence implicating nicotine in various cardiovascular disease mechanisms. A recent review of the evidence indicates the following.[6] For adverse effects on lipids, there is some suggestive evidence in animals. There are no data showing that nicotine produces lipid abnormalities in humans. There is no evidence that nicotine produces sustained hypertension. For endothelial injury, there is evidence that nicotine injures endothelial cells in vitro and in animals. There is no clear evidence in humans. For thrombosis, there is one suggestive animal study that examined effects of high dose nicotine. Most studies of nicotine effects on thrombosis have been negative. In conclusion, for long term nicotine use it is possible but not probable that nicotine will cause or aggravate atherosclerosis.

Considering acute ischaemic events, nicotine increases heart rate, transiently increases blood pressure and increases myocardial work. Thus nicotine produces haemodynamic effects that could aggravate pre-existing coronary heart disease. Thrombosis, as discussed previously, is a possible effect of nicotine but is of questionable relevance after nicotine exposure in people. There is good evidence that nicotine can constrict coronary blood vessels and therefore impair coronary perfusion. Arrhythmogenesis is theoretically a concern because of

catecholamine release, but such arrhythmias, if they occur, are uncommon.

It is hard to assess nicotine as a cause of cardiovascular disease experimentally because there are no good animal models and because no humans have been treated long term with nicotine. A potentially useful analysis is the epidemiology of snuff use in Sweden. Snuff users have plasma or urine nicotine and cotinine levels as high or higher than cigarette smokers.[7] A recent epidemiological study reported that snuff dippers had the same odds ratio for myocardial infarction as those who did not use tobacco.[8] In comparison, the odds ratio for cigarette smokers was substantially higher than that of either snuff users or those who used no tobacco.

Experimental studies of snuff use and studies with transdermal nicotine indicate that neither activates coagulation nor causes as much catecholamine release as smoking.[9,10] There may be other components of cigarette smoke that cause thrombosis, or perhaps the rapid delivery of nicotine through smoking cigarettes, which results in higher concentrations of nicotine in the arterial circulation than are produced with slower absorption products, is responsible for activation of platelets. In any case, there is no evidence that nicotine treatment – at least with slow release nicotine formulations – produces a hypercoagulable state (which is probably the most important single factor in smoking causing acute myocardial infarction and stroke). The available data suggest that nicotine maintenance treatment would not be a significant contributor to cardiovascular disease.

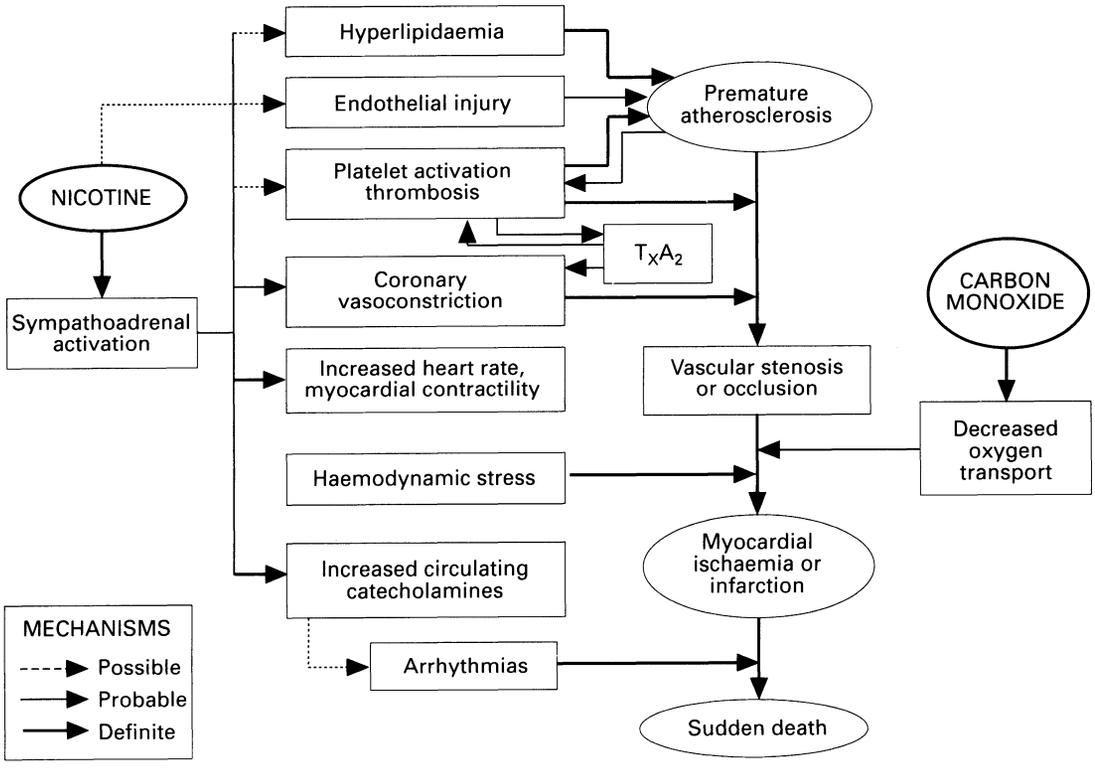
A discussion of the possible toxicity of nicotine during pregnancy is beyond the scope of this brief paper but has been reviewed recently.[11] In summary, nicotine could have adverse effects on pregnancy and fetal development as mentioned previously, but as explained for nicotine and cardiovascular disease, nicotine absorbed from cigarette smoking is much more likely to cause such injury than is nicotine derived from nicotine replacement therapy.

Over-the-counter nicotine

Next I would like to discuss the safety of over-the-counter nicotine replacement products. One question is whether nicotine use and concomitant cigarette smoking is reasonably safe. A second question is whether nicotine use by high risk populations, such as pregnant women or people with cardiovascular disease, is reasonably safe.

On the first issue, a few cases of people developing myocardial infarction while smoking cigarettes and taking patches have been widely publicised. These cases raised an enormous amount of concern, among both patients and physicians, that if a person smoked a cigarette while using a patch, they might have a heart attack and die. This concern has probably inhibited some physicians from prescribing and some patients from accepting the use of nicotine replacement products.

Is there evidence to support this concern? I have not found much evidence that smoking a cigarette while using a patch produces any higher risk of cardiovascular events than smoking a cigarette alone. Two lines of evidence suggest that there will not be an increased risk. First, Sachs *et al* have reported that when someone smokes while using nic-



Schematic summary of possible mechanisms by which nicotine could contribute to coronary heart disease. Reprinted from Benowitz, 1991.[6]

otine patches, the level of smoking is reduced so that the overall nicotine exposure is less than it was when they were smoking before starting to use patches (Sachs D, personal communication). Second, there are studies suggesting that the cardiovascular dose-response curve with increasing nicotine levels is flat. That is, progressively higher levels of nicotine do not produce progressively greater cardiovascular responses. In one dose-response study we studied effects of low nicotine cigarettes versus high nicotine cigarettes. The low nicotine cigarettes were experimental samples that did not contain much nicotine.[12] Measurement of blood nicotine levels throughout the day in subjects smoking 30 cigarettes per day showed a fourfold difference in nicotine levels. However, both the high nicotine and and the low nicotine cigarette conditions, despite the fourfold different nicotine levels, produced the same degree of heart rate acceleration through the day, and the same increase in catecholamine concentrations. These data are consistent with a flat dose-response relation. A second study was done looking at the suppression by intravenous nicotine of spontaneous cigarette smoking.[13] Subjects received intravenous nicotine for 14 hours, the dose calculated to match the daily dose of nicotine that they normally took from cigarette smoking. Subjects were studied during nicotine infusion with no smoking and then during ad libitum smoking. Intravenous nicotine suppressed nicotine intake from ad libitum smoking by about 25%. Therefore the total dose of nicotine with combined intravenous nicotine and smoking was on average 175% of the dose with just smoking alone. The heart rate response and the catecholamine release response was virtually the same with intravenous nicotine alone, cigarette smoking alone, and the combination of both. This study further supports the view that there is a flat cardiovascular dose-response curve for nicotine. These studies suggest that there is little or no added risk of smoking while on the nicotine patch compared to cigarette smoking alone.

Another type of safety concern about over-the-counter nicotine is the possibility that people will use the product to relieve withdrawal symptoms when they are unable to smoke, making it easier for them to continue to be smokers in a world with an increasing number of environmental restrictions. Thus over-the-counter nicotine could in theory reduce the likelihood of smoking cessation for the population. To the best of my knowledge there are no data showing that this occurs, but the possibility should be examined when over-the-counter nicotine becomes available.

Nicotine therapy in high risk populations

I want next to discuss the risks versus the benefits of nicotine in high risk populations. The table summarises the issues. Cigarette smoking delivers nicotine rapidly to the body, resulting in higher arterial levels than nicotine replacement. Smoking also delivers carbon monoxide and a variety of other toxic compounds.

The risks of smoking are well established. There are theoretical risks of nicotine, but no clear human evidence that I have seen of nicotine related injury. There are no benefits of cigarette smoking in people with heart disease or during pregnancy. The benefits of nicotine replacement are either smoking cessation or maybe smoking fewer cigarettes.

If one analyses benefits and risks in this way, then even in the highest risk populations people are generally better off receiving nicotine replacement treatment than smoking cigarettes. I have no reservations about the use of nicotine replacement treatment in high risk patients who are otherwise unable to stop smoking. If over-the-counter drugs are used instead of smoking cigarettes in high risk patients, I do not have great concern.

Modification of tobacco products

My final comments will address issues of modification of cigarettes to reduce adverse health consequences. Are currently marketed low yield cigarettes less harmful than high yield cigarettes? Hughes has presented some data suggesting that maybe they are for lung cancer (this issue, p. S33). I need to point out that the data presented by Hughes are based on older style cigarettes smoked 20 or more years ago. These cigarettes were primarily non-filtered, high yield cigarettes. In contrast, almost all modern cigarettes are filtered, and the yields of tar and other toxins are much lower than they were 20 years ago. I am aware of no data showing that among the currently marketed cigarettes there is a dose–response

Benefits versus risks of nicotine replacement treatment in high risk patients

	Cigarette smoking	Nicotine replacement
Exposure	● Nicotine: rapid delivery high doses ● Carbon monoxide ● 4000 other chemicals	● Nicotine: slow delivery low–moderate doses
Risks	● Well established – acute myocardial infarction – sudden death – reproductive disorders	● Possible – haemodynamic aggravation of myocardial ischaemia (no increased thrombosis) – aggravation of utero-placental ischaemia
Benefits	● None	● Smoking cessation ● Smoking fewer cigarettes

relation indicating a reduction of risk when smoking lower yield cigarettes. Therefore, I am sceptical about lower yield cigarettes as a viable approach to nicotine reduction.

The last issue is whether a regulatory strategy to reduce the content of nicotine in cigarettes is safe. Henningfield and I proposed gradually reducing the content of nicotine in cigarettes in order to make cigarettes non-addictive.[14] Such a strategy, if it worked, would reduce the prevalence of cigarette smoking and substantially reduce harm. There are of course concerns about compensatory smoking of cigarettes during the weaning phase, which could result in periods with greater exposure to tar and carbon monoxide. The magnitude of this problem would need to be addressed as the strategy was implemented.

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1 Doll R, Peto R. Cigarette smoking and bronchial carcinoma: dose and time relationships among regular smokers and lifelong non-smokers. *J Epidemiol Community Health* 1978; **32**: 303–13.
2 Rosengren A, Wilhelmsen L, Wedel H. Coronary heart disease, cancer and mortality in male middle-aged light smokers. *J Intern Med* 1992; **231**: 357–62.
3 Wilhelmsen L. Coronary heart disease: epidemiology of smoking and intervention studies of smoking. *Am Heart J* 1988; **115**: 242–9.
4 Willett WC, Green A, Stampfer MJ, Speizer FE, Colditz GA, Rosner B, *et al*. Relative and absolute excess risks of coronary heart disease among women who smoke cigarettes. *N Engl J Med* 1987; **317**: 1303–9.
5 Benowitz NL, Jacob P III, Kozlowski LT, Yu L. Influence of smoking fewer cigarettes on exposure to tar, nicotine, and carbon monoxide. *N Engl J Med* 1986; **315**: 1310–3.
6 Benowitz NL. Nicotine and coronary heart disease. *Trends Cardiovasc Med* 1991; **1**: 315–21.
7 Holm H, Jarvis MJ, Russell MAH, Feyerabend C. Nicotine intake and dependence in Swedish snuff takers. *Psychopharmacology* 1992; **108**: 507–11.
8 Huhtasaari F, Asplund K, Lundberg V, Stegmayr B, Wester PO. Tobacco and myocardial infarction: is snuff less dangerous than cigarettes? *BMJ* 1992; **305**: 1252–6.
9 Wennmalm A, Benthin G, Granström EF, Persson L, Petersson A-S, Winell S. Relation between tobacco use and urinary excretion of thromboxane A_2 and prostacyclin metabolites in young men. *Circulation* 1991; **83**: 1698–704.
10 Benowitz NL, FitzGerald GA, Wilson M, Zhang Q. Nicotine effects on eicosanoid formation and hemostatic function: comparison of transdermal nicotine and cigarette smoking. *J Am Coll Cardiol* 1993; **22**: 1159–67.
11 Benowitz NL. Nicotine replacement therapy during pregnancy. *JAMA* 1991; **266**: 3174–7.
12 Benowitz NL, Kuyt F, Jacob P. Influence of nicotine on cardiovascular and hormonal effects of cigarette smoking. *Clin Pharmacol Ther* 1984; **36**: 74–81.
13 Benowitz NL, Jacob P III. Intravenous nicotine replacement suppresses nicotine intake from cigarette smoking. *J Pharmacol Exp Ther* 1990; **254**: 1000–5.
14 Benowitz NL, Henningfield JE. Establishing a nicotine threshold for addiction – the implications for tobacco regulation. *N Engl J Med* 1994; **331**: 123–5.

Public health implications

Judith K Ockene

I am pleased to be wearing my public health hat. Sometimes I wear my clinician's hat, and the two overlap quite a bit. Those of us who see ourselves as public health practitioners believe that we have a responsibility for developing and delivering smoking intervention treatments and policies which decrease risk for as many people as possible. That is the bottom line when we consider public health approaches.

Earlier we heard that a major problem is lack of success in smoking cessation for the poorer, less educated smokers in our country; and that is the issue on which I shall focus most of my comments. Attention to public health requires that we attend to those individuals who are most in need of assistance for making changes and are most able to benefit from our efforts. From a public health perspective, I believe that we do not necessarily lack appropriate and adequate interventions. There are in fact interventions which are effective for all groups of smokers when delivered as intended.

The problems in the public health arena are lack of adequate ways of delivering interventions which are appropriate and acceptable to the providers and consumers who need them, and lack of adequate access to treatment. The latter includes lack of adequate methods of delivery. Improved methods of delivery improve access.

An optimal public health approach could improve delivery of services and access for all consumers. This approach includes five components: the first component, education for the smokers and providers about smoking treatment, is the most important aspect of public health. Education must be delivered in a form or mode which is acceptable to the target population. For example, for a low income adolescent inner city population, it is important for education and other interventions to be delivered in places where inner city youth gather, and the messages need to be in a form that they can hear. For example, Dr Vic Strecher told me about a wonderful rap group which he heard which put antismoking messages into their music. Another example is the media campaign in Massachusetts which has developed targeted educational messages directed at particular populations such as teenagers to grab their attention.

The second component, development of social norms and an environment that supports change, is necessary since individual change (for smokers and health care providers) does not occur in a vacuum.

The third component, coordination and integration of services and efforts in multiple community channels, which include worksites, health care settings, media and voluntary organisations, allows services and programmes to optimise each other.

The fourth component, the creation of infrastructures, allows for and facilitates the delivery of messages and services for health

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