TOBACCO CONTROL
AN INTERNATIONAL JOURNAL

Editorial

Applying the risk/use equilibrium: use medicinal nicotine now for harm reduction

Both the recent Institute of Medicine (IOM) report[1] and the article by Henningfield and Fagerstrom[2] in this issue of *Tobacco Control* consider the value of adding harm reduction products to the main public health strategies for dealing with tobacco use—prevention, cessation, and protection of non-smokers from tobacco smoke pollution.[3 4] Harm reducing products are those that lower total tobacco caused morbidity and mortality, even though these products might involve continued exposure to one or more tobacco related toxicants. The IOM committee developed a testing strategy to assess which products (tobacco or pharmaceutical) are truly harm reducing, along with surveillance and regulatory principles for the protection of public health. Henningfield and Fagerstrom[2] discussed the possible benefits from an uncontrolled harm reduction "intervention" in Sweden involving Snus (Swedish moist snuff) and to some extent nicotine replacement pharmaceuticals or medicinal nicotine (MN).

It will take years, if ever, before any battery of IOM-type tests will be in place. Given the probability of legal and political battles, the final form of testing and regulation may be far from adequate, leading to further decades of the promotion of ostensibly reduced risk products falsely reassuring tobacco users. Cigarette smoking remains the single leading preventable cause of death in most developed countries[5] and a major cause of current and future deaths in developing countries.[6] For health, non-smokers should never start smoking, and current smokers should become former smokers as soon as possible. Harm reduction, if done well, offers additional promise. Once it was hoped that lower tar cigarettes would have harm reducing properties and be good for the public's health,[7] but, on current evidence, they have been a public health disaster.[8–11]

Strongly prefer harm reduction products with the largest effects to those with small effects

One harm reduction strategy is to alter cigarettes to try to reduce or eliminate toxic ingredients. Such altered cigarettes are of obvious interest to the cigarette industry. But there are serious practical challenges to assessing the impact of small changes. Scientifically, smaller effects are harder to identify than are larger effects. Reliably finding smaller effects requires more reliable measures and larger samples.[12] In other words, more expensive, longer term studies will be needed to determine, for example, if a product change has caused a 5% reduction in risk than an 80% reduction. The proposed IOM testing methods need to be applied to these new tobacco products before any recommendations can be made about novel, small change, reduced risk products; therefore, it will be years before it will be possible to assess with confidence the health risks of changes in cigarette formulations or other burned/heated tobacco products (for example, Eclipse, Accord, Advance).

Our strategy is to start with the least risky nicotine delivery products and try to judge if it is reasonable at the present time to recommend that smokers use them for harm reduction. We have concluded that: (1) smokers who cannot or will not stop using nicotine in cigarettes should be encouraged to use MN as their only source of nicotine; and (2) never smokers should not be encouraged to use nicotine in any form. We are not advocating the mixing of cigarettes and MN.

From the point of view of someone treating an individual with a health problem, risks and benefits are weighed, and decisions are made on the basis of current evidence—often flawed and inconclusive. For the individual smoker, there is no doubt that MN, in the form of pharmaceutically tested products such as gum, patch, nasal spray, is less dangerous than continuing smoking. We concur with the IOM report "that for persons addicted to nicotine, a nicotine containing drug product is preferable to a cigarette or other tobacco containing product as a chronic source of nicotine"(pages 7–20).[1] Henningfield and Fagerstrom[2] also suggest that medicinal nicotine may be preferred to Snus as a less dangerous product.

The case for the individual smoker is clear, but the case for public health has been questioned. In discussions of harm reduction products for cigarettes, we have often heard participants (including some of us) argue that a less dangerous product might encourage use so much that the reduced risk for individuals sums to greater risk for the entire population. What if more people use MN?

Applying the risk/use equilibrium

To evaluate the possible problems caused by increased use of a less dangerous product, it is helpful to consider what might be called *the risk/use equilibrium*—an equilibrium achieved by increasing use as risk decreases. Maintaining this equilibrium constitutes a public health stalemate. To the extent use rises faster than risk is decreased, public health will be increasingly disadvantaged. To the extent risk is decreased faster than use rises, public health will be advantaged. Figure 1 shows a plot of the relation between level of risk and the increase in the number of users (as a multiplier) needed to achieve an equilibrium, or, in other words, no increased population level risks.

MORTALITY RISKS FROM MEDICINAL NICOTINE

A carcinogen-free, unburned nicotine source, free of all other smoke toxins, is not widely expected to cause cancer,

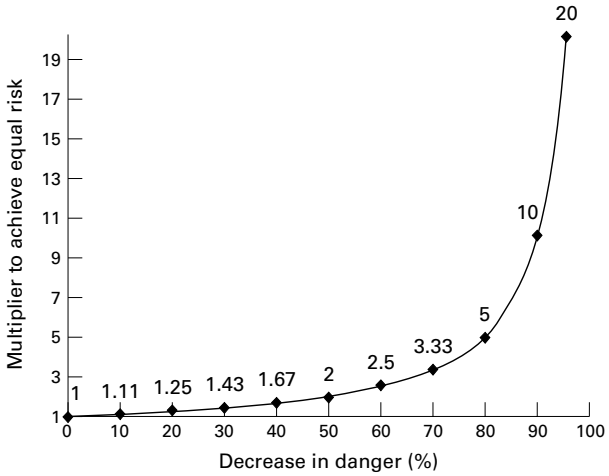

Figure 1 The risk/use equilibrium. Each point on this curve indicates the multiplier needed to achieve a constant level of population risk, given specific levels of decreased danger per user. For example, if 100 individuals used a product with full danger (for example, killing 100% of users), 10 times that number (1000 individuals) would need to use a product that had 90% decreased danger, to achieve an equal health problem (100 dead in each instance). The formula is Y = 100/100−X, where Y = multiplier and X = decrease in danger, expressed in percentages. If danger is 0.1%, use would have to increase by 1000 times to produce a problem of the same magnitude as the full risk product (not plotted on figure). For a given risk on the curve, use that is increased by a smaller multiplier represents a public health benefit, and use that is increased by a larger multiplier represents a public health (population level) cost. (See text for more details.)

chronic obstructive lung disease, or fires—all causes of tobacco attributable mortality.[13–15] (Nicotine should be avoided during pregnancy, but cigarettes cause greater problems for reproductive health.[1 16]) Most concerns about mortality effects in users of MN focus on possible effects on cardiovascular disease,[1 16] so we will take a closer look at MN and cardiovascular disease.

The toxicological literature is mixed on the relative dangers of nicotine alone versus cigarette smoke for cardiovascular disease. Although nicotine can increase heart rate, blood pressure, and cardiac contractility, MN does not seem to produce many of the cardiovascular risks of cigarette smoke.[1 16] Unlike cigarettes, MN does not appear to promote platelet aggregation.[17 18] MN has no carbon monoxide. MN (gum) was shown to not have adverse effects on coronary circulation.[19] MN (nasal spray) was found to not have adverse effects on blood lipids (for example, high density:low density lipoprotein cholesterol ratio).[20]

Epidemiological research provides a better estimate of actual cardiovascular risks from MN. Although there were some early media reports of cardiovascular problems caused by MN (in particular, the nicotine patch),[21] subsequent research supports that MN has very low cardiovascular risk. Up to five years of nicotine gum use in the Lung Health Study was unrelated to cardiovascular diseases or other serious side effects.[22 23] Other research has found no excess risk of myocardial infarction from the nicotine patch in the general population[24] or even in patients with cardiovascular disease.[25] A meta-analysis of 35 clinical trials (5501 active patch, 3752 controls) found no evidence of cardiovascular or other life threatening adverse effects caused by MN, and noted that: "The results of this meta-analysis indicate that very large studies would be needed to assess the effect of the patch, if any, on serious, rare outcomes."[26] Based on current epidemiological evidence (which might change with more data on longer term use), MN has small to negligible effects on cardiovascular disease in former smokers. Some may say that it cannot be established that MN is "safe" (without any excess risk). This may be true, but it is fatuous to treat such a statement as an argument, in and of itself, against the use of this low risk product for both individual and public health care. We think the risk/use equilibrium needs to be considered.

HOW MANY PEOPLE WOULD USE MEDICINAL NICOTINE?

MN use by never smokers is likely to be rare. In a study of nicotine replacement therapies in the UK and Sweden, Ramstrom[27] found no cases where Nicorette gum was being used by someone who had not used tobacco previously. Note that over-the-counter (OTC) MN has been available for several years in the USA, and there is no evidence of emergence of a MN abuse problem in never smokers.[28] We find it hard to expect that more that 10% of former smokers might start using MN—but many of them might be spared from returning to cigarettes by using MN. Fifty per cent use of cigarettes by adults (males and females combined) appears to be close to a maximum use levels for cigarettes world wide,[29] but it would be unlikely that MN would ever be used by more half of smokers. Summing the projected use of MN by current and former smokers, we would expect a lower limit on use of about 10% and an upper limit of about 35% of adults.

POPULATION LEVEL RISK

We have not put an exact number on the mortality risks, if any, from MN, but our best estimate is that the risks of these often OTC medications are extremely small. For example, if the risk were less than 1/10 000, use would have to increase by over an impossible 10 000 times to cause an equivalent level of problems! On current knowledge, MN use could not increase to a degree that there would be a net public health loss.

The complete public health picture is, of course, somewhat more complicated. Except if MN prevented never smokers from becoming smokers, never smokers who started using MN would be increasing risk somewhat, not decreasing it. As noted above, however, increased use by never smokers and ex-smokers is an unlikely outcome unless the MN industry were to embark on marketing efforts designed to encourage never smokers and ex-smokers to take up MN. On current knowledge, we would not recommend that smokers use MN to reduce cigarette intake. Mixed use of cigarettes and MN will occur, despite recommendations to the contrary. A much more complex and complete model of use and risk is being developed[30] that will estimate risks of different patterns of starting, continuing, and quitting product use. Such a model may be important for judging the value of harm reduction products with less promising risk reducing effects than MN.

Use medicinal nicotine for harm reduction now

The public health community should send a strong message now that the best harm reduction strategy for current smokers, after abstinence, is MN. While others will be promoting tinkering with cigarettes to reduce tobacco risks, we think these modifications are unlikely to produce worthwhile changes in risk and will take years of research to evaluate their actual level of risk. Henningfield and Fagerstrom[2] show evidence that Swedish Snus offers harm reduction compared to cigarettes, but we would particularly support the use of MN as a more powerful harm reduction product carrying less public health risk. As has been pointed out by others,[31] the current regulatory system is upside down, with the more dangerous products (that is, tobacco products) receiving the least regulation and the least dangerous products (that is, MN) subject to the most stringent constraints. If tobacco companies are

unregulated or under regulated, they may well find ways to drown out the messages of medical and public health professionals regarding the least dangerous form of nicotine delivery. Medical and public health authorities should advocate for MN products that provide doses of nicotine in forms that are as affordable and reinforcing as the more toxic tobacco products. They should also advocate for the long term use of MN by those who need it, as has been advocated by Rodu and Cole.[32] Considerable work needs to be done to inform consumers that MN is the least toxic way to get nicotine. One anecdotal report, for example, suggests that some smokers believe that MN is more likely to cause heart attacks than traditional cigarettes.[33] Many adults may perceive MN as a sign of weakness, with tobacco use associated with freedom and the pursuit of pleasure (KM Cummings, personal communication, April 2000). Such an image needs to be changed. If empirical evidence related to MN changes, and making MN more reinforcing might lead to more adverse effects, advice may need to change. For now, we think it is urgent to promote complete substitution of medicinal nicotine for cigarettes for harm reduction in smokers.

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Lynn Kozlowski had some research funding nine years ago from a manufacturer of medicinal nicotine and has consulted with Pinney Associates who provides consultative services to manufacturers of medicinal nicotine. Gary Giovino has also provided consultative services to Pinney Associates. Pennifer Erickson has consulted widely for the pharmaceutical industry related to measures of quality of life.

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