

- cessation trial after one year. *Br J Addict* 1992; 87: 1189-94.
- 48 Cinciripini PM, Lapitsky LG, Wallfisch A, Mace R, Nezami E, Van Vunakis H. An evaluation of a multicomponent treatment program involving scheduled smoking and relapse prevention procedures: Initial findings. *Addict Behav* 1994; 19: 13-22.
- 49 Shapiro D, Schwartz GE, Tursky B, Shnidman SR. Smoking on cue: a behavioral approach to smoking reduction. *J Health Soc Behav* 1971; 12: 108-12.
- 50 Fant RV, Gross J, Stitzer ML. Effects of smoking exposure on subsequent desire to smoke. Poster presented at the annual meeting of Society of Behavioral Medicine, San Diego, March, 1995.
- 51 Rennard SI, Daughton DM, Thompson AB, Floreani AA, Romberger DJ, Millatmal T. The effects of nicotine replacement therapy on cigarette smoking reduction. Abstract presented at the American Lung Association, American Thoracic Association Conference, Boston, MA, May, 1994.
- 52 Hughes GH, Hymowitz N, Ockene JK, Simon N, Vogt TM. The multiple risk factor intervention trial (MRFIT). *Prev Med* 1981; 10: 476-500.
- 53 US Department of Health and Human Services. *Reducing the health consequences of smoking: 25 years of progress. A report of the Surgeon General*. Rockville, Maryland: Public Health Service, Centers for Disease Control, Office on Smoking and Health, 1989. (DHHS Publication No (CDC) 89-8411.)
- 54 Baile WF, Gibertini M, Ulschak F, Snow-Antle S, Hann D. Impact of a hospital smoking ban: changes in tobacco use and employee attitudes. *Addict Behav* 1991; 16: 419-26.
- 55 Frederiksen LW, Peterson GL, Murphy WD. Controlled smoking: development and maintenance. *Addict Behav* 1976; 1: 193-6.
- 56 US Department of Health and Human Services. *The health consequences of smoking: cancer. A report of the Surgeon General*. Rockville, Maryland: Public Health Service, Centers for Disease Control, Office on Smoking and Health, 1982. (DHHS Publication No. (PHS) 82-50179.)
- 57 Townsend J, Roderick P, Cooper J. Cigarette smoking by socioeconomic group, sex, and age: effects of price, income, and health publicity. *BMJ* 1994; 309: 923-7.
- 58 Prochaska JO, Goldstein MG. Process of smoking cessation: implications for clinicians. *Clin Chest Med* 1991; 12: 727-35.
- 59 Sobell LC, Sobell MB, Nirenberg TD. Behavioral assessment and treatment planning with alcohol and drug abusers: a review with an emphasis on clinical application. *Clin Psychol Rev* 1988; 8: 19-54.

## Panel discussion

Moderator: Jack E Henningfield

Panellists: Richard D Hurt, Cynthia S Rand, Frank J Vocci

### Jack E Henningfield

I am going to put Dr Vocci on the spot. Frank, you are one of the coauthors of the *Guidelines for medications development* which tried to level the playing field. With what you have heard today, what do you think about harm reduction with respect to tobacco?

### Frank J Vocci

In the opiate field, we have somewhat acquiesced with the idea of total abstinence for all opiate users. If we can get people into treatment, we know that a certain proportion will stop using opiates, but then there is a subgroup that will not, but will reduce their use. We have somehow stuck with them and have started to accept those patients more.

I think if you use that type of a strategy, you have to start looking at these partial responders as people who are possibly giving the best response that they can. If you are conducting clinical trials in smoking cessation, you could look at secondary indications, like reduction of use, because for every drug that produces cessation, there is going to be a subgroup with reduced use. This subgroup is probably embedded within the clinical trial. All you need to do is to analyse the data a little differently and do a secondary analysis. We have categorised these people originally as failures, and perhaps we just have to start thinking differently: if you can get a sustained reduction of whatever the determined magnitude is for a long enough period of time, you should be able to show a reduction in harm.

There is a tension developing between these types of proximal endpoint and some of the things I am hearing lately from Robert Temple at the FDA, who feels that perhaps we should be looking at different endpoints. The other

day he made the analogy of the congestive heart failure trials, saying that instead of looking at cardiovascular indices such as ejection fraction improvement we should perhaps be doing large scale clinical trials which would show the hospital admission rate in people on a particular treatment, and how soon these people die from congestive heart failure. Perhaps we should look at these very gross endpoints, and look at them in large populations rather than doing sophisticated modellings that may or may not show harm reduction in the disease process. It is one of the issues FDA is concerned about in clinical trials – you can have a very fancy clinical measure that does not necessarily translate to patient benefit in the long term.

Philosophically, I sympathise with this concept of harm reduction. I do not think you are going to get everyone who is a smoker to stop smoking, and I think we have to start thinking about what the magnitude and duration of a reduction are that will produce a meaningful benefit in whatever indication we are looking at, whether it is a reduction of cardiovascular, pulmonary, or cancer risk.

### Jack E Henningfield

Dr Rand, the lung health study you worked on had facets that might be construed as harm reduction approaches in so far as gum was relatively freely available for a long time. What are the pros or cons from your perspective?

### Cynthia S Rand

To orient those who may be unfamiliar with it, the lung health study, for which final results were published in *JAMA* in November 1994, enrolled 6000 people with early chronic ob-

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structive pulmonary disease (COPD), 4000 of whom got a special treatment programme. Our goal was absolute smoking cessation. All of us who designed the intervention clearly worship at the church of total cessation as the only cessation, and anything less than that was failure, and we certainly counted our success by the number of absolute quits.

In terms of our final results, we had projected that we would have the maximum impact on pulmonary function among those people who quit in the initial smoking cessation programme and those who remained smoke-free through the entire five year trial. Those were a population that we referred to as our sustained quitters, those who never relapsed.

To achieve these goals, at the time we used state-of-the-art treatment – the comprehensive, multicomponent behavioural programme that everyone has described. When we began the trial, Peggy O'Hare, who had been one of the key people in designing the intervention, had projected how much nicotine gum we would need per participant, and we had calculated that it would be four or five boxes a person. Five years later, after we had gone through several hundred thousand boxes of gum, we realised we had grossly miscalculated. We took the perspective that we would use replacement therapy intensively because it was important to help this high risk population remain smoke-free, and our participants took us up on that offer of use of free gum.

At the end of one year in the lung health study, we had a confirmed smoking cessation rate of about 34% of all participants. Of that population, however, about 40% were still using nicotine gum at one year. When gum was available and offered free of charge, we certainly had a substantial subset who chose to use it. It was a continual source of debate, and underlying this was the issue of the morality and the appropriateness of sustaining people.

We had never begun the trial with the idea of a methadone-like model of shifting people to nicotine replacement. However, our participants seemed quite ready and willing, given the availability of nicotine gum, to drop right into that model. We maintained over the course of the five years quite a significant subset of individuals who used nicotine gum.

About the middle of the trial, we put additional efforts into reducing gum use. We began to require that they have a prescription from their private physician, although we continued to provide it free of charge, and we placed a greater emphasis on stopping, based on the idea that it was wrong to keep these people on the gum.

How do you feel about the concept of maintaining someone on nicotine replacement, even if it works? We did succeed by the end of the trial in reducing the percent of long term nicotine gum users to something under 10%.

What was the result in terms of harm reduction in this population? For those who quit, the sustained non-smokers, they had only one quarter of the loss of pulmonary function over the course of five years than those who continued to smoke. They lost on average

about 72 ml over the period of the trial compared to over 300 ml for the sustained smokers.

What about the people that went in and out, though? We had a group that we called intermittent smokers. Some of these both smoked and used gum. Some were people who cycled through quitting and relapsing. They ended up right in the middle in terms of loss of lung function.

From a harm reduction perspective, these people who were partial failures were also partial successes because they had significant benefit. The question I would ask of harm reduction is that, while it obviously makes sense from a policy perspective to reduce harm, what does that do to cessation? Had we stated at the beginning, "All right. Well, we would like you to stop, but if you can't stop, what about cutting down?" I do not think we would have done as well. I think most of those people desperately wanted to stop. We were happy with what we got, but I suspect we would have been much less successful had we taken a more ambivalent approach to our ultimate goal.

#### **Jack E Henningfield**

Dr Hurt, what do you think of muddying up the message?

#### **Richard D Hurt**

I am not ready at this point to abandon our intervention efforts until we fully exploit them. We need to push intervention technology to the edge and then disseminate that information in a way that makes a difference before we accept another way of dealing with this very difficult problem.

For the interventionists in the audience, I think you will agree that we already do harm reduction in treating the patients that we see. Stopping smoking is a process, and not everyone gets it right the first time. We use the stages of change to measure progress. We do treat patients with long term nicotine replacement treatment if they are in danger of relapse to smoking because we recognise that the continued use of cigarettes is much more harmful than continued use of nicotine replacement treatment in those individuals. So we already do harm reduction to some degree.

My second point is that we have limited resources. All of us are competing for a shrinking pot of money, and to divert resources from the interventionists who deal with individual patients on a day to day basis and muddying the water by invoking harm reduction would be a serious move backward, and I think one that actually endorses the addicted patient's attitude. It is akin to recommending to alcoholics that they switch to beer or to wine. We used to recommend that patients cut down on their smoking, but we found that it did not work very well.

I also believe that harm reduction appears to endorse the position of the tobacco industry and their minions. I am not sure that the FDA

or the pharmaceutical industry is ready to jump into that relationship. If they are, it would be very interesting.

I recall a few years ago at a meeting in Cambridge when we were told that we already knew enough about smoking intervention and that we did not need more intensive interventions like inpatient treatments for people with severe nicotine dependence. I disagreed with that then, and I more strongly disagree with that now. We do need more intensive interventions for patients who are more severely addicted, and we need to work out how to do it, and then we need to disseminate that technology to the rest of the treatment community.

We are at the very beginning of this process. We are using rudimentary tools in dealing with a very difficult addiction. We only have a few drugs to use and there is much to learn about intervention.

For the health care providers in the audience, we need to think about how we can incorporate an integrated approach to nicotine dependence for all the patients that we see in each hospital and medical centre around the country. Most of the smokers come in contact with the medical care community on an annual basis, so this approach could reach many smokers.

Physicians play a key role, but we need to use mid-level practitioners, such as counsellors rather than physicians, to do the bulk of this work. They do better at more intensive counselling than the physicians do. We also need to systematise these interventions so that they become a part of the health care delivery system and not have them off in some other part of the medical system. We also need to communicate realistic expectations so we do not generate disappointment among patients or health care providers.

#### **Jack E Henningfield**

What would need to be done to collect those kinds of data? The obvious thing to do is to demonstrate actual reduction of disease. In the area of heart attacks, this might be possible because it is within the life cycle of a research project. For lung cancer, it is probably not.

#### **Richard D Hurt**

Dr Vocci and I were talking about this before we started. If you were going to use reduction in lung cancer rates as a measuring stick in your approval process, it would make approval impossible. That is an undoable study because it is going to take too long to do it. No one can fund that.

#### **Jack E Henningfield**

In the absence of data, what kinds of markers?

#### **Richard D Hurt**

I don't know. We can go back and look at some of the use patterns within the data we have, and Dr Rand just mentioned one where there is clear reduction in harm in those people who have reduced their consumption of cigarettes over time in the lung health study. We surely have information about the end-of-treatment level of smoking. We could do a study to find out what happened to them later on – whether they reverted back to their previous levels of smoking.

#### **Jack E Henningfield**

I am hoping is that you and others, including pharmaceutical companies, may have some of the data that have just not been reported. I do not think all these data have been thrown away. There are some potential gold mines out there.

#### **Richard D Hurt**

I agree.

#### **Cynthia S Rand**

But let me throw out the cautionary note that if you want to go back and do secondary data analysis and look at the number of people who have managed to achieve reduced smoking levels or some modification of their smoking habits, I think that there is a danger in extrapolating from studies where the goal was smoking cessation. You may achieve a certain rate and assume that you would have got the same results had your message been moderate harm reduction.

Harm reduction is a valuable and important byproduct of a focused intervention where the goal is smoking cessation, and it may well be important for policy. For example, when we assess the cost-effectiveness of our treatments, particularly very costly ones like the lung health study, it is of critical importance to produce data that show a clear benefit in our population, like the reduction in loss of pulmonary function.

I am much less clear about whether we want to soften or make ambivalent our message and our goal and whether we really can conclude from existing data what the result of that would be. I think that requires new research.

## Questions and answers

**CALVIN FUHRMANN:** Let me represent to you that if I put a person with angina on a treadmill and exercise them and then give them 1–3% carboxyhaemoglobin, I can significantly reduce the endpoint of their exercise. An immediate benefit of reducing the number of cigarettes is to reduce carbon monoxide. In every other model we have, such as hypertension or cholesterol, we have accepted cutoff points or markers for risk reduction. So why not for smoking?

**RICHARD D HURT:** I think there is one major difference. When you are dealing with a drug of dependence, the mentality of the individual has a lot to do with what happens in the intervention. Hypertension, diabetes, I treat all of those things, too, but the individual who is addicted to a drug has a different mentality. With cigarette smoking, the ultimate goal must be to get them to stop altogether.

**JED ROSE:** I have a comment about the notion of cigarettes which deliver nicotine without significant tar. I was struck, Dr Henningfield, by your first slide which showed that a little more than half of all deaths attributed to smoking were due to cancer as opposed to heart disease, and if you can really eliminate virtually all of the carcinogens in smoke, then it seems extremely likely that it would have a major impact on public health.

So I am a little distressed at the fact that that approach might be dismissed because you cannot design the trial to show that lung cancer rates are reduced in 15 years. We know enough about carcinogens and tar to have a strong suspicion that tar is the main contributor to cancer, and since cancer accounts for more than half of the disease or deaths due to smoking, if you could eliminate that, might that not be as good as getting half the people to stop altogether, in terms of public health?

**CORINNE G HUSTEN:** I just wanted to address the issue of reducing the number of cigarettes as a sanctioned endpoint. I think it is true that it can be a beneficial side effect of our efforts to promote cessation, but I have some reservations about using that as an explicit endpoint.

Some of this has already been said. I do not think we have maximised our efforts as far as cessation goes, and I think until we do that it would be premature to give up on cessation as our endpoint. Also, the fact is that prevalence is going down in nearly all the demographic subgroups and the prevalence of cessation is increasing. It may not be doing so as rapidly as we would like, but we are still making progress.

Secondly, I have concerns because I am not sure that reduction in use is really harm reduction when it comes to number of cigarettes, because at least for lung cancer there is some suggestion that duration is a stronger risk factor than number of cigarettes. While it may be the square of the number of cigarettes per day, it may be the duration to the fourth or fifth power. So we may not really be reducing harm when we talk about decreasing the number of cigarettes, especially if it keeps people from quitting instead.

Thirdly, there are chippers and people who seem to smoke small numbers of cigarettes for long periods of time, but there is also evidence that a fair number of people show indicators of addiction at very low levels of cigarette use. So I am not sure we are really accomplishing all that much by telling people to cut down.

Finally, I am concerned that an explicit message of reduction might send a really dangerous message to our children. They already start saying, “Well, I can stop any time I want”, and if we also have a strong message out there that cutting down is an endpoint, I think it would only reinforce the idea that they can start and then control their use whenever they want.

**JOHN R HUGHES:** I hope that everyone who has opinions about this feels that their opinions are going to be swayed by data. My point is these questions are eminently researchable. Dr Rand, what if you did a trial where to a third of the people you said, “Cessation is the only way to go”, to another third you said, “Cessation is the way to go, but if you cannot make it, reducing would be really nice”, while to the final third one, you said, “Why don’t you reduce, and if you can quit, that would be great, too”. I just hope that we as a group do not make the same mistake that many areas of psychiatry and chemical dependency have done, where philosophy comes first and data come second.

**PETER REUTER:** Two phrases have come out that bother me. One is “muddying the waters”, and the other is a notion that we have to make a choice between harm reduction and cessation. I think those are just false distinctions.

You have a very fragile technology, and you are developing it. It does not mean that there is not another fragile technology that shouldn’t get developed around the same time, and it is not clear that even at the policy level differentiation is not allowed. There are some settings in which the message is one thing and another one in which the emphasis of the message might be different.

**RONALD M DAVIS:** I agree with Dr Hughes that we do need data in all of these areas, but until we have those data, I will get a couple of my concerns out on the table, and if nothing else, they will point out some other areas of potential research.

First of all, to pick up on Dr Husten's point about the message that a harm reduction strategy sends to children, I would make the point that a lot of children of course try their first couple of cigarettes and have a pretty violent reaction to them and, therefore, do not go any further in smoking or moving toward nicotine dependence. If we had cigarettes with much less initial toxicity, might we increase the number of children who can get beyond their first couple of nausea-inducing cigarettes? That is an area that also could be easily researched.

On the issue of adults, though, and this question of safe haven, I agree on the critical importance of examining this. We do not really know whether low tar/low nicotine cigarettes increase quitting by providing sort of a step down approach to lower and lower levels of nicotine to cessation, or whether they decrease quitting because health conscious smokers feel they have done their job in reducing their own personal health risk.

We ought to look at who has done the research, and it is likely that the tobacco industry has done it. Of course, they will not share their research with us, but as a proxy to their research, we can look at their advertising and marketing techniques. One thing that has struck me for many years is the proportion of their advertising and promotional expenditures that go toward low tar cigarettes, and the Federal Trade Commission data show that the cigarette industry has always spent a much higher percentage of their advertising dollar for low tar cigarettes, that is, those yielding 15 mg or less of tar, than the market share of those cigarettes would seem to justify.

For example, if the low tar cigarettes occupy about 50% or 55% of the total cigarette market, then they have been spending about 65%, 70%, or 75% of their advertising dollars to advertise those low tar cigarettes. Why is that? I think there are two possible explanations. One is that that segment of the market is simply more competitive; the other is that the cigarette industry is intentionally trying to increase the low tar market because that will keep more smokers, particularly health conscious smokers, in the smoking population. We need to look at these realities.

**RICHARD D HURT:** The third reason may be that it is an entry level drug. Low tar/low nicotine cigarettes do not make the kid sick – they are like Skoal Bandits.

**LORI D KARAN:** I was involved in the HIV/AIDS field when we started discussing needle exchange programmes, and there was much debate about whether that muddied the waters about drug use. A lot of good studies found that people sought more treatment and there was more engagement in treatment,

probably meshing well with the stages of change model. I think as we understand more about the neurophysiology and the mechanisms of addiction, we will be able to understand for whom we need to tailor nicotine maintenance, for example, subpopulations and treatment matching, and that will further refine our treatments and goals.

**JACK E HENNINGFIELD:** That is interesting. I had not thought of how this may or may not fit into the stages of change model.

**MARTIN JARVIS:** On the issue of reductions in cigarette consumption as an alternative endpoint, I think we do actually have some data on that, Dr Hughes. We should remember the multiple risk factor intervention trial (MRFIT) experience, where they did design reductions in cigarette consumption as one of their planned endpoints. In the end, they abandoned it because they found no reduction in effective exposure by thiocyanate measurement in people who reported reductions in cigarette consumption. I think we have to distrust reported reductions in cigarette consumptions and outcome measure.

**JOHN R HUGHES:** You are absolutely right, and I did say it was going to be quick and dirty, but I think that is a good point. I did not mean to suggest that all the reduction data looked that way. I think there is enough controversy to suggest further studies. So if anybody took the impression that this always works, let me correct it.

**PETER REUTER:** Finding that needle exchange programmes bring more users into treatment is important. It does not deal with the fears that I think touch on something said here, which is that it is still focused on the harm to the user, not to the community. The claim about needle exchange is that it muddies the message about drug use, and none of the studies, I think, is able to do a very good job at dealing with that concern.

**PAUL M CINCIRIPINI:** I have two quick points, and both of them speak to Dr Rand's issues about smoking reduction. First, even when you remove the people who are abstinent and look at those who are left over, the reduction in smoking occurs in the most effective treatment groups substantially more than it does in the less effective treatment groups.

Second, no one has mentioned a paper by Sharon Hall, from about two years ago, on commitment to abstinence being a very important precondition for long term cessation of smoking, as well as heroin and alcohol use.

**DAVID G GILBERT:** I would like to preface my comment with the fact that we have nearly a billion people smoking worldwide, and it is important for us to consider that larger community in terms of harm reduction.

A more parochial or local issue would be labelling cigarettes and potentially taxing the

tar, as Dr Hughes mentioned. I think, however, it would probably also be important to tax the tar to nicotine ratio to allow for any compensation that might happen with your lower tar delivery cigarettes. One benefit, I believe, of that would be that it would shape the tobacco companies and the consumer into producing and smoking less harmful cigarettes.

**CLIFF DOUGLAS:** As a policy and legal rather than a scientific or research person, all of this seems to say that we need FDA regulation. When you get right down to it, we cannot do anything effectively without having full disclosure and full information. The people or the entities whom we are all relying on for most of our information are the tobacco companies. I would also point out that the Henningfield and Benowitz paper, looking at the possibility of phasing nicotine out of cigarettes, is something we have not talked about, but should be part of any discussion at this point, now that we know that tobacco manufacturers exercise complete control over the drug.

**C TRACY ORLEANS:** I resonate very much

with the points of view espoused by Drs Rand and Hurt on the need to retain the goal of absolute abstinence and to pursue the improvement of those technologies and their dissemination. I also want to point out that harm reduction does not solve anything for us in this country because it is going to require yet another level of triage monitoring. We cannot get providers now to give a 90 second message about stopping smoking or about the proper use of transdermal nicotine or quitting methods that really maximise the efficacy of the tools we now have. Patients who appear suitable for a harm reduction strategy remain in need of treatment. We are going to face the same practical realities of cost and physician support.

**JACK E HENNINGFIELD:** If anyone came in here thinking this is just like any other area of medicine where if you have something that mitigates disease you have something good, now you know better. It is a complicated issue where there may be unpublished data that will bear on the issue; if you have such data, please bring it out.