Panel discussion

Moderator: John R Hughes
Panellists: John C Ball, Carl C Peck, Stephen I Rennard

University of Vermont Human Behavioral Pharmacology Laboratory, Burlington, Vermont, USA
J R Hughes

University of Maryland School of Medicine, Department of Psychiatry, Baltimore, Maryland, USA
J C Ball

Center for Drug Development Science, Georgetown University Medical Center, Washington DC, USA
C C Peck

University of Nebraska Medical Center, Pulmonary and Critical Care Medicine, Omaha, Nebraska, USA
S I Rennard

John C Ball

I have been working in methadone maintenance treatment programmes for many years, and there are some differences between that field and what we are discussing here. I think the concept of harm reduction, as Dr Henningfield anticipated, is very useful in terms of encouraging discussion and debate, and breaking us loose, perhaps, from a preoccupation with smoking cessation. But other than that, I think the concept muddies the water tremendously because it does not have a clear cut goal.

We have a semantic problem with the term "harm reduction." Some people say all medicine is harm reduction. I think it is. Harm reduction can mean just a decrease in the number of cigarettes. It can mean a decrease in the amount of nicotine. It can mean – as used by many advocates in the drug abuse fields – less treatment and cheap treatment.

We normally do not talk in the United States about methadone maintenance as being harm reduction. We talk about methadone maintenance as long term treatment and rehabilitation, and very good data show that the more money and resources put into the programme, the better the outcome. So it is not, as it is in some places in Europe, just giving out methadone. Even in Europe harm reduction can mean different things.

So I think the term has tremendous semantic problems with it, and my own suggestion is to drop the term fundamentally and replace it. I like the term "improvement" a great deal more than I do "harm reduction." What do you mean? What kind of harm? But if you talk about health improvement or less adverse effects, such as a reduction in mortality or morbidity, you are sending a clearer message.

So where does this leave us? This leaves us with talking about alternative strategies and what these specific strategies are and what their goals are. And then, as Dr Hughes said, it becomes a research question.

Also, we need realistic expectations, which our experience in other drug treatments has shown. To think that you are going to do great things in five years is unrealistic, and I worry because you set yourself up for failure. Realistic expectations require a solid understanding of the populations that you are dealing with, and to be able to forecast in terms of 10–15 years from the present.

John R Hughes

Dr Peck, what is your thought about someone coming to the FDA with a pharmacological agent aimed purely at harm reduction? That is, a drug designed not to achieve cessation of smoking, but for reducing harm from smoking.

Carl C Peck

You could not be at a luckier moment in history. There were days at the FDA in the sixties and seventies and perhaps in the early eighties when you would have been met with a rigid, unhelpful, unimaginative bureaucracy, not necessarily populated with the best and the brightest, who would have thrown up a lot of roadblocks. You will hear some perspectives this spring in congressional debates about regulatory agencies that will sound as if the agency is still the same, but it is not.

At this meeting there are eight FDA heroes who helped to get levo-α-acetylmethadol (LAAM) approved within 18 days of receipt at the agency. If you want data, Charles Grudzinskas, director of NIDA's medication development division, has published a paper[1] documenting how this drug development process evolved and how the agency was so responsive, along with the medications development program at NIDA.

If there are data to support the intended claim, derived under adequate and well controlled trials, this is a good moment for expedited development and FDA review.

1 Grudzinskas CV, Wright C. An 18-day approval becomes reality. *Pharm Exec* 1994: 74–80.

John R Hughes

Dr Rennard, as a pulmonologist you see a lot of people who have severe chronic obstructive pulmonary disease and will not stop smoking. Would harm reduction be a reasonable alternative with those people?

Stephen I Rennard

Whether it is a reasonable alternative or not requires some data, but I think it is certainly an option that should be considered. If you are faced with a patient with a medical problem who has some complicating factor, such as smoking, and you can address that problem

and improve their health, that would seem to me to be an option that should be considered.

What you need, of course, are the data that support the idea that the reduction of smoking, as opposed to cessation, would in fact have some kind of measurable therapeutic benefit. You certainly would like to have something to offer to patients, not just patients with significant lung disease, but heart disease or other diseases where smoking is a complicating factor. These are patients who know they are suffering the lifetime consequences of some self inflicted injury and may have failed the very best of smoking cessation attempts that they initiated with the best of intentions. We really have relatively little to offer those patients. So I think that being able to offer them reduction, at least conceptually, gives us another possibility.

We are very interested in whether smoking reduction can be achieved. You presented our data showing that some smoking reduction can be achieved with nicotine replacement. It seems that nicotine replacement is slightly more beneficial than trying to reduce smoking with placebo alone. This is to be expected on the basis of the work of Drs Hughes and Benowitz, and many others here.

Also in that study, we tried to get some measure of health benefit. Our study was of people who were normal smokers. If they had any measurable health problems, they were excluded from our study. We also excluded anybody who was interested in smoking cessation. If they were interested in smoking cessation, we encouraged them to stop and disqualified them from participating in the study. So we were dealing with people who had no intention of stopping, and even so they were able to achieve a reduction.

We were able to achieve statistically significant improvement in measures of lower respiratory tract inflammation. Pulmonologists were concerned with this, and we believe that this kind of inflammation contributes to bronchitis and emphysema. So we could show some biological benefits that were statistically significant in that study, at least providing some conceptual support that reduction might have medical benefits.

I suspect that more tangible clinical results would be required before you could really advocate reduction as a therapeutic endpoint, but certainly our data would support that kind of approach conceptually.

Questions and answers

CYNTHIA S RAND: One of the words that has been missing from the alternatives we are talking about – and it is curious that it is missing because you hear it so often when you talk to smokers – is pleasure.

We are talking a lot about what are essentially negative reinforcement models. We are talking a lot about getting people to avoid bad things happening to them. But we haven't said much about reinforcement in the sense of replacing the pleasure that comes from smoking. Some of us may be uncomfortable with that.

In terms of pharmacological alternatives and balancing the issues of abuse potential, I should be interested in the panelists' thoughts about the possible future for a safe, pleasurable drug. Nicotine provides the positive reinforcement that so many of the participants in our programmes say is missing and that is part of what keeps them smoking, not just avoiding withdrawal.

JOHN R HUGHES: Jed Rose is doing some work with citric acid aerosols and other types of aerosols that replace some of those sensory aspects. And one could add pharmacological therapy, too. I think that your notion is a good one. It might cause a blurring between the pharmaceutical and consumer product industry, as Dr Warner mentioned, and that is something to be aware of.

TERRY PECHACEK: When the public health community of the United States killed Premier, Michael Russell caught me in the hallway and told me what fools we were. We are approaching the situation where Eclipse is one of many products that are in the pipeline of the tobacco industry. And the initial public health response to the information about it was, "Kill it. Kill it quickly." How would the panel react to this position?

KENNETH E WARNER: That experience with Premier is very telling and important because it shows the gap in understanding about and between the tobacco industry and the public health community. As I understand it, RJ Reynolds went into a private meeting with the Surgeon General and essentially said, "We have taken the cancer stuff out of the cigarettes, will you guys get off of our backs?" The answer is that the public health community would not get off of their backs, and I think they were really surprised by that. You are raising a very important question because we are going to see more of these products.

I am concerned about Eclipse in some ways more than about Premier because I think it has been designed to avoid the FDA regulatory mechanism which they found they might have to confront with Premier®. Premier® is obviously a drug delivery system, and not a cigarette. Eclipse® is designed to look more like a cigarette, and they are trying to evade that particular realm of the regulatory business.

We are talking about extremes here. We have the Benowitz/Henningfield proposal that we ought to reduce the nicotine in cigarettes to non-addictive levels, if there are such levels. Couple that with the possibility that we are going to have all kinds of over-the-counter nicotine substitutes available and it becomes a terrifically interesting area. We have to think very seriously, as a public health community, about how we should react to this. I do not know the answer, but I think we are hearing a lot of the questions here.

NEAL L BENOWITZ: The goal is the same for both strategies. It is to reduce tobacco health consequences, and if people are not addicted to cigarettes, they do not become addicted smokers and then suffer those consequences. If they just use plain nicotine without anything else toxic, it accomplishes that as well.

I would just emphasise that the focus should not really be on nicotine. Nicotine is just the vehicle that maintains addiction, and that is sort of the tool we are dealing with, but the goal is to reduce the tobacco related disease.

RON TODD: We have not done a very good job on cessation. We do not have a good national network. When smokers reach the point when they are ready to stop, there is really no good infrastructure nationwide nor any kind of cohesive effort to address the issue. There is a lot that we can do to find better methods, but we must also produce a more cohesive national approach to the issue. At the moment we have a hotchpotch of the Cancer Society, the Lung Association, and whoever else happens to get involved in cessation. We are not well orchestrated.

Secondly, I do not think risk reduction or harm reduction needs to be an end to the means. Cessation appears to be somewhat of a continuum. Perhaps reduction can be an interim step on the way to quitting for the more addicted smokers.

A term that I have heard today that I don't agree with is "for smokers who cannot quit." I do not think there really is such a thing as a smoker who cannot quit. I think there are many smokers whom we will not be able to reach, but I think that we have to be as creative as we can.

C TRACY ORLEANS: I want to add another economic model to the one that Dr Warner presented. What I am hearing about now, in the dawning of a new era of disease state management, has a lot to do with return on investment, and I have personally seen managed care organisations really fight a systematic introduction of tobacco intervention strategies because the return on investment is too delayed. In the rush to quality managed care, at least to top rated managed care, we now find that if return on investment is not achieved in 18 months, it is not thought of as a high priority programme.

I think we all need to do better cost-effectiveness research, and one of the results of the emphasis on return on investment short term is that we shall see better treatments, I hope, for the high risk medical populations where that return is greatest – the post-myocardial infarction patient and the pregnant smoker, for example.

KENNETH E WARNER: We should keep in mind it is not simply a matter of having a short time horizon. It may well be that for most managed care organisations you do not get a positive return on investment for a very simple reason: you lose a lot of the people who you helped to quit. Maybe with the high risk patient you get a better return because they remain with you.

On an optimistic note, it has struck me that there is going to be an incentive for these mega-health care organisations that are evolving all around the country to take an interest in the health of their clients because they will have them for a long time.

DAVID SWEANOR: As a lawyer who has been involved in the economics of this subject for quite some time, I think we have to look at the sort of regulatory framework that is possible for alternative nicotine delivery, but at the same time, what can we do to make tobacco a less effective nicotine delivery device? I had seen this morning that the total market for alternative nicotine delivery, nicotine patches and gum, is about $200 million. The total market for cigarettes in this country is about $50 billion. That is not a big market penetration, and it seems to me that there is the potential here to do something that is not only very good for public health, but makes a lot of money for some of the people who are doing these things.

I would like to hear more from the pharmaceutical companies about some of their concerns. I have heard in talking to some of them individually that they do not want to get involved any further in this for fear of the image of being nicotine suppliers. They do not want to be seen to be like tobacco companies, and they have concerns over product liability if they say, "Hooray, we have got a product that will only kill 20000 Americans a year".

CHARLES W GORODETZKY: It is hard to respond to a generalisation. I think that there have been some image issues in the pharmaceutical industry of getting involved with "an addictive product," and getting involved with a product for the treatment of substance abuse. It extends broader than just the area of smoking cessation. It extends over into the whole area of development of medications for the treatment of substance abuse.

Some of the issues are economic in a way that is beyond me since I am in the clinical research area of the industry, but the industry is certainly under the same kind of economic pressures that many other industries are under: those of constrained resources. A company has to look at where it is going to divide the resources it has what is going to be the economic payoff. We are looking at 46 million smokers in the United States. We are looking at a much larger number, in the billions perhaps, worldwide, and it sounds like a lot of folk.

When we place this in the broader economic context of a company as a whole, seeing what kind of resources are available, what areas they want to work in, and putting them in order of priority, the development of medication for treating smoking addiction tends to come out more on the lower side than on the higher side.

MURRAY JARVIK: I want to ask Dr Benowitz about the scheme that he and Dr Henningfield have for a non-addicting cigarette, which would be produced by regulation. How would you get Congress to regulate for cigarettes of this kind? And secondly, how would you prevent people from rolling their own or, for that matter, from a black market arising for cigarettes from Mexico or Canada?

NEAL L BENOWITZ: It is technologically possible because with the current process, nicotine is in fact extracted and re-added. That process certainly could be mandated as part of the regulation process just by measuring nicotine content in tobacco and saying that it had to be reduced by a certain percentage. I think it is clearly feasible to do that.

In terms of rolling your own, obviously if tobacco is available, one could roll one's own. Black marketing is not so much of concern to me. The big issue that this proposal is trying to address is the children who almost invariably experiment with cigarettes, and who mostly don't want to become addicted smokers. Most of them see that smoking a few cigarettes in adolescence is not going to be harmful for life, and they are probably right if they could stop within three or four years, when the urge to smoke dies down.

If there was a way to make cigarettes so that children would not be addicted by the age of 20, then I think the risk would be tremendously reduced, and that is the rationale for it.

If people want to get black market cigarettes, that does not bother me because if there are 10% or 20% of hard core smokers who must have cigarettes and will pay more for them, then let them. It certainly reinforces the addictive aspect of nicotine if people do that. But even if you could reduce the number of

smokers by 80%, we would have made a phenomenal jump.

RONALD M DAVIS: I want to respond to Dr Warner's point about whether taxpayers or insurance companies ought to be paying for smoking cessation, especially since you raised that question at each of these three conferences, and I did not have a chance to respond the previous two times.

I think there is an important flaw in your analogy between trying to get people to eat a lot of fruit and helping people quit smoking. While both are prevention strategies, smoking cessation is also treatment of a substance use disorder. So I think what our goal should be is to have third party payers address smoking cessation just as they would the treatment of other medical problems, and certainly to address smoking cessation to the same degree as they would treatment of other substance use disorders.

In my previous life at the Office on Smoking and Health, we dealt with this issue when we released the 1988 Surgeon General's report on nicotine addiction and the 1990 report on the health benefits of smoking cessation. What the Department of Health and Human Services said at that time was that we ought to have third party payers cover treatment of nicotine addiction to the same extent as they cover treatment of addiction to illicit drugs and alcohol. So I think that that sort of framework would argue for third party payers to cover treatment of smoking.

MICHAEL C FIORE: Whatever smoking cessation strategy is adopted, harm reduction included, it is doomed to failure if we have our current system in which health care providers are not active participants in smoking cessation in a consistent manner and on a regular basis with smokers who present to the health care setting. Like Dr Davis, I would say that other medical conditions like hypertension or hyperlipidaemia are better as comparisons.

Until clinicians are reimbursed for providing such services, particularly as we move to a managed care environment where so many people today are getting that care, they will not receive it.

KENNETH E WARNER: Unfortunately this would require a long and complicated answer that involves some basic economic understanding, and it is why I think we have a problem in our health care system in general.

I would agree with what Dr Davis said. As long as we are going to treat and reimburse for everything else, why not do this? This is certainly every bit as cost-effective and reasonable as anything else we do.

It is a bigger, broader question of why we feel that in the medical arena that we have to have everything paid for in order to make it worth doing. If enough people thought that smoking cessation was something they wanted to do and that it was worth the money to them, and they went to their physicians with cash in hand and said I will pay you for this therapy, you would see physicians providing the service.

In a managed care environment, if you get large organisations that truly have an interest in health; these are not going to need to be reimbursed for smoking cessation, per se. They are going to provide smoking cessation services because it makes financial sense to them if they are going to deal with those lives a decade down the line.

What I am doing is to vent some concern and disappointment about our conventional method of funding health care in general. I would like to see health insurance used to cover big, unpredictable expenses, and have some of us bear a little bit of the responsibility for our own health care costs until they start to get too burdensome, but that is a more general issue.

JUDITH K OCKENE: In managed care there are guidelines that indicate whether or not certain services should be provided; it is not necessarily at issue that that there is reimbursement for those services, but that they are part of what should happen in the setting. With managed care, we are getting more guidelines for what should be provided to the *individual*. I think the wider coverage is more of an issue in the non-managed care setting, such as Medicaid, where I think it is important.

JACK E HENNINGFIELD: First on RJR's Premier because I was berated for my role in that: I think the main issue there for me was that when a tobacco company develops a high-tech drug delivery system it should be treated like a pharmaceutical company. Why should it develop a high-tech device and then get a regulatory free ride, even though it may be useful? If it is useful, then prove it and put it on the market.

Secondly, how you would go to the FDA with a claim for a risk reduction or a health improvement? With smoking cessation, it is pretty simple in one sense: a statistically significant difference. With risk reduction, I think we are going to have to think about whether the effect is not just statistically significant but biologically meaningful. So a reduction of 40 cigarettes to 30 or 20 might be significant in a given population, but not have enough biological meaning. Thus we may have to apply a different standard.

JOHN R HUGHES: How did they do it with cholesterol lowering drugs? Did they have to show that it would decrease cholesterol by a certain amount to get it approved or did they just show that it decreased it somewhat and any little helps?

JACK E HENNINGFIELD: I don't know about the cholesterol lowering drugs, but with food labelling, for example, to get a product into a healthier food category, you have to demonstrate that it has a biologically meaningful effect in the diet.

JOHN R HUGHES: My only question is where would you draw the line. Let's say I get carbon monoxide to go from 30 down to 20. Is

that significant or not? I can't answer that. Dr Peck, do you have any comments on that?

CARL C PECK: Yes, I do. First of all, Michael Weintraub, who I think is still in the audience, is the senior FDA official representing the Center for Drugs. One of his areas of expertise is obesity treatment, and he has pointed out to me that the efforts to reduce the morbid effects of obesity have a long history of drug development, with excess body mass as a surrogate endpoint towards normalcy, but not requiring a return to normalcy.

In fact, there is a more general paradigm that the agency has employed in many instances by using a surrogate marker as a substitute for a hard to realise clinical event. Blood pressure measurements are used as a marker for the risk of stroke and heart failure. More recently, with controversy, has been the use of CD4 counts in the treatment of HIV, and in between there is a whole gamut of markers that have been used, some imperfectly and some with ill effects. For example, drugs to treat irregular heart beat took a nose dive a couple of years ago when the placebo group fared better than the treatment group in a major clinical trial.

But the notion of presenting the agency with a labelling claim and data to support it for reducing the risk is, I think, certainly tenable, and it would be a matter of negotiating with the agency in advance about the validity of the surrogate marker, whether it be nicotine levels or cotinine levels or something else. This whole area needs to be negotiated and debated and probably brought before a public advisory committee to develop a strategy for it, but it is certainly within the realm of possibility.

MITCHELL A NIDES: We have some data from the lung health study that I think support the long term use of nicotine gum. We had many people who were long term users of gum over five years. When you look at morbidity and mortality data in that group, they show that there is no real risk from long term nicotine gum use.

On the issue of flexibility that Dr Gorodetzky mentioned, when we submitted those data to *Archives of Internal Medicine*, the paper was rejected on the basis that nicotine gum is now passé and nobody uses it, so why publish about it?

Nicotine gum is still, I think, a viable force in nicotine replacement. Regarding nicotine patches, if they do go over the counter, we have to make a concerted public relations effort to explain that people are not going to die if they smoke one cigarette while they are on the patch. I do a lot of patch studies and talk to a lot of smokers, and without fail, they all saw the headlines that said they would die if they smoked, but nobody has heard anything about the data that show they are better off if they smoke and use the patch at the same time.

DAVID P L SACHS: This is a thought and a question for both Drs Warner and Ockene, and anybody else who wishes to respond. I raise this point as a 20 year research veteran in this field and also wearing my hat as a pulmonologist and the former medical director of respiratory therapy at University Hospitals of Cleveland and former associate chief of the medical ICU there.

When I started in this field, there really was very little, if anything, that one could label as effective treatment as shown by randomised controlled trials. Now we are at the other end of the spectrum where every nicotine patch study to date that has been published, even if it does not show a significant difference between active and placebo, shows a trend in that direction.

So I would like to have some insight, if anybody has it, into why there is this amazing lacuna in managed care planning and in the insurance industry. Any managed care plan will currently pay tens, if not hundreds, of thousands of dollars for a coronary artery bypass operation. What is the return on that investment, and why will they pay for that when they will not pay for fundamentally effective treatment that is now in the medical literature?

KENNETH E WARNER: I think that is easy. You are preaching to the choir. We have known for a long time there is a difference between prevention and secondary and tertiary care treatment as it is perceived by the medical profession, and prevention gets the double standard.

William Foege said years ago that for a surgical innovation to be accepted into practice it has to be shown to be safe; a medical innovation has to be shown to be safe *and* effective; a prevention intervention needs to be safe and effective *and* cost-effective. He was wrong about that. It needs to be safe, effective, and money making, which is a much stronger statement than cost-effectiveness.

The reality of life is you have got a double standard of care out there: if you do not do the coronary artery bypass, you are going to be in deep yogurt. If you do not provide smoking cessation, you are not going to be in deep yogurt. For new procedures to insinuate their way into medical practice, there is going to have to be an economic incentive.

JUDITH K OCKENE: I did not think the data were that alarming. At least the data we saw this morning from Mr Pinney indicated that close to 50% of the managed care organisations were covering nicotine replacement therapy. Granted, we still have a way to go.

And I would say that we have very similar data that are a bit more promising. We just did a survey in Massachusetts of managed care organisations in the last couple of months and found that about 70% were covering nicotine replacement. We had several of the managed care organisations knocking on our door asking how they can better put this into practice in their health maintenance organisation (HMO). So I do not think the picture is quite so bleak,

and I will take a slightly more optimistic approach with regard to some of our managed care colleagues.

SHARON SCHMIDT: I want to thank Dr Peck for his comments about our division. It was under Dr Peck that Dr Harter was allowed to set up the Division of Pilot Drug Evaluation to work with companies in different ways so that reviews could get done faster, and I think we have done that. But it was not just our reviewing. It was the companies we are talking about working as a team. I think the companies worked very well with us in getting submissions to us quickly and in a form that we could review quickly.

Also, the individual investigators have been very helpful in getting information to us, and now we are moving into another era, with Dr Weintraub joining our team. I want to thank everyone who helped us get these products out quickly.