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Product implications

Charles W Gorodetzky

I shall begin with my conclusion: the major product implication of alternative treatment goals is the maintenance of flexibility. We need to develop a variety of pharmacotherapeutic options to allow individualised treatment, both for the particular smoker and for a particular treatment goal.

I refer to flexibility here over a number of different dimensions, which I refer to as corollaries of flexibility. The table shows these major areas of concern. The first and obviously most important of those corollaries of flexibility or dimensions of concern, is the pharmacotherapeutic agent, per se.

The figure shows cigarettes as well as the currently available, and perhaps soon to be available, nicotine replacement medications along a continuum of those that are the shortest acting and most rapid to reach their peak to those that are of longest duration and reach their peak the slowest. The first line indicates the dosage form; the second line shows the number of dosage units (cigarettes, sprays, pieces, systems) used per day; the third line is the approximate time to reach peak concentration; and the last line indicates approximate duration of significant plasma levels of nicotine.

Of course, there are also several other important variables along this continuum, including the total administered dose, the degree of active patient participation, or the degree to which the medication is passive, as well as the side effect profile. Active participation by the patient is indicated to some degree by the frequency of administration. Those dosage forms on the left side of the continuum, requiring most frequent administration, involve the most active patient participation, while those requiring less frequent dosing, often referred to as passive medications, appear on the right side. Transdermal nicotine replacement, with only one daily dose, is currently the form requiring the least patient participation.

Corollaries of flexibility

- Pharmacotherapeutic options
  - Nicotine replacement
  - Non-nicotine products
  - Combination products
- Dynamic clinical status
- Research implications
- Who is the treater?
- Commercial implications

The total administered dose per unit is quite variable. Transdermal systems have 7, 14, and 21 mg available, while the gum provides 2 and 4 mg per piece. Nasal spray, as I understand, will be about 0.5 mg per spray per side,[1] (about 1 mg per administration), and the average amount of nicotine obtained from a cigarette is estimated to be about 1 mg.

Where are we going to go in the future here? What are we going to need? Although it is not totally clear at present, I propose that what we need is more products along this continuum. The continuum of nicotine replacement currently available, or soon to be available, goes roughly from the short acting nasal spray on the left to transdermal systems on the right. As referred by others, I think we are going to need some dosage form (or forms) even more rapid acting than the nasal spray. Perhaps we need something that begins to approach the rapid onset and short duration of the nicotine in the cigarette. Perhaps the low tar, high nicotine cigarette itself will be useful. Possibly it will be something on the order of a pure nicotine cigarette of some sort, and reference has been made to those as well.

Central Nervous System, Marion Merrell Dow Inc, PO Box 9627, Kansas City, Missouri, USA
C W Gorodetzky

Correspondence to: Dr Charles D Gorodetsky

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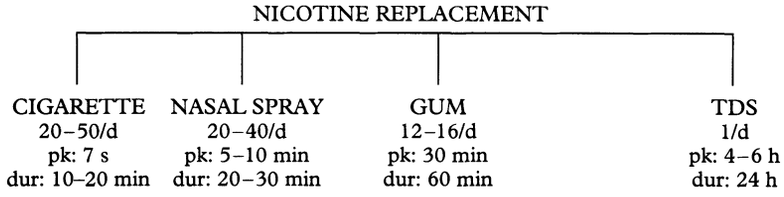

Cigarettes and nicotine replacement medications on a continuum from short acting (left) to long acting (right). TDS = transformed systems; pk = time to peak concentration; dur = duration of significant plasma nicotine concentrations.

We may need other things also along this continuum. For example, an inhaler might be useful,[2] as might other transmucosal kinds of administration, and perhaps oral dosage forms that would give us additional options. In addition, we may want to push the continuum to the right as well. Possibly even lower dose, longer duration kinds of medications than currently available transdermal systems will provide useful options for nicotine replacement.

What about total dose? Several people have referred to the need for higher dose nicotine replacement for use especially in more highly dependent smokers. With currently available medications, we have to go to techniques like use of multiple patches in order to get closer to 100% nicotine replacement. A high dose patch, if it could be done, in a size that would be acceptable to the patient would probably be beneficial.

As well as nicotine replacement, we also are interested in non–nicotine products. These may be closely related to nicotine, such as, for example, cotinine,[3] lobeline, or other nicotine agonists. However, they may be totally non-nicotine-related products, like antidepressants, such as bupropion, for example, and perhaps other psychotherapeutic agents.

We should also pay attention to the potential of combinations. These may be combinations of currently available nicotine replacements; or they may be combinations of non-nicotine products with nicotine replacements. For example, an antidepressant such as bupropion might be tried in combination with a nicotine replacement medication; work by Rose and his colleagues[4] has looked at mecamylamine and mecamylamine/nicotine combinations.

Although continued development in this area could lead to a large number of products, it could also provide pharmacotherapies with specific advantages in particular situations. After careful clinical research, significant effort will be required to educate consumers. When talking about product implications of alternative treatment goals, I should probably add here an additional related group of products, the diagnostic products. These might provide, for example, a measure of level of dependence, a characterisation of particular types of smokers or smoking typology, or diagnostics for detecting and following tobacco related illnesses, perhaps even at earlier stages than are currently possible.

Another corollary of flexibility is the dynamic clinical status of tobacco dependence, a topic which several others have already addressed. It relates to the issue of stage of change, stage of motivation; and this is not necessarily a unidirectional kind of change. People go up and down; this is a chronic relapsing illness. There are exacerbations and remissions; and it may well be that different products will be necessary at different points along that way, depending on the clinical status of the patient and the particular treatment goal. I am referring here to a clinical continuum.

There are also research implications as they apply to products under consideration for alternative treatments. This reinforces earlier comments by Hughes and others. It is not enough just to have the products. We have to learn how to use those products.

When we consider how we develop drugs in the pharmaceutical industry, quite logically and reasonably, we usually pick a single indication, one that is feasible and which represents an unmet medical need, and explore that with the appropriate clinical trials to get regulatory approval. No one would claim that this approach exhausts all the therapeutic potential for any of these agents; and that is certainly true of the nicotine replacement agents currently on the market. We need to learn a great deal more than we now know about the use of these products. I certainly support what others have been saying about the need for additional clinical research to explore much more completely how we can make optimal use of the currently available medications. On the other hand, I also support the need for to develop new medications, new options, new agents to work within the clinical continuum, and along the continuum of nicotine replacement.

Another area to consider is who is the treater? Again, this is an issue that has been noted by others. Certainly physicians and other health care professionals working alone and in combination will continue to be treaters. Also, as we move towards over-the-counter (OTC) availability, with potential OTC approval of a number of nicotine replacement medications, smokers themselves will be doing the treating. We need to determine how this factor will relate to the products that might be available, and to the appropriate use of a variety of pharmacotherapeutic interventions.

This might be an appropriate place for me also to note the issues of accessibility. A provocative remark was made earlier relating to the problem of accessibility. As this person noted, several treatment options, not only pharmacotherapeutic agents but the pro-

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grammes themselves, are often not easily available to many people, for example to the African-American community and to a variety of ethnic minorities, in fact to many of those who need them the most.

How can we have some impact on that problem? I believe it is a challenge to the pharmaceutical industry, working in concert with our treatment colleagues and with those in regulatory agencies, to work creatively in marketing our products so that we do maximise treatment accessibility, especially to those populations that have not had previous access. I include in that a consideration of economic factors. I do not disagree with the contention that people should indeed pay for their own treatments. However, there may be ways in which we can tackle being presented with a $55 bill at one go to get patches, especially for people who perhaps can only afford such expense in small portions. I think part of the challenge to the pharmaceutical industry and part of the product implications of alternative treatment goals is to work creatively in this marketing arena.

A few issues about commercial implications should be considered. From the broad pharmaceutical industry perspective, I see both positive and negative factors in terms of attraction of this market. Certainly, wider accessibility through OTC, with a broader range of treatment options, is something that makes this more rather than less attractive to the industry. On the other hand, when one gets increasing numbers of products, this tends to fractionate the market, making it less likely that any one product or brand will dominate, and making it less attractive, especially to the larger companies.

I think what we are going to see (and are already seeing to some degree) is a lot more initiatives arising from smaller companies, perhaps with larger company partners to assist in clinical development and marketing. And I do not see this necessarily as a negative development. In fact, throughout the industry small companies are taking interesting discovery and development initiatives, not only in CNS but also in other therapeutic areas. I think that this is positive from the perspective of broadening the base of people interested in applying their scientific creativity to the problems of developing new treatment options.

In response to a comment concerning the profit motive of the pharmaceutical industry, let me answer from the perspective of my own experience. I think that making money is partly what the industry is about, as is all industry, and I do not think there is any need to apologise for that. However, in the 11 years that I have been in this industry, I can quite honestly say that I have seen a major motivation derived from the desire to do something to help meet unmet medical needs. And this desire goes well beyond its economic implications: it constitutes an important part of the day-to-day working environment of industry scientists.

Lastly, let me end with a challenge. As I see it, the prime challenge is to broaden our conceptual treatment framework. I have purposely not used the term "harm reduction" here because I believe, as mentioned earlier, that this is not an either/or situation. We are not talking about harm reduction strategies *or* treatment for smoking cessation, but rather a broad concept encompassing both approaches. Harm reduction is practised in the use of a broad range of potential treatments, tailored for use depending on the particular patient, clinical status of the disease, and treatment goal. Perhaps what we are talking about here is not a major qualitative change, but rather a quantitative change, maybe with some shade of qualitative change.

Secondly, I see a challenge to work together across industry, government, and health care providers, to develop the widest range of effective treatments. Although it might sound a little simplistic, I truly believe that unless we do work together in the treatment of tobacco dependence it is going to be very difficult to make much progress. This was alluded to earlier in comments about fractionation – fractionation in a whole variety of programmes – and I think this is a possibility here as well if we do not work together closely.

We must develop new products to meet the needs as defined by the academic community, by government, and by meetings such as this. We have to work closely with the regulatory agencies as we develop guidelines for how best to develop drugs so they can be approved in a timely manner. Also, we need to work with policy makers, again in a coordinated effort, to make policy decisions truly based on scientific information. I think putting all these together, we can make a difference, both for the individual and for the public health.

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