Nicotine withdrawal medications*

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As an active researcher in the tobacco dependency field for nearly 20 years, I have seen our knowledge of the pathogenesis and pathophysiology of tobacco dependence grow by leaps and bounds. As our knowledge into basic behavioural and physiologic mechanisms has grown, so has our ability to improve treatment tools. Nonetheless, although we have ever more effective tools available which patients can use to help them stop smoking, there is no magic bullet that is going to make the smoker quit.

Nicotine replacement therapy, currently the most effective tool at our disposal to treat tobacco dependence, is an integral part of smoking cessation treatment. However, since each smoking patient has individual needs which must be met in order to stop smoking successfully, individualisation of treatment is a necessity for sustained smoking cessation. First, though, let us review some basic nicotine replacement therapy facts. Earlier in this conference, we reviewed material which shows that there are two fundamental, inter-linked forces driving cigarette smoking: psychological dependency and nicotine dependency. However, it is artificial to think of these driving forces as being different, because in reality they both describe various factors which affect neurotransmitter activity in the brain. Intrinsic mood states, external events (such as a pleasurable encounter with a friend), or drugs of abuse all affect brain neurochemical activity and thus change the way we feel, how we think, and how we respond to the world around us.

In the context of cigarette smoking, a large number of external factors, such as neutral habit situations, can affect neurotransmitter release rates in the brain, which serve to link smoking with those activities, and those activities with smoking. For example, having a cup of coffee, making a phone call, having a cocktail, being around other smokers, or after a meal, all can serve as factors altering brain neurotransmitters. Additionally, negative mood situations, such as anger, anxiety, stress, or boredom, also affect neurotransmitter release rates.

Similarly, abrupt withdrawal of nicotine can alter neurotransmitter activity and thus change cortical function so that the smoker experiences one or more physiological, nicotine-mediated withdrawal symptoms: anxiety, irritability, restlessness, anger, difficulty concentrating, hunger, or craving for cigarettes.

On the nicotine dependency side of the equation, the smoker has two nicotine medications available to ameliorate nicotine with-

drawal symptoms: nicotine polacrilex (frequently referred to as 'nicotine gum') and nicotine transdermal systems ('patch') (see table). Various interventions which have been effective in helping the smoker deal with the psychological dependency side of the equation range from self-help to intensive multi-component behaviour modification techniques. As noted in the presentation by Dr Abrams, the literature clearly shows that the more intensive the behavioural intervention, the higher both the end-of-treatment smoking cessation rates and the long-term quit rates. However, time to provide treatment also increases, which means that the cost does, too. Moreover, what has clearly been shown in multiple studies over the last 10 to 15 years is that when nicotine polacrilex is added to a behavioural intervention, the results are consistently doubled or tripled. As we shall see, the relationship between intensity of behavioural intervention and nicotine patch with treatment effectiveness is a bit more complicated.

Both pharmaceutical company-funded and federally funded research are actively investigating the potential efficacy of a wide range of other nicotine withdrawal medications. These extend from the anti-anxiety agent, buspirone, to different routes of nicotine administration, such as nasal spray and vaporiser. The limited time available to me today precludes discussion of all of these. Consequently, I am

Table Proposed pharmacologic classification of nicotine withdrawal (smoking cessation) medications

1	Class: nicotine
A	Subclass: nicotine reduction medications
	Nicotine polacrilex (Nicorette)
	Nicotine transdermal patch (Habitrol, Nicoderm, Nicotrol, ProStep)
	Nicotine nasal spray*
	Nicotine vaporiser*
	Nicotine lozenge*
B	Subclass: Nicotine replacement medications
	? Nicotine aerosol**
2	Class: non-nicotine
A	Subclass: anxiolytics
	Buspirone (BuSpar)*
B	Subclass: antidepressants
	Doxepine (Sinequan)*
C	Subclass: nicotine analogues
	Lobeline (CigArrest, others)*
D	Subclass: sympathomimetics
	Phenylpropanolamine (Entex, Ornade, others)*

This table is not intended to be complete and exhaustive; rather, it is designed to provide a basic classification system for nicotine withdrawal, or smoking cessation, medications that can grow and expand as our knowledge, insight, and scientific database expands.

* Not yet clearly established scientifically for this indication and not approved by the FDA for this indication
** Hypothetical

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going to focus on the one medication class proven as an effective adjunct in the medical management of tobacco dependency: the nicotine reduction pharmaceuticals. This is an appropriate name for them since the peak arterial blood levels which they deliver to the brain, the heart, and other organs are only about one-fifth of the peak blood levels provided by the tobacco cigarette.^{1,2}

At present there are four different nicotine patches available on the US market: Habitrol[™], Nicoderm[®], Nicotrol[™], and ProStep[™], and two nicotine polacrilex doses: 2 mg and 4 mg.

There are similarities and differences in the way these two types deliver their nicotine to the central nervous system and the body. The nicotine in nicotine polacrilex is slowly absorbed across the buccal epithelium in the mouth until it reaches the submucosal capillary bed, whence the nicotine enters the systemic venous circulation at a very slow rate. Similarly, nicotine in the patch is slowly absorbed across the epidermis into the dermal capillary bed, which is also on the systemic side of the circulation.

Potential therapeutic advantages of nicotine polacrilex include the ability of the patient to, within a narrow range, up-regulate or down-regulate nicotine intake relatively rapidly and easily, although not nearly as rapidly or easily as via cigarette smoking. A potential therapeutic disadvantage of nicotine polacrilex, however, is that in order to achieve effective therapeutic blood levels, recent studies^{3,4} have shown that subjects need to be using, on average, 12–16 pieces of this medication per day, whether using the 2 or the 4 mg dose. This can be a stumbling block in patient compliance with treatment.⁵

The nicotine transdermal patch is a step in the right direction for enhanced compliance, since it needs to be used only once per day. Moreover, the nicotine patch provides relatively steady administration of nicotine throughout the day. One potential disadvantage of the nicotine patch is that this steady nicotine level may be far too low for many patients; additionally, there is no way to 'turbo-charge' the patch for a quick 'hit', as with cigarettes, or to provide even a much less intense 'mini-hit', as from nicotine polacrilex.

The nicotine reduction pharmaceuticals are very safe medications; much safer, in my clinical experience as a pulmonologist and critical care medicine specialist, than many other commonly used prescription medications for other medical conditions. In fact, initial evidence indicates they are safe even when the two types, polacrilex and patch, are used in combination with each other⁶ or in doses higher than those regularly used today.

In the last year, concern has been raised that patients who smoke while wearing their nicotine patch might subject themselves to an added heart attack risk, presumably based on the idea that this would somehow produce 'toxic' nicotine blood levels. To assess this, we examined a database from one of our large nicotine patch trials.⁷ At each visit, serum

Figure 1 Maximum serum cotinine (mean $\pm$ SD) in all subjects who smoked while wearing their assigned, active nicotine patch ($n = 68$). See text for details. (Unpublished data.)

nicotine and serum cotinine were measured. Of the 113 subjects who were assigned to the active 30 cm² nicotine patch condition, 68, or 60 %, smoked while wearing their active patch.

Figure 1 shows the maximum serum cotinine level (a marker of total nicotine intake) in subjects who both smoked and wore their active nicotine patch. During the baseline period, when subjects were only smoking cigarettes, their mean serum cotinine level was 314.6 ng/ml. During the treatment phase, when these subjects smoked while wearing their patch, their serum cotinine level fell by 20 %, down to 251.3 ng/ml. Thus, it does not seem likely that subjects who smoked while wearing their nicotine patch were in any way exposing themselves to dangerously high levels of nicotine.

I am now going to review briefly some of the extensive literature documenting the efficacy of nicotine polacrilex, and I am going to do so, building on the presentation of Dr Abrams, by looking at several different levels of behavioural therapy intensity.

In 1983, Russell⁸ showed that single-shot, simple, 60-second, physician advice to stop smoking plus the offer of a prescription of nicotine polacrilex more than doubled the objectively validated, sustained, 1-year abstinence rate from 4.1 % to 8.8 % ($p < 0.001$) (see figure 2). This despite the fact that only 50 % of subjects randomised to the medication condition even filled the prescription.

Increasing the intensity of behavioural intervention, Fagerström⁹ (see figure 3) showed that increasing psychological intervention to simple physician advice plus three physician follow-up visits during the first month plus a 3-month follow-up letter significantly boosted sustained abstinence (without any nicotine reduction medication usage) from 3 % to 15 %. Those subjects randomly assigned to receive the 2 mg dose of nicotine polacrilex, in addition to the same physician-provided "behavioural intervention", showed sustained, objectively verified, 1-year abstinence of 27 % – almost double the physician-delivered behavioural intervention alone.

Not all studies endeavouring to replicate the Russell study have consistently shown the same kinds of results.^{10–12} Careful analysis of

Figure 2 Pharmacological and psychological treatment synergism: simple physician advice. Multiplicative effect of nicotine polacrilex on basic physician advice. Adding the offer of a prescription for 2 mg nicotine polacrilex (pharmacological intervention) to simple physician advice plus an educational leaflet (psychological intervention) increased the 1-year, objectively verified, sustained abstinence two-fold. (Graph created with data from Russell MAH, et al. BMJ 1983; 287: 1782-5.)

Figure 3 Pharmacological and psychological treatment synergism: simple physician advice and medical follow-up. Multiplicative effect of nicotine polacrilex on basic physician advice and follow-up. Adding 2 mg nicotine polacrilex (pharmacological intervention) to simple physician advice + three follow-up contacts by the general practitioner (psychological or behavioural intervention) almost doubled 1-year, objectively verified, sustained abstinence. (Graph created with data from Fagerström KO. Prev Med 1984; 13: 517-27.)

those papers that have failed to show significant differences in the active medication results compared to either the control or placebo condition shows them generally to suffer from one or more of the following design limitations: 1) Too small a sample size, reducing power to as low as 0.25; 2) Failure of a substantial percentage of the subjects assigned to the medication condition to use the medication at all; 3) Failure to use it in sufficient dosages; or failure to use the assigned medication for a long enough time period; 4) Other pertinent compliance problems; or 5) Study physician compliance problems. For example, in one widely quoted study,¹¹ approximately 55% of active medication subjects used less than one box of nicotine polacrilex. This represents severe underdosing; and we cannot conclude lack of efficacy from those data alone.

In fact, when nicotine actually gets into the circulation, in an adequate dose, it consistently increases the long-term treatment results of the behavioural intervention, no matter what the behavioural intervention.¹³

Increasing the intensity of behavioural intervention one more notch, Jarvis¹⁴ showed that when all subjects received 6 weeks of well-run, comprehensive group counselling, as the psychological intervention, but with half randomly assigned in double-blind fashion to receive 2 mg nicotine polacrilex and the other half placebo, then the sustained 1-year abstinence rate was significantly increased and somewhat more than doubled to 38% (figure 4). Note two things, though. First, a family physician, working with patients motivated to quit, but not using any nicotine reduction medication, can achieve 1 year sustained abstinence rates of 15% (figure 3) – similar to the 16% rate resulting from a well-run group counselling programme alone, also using patients motivated to quit and not using nicotine reduction medication (figure 4). Second, when the family physician adds the 2 mg nicotine polacrilex into the visit and follow-up visit regimen, the result almost doubles. While

perhaps not quite as high as that achieved with well-run group counselling programme plus nicotine polacrilex, the results are not that disparate, either.

Which treatment plan is more accessible to the average patient, more responsive to the patient's time-window of opportunity, easier to administer, more cost-effective? I pose these as questions for all of us to think about.

To bring this presentation to a close, I shall now briefly review one of the four^{7,15-17} recent nicotine patch trials that are either published or in press which present long-term results (6 or more months after Target Quit Date).

The Palo Alto Center for Pulmonary Disease Prevention study was randomised, double-blind, and placebo-controlled. Study design details are described elsewhere.⁷ In brief, we enrolled 220 healthy men and women. Each subject set a specific and individualised Target Quit Date 2 weeks after meeting all study enrollment criteria. After their Target Quit Date, they received 3 months of nicotine patch treatment with the highest dose of this particular patch (30 cm², delivering 15 mg/16 h). All subjects then underwent a 6-week patch tapering phase. Abstinence was defined as 0 cigarettes per day (by self-report) plus CO ≤ 9 ppm at each visit. After patch use had stopped, an additional objective validation check was serum cotinine ≤ 15 ng/ml.

The behavioural intervention was a standard medical practice model, which any primary care physician could use. There was absolutely no group counselling, behaviour modification, or psychological counselling. Subjects received a self-help audio book,¹⁸ developed for the American Academy of Family Physicians, to use in the 2-week preparation period before the Target Quit Date, to develop an action plan for coping more effectively with external triggers for smoking a cigarette.

Each subject received physician reinforcement of the subject's wisdom in deciding to stop smoking. Also, the examining physician provided clear, individualised review of the

Figure 4 Pharmacological and psychological treatment synergism: comprehensive psychological counselling. Multiplicative effect of nicotine polacrilex (vs placebo) on comprehensive group counselling. Adding 2 mg nicotine polacrilex (pharmacological intervention) to a well-run, 6-week, comprehensive group counselling programme (psychological or behavioural intervention) more than doubled the sustained, objectively verified, 1-year abstinence rate. (Graph created with data from Jarvis MJ, et al. BMJ 1982; 285: 537-40.)

specific medical benefits that subject could reasonably expect to gain by stopping smoking. (NB: This step took only 1 to 2 minutes during the traditional medical physical examination.) After the Target Quit Date, each patient received, but only on an as-needed basis, brief, 5 to 10 minutes of common sense, medical-type advice.

The 1-year survival curve from Target Quit Date for all subjects shows that the differences during active treatment, tapering, and the 7.5 month follow-up period after patch use was discontinued, were significantly different compared to placebo (see figure 5). Six months after the Target Quit Date, 34% of active patch subjects were sustained non-smokers, compared to only 12% who had received the placebo patch ($p < 0.0001$). We have recently completed analysis of data collected at 1-year follow-up from the end of patch treatment. The results are virtually identical to those we reported at 1-year from Target Quit Date, which were 25% vs 9% ($p = 0.0001$).⁷ We have also just recently completed a 3-year follow-up on these subjects. Data have not been analysed but were collected within the double-blind design. Our preliminary analysis is showing minimal further relapse.

Our results at 6 months are at least as strong as those reported by the Transdermal Nicotine Study Group at 6 months: 26% (active) vs 12% (placebo) ($p \leq 0.05$).¹⁶ The Transdermal Nicotine Study Group trial, however, used a much more intensive behavioural intervention: weekly group counselling sessions for the first 6 weeks treatment, followed by three further group sessions for the next 6 weeks of treatment.

Garvey's Harvard Normative Aging Project¹⁹ (figure 6) reported the natural history of smoking relapse in the absence of any structured intervention – behavioural, pharmacological, or otherwise. A total of 234 subjects who had set their own Target Quit Date, were

Figure 5 Palo Alto Center for Pulmonary Disease Prevention Nicotine Patch trial: time to relapse in 220 smokers using 16-hour nicotine skin patch or placebo patch. The first 2 weeks were not considered in the analysis of efficacy. The time to relapse is shown as the percentage of 220 smokers continuing to abstain from smoking at each follow-up visit in the nicotine patch group (filled circles, $n = 113$) and the placebo patch group (open circles, $n = 107$); non-smoking defined at each visit as explicit verbal confirmation of no smoking since the last visit + CO ≤ 9 ppm at each visit + serum cotinine ≤ 15 ng/ml after Week 18. $p = 0.0001$ by the Log-Rank Test. (From Sachs DPL, et al. Arch Int Med 1993; 153:1881-90, used with permission. Copyright 1993, American Medical Association.)

Figure 6 Natural history of smoking relapse. This study tracked the number of days to relapse in a population of 234 individuals who set a target quit date and then stopped without the assistance of any formal intervention or treatment programme. The relapse curve became asymptotic at one year. (Adapted from Garvey AJ, et al. Addict Behav 1992; 17: 367-77, with kind permission from Pergamon Press Ltd, Oxford, UK).

tracked to determine when they relapsed. At 2 weeks, fully 50% had relapsed, and 60% had relapsed at the end of the first month. Looking at the results in the placebo group from our trial you will note that 40% had relapsed at the end of 2 weeks – not that dissimilar from Garvey's study that was deliberately not a treatment trial. In Garvey's study, 85% had relapsed at 1 year – again, similar to the 91% relapse we saw at 1 year in our placebo patch-treated subjects.

In the Palo Alto Center study, we also analysed several different subgroups, including high-dependent and low-dependent smokers. To our knowledge, this is the first study to do this. Of the 220 subjects in our trial, 98 (45%) were low-dependent, as measured by a Fagerström Tolerance Questionnaire (FTQ) score of 6 or less. At the end of the patch treatment and tapering phase, 53% of the low-dependent active group were sustained abstainers compared to only 16% receiving placebo ($p < 0.001$) (figure 7).⁷ Although the active patch

Figure 7 Palo Alto Center for Pulmonary Disease Prevention Nicotine Patch Trial: time to relapse for the 98 low-dependent subset (defined as Fagerström Tolerance Questionnaire Score ≤ 6) of the 220 smokers in figure 5 using 16-hour nicotine skin patch (filled circles, $n = 49$) or placebo patch (open circles, $n = 49$). $p = 0.0001$ by the Log-Rank Test. (From Sachs DPL, et al. Arch Intern Med 1993; 153: 1881–90, used with permission. Copyright 1993, American Medical Association.)

curve appeared to be stabilising and reaching an asymptote by the end of the Tapering Phase at Week 18, fully one-third relapsed over the next 7.5 months after stopping active treatment, producing a 1-year sustained abstinence result of 35% in the low-dependent subgroup. However, those low-dependent smokers who had received the placebo were virtually doomed to failure 1 year later, with only 4% successfully achieving long-term abstinence.⁷

Those subjects who were high-dependent, that is, had a FTQ score of 7 or higher, showed a different pattern: as long as they were receiving patch treatment, either the full dose or the tapering doses, they showed significantly better results, 1.5 to 2-fold better than those receiving placebo patch ($p = 0.0131$). Once off patch, high-dependent placebo-treated subjects showed virtually no further relapse over the next 7.5 months. When active-patch treatment stopped for high-dependent subjects, however, relapse was high; six weeks after stopping patch use, there was no longer any significant difference between active and placebo patch groups ($p = 0.07$; see figure 8).⁷

We broke these 122 high-dependent smokers into a further subgroup, namely, those 71 high-dependent smokers who also had a baseline cigarette smoking cotinine > 250 ng/ml.²⁰ From Week 6 through Week 15, which included the first, 3-week, tapering dose, this subgroup of smokers showed stable sustained abstinence of 44% (see figure 9). When they went to the last 3-week tapering dose, utilising the 10 cm² patch, fully 50% of those who had been abstinent, for over 2 months, relapsed. Over the next 6 weeks, when patch use was discontinued entirely, another 50% relapsed.

These data on high-dependent smokers indicate to us that these smokers needed one or more of the following modifications to the treatment plan: 1) a higher-dose patch during the first 3 months of treatment, 2) a longer duration of treatment, 3) a more gradual tapering phase, with smaller dose decrements at each dose reduction, 4) a longer tapering

Figure 8 Palo Alto Center for Pulmonary Disease Prevention Nicotine Patch Trial: time to relapse for the 122 high dependent subset (defined as Fagerström Tolerance Questionnaire Score ≥ 7) of the 220 smokers in figure 5 using 16-hour nicotine skin patch (filled circles, $n = 64$) or placebo patch (open circles, $n = 58$). $p = 0.0131$ by the generalised Wilcoxon Test (Breslow Test), which places more emphasis on the first part of the survival curve; $p = 0.07$ by the Log-Rank Test which places more emphasis on the last part of the survival curve. (From Sachs DPL, et al. Arch Intern Med 1993; 153: 1881–90, used with permission. Copyright 1993, American Medical Association.)

Figure 9 Palo Alto Center for Pulmonary Disease Prevention Nicotine Patch Trial: time to relapse for the 71 subjects who, at baseline, were both high dependent and had high serum cotinine (defined as Fagerström Tolerance Questionnaire score ≥ 7 + serum cotinine during baseline cigarette smoking ≥ 253 ng/ml) of the 220 smokers in figure 5 using 16-hour nicotine skin patch (filled circles, $n = 40$) or placebo patch (open circles, $n = 31$). $p = 0.0453$ by the Log-Rank Test. (This graph was presented at the 53rd Annual Meeting of the Committee on Problems of Drug Dependence, June 1991.²⁰)

phase, 5) a more intensive behavioural intervention, or 6) all of the above.

These data on nicotine-dependent subgroups stress the need to individualise the treatment for tobacco dependence, and further emphasise the conclusion that one size does not fit all. But then why should it? It does not in the management of any other medical condition that I treat: asthma, hypertension, angina, or cardiac arrhythmia, for example. By what conceivable pharmacologic rationale should we not be individualising the speed of tapering nicotine reduction pharmaceuticals? There is none. In fact, nicotine reduction therapy, whether with nicotine patch or nicotine polacrilex, must be tailored and individualised, based on how a patient responds.

Let me provide some examples. If, after decreasing the nicotine patch dose from 30 to 20 cm², the patient reports having a severe increase in withdrawal symptoms, then that

patient will be at higher risk for either slipping, that is, having one or more cigarettes, or actually relapsing. This prelude to a relapse could most likely be aborted by having the patient go back up to the 30 cm² patch dose to restabilise, then tapering more gradually. As another example, if after reducing from the 30 to the 20 cm² patch, the patient reported actually having one or two cigarettes, then clearly this patient should have the dose increased back to the 30 cm² patch dose until restabilised – at least a two to four week period; then resuming tapering, but doing so more gradually. This model is, of course, no different to the empirical model that chest physicians use when tapering a successfully treated asthmatic off of corticosteroid medication.

The data reviewed and presented today clearly show that the nicotine reduction subclass of medications effectively doubles or triples abstinence results during treatment and that this benefit persists after medication use stops. Patients need a range of treatment options in order to benefit the most, as is the case in treating virtually every other medical condition. Forcing patients into a restricted and restrictive treatment mode with many hurdles might save money in the short term, but will waste 10 to 100 times more money in the long term. We do not say to the physician that a bronchodilator can only be used for 3 months, and if the patient's asthma flares and she dies, so what! We can ill afford to apply the same illogic in the management of tobacco dependence.

The data show that patients benefit from a diversity of therapeutic options. It is important that they have this wide range of treatment options available, so that the primary goal, stopping cigarette smoking, is achieved. Having said that, I must also say this: based on the data available today in 1993, a behavioural or medical treatment for tobacco dependence simply cannot be regarded as either complete or comprehensive unless it includes a nicotine reduction medication, such as nicotine polacrilex or patch. In addition, treatment must be tailored to meet the needs of the individual patient. One size, indeed, does not fit all. Only by individualising the treatment plan, as we do for all other medical conditions, will the patient achieve the best treatment result, and, in the

case of managing tobacco dependence, will health care cost reductions be the greatest.

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