Tobacco Dependence Treatment: Time To Change the Paradigm

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Fifty years ago, I asked my radiologist father why many of my grade school friends shunned another who had asthma. "Well, David," he responded, "most people, and many physicians, believe that a psychiatric disorder or a personality flaw causes asthma, even though the scientific evidence does not support that."

Last summer, while presenting “Medical Management of Tobacco Dependence” at the house-staff noon conference at Stanford Medical, I related this story. Their eyes popped. Jaws dropped. They were astounded that 50 years ago anyone could have thought asthma was a psychiatric disease. After they recovered from their shock, I said I hoped that 20 years hence no one would believe the use of cigarettes was a manifestation of a flaw in character or a weak will. Rather, everybody—physicians and non-physicians—would approach tobacco dependence for the chronic medical disease it is, and recognizing cigarette use as the primary symptom of tobacco dependence.

In this article of CHEST (see page 979), Bars et al1 start the transformation in a phase II, open-label, proof-of-concept study testing the hypothesis that the number of cigarettes smoked per day determines the severity of tobacco dependence and consequently provides a way to provide more effective, individualized pharmacotherapy, rather than the standard “one-dose-fits-all” approach. Individualizing medication types, doses, and delivery systems, as well medication duration of use, is common in medical practice; clinical therapeutics for tobacco dependence, however, is mired in outdated pharmacotherapeutic concepts. The clinical trial by Bars et al1 on tobacco dependence is one of the first to break out of that mold, using a treatment paradigm similar to asthma: individualizing treatment based on disease severity.

For having the scientific guts to break with entrenched (and non-scientifically validated) tradition within the field of tobacco dependence, these authors are to be commended. Their findings are of critical importance to developing a more practical and more clinically effective treatment model for improving medical treatment of tobacco dependence.

Despite the documented safety and effectiveness of any pair-wise combination of US Food and Drug Administration-approved tobacco dependence medications, boosting treatment effectiveness an additional 50 to 100% over either medication alone,2–9 physicians do not routinely use medication combinations to improve outcome results. The most likely reason for this omission is the lack an algorithm to determine what medication combinations to use and when, hence the importance of the present study.

The authors1 chose number of cigarettes smoked per day as the independent variable to determine the initial medication doses and delivery systems. Thus, the “average” tobacco-dependent patient, comprising 50% of this group from the New York Fire Department (FDNY), smoked 20 to 30 cigarettes per day as the independent variable to determine the initial medication doses and delivery systems. Thus, the “average” tobacco-dependent patient, comprising 50% of this group from the New York Fire Department (FDNY), smoked 20 to 30 cigarettes per day and would have started treatment on two different nicotine medications: an oral inhaler at ≤12 cartridges per day, and a patch delivering 15 mg of nicotine over 16 h. Since each inhaler cartridge can deliver up to 4 mg of nicotine, the total daily nicotine dose for the typical FDNY firefighter could have been 63 mg of nicotine per day, a threefold- to fourfold-higher dose than nicotine patch labeling would recommend. Informatively,
slightly > 10% of the firefighters smoking 20 to 30 cigarettes per day actually used a more intense regimen, since only 44%, not 50%, used the initial regimen.

The nicotine patch functions like an asthma controller medication and generally cannot relieve acute, breakthrough, nicotine-withdrawal symptoms. Nicotine patch takes a long time to reach maximum serum concentration (T\text{Max}) [both arterial and venous] of 6 to 8 h.\textsuperscript{10} The nicotine inhaler is 16 times faster: T\text{Max} = 30 min.\textsuperscript{11,12} This oral inhaler delivers nicotine to the brain faster and can thus relatively acutely relieve breakthrough nicotine-withdrawal symptoms. The nicotine oral inhaler does function precisely like an asthma rescue inhaler.

In contrast, the light-smoking NYFD members, smoking only one to five cigarettes per day, comprised 5% of the study population. They would have started on only the nicotine inhaler, up to six cartridges per day, delivering only \( \leq 24 \text{ mg of nicotine per day} \): a 62% less total daily nicotine dose than the typical tobacco-dependent patient in this cohort would receive. This approach is similar to using an albuterol inhaler as an as-needed rescue medication to treat mild, intermittent asthma.

The heavy-smoking FDNY firefighter, smoking > 40 cigarettes per day and comprising only 5% of the study population, would have started on one controller medication (a higher patch dose [two patches], delivering 30 mg of nicotine over 16 h) and also two different nicotine-withdrawal symptom rescue medications: the oral inhaler (\( \leq 12 \text{ cartridges per day} \)) and the nicotine nasal spray for immediate/crisis withdrawal symptom relief. Most importantly, as the authors\textsuperscript{1} point out, four times more firefighters than predicted—even though smoking < 40 cigarettes per day—needed this unique, high-dose nicotine medication paradigm in order to keep nicotine-withdrawal symptoms adequately suppressed. This group would have used a total nicotine medication dose of 78 to 100 mg of nicotine per day, four to seven times more than the ubiquitous, nonscientifically determined nicotine patch labeling states: 15 mg over 16 h or 21 mg over 24 h. Because nicotine medication doses were individualized, side effects were nil.\textsuperscript{1}

Finally, the protocol allowed for the addition of a second controller medication, sustained-release bupropion, 150 mg, bid. As Table 1 in the article by Bars et al\textsuperscript{1} stated, 14% of enrollees used sustained-release bupropion, with most smoking > 40 cigarettes per day. Thus, it would appear that 14% of the firefighters needed two controller medications, including 30 mg of nicotine over 16 h transdermally, and up to 88 mg of additional nicotine via rescue medication delivery systems to keep nicotine-withdrawal symptoms under adequate control.

Bupropion has a unique CNS mechanism of action. It is both a dopamine and norepinephrine reuptake inhibitor but without effect on serotonin.\textsuperscript{13} Nicotine, in contrast, activates multiple CNS pathways to release dopamine and norepinephrine, as well as other neurotransmitters.\textsuperscript{14} These two tobacco dependence-controller medications, sustained-release bupropion and nicotine patch, each acting via different pharmacologic mechanisms of action in the CNS, are similar to using two controller medications in asthma.

Use of an algorithm of this type confirms two important points: (1) individualizing and tailoring medication combinations and doses, similar to the current asthma standard-of-care, improves tobacco dependence treatment effectiveness. Essentially every published study heretofore found that treatment effectiveness was inversely proportional to the number of cigarettes smoked per day. The worst smoking cessation rates were seen in those who, pretreatment, had smoked > 20 cigarettes per day. Moreover, the number of cigarettes smoked per day, pretreatment, inversely predicted the percentage not smoking at any time after treatment start. Dale et al\textsuperscript{15} found this relationship highly significant (\( p < 0.0001 \)) across all doses of sustained-release bupropion studied. Table 1\textsuperscript{15} shows that 33% of patients randomized to placebo who had smoked \( \leq 19 \) cigarettes per day had stopped smoking at the end of study drug treatment, while only 4% who had smoked \( \geq 40 \) cigarettes per day could stop. Figure 4 in the study by Bars et al\textsuperscript{1} demonstrates that the novel approach eliminates that inverse relationship. At 3 months, approximately 50% of those who had smoked 6 to 19 cigarettes per day had stopped, as had approximately 50% who had smoked > 40 cigarettes per day. Even more remarkable, at the 12-month evaluation point,\textsuperscript{1} 9 months after all treatment had stopped, treatment effectiveness was directly proportional to the pretreatment number of cigarettes smoked per day: approximately 30% of those who had smoked 6 to 19 cigarettes per day had stopped, but nearly twice that (approximately 50%) who had smoked > 40 cigarettes per day had stopped. This finding is truly remarkable and without precedent. If subsequent, randomized, double-blind studies confirm the unique, individualized approach of Bars et al,\textsuperscript{1} we will be able to safely provide far more effective tobacco dependence treatment for the patients in our office.

(2) Individualizing the dose of nicotine to as high as \( \geq 100 \text{ mg/d} \) is safe, with no study participant having a serious adverse drug event. The adverse events reported were of mild intensity and little
consequence.1 If anything, these adverse events seemed to relate more to resuming cigarette smoking, rather than use of nicotine medications.1 The adverse events of greatest potential cardiac concern, chest pain and palpitations, fell significantly over time, and particularly—surprise!—among those who stopped smoking.1 It appears that even use of up to 100 mg of nicotine per day in the heaviest of smokers did not produce toxicity.1

This study provides strong, compelling evidence that individualizing pharmacotherapy can substantially improve tobacco dependence treatment effectiveness, with the heaviest cigarette users enjoying 50% treatment effectiveness—results unheard of before the present study. The authors1 rightly point out that their approach, based on number of cigarettes smoked per day at study entry, although intuitive and easy to employ, was not optimal. Rather, the intensity of nicotine withdrawal, as easily measured by the Fagerström Test for Nicotine Dependence,16 and the intensity of nicotine-withdrawal symptoms, after stopping smoking, should provide a superior algorithm to optimize treatment results.

This study shows us it is time to shed the artificial and scientifically invalid dose and duration-of-use constraints posed by nicotine medication labeling and focus our attention—30 years after nicotine polacrilex gum arrived on the global market—where it should be: combining these valuable and safe medications, including nicotine and bupropion, in the most effective ways and using them as long as necessary17–19 to improve smoking cessation rates and optimize tobacco dependence treatment outcome. After all, providing effective treatment so that our patients have the proper tools to stop smoking is the only way to prevent the progression of COPD.20,21

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References
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