

PRESCRIPTION FOR CONFLICT

Smoking-cessation strategies are perversely dominated by ineffective nicotine-replacement therapies.

By John Luik

A group of spine specialists recently challenged the research of colleagues on Medtronic's bone-growth product, Infuse, calling the research misleading and biased. ("Spine Experts Repudiate Medtronic Studies," Barry Meier and Duff Wilson, *The New York Times*, June 29, 2011)



Such questioning of experts' research capabilities and integrity, and the effectiveness of medical devices and therapies, is increasingly common, in large part because of the revelation of an ongoing pattern of "science for hire," in which researchers' objectivity appears to have been compromised by the fact that their work has been commissioned and funded—and in some cases even written—by the pharmaceutical industry and its consultants.

Instead of pursuing disinterested science, the pharmaceutical industry seems increasingly willing to stack the deck in its favor in order to win regulatory approval—and with it billions of dollars in potential sales—for its products.

In a sense this represents a substantial departure from what was expected of science in general, and biomedical and pharmaceutical research in particular. Such bias and misrepresentation was previously associated only with "rogue" industries such as tobacco, which supposedly distorted science relating to smoking and smoking prevention and then lied about it.

The reasons for such differences in behavior among the legitimate scientific community, public health advocates and the pharmaceutical industry on the one hand, and the "rogue" tobacco industry on the other, were to be found in the fact that the tobacco industry was engaged in self-interested activities of questionable morality. It made products designed not to help and heal but to kill its customers.

Self-interested by nature, the tobacco industry produced

dubious, if not corrupted, science while the pharmaceutical industry, in conjunction with the public health community, worked tirelessly for the public good through reputable and reliable science.

The recent scandals involving Big Pharma have upended this tidy picture. What has become increasingly clear is that the drug industry and its public health partners too have commercial interests, and with such interests comes the same incentive to distort science. There is no more reason to assume that Big Pharma produces good and disinterested science simply because it is Big Pharma than that Big Tobacco produces corrupted and untrustworthy science just because it is Big Tobacco. Rather, the science of each must be judged on its own merits.

Unfortunately, this has rarely happened. Over the past quarter century Big Pharma has increasingly entered what was previously the sole preserve of Big Tobacco—the nicotine business—through the development and marketing of nicotine replacement therapies (NRT), including gums, patches, nasal sprays, inhalers and lozenges. Its efforts have been brilliantly successful, not only as a billion-dollar business (\$1.7 billion in 2006 alone, according to Euromonitor), but also in convincing policymakers that smoking cessation requires the assistance of white coats and their nostrums.

In the process, Big Pharma's products and business strategy have largely escaped critical evaluation. Chapman and MacKenzie's 2010 article "The Global Research Neglect of Unassisted Smoking Cessation: Causes and Consequences," published in *PLOS Medicine*, is one of the few articles to scrutinize the issue with sufficient rigor.

I will attempt to fill this void by looking at two aspects of Big Pharma's nicotine business—its NRT products and its enormous financial support for the antitobacco movement, which has made switching smokers to NRT a major pillar of its campaigns. As we shall see, there is a close connection between the

two. More disturbing, it is not clear that Big Pharma's intervention in the nicotine business has helped smokers stop smoking.

The effectiveness of NRT

Over the past 25 years, the public health community has come to support NRT as the most effective way to stop smoking. For instance, the U.K. government in its 2010 tobacco strategy claimed that "Those who are most successful in quitting use a combination of behavioral and medicinal support." In the United States, the government's *Clinical Practice Guideline for Treating Tobacco Use and Dependence* of June 2000 also advocates NRT. The clear belief is that planned quitting, using "medicinal support," is more likely to succeed than "cold turkey" smoking cessation. Big Pharma has thus successfully established the medicinal paradigm in which smokers wishing to stop need NRT. The problem with this position is that it fails the most basic test of evidence-based medicine—it is contradicted by much of the published literature, which suggests that NRT has a low rate of success compared with unassisted, cold-turkey quitting. Indeed, in real-world situations, NRT often performs below the levels reported during FDA approval studies.

So what does the scientific evidence about NRT suggest? Using data from the 2000 National Health Interview Survey, Lee et al. reported 75.7 percent of successful quitters (abstinent for seven-24 months) stopped cold turkey without pharmaceutical assistance, as compared with 12.4 percent who used nicotine patches or gum ("Factors associated with successful smoking cessation in the United States," *American Journal of Public Health*).

In a study of California smokers, Pierce et al., noted that pharmaceutical aids "were not associated with a clinically meaningful long term improvement in successful cessation." ("Impact of over-the-counter sales on effectiveness of pharmaceutical aids for smoking cessation," *Journal of the American Medical Association*, 2002)

According to Pierce et al. "only about half of California aid users managed to discontinue smoking even for a day after they stopped using the aid." The authors concluded the effectiveness of NRT in clinical trials does not appear to be replicated in general populations of smokers in real-world situations.

Ferguson et al. found that most of those who quit smoking without planning used neither behavioral nor medicinal support, and most significantly, unplanned attempts to quit were twice as successful as planned attempts using NRT. ("Unplanned quit attempts—results from a U.S. sample of smokers and ex-smokers," *Nicotine & Tobacco Research*, 2009)

Schnoll et al. found that the one-year abstinence rate for those using patches was only 0.8 percent of the sample ("Effectiveness of extended-duration transdermal nicotine therapy," *Annals of Internal Medicine*, 2010). This compares with unaided quit attempts that yield one-year abstinence rates of between 3 and 11 percent, according to Gritz et al. ("Unaided smoking cessation: Great American Smokeout and New Year's Day quitters," *Journal of Psychosocial Oncology*, 1989)

In a comprehensive review of the effectiveness of NRT in cessation in the U.S., Cummings and Hyland concluded that sales of NRT were associated with a modest decrease in cigarette consumption immediately following the introduction of the prescription nicotine patch in 1992. "However, no statistically significant effect was observed after 1996." ("Impact of nicotine replacement therapy

on smoking behavior," *The Annual Review of Public Health*, 2005)

Using data from the 1986 *Adult Use of Tobacco Survey*, Fiore et al. reported that among smokers who had attempted cessation within the previous 10 years, 47.5 percent of persons who tried to quit on their own were successful, whereas only 23.6 percent of persons who used cessation programs succeeded. ("Methods used to quit smoking in the United States—Do cessation programs help?" *JAMA* 1990)

Walsh found that "despite optimistic predictions when nicotine replacement therapy [OTC/NRT] ... was switched to over-the-counter availability, population surveys have failed to demonstrate a positive impact on long-term smoking cessation ... the superiority of OTC/NRT over unaided smoking cessation has not been demonstrated convincingly." ("Over-the-counter nicotine replacement therapy: a methodological review of the evidence supporting its effectiveness," *Drug Alcohol Review*, 2008)

West et al. found that almost half of a group of British smokers' quit attempts were unplanned and that unplanned attempts were more likely to be successful at the six-month mark ("Catastrophic pathways to smoking cessation: findings from national survey," *British Medical Journal*, 2006).

Examining smoking prevalence in Australia, Wakefield et al. reported that NRT had no statistically significant effect on smoking prevalence. ("Impact of tobacco control policies and mass media campaigns on monthly adult smoking prevalence," *American Journal of Public Health*, 2008)

Chapman and MacKenzie note that unassisted cessation continues to lead the next most successful method (nicotine replacement therapy) by a wide margin ("The global research neglect of unassisted smoking cessation: causes and consequences," *PLOS Medicine*, 2010). They write that the population level analyses of the impact of the proliferation, deregulation and widespread promotion of NRT and other pharmacotherapies have failed to show any significant, sustained impact on smoking prevalence, despite the conclusions of clinical trials.

Then why NRT?

Considering that unassisted cessation is the most successful way to quit smoking and given the abysmal success rate at six and 12 months for over-the-counter NRT (generally 5-7 percent), why do governments and the antismoking movement continue to push NRT?

First, research on smoking cessation is dominated by the medical model in which NRT is portrayed as the only way to successful quitting. Chapman and MacKenzie report that 91.3 percent of recent intervention studies focused on assisted cessation. Big Pharma's deep pockets provide enormous funding for NRT research. "This greater availability of funding for certain sorts of research produces a distorted research emphasis on pharmacotherapy that ... concentrates both scientific and public discourse on cessation around assisted pharmacotherapy," write Chapman and Mackenzie. In their 2009 analysis of cessation research, they report that "of the 84 papers for which competing interest information was available, ... 48 percent of pharmacotherapy intervention studies, ... 10.3 percent of non-pharmacotherapy intervention studies and 0 percent of unassisted cessation studies had at least one author declaring support from a company manufacturing cessation products and/or research

funding from such a company ...”

Further there is also the question of whether the source of cessation research funding influences the outcomes of NRT trials and research. Etter et al. looked at all the randomized controlled trials for nicotine gum and patches that were included in the Cochrane review (“The impact of pharmaceutical company funding on results of randomized trials of nicotine replacement therapy for smoking cessation: a meta-analysis,” *Addiction* 2007). They found that compared with independent trials, industry-supported trials were more likely to produce statistically significant results and larger odds ratios.

Second, NRT continues to dominate smoking cessation because it is sold to policymakers, and to a lesser extent the general public, on the basis of clinical trials rather than on real-world situations. But there is a significant difference between the success of participants in clinical trials and smokers trying to quit smoking outside of such trials. The most significant difference is the amount of resources provided to participants in such trials in the form of counseling, phone calls, etc.

Consider, for example, the much-advertised smoking cessation medication Chantix. Chantix was approved by the FDA in part on the basis of clinical trials that reported six-month abstinence rates that in some cases reached 33.5 percent. However, more recent studies, which still provided participants with eight counseling sessions, reported only a 14 percent six-month abstinence rate (“Efficacy of Varenicline to prompt quit attempts in smokers not currently trying to quit: A randomized placebo-controlled trial,” Hughes et al., *Nicotine and Tobacco Research*, 2011). Indeed, as Michael Siegel of the Boston University School of Public Health notes, one would well wonder what the abstinence rate for Chantix users would be if no counseling session were provided (*The Rest of the Story*, blog, June 14, 2011). “This research suggests that as the number of support sessions falls and the intervention approaches a real-world situation, the effectiveness of the medication falls quite drastically,” writes Siegel. “The rest of the story is that tobacco control advocates and researchers are grossly overestimating the effectiveness of existing, FDA-approved pharmaceutical smoking cessation aids ... because the clinical trial setting ... does not simulate the real-life situation in which most of the population is using these drugs.”

Third, there is the question of money. It is not simply that Big Pharma provides enormous support for research on NRT, and that this research shows a much higher rate of NRT-cessation success than does non-industry-funded research, but also that the industry provides significant amounts of money directly to the antismoking movement. This raises the question of whether such support leads the public health community and the antismoking movement to uncritically trumpet the benefits of NRT to the exclusion of unassisted smoking cessation.

This connection between Big Pharma and the antismoking and public health communities is hardly a secret, though its implications are little discussed. For instance, in 1999 the World Health Organization launched a partnership with the pharmaceutical industry on smoking cessation. The partnership involved GlaxoWellcome, Novartis and Pharmacia & Upjohn. The American Cancer Society also entered into a partnership with Smithkline Beecham in which the society’s name and logo could be used in advertisements for Nicoderm, while the American Lung Association had a similar arrangement with McNeill Industries (a Johnson &

Johnson subsidiary) for its smoking-cessation product Nicotrol. As antismoking activist Michael Siegel has pointed out, the Campaign for Tobacco-Free Kids, the American Cancer Society, the American Heart Association, the American Lung Association, Action on Smoking and Health, the American Academy of Pediatrics and the American Legacy Foundation all have or have had financial associations with Pfizer, the maker of the NRT product Chantix. (*The Rest of the Story*, June 27, 2011)

The influential Robert Wood Johnson Foundation, whose assets consist to a large extent of Johnson & Johnson stock (about 40 million shares with a value of \$3 billion), focuses considerable attention on preventing tobacco use and encouraging smoking cessation. It provides grants for antismoking initiatives such as cost-benefit analyses of NRT and research supporting the constitutionality of tobacco advertising bans, public smoking bans and higher tobacco excise taxes.

Interestingly, the foundation began making grants to antismoking groups in 1991, when the U.S. government approved the sale of prescription nicotine patches. According to the foundation’s records, it has disbursed some \$450 million to antismoking initiatives, including \$84 million to the Campaign for Tobacco-Free Kids. (See *Velvet Glove, Iron Fist*, Snowden, Oct. 17, 2010.)

Nor has Big Pharma’s largess been confined to the United States. Johnson & Johnson’s competitors in the NRT business, Pfizer and GlaxoSmithKline, have dispensed millions of dollars to support antismoking groups and initiatives worldwide. The Pfizer Foundation in 2009-2010 gave \$33 million to a variety of antismoking groups. It is obviously in the interest of NRT manufacturers to support the World Health Organization’s Framework Convention on Tobacco Control, as it is essentially an export of developed-world tobacco control policies, with their built-in support for NRT-provisioned smoking cessation.

The usefulness to NRT suppliers of tobacco control measures can be seen in a number of areas. Public smoking bans provide but one example of how the commercial interests of Big Pharma and the public policy objectives of the antismoking movement intersect. By restricting smoking in public places, smokers are pushed to either stop smoking or find alternatives—both of which are conveniently available through NRT. Smoking bans and measures such as higher cigarettes taxes serve to disrupt the current nicotine market and move it from one dominated by Big Tobacco to one more open to alternative suppliers of nicotine. It makes sense for Big Pharma to support such bans and the organizations pushing for them. “What could be better for a seller of nicotine drugs than smoking bans, the demonization of the tobacco industry and higher cigarette prices?” writes Chris Snowden in *Velvet Glove, Iron Fist*.

In return for Big Pharma’s support, the antismoking movement champions tobacco control policies that ultimately support the drug industry’s commercial objectives. This can be seen in a number of policy proposals pushed by the antismoking movement and the public health community.

In a speech at the 11th Global Conference on Tobacco or Health in 2000, then-WHO Director General Gro Brundtland noted that the best way to help people stop using tobacco was to raise its price, control smuggling, avoid tobacco advertising—and make NRT available.

A comprehensive proposal for a nicotine policy put forward in

2005 by some of the leading lights of the antismoking movement reflects how neatly the interests of Big Pharma are advanced by the antismoking movement.

According to Gray et al., the primary goal of nicotine policy in the short term is a liberalization of the market for “clean” nicotine—read NRT—while in the moderate term clean nicotine would overtake cigarettes as the primary source of nicotine (“Toward a comprehensive long term nicotine policy,” *Tobacco Control*, 2005).

In the longer term, the move to clean nicotine would be facilitated by the “progressive reduction in the nicotine content of cigarettes, with clean nicotine freely available to take the place of tobacco as society’s main nicotine source,” according to the authors.

In effect, here we have Big Pharma’s strategic goal of capturing for NRT the nicotine market currently held by cigarettes brazenly pushed as public policy by the antismoking movement.

Indeed, the competing-interest statement at the end of the article makes clear not only how deeply connected with Big Pharma but also how deeply conflicted and non-objective the interests of these antismoking activists can be. Of the eight authors, five have some current or past connection with not just the pharmaceutical industry, but the NRT end of that industry. Benowitz, for instance, “has consulted for several pharmaceutical companies that market smoking-cessation medications.” Dresler was “the medical director for Research and Development for GlaxoSmithKline Consumer Healthcare working on nicotine-replacement therapy products,” while Henningfield “provides consulting services regarding treatment for tobacco dependence to GlaxoSmithKline Consumer Health Care.”

Instead of pushing tobacco control policies that will benefit their commercial interests themselves, the three makers of NRT can leave the advocacy of such policies to the supposedly neutral, objective and disinterested antismoking movement. If this were Big Tobacco, one might be tempted to say that the industry was using a “front group” to push its agenda.

Fourth, NRT continues to dominate smoking cessation because of the pernicious effect of the addiction model of smoking. Because smokers are continually told that tobacco use is addictive—indeed, more addictive than hard drugs like heroin and cocaine—they are encouraged to believe that the only effective way in which to stop smoking is through a professionally administered pharmaceutical intervention.

By convincing smokers that they are addicted—read powerless to stop smoking on their own—the move to NRT as the only way to combat this addiction is seen as normative. Unassisted smoking cessation is seen as ineffective since smokers’ confidence in their ability to succeed is undermined by their belief that they are addicted. As Chapman and MacKenzie note, “The persistent messaging that nicotine addiction is refractory and stopping unaided will be futile deflects attention away from what is by far the most common story of cessation: people doing it without professional or therapeutic help.”

Unwelcome consequences

The dominance of NRT in smoking cessation has several unwelcome consequences. First, and most obvious, are the dangers that some NRT products represent. For instance, in a recently published study, Singh et al. reported that the smoking-cessation drug Varenicline (also known as Chantix) was associated with a significantly increased risk of serious adverse cardiovascular events com-

pared with placebo. (“Risk of serious adverse cardiovascular events associated with Varenicline: a systematic review and meta-analysis,” *Canadian Medical Association Journal*, July 2011)

Indeed, the FDA in June issued a warning, based on an analysis of a small clinical trial, noting that Chantix appeared to be associated with an increase in heart attacks in patients with an existing cardiovascular disease.

The Singh et al. study found that Chantix represented a 70 percent increase in cardiovascular incidents, such as heart attacks, compared with a placebo. As Siegel notes, “for every 30 patients treated with Chantix, this article predicts that three people will quit smoking successfully due to the Chantix but that one person will have a serious cardiovascular event like a heart attack.” (*The rest of the story*, July 5, 2011)

Pfizer, in damage control mode, plays down the risks. But in a July 4 interview with *MedPage Today*, Singh noted that “In absolute terms, it is a small difference. However, when you consider the difference from a population perspective, you get a very different picture. It is estimated that 7 million people in the U.S. were using Chantix last year. If you apply our results to the total number of users, I estimate that there were 62,500 cardiac events that were linked to use of Chantix. That is not a small number by any standards.”

Second, given that the most successful quitting method is unassisted cessation, the dominance of NRT in the smoking-cessation market and its endorsement by the public health community does not serve the interest of smokers who wish to quit, but those of Big Pharma.

The dominance of NRT is not supported by the research data. Rather, it effectively pushes smokers away from the most successful way to quit. By pushing smokers who wish to quit to NRT, the public health community and the antismoking movement paradoxically reduce these smokers’ chances of stopping smoking and thereby increase their chances of dying from smoking. In an uncharitable reading, smokers are quite literally sacrificed to the interests of Big Pharma and their antismoking partners.

Third, given the fact that NRT is not supported by scientific evidence and given the fact that the connection between Big Pharma and the antismoking movement is little known, the triumph of NRT and the commercial interests of its makers corrupts the public policy process, which should be evidence-based and transparent.

Smokers and the general public are being told a story—the superiority of NRT over unassisted quitting—that is scientifically untrue, but the reason for this misrepresentation is not apparent. Smokers deserve unbiased and accurate information about something that could literally save their lives. And the rest of us need to be confident that public policies serve our interests and not just those of commercial interests such as the pharmaceutical industry.

Finally, the ill effects of the “bargain” between Big Pharma, the antismoking movement and the public health community go beyond the question of smoking-cessation and NRT. By considering tobacco-control policies only through the lens of self-interest, Big Pharma ends up championing and funding policies that have little proven effectiveness and ignoring policies that might genuinely prevent and reduce tobacco use.

Instead of pushing the antismoking movement to critically examine its approach to tobacco control, Big Pharma’s blank checks permit it to continue business as usual. And that is a tragedy for smokers and nonsmokers alike.

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