The Gum, the Patch, the Pill: The Safety and Efficacy of "Smoking Cessation" Drugs

By Wanda Hamilton
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> ***"The low quit rates associated with unaided and nonpharmacological quit attempts demands that pharmacological treatment be offered to all smokers planning to quit unless there is a medical contraindication."*** Okuyermi KS, Ahluwalia JS, Harris KJ, "Pharmacotherapy of Smoking Cessation," *Archives of Family Medicine*, 9(3), March 2000. This "Clinical Review" was funded by the National Cancer Institute and the Robert Wood Johnson Foundation. Dr. Ahluwalia has been funded by and received honoraria from Glaxo Wellcome, SmithKline Beecham, and Johnson & Johnson subsidiary McNeil Consumer Products, all companies that market smoking cessation drugs.
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> ***"Of quitters polled, 59 percent quit 'cold turkey,' while 11 percent used nicotine replacement therapy."*** "Attitudes and Behaviors Related to Smoking Cessation: A Survey of Current and Former Smokers," Gallup poll released Oct. 20, 1998. The poll also found that only 36 percent of current smokers are very interested in quitting.
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> ***"…interest in giving smokers up to $600 apiece for nicotine patches and other quitting aids, for instance, might subsidize manufacturers of such products, but may do little to help most addicts. Studies show that only 10 to 15 percent of smokers give up the habit by using nicotine gum or patches."*** Catherine Clabby, "Pact doesn't assure smokers a happy ending," *Raleigh News & Observer*, June 26, 1997.

The 1988 U.S. Surgeon General's report deeming tobacco use an addiction initiated a boom in the smoking cessation business, especially for the drug industry. By the mid-1990s, when the anti-tobacco organizations became partners with the pharmaceutical conglomerates in pushing smoking cessation (and smoking cessation drugs), the boom intensified.

At the end of 1995, sales of nicotine-based cessation drugs were roughly $200 million in the U.S. and by the end of 2000 U.S. sales had more than tripled to roughly $700 million. Considering that these figures do not include sales for Zyban, the non-nicotine cessation drug, or increasing global sales outside the U.S., it is easy to see that smoking-cessation drugs are a multi-billion-dollar business, one with even bigger potential profits in the future as the World Health Organization pushes smoking cessation globally.

The Development of Smoking Cessation Drugs

In 1971 Pharmacia developed the first nicotine replacement product for smoking cessation, nicotine-laced chewing gum. The gum was launched for use in Switzerland in 1978, and in 1984 it was approved by the U.S. Food and Drug Administration (FDA) as a smoking cessation prescription drug. SmithKline Beecham subsequently marketed the gum as Nicorette.

The patch was developed by Duke University researcher Jed Rose in the early 1980s. Manufactured by Pharmacia, the patch has been marketed in the U.S. as Nicotrol by a Johnson & Johnson subsidiary and as Nicoderm by SmithKline Beecham. The FDA approved Nicotrol and Nicoderm as prescription smoking cessation drugs in 1991, and in 1996 the FDA did away with the prescription requirement for the patches and the gum, approving them for over-the-counter sale directly to consumers.

The nicotine inhaler and nicotine spray have also been approved as smoking cessation drugs by the FDA, but to date the agency as not approved them for over-the-counter sale. Ironically, the nicotine inhaler evolved from a "smoke-free" cigarette. Sold under the brand name Favor in the 1980s, the cigarette was forced off the market by the FDA in 1987 because it was deemed a "drug delivery device." Just ten years later the FDA approved Johnson & Johnson's Nicotrol inhaler as a nicotine delivery device which could be used for smoking cessation.

Orally ingestible nicotine drugs have been developed but have not yet been clinically tested. One of the two Duke University inventors of this cessation drug is Jed Rose, who also invented the nicotine patch.

Glaxo Wellcome's Zyban, the only non-nicotine smoking cessation drug currently approved by the FDA, was originally developed as the anti-depressant Wellbutrin. The FDA approved Wellbutrin, the trade name for the drug bupropion, in 1985, but it was subsequently removed from the market because of concerns about drug-induced seizures. Wellbutrin was reintroduced as an anti-depressant in 1989. When researchers noted that some of those taking the drug quit or reduced their smoking, Glaxo Wellcome began clinically testing it as an aid for smoking cessation. The FDA approved Zyban as a prescription smoking cessation aid in May 1997 and approved the combined use of Zyban and the nicotine patch in 1999. Bupropion is currently marketed by GlaxoSmith Kline as an anti-depressant under the trade name Wellbutrin and as a smoking cessation drug under the name Zyban.

FDA Approval

In order for any drug or drug delivery device to be marketed in the U.S., it must first be approved by the FDA. To gain FDA approval, the pharmaceutical company intending to market a specific drug must conduct clinical tests to demonstrate that the drug is both safe for use and that it works for the purpose for which it is intended. Once clinical testing is complete, the results are presented to an FDA panel of experts for evaluation. If the panel believes the clinical test results demonstrate both safety and efficacy, the drug is recommended for approval, and the pharmaceutical company is then free to market its drug under conditions determined by the FDA (prescription or over-the-counter sales, recommended uses and doses, mandated warnings, duration of use, etc.).

On its face, the system appears to be a good one for protecting consumers from unsafe drugs and fraudulent claims about the curative powers of drugs. However, in practice the system is far from perfect. Sometimes political pressure is brought to bear on the FDA to

approve—or not approve—a given drug. Sometimes there are financial ties between members of FDA panels and pharmaceutical companies seeking drug approval, and occasionally cases of outright graft have been uncovered at the FDA. But even when the approval process is uncorrupted by political interference or competing financial interests on the part of FDA employees or scientific panel members, there is still one major problem: the clinical trials are financed by and heavily influenced by the drug companies themselves. The FDA itself does none of the testing; FDA scientific panels merely examine the clinical test results the drug companies present to them, and the companies are not likely to present results which are not favorable to the companies' products.

In the case of smoking cessation drugs, the results of the company-funded clinical tests had to demonstrate that the drugs were generally safe and that they were effective for smoking cessation. The FDA standard for approval for "efficacy" was that at six weeks the drugs had to show significantly better rates than placebos (nothing) for 28 days of continuous smoking abstinence in test subjects. The fact that at the end of a year, many of those test subjects were smoking again did not enter into the FDA approval process, and the pharmaceutical companies were able to list the quit rates at six weeks on their drug labels.

To date the FDA has approved only five drugs for smoking cessation: Nicorette gum, the Nicoderm and Nicotrol patches, the Nicotrol inhaler and nasal spray, and Zyban. Of these, the gum, the patches and Zyban are the most widely used, but just how safe and efficacious are they?

The Patch and the Gum: Safe but Ineffective

Called "nicotine replacement therapy" (NRT), the patch, the gum, the inhaler, and the nasal spray all have about the same level of efficacy, which is to say that none of them is efficacious, at least in the long term.

- **"In their trial of 4 nicotine replacement therapy (NRT) products, Hajek and colleagues concluded that there were no notable differences in general efficacy among the tested nicotine patch, gum, nasal spray and inhaler**." Letter, "Continued Dependence on Nicotine Replacement Therapy Should Be Reported and Discussed in Smoking Cessation Trials," *Archives of Internal Medicine*, July 10, 2000.

- **"The initial report of this trial [The Trasdermal Nicotine in Cardiac Patients Study] described the safety of the therapy in this high-risk outpatient population; however, 24 weeks after randomization, only 14 percent of the subjects in the nicotine-treatment group and 11 percent of those in the placebo [no nicotine] group were abstinent from smoking…."**

  "At 48 weeks after randomization, 10 percent of subjects in the nicotine group and 12 percent of those in the placebo group were abstinent." Joseph AM, Antonnucio D, "Lack of Efficacy of Transdermal Nicotine in Smoking Cessation," Letter, *New England Journal of Medicine*, 341(15), Oct. 7, 1999. In other words, at 48 weeks, those using nothing had a higher quit rate than those using the patch. Joseph and Antonnucio point out that another recent study also showed no efficacy for the patch, and they suggest that clinical trials which did show efficacy might have selected optimal subjects or that trials with negative outcomes might not have been published.

- **"At the annual meeting of the Society for Research on Nicotine and Tobacco conference held in San Diego, CA, Scott Leischow, PhD., Associate Professor of Public Health for the University of Arizona, presented research findings indicating that over-the-counter (OTC) nicotine patches resulted in low quit rates of 4-5% at one year, which is in the range of naturally occurring smoking cessation. Published in the January/February 1999 issue of the American Journal of Health Behavior, the study also found that brief physician intervention did not improve on these rates."** "New Smoking Study Questions the Effectiveness of the Nicotine Patch," PR Newswire, Mar. 24, 1999.

- **"The self-reported continuous quit rate among patients originally assigned 21 mg (20.2%) was significantly higher than rates for patients assigned 14 mg (10.4%), 7 mg (11.8%), or placebo patches (7.4%)…. Relapse rates among the various treatment conditions were similar after 1 year postcessation."** Daughton DM, Fortmann SP, Glover ED, Hatsukami DK, et al, "The smoking cessation efficacy of varying doses of nicotine patch delivery systems 4 to 5 years post-quit day," *Preventive Medicine*, 28(2): 113-8, Feb 1999.

- **"However, there was no statistically significant difference between the two groups of smokers [one group on the nicotine patch and one group on a placebo patch] after one year of follow-up."** Perng RP, Hsieh WC, Chen YM, et al, "Randomized, double-blind, placebo-controlled study of transdermal nicotine patch for smoking cessation, " *J Formos Med Assoc* 97(8): 547-51, Aug. 1998.

- **"There was no difference between nicotine and placebo groups…. Nicotine patches had no influence on smoking cessation during pregnancy…."** Wisbord K, Henriksen TB, Jespersen LB, Secher NJ, "Nicotine patches for pregnant smokers: a randomized controlled study," *Obstet Gynecol* 96(6): 967-71, Dec 2000.

- **"We conclude that transdermal nicotine patches are of limited efficacy in achieving long-term smoking cessation and that the relative costs and benefits of this treatment are not adequately specified."** Mankani SK, Garabrant DH, Homa DM, "Effectiveness of nicotine patches in a workplace smoking cessation program. An eleven-month follow-up study," *J Occup Environ Med*, 38(2): 184-9, Feb. 1996.

- **"However, users of nicotine gum and patches were found to be less likely to have given up smoking than non-users."** Buck D, Morgan A, "Smoking and quitting with the aid of Nicotine Replacement Therapies in the English adult population," *European Journal of Public Health* 2001, Vol 11, Issue 2, pp. 211-217.

By 1997, when it became obvious that the FDA approved nicotine-based cessation drugs were not very efficacious in the long term, an FDA panel urged that the labels for these drugs be changed to reflect the low long-term efficacy. The marketers and manufacturers of the drugs (Pharmacia, SmithKline Beecham, and Johnson & Johnson subsidiary McNeil) argued vehemently against any such labeling changes:

> ***"The standard for approval of smoking cessation products, 28 day continuous abstinence at six weeks, and the labeling that has resulted from this standard, allows ample room for companies to market their products in a responsible way."***
> George Quesnelle, VP of medical marketing and sales for SmithKline. Quoted in "FDA Panel Urges Changes in Nicotine Patch and Gum Labels," Reuters, June 10, 1997.

So how could the FDA approve—and continue to approve—these "nicotine replacement" products as efficacious for smoking cessation when in fact at the end of a year or less they work no better than a piece of adhesive tape? Part of the answer is the FDA

standard for "efficacy" in smoking cessation drugs. The company-funded clinical trials only had to demonstrate that these drugs were significantly better than placebo at six weeks. The rest of the answer is that the clinical trials were funded by the pharmaceutical companies, and, as Joseph and Antonnucio suggest above, optimal subjects may have been selected for the trials or the trials with negative outcomes may have been suppressed.

An example of how the results of early clinical trials vary from those done after FDA approval lies in two studies by Michael Fiore and D. E. Jorenby of the Center for Tobacco Research and Intervention at the University of Wisconsin Medical School. Fiore and Jorenby have both received funding from various pharmaceutical companies and their adjuncts (e.g. The Robert Wood Johnson Foundation). In 1994, they found that the nicotine patch was very efficacious: "The nicotine patch is an effective smoking cessation aid and has the potential to improve public health significantly."

> ***"Across 17 studies meeting inclusion criteria, overall abstinence rates for the active patch were 27% (vs 13% for placebo) at the end of treatment [6 weeks] and 22% (vs 9% for placebo) at 6 months…. The 16-hour and 24-hour patches appeared equally efficacious, and extending treatment beyond 8 weeks did not appear to increase efficacy. The pooled abstinence data showed that intensive behavioral counseling had a reliable but modest positive impact on quit rates."*** Fiore MC, Smith SS, Jorenby DE, Baker TB, "The effectiveness of the nicotine patch for smoking cessation. A meta-analysis," JAMA, 271(24): 1940-7, June 22, 1994.

In March 1998, Glaxo Wellcome (makers of Zyban) awarded $1 million to the University of Wisconsin Center for Tobacco Research and Intervention to support a professorship in tobacco dependence. The award went to Michael Fiore. In 1999, the results of a clinical trial for Zyban (funded by Glaxo Wellcome) appeared in the *New England Journal of Medicine:*

> ***"RESULTS: The abstinence rates at 12 months were 15.6 percent in the placebo group, as compared with 16.4 percent in the nicotine-patch group, 30.3 percent in the bupropion [Zyban] group, and 35.5 percent in the group given bupropion and the nicotine patch…. CONCLUSIONS: Treatment with sustained-release bupropion alone or in combination with a nicotine patch resulted in significantly higher long-term rates of smoking cessation than use of either the nicotine patch alone or placebo. Abstinence rates were higher with combination therapy than with bupropion alone, but the difference was not statistically significant."*** Jorenby DE, Leischow SJ, Nides MA, Rennard SI, Johnston JA, Hughes AR, Smith SS, Muramoto ML, Daughton DM, Doan K, Fiore MC, Baker TB, "A controlled trial of sustained-release bupropion, a nicotine patch, or both for smoking cessation, *NEJM*, 340(9): 685-91, Mar 4, 1999. The study also noted that 34.8 percent of the study participants discontinued one or both medications, the 23.3% who stopped because of adverse "events" were in either the bupropion-alone group or in the bupropion-plus-patch group.

So in this study, which was one of only two clinical trials submitted to the FDA for approval of Zyban as a smoking-cessation drug, the patch and the placebo had about the same results, a far cry from Fiore's and Jorenby's glowing reports of the efficacy of the patch in 1994. Apparently the "efficacy" of the patch depends on which pharmaceutical company is doing the funding.

Zyban (bupropion): Less Safe and Not Very Effective

> ***"My daughter was fit and healthy before she started taking this drug, but now the doctors say she has to be on medication for the rest of her life. I am blaming Zyban for this,"*** Susan Sinclair, quoted in "Ban anti-smoking pill that wrecked my life," *Northern Echo* (UK), July 23, 2001.

Though the patch and other nicotine-based cessation drugs have few, if any, side effects (a skin rash is the most common negative side effect of the patch), Glaxo Wellcome's Zyban has many. In addition, it can interact with a number of other drugs. For these reasons, the FDA has approved its use only as a prescription drug.

Included in the long list of drugs that can interact with bupropion are alcohol, cocaine, corticosteroids, kava kava, medications or herbal products for weight loss, medicines for difficulty sleeping, nicotine, phenobarbitol, some medicines for heart rhythm or blood pressure, some medicines for pain, and St. John's wort.

Among the most common serious side effects are seizures (a dose-dependent risk, according to Glaxo Wellcome), confusion, vomiting, and hives. Less common side effects are blurred vision, difficulty breathing, fast or irregular heartbeat, increased blood pressure, and hallucinations. It can also cause loss of appetite, loss of sexual drive, agitation, anxiety, constipation, wakefulness, dizziness, dry mouth, headache, nausea, tremors, chest pain, and abdominal pain. It may cause changes in menstruation in women and is not recommended for those with liver problems, since metabolites of bupropion may accumulate in the liver.

Despite all these possibly serious side effects, it was approved by the FDA as a smoking cessation aid. Further, the U.S. Public Health Service Clinical Practice Guidelines released in June 2000, recommend Zyban as "an option for first-line use as an alternative to nicotine-replacement therapy." It should be noted that Michael Fiore, who was one of the researchers on the pivotal Glaxo Wellcome-funded Jorenby study which led to FDA approval for Zyban, was also the lead author of the U.S. PHS Clinical Practice Guidelines. Fiore has also received significant additional funding from Glaxo Wellcome and is a paid consultant to the company.

British guidelines released in December 2000 adopted a more cautious approach to Zyban, highlighting the limited evidence about the drug's effectiveness in the absence of behavioral support. An editorial in the July 8, 2000 *BMJ* was far more enthusiastic and called for the UK National Health Service to include bupropion on the list of reimbursable prescriptions. The authors of the editorial, John Britton and Martin Jarvis, have both received honoraria and other funding from Glaxo Wellcome, the drug's manufacturer, and the editorial itself drew some highly critical responses:

> ***"Britton and Jarvis could have pointed out that half of patients who successfully stop smoking with the aid of bupropion will start again within 12 months of coming off the drug. They could also have referred in more detail to the side effect profile and the number of patients for whom the drug will be unsuitable. Bupropion may have a 1 in***

> ***1000 risk of inducing seizures (product information from Glaxo Wellcome, the manufacturer of the drug). This may be an acceptable risk for drugs to treat disease but is less so for lifestyle drugs."*** Harrison C, "Bupropion may not be as good as editorial implies," Letter, BMJ, Feb 17, 2001.
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> ***"Britton and Jarvis's editorial on bupropion does not mention that the drug is an amphetamine derivative…. Bupropion has been released in the United Kingdom on the strength of only two American clinical trials financed by the manufacturer [the highly-positive Jorenby and Fiore study and the Hurt/Sachs/Glover study]…. Bupropion is being foisted on an unsuspecting British public with little evidence that it works much better than placebo."*** Kinnell HG, "Drug is almost identical in structure to diethylpropion, a controlled drug," *BMJ,* Feb 17, 2001.

In the first year after Zyban was released in the UK as a prescription drug for smoking cessation, 40 people died after taking it and thousands of others reported serious negative reactions. As a result, the country's Committee on Safety of Medicines ordered changes to the prescribing regimen and stronger warnings about its use ("Anti-smoking drug must carry stricter warnings," James Meikle, *The Guardian*, June 1, 2001).

The reported deaths and masses of complaints about Zyban didn't prevent the BMJ from publishing another editorial in May 2001 supporting the use of nicotine replacement products and bupropion for those who smoke 10 – 15 cigarettes a day or more. Time Coleman and Robert West, the writers of the editorial, both received funding from Glaxo Wellcome and the pharmaceutical companies manufacturing nicotine replacement products.

In Canada, too, there have been reported deaths by Zyban users, and some experts feel the side effects are too serious for the drug to be used for smoking cessation:

> ***"It is very unusual to get 300-plus adverse drug-reaction reports in the first year of marketing a drug. The question is whether the benefit of the drug justifies the risk…and the answer is no."*** Rick Hudson, a medical consultant to British Columbia's Pharmacare program, quoted in Krista Foss, "The hidden cost of kicking the habit," *Toronto Globe and Mail,* Aug. 31, 1999.

Australia also has had reports of deaths and negative reactions in Zyban users:

> ***"A federal Government committee monitoring the anti-smoking drug Zyban has had almost 800 reports of adverse reactions in the seven months since the drug became available [in Australia]…. There have been nine deaths which may be associated with the use of the drug."*** "Hundreds of adverse effects to anti-smoking drug Zyban reported," Australian Broadcasting Corporation, June 17, 2001.
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> ***"Authorities at Sydney's Westmead Hospital say at least one person a week is admitted suffering from side effects after using the drug."*** Australian Broadcasting Corp., June 18, 2001.

Interestingly, there are few if any media reports on the adverse reactions to Zyban in the U.S., and despite the known risks of the drug, clinical trials on children and pregnant women are continuing in the United States. The National Cancer Institute and pharmaceutical interests are funding Zyban smoking cessation clinical trials on children

as young as 13 at the University of Arizona and at Children's Hospital in Pittsburgh. Bupropion is also being clinically tested on adolescents with attention deficit hyperactivity disorders.

Glaxo Wellcome also maintains a pregnancy registry for pregnant users of bupropion. The purpose of the registry is "to gain more information about the potential teratogenicity [the potential for causing fetal malformations and birth defects] of these drugs during pregnancy" (White AD, Andrews EB, "The Pregnancy Registry program at Glaxo Wellcome Company, " *J Allergy Clin Immunol*, Feb 1999; 103 (2 Pt 2): S362-3).

Despite all its serious side effects, is Zyban really effective for smoking cessation? The two Glaxo Wellcome funded clinical trials (Jorenby/Fiore and Hurt/Sachs/Glover/Offord, which were submitted to the FDA to demonstrate the drug's efficacy) found supportive evidence for efficacy.

- **Jorenby**: Zyban resulted in a 30.3 percent quit rate at 12 months, compared to 16.4 percent in the nicotine patch group and 15.6 percent in the placebo group. This meant that Zyban was almost twice as effective as either the patch or nothing at the end of a year. However, 11.9 percent of those in the Zyban group stopped treatment because of "adverse events," and another 11.4 percent in the Zyban plus patch group discontinued because of "adverse events." [Jorenby DE, Leischow SJ, Nides MA, Rennard SI, Johnston JA, Hughes AR, Smith SS, Muramoto ML, Daughton DM, Doan K, Fiore MC, Baker TB, "A Controlled trial of sustained-release bupropion, a nicotine patch, or both for smoking cessation," *New England Journal of Medicine*, Mar 4, 1999].

- **Hurt/Sachs/Glover/Offord:** Zyban resulted in quit rates at 12 months of 19.6 percent for those taking 100 mg, 22.9 percent of those taking 150 mg, and 23.1 percent of those taking 300 mg of Zyban. This compared to 12.4 percent of those taking only placebo. "The rates for the 150 mg group and the 300 mg group—but not the 100 mg group—were significantly better than those for the placebo group." (Hurt RD, Sachs DP, Glover ED, Offord KP, et al, "A comparison of sustained-release bupropion and placebo for smoking cessation," *New England Journal of Medicine*, Oct 23, 1997).

These two studies found far higher cessation rates for Zyban takers at the end of a year than subsequent studies have. Nevertheless, in the Jorenby study Zyban was *not* effective as a smoking cessation drug in 70 percent of those taking it, even after a fairly large number of participants had dropped out because of "adverse events." And in the Hurt/Sachs study Zyban was not effective as a smoking cessation drug—even at maximum dosage—for 77 percent of those taking it. Those on the minimum dosage of Zyban did not do significantly better than those on nothing, so at low doses the drug was completely ineffective as a smoking-cessation medication.

A more recent study funded by Glaxo Wellcome (now GlaxoSmith Kline) found that Zyban was no more effective at helping people give up smoking than the gum or the patch:

> ***"Ms Renee Bittoun, director of the Smoking Research Unit at Sydney University [Australia], said she could not reveal the precise results of the study, which was sponsored by the drug's manufacturer, GlaxoSmith Kline, because her contract would not allow it…. But the study did not show that Zyban was any more effective at helping***

> ***people give up smoking than the gums or patches, she said."*** Judith Whelan, "Anti-smoking drug all puff, says tester," *Sydney Morning Herald*, June 1, 2001.

So the question is: Given that Zyban does *not* help the vast majority of people using it to quit smoking, even according to company-funded trials, is it worth the risks it imposes? The answer is that it is not, at least not for those who have been harmed by the drug:

> ***"I would rather die after 35 years of smoking than overnight from taking a Zyban tablet."*** Alan Gardiner, a UK smoker who had a massive seizure after using Zyban to quit smoking. Quoted in "Zyban…Over 37 Deaths," *The Daily Record*, June 1, 2001.