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Tobacco Addiction: Diagnosis and Treatment

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Abstract

Tobacco use is associated with 5 million deaths per year worldwide and is considered as one of the leading causes of premature death. Comprehensive tobacco control programs can significantly reduce the prevalence of tobacco use. An important component of a comprehensive program is the provision of treatment for tobacco addiction. Treatment involves targeting multiple aspects of addiction including the underlying neurobiology and behavioral processes. Furthermore, building an infrastructure in health systems that encourage and facilitate cessation and expanding the accessibility of treatments are necessary. While current pharmacological and behavioral treatments are effective in improving cessation success, the rate of relapse to smoking remains high, demonstrating the strong addictive nature of nicotine. The future of treatment resides in better patient matching to treatment, combination or novel medications, and conceptualizing nicotine addiction as a chronic disorder which may require long-term treatment.

Keywords

Tobacco Addiction; Tobacco Addiction Treatment

Scope of the world wide tobacco problem

Over 50 years have passed since lung cancer was confirmed to be caused by cigarette smoking and since then, a vast spectrum has been added to the list of diseases caused by smoking and involuntary exposure to cigarette smoke (1, 2). The world-wide production and

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Dr. Hatsukami wrote the first draft of the manuscript. Each of the authors wrote a component of the manuscript, and reviewed and revised the final manuscript.

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Dorothy Hatsukami advised Pfizer on varenicline and was paid an honorarium for the consultation. She also received a grant to conduct nicotine vaccine trials for Nabi Biopharmaceuticals. Lindsay Stead and Prakash Gupta have no conflicts of interests.

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consumption of cigarettes however, has continued to increase unabated during this period. Currently there are about 1.2 billion smokers in the world and half of these smokers today will die of smoking caused diseases (www.who.int/tobacco/en/). Smoking is responsible for 5 million deaths per year and if current patterns of smoking continue, it is projected to kill 10 million smokers per year in the year 2020. The prevalence varies a great deal, from less than 5% to over 55% in different countries. Prevalence varies greatly between men and women so it is important to examine the prevalence separately in the two sexes.

Based on the analyses of the World Health Organization and American Cancer Society database, Tables 1a and 1b show the distribution of prevalence of smoking among adult men and women in different countries of the world. These prevalence rates are not strictly comparable: samples may not be representative of the population of the country, time period to which they refer may be different, the definition of smoking may be different (e.g. smoking of at least one cigarette a day for a specified time period vs. smoking of at least 100 cigarettes in lifetime) and even age cut offs may be different. Despite limitations, they are the best data available.

It is clear that more men smoke compared to women. Among men, prevalence seems to be moderate to low in industrialized countries and in sub-Saharan Africa. The prevalence seems generally high in Eastern Europe and Asia. About 45% of the global population lives in countries where the prevalence of smoking among males is greater than 45%, and about 92% of the global population lives where prevalence among men is more than 25%. In contrast, among women, only about 10% of the global population lives in a country where the prevalence is greater than 24%. The prevalence among women is low among some of the most populous countries of the world (China, India, Indonesia, and Nigeria) and in general, in countries of Asia, whereas high prevalence is reported from several industrialized countries.

The best way to stop this global epidemic of smoking is to have strong tobacco control programs to prevent and to help cigarettes smokers quit smoking. For long term benefits, success of tobacco control would be measured by the reduction in the number of persons initiating smoking. In the shorter term (i.e., over the next thirty years), the main determinant of significantly reducing the accelerated increase of tobacco-related morbidity and mortality would be if smokers were able to quit smoking (3). Although smoking is a global problem and the burden of tobacco-related death and disease has been shouldered by developing countries, most of the evidenced-based treatments have been from studies conducted in developed countries. Nonetheless, these treatments may be generalized to developing countries and efforts are underway to develop culturally sensitive interventions that are based on the principles of these evidence-based treatments. This article will provide descriptions on the diagnosis of tobacco addiction, the biobehavioral basis for this addiction, and the evidence-based treatments.

Search Strategy

We focused the review on existing meta-analyses which have been conducted on treatments and conducted a MEDLINE (PubMed) search for articles that were not covered by the meta-

analyses, with a primary focus on medication treatments. Search terms included smoking cessation, tobacco cessation, nicotine replacement therapy (smoking cessation and nicotine gum, nicotine patch, nicotine lozenge, nicotine nasal spray, nicotine inhaler or sublingual nicotine), smoking cessation and antidepressants, smoking cessation and varenicline [Chantix], bupropion [Zyban], clonidine or nortriptyline, nicotine vaccine or immunotherapy, and rimonabant (CB1 antagonist). These articles were examined for other related articles. Only those studies that were considered to be of sufficient sample size and rigorous methodology and to add to the content of the manuscript were selected.

Diagnosis

The 1988 Surgeon's General report, *The Health Consequences of Smoking: Nicotine Addiction* (4), described three major conclusions: 1) cigarettes and other forms of tobacco are addictive, 2) nicotine is the drug that causes this addiction, and 3) the pharmacological and behavioral processes that determine tobacco addiction are similar to those that determine addiction to drugs such as heroin and cocaine (pg. 9). The primary difference between nicotine addiction and addiction to other drugs is the lack of behavioral disruption associated with tobacco use; but the lack of this drug effect by no means signifies less addictive capabilities of nicotine.

Criteria for nicotine dependence have been described in the *Diagnostic Statistical Manual IV* (DSM IV) (5) and the *International Classification of Diseases, 10th Revision* (ICD-10; 6). Table 2 lists these characteristics and the core features include a repeated or compulsive administration of the drug, impaired control over use as manifested by continued use despite of negative consequences or by repeated relapse to use after quit attempts, a high motivation to seek the drug, a greater value given to the use of the drug over other activities, and the manifestation of physical dependence, that is, tolerance and withdrawal. There has been debate as to whether the DSM IV and ICD-10 diagnostic criteria are sufficiently valid measures of nicotine dependence. Studies have demonstrated that these diagnostic criteria do not have adequate predictive validity, such as their ability to predict relapse to smoking. Diagnosis based on these criteria is also limited because of its unidimensional and categorical nature, rather than reflecting the potentially multidimensional and continuous aspects of addiction. The most widely used dependence measure is the Fagerstrom Tolerance Questionnaire (7, 8), or the recent modified version, the Fagerstrom Test for Nicotine Dependence (9; see Table 3 for illustration of items for this scale). Although this scale tends to be unidimensional, it often predicts relapse to smoking (10) and the items that contribute the most to the prediction of relapse is the number of cigarettes smoked and time to first cigarette (11). These two items, which constitute the Heaviness of Smoking Scale (12), may be a useful measure of dependence in a clinic office setting and helpful in determining the dose of nicotine replacement treatments (e.g., nicotine lozenge or gum). Regardless of whether or not a smoker meets DSM IV or ICD-10 criteria for nicotine dependence or scores high on the FTND, all smokers should be provided treatment for smoking cessation.

Pathophysiology

The addiction to nicotine is a consequence of the speed and magnitude of nicotine delivery, the clearance of nicotine, its effect on the brain, the development of physical dependence, and the occurrence of associative learning where stimuli linked with smoking trigger tobacco use. The speed and amount of nicotine delivery is dependent on the amount of nicotine in the product, the alkalinity of the product, and the route of administration. Nicotine, 3-(1-methyl-2-pyrrolidinyl) pyridine, is a volatile alkaloid in the tobacco plant and its absorption and renal secretion is highly pH dependent. Higher alkalinity is associated with greater absorption in the non-ionized state, which crosses cell membranes more rapidly than ionized nicotine (13, 14). The fastest rate and greatest amount of nicotine delivery is through cigarettes. Nicotine, when inhaled, enters the lungs where there is a large surface area of small airways and alveoli, undergoes dissolution in pulmonary fluid at a high pH, is transported to the heart and then immediately passes to the brain (13, 15).

Nicotine is metabolized to cotinine primarily by C-oxidation via CYP2A6 metabolizing enzymes. Cotinine is further hydroxylated to *trans* 3-hydroxycotinine also via CYP2A6 enzymes. CYP2A6 activity varies significantly among individuals, which may affect smoking behaviors (16–21). Nicotine is also metabolized by two other pathways: glucuronidation and N-oxidation via UGT and FMO isoenzymes, respectively, which also may significantly influence the circulating levels of nicotine in a smoker and the amount of nicotine which reaches the brain (22).

Nicotine targets various nicotinic acetylcholine receptor (nAChRs) subtypes, which are found in the periphery and in the central nervous system (e.g., 23, 24). Of the various types of nAChRs that exist in the central nervous system (CNS), members of the so-called bungarotoxin-insensitive subtypes, which are composed of alpha and beta subunits and includes the ubiquitous $\alpha 4\beta 2$ -containing subtype, have been extensively implicated in the behavioral effects of nicotine, including its dependence-related effects such as nicotine self-administration and neurotransmitter release (i.e., dopamine, 25, 26, 27). Bungarotoxin-insensitive nAChRs such as homomeric $\alpha 7$ subtype appear to influence the release of the excitatory transmitter, glutamate (27, 28). Neuronal interactions and the circuitry involved in nicotine-dependence are being progressively elucidated (e.g., 25, 29, 30). For example, differential effects of nicotine at its receptors on gamma aminobutyric acid (GABA)-containing neurons, which mediate inhibition, and on glutamate-containing cells has been implicated in prolonging the effects of drug on synaptic function (31). Nicotine administration also increases the extracellular noradrenaline in various parts of the brain (32–35); however, the effects of nicotine on neurotransmitters such as serotonin or other CNS neurotransmitter systems such as the endocannabinoids and neuropeptides have been less studied. The release of all these various neurotransmitters leads to the arousal, mood modulation, performance enhancement, analgesic and weight loss effects associated with tobacco use (4, 13).

With chronic or even acute administration of nicotine, neural adaptations occur to attain homeostasis resulting from the increased activity on the nAChR receptor sites and increased concentration of neurotransmitters. Although some nAChR subtypes are upregulated by

chronic nicotine treatment, that is, their numbers increase, receptors also become desensitized or inactivated, one potential mechanism leading to the development of tolerance (13, 36, 37). Because the body develops a homeostatic response, upon abstinence from the drug, the smoker experiences withdrawal symptoms. These withdrawal symptoms include negative affect such as irritability, frustration or anger, anxiety, dysphoric or depressed mood, restlessness, difficulty concentrating, insomnia, decreased heart rate, and increased appetite (5). Other possible symptoms may include constipation, cough, dizziness, increased dreaming and mouth sores (38). Among tobacco users, withdrawal symptoms, with the exception of weight, peaks during the first week of abstinence and then gradually decreases to baseline levels by two to four weeks (38–40); although more recent studies have found withdrawal to be persistent and elevated for several months after quitting (41, 42). Weight, on the other hand, may increase over the course of six months, and then decrease or be sustained (43). Studies have also shown individual variations in the intensity, slope and variability of symptoms (44). Symptoms of greater intensity, positive slope and variability have been observed to predict relapse to smoking (45, 46) and symptoms of craving and negative affect were the most likely to be associated with relapse (47, 48). The experience of withdrawal symptoms was also found to make the abstaining smoker more reactive to environmental events that engender emotional reactions (49).

In addition to the physiological basis for addiction, there are behavioral or learning factors that sustain addiction. Stimuli in the environment become associated with the positive reinforcing effects of nicotine and withdrawal symptoms. Over time and through associative learning, these stimuli begin to control behavior, such that when a tobacco user is exposed to these stimuli, they evoke craving for the drug or drug seeking behavior. These stimuli could include smoking cues such as other smokers, an ashtray or a lighter; negative affect such as irritability, depressed mood or anxiety; situational cues such as a bar or after finishing a meal; alcohol use; or sensory cues from smoking such as the harshness in the throat and lungs and the taste (50–52). This associative learning has been considered by some to make as important a contribution to nicotine addiction as the direct effects of the drug itself (26, 53–56). Nicotine has also been observed to enhance the reinforcing effects of stimuli or other reinforcers that are not associated with the administration of nicotine, a phenomenon which also contributes to the addiction to nicotine (57–59).

Susceptibility

Besides the effect of nicotine on the brain, the experience of nicotine withdrawal and the associative learning processes, other factors play a contributory role in whether tobacco use is initiated or sustained. These factors include the environmental culture (access and availability of tobacco products, tobacco use bans, cost, social acceptability and modeling) and the characteristics of the individual (e.g., genes, co-morbid psychiatry disorders, and personality features). With regard to the latter factors, initiation of smoking behavior and transition to dependence (i.e. persistent smoking) has been found to show strong heritability (60). The reported heritability coefficients range from 30% to greater than 80% (a mean of approximately 60% for initiation and 70% for progression to dependence). The potential candidate gene variants include cholinergic nicotine receptor genes such as *CHRNA3* ($\beta 3$ nicotinic receptor subunit) and *CHRNA5* ($\alpha 5$ nicotinic receptor subunit); dopamine pathway

genes such as dopamine D2 and D4 receptor (*DRD2* and *DRD4*) and dopamine transport (*DAT*) genes; serotonin pathway genes such as tryptophan hydroxylase, *TPH* (associated with serotonin biosynthesis) and serotonin transporter, *5HTTLPR* (associated with serotonin reuptake) genes; monoamine oxidase (MAO-A) and dopamine beta hydroxylase genes affecting norepinephrine pathways; and genes involved in the metabolism of nicotine such as P540 *CYP2A6* (61–63). What is inherited may be differences in response to nicotine, differences in responsiveness of the various neurotransmitter pathways, or behavioral traits, such as novelty or sensation seeking, impulsivity, hostility or harm avoidance (61). Furthermore, co-morbid psychiatric disorders may predispose a smoker to begin or persist in smoking. A population survey found that 41% of individuals with mental illness smoked cigarettes. Those with past-month illness were estimated to consume over 40% of the cigarettes smoked by the sample (64). Similarly, in a larger study, nicotine dependent individuals with comorbid psychiatric disorder accounted for 34% of all cigarettes smoked in the United States (65). Studies have observed a higher prevalence of alcohol and drug dependence, depression and anxiety disorders among daily or dependent smokers compared to non-smokers or non-dependent smokers (66–71) and the more severe the dependence, the higher the likelihood for psychiatric disorders (71).

Treatments

Treatments are targeted towards dealing with the physical addiction to nicotine, the psychological reliance on the effects of nicotine, and the behavioral aspects of tobacco use. Several meta-analyses have been conducted that describe evidence-based treatment approaches. The reader is referred to the Cochrane Collaboration Tobacco Addiction Group reviews on tobacco cessation (www.cochrane.org/reviews/en/topics/94.html#topic_2), the United States Public Health Service (U.S. PHS) *Clinical Practice Guideline Treating Tobacco Use and Dependence* (72), and the English Health Development Agency Guidelines (73) for more specific details.

Physician's role

In the U.S., although more than 70% of smokers want to quit each year and 45% make a quit attempt, less than 5% in the general population are successful (74). Proportions are similar in the UK (75). Although the majority of smokers will quit on their own (76), the physician and other health care professionals can have a powerful impact in helping to facilitate the cessation of tobacco products and can enhance cessation rates by 3 to 5 fold above 5% (72). Even brief advice to quit by a health care professional leads to a small (by 2.5%) but significant increased absolute rate of cessation compared to no advice (77). In the U.S., 70% of smokers see primary care physicians each year (72) and in the UK 78% of the population see a GP annually (National General Practice Morbidity Survey, 78). Therefore, health care providers are in an extraordinary position to provide effective treatments. The U.S. PHS Clinical Practice Guideline recommended providing evidence-based counseling and pharmacotherapies (if not contraindicated) for all smokers and also recommended institutional changes that would facilitate the provision of these services. Institutional changes can involve a system that routinely identifies tobacco users and documents tobacco use status at each clinic visit. It also involves other system-wide changes in the health

systems (see Table 4). Health care providers can also provide their patients with a brief intervention that has been described as the 5 As (see Table 5). Assistance for cessation involves both counseling and pharmacotherapies.

Counseling

Counseling involves motivating the tobacco user to quit by examining the consequences from smoking. It also involves educating the tobacco user about the beneficial health effects from smoking cessation (2), beneficial effects which can be experienced even when cessation occurs at an older age (79, 80). Components of effective counseling include problem solving, that is, discussing methods and coping skills to deal with high risk situations for tobacco use, and obtaining support from others for cessation efforts (72). In the event that physician care or personnel to provide smoking cessation are unavailable, tobacco users can be referred to smoking cessation specialists (73) or telephone quit lines. Telephone quitlines are most effective if they proactively provide frequent personal counseling (81). One of the major advantages of quitlines, besides its efficacy, is its accessibility and reach to a large population of diverse tobacco users (82–84). In the United States, a national network of tobacco cessation quitlines (1-800-QUITNOW) has been established that can refer tobacco users to their own regional quit line. The UK and Australia also have quit lines.

Pharmacotherapies

Pharmacotherapies for nicotine dependence can enhance quit rates by about two to three fold (e.g., 72). Therefore, according the UK and U.S. PHS guidelines, all smokers should be considered for pharmacotherapies, but with special consideration given to smokers with certain medical conditions, to smokers who smoke less than 10 cigarettes per day, to pregnant/breast feeding women, and to adolescents. Table 6 describes the various medicinal treatments that are available to treat cigarette smoking. The UK clinical practice guidelines recommend nicotine replacement therapies (NRTs) and bupropion as a first line therapy (73), although in New Zealand and Germany, bupropion is recommended as a second-line therapy (85, 86). In the U.S., first line therapies are those medications that have been approved by the Food and Drug Administration (FDA) and include all NRTs and bupropion (72). Second line therapies have demonstrated efficacy but have not been approved by the FDA and include clonidine and nortriptyline. The guidelines have not addressed the status of varenicline as a first-line therapy due to its recent introduction into the market.

Nicotine replacement therapies—NRTs are delivered transdermally, orally (gum, lozenge/sublingual tablets, inhaler) or nasally. The principle rationale for using medicinal nicotine is to replace nicotine in tobacco users in a way that replaces some of its effects while also reducing the addiction potential (e.g., reducing amount and speed of nicotine delivery) and toxicity associated with tobacco use. The use of medicinal nicotine leads to the reduction in withdrawal symptoms. In addition, it is also speculated that medicinal nicotine, particularly the patch, may be associated with desensitizing nicotinic receptors, resulting in reduced reinforcement from cigarette smoking (87). General and medication-specific precautions and side effects are described in Table 7.

The Cochrane meta-analysis (88) pools studies of all types of NRT with six month or longer follow-up using sustained and validated outcomes where available. The meta-analysis includes both early efficacy studies and pragmatic trials in a range of settings and populations, with different levels of common behavioural support. Table 8 gives estimated pooled odds ratio derived from applying the quit rates of active nicotine medication to the median long term quit rate for the placebo groups receiving only behavioural support. Table 8 also provides estimates of the abstinence rates achievable if the estimated odds ratios are applied to a range of control group quit rates. The quit rates that can be expected in the absence of pharmacotherapy will depend on the motivation and level of dependence of the smokers and the amount of behavioural support provided, as well as the definition of abstinence and period of follow-up. The pooled odds ratio for 104 NRT studies is 1.8, 95% CI 1.7, 1.9. The meta-analysis includes any type of NRT product, and the odds ratios for different types do not differ statistically. In a head-to-head comparison of gum, patch, nasal spray and inhaler in a randomized clinical trial, no significant differences were found at the 3 month follow-up, with 12-week continuous abstinence rates ranging from 20% to 24% (89). Studies examining the effects of 4 mg versus 2 mg nicotine gum in highly dependent smokers have found that 4 mg gum is more efficacious than 2 mg gum (4 studies, OR 2.2, 95% CI 1.5 to 3.3, 88). Trials comparing two patches to a single patch for heavy smokers suggest only a small benefit (six studies, OR 1.2, 95% CI 1.0, 1.4; 88). In a clinical trial with the nicotine lozenge, low dependence smokers (time to first cigarette was greater than or equal to 30 minutes) were randomly assigned to 2 mg nicotine lozenge or placebo; and high dependent smokers were randomized to 4 mg nicotine lozenge or placebo (90). Table 9 shows the results from this study and clearly shows the lower placebo quit rates for high compared to low dependent smokers and the improved efficacy with the active medication.

Most of these approved NRT products are over-the-counter (OTC), and while the absolute abstinence rates associated with the OTC use of these products are lower than observed in clinical trials with behavioral treatment, the abstinence rates with the patch is still better than placebo (OR 1.8, 95% CI 1.2, 2.8, 11.8% vs. 6.7%, respectively) (72). In a more recent meta-analysis (91), OTC nicotine patch continued to demonstrate improved efficacy over placebo (OR 2.5, 95% CI 1.8, 3.6), and furthermore, similar quit rates were observed between OTC patch and prescription NRTs (OR 1.4, 95% CI 0.6, 3.3). The mean quit rate at 6 months across the studies for OTC nicotine replacements was 7%. However, in an analysis of a large population based tobacco survey, non users of pharmaceutical aids did as well as users of NRT leading the authors to conclude a lack significant effect on long-term cessation with the introduction of these products over-the-counter (92). However, this study has been criticized for being cross-sectional and being based on self-report (93). Furthermore, a potential bias is introduced when smokers self-select to use pharmacological tools to aid cessation. For example, smokers choosing to use NRT may have been more dependent than nonusers of NRT (94). A more recent study of 'real-world' effectiveness used a prospective longitudinal design (95). In this study smokers who used NRT with no behavioral support doubled their odds of 6 months abstinence compared to non users, adjusting for nicotine dependence, with a difference in success rates of approximately 4%.

Non-nicotine based treatments—Bupropion Sustained Release (SR) is a non-nicotine based medication that is also being used as an antidepressant. Bupropion is thought to target the neurochemistry of nicotine addiction by blocking the reuptake of dopamine and noradrenaline and therefore increasing their levels in the synapse. It is also considered to function as a noncompetitive nicotinic AChR antagonist (96). Clonidine and nortriptyline, the second line therapies, also affect the noradrenergic system. Clonidine, which is α_2 adrenergic autoreceptor agonist, decreases noradrenergic activity and firing in the locus ceruleus. Nortriptyline is a reuptake inhibitor, primarily of noradrenaline but also serotonin. Table 10 shows the precautions for and side effects from these medications. Meta-analyses conducted for clinical trial results show similar odds ratios, ranging from 1.9 to 3.2, across these non-nicotine pharmacotherapies (see Table 8).

The cessation effects of both nortriptyline and bupropion seem to be independent of their anti-depressant properties as studies show efficacy in populations of smokers with and without depression (97). Three trials have directly compared bupropion and nortriptyline (98–100). None showed significant differences and the pooled odds ratio, though favouring bupropion, was non significant (OR 1.4, 95% CI 0.9, 2.3). Although bupropion produced significantly higher cessation rates than nicotine patch in one trial (101), this has not been replicated. Indirect comparisons of odds ratios from meta-analyses suggest that NRT, bupropion and nortriptyline have similar efficacy. Clonidine is observed to be as efficacious as the other medications in promoting cessation, but the high incidence of side effects may be a deterrent for considering this medication as a primary therapy. One report stated that clonidine should be potentially targeted to a subgroup of smokers who can benefit from the sedative side effects, such as smokers who report experiencing anxiety or agitation when they stop smoking (102).

More recently, a medication that targets a specific nicotinic receptor subtype has been approved by the Food and Drug Administration and other national licensing authorities. This drug is varenicline, a potent $\alpha_4 \beta_2$ partial agonist, which provides tobacco withdrawal relief by its agonist action and blocks the reinforcing effects of nicotine by its antagonist action (103, 104). Four clinical cessation trials have been reported to date: two Phase II which included dose ranging and titration arms (105, 106) and two phase III cessation trials (103, 104). The two cessation trials were double-blind, placebo-controlled and enrolled smokers interested in quitting who were randomized to varenicline (1 mg bid), or placebo for a 12-week treatment phase (103, 104). Three of the trials included a bupropion (150 mg bid) treatment arm (103, 104, 105). A meta-analysis pooling all four studies (107) estimates an OR of 3.2 (95% CI 2.4, 4.3) for continuous abstinence at 52 weeks. Of the three trials comparing varenicline to bupropion, two had significant effects on long term abstinence and the pooled OR showed a significant effect for varenicline (OR 1.7, 95% CI 1.3, 2.2). In a recent trial, smokers were assigned to varenicline vs. placebo for 52 weeks. The 7-day point prevalence was 37% vs. 8%, respectively at week 52 (108). The major side effect for varenicline was nausea; about 30% of participants experienced this symptom. As with any new pharmacotherapy, clinical experience with varenicline and further pragmatic trials will be valuable to confirm the effects seen in initial trials, and to exclude the possibility of rare adverse events.

Combination medications—Studies have also examined combination of medications to improve efficacy. The combination of nicotine patch (which can offer a steady concentration of nicotine over the course of the day) and the use of ad libitum nicotine (which can help to deal with high risk situations or experiences with increased craving) has led to increased efficacy over single products (seven studies, OR 1.4, 95% CI 1.1, 1.8; 88). One study found a combination of bupropion and nicotine patch to be more efficacious than patch only, but not bupropion alone (101). Three other trials comparing a combination to patch alone have not replicated this result (109–111). A combination of nortriptyline and nicotine patch resulted in higher success rate compared to the nicotine patch alone (23% vs. 10% at 6 months; 112), but another study showed inconsistent effects of a combination of nicotine patch and nortriptyline over nicotine patch alone, with significant differences in the short-term, but no long-term differences (113). To date, the results suggest that there is no evidence to strongly support combining a nicotine and non-nicotine therapy, however, the combination of nicotine patch with an ad libitum form of NRT may confer some benefit (73).

Relapse prevention—Pharmacotherapies could also be considered for relapse prevention, that is, using medications to sustain abstinence rates. In a study examining the use of bupropion in individuals who quit smoking, one year use of bupropion led to significantly higher rates of success than placebo during treatment assignment (114), however this and another study (115) did not show that bupropion would sustain long term abstinence post-medication (OR 1.2, 95% CI 0.8, 1.7; 116). In other studies, no differences were observed between bupropion versus placebo both during and after relapse prevention intervention (117, 118). In a study by Hall and colleagues, one year continued use of nortriptyline appears to improve continuous abstinence rates over the course of a year compared to 8 weeks of nortriptyline (plus 8 week nicotine patch therapy in both conditions); however, no differences were observed in point prevalence abstinence at one year (113). What was remarkable in this study was that extended treatment, which included psychological counseling and pharmacotherapy, resulted in an abstinence rate (50%) that is dramatically higher than in the current literature. Varenicline has also shown some efficacy as a relapse prevention agent. In a clinical trial examining sustained abstinence, smokers were assigned to 12-weeks of varenicline and those who achieved abstinence were then randomized to double-blind trial of varenicline versus placebo for 12 weeks (119). The continuous abstinence rates from weeks 13 to 24 and weeks 13 to 52 were significantly higher for varenicline compared to placebo but the effect was relatively modest (OR at 52 weeks 1.3; 95% CI 1.1, 1.7) and there was some indication that the extended treatment deferred rather prevented relapse. To date, there is no strong evidence to suggest that prolonged use of pharmacotherapy is necessary, except perhaps for those who are trying to maintain abstinence (73).

Recycling smokers—Recycling medications may be indicated in smokers who have relapsed, as would be the case in treating many other diseases. Studies have examined repeated use of the same medication or use of different medications for the subsequent quit attempts. To date, repeated use of the nicotine patch shortly after prior cessation failure with the patch did not lead to significant cessation rates (0% to 1.6% sustained abstinence at 26

weeks, (120, 121). On the other hand, repeated use of bupropion in smokers who had previously failed to quit with bupropion led to significantly greater continuous abstinence rates compared to placebo (12% vs. 2%; 122). A recent study showed that smokers who reported previous use of medications (nicotine gum, patch, inhaler and bupropion) showed as much success with nicotine lozenge compared to placebo as those who did not have a previous history with smoking cessation medications (123). Similarly, in another study, smokers who reported a past history of nicotine replacement therapy demonstrated as much efficacy with bupropion alone, nicotine patch alone, and bupropion plus nicotine patch as those without a past history of nicotine replacement therapy; and among those with a past history of using nicotine replacements, the active medications led to significantly better results than placebo (124). However, in one prospective study, treating smokers who have not been successful with nicotine replacement agents with bupropion did not show significant increases in efficacy compared to placebo (115, 118), nor was treating smokers who were not successful with bupropion with a nicotine replacement treatment (118). Perhaps the differences among these study results can be accounted for in part to differences in subject recruitment—smokers who failed abstinence in a prior clinical trial vs. smokers with and without a history of prior medication use who are entering a new clinical trial. These results would suggest that smokers who are highly motivated to make another quit attempt, even with prior cessation failures on medication, may benefit from another course of pharmacotherapy.

Cigarette reduction—Some smokers may not be ready or desire to quit. Another method of intervention is reducing cigarette consumption through the use of pharmacotherapies. The use of nicotine replacement agents compared placebo has led to a higher percent who could achieve 50% reduction in cigarettes (88), although the extent of reduction is unlikely to confer beneficial health effects. Smokers engage in significant compensatory smoking so that a 50% or greater reduction in cigarette consumption, only results in a 30% reduction in biomarkers for toxicant exposure (125, 126) and modest reductions in biomarkers for cardiovascular risk (127). Epidemiological, longitudinal studies have shown that cigarette reductions of 50% or greater does not lead to a significantly reduced risk for fatal and non-fatal myocardial infarction compared to smokers who did not reduce their cigarette smoking (Hazard Ratio [HR] 1.2; 95% CI 0.9, 1.4) (128) or reduced risk for hospitalizations for chronic obstructive pulmonary disease (HR 0.9, 95% CI 0.7, 1.2) (129). However, reducers did experience risk reduction in lung cancer risk compared to continuous smokers, but only by 25% (HR 0.7, 95% CI 0.5, 1.0) (130). Other studies have shown either an improved or no effect on disease risk with cigarette reduction (131). Therefore, reduction in smoking may be seen more as a stepping stone towards cessation and studies show that recommending cigarette reduction has not conferred any detrimental effects and a potential facilitation of smoking cessation (131). Recently, the use of nicotine gum and nicotine inhaler has been approved for cigarette reduction as a means for cessation in 13 European countries.

Summary—To summarize, the following conclusions can be made regarding the use of pharmacotherapies:

- At present the choice between pharmacotherapies should be based on examining the precautions, side effect profiles, the patient's previous experience with the

medication, and patient preference (73). As noted in Table 6, higher starting doses of nicotine replacement products are recommended for smokers who smoke 25 cigarettes per day or those who smoke within the first 30 minutes in the morning.

- To date, a combination of medications that includes nicotine patch and ad libitum nicotine replacement may improve efficacy over a single NRT in helping heavily dependent smokers quit smoking; however, a combination of nicotine and non-nicotine therapies may not enhance treatment effect.
- Continuing smokers on medications for a prolonged period of time in smokers who are trying to maintain abstinence may be beneficial, but there is no evidence to suggest that all smokers should be given long term treatment.
- Even if smokers experienced failed attempts at quitting using medications in the past, repeating the use of medications in those highly motivated to make another quit attempt may improve treatment success.
- Using medications to reduce smoking among those smokers not interested in quitting does not deter cessation attempts and may in fact facilitate them; however, cessation should remain the primary end goal.

Future directions: Novel medications and pharmacogenetics

Although currently available pharmacotherapies have been shown to improve success rates, the absolute cessation rate remains relatively low—around 20%. Several other medications have undergone clinical trials and many others that target specific neurotransmitters or metabolic enzymes (e.g., gabaergic drug or MAO inhibitors) or specific nicotinic receptor subtypes (e.g., $\alpha 7$) are undergoing development or testing in Phase I/II trials. Two medications bear mentioning because of their novel mechanism of action or target site and promising results. The first is the nicotine vaccine, which stimulates the immune system to develop anti-nicotine antibodies. Study results have shown that the nicotine vaccine reduces the early distribution of nicotine to the brain in rats, by up to 65%, in clinically relevant acute and chronic nicotine doses (132). Furthermore, anti-nicotine vaccination in rats has been found to prolong the half-life of nicotine by 3 to 6 fold (133), resulting in gradual decrease in nicotine concentrations which may serve to make the effects of the vaccine act like a nicotine patch, in which low doses of nicotine are delivered to the brain. Vaccination of rats against nicotine (or passive immunization with nicotine-specific IgG to simulate vaccination) attenuates physiological and behavioral responses to nicotine (134). In addition, vaccinated rats have also demonstrated reduced nicotine-induced dopamine release in the brain (135). Several preliminary human studies have been conducted. One published study (136) showed that the vaccine was safe and well tolerated and, although not intended as a treatment study, the highest dose of the vaccine (200 μ g) led to significantly higher 4-week continuous abstinence rates than the other vaccine doses and placebo.

Another promising medication that has undergone large clinical trial is a selective cannabinoid CB1 receptor antagonist, rimonabant. The CB1 antagonist reduces the nicotine-induced increase in dopamine turnover in the nucleus accumbens and nicotine self-administration in animals (137), and reduces nicotine-seeking behavior in response to

nicotine-related cues after weeks of abstaining from the drug (138). This medication is marketed in some European countries to treat metabolic syndrome and is being considered for the treatment of smoking. Three large double-blind, placebo controlled clinical trials have been conducted in the United States and Europe. In these trials 784 and 783 smokers, respectively, were randomly assigned to: 5 mg of the CB1 antagonist, 20 mg of the CB1 antagonist or placebo for 10 weeks (139, 140). In a pooled analysis, significant end-of-treatment effects were observed for 20 mg CB1 antagonist vs. placebo (22.0% vs. 15.0%, $p=0.0003$) and a significantly reduced weight gain among the non-obese abstainers (0.8 kg vs. 2.5 kg, $p < 0.0003$; 139).

One area of research that is receiving considerable attention is pharmacogenetics, that is matching treatments based on the genotypes. To date, the limited research has shown that polymorphisms on specific genes associated with neurobiological effects of nicotine or metabolism of nicotine may affect treatment response to certain medications. For example, with regards to the use of bupropion in treatment, smokers who possessed a variant of a gene, *P450-CYP2B6*, which may be associated with a slower metabolism of nicotine, experienced a higher relapse rate compared to smokers without this variant. Bupropion was found to mitigate this effect, but only in women (61). In a further analysis, smokers homozygous for the -141C Ins C allele of the dopamine receptor D2 promoter regions of the gene (*DRD2*-141C Ins/Del) responded significantly better to bupropion than smokers who carried the -141C Del C allele (141). The common -141C Ins C allele is associated with greater transcriptional efficiency than the -141C Del C allele (142).

Studies also show that smokers may vary in their responses to nicotine replacement agents based on their genetic profile. One trial examined the role of a mu-opioid receptor gene, *OPRM1*. The mu-opioid receptor is the primary site of action for the endogenous opioid peptide, beta-endorphin, which is released after nicotine is administered (29). Smokers who possess the *Asp40* variant of the *OPRM1* gene, which has been associated with increased binding affinity of beta-endorphins in one study (143) but not others (144, 145), tend to be more likely to be abstinent and more likely to respond to transdermal nicotine during but not after treatment than smokers who are homozygous for *Asp40* (146). The authors suggested that individuals with this variant gene may be candidates for long term nicotine patch treatment. A recent study, however, demonstrated an opposite effect in which smokers homozygous for *Asp40* showed greater abstinence with the nicotine versus placebo patch and those smokers with the variant showed no differences between the patches (147), illustrating the rapid changing nature of this field. Other studies have found that smokers with both *DRD2* A1 allele, which is associated with reduced number of *DRD2* receptors in the corpus striatum (148), and dopamine beta-hydroxylase (*DBH*) A allele responded significantly better to transdermal nicotine than placebo and smokers with the other genotypes did not (149). Pharmacogenetics for tobacco addiction is an evolving and relatively new area and therefore, genotyping smokers at this point is premature; however, this area of research is likely to provide valuable data on a potential method for matching patients to treatment.

Conclusion

It is important to keep in mind that nicotine or tobacco addiction should be treated as a chronic disorder. Treatment may require persistent efforts in trying to assist tobacco users in their attempts at quitting. Relapse should be seen as a likely event. Among smokers who quit without treatment, the percent who can achieve abstinence for at least one week is 25–51% and at least three months is 10–20%. By six months, only 3–5% have achieved prolonged abstinence (150). Treatment can improve these outcomes. Treatment may involve using various avenues of counseling and different kinds of pharmacotherapy. It also may involve the use of multiple medications. However, it is clear that effective treatments are available and promising new treatments are being developed. The most critical component of care is the actual delivery of such treatments. Delivery of treatments can be facilitated by developing the infrastructure to promote the identification of smokers at each clinic visit, by training health care professionals on nicotine addiction treatments, by providing smoking cessation medicinal products on the formulary, and by providing health care coverage for tobacco cessation.

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Smoking Prevalence Among Adult Males From 147 Countries

Table 1a

Prevalence (%)	No. of countries	Percent of countries	Combined population across countries		Some large countries
			Number	Percent of population	
<25	26	17.7	467,405,158	8.1	Nigeria, Iran, Sudan, Tanzania, Canada
25 – 35	30	20.4	1,733,797,361	29.9	India, US, France, UK, Italy, Columbia, Morocco
35 – 45	39	26.5	988,527,769	17.1	Brazil, Pakistan, Germany, Egypt, Thailand, Myanmar
45 – 55	28	19.0	2,017,020,322	34.8	China, Bangladesh, Japan, Philippines, Vietnam, Turkey
55+	24	16.3	590,227,552	10.2	Indonesia, Russia, Ukraine, Kenya

SOURCE: Based on World Health Organization and American Cancer Society Database

Minimum prevalence = 7.0%

Maximum prevalence = 77.0%

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Smoking Prevalence Among Adult Females From 149 Countries

Table 1b

Prevalence (%)	No. of countries	Percent of countries	Combined population across countries		Some important countries
			Number	Percent of population	
< 4	36	24.2	3,220,581,420	55.1	China, India, Indonesia, Nigeria, Vietnam, Iran, Thailand
4 – 14	37	24.8	1,031,593,028	17.6	Pakistan, Russia, Japan, Philippines, Turkey, Congo
14 – 24	43	28.9	1,022,297,825	17.5	US, Bangladesh, Egypt, France, Italy, Myanmar
24+	33	22.1	572,828,144	9.8	Brazil, Germany, UK, Spain, Kenya

SOURCE: Based on World Health Organization and American Cancer Society Database

Minimum prevalence = 0.5%

Maximum prevalence = 80.0%

Table 2

Criteria for Substance (Nicotine) Dependence based on the Diagnostic Statistical Manual Version IV and the International Classification of Diseases Revision 10

DSM-IV	ICD-10
A maladaptive pattern of substance use, leading to clinically significant impairment or distress, as manifest by three (or more) of the following, occurring at any time in the same 12-month period	
☐ Tolerance—need increased amounts of substance to achieve desired effect, or diminished effect with continued use of same amount	☐ Increased tolerance
☐ Withdrawal	☐ Sometimes, physical withdrawal
☐ Substance often taken in larger amounts or over a longer period than intended	☐ A strong desire to take the drug
☐ Persistent or unsuccessful efforts to cut down or control substance use	☐ Difficulty controlling use
☐ Great deal of time spent in activities necessary to obtain the substance or recover from its effects	
☐ Important social, occupational, or recreational activities given up or reduced because of substance use	☐ Higher priority given to drug use than to other activities and obligations
☐ Substance use continued despite knowledge of having a persistent or recurrent physical or psychological problem likely to have been caused or exacerbated by the substance	☐ Persisting use despite harmful consequences

SOURCE: Adapted from Royal College of Physicians of London, 2000, Reference #(151)

Table 3

The Fagerström Test for Nicotine Dependence (9)

Items and scoring for Fagerström Test for Nicotine Dependence (FTND)		
Questions	Answers	Points
1. How soon after you wake up do you smoke your first cigarette?	-Within 5 minutes	3
	-6–30 minutes	2
	-31–60 minutes	1
	-After 60 minutes	0
2. Do you find it difficult to refrain from smoking in places where it is forbidden, e.g., in church, at the library, in cinema, etc.?	-Yes	1
	-No	0
3. Which cigarette would you hate most to give up?	-The first one in the morning	1
	-All others	0
4. How many cigarettes/day do you smoke?	-10 or less	0
	-11–20	1
	-21–30	2
	-31 or more	3
5. Do you smoke more frequently during the first hours after waking than during the rest of the day?	-Yes	1
	-No	0
6. Do you smoke if you are so ill that you are in bed most of the day?	-Yes	1
	-No	0

Table 4

System-Level Interventions for Health Systems

Implement a tobacco user identification system in every clinic.
Provide education, resources, and feedback to promote provider intervention.
Dedicate staff to provide tobacco dependence treatment and assess the delivery to this treatment in staff performance evaluations.
Promote hospital policies that support and provide inpatient tobacco dependence services.
Include tobacco dependence treatments (both counseling and pharmacotherapy), identified as effective in the Public Health Service Clinical Practice Guideline (72), as paid or covered services for all subscribers or members of health insurance packages.
Reimburse physicians and specialists for delivery of effective tobacco dependence treatments and include these interventions among the defined duties of physicians.

SOURCE: Reprinted from Fiore et al., 2002, Reference #(84)

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Table 5**The 5 A's for Brief Intervention to Treat Tobacco Dependence**

Ask about tobacco use	Identify and document tobacco use status for every patient at every visit
Advise to quit	In a clear, strong, and personalized manner, urge every tobacco user to quit
Assess willingness to make a cessation attempt	Is the tobacco user willing to make a cessation attempt at this time?
Assist in cessation attempt	For the patient willing to make a cessation attempt, use counseling and pharmacotherapy to help him or her quit
Arrange follow-up	Schedule follow-up contact, preferably within the first week after the cessation date

SOURCE: Data from Fiore et al., 2000, Reference #(72); reprinted from Fiore et al., 2002, Reference #(84)

Table 6**Pharmacotherapies**

First-line therapies	Dose	Instructions for Use
Nicotine replacement therapies		
Nicotine patch	21mg, 14 mg, 7 mg 15 mg, 10 mg, 5 mg	24 hour application, 21 mg 4–6 weeks, 14mg 2 weeks, 7 mg 2 weeks 16 hour application, 15 mg 6 weeks, 10 mg 2 weeks, 5 mg 2 weeks.
Nicotine gum	2mg (<25 cpd) 4 mg (25 cpd) (1 and 2 mg delivered, respectively)	1 piece every 1–2 hours for 6 weeks, every 2 to 4 hours for 3 weeks and every 4 to 8 hours for 3 weeks Maximum=24 pieces
Nicotine inhaler	10 mg cartridge (4 mg delivered, 2 mg absorbed)	6 to 16 cartridges per day for 12 weeks, gradual reduction 6–12 weeks
Nicotine nasal spray	0.5 mg in each nostril	1–2 doses per hour, 12 to 26 weeks of treatment Maximum =40 doses per day
Nicotine lozenge	2 mg (30 mins to first cigarette in a.m.) 4 mg (< 30 mins to first cigarette in a.m.)	1 lozenge every 1–2 hours for 6 weeks, every 2–4 hours for 3 weeks, and every 4–8 hours for 3 weeks Maximum=20/day
Nicotine microtab	2 mg	1 (<20cpd) – 2 (20cpd) per hour for 12 weeks, followed by gradual reduction Maximum = 40/day
Non-nicotine products		
Bupropion SR	150 mg b.i.d ¹	1 week prior to quit, 150 mg q AM for 3 days then 150 mg b.i.d, 7–12 weeks of treatment
Varenicline	1 mg b.i.d	1 week prior to quitting, 0.5 mg once a day for days 1–3, 0.5 mg twice/day for days 4–7, 1 mg twice/day for 12 weeks, and an additional 12 weeks for quitters
Second-line therapies		
Clonidine	Oral=0.15–0.75 mg/day Patch=0.1–0.2 mg/day	Initiate on quit date or up to 3 days before quit date, initial dose 0.1 mg b.i.d PO or 0.1 mg/day transdermal, increasing by 0.1 mg/day per week, 3–10 weeks of treatment, down titrate dose over 2–4 days
Nortriptyline	75–150 mg/day	Initial dose 25 mg/day and up titrate to 75–150 mg/day 10–28 days prior to quit date, 12 weeks of treatment

SOURCE: Information gathered from AHFS Drug Information, 2004, Fiore et al., 2000, Reference #s (72 and 145), Pfizer Labs U.S.

http://www.pfizer.com/pfizer/download/uspi_chnatix.pdf.

¹No significant differences in cessation rates were observed between the recommended 300 mg dose and the 150 mg dose (OR 1.07, 95% CI 0.87, 1.32;) (97).

Table 7**Side Effects and Precautions for Nicotine Replacement Products**

Product	Most Frequent Side Effects	Precautions
All NRTs		1) Cardiac disease, myocardial infarction, irregular heartbeat, ¹ 2) peptic ulcers, 3) insulin-dependent diabetes, 4) uncontrolled hypertension, 5) drug therapy for depression or asthma, 6) pregnancy or lactation, 7) hyperthyroidism, pheochromocytoma or Type I diabetes mellitus
Nicotine gum	Jaw ache, mouth soreness, dyspepsia, hiccups	Dental conditions exacerbated by chewing gum; history of esophageal, oral or pharyngeal inflammation
Nicotine Inhaler	Local irritation of mouth and throat, coughing and rhinitis	Allergy to menthol, bronchospastic disease
Nicotine Patch	Local skin reaction, sleep disruption	Allergic to tape or dermatological condition
Nicotine Spray	Nasal and airway irritation	Severe reactive airway disease, chronic nasal disorder
Nicotine Lozenge and sublingual tablets	Hiccups, mouth or throat irritation, heartburn or dyspepsia	

SOURCE: Information gathered from AHFS Drug Information, 2004, Physicians' Desk Reference 60th Edition, 2006, Fiore et al., 2000, Reference #s (72, 152, 153).

¹ Treatment with nicotine patches has been examined with smokers who have cardiovascular disease and the medications have been found to be safe (154).

Table 8

Estimates of Efficacy of Pharmacotherapies

Medication	Odds Ratio (95% CI)	Placebo+support Abstinence Rate ¹ Median (Interquartile Range)	Estimated Abstinence with Pharmacotherapy (95% CI) ² [Range] ³
Nicotine replacement therapy (104 studies) (88)	1.8 (1.7, 1.9)	11% (7 – 17)	18% (17, 19) [11% – 28%]
Bupropion (31 studies) (97)	1.9 (1.7, 2.2)	10% (6 – 14)	17% (15, 19) [10% – 26%]
Varenicline (4 studies) (107)	3.2 (2.4, 4.3)	7% (5 – 9)	18% (15, 23) [10% – 30%]
Nortriptyline (6 studies) (97)	2.3 (1.6, 3.4)	10% (6 – 14)	21% (15, 28) [9% – 36%]
Clonidine (n=6 studies) (102)	1.9 (1.3, 2.7)	13% (11 – 22)	22% (17, 30) [14% – 44%]

¹ Abstinence rates from control groups of trials with 6 months follow-up, strictest available criteria for abstinence with losses to follow-up treated as smokers

² Estimated abstinence rates with 95% CI from applying column 2 odds ratio (95% CI) to column 3 median placebo quit rate. For example, the median control group quit rate across all NRT trials is 11% and the estimated odds ratio is 1.8 (95% CI 1.7, 1.9), giving an estimated quit rate on active therapy of 18% (95% CI 17%, 19%)

³ Range derived from applying lower 95% CI for odds ratio to lower quartile of placebo quit rate range, and upper 95% CI for OR to upper quartile placebo quit rate range. For example, in the lower quartile, if a quit rate of only 7% is expected without NRT, and the odds ratio is only 1.7, then the estimated quit rate with active therapy would be 11% for the lower range.

Table 9

Nicotine Lozenge Efficacy: 6 Month Continuous Abstinence Rates N=450–459 in Each Group (90)

Level of Dependence	OR	Placebo	Active
Low Dependence ¹ 2 mg lozenge	2.0 (1.4–2.8)	14.4%	24.2%
High Dependence ² 4 mg lozenge	2.8 (1.9–4.0)	10.2%	23.6%

¹Time to first cigarette ≥ 30 min²Time for first cigarette < 30 min

Table 10

Side Effects and Precautions for Non-nicotine Medicines

Product	Most Frequent Side Effects	Precautions
Bupropion ¹ 150 mg bid/day	Dry mouth, insomnia	Seizure disorder or predisposition towards seizure disorder, concomitant use of Wellbutrin, diagnosis of bulimia or anorexia nervosa, concomitant or recent use of MAO inhibitors
Varenicline	Nausea/vomiting, sleep disturbance, flatulence	* Severe renal impairment, * pregnancy
Clonidine	Dry mouth, drowsiness, dizziness, sedation, constipation, lower blood pressure, rebound hypertension	* Pregnancy
Nortriptyline	Dry mouth, sedation, blurred vision, urinary retention, lightheadedness, shaky hands, cardiotoxicity with overdose	Cardiovascular disease, * pregnancy

* Conditional (consider benefit to risk ratio)

NOTE: MAO=Monoamine Oxidase; **SOURCE:** Information from Fiore et al., 2000, Reference #(72), Pfizer Labs U.S.

http://www.pfizer.com/pfizer/download/uspi_chnatix.pdf.