Published in final edited form as:
Pharmacol Ther. 2009 July ; 123(1): 1–16. doi:10.1016/j.pharmthera.2009.03.011.

Tobacco dependence and withdrawal: Science base, challenges and opportunities for pharmacotherapy☆

Jack E. Henningfield[a,*], **Saul Shiffman**[b], **Stuart G. Ferguson**[b], and **Ellen R. Gritz**[c]

[a]Pinney Associates, Bethesda, Maryland, The Johns Hopkins University School of Medicine, Baltimore, United States

[b]Pinney Associates, Pittsburgh, Pennsylvania, University of Pittsburgh, Pittsburgh, Pennsylvania, United States

[c]The University of Texas M.D. Anderson Cancer Center, Houston, Texas, United States

Abstract

Several pharmacotherapies for tobacco dependence and withdrawal have been approved by the Food and Drug Administration to aid smoking cessation. These medicines double to triple the odds of cessation compared to placebo, with the diversity in chemical entity (e.g., nicotine, varenicline, bupropion) and route (e.g., nicotine gum and transdermal patch) providing options for people who find a given medication unacceptable or ineffective. Treatments in development include vaccines, combinations of existing products, and new indications, such as reduced tobacco use and exposure. These therapies have been developed on the foundation of research on the neuropharmacology of tobacco dependence and withdrawal. Ongoing research is expected to contribute to more efficacious use of existing therapies and the development of new approaches. This article addresses these developments as well as the challenges to medication development. Challenges include understanding the population-based and individual differences in the vulnerability to dependence and responsiveness to various treatment options, which could contribute to effective treatment to patient matching. Research on the CNS effects of administration and withdrawal of nicotine and other tobacco product constituents is expanding, providing the basis for more effective therapeutic approaches and new medications development. Additionally, whereas medications are approved on the basis of standardized assessments of efficacy and safety in clinical trials, the public health impact of medications depends also on their appeal to smokers and their effectiveness in actual use settings. Research on more effective medication use along with policies that support improved access and utilization are vital to conquering the tobacco epidemic.

☆Financial support and acknowledgment. JEH salary support for work on this manuscript was provided by Pinney Associates and The Johns Hopkins University School of Medicine, Innovators Combating Substance Abuse Awards Program, supported by the Robert Wood Johnson Foundation. The efforts of ERG were supported by NIH grant, An Innovative Telephone Intervention for HIV +Smokers, R01 CA097893. JEH, SS, and SGF provide consulting support to GlaxoSmithKline Consumer Healthcare through Pinney Associates on an exclusive basis regarding tobacco dependence treatment; GSK had no editorial input into this manuscript. JEH and SS have a financial interest in a potential new oral nicotine replacement therapy product.

*Corresponding author. Pinney Associates, Research and Health Policy, 3 Bethesda Metro Center, Suite 1400, Bethesda, MD 20814, United States. Tel.: 301718 8440; fax: 301718 0034. jhenning@pinneyassociates.com (J.E. Henningfield).

Keywords

tobacco; nicotine; treatment; drug; pharmacotherapy; mechanism; brain; nicotine replacement therapy; varenicline; bupropion; gum; patch; lozenge; inhaler; nasal; policy; efficacy; epidemiology; withdrawal; brain imaging; receptors

1. Introduction

Pharmacotherapy for tobacco dependence and withdrawal is vital to reversing the epidemic of tobacco-caused disease and premature mortality in the United States and globally (US DHHS, 2000; WHO, 2004; Bonnie et al., 2007). Behavioral therapies for helping smokers quit are also available and may be the best option for some tobacco users. However, these therapies are rarely used and generally require trained intermediaries to provide the service. These are not addressed in the present review (but see Fiore et al., 2000; Abrams et al., 2003; Fiore et al., 2008). Medications approved by major drug regulatory agencies such as the U.S. Food and Drug Administration (FDA) roughly double to triple the success in smoking cessation attempts and can thereby contribute substantially to improved health and reduced risk of premature mortality (Fiore et al., 2000, US DHHS, 2000; Fiore et al., 2008; Fant et al., 2009). Presently approved medications include several types of nicotine replacement therapy, bupropion, and varenicline; several other medications are recognized as effective in clinical practice guidelines though they have not been approved or labeled for smoking cessation (Fiore et al., 2008; WHO, 2008b).

New pharmacotherapies known to be under development include nicotine vaccines, new chemical entities, new nicotine delivery systems, and new indications and modalities of use for approved drugs. Active developers range from government grant supported small research and business operations to major multinational pharmaceutical companies. Nonetheless, despite the promise and established benefit of pharmacotherapy, controversy continues to emerge with questions about real world effectiveness, use in certain populations, and safety-benefit ratio of various modalities of use. The science base for the pharmacotherapy, challenges for new medications development, and opportunities for contributing to public health are therefore timely to consider.

For health professionals, scientists, pharmaceutical developers, health care payers, and tobacco dependent people, the primary questions regarding pharmaceutical products are their efficacy, acceptability, and safety. There is little question that more effective and acceptable treatments and more effective ways of using existing treatments would lead to increased willingness to pay for them by individuals and health care providers. A source of complication and opportunity for medications development is that it is evident that there are numerous potential mechanisms by which medications may exert beneficial effects with probably no single approach emerging as effective and acceptable for all. In turn, this implies that the relatively narrow model used by the FDA and other major drug regulatory authorities for demonstrations of efficacy needs to be expanded. For example, it appears likely that some medications might emerge as best suited for chronic use to sustain abstinence while others are better suited to enabling cessation and/or treating withdrawal to sustain occupational performance during intermittent abstinence required by smoke free policies. Still other possibilities are apparent and are discussed in this review. The present review is especially focused on research and development needs, opportunities and challenges in the development of medications to meet global needs and contribute to the reversal of the epidemic of tobacco disease.

The difficulty characterizing relevant medications under a single rubric is exemplified by the question of how to describe these medications. Many reviews refer to them as “smoking cessation medications,” which implies a particular use of such medications. The present review will refer to them as “tobacco dependence treatment medications,” recognizing the multitude of ways in which dependence might ultimately be treated. The review begins with a brief overview of the public health rationale and twenty-first century support for an expanded pharmaceutical armamentarium, followed by a summary of the fundamental clinical symptomology and neurobiology of tobacco dependence and withdrawal. Presently approved medicines and their basis for approval will be described to help understand the controversies that surround them as well as to further develop the foundation for new medications development. The needs of several key special populations and unique challenges which they raise will be described because these provide still more opportunities for development. Finally, we offer recommendations for consideration for expanding the range of potential medication types, as well as the indications and applications of medications to address the enormous diversity of needs of the hundreds of millions of people who may benefit from their use for many decades to come.

2. Public health rationale and global considerations for medications development

The human cost of tobacco use is well known: Tobacco use and exposure results in approximately 442,000 deaths annually in the United States and 5 million world wide, with the annual global death toll expected to increase to approximately 10 million by the 2020s (WHO, 2007). Although prevention of tobacco use initiation and addiction are vital to long range reduction in morbidity and mortality, only dramatically increased cessation rates will turn the tide of the ongoing health disaster because the major health benefits of prevention are delayed by several decades (Henningfield & Slade, 1998; World Bank, 1999; World Health Organization, 2004), whereas cessation yields more immediate benefits. Therefore, both the World Health Organization and World Bank support increased treatment access and utilization (World Bank, 1999; WHO, 2004).

For tobacco users who have not yet experienced serious tobacco attributable disease, cessation of tobacco use offers many important benefits to health in the near and long term. For example, nearly one third of smoking attributable premature mortality is due to cardiovascular events, the risk of which can fall to near nonsmoker levels within two years or less of smoking cessation (US DHHS, 1990, 2004). This extremely favorable benefit-to-risk ratio compared to the very low overall risks of medications, and the substantial benefits of smoking cessation contribute to why the U.S. Public Health Service clinical practice guideline as well as many experts strongly advocate offering treatment to most people who can not quit on their own (Fiore et al., 2000; US DHHS, 2000; Royal College of Physicians, 2000; Fiore et al., 2008; Fant et al., 2009).

Ongoing and globally emerging public health efforts can dramatically increase tobacco cessation efforts and reduce initiation of tobacco use (WHO, 2004). For example, in countries with established anti-tobacco education, such as the United States, more than 80% of cigarette smokers are interested in quitting smoking with more than 40% attempting to quit every year (Shiffman et al., 2008a). Unfortunately, without treatment, approximately 3% achieve even one year abstinence rates, and many who do achieve one year abstinence will relapse within the next two years (Giovino et al., 1995; US DHHS, 2000; WHO, 2004).

The public health and economic benefits of smoking cessation are dramatic and well established. The economic costs associated with tobacco-related morbidity and mortality in the US alone were estimated at approximately $158 billion (CDC, 2002). Smoking cessation

reduces the risk of disease, complicated pregnancy, occupational absenteeism, and premature mortality, with the magnitude of these benefits inversely related to age and/or years of tobacco use (US DHHS, 1989, 2000). Many people can and do achieve lasting cessation without formal treatment intervention, but the overall rates of success are low and generally only follow several decades of tobacco use and repeated cessation efforts. This results in an increase in tobacco attributable mortality globally, which has only recently appeared to begin to level off and possibly decline in Sweden and states such as California, where substantial increases in smoking cessation rates have been achieved over the past two decades (Tomar et al., 2003; Gray, 2004; Koop, 2004; Barnoya & Glantz, 2004). In the United States, the combined benefits of cessation and prevention have already prevented several million premature deaths and are considered one of the top ten public health achievements of the 20th century (CDC, 1999).

As noted, most smoking cessation efforts end in a failure to sustain abstinence. Because intervention with evidence-based pharmacotherapy roughly doubles to triple the rate of successful long term cessation, it is advocated for all cigarette smokers by the U.S. Public Health Service (Fiore et al., 2008) and by other organizations that have developed evidence-based recommendations (WHO, 2004). The World Health Organization advocates expanded access to and utilization of evidence-based treatments globally, as expressed in a monograph (WHO, 2004) and through an international treaty called the World Health Organization Framework Convention on Tobacco Control (WHO, 2008a, 2008b).

Although expanded access to and utilization of existing evidence-based treatments have the potential to reverse the tobacco epidemic, it is clear that existing treatments are either not acceptable or not effective for many people and that new treatments and modalities of use will be needed to substantially increase overall cessation rates. Advances in the understanding of the pathophysiology of tobacco addiction, specifically the disorders of dependence and withdrawal, as well as the cognitive and psychiatric benefits many people appear to achieve through nicotine self-administration provide a scientific foundation for development of new treatments.

3. Diseases and symptoms targeted for medications development

What is commonly referred to as tobacco addiction or tobacco dependence has been clinically delineated into two specific diagnosable diseases: dependence and withdrawal (American Psychiatric Association, 2000; World Health Organization, 1992). Tobacco dependence and withdrawal were classified as medical diseases or disorders by the World Health Organization in 1992 (WHO, 1992) and American Psychiatric Association in 1980 (APA, 1980). Although, not life-threatening in their own right, dependence and withdrawal contribute to morbidity and mortality because they promote the continuous and prolonged daily tobacco use that propels disease rates to high levels.

The disorders of intoxication and abuse are recognized by the WHO (1992) but not by the APA (2000). Whereas these are theoretically viable targets for treatment development, they do not appear a priority from a public health or commercial perspective. Intoxication is a pharmacological effect of nicotine that is not uncommonly experienced by first time tobacco users. However, it appears relatively rare in regular tobacco users and is generally short-lived and does not appear to warrant treatment other than a reduction or termination of nicotine intake. It is yet to be determined whether there is any clinical advantage to differentiating tobacco abuse from tobacco dependence with respect to treatment approached.

Since 1987, the APA has used the terms “nicotine dependence” and “nicotine withdrawal,” placing emphasis on the drug which defines the disorders as psychoactive substance

dependence disorders (APA,1987, 1994, 2000), whereas the WHO continues to refer to "tobacco dependence" and "tobacco withdrawal" by emphasizing the importance of the tobacco delivery system in the dependence process and adverse effects. However, the diagnostic criteria across the two organizations for each of these disorders are similar, and the symptoms that comprise dependence and withdrawal may be considered targets for pharmacotherapy.

In brief, dependence refers to the chronic, maladaptive and relapsing pattern of chronic tobacco *use* that meets the same criteria that are applied to other forms of drug dependence; physiological dependence and abstinence associated withdrawal are often seen but are not necessary to the diagnosis of dependence (WHO, 1992; American Psychiatric Association, 2000). The major symptoms of dependence include difficulty abstaining when tobacco is not allowed, relapse following cessation, and higher levels of use than desired. Withdrawal is also a potential symptom of dependence. Each of these symptoms is a potential target for drug development. All drugs that have been approved for smoking cessation have been demonstrated to be effective in reducing nicotine self-administration by animals and/or humans, and provide some degree of substitution with respect to psychoactive or discriminative effects of nicotine (Buchhalter et al., 2007).

Withdrawal is the time-limited syndrome of signs and symptoms that begin to emerge within a few hours of discontinuation of nicotine intake, with prominent symptoms including dysphoric mood, anxiety, anger, difficulty concentrating, sleep disturbance, and weight gain (WHO, 1992; American Psychiatric Association, 2000; Hughes, 2007a). Powerful recurring cravings are typically prominent during withdrawal but also occur during ad libitum smoking, sometimes precipitated by the sight of a cigarette or a smoking associated situation, without the emergence of withdrawal symptoms (Shiffman et al., 2002). Withdrawal and craving constitute potential targets for drug development; craving in particular stands out as the single symptom most important for labeling, marketing, and potential claims. All drugs approved for smoking cessation provide some degree of relief of craving and withdrawal symptoms.

As with other drug addictions, the relationship between withdrawal and drug seeking is complex and variable (US DHHS, 1989; Hughes 2007c). There is no question that withdrawal associated discomfort, dysfunction (e.g., cognitive and mood), and cravings can precipitate tobacco use and relapse. However, it is also known that relapse may occur in the absence of apparent withdrawal symptoms and withdrawal is suffered and survived by many without relapse to tobacco use (US DHHS, 1989; Hughes, 2007a, 2007b, 2007c). Withdrawal severity is a good predictor of treatment failure, but even when withdrawal is nearly eliminated by treatment, most smokers still resume smoking (Ferguson et al., 2006). Withdrawal can also be treated and effectively alleviated in the absence of efforts to establish lasting smoking cessation, such as in the case of people in research studies and demanding occupational settings who were not attempting to quit smoking but were given nicotine replacement medications to block withdrawal and sustain performance (Fiore et al., 1994, 2008).

4. Approved medications to aid smoking cessation by treatment of dependence and withdrawal

There is a broad range of medications that are presently available and have been approved by the U.S. FDA and/or other major medicines regulatory authorities worldwide (Fiore et al., 2000; US DHHS, 2000; Royal College of Physicians, 2000; Fant et al., 2009). Although unmet needs remain, what has been accomplished, especially since the early 1990s, is impressive by the standards of many other areas of medications development. Three

categories of medications are summarized in Table 1: nicotine delivering or nicotine replacement medications (NRT), the antidepressant bupropion, and the nicotinic agonist varenicline. Outside of the United States, a sublingual nicotine tablet has also been approved in several countries.

All of the medications listed in Table 1 have been evaluated in rigorous smoking cessation trials demonstrating significant improvement in abstinence rates compared to placebo, frequently demonstrating persisting superiority over placebo for 6 months or more after treatment has ended. They all reduce symptoms of withdrawal, although nicotine gum and patch have been the most thoroughly studied and well documented as efficacious for relief of withdrawal. The medicines are typically referred to as smoking cessation medicines because smoking cessation is the primary approved indication by FDA and other medicines regulatory agencies. However, some expert reviews such as from the World Health Organization and the U.S. Public Health Service explicitly refer to both “treatment of tobacco dependence” and “smoking cessation” (Fiore et al., 2000; WHO, 2003; Fiore et al., 2008), and labeling often refers to the uses of the medicines to reduce withdrawal. For example, the U.S. labeling for these products describes their use as “reduction of craving and withdrawal associated with smoking cessation” (Thomson, 2008).

Nicotine based medications for treating these medical disorders have been established as safe and effective in more than 100 clinical trials, as documented in several Cochrane Reviews, United States Public Health Service reviews, and other expert committee based reviews (US DHHS, 2000; WHO, 2004; Fiore et al., 2008; Stead et al., 2008). Since the approval of an oral chewing gum type of nicotine delivering medicine by the United States Food and Drug Administration (FDA) and other national drug regulatory agencies in the 1980s, numerous other nicotine delivering forms including lozenges, transdermal patches, a nasal spray and oral inhaler have been approved by FDA and other drug regulatory agencies world wide (WHO, 2004).

Two additional medication types, bupropion and varenicline, have been approved by many drug regulatory agencies based on the results of strongly supportive clinical studies (Henningfield et al., 2005). A third category of medication — cannabinoid receptor blockers —appears effective for obesity treatment but less consistently effective for smoking cessation than the approved medications. Whether these will prove to be a strong smoking cessation aid under certain conditions is not clear. However, potential side-effects such as suicidal ideation may preclude its approval. Rimonabant is a cannabinoid 1 receptor (CBN-1) blocker (Henningfield et al., 2005) and was approved by the European Commission as an aid to weight loss for obesity in 2006. Safety and efficacy concerns have led FDA to require further study (Harris, 2008). However, whether it is approved for tobacco dependence treatment or not, it represents another mechanism of potential action for such medications.

Several other medications are recognized to be effective as potential second line medications for smoking cessation by evidence-based reviews and clinical practice guidelines (Fiore et al., 2000; US DHHS, 2000; Royal College of Physicians, 2000; Henning-field et al., 2005). These are the antidepressant nortryptiline and the antihypertensive clonidine (Fiore et al., 2000; US DHHS, 2000; WHO, 2004; Henningfield et al., 2005). Naltrexone also shows promise at least in combination with transdermal nicotine under certain dosing conditions (Krishnan-Sarin et al., 2003). The nicotinic agonist, cytisine, which has similar actions as varenicline, also appears effective for smoking cessation (Etter, 2006). Whether or not these medications would be approved for smoking cessation by regulatory agencies is not known, but (to the knowledge of these authors) applications for approval as smoking cessation aids have not been submitted. This is not surprising because applications would undoubtedly

require many millions of dollars committed for clinical trials and submission packages meeting regulatory standards with market potential limited by the fact that they are off patent and produce side effects that would likely limit their use.

Several other medications are in various stages of development. Perhaps the most interesting class is comprised of vaccines that appear capable of producing relatively long term (e.g., many days) reductions in reinforcing actions of nicotine. These raise the intriguing possibility that the most appropriate or at least an appropriate indication may be in relapse prevention for persons able to achieve cessation using other treatments but requiring assistance to sustain abstinence.

5. Controversy: efficacy versus real world effectiveness

A controversy in the evaluation of tobacco dependence treatment medications is the generalizability from clinical studies to real-world use. This is a universal issue in drug therapy, where clinical effectiveness is sometimes thought to degrade when a medication comes into widespread real-world use. The issue has been raised in the case of nicotine replacement therapy (NRT) products that were switched to over-the-counter status, namely the nicotine patch and gum. NRT products have been tested in over one hundred clinical trials, comprising over 35,000 smokers, and have been found to be efficacious (Silagy et al., 2004; Stead et al., 2008). Importantly, the studies include effectiveness trials in which smokers purchased and used the medications without instruction (other than labeling), counseling, or supervision, much as they would in an OTC environment. However, despite these findings, some researchers have questioned whether NRT is “effective” (as opposed to efficacious) —that is, whether NRT helps people quit smoking when it is used under real-world OTC conditions. Fueling these concerns have been epidemiological analyses of overall population-based cessation rates and comparisons between the cessation rates in people using NRT, and those quitting unassisted (e.g., Pierce & Gilpin, 2002). It is argued that if NRT is effective, then a) we should observe decreases in smoking prevalence since these products have became available; and b) people who report using NRT to quit smoking should have higher rates of cessation than those who report attempting to quit unassisted (“cold turkey”). Findings on these issues have been inconsistent, raising the concern that OTC NRT is not effective.

However, methodological shortcomings of population-based analyses mean that they are not adequate tests of either of the two hypotheses mentioned above. With regard to NRT’s impact on overall prevalence, the impact of NRT on prevalence depends heavily on its utilization. In fact, with NRT being used in only about 25% of quit efforts, and absolute quit rates being modest, its effect on population cessation rates would be smaller than the margin of error in such studies (West et al., 2005). Clearly, therefore, it should not be surprising that such an effect has not been observed in population-based analyses.

The other questions about the impact of OTC NRT have arisen as a result of cross-sectional retrospective population case control studies comparing success rates among smokers who did and did not use NRT in their quit attempt. Although some studies of this design find greater success rates in those using NRT (Pierce et al., 1995), others do not (Pierce & Gilpin, 2002; Alberg et al., 2005), which has led some to question the effectiveness of OTC NRT. However, two significant issues make it difficult to draw any valid inferences from such studies. The first is that retrospective recall of quit attempts in such surveys can introduce systematic bias. Particularly as many quit attempts are spontaneous and often short-lived, unsuccessful unaided quit attempts are easily forgotten; in contrast, when a smoker takes the unusual step of procuring and using treatment, quit attempts are remembered even when they fail. The result is a biased inflation of success rates in unaided

treatment. Indeed, a prospective population-based study that minimized reliance on recall recently found that NRT was as effective in OTC use as it was in controlled clinical trials (West & Zhou, 2007). This is consistent with the findings from controlled prospective effectiveness trials of OTC NRT, which found that OTC NRT was more effective than placebo and as effective as prescription NRT (Hughes et al., 2003). The second is that these population surveys are subject to indication bias (Miettinen, 1983) which occurs where treatments are administered based on the patient's preference.

In contrast to clinical trials, where the effects of treatment or no treatment (placebo) are compared in similar populations (based on randomization), in the real-world, smokers decide whether they will use or not use NRT themselves. Naturally, NRT is largely adopted primarily by those who feel they cannot quit on their own, whereas those who feel able to quit easily quit without treatment. Indeed, NRT is used by smokers who are more nicotine-dependent, suffer more psychopathology, and have lower self-efficacy for quitting (Shiffman et al., 2005). Such dynamics — the least able to quit are most likely to select treatment — affect all treatments, not just NRT: analyses of national data show similarly that smokers who elect to undertake behavioral treatment also have lower success rates than those who do not (Shiffman et al., 2008a,2008b). This finding also undercuts Pierce and Gilpin's (2002) argument that NRT's efficacy was reduced in the OTC environment because it was no longer accompanied by behavioral treatment. But using retrospective data from self-selected samples makes all treatment, including behavioral treatment, appear to be ineffective (Shiffman et al., 2008a,2008b). This demonstrates why cross-sectional surveys are not appropriate for assessing treatment effectiveness.

6. Neurobiology of tobacco dependence and withdrawal: the potential targets for and mechanisms of pharmacotherapy suggest new models for predicting efficacy

The neurobiology of tobacco dependence and withdrawal is complex and the understanding is rapidly evolving as research advances on many fronts. As relates to the actions of nicotine that contribute to tobacco dependence and withdrawal, the scientific discovery process over the past few decades provides a strong foundation for progress toward an expanded range of treatment medications (Royal College of Physicians, 2000; US DHHS, 2004; Henningfield & Benowitz, 2004; Koob and Le Moal, 2006; Buchhalter et al., 2007). The following summary highlights aspects of the neurobiology that we feel are useful to consider in evaluating potential indications for treatment and assessment of their efficacy.

Nicotine is the drug in tobacco products that is critical in the development of dependence, withdrawal, tolerance, and many effects that smokers variously describe as useful, if not key, to why the continue to use tobacco. Decades of research have supported the observation of Lewin in the 1920s (translated in English in the 1930s and reprinted several times since), that "the decisive factor in the effects of tobacco, desired or undesired, is nicotine…" (1998). The multitude of effects of nicotine that contribute to tobacco dependence have been reviewed elsewhere and include the effects of tobacco use and deprivation on mood and affect, cognition, weight and appetite control, and other effects that the U.S. Food and Drug Administration and other organizations cite in defining tobacco use as a form of drug use (US DHHS, 1988; FDA, 1995, 1996; Royal College of Physicians, 2000).

Nicotine withdrawal can occur independently of dependence, as is the case with other dependence producing drugs, and is not necessarily mediated by the same mechanisms or neurosubstrates as dependence. The nicotine withdrawal syndrome includes impairments in mood and cognitive ability, increased appetite, heightened aggressiveness, disturbed patterns

of sleep, and powerful cravings (APA, 2000). Physiological correlates include reduced heart rate, perturbation of a variety of neurohormones, alterations in electroencephalographic theta power, and alterations in regional brain activity, and disruptions in learned behaviors (Koob & Le Moal, 2005; Buchhalter et al., 2007). Although withdrawal symptoms are drug class-specific, some are common across drug classes, such as the abstinence-associated decreases in DA levels in the nucleus accumbens, which have also have been observed with ethanol, morphine, cocaine, and amphetamine (Rossetti et al., 1992; Weiss et al., 1992).

Taken together, the emerging understanding of the neurobiology of tobacco dependence and withdrawal, and of the nicotine effects that contribute to tobacco use such as desirable enhancement of attention and mood (at least for some individuals), suggests that there are diverse potential mechanisms by which medicines could support efforts to reduce if not cease tobacco use completely. This is relevant for the development of diverse laboratory preclinical and human models for drug screening as has been discussed by Lerman et al. (2007).

Animal studies of nicotine self-administration and human studies of patterns of development of cigarette smoking suggest that individual differences exist but that certain conditions of exposure, including access to behaviorally active doses of nicotine, carry a high risk of development of self-administration (e.g., Lanza et al., 2004). This risk appears to be conferred by the diverse effects of nicotine, which directly and indirectly reinforce continued tobacco use and dependence. The effects of nicotine are mediated by its binding to muscular and neuronal receptors, but it is the neuronal nicotinic receptors (nAChR) that appear most crucially involved in the CNS effects of tobacco including dependence and withdrawal.

Although nicotine can directly serve as a reinforcer for animals and humans, and in humans this is associated with pleasurable CNS effects, it is not clear that direct reinforcing actions of nicotine from nicotine replacement medications are essential for efficacy because transdermal nicotine can reduce withdrawal and aid cessation even at doses too low to discriminate. This observation does not in itself rule out the possibility that medication delivered nicotine can provide direct reinforcing effects because other drugs of abuse can also be reinforcing at subdiscriminable levels (Lamb et al., 1991), but it does suggest that the medications can be effective at doses that produce very weakly discriminable and/or reinforcing effects.

There are a number of neural mechanisms by which a medication may alleviate withdrawal symptoms, simulate some of the reinforcing effects of nicotine, or block the reinforcing effects of nicotine. The most obvious is the nicotinic receptor itself, where nicotine replacement medications act. However, as reviewed by Picciotto, many, if not most, of the effects of nicotine in the brain are likely to be mediated through neuromodulation in which nicotine potentiates the release of neurotransmitters including acetylcholine, dopamine, glutamate, GABA, norepinephrine, and serotonin (Picciotto et al., 1998a; Koob & Le Moal, 2005, 2006). By selectively activating or blocking these neurotransmitters, one might be able to mimic or block some of the reinforcing effects of nicotine.

Various subpopulations of nAChRs in the brain are likely to mediate different aspects of the cause and associated symptoms of dependence and withdrawal. For example, nicotine-induced dopamine release that appears especially critical in its reinforcing effects is dependent on the β2 subunit (Picciotto et al., 1998a). However, the cascading release and perturbation of a variety of neurotransmitters in addition to dopamine undoubtedly contributes to the development and persistence of tobacco dependence. For example, activation of CNS nicotinic receptors leads to the release of serotonin (5-HT), glutamate

(Glu), γ-aminobutyric acid (GABA), and endogenous opioid peptides (George and O'Malley, 2004). Neurosubstrates involved in nicotine reinforcement include the mesolimbic dopaminergic neurons at the ventral tegmental area (VTA) and nucleus accumbens (Nisell et al., 1995). In the VTA, nicotine appears to act via presynaptic α7 nAChRs located on Glu afferents (Mansvelder & McGehee, 2000), thereby increasing Glu release, which in turn stimulates DA release in the nucleus accumbens (Schilstrom et al., 1998a,1998b; Mansvelder & McGehee, 2000). Multiple studies suggest α7 nAChR subunits and/or α4β2 nAChR subtypes have a role in nicotine reinforcement, DA release, and the anxiolytic effects (Picciotto et al., 1998b; Sharples et al., 2000; Markou & Paterson, 2001; Cheeta et al., 2001) that contribute to continued tobacco use (CDC, 1988). Another neurosubstrate that may mediate nicotine reinforcement is the GABA neurotransmitter system (Koob & Le Moal, 2006). Still other neurosubstrates that may mediate nicotine reinforcement involve the hypothalamic–pituitary–adrenal (HPA) axis and corticotropin-releasing factor (CRF; also abbreviated CRH for corticotropin-releasing hormone), a neuropeptide neurotransmitter involved in stress responses (Sarnyai et al., 2001; Koob & Le Moal, 2006). CRF transmission in the paraventricular nucleus of the hypothalamus (PVN) has been hypothesized to mediate the effects of acute nicotine exposure on the HPA in rodents and humans (Koob & Le Moal, 2006). Thus, there is a rich set of potential targets for development of pharmacological treatments for tobacco dependence.

Nicotine exposure also leads to changes in brain structure, if not function, that may contribute to the persistence of the dependence process. For example, chronic nicotine administration desensitizes and inactivates nAChRs which leads to up-regulation of nAChR sites (Mansvelder et al., 2002; George & O'Malley, 2004; Koob & Le Moal, 2006). This nicotine-induced up-regulation of nAChRs has been observed in the rodent brain (Sanderson et al., 1993; Flores et al., 1997), human brain (Benwell et al., 1988; Breese et al., 1997; Perry et al., 1999), and human blood leukocytes (Benhammou et al., 2000), and is dose dependent (Breese et al., 1997; Benhammou et al., 2000). Chronic nicotine exposure can increases nAChR numbers (Marks et al., 1992; Buisson & Bertrand, 2001) and function (Rowell & Wonnacott, 1990). Further complicating understanding of the neurobiology of tobacco dependence is that different nAChR subtypes vary in their sensitivity to nicotine, as evidenced by differential degrees and rates of desensitization and up-regulation (Watkins et al., 2000; Koob & Le Moal, 2006). For instance, nAChRs composed of α4β2 subunits desensitize slowly (Leonard & Bertrand, 2001a) while α7 receptors desensitize rapidly (Leonard & Bertrand, 2001b). Thus behavioral observations may reflect the combined effects of complex adaptations of different nAChR types (Koob & Le Moal, 2006).

It appears plausible that the withdrawal syndrome associated with smoking cessation reflects the 200% to 400% increase in nicotine receptors that occurs during chronic smoking (Perry et al., 1999), many of which are abruptly left unoccupied when smokers quit. In turn, nicotine replacement therapy may provide its benefits, in part, by occupying these receptors, and thus contributing to stabilized physiological functioning while the person behaviorally adapts to daily functioning without "aid" of tobacco (Ferguson et al., 2006). In practice, people treated with nicotine delivering therapy are often stabilized for a several weeks and then the dose is gradually reduced according to the needs of the user. A small percentage of people use longer than 1 year (Shiffman et al., 2003a,2003b) and it is not clear if this is driven by a need for continued nicotine due to potential CNS effects of prior nicotine exposure such as receptor up-regulation. By self-report, most long-term users state that their continued use is intended to ward off relapse to smoking (Shiffman et al., 2003a,2003b). Many public health professionals (e.g. Henningfield & Slade, 1998; Shiffman et al., 1998; Hughes, 2000; Fagerstrom 2005; Royal College of Physicians, 2007) have urged that long term nicotine replacement be considered for smokers who appear to need it to sustain tobacco abstinence.

Varenicline is an example of a smoking cessation medication that was designed to produce a complex modulation of nicotinic receptor subtypes. It is a partial agonist at alpha 4 beta 2 receptors, and is also a full agonist at alpha 7 receptors and also acts at alpha 3 beta 4 receptors (Mihalak et al., 2006). These actions do not imply that varenicline is necessarily more effective than nicotine-based medications or other medications, but it is plausible that its different pharmacology will at least provide an alternative for people for whom other medications are either not effective or efficacious. As the mechanisms of nicotine's addictive effects become increasingly well understood, laboratory models potentially will emerge as stronger predictors of clinical efficacy, and further advances in medications should be enabled. In fact, as discussed by Lerman et al. (2007), a variety of preclinical and clinical models are emerging for the preliminary screening of putative medications bringing clinical medicine a step closer to the time that a genetic screen might be used practically to help predict which medicines would produce the best response in individuals (Lerman et al., 2007). However, the link between most current models and clinical outcomes is not well established. The value of such models may increase further as we continue to unravel the undoubtedly complex and myriad mechanisms by which tobacco use exerts its addictive control over behavior.

6.1. Non nicotinic factors may contribute to dependence by acting independently and by modulation of the effects of nicotine

Despite the prominence of nicotine in defining and explaining tobacco use and dependence, it is growing ever clearer that a full explanation of dependence, withdrawal and other effects of tobacco use is not accounted for simply by the actions of nicotine at nicotinic receptors. Analysis by the U.S. Food and Drug Administration, World Health Organization advisory committees, and others have concluded that tobacco products are designed and manufactured to maximize their attractiveness, palatability, and addictiveness through numerous ingredients and design features which contribute to sensory effects, produce their own neuropharmacological effects, or modify the chemical form of nicotine (Food and Drug Administration, 1995, 1996; World Health Organization, 2001; Henningfield et al., 2003a, 2003b; Henningfield et al., 2004; World Health Organization, 2007). In fact, the dose, speed of delivery, and pattern of nicotine delivery are crucial determinants of the observed effects; ingredients and design features of tobacco products can indirectly control dose and speed of absorption, as well as exert their own effects that may contribute to the dependence process; ingredients and design features may also contribute to sensory stimulation that is important in the addictive process (Henningfield et al., 2004; Rose, 2006). These have been reviewed elsewhere and include substances that are added to tobacco products to enhance the ease of nicotine self administration such as menthol and chocolate, as well as substances that occur in tobacco products but can be manipulated in tobacco product manufacturing to increase the reinforcing effects by increasing free-base nicotine formation (ammonia compounds) or by potentiating the reinforcing effects (acetaldehyde) (FDA, 1995, 1996; US DHHS, 2001; Henningfield et al., 2003a,2003b; Wayne et al., 2004, 2006; DeNoble & Mele, 2006; Rabinoff et al., 2007; Wayne et al., 2008).

One of the many implications of these observations is that medications simply delivering nicotine or which act via other CNS pathways should not be expected to fully replace the reinforcing and other CNS effects of tobacco use, regardless of the dose or delivery system, although systems that provide more rapid delivery and more readily controllable doses may be more desirable to tobacco users attempting to achieve and sustain abstinence. Another implication is that it is a least theoretically possible that medications that replaced or blocked effects of non-nicotinic components in tobacco product emissions might be effective for smoking cessation. An example, albeit a non-drug product example, is the use

of citric acid aerosol to partially mimic the throat burn produced by tobacco smoke inhalation and thereby diminish craving (Rose & Hickman, 1987).

7. New pharmacotherapy: challenges and opportunities

Even as the diversity of medications and their utilization have increased over the past few decades, so too has the science foundation for developing new pharmacotherapies to address unmet clinical and public health needs. As suggested by the diversity of current medications and their applications, there are many potential paths for pharmacotherapy. At least three nonexclusive areas of new pharmacotherapy development can be delineated (1) new chemical entities and formulations, (2) new indications for existing and new chemical entities, (3) special populations, which may be similar to new indications from a regulatory perspective but we believe warrants its own focus because the new indications that will be discussed are not necessarily appropriate for all of the special populations that will be discussed.

7.1. New chemical entities and formulations

Table 2 summarizes several categories of potential new formulations of nicotine and new chemical entities as well as potential tobacco dependence indications for drugs approved for other diseases. Nicotine itself is likely to remain a mainstay chemical entity for pharmacotherapy due to its established broad range of efficacy and safety in acute and long term use. However, compared to tobacco products, medicinal nicotine delivery systems in general are relatively low dose, slow onsetting, and less responsive to moment to moment dosing manipulations to which tobacco users are accustomed (Henningfield & Slade, 1998; Slade & Henningfield, 1998). This does not mean that all smokers require more flexible and aggressive nicotine delivery systems. However, for those who could so benefit, a broader range should be available, and modification of the formulation for established drugs has emerged in the past decade as an area of pharmacotherapeutics with enormous activity and potential. These delivery systems range from relatively small variations on nicotine gum that enable faster relief of craving (Niaura et al., 2005) to lung delivered nicotine. Of course more aggressive, rapid and higher delivering dosage systems will carry heavier burdens to assess safety and addiction potential. Furthermore, they may be regulated as addictive drugs under regulatory frameworks such as the Controlled Substance Act in the United States or the Psychotropic Convention of the United Nations (Spillane & McAllister, 2003; Balster & Bigelow, 2003; Schuster & Henningfield, 2003; Buchhalter et al., 2008). However, because of the potential clinical and public health need and market potential, these factors should not be insurmountable barriers.

In addition to new nicotine delivery systems, there is clearly great opportunity for the development of new chemical entities, and in this area as well there is a strong science base and already several medications established as efficacious. Animal and human models for evaluation of potential medications provide a foundation for exploration and development of medications to meet a broad range of targets of potential interest (Lerman et al., 2007). Pharmacotherapies include vaccine-like approaches to provide long term mitigation of the central reinforcing effects of nicotine (by excluding nicotine from the brain), selective nicotinic receptor acting drugs, and drugs targeted to either substitute for or prevent various effects of tobacco self-administration and withdrawal that contribute to dependence. Additionally, the efficacy of the antidepressants bupropion and nortryptiline, as well as clonidine, demonstrate that medications already approved for indications other than those related to tobacco might be useful for treating dependence and/or withdrawal. This approach was described by Jarvik and Henningfield as “symptomatic treatment” and has additional precedent in treatment of other addictions (Jarvik & Henningfield, 1988; US DHHS, 1988).

7.2. New indications

The current primary indication for treating tobacco dependence, “aid to cessation,” provides a well established path from laboratory to market but may not be most appropriate for all potential tobacco dependence medications (Shiffman et al., 1998). Several categories of such medications are summarized in Table 3. Some of these indications have been approved as medications for treating dependence and/or withdrawal to other addictive drugs including opioids, alcohol and sedatives (US DHHS, 1988; Henningfield & Slade, 1998).

In fact, some indications may promote cessation whether or not cessation is their basis for approval or use, and it is plausible that regulatory approval for a non-cessation indication would require labeling and marketing that promoted eventual cessation using an appropriate therapy. Alternatives that have been proposed have been discussed elsewhere and are largely based on models and indications that have gained precedents with other drug addictions and have been recommended for consideration by the U.S. FDA (Henningfield & Slade, 1998; Slade et al., 2000; Robert Wood Johnson, 2007). These include the following: treat withdrawal, decrease use, prevent relapse or prolong abstinence, and reduce to quit smoking (Henningfield & Slade, 1998).

The precedent for treatment of withdrawal as a stand-alone indication is the use of various opioids for opioid detoxification and withdrawal relief, and benzodiazepines for alcohol and sedative withdrawal. Drug withdrawal is neither necessary nor sufficient for the determination that drug dependence is present, but it can contribute to dependence severity, pose a barrier to maintaining abstinence and can be a debilitating disorder in its own right (American Psychiatric Association, 2000; Koob & Le Moal, 2006). Nicotine withdrawal can include debilitating emotional distress, heightened aggressiveness, difficulty concentrating, and impaired mental performance. It can also contribute to the severity of dependence. Even in persons not attempting to quit, withdrawal due to abstinence from smoking can impair social and occupational functioning. The severity of emotional disturbance in nicotine withdrawal can be on par with that seen in other psychiatric diseases (Hughes, 2007b), and the cognitive and behavioral disruption seen in nicotine withdrawal is so serious that the Federal Aviation Administration considered whether forbidding smoking in airline cockpits might endanger flight safety (Fiore et al., 1994). For many occupations, such as security personnel, transportation workers, and construction workers, such deficits could pose safety concerns. For others, the cognitive deficits associated with nicotine withdrawal are intolerable impediments to their occupational and social performance. Yet increasingly, as buildings, campuses, hospitals, and other settings adopt clean air policies, people who are not yet able to achieve complete cessation are placed into nicotine withdrawal. The tobacco industry has quickly responded with new smokeless chewing products and marketing targeting their needs with messages such as “for when you can’t smoke” and images such as various work place settings, long airline flights, and shopping malls. These products can be harmful, and do not provide guidance intended to promote eventual cessation of either the smokeless product or cigarettes. Nonetheless, there is a substantial body of evidence (Heishman et al., 1994; Henningfield & Slade, 1998) that nicotine replacement products can mitigate and treat withdrawal, and thus might find some use in this context.

There are also other types of use and indications that might directly support or lead to smoking cessation and/or reduce disease risk in the absence of complete cessation. For example, it is plausible that nicotine vaccines might be beneficial if used as long term maintenance for relapse prevention and tobacco abstinence, whether or not they were optimal or approved for smoking cessation. Using a medication to reduce smoking in persons not presently ready or able to completely quit smoking is possible and evidence suggests that such use promotes eventual cessation (Shiffman et al., 1998; Hughes, 2000; Fagerstrom, 2005; Hughes & Carpenter, 2006). Such an approach might similarly stand

alone as a long-term exposure reduction approach (Shiffman et al., 1998) or as reduction towards cessation. Other variants on use may promote cessation through relatively straightforward evidenced-based labeling.

8. Alternate applications of approved products

As discussed elsewhere, tobacco dependence treatment products have been evaluated and found effective in promoting smoking cessation even when used in ways that are not included in the labeling approved by most drug regulatory agencies such as FDA (Henningfield et al., 2005; Stead et al., 2008). Two general approaches have been studied in a variety of settings. First is the combination of nicotine replacement medications, of which the most compelling is some combination of patch to provide relatively steady passive delivery, and a relatively fast acting acute nicotine replacement medication (e.g., gum, nasal spray, inhaler) to function as rescue medication for immediate relief of breakthrough cravings (Shiffman et al., 1997; Sweeney et al., 2001). This is analogous to the use of combinations of extended relief opioids for chronic pain with short acting opioids for breakthrough pain (Bennett et al., 2005a,2005b). Clinical trials have demonstrated incremental efficacy of patch plus gum and other acute dosage forms compared to either product alone (Stead et al., 2008). These data suggest that the benefit is not simply a function of increased total daily nicotine (Henningfield et al., 2005). The fact that adding an acute dosing form to patch regimens yields substantial incremental benefit, whereas adding another patch yields less benefit, suggests that the mechanism is not simply an increase in nicotine dose, but the combination of steady-state dosing and acute dosing to provide for use as rescue medication. Bupropion in combination with nicotine patch appears to be more efficacious than the nicotine patch alone (although other studies have found no incremental benefit from this combination; e.g., Jorenby et al., 1999; Simon et al., 2004), possibly because the two medications act via different pharmacological mechanisms. However, this use is approved in bupropion labeling (Fiore et al., 2000, 2008).

Another application of nicotine replacement medications that is not endorsed in medications labeling is pretreatment with the medications to either facilitate abrupt cessation on the planned quit date (Shiffman & Ferguson, 2008) or enable reduction of smoking as a strategy to achieve eventual complete cessation (Henningfield et al., 2005). Variations on these approaches have been demonstrated to be effective in several trials (Stead & Lancaster, 2007; Stead et al., 2008).

8.1. Special populations

Most clinical trials of medication efficacy, whether sponsored for drug registration, or by independent and government supported research, have evaluated adult cigarette smokers without other major active illness and thus the clinical practice guideline recommendations are on a strong foundation for these populations. Populations with major chronic diseases have been little studied even though some of these would have much to benefit by smoking cessation (Gritz et al., 2007). For example, cancer patients have been little studied even though smoking cessation can improve prognosis in some cases as well as quality of life (Gritz et al., 2008). People with psychiatric co-morbidities such as depression, schizophrenia, and other forms of substance abuse are at great risk for tobacco dependence and premature mortality caused by tobacco (Lasser et al., 2000; Ziedonis, 2007), but are often excluded from clinical trials.

Each special population raises different issues and there are also areas in which special caution is required. For example, whereas exposure reduction might be an acceptable path towards reducing risk in some populations, it is not clear what level of smoke exposure would be acceptable in persons with respiratory disease or various cancers, and until data are

obtained to the contrary it seems reasonable that the strongest efforts be made to help such patients achieve total and lasting abstinence from tobacco smoke. On the other hand, for individuals who appear to find it virtually impossible to completely quit tobacco use in the near term, strong efforts to reduce their intake to the greatest extent possible should be considered even though the benefits are uncertain. Whether medications can be appropriately used to aid smoking reduction in special populations seems likely to require personal evaluation and monitoring until further data are collected. The medications may not all be equally safe or appropriate depending upon the disease condition either, but it is beyond this paper to speculate or draw preliminary conclusions other than this one.

Table 4 presents some of the special populations that might be considered for indications, or at least for study to inform practice guideline developers and clinicians which medications might be most or least appropriate.

The labeling of tobacco dependence treatment medications in the United States and many countries primarily address three special populations by way of noting that use poses special concerns that should be considered by a doctor. These are pregnant women, adolescents, and people with histories of heart disease. In fact, although these and other populations discussed below pose various challenges to treatment, they have much to gain. In some cases the benefit to risk ratio may be similar or better than for the general adult population of cigarette smokers because the risk of unmitigated smoking or resumption of smoking is so serious. It is vital to address the needs of these and other populations from medical, public health and humanitarian perspectives. Following is a summary of key issues related to assessing the complex benefit to risk evaluations and clinical needs posed by prominent special populations.

8.2. Pediatric tobacco dependence

Tobacco use is sometimes referred to as a pediatric disease (Slade, 1993; Food and Drug Administration, 1996) because it most typically onsets by adolescence with symptoms of dependence and withdrawal commonly evident: failed efforts to quit smoking occur in about one half of cigarette smokers by age 18, at least in the United States as discussed in Reports from the U.S. Surgeon General and Institute of Medicine (US DHHS, 1994; Lynch & Bonnie, 1994). Prior to these reports, interventions for youth tobacco use were almost exclusively prevention focused with messaging to quit if you started, but there was little by way of systematic youth treatment available or even under investigation. Those reports triggered review articles, National Institutes of Health supported research, and a commitment by the Robert Wood Johnson Foundation (Clayton et al., 2000; Henningfield et al., 2000; Moolchan et al., 2000) to develop the science foundation for treatment of pediatric addiction. This research suggests that pediatric symptoms of dependence and withdrawal are generally the same as for adults, but there are differences that might be of importance in adapting treatment to the needs of youth and these differences are only recently beginning to be systematically explored (Shadel et al., 2000; Colby et al., 2000a,2000b; Mayhew et al., 2000; Henningfield et al., 2000; Flay & Clayton, 2003).

Because unremitting pediatric tobacco addiction carries an approximate 50% risk of premature mortality that can be largely eliminated by smoking cessation, the potential important benefit of treatment of young people is great (US DHHS, 1994; Lynch & Bonnie, 1994; Henningfield et al., 2000). Unfortunately, evidence of efficacy of current pharmacotherapy for treatment of adolescents is itself in its infancy, with studies just beginning to reveal potential differences in the treatment needs of the young and how to best address them (Sussman et al., 1999; Henningfield et al., 2000; Moolchan et al., 2000). Furthermore, although tobacco dependence treatment medications are generally very safe, they are not without risks and risks such as suicidal thinking and behavior for bupropion and

varenicline, and the possibility that giving a nicotine replacement product might increase nicotine tolerance and dependence in a young person who is at early stages of dependence, must be factored into the risk side of the benefit to risk equation. Furthermore, some young cigarette smokers quit smoking in early adulthood without medical treatment support (US DHHS, 1994; Henningfield et al., 2000; American Legacy Foundation, 2003). Estimates of spontaneous cessation vary widely from about 4% to 6% for daily smokers to about 21% to 33% for occasional smokers (US DHHS, 1994; American Legacy Foundation, 2003). Nonetheless, the seriousness of persisting tobacco use has led to strong calls for youth treatment development and utilization (US DHHS, 1994; Lynch & Bonnie, 1994; Jacobson et al., 2001; American Legacy Foundation, 2003; Henningfield et al., 2003a,2003b). It does appear that the amount of smoking is a key factor, but there is not a well validated algorithm for guiding treatment selection or use at this point. Development of a pediatric indication for tobacco dependence treatment would fulfill a medical and public health need that is increasingly recognized.

8.3. Pregnant women

The risks of unremitting cigarette smoking during pregnancy are severe and frequent and include low birth weight, preterm delivery, spontaneous abortion, stillbirth, and sudden infant death syndrome (US DHHS, 2001). Most of these adverse outcomes are reduced by smoking cessation with greater benefits the earlier in pregnancy that cessation occurs (US DHHS, 2000; US DHHS, 2001; Ershoff et al., 2004; Cnattingius, 2004). In general the well established high risk of unremitting smoking compared to the striking benefits of cessation and relatively low risk of the medications supports the use of medications during pregnancy and beneficial outcomes on pregnancy have been documented with tobacco dependence treatment such as nicotine replacement, even when complete tobacco abstinence was not achieved (Windsor et al., 2000; Benowitz & Dempsey, 2004).

Nonetheless, because the medications themselves do carry risks it is generally advocated that pregnant women be treated without medication, with medication used if that fails, or if the health professional determines that cessation without pharmacotherapy is unlikely. When medication is used the lowest plausibly effective dose is recommended (Fiore et al., 2000; Windsor et al., 2000; Benowitz and Dempsey, 2004; Haviland et al., 2004; Orleans et al., 2004; Fiore et al., 2008). If pharmacotherapy appears needed, it must not be unduly delayed, however, because, each day of continued smoking appears to increase the risk of adverse effects. The treatment balancing act is further complicated by data showing that pregnant women metabolize nicotine more quickly than non-pregnant women, thus suggesting that if they are treated with nicotine replacement medications they will need higher than typical doses (Benowitz & Dempsey, 2004). There is no question of the serious medical and public health need for improved treatment during pregnancy and for medications labeled with evidenced based algorithms for dosing.

8.4. Other major and chronic diseases

It has been increasingly recognized that tobacco dependence treatment of persons who have developed various diseases is desirable and important (Gritz et al., 1995; Gritz et al., 2007). The approximate 50% risk of premature mortality among cigarette smokers is accompanied by extremely high rates of serious illness including cardiovascular disease, chronic obstructive pulmonary disease, diabetes, asthma, cancer, as well as diseases in which tobacco use may have been associated with prognosis but is not a causal factor such as HIV/AIDS. Other diseases in which cigarette smoking is a negative factor in prognosis include people with diabetes, bone fractures, osteoporosis, injury and surgery leaving significant wounds (US DHHS, 2000; Robbins et al., 2007). In these populations, continued tobacco use can hinder treatment efforts by a variety of mechanisms, including contributing to

disease progression, worsening disease symptoms, and complicating medication dosing due to pharmacologic interactions such as increased metabolism of the medications (Cone et al., 2004; Gritz et al., 2007, 2008).

In addition to potential direct health benefits, smoking cessation is often accompanied by improved prognosis and quality of life in populations with other major diseases (Gritz et al., 2005). In contrast to the well established risks of tobacco use, the risks of the medications, in general, are substantially lower, and in some cases only theoretical, based on dosing assumptions from animal studies and some human studies, but with relatively little direct evidence of harm by the medications in these populations. For example, although nicotine itself is thought to contribute to the risks of tobacco use for myocardial infarction and other heart disease (US DHHS, 1988; Benowitz, 1998) nicotine replacement therapy appears to carry very low real world cardiovascular risk in people, even among those with histories of cardiovascular disease (Joseph et al.,1996; Benowitz,1998; Kimmel et al., 2001; McRobbie and Hajek, 2001). Similarly, although it has been suggested that nicotine itself may promote cancer through inhibition of apoptosis or other mechanisms (e.g., Dasgupta et al., 2006), there is not sufficient evidence to consider nicotine a carcinogen (Benowitz, 1998; International Agency for Research on Cancer, 2007). This is not to imply that potential adverse effects of medications should be dismissed, they should be considered and studied on a disease by disease basis, with the benefits and risks of the medicines thoroughly evaluated (Gritz et al., 2005).

For diseased populations such as persons with cancer, efficacy markers might include quality of life and response to treatments for cancer or their other disorders. For example, cigarette smoking increases dosing needs for a variety of medications due to its hepatic stimulating effects. It is not known if smoking cessation simply results in smaller doses of other medications being needed or if it might actually result in improved response. Cancer patients who smoke have poorer response to some chemotherapy medications, have more side effects from radiotherapy and poorer wound healing (Gritz et al., 2008). Data suggesting improved quality of life for patients with cancer, including those with advanced disease, suggest that these populations merit attention as high priority for humanitarian reasons, regardless of whether or not the treatments result in complete smoking cessation or prolongation of life. It is not clear, which if any, of these populations would significantly benefit from reduction but not complete abstinence from smoking and data are needed on this issue to guide clinical practice.

A variety of factors can operate to either improve or impede efforts to achieve abstinence from tobacco when co-occurring diseases are present. For example, co-occurring disease is a recognized category of factors associated with spontaneous remission (US DHHS, 1988), suggesting that the disease state may provide an important source of motivation, often referred to as a “teachable moment” (Gritz et al., 2006). Conversely, adverse emotional states associated with the disease and the perception that “it is too late to benefit from quitting” may undermine cessation efforts. Whether it is practically viable or commercially feasible to develop specific indications for tobacco dependence pharmacotherapy for persons with co-occurring disease is not clear. However, it would be of enormous medical and public health value to have a stronger foundation for medications labeling and guidance.

8.5. Psychiatric co-morbidities including substance use disorders

It has been estimated that 44% of all cigarettes in the United States are smoked by persons with a co-occurring psychiatric disorder (including depression, schizophrenia, alcohol and other drug dependence) (Lasser et al., 2000; Ziedonis, 2007). Thus it is not surprising that people with psychiatric disorders have a roughly three-fold increase in risk of respiratory disease and lung cancer and two-fold increase in risk of cardiovascular mortality compared

to persons without psychiatric disorders (Dalack & Meador-Woodruff, 1999; Brown et al., 2000; Joukamaa et al., 2001; Curkendall et al., 2004; Ziedonis, 2007). In fact, persons with alcohol dependence and other addictions are more likely to prematurely die of smoking related disease than from causes attributable to their other addictions (Hurt et al., 1996; Hurt, 2002). These observations, along with the fact that many hospitals and their psychiatric and addiction treatment units are adopting nonsmoking policies, are increasing the pressure to find acceptable and effective treatment for tobacco dependence in psychiatric populations. This is not a small challenge, as there appear to be widespread assumptions that smoking cessation will be counterproductive to addiction and other psychiatric treatment. Recent studies of smoking cessation in people with alcohol dependence suggest that this is not the case, but systematic research in this area of medicine and public health is relatively recent leaving many questions unanswered (Ziedonis, 2007). Furthermore, tobacco dependence treatment in such populations has not been addressed in labeling of currently approved pharmacotherapeutics (e.g., Asher et al., 2003; Ziedonis, 2007). Nonetheless, progress has been made in advancing treatment of tobacco dependence and withdrawal in psychiatric populations (e.g., American Psychiatric Association, 1994; Ziedonis et al., 1994; Ziedonis & Williams, 2003; Lemon et al., 2003; Williams & Ziedonis, 2004; Montoya et al., 2005; Hughes & Kalman, 2006). One possible impediment to the use of some medications in psychiatric populations are early indications that two medications, varenicline and bupropion, may themselves promote the psychiatric symptoms of suicidal ideation (Food and Drug Administration, 2009).

8.6. Treatment development for users of tobacco products other than cigarettes

At present, there is no product approved for treatment of dependence and withdrawal resulting from use of tobacco products other than cigarettes. This may not be surprising, given that cigarette smoking is the most prevalent and harmful form of tobacco use in most countries. However, as the prevalence of other conventional products, and potentially new products emerges, so too will the pressures from public health organizations to provide treatment.

Treatment development for other forms of tobacco used carries a variety of challenges. For example, the patterns of use of other products are more variable and less well-understood. It is well established that virtually any widely marketed cigarette is capable of readily delivering from approximately 1–3 mg of nicotine and that cigarette per day and time to the first cigarette smoked upon waking provide reasonable proxy measures of dosing needs for nicotine delivering medications. In contrast, cigars are known to contain anywhere from approximately 10 to over 200 mg of nicotine; smokeless tobacco products from less than 1 mg per typical unit dose (e.g., pouch or “pinch”) to more than 10 mg of readily absorbable nicotine. Nicotine content data and patterns of use of bidis and kreteks have not been extensively studied (Malson et al., 2001. Waterpipe smokers can also obtain very high levels of nicotine but appear to display very different patterns of use (WHO, 2006). Taken together, this means that one of the core elements of treatment development, determination of dosing needs for the purpose of clinical trials and labeling, does not have a strong scientific foundation. An economic barrier to development of such indications is the fact that the population using forms of tobacco other than smoking is relatively small, reducing the potential sales of a product, and thus possibly creating an unfavorable climate for investing in such clinical development. Developing dosing algorithms and adapting treatment approaches to forms of tobacco dependence other than cigarette smoking is of great and increasing public health importance.

9. Discussion

Pharmacotherapy for smoking cessation is important in medicine, public health and research and development. There are few areas of public health and disease control in which pharmacotherapy has such enormous potential to contribute, or is as broadly recognized as needed by medical societies, governmental reports, and an international treaty. Tobacco-caused morbidity and mortality is epidemic accounting for nearly one in five deaths in the United States and one in ten globally (Mokdad et al., 2004; WHO, 2008b) and is broadly recognized as a national and global public health disaster (Boyle et al., 2004; Koop, 2004; Leischow, 2009). Furthermore, the scale of the epidemic is rapidly increasing globally and can be reversed in coming decades only by greatly increased smoking cessation. Reversal of the tobacco epidemic in the United States and globally could be facilitated by greater access to and utilization of existing treatments and new pharmacotherapy.

These conclusions are supported by major reports from national and international organizations (World Bank, 1999; US DHHS, 2000; Royal College of Physicians, 2000; Fiore et al., 2000; World Health Organization, 2004; Fiore et al., 2008) and the international tobacco treaty — the World Health Organization Framework Convention on Tobacco Control (2007, 2008a). Although the United States has not yet ratified the treaty, the U.S. is a signatory to the treaty implying that ratification may be forthcoming. Article 14 of the treaty requires parties to the treaty to make comprehensive treatment, including medicines, widely available (WHO, 2008a). This will be an ongoing process occurring over decades but already, many nations are responding by making pharmaceutical and other forms of treatment more widely available, especially to low income populations.

Recognition that tobacco use is driven by the neurobiological diseases of dependence and withdrawal provides a rational basis for treatment development and also supports the inclusion of pharmacotherapy for dependence and withdrawal along with pharmacotherapy for other medical disorders. In fact, the need to prevent public health and economic devastation caused by tobacco use supports treatment as a high priority in health care. Pharmacotherapy for tobacco dependence is also cost effective when compared to many widely supported forms of pharmacotherapy for diseases such as hypertension, hypercholesterolemia, as well as preventive periodic screening such as mammography or Papanicolaou smears (Oster et al., 1986; Fiscella & Franks, 1996; Fiore et al., 2000; Song et al., 2002, Woolacott et al., 2002; Cornuz et al., 2003; Gilbert et al., 2004; Fiore et al., 2008). Furthermore, costly diseases with very poor prognoses such as lung cancer and emphysema could be prevented by tobacco dependence treatment.

The economic incentives for treatment development are also increasing, although the economic picture is complex. For example, the tobacco market is near 100 billion dollars in the United States and probably in excess of one half trillion world wide, with much of this in the form of daily and weekly cash outlays by tobacco users for products that many would like to cease using. In contrast, the market for evidence-based pharmaceutical treatment in the United States was little more than 1 billion at the turn of the century and less than 3 billion globally. Whereas the economic market is far from commensurate with the scope of the public health needs, it has continued a steady growth over the past two decades and growth appears likely to further increase along with increasing documentation of the benefits of treatment and treatment provision by health care systems. On current course, the global market for prescription tobacco dependence treatments is projected to increase from approximately 1 billion U.S. dollars to more than 4 billion within the next decade (Report Buyer, 2007) and this is on top of the market for approved nonprescription products such as nicotine gum, lozenge, and patch, which have a current market of approximately one billion dollars in the U.S. and more than 1 billion outside of the U.S., with steady growth projected.

Despite the vagaries and uncertainties of the economic market potential, the science base in this area is strong and the opportunity to serve public health through pharmaceutical development is enormous. It was not until the 1980s that tobacco dependence and withdrawal were determined to be diseases. At that time hypotheses were emerging about the potential role of central nicotinic receptors; animal models for dependence (e.g., self-administration) and withdrawal were being developed and validated; and brain imaging studies to better understand the neurobiology of tobacco dependence were just getting underway. Today, there are well-validated animal and human models for various aspects of dependence and withdrawal, a broad range of neuroimaging techniques that can be applied, advances in the study of the molecular genetics of nicotine actions at various receptors and receptor subtypes, and a variety of pharmacological tools to employ in pharmaceutical development and screening (e.g., Lerman et al., 2007). It is truly conceivable that on the back of this knowledge science and medicine may find a path to the goal of former Surgeon General C. Everett Koop: to have the end of the 21st century be like the end of the 19th century, when lung cancer was rare and tobacco disease was hardly known (Koop, 2003).

References

Abrams, DB.; Niaura, R.; Brown, RA.; Emmons, KM.; Goldstein, MG.; Monti, PM. The Tobacco Dependence Treatment Handbook: a Guide to Best Practices. New York: The Guilford Press; 2003.

Alberg AJ, Patnaik JL, May JW, Hoffman SC, Gitchell J, Comstock GW, et al. Nicotine replacement therapy use among a cohort of smokers. J Addict Dis. 2005; 24:101–113. [PubMed: 15774414]

American Legacy Foundation. Youth tobacco cessation: Results from the 2000 National Youth Tobacco survey. Washington, DC: American Legacy Foundation; 2003.

American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 3. Washington, DC: American Psychiatric Association; 1980.

American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 3. Washington, DC: American Psychiatric Association; 1987. Revised

American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 4. Washington, DC: American Psychiatric Association; 1994.

American Psychiatric Association. Diagnostic and statistical manual — IVTR. Washington, D.C: American Psychiatric Association; 2000.

Asher MK, Martin RA, Rohsenow DJ, MacKinnon SV, Traficante R, Monti PM. Perceived barriers to quitting smoking among alcohol dependent patients in treatment. J Subst Abuse Treat. 2003; 24:169–174. [PubMed: 12745034]

Balster RL, Bigelow GE. Guidelines and methodological reviews concerning drug abuse liability assessment. Drug Alcohol Depend. 2003; 70:S13–S40. [PubMed: 12759195]

Barnoya J, Glantz S. Association of the California tobacco control program with declines in lung cancer incidence. Cancer Causes Control. 2004; 15:689–695. [PubMed: 15280627]

Benhammou K, Lee M, Strook M, Sullivan B, Logel J, Raschen K, et al. [(3)H]Nicotine binding in peripheral blood cells of smokers is correlated with the number of cigarettes smoked per day. Neuropharmacology. 2000; 39:2818–2829. [PubMed: 11044752]

Bennett D, Burton AW, Fishman S, Fortner B, McCarberg B, Miaskowski C, et al. Consensus panel recommendations for the assessment and management of breakthrough pain part 1: assessment. Pharmacol Ther. 2005a; 30:296–301.

Bennett D, Burton AW, Fishman S, Fortner B, McCarberg B, Miaskowski C, et al. Consensus panel recommendations for the assessment and management of breakthrough pain part 2: management. Pharmacol Ther. 2005b; 30:354–361.

Benowitz, NL. Cardiovascular toxicity of nicotine: pharmacokinetic and pharmacodynamic considerations. In: Benowitz, NL., editor. Nicotine safety and toxicity. New York: Oxford University Press; 1998. p. 19-27.

Benowitz N, Dempsey D. Pharmacotherapy for smoking cessation during pregnancy. Nicotine Tob Res. 2004; 6(Suppl 2):S189–S202. [PubMed: 15203821]

Benwell ME, Balfour DJ, Anderson JM. Evidence that tobacco smoking increases the density of (−)-[3H]nicotine binding sites in human brain. J Neurochem. 1988; 50:1243–1247. [PubMed: 3346676]

Bonnie, RJ.; Stratton, K.; Wallace, RB., editors. Institute of Medicine of the National Academies. Washington DC: The National Academies Press; 2007. Ending the tobacco problem: A blue print for the nation.

Boyle, P.; Gray, N.; Henningfield, JE.; Seffrin, J.; Zatonski, W. Tobacco and Public Health: Science and Policy. Oxford, UK: Oxford University Press; 2004.

Breese CR, Marks MJ, Logel J, Adams CE, Sullivan B, Collins AC, et al. Effect of smoking history on [3H]nicotine binding in human postmortem brain. J Pharmacol Exp Ther. 1997; 282:7–13. [PubMed: 9223534]

Brown S, Inskip H, Barraclough B. Causes of the excess mortality of schizophrenia. Br J Psychiatry. 2000; 177:212–217. [PubMed: 11040880]

Buchhalter, AR.; Fant, RV.; Henningfield, JE. Nicotine. In: Sibley, DR.; Hanin, I.; Kuhar, M.; Skolnick, P., editors. Handbook of contemporary neuropharmacology. John Wiley & Sons, Inc; 2007. p. 535-566.

Buchhalter AR, Fant RV, Henningfield JE. Novel pharmacological approaches for treating tobacco dependence and withdrawal: current status. Drugs. 2008; 68:1067–1088. [PubMed: 18484799]

Buisson B, Bertrand D. Chronic exposure to nicotine upregulates the human (alpha)4(beta)2 nicotinic acetylcholine receptor function. J Neurosci. 2001; 21:1819–1829. [PubMed: 11245666]

Centers for Disease Control. Nicotine addiction: a report of the Surgeon General. The Health Consequences of Smoking. 1988:241–375.

Centers for Disease Control and Prevention. Ten great public health achievements — United States, 1900–1999. MMWR: Morb Mort Wkly Rep. 1999; 48:241–243.

Centers for Disease Control and Prevention. Annual smoking-attributable mortality, years of potential life lost, and economic costs — United States, 1995–1999. MMWR: Morb Mort Wkly Rep. 2002; 51:300–303.

Cheeta S, Tucci S, File SE. Antagonism of the anxiolytic effect of nicotine in the dorsal raphe nucleus by dihydro-beta-erythroidine. Pharmacol Biochem Behav. 2001; 70:491–496. [PubMed: 11796148]

Clayton RR, Ries MK, Abrams DB. Introduction to tobacco, nicotine, and youth: the tobacco etiology research network. Drug Alcohol Depend. 2000; 59(Suppl 1):S1–S4. [PubMed: 10773433]

Cnattingius S. The epidemiology of smoking during pregnancy: smoking prevalence, maternal characteristics, and pregnancy outcomes. Nicotine Tob Res. 2004; 6(Suppl 2):S125–S140. [PubMed: 15203816]

Colby SM, Tiffany ST, Shiffman S, Niaura RS. Are adolescent smokers dependent on nicotine? A review of the evidence. Drug Alcohol Depend. 2000a; 59(Suppl 1):S83–S95. [PubMed: 10773439]

Colby SM, Tiffany ST, Shiffman S, Niaura RS. Measuring nicotine dependence among youth: a review of available approaches and instruments. Drug Alcohol Depend. 2000b; 59(Suppl 1):S23–S39. [PubMed: 10773436]

Cone, EJ.; Fant, RV.; Henningfield, JE. Nicotine and tobacco. In: Mozayani, A.; Raymon, LP., editors. Handbook of drug interactions: a clinical and forensic guide. Totowa, New Jersey: Humana Press; 2004. p. 463-492.

Cornuz J, Pinget C, Gilbert A, Paccaud F. Cost-effectiveness analysis of the first-line therapies for nicotine dependence. Eur J Clin Pharmacol. 2003; 59:201–206. [PubMed: 12759795]

Curkendall SM, Mo J, Glasser DB, Rose SM, Jones JK. Cardiovascular disease in patients with schizophrenia in Saskatchewan, Canada. J Clin Psychiatry. 2004; 65:715–720. [PubMed: 15163261]

Dalack GW, Meador-Woodruff JH. Acute feasibility and safety of a smoking reduction strategy for smokers with schizophrenia. Nicotine Tob Res. 1999; 1:53–57. [PubMed: 11072388]

Dasgupta P, Kinkade R, Joshi B, Decook C, Haura E, Chellappan S. Nicotine inhibits apoptosis induced by chemotherapeutic drugs by up-regulating XIAP and surviving. Proc Natl Acad Sci U S A. 2006; 103:6332–6337. [PubMed: 16601104]

DeNoble VJ, Mele PC. Intravenous nicotine self-administration in rats: effects of mecamylamine, hexamethonium and naloxone. Psychopharmacology (Berlin). 2006; 184:266–272. [PubMed: 16088413]

Ershoff D, Ashford TH, Goldenberg R. Helping pregnant women quit smoking: an overview. Nicotine Tob Res. 2004; 6(Suppl 2):S101–S105. [PubMed: 15203814]

Etter JF. Cytisine for smoking cessation: a literature review and a meta-analysis. Arch Int Med. 2006; 166:1553–1559. [PubMed: 16908787]

Fagerstrom KO. Can reduced smoking be a way for smokers not interested in quitting to actually quit? Respiration. 2005; 72:216–220. [PubMed: 15824536]

Fant, RV.; Buchhalter, AR.; Henningfield, JE. Pharmacotherapy for tobacco dependence. In: Henningfield, JE.; London, ED.; Pogun, S., editors. Nicotine Psychopharmacology. Berlin Heidelberg: Springer-Verlag; 2009. p. 488-510.

Ferguson SG, Shiffman S, Gwaltney CJ. Does reducing withdrawal severity mediate nicotine patch efficacy? A randomized clinical trial. J Consult Clin Psychol. 2006; 74:1153–1161. [PubMed: 17154744]

Fiore, MC.; Bailey, WC.; Cohen, SJ.; Dorfman, SF.; Goldstein, MG.; Gritz, ER., et al. Clinical practice guideline. Rockville, MD: U.S. Department of Health and Human Services. Public Health Service; 2000. Treating tobacco use and dependence.

Fiore, MC.; Bailey, WC.; Cohen, SJ.; Dorfman, SF.; Goldstein, MG.; Gritz, ER., et al. Clinical practice guideline. Rockville, MD: U.S. Department of Health and Human Services. Public Health Service; 2008. Treating tobacco use and dependence.

Fiore, MC.; Shi, FY.; Heishman, S.; Henningfield, JE. The effect of smoking and smoking withdrawal on flight performance: a 1994 update to Centers for Disease Control and Prevention National Center for Chronic Disease Prevention and Health Promotion Office on Smoking and Health (Rep No 9386129). 1994.

Fiscella K, Franks P. Cost-effectiveness of the transdermal nicotine patch as an adjunct to physicians' smoking cessation counseling. JAMA: J Am Med Assoc. 1996; 275:1247–1251.

Flay BR, Clayton RR. Contexts and adolescent tobacco use trajectories. Addiction. 2003; 98:iii–iv. [PubMed: 14984236]

Flores CM, Davila-Garcia MI, Ulrich YM, Kellar KJ. Differential regulation of neuronal nicotinic receptor binding sites following chronic nicotine administration. J Neurochem. 1997; 69:2216–2219. [PubMed: 9349569]

Food and Drug Administration. Regulations restricting the sale and distribution of cigarettes and smokeless tobacco products to protect children and adolescents; proposed rule analysis regarding FDA's jurisdiction over nicotine-containing cigarettes and smokeless tobacco products; notice. Fed Regist. 1995; 60:41314–41792.

Food and Drug Administration. Regulations restricting the sale and distribution of cigarettes and smokeless tobacco to protect children and adolescents; final rule. Fed Regist. 1996; 61:44396–45318.

Food and Drug Administration. The smoking cessation aids varenicline (marketed as Chantix) and bupropion (marketed as Zyban and generics): suicidal ideation and behavior. FDA Saf Newslett. 2009; 2(1):1–4.

George TP, O'Malley SS. Current pharmacological treatments for nicotine dependence. Trends Pharmacol Sci. 2004; 25:42–48. [PubMed: 14723978]

Gilbert AR, Pinget C, Bovet P, Cornuz J, Shamlaye C, Paccaud F. The cost effectiveness of pharmacological smoking cessation therapies in developing countries: a case study in the Seychelles. Tob Control. 2004; 13:190–195. [PubMed: 15175539]

Giovino GA, Henningfield JE, Tomar SL, Escobedo LG, Slade J. Epidemiology of tobacco use and dependence. Epidemiol Rev. 1995; 17:48–65. [PubMed: 8521946]

Gray, N. Global tobacco control policy. In: Boyle, P.; Gray, N.; Henningfield, JE.; Seffrin, J.; Zatonski, W., editors. Tobacco and public health: Science and policy. Oxford, UK: Oxford University Press; 2004. p. 659-668.

Gritz ER, Dresler C, Sarna L. Smoking, the missing drug interaction in clinical trials: ignoring the obvious. Cancer Epidemiol Biomark Prev. 2005; 14:2287–2293.

Gritz ER, Fingeret MC, Vidrine DJ, Lazev AB, Mehta NV, Reece GP. Successes and failures of the teachable moment: smoking cessation in cancer patients. Cancer. 2006; 106:17–27. [PubMed: 16311986]

Gritz, ER.; Fiore, MC.; Henningfield, JE. Smoking and cancer. In: Murphy, GP.; Lawrence, W.; Lenhard, RE., editors. American Cancer Society textbook of clinical oncology. 2. Atlanta: American Cancer Society; 1995. p. 146-163.

Gritz, ER.; Lam, CY.; Vidrine, DJ.; Fingeret, MC. Cancer prevention: tobacco dependence and its treatment. In: Devita, V.; Lawrence, T.; Rosenberg, S., editors. Cancer: principles and practice of Oncology. 8. 2008.

Gritz ER, Vidrine DJ, Fingeret MC. Smoking cessation a critical component of medical management in chronic disease populations. Am J Prev Med. 2007; 33:S414–S422. [PubMed: 18021917]

Harris, G. FDA requiring suicide studies in drug trials. 2008. Retrieved January 22, 2009, from: http://www.nytimes.com/2008/01/24/washington/24fda.html

Haviland L, Thornton AH, Carothers S, Hund L, Allen JA, Kastens B, et al. Giving infants a great start: launching a national smoking cessation program for pregnant women. Nicotine Tob Res. 2004; 6(Suppl 2):S181–S188. [PubMed: 15203820]

Heishman SJ, Taylor RC, Henningfield JE. Nicotine and smoking: A review of effects on human performance. Experimental & Clinical Psychopharmacology. 1994; 2(4):345–395.

Henningfield, JE.; Benowitz, NL. Pharmacology and nicotine addiction. In: Boyle, P.; Gray, N.; Henningfield, JE.; Seffrin, J.; Zatonski, W., editors. Tobacco and public health: science and policy. Oxford: Oxford University Press; 2004. p. 129-147.

Henningfield JE, Benowitz NL, Ahijevych K, Garrett BE, Connolly GN, Wayne GF. Does menthol enhance the addictiveness of cigarettes? An agenda for research. Nicotine Tob Res. 2003a; 5:9–11. [PubMed: 12745502]

Henningfield JE, Benowitz NL, Connolly GN, Davis RM, Gray N, Myers ML, et al. Reducing tobacco addiction through tobacco product regulation. Tob Control. 2004; 13:132–135. [PubMed: 15175528]

Henningfield JE, Fant RV, Buchhalter AR, Stitzer ML. Pharmacotherapy for nicotine dependence. CA: Can J Clin. 2005; 55:281–299.

Henningfield JE, Michaelides T, Sussman S. Developing treatment for tobacco addicted youth — Issues and challenges. J Child Adolesc Subst Abuse. 2000; 9:5–26.

Henningfield JE, Moolchan ET, Zeller M. Regulatory strategies to reduce tobacco addiction in youth. Tob Control. 2003b; 12(Suppl 1):I14–I24. [PubMed: 12773782]

Henningfield JE, Slade J. Tobacco-dependence medications: public health and regulatory issues. Food Drug Law J. 1998; 53(suppl):75–114. [PubMed: 10342981]

Hughes JR. Reduced smoking: an introduction and review of the evidence. Addiction. 2000; 95(Suppl 1):S3–S7. [PubMed: 10723815]

Hughes JR. Effects of abstinence from tobacco: etiology, animal models, epidemiology, and significance: a subjective review. Nicotine Tob Res. 2007a; 9:329–339. [PubMed: 17365765]

Hughes JR. Effects of abstinence from tobacco: valid symptoms and time course. Nicotine Tob Res. 2007b; 9:315–327. [PubMed: 17365764]

Hughes JR. Measurement of the effects of abstinence from tobacco: a qualitative review. Psychol Addict Behav. 2007c; 21:127–137. [PubMed: 17563132]

Hughes JR, Carpenter MJ. Does smoking reduction increase future cessation and decrease disease risk? A qualitative review. Nicotine Tob Res. 2006a; 8:739–749. [PubMed: 17132521]

Hughes JR, Kalman D. Do smokers with alcohol problems have more difficulty quitting? Drug Alcohol Depend. 2006b; 82:91–102. [PubMed: 16188401]

Hughes JR, Shiffman S, Callas P, Zhang J. A meta-analysis of the efficacy of over-the-counter nicotine replacement. Tob Control. 2003; 12:21–27. [PubMed: 12612357]

Hurt RD. Pharmacotherapy for alcoholic smokers. Alcoholism: Clin Exp Res. 2002; 26:1939–1941.

Hurt RD, Offord KP, Croghan IT, Gomez-Dahl L, Kottke TE, Morse RM, et al. Mortality following inpatient addictions treatment. Role of tobacco use in a community-based cohort. JAMA: J Am Med Assoc. 1996; 275:1097–1103.

International Agency for Research on Cancer. IARC monographs on the evaluation of carcinogenic risks to humans. Vol. 89. Lyon, France: World Health Organization; 2007. Smokeless tobacco and some tobacco-specific N-Nitrosamines.

Jacobson, PD.; Lantz, PM.; Warner, KE.; Wasserman, J.; Pollack, HA.; Ahlstrom, AK. Combating teen smoking. Ann Arbor: The University of Michigan Press; 2001.

Jarvik ME, Henningfield JE. Pharmacological treatment of tobacco dependence. Pharmacol Biochem Behav. 1988; 30:279–294. [PubMed: 3051049]

Jorenby DE, Leischow SJ, Nides MA, Rennard SI, Johnston JA, Hughes AR, et al. A controlled trial of sustained-release bupropion, a nicotine patch, or both for smoking cessation. New Engl J Med. 1999; 340:685–691. [PubMed: 10053177]

Joseph AM, Norman SM, Ferry LH, Prochazka AV, Westman EC, Steele BG, et al. The safety of transdermal nicotine as an aid to smoking cessation in patients with cardiac disease. New Engl J Med. 1996; 335:1792–1798. [PubMed: 8943160]

Joukamaa M, Heliovaara M, Knekt P, Aromaa A, Raitasalo R, Lehtinen V. Mental disorders and cause-specific mortality. Br J Psychiatry. 2001; 179:498–502. [PubMed: 11731351]

Kimmel SE, Berlin JA, Miles C, Jaskowiak J, Carson JL, Strom BL. Risk of acute first myocardial infarction and use of nicotine patches in a general population. J Am Coll Cardiol. 2001; 37:1297–1302. [PubMed: 11300438]

Koob GF, Le Moal M. Plasticity of reward neurocircuitry and the 'dark side' of drug addiction. Nat Neurosci. 2005; 8:1442–1444. [PubMed: 16251985]

Koob, GF.; Le Moal, M. Neurobiology of addiction. Amsterdam, NL: Elsevier; 2006.

Koop CE. Tobacco addiction: Accomplishments and challenges in science, health, and policy. Nicotine & Tobacco Research. 2003; 5:613–619. [PubMed: 14577977]

Koop, EC. Tobacco: the public health disaster of the twentieth century. In: Boyle, P.; Gray, N.; Henningfield, JE.; Seffrin, J.; Zatonski, W., editors. Tobacco and public health: science and policy. Oxford, UK: Oxford University Press; 2004. p. v-xvii.

Krishnan-Sarin S, Meandzija B, O'Malley S. Naltrexone and nicotine patch smoking cessation: a preliminary study. Nicotine Tob Res. 2003; 5:851–857. [PubMed: 14750508]

Lamb RJ, Preston KL, Schindler CW, Meisch RA, Davis F, Katz JL, et al. The reinforcing and subjective effects of morphine in post-addicts: a dose–response study. J Pharmacol Exp Ther. 1991; 259:1165–1173. [PubMed: 1762068]

Lanza ST, Donny EC, Collins LM, Balster RL. Analyzing the acquisition of drug self-administration using growth curve models. Drug Alcohol Depend. 2004; 75:11–21. [PubMed: 15225885]

Lasser K, Boyd JW, Woolhandler S, Himmelstein DU, McCormick D, Bor DH. Smoking and mental illness: A population-based prevalence study. JAMA: J Am Med Assoc. 2000; 284:2606–2610.

Leischow SJ. JAMA: J Am Med Assoc. 2009; 301:1058–1060.

Lemon SC, Friedmann PD, Stein MD. The impact of smoking cessation on drug abuse treatment outcome. Addict Behav. 2003; 28:1323–1331. [PubMed: 12915172]

Leonard S, Bertrand D. Neuronal nicotinic receptors: from structure to function. Nicotine Tob Res. 2001a; 3:203–223. [PubMed: 11506765]

Leonard S, Bertrand D. Neuronal nicotinic receptors: from structure to function. Nicotine Tob Res. 2001b; 3:203–223. [PubMed: 11506765]

Lerman C, LeSage MG, Perkins KA, O'Malley SS, Siegel SJ, Benowitz NL, et al. Translational research in medication development for nicotine dependence. Nat Rev Drug Discov. 2007; 6:746–762. [PubMed: 17690709]

Lewin, L. Phantastica: a classic survey on the use and abuse of mind-altering plants. Rochester, VT: Park Street Press; 1998.

Lynch, BS.; Bonnie, RJ. Toward a youth-centered prevention policy. In: Lynch, BS.; Bonnie, RJ., editors. Growing up tobacco free: preventing nicotine addiction in children and youths. Washington, DC: National Academy Press; 1994. p. 3-25.

Malson JL, Sims K, Murty R, Pickworth WB. Comparison of the nicotine content of tobacco used in bidis and conventional cigarettes. Tob Control. 2001; 10:181–183. [PubMed: 11387541]

Mansvelder HD, Keath JR, McGehee DS. Synaptic mechanisms underlie nicotine-induced excitability of brain reward areas. Neuron. 2002; 33:905–919. [PubMed: 11906697]

Mansvelder HD, McGehee DS. Long-term potentiation of excitatory inputs to brain reward areas by nicotine. Neuron. 2000; 27:349–357. [PubMed: 10985354]

Markou A, Paterson NE. The nicotinic antagonist methyllycaconitine has differential effects on nicotine self-administration and nicotine withdrawal in the rat. Nicotine Tob Res. 2001; 3:361–373. [PubMed: 11694204]

Marks MJ, Pauly JR, Gross SD, Deneris ES, Hermans-Borgmeyer I, Heinemann SF, et al. Nicotine binding and nicotinic receptor subunit RNA after chronic nicotine treatment. J Neurosci. 1992; 12:2765–2784. [PubMed: 1613557]

Mayhew KP, Flay BR, Mott JA. Stages in the development of adolescent smoking. Drug Alcohol Depend. 2000; 59(Suppl 1):S61–S81. [PubMed: 10773438]

McRobbie H, Hajek P. Nicotine replacement therapy in patients with cardiovascular disease: guidelines for health professionals. Addiction. 2001; 96:1547–1551. [PubMed: 11784452]

Miettinen OS. The need for randomization in the study of intended effects. Stat Med. 1983; 2:267–271. [PubMed: 6648141]

Mihalak KB, Carroll FI, Luetje CW. Varenicline is a partial agonist at alpha4beta2 and a full agonist at alpha7 neuronal nicotinic receptors. Mol Pharmacol. 2006; 70:801–805. [PubMed: 16766716]

Mokdad AH, Mark JS, Stroup DF, Gerberding JL. Actual causes of death in the United States, 2000. JAMA: J Am Med Assoc. 2004; 291:1238–1245.

Montoya ID, Herbeck DM, Svikis DS, Pincus HA. Identification and treatment of patients with nicotine problems in routine clinical psychiatry practice. Am J Addict. 2005; 14:441–454. [PubMed: 16257881]

Moolchan ET, Ernst M, Henningfield JE. A review of tobacco smoking in adolescents: treatment implications. J Am Acad Child Adolesc Psych. 2000; 39:682–693.

Niaura R, Sayette M, Shiffman S, Glover ED, Nides M, Shelanski M, et al. Comparative efficacy of rapid-release nicotine gum versus nicotine polacrilex gum in relieving smoking cue-provoked craving. Addiction. 2005; 100:1720–1730. [PubMed: 16277632]

Nisell M, Nomikos GG, Svensson TH. Nicotine dependence, midbrain dopamine systems and psychiatric disorders. Pharm Toxicol. 1995; 76:157–162.

Orleans T, Melvin C, Marx J, Maibach E, Vose KK. National action plan to reduce smoking during pregnancy: the National Partnership to Help Pregnant Smokers Quit. Nicotine Tob Res. 2004; 6(Suppl 2):S269–S277. [PubMed: 15203827]

Oster G, Huse DM, Delea TE, Colditz GA. Cost-effectiveness of nicotine gum as an adjunct to physician's advice against cigarette smoking. JAMA: J Am Med Assoc. 1986; 256:1315–1318.

Perry DC, Davila-Garcia MI, Stockmeier CA, Kellar KJ. Increased nicotinic receptors in brains from smokers: membrane binding and autoradiography studies. J Pharmacol Exp Ther. 1999; 289:1545–1552. [PubMed: 10336551]

Picciotto MR, Zoli M, Rimondini R, Lena C, Marubio LM, Pich EM, et al. Acetylcholine receptors containing the beta2 subunit are involved in the reinforcing properties of nicotine. Nature. 1998a; 391:173–177. [PubMed: 9428762]

Picciotto MR, Zoli M, Rimondini R, Lena C, Marubio LM, Pich EM, et al. Acetylcholine receptors containing the beta2 subunit are involved in the reinforcing properties of nicotine. Nature. 1998b; 391:173–177. [PubMed: 9428762]

Pierce JP, Gilpin EA. Impact of over-the-counter sales on effectiveness of pharmaceutical aids for smoking cessation. JAMA: J Am Med Assoc. 2002; 288:1260–1264.

Pierce JP, Gilpin E, Farkas AJ. Nicotine patch use in the general population: results from the 1993 California Tobacco Survey. J Natl Cancer Inst. 1995; 87:87–93. [PubMed: 7707395]

Rabinoff M, Caskey N, Rissling A, Park C. Pharmacological and chemical effects of cigarette additives. Am J Public Health. 2007; 97:1981–1991. [PubMed: 17666709]

Report Buyer. Pipeline insight: substance dependence — part I: nicotine. 2007. Retrieved February 9, 2009, from: http://www.reportbuyer.com/pharma_health-care/company_reports_pharmaceutical_/pipeline_insight_substance_dependence_part_i_nicotine.html

Robbins J, Aragaki AK, Kooperberg C, Watts N, Wactawski-Wende J, Jackson RD, et al. Factors associated with 5-year risk of hip fracture in postmenopausal women. JAMA: J Am Med Assoc. 2007; 298:2389–2398.

Robert Wood Johnson Foundation. Tobacco Control Policy. San Francisco: John Wiley & Sons, Inc; 2007.

Rose JE. Nicotine and nonnicotine factors in cigarette addiction. Psychopharmacology (Berlin). 2006; 184:274–285. [PubMed: 16362402]

Rose JE, Hickman CS. Citric acid aerosol as a potential smoking cessation aid. Chest. 1987; 92:1005–1008. [PubMed: 3677804]

Rossetti ZL, Melis F, Carboni S, Diana M, Gessa GL. Alcohol withdrawal in rats is associated with a marked fall in extraneuronal dopamine. Alcoholism: Clin Exp Res. 1992; 16:529–532.

Rowell PP, Wonnacott S. Evidence for functional activity of up-regulated nicotine binding sites in rat striatal synaptosomes. J Neurochem. 1990; 55:2105–2110. [PubMed: 2230812]

Royal College of Physicians. Nicotine addiction in Britain: A Report of the Tobacco Advisory Group of the Royal College of Physicians. London, UK: Royal College of Physicians of London; 2000.

Royal College of Physicians. Harm reduction in nicotine addiction: Helping people who can't quit. London, UK: Royal College of Physicians of London; 2007.

Sanderson EM, Drasdo AL, McCrea K, Wonnacott S. Upregulation of nicotinic receptors following continuous infusion of nicotine is brain-region-specific. Brain Res. 1993; 617:349–352. [PubMed: 8402163]

Sarnyai Z, Shaham Y, Heinrichs SC. The role of corticotropin-releasing factor in drug addiction. Pharmacol Rev. 2001; 53:209–243. [PubMed: 11356984]

Schilstrom B, Nomikos GG, Nisell M, Hertel P, Svensson TH. N-methyl-D-aspartate receptor antagonism in the ventral tegmental area diminishes the systemic nicotine-induced dopamine release in the nucleus accumbens. Neuroscience. 1998a; 82:781–789. [PubMed: 9483535]

Schilstrom B, Svensson HM, Svensson TH, Nomikos GG. Nicotine and food induced dopamine release in the nucleus accumbens of the rat: putative role of alpha7 nicotinic receptors in the ventral tegmental area. Neuroscience. 1998b; 85:1005–1009. [PubMed: 9681941]

Schuster CR, Henningfield J. Conference on abuse liability assessment of CNS drugs. Drug Alcohol Depend. 2003; 70:S1–S4. [PubMed: 12759193]

Shadel WG, Shiffman S, Niaura R, Nichter M, Abrams DB. Current models of nicotine dependence: what is known and what is needed to advance understanding of tobacco etiology among youth. Drug Alcohol Depend. 2000; 59(Suppl 1):S9–S22. [PubMed: 10773435]

Sharples CG, Kaiser S, Soliakov L, Marks MJ, Collins AC, Washburn M, et al. UB-165: a novel nicotinic agonist with subtype selectivity implicates the alpha4beta23 subtype in the modulation of dopamine release from rat striatal synaptosomes. J Neurosci. 2000; 20:2783–2791. [PubMed: 10751429]

Shiffman S, Brockwell SE, Pillitteri JL, Gitchell JG. Smoking cessation attempts and use of smoking cessation treatments in the United States. Am J Prev Med. 2008a; 34:102–111. [PubMed: 18201639]

Shiffman S, Brockwell SE, Pillitteri JL, Gitchell JG. Individual differences in adoption of treatment for smoking cessation: demographic and smoking history characteristics. Drug Alcohol Depend. 2008b; 93:121–131. [PubMed: 17996399]

Shiffman S, Di Marino ME, Sweeney CT. Characteristics of selectors of nicotine replacement therapy. Tob Control. 2005; 14:346–355. [PubMed: 16183986]

Shiffman S, Engberg J, Paty JA, Perz W, Gnys M, Kassel JD, et al. A day at a time: Predicting smoking lapse from daily urge. J Abnorm Psychology. 1997; 106:104–116.

Shiffman S, Ferguson SG. Nicotine patch therapy prior to quitting: A meta-analysis. Addiction. 2008; 103:557–563. [PubMed: 18339101]

Shiffman S, Gwaltney CJ, Balabanis MH, Liu KS, Paty JA, Kassel JD, et al. Immediate antecedents of cigarette smoking: an analysis from ecological momentary assessment. J Abnorm Psychology. 2002; 111:531–545.

Shiffman S, Hughes JR, Di Marino ME, Sweeney CT. Patterns of over-the-counter nicotine gum use: persistent use and concurrent smoking. Addiction. 2003a; 98:1747–1753. [PubMed: 14651507]

Shiffman S, Hughes JR, Pillitteri JL, Burton SL. Persistent use of nicotine replacement therapy: an analysis of actual purchase patterns in a population based sample. Tob Control. 2003b; 12:310–316. [PubMed: 12958394]

Shiffman S, Mason KM, Henningfield JE. Tobacco dependence treatments: review and prospectus. Annu Rev Public Health. 1998; 19:335–358. [PubMed: 9611623]

Silagy C, Lancaster T, Stead L, Mant D, Fowler G. Nicotine replacement therapy for smoking cessation. Cochrane Database Syst Rev. 2004; 2004:CD000146. [PubMed: 15266423]

Simon JA, Duncan C, Carmody TP, Hudes ES. Bupropion for smoking cessation: a randomized trial. Arch Int Med. 2004; 164:1797–1803. [PubMed: 15364675]

Slade J. Adolescent nicotine use and dependence. Adolesc Med. 2004; 4:305–320. [PubMed: 10356217]

Slade J. Adolescent nicotine use and dependence. Adolescent Medicine. 1993; 4(2):305–320. [PubMed: 10356217]

Slade, J.; Bickel, WK.; Crowley, TJ.; Ferrence, R.; Henningfield, JE.; Houston, TP., et al. The role of managing nicotine in controlling the tobacco epidemic. In: Ferrence, R.; Slade, J.; Room, R.; Pope, M., editors. Nicotine and public health. Washington, D.C: American Public Health Association; 2000. p. 483-501.

Slade J, Henningfield JE. Tobacco product regulation: context and issues. Food Drug Law J. 1998; 53(suppl):43–74. [PubMed: 10342980]

Song F, Raftery J, Aveyard P, Hyde C, Barton P, Woolacott N. Cost-effectiveness of pharmacological interventions for smoking cessation: a literature review and a decision analytic analysis. Med Decis Mak. 2002; 22:S26–S37.

Spillane J, McAllister WB. Keeping the lid on: a century of drug regulation and control. Drug Alcohol Depend. 2003; 70:S5–12. [PubMed: 12759194]

Stead LF, Lancaster T. Interventions to reduce harm from continued tobacco use. Cochrane Database Syst Rev. 2007:CD005231. [PubMed: 17636791]

Stead L, Perera R, Bullen C, Mant D, Lancaster T. Nicotine replacement therapy for smoking cessation. Cochrane Database Syst Rev. 2008:CD000146. [PubMed: 18253970]

Sussman S, Lichtman K, Ritt A, Pallonen UE. Effects of thirty-four adolescent tobacco use cessation and prevention trials on regular users of tobacco products. Subst Use Misuse. 1999; 34:1469–1503. [PubMed: 10468104]

Sweeney CT, Fant RV, Fagerstrom KO, McGovern JF, Henningfield JE. Combination nicotine replacement therapy for smoking cessation: rationale, efficacy and tolerability. CNS Drugs. 2001; 15:453–467. [PubMed: 11524024]

Thomson, ISI. Physicians' desk reference. 2008. Retrieved February 9, 2009, from: http://www.pdr.net/login/Login.aspx

Tomar SL, Connolly GN, Wilkenfeld J, Henningfield JE. Declining smoking in Sweden: is Swedish Match getting the credit for Swedish tobacco control's efforts? Tob Control. 2003; 12:368–371. [PubMed: 14660769]

U.S. Department of Health and Human Services. Reducing the health consequences of smoking: 25 years of progress: a report of the Surgeon General. Rockville, Maryland: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health; 1989.

U.S. Department of Health and Human Services. Rep No (CDC) 90-8416. U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control, Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health; 1990. The health benefits of smoking cessation — Report of the Surgeon General.

U.S. Department of Health and Human Services. Preventing tobacco use among young people: a report of the Surgeon General. Atlanta: U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health; 1994.

U.S. Department of Health and Human Services. Reducing tobacco use: a report of the Surgeon General. Atlanta, Georgia: U.S. Department of Health and Human Services, Centers for Disease

Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health; 2000.

U.S. Department of Health and Human Services. Women and smoking: a report of the Surgeon General. Washington, DC: U.S. Government Printing Office; 2001.

U.S. Department of Health and Human Services. Health consequences of smoking — A report of the Surgeon General. 2004.

U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control, Center for Health Promotion and Education, & Office on Smoking and Health. The health consequences of smoking: nicotine addiction. A report of the Surgeon General. Rockville, MD: U.S. Government Printing Office; 1988.

Watkins SS, Koob GF, Markou A. Neural mechanisms underlying nicotine addiction: acute positive reinforcement and withdrawal. Nicotine Tob Res. 2000; 2:19–37. [PubMed: 11072438]

Wayne GF, Connolly GN, Henningfield JE. Assessing internal tobacco industry knowledge of the neurobiology of tobacco dependence. Nicotine Tob Res. 2004; 6:927–940. [PubMed: 15801568]

Wayne GF, Connolly GN, Henningfield JE. Brand differences of free-base nicotine delivery in cigarette smoke: the view of the tobacco industry documents. Tob Control. 2006; 15:189–198. [PubMed: 16728749]

Wayne GF, Connolly GN, Henningfield JE, Farone WA. Tobacco industry research and efforts to manipulate smoke particle size: implications for product regulation. Nicotine Tob Res. 2008; 10:613–625. [PubMed: 18418784]

Weiss F, Markou A, Lorang MT, Koob GF. Basal extracellular dopamine levels in the nucleus accumbens are decreased during cocaine withdrawal after unlimited-access self-administration. Brain Res. 1992; 593:314–318. [PubMed: 1450939]

West R, DiMarino ME, Gitchell J, McNeill A. Impact of UK policy initiatives on use of medicines to aid smoking cessation. Tob Control. 2005; 14:166–171. [PubMed: 15923466]

West R, Zhou X. Is nicotine replacement therapy for smoking cessation effective in the “real world”? Findings from a prospective multinational cohort study. Thorax. 2007; 62:998–1002. [PubMed: 17573444]

Williams JM, Ziedonis D. Addressing tobacco among individuals with a mental illness or an addiction. Addict Behav. 2004; 29:1067–1083. [PubMed: 15236808]

Windsor R, Oncken C, Henningfield J, Hartmann K, Edwards N. Behavioral and pharmacological treatment methods for pregnant smokers: issues for clinical practice. J Am Med Women’s Assoc. 2000; 55:304–310. [PubMed: 11070654]

Woolacott NF, Jones L, Forbes CA, Mather LC, Sowden AJ, Song FJ, et al. The clinical effectiveness and cost-effectiveness of bupropion and nicotine replacement therapy for smoking cessation: a systematic review and economic evaluation. Health Technol Assess. 2002; 6:1–245.

World Bank. Curbing the epidemic: governments and the economics of tobacco control. Washington, DC: World Bank; 1999.

World Health Organization. The ICD-10 classification of mental behavioural disorders. Geneva: World Health Organization; 1992.

World Health Organization. Advancing knowledge on regulating tobacco products (monograph). Geneva, Switzerland: World Health Organization; 2001.

World Health Organization. Policy recommendations for smoking cessation and treatment of tobacco dependence. Geneva: World Health Organization; 2003.

World Health Organization. The millennium development goals and tobacco control. Geneva, Switzerland: World Health Organization; 2004.

World Health Organization. Advisory note waterpipe tobacco smoking: health effects, research needs and recommended actions by regulators. 2006. Retrieved February 9, 2009, from: www.who.int/tobacco/global_interaction/tobreg/Waterpipe%20recommendation_Final.pdf

World Health Organization. The scientific basis of tobacco product regulation. Geneva, Switzerland: World Health Organization; 2007.

World Health Organization. Framework convention on tobacco control. 2008a. Retrieved February 10, 2009 from: http://www.who.int/fctc/en/

World Health Organization. WHO report on the global tobacco epidemic, 2008: The MPOWER package. 2008b. Retrieved February 11, 2009, from: http://www.who.int/tobacco/mpower/en/

Ziedonis, DM. Unpublished manuscript. 2007. Tobacco dependence and psychiatric illness.

Ziedonis DM, Kosten TR, Glazer WM, Frances RJ. Nicotine dependence and schizophrenia. Hospit Commun Psychiatry. 1994; 45:204–206.

Ziedonis DM, Williams JM. Management of smoking in people with psychiatric disorders. Curr Opin Psychiatry. 2003; 16:305–315.

Table 1

FDA approved pharmacotherapies for the treatment of tobacco dependence.

	Pharmacological agent	Doses and allocation	Typical dosing & schedule	Comments
Nicotine replacement therapies				
Gum[a]				
Nicorette® (GSKCH; Pfizer, Novartis, numerous store brands) in a variety of flavors	Nicotine	2-mg: <25 cpd[b]	Maximum dose/day, e.g., 24 pieces with 1 dose recommended per hour and gradually tapering to low levels across several months	Acute dosing formulation useful for relieving acute craving and withdrawal.
		4-mg: ≥25 cpd	Same as above	
Lozenge[c]				
Commit® (GSKCH)	Nicotine	2-mg: TTFC>30 min	Maximum dose/day, e.g., 20 lozenges within one dose recommended every 1–2 h and gradually tapering to low levels across several months	Acute dosing formulation useful for relieving acute craving and withdrawal.
		4-mg: TTFC≤30 min	Same as above	
Patch[d]				
Habitrol® (Novartis)	Nicotine	7-mg	>10 cpd dosing schedule	Sustained dosing formulation useful for reducing background craving.
		14-mg: ≤10 cpd	Weeks 1–4: 21-mg/day	
		21-mg: >10 cpd	Weeks 5–6: 14-mg/day	
			Weeks:7–8: 7-mg/day	
			≤10 cpd dosing schedule	
			Weeks 1–6: 14-mg/day	
			Weeks 7–8: 7-mg/day	
NicoDerm® CQ® (GSKCH)	Nicotine	7-mg	>10 cpd dosing schedule	Sustained dosing formulation useful for reducing background craving.
		14-mg: <10 cpd	Weeks 1–6: 21-mg/day	
		21-mg: >10 cpd	Weeks 7–8: 14-mg/day	
			Weeks 9–10: 7-mg/day	
			≤10 cpd dosing schedule	
			Weeks 1–6: 14-mg/day	
			Weeks 7–8: 7-mg/day	
Nicotrol 16 h patch (Pfizer)	Nicotine	5-mg	Weeks 1–6: 15-mg patch/day	Sustained dosing formulation useful for reducing background craving.
		10-mg	Weeks 7–8: 10-mg patch/day	
		15-mg: >10 cpd	Weeks 9–10: 5-mg patch/day	
Inhalator				
Nicotrol® Inhaler (Pfizer)	Nicotine		Up to 12 weeks (initial treatment): 6–16 cartridges/day	Prescription required in U.S.
Nasal spray				
Nicotrol® (Pfizer)	Nicotine		Minimum doses/day: 8 sprays	Prescription required in U.S

	Pharmacological agent	Doses and allocation	Typical dosing & schedule	Comments
			Recommended doses per/h: 1–2 sprays Maximum doses/h: 5 sprays Maximum doses/day: 40 sprays Maximum duration of treatment: 12 weeks	
Non-nicotine based pharmacotherapies				
Zyban® sustained-release tablets (GSK)	Bupropion hydrochloride		Maximum dose/day: 300 mg (2×150 mg/day) First 3 days: 150 mg/day After 3 days: 300 mg/day (2×150 mg/day) Treatment duration: at least 7–12 weeks but longer as indicated Treatment initiation: at least 1 week before quitting (i.e., quit during second week of treatment)	Prescription required in U.S. Non-nicotine pharmacotherapy useful for reducing withdrawal.
Chantix™ tablets (Pfizer)	Varenicline, a nicotinic agonist available as the tartrate salt		Maximum dose/day: 2 mg (1 mg/AM, 1 mg/PM) Days 1–3: 0.5 mg/day Days 4–7: 1 mg/day (0.5 mg/AM, 0.5 mg/PM) Day 8 to end of treatment: 2 mg/day (1 mg/AM, 1 mg/PM) Treatment initiation:1 week before quitting Treatment duration: 12 weeks or longer as indicated	Prescription required in U.S. Partial agonist selective for $\alpha_4\beta_2$ nicotinic acetylcholine receptor subtypes useful for reducing craving and withdrawal symptoms.

[a] Generic gums (e.g., Perrigo, Watson) are available and follow the label of the “innovator” product.

[b] Cpd — cigarettes per day.

[c] Generic lozenges (e.g., Perrigo) are available and follow the label of the “innovator” product.

[d] Generic patches (e.g., Perrigo [former ProStep]) exist and follow the label of the “innovator” product.

Table 2

Pharmacotherapy opportunities: new chemical entities and formulations.

Type or class	Science base	Challenges & opportunities	Comment
Lung delivered nicotine	Lung delivery is the mode of delivery for most tobacco users.	Palatable delivery with an acceptably safe profile for chronic use	Achievement of desirable medical goals may result in abuse liability that would warrant controlled substance scheduling.
Nicotine delivery with greater user control over dosing to meet daily and momentary needs	Individual dosing needs and needs within the day vary widely and are presently met by tobacco products.	Providing flexibility while minimizing risks for user and non-intended users such as children and infants	
Diverse nicotinic targeted drugs	Cytisine and varenicline have established proof of concept, many more possibilities exist.	The range possibilities is vary large, with multiple plausible paths to success.	Benefits might be target, e.g., some might be more effective at relieving withdrawal than reducing reinforcing effects of smoking or vice versa.
Non nicotinic drugs, including cannabinoid receptor blockers (e.g., rimonabant-like drugs), and selective dopaminergic inhibitors or agonists	Diversity in reasons for tobacco use and withdrawal effects suggests that for some individuals, addressing individual factors will be sufficient to aid withdrawal.	Clinical trials may need to be designed with as much emphasis on targeted symptoms as smoking cessation.	Indications and claims may differ substantially offering potential “exclusive” markets.
Vaccine type	Animal and human studies indicate potential efficacy in reducing reinforcing effects of nicotine and aiding cessation.	Depending upon the pharmacological profile of the medications, they may be suited as well if not better for maintaining abstinence and/or aiding tobacco users at early stages of dependence from progressing.	Current vaccine development is not pursuing the prophylactic model of immunization of young people but rather as treatment of dependence but that could change. Publically presented data suggest that safety and tolerability issues are manageable and that this category of product is viable within five years.
Antagonists	Nicotine antagonists can block nicotine reinforcing effects in humans and animals and alone or in combination with nicotine may aid cessation.	A nicotine antagonist with an acceptable profile of effects (e.g., mecamylamine causes a high rate of constipation, dizziness, and sedation) would need to be identified.	Whether an acceptable full antagonist can be developed is not clear but selective partial agonist antagonist combinations merit exploration.
Medications approved for other indications	Increased understanding of the importance of symptoms of withdrawal and potential factors in self-administration (e.g., stress, anxiety, cognitive dysfunction) suggest that treatment of these symptoms might support smoking cessation.	An increasing range of drugs for treating mood and cognitive disorders is available and might be evaluated in paradigms designed to for tobacco withdrawal and dependence.	Intellectual property rights and medicinal claims would depend on the approach, status of the drug, and other factors, but this may also be a legitimate way to extend use of existing drugs as occurred with respect to approval of the antidepressant bupropion for smoking cessation.
Pharmacogenetic based approaches	Increasing data on genetic differences in nicotine metabolism, addiction risk and treatment needs provide an initial platform for further research.	These approaches might be based on existing and forthcoming medications or might involve new chemical entities.	

Table 3

Cessation and beyond: new indications and applications.

Indication or application	Considerations for trial design	Comment
Cessation	Current 6 week abstinence model has served and probably should continue as basic model.	This model has been used to justify limited time use, e.g., 6 months. Are longer trials or postmarketing surveillance needed to justify labeling for extended use?
Relapse prevention	Could involve chronic and long term drug administration or acute use as needed to avoid relapse. Long term trials, e.g. 1–3 years, with large populations may be required. Innovative approaches include: (1) targeting populations at very high risk of relapse; (2) surveillance in users following restricted marketing approval as allowed in US FDA fast-track drug approval protocols.	This could be an added indication to a medication approved for cessation but used differently or a new dose, formulation or entity, used analogously as “break through pain” (“rescue analgesics) for people with chronic pain who may or may not be maintained on a pain medication.
Maintenance of abstinence	Generally conceived as long term chronic drug use. Long term trials, e.g. 1–3 years, with large populations may be required. Innovative approaches include: (1) targeting populations at very high risk of relapse; (2) surveillance in users following restricted marketing approval as allowed in US FDA fast-track drug approval protocols.	This could be an added indication to a medication approved for cessation but used differently or a new dose, formulation or entity. For NRT and certain other approved medications with extensive use histories, long term safety concerns should not preclude such use.
Tobacco toxin exposure reduction	Trials must demonstrate reduction with plausible health benefit if sustained without complete cessation but must support or at least not undermine eventual cessation.	How the products are marketed and application of emerging risk minimization protocols may be vital to reducing unintended consequences such as undermining cessation.
Reduce to quit smoking	Trials must demonstrate reduction with plausible health benefit if sustained without complete cessation but must demonstrate significant smoking cessation.	Labeling and guidance would need to make clear that cessation was the ultimate goal. The concept would be to reach people for whom abrupt cessation is not achievable or acceptable.
Treatment of dependence on cigarette like products that are spreading in Western countries and common in SE Asia and India, e.g., clove cigarettes, bidis, kreteks.	Dependence process appears similar to cigarettes for cigarette-like products with nicotine primarily inhaled at apparently comparable dose levels suggesting similar trial designs as for cigarette indications.	It is possible that the major adaptation will be the supportive behavioral programs because patterns of use may differ somewhat.
Treatment of dependence on cigars and possibly waterpipes	Some cigar smokers inhale but many absorb nicotine more gradually by holding smoke in the mouth and probably by holding the unlit cigar in the mouth. Nicotine dosing capacity of a single cigar can range from a few to more than 100 mg and patterns of use can range from several cigars per day to a few per week. Waterpipe smokers similarly can absorb large doses but typically in 1–3 sessions per day. Cigarette based trial designs will need to be adapted.	As the dangers of cigar smoking are increasingly recognized there will be increasing pressures for at least dependent smokers to seek treatment, though this will probably not be appropriate for special occasion intermittent cigar smokers. Whereas waterpipe smoking was most common in the Middle East and Asia throughout the 20th century, the 21st century has witnessed rapid spread to the West, particularly in college campus settings suggesting increasingly concerns over the next decade or so.
Treatment of dependence on noncombusted oral tobacco products, e.g., snuff, chewing tobacco, and Swedish snus	Nicotine delivery is slower onsetting than from inhaled smoke but doses can be very high, e.g., popular snuff brands in the US can deliver 10–20 mg per “dip” which is typically repeated 5–10 times/day. Cigarette based trial designs will need to be adapted. Seasonal use occurs with many athletes and it is not clear how trial designs would be adapted to such populations.	The oral tobacco using population is increasing and will probably continue to do so as some smokers switch to such products, in part due to their marketing “for when you can’t smoke”. Although health risks are lower than for combusted products, the health risks are serious.

Table 4

Special populations.

Indication or application	Considerations for trial design	Comment
Pediatric indications	Youth develop dependence and withdrawal with 50% trying to quit and most regretting having started before age 18, however, patterns of use and behavioral and social factors may require adaptations of clinical trial designs used for adults.	The safety benefit ratio will be an important consideration due to the fact that one third or more youth in some countries (e.g., the US) discontinue smoking in early adulthood without treatment.
Pregnant women	Outcomes may include neonatal weight, pregnancy complications.	Safety concerns exist but have been partially addressed through labeling of current medications and extensive real world experience.
Cancer patients	Trials may need to focus as much on quality of life as cessation. Treatment and disease-related outcomes may be cancer organ site and trial specific.	Safety concerns including effects on cancer prognosis might be preliminarily addressed with biomarkers but resolution may require post-marketing studies.
Respiratory disease	Trials may need to focus on potential indirect respiratory benefits and quality of life.	Safety concerns including effects on lung disease prognosis might be preliminarily addressed with biomarkers but resolution may require post-marketing studies.
Heart disease patients	Major premarketing outcomes may be the absence of exacerbation of heart disease.	Safety concerns including effects on heart disease prognosis might be preliminarily addressed with biomarkers but resolution may require post-marketing studies.
People with psychiatric co-morbidities, e.g. depression, schizophrenia, anxiety	Trials will need to minimize risk of adverse impact of other psychiatric disease and treatment and presumably need to demonstrate no adverse impact and/or how to minimize adverse impact.	It is likely that although psychiatric co-morbidities are grouped in this table that approaches will vary across condition and indications may be condition specific (e.g., for patients with depression).
People with other drug dependence disorders	Trials will need to minimize risk of adverse impact of other psychiatric disease and treatment and presumably need to demonstrate no adverse impact and/or how to minimize adverse impact.	It is likely that although drug dependence disorders are grouped in this table that approaches will vary across condition and indications may be condition specific (e.g., for patients with alcohol dependence).