

Special Article – Tobacco and Smoking Cessation

Tobacco Dependence Treatment: Pharmacist's Role

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Abstract

Smoking prevalence and tobacco-related mortality have steadily declined in the recent decades. However, the use of e-cig and other nicotine-containing products used for smoking cessation and other reasons is on the rise. Chronic use of tobacco products leads to serious health issues, yet a limited number of pharmacotherapies are available to treat smoking related disorders. These pharmacotherapies in some cases are not effective or cause similar side effects as nicotine. Recently, with the inception of SB 493, pharmacists are authorized to be actively involved in smoking cessation. For example, California's legislature granted pharmacists authority to furnish FDA-approved nicotine replacement therapies through SB 493. Thus, pharmacists must complete a training course approved by the board of pharmacy, as well as annual continuing education on tobacco cessation to be able to make the appropriate decision which product to choose for their patients. In this review, we attempted to review the available pharmacotherapies for smoking cessation and discuss the role that pharmacists play to help patients benefit from these products.

Keywords: Tobacco dependence; Smoking cessation; Treatment; Pharmacist role; SB 493

Scope of the Tobacco Dependence

Since its inception in 1964 the Surgeon General's report, *Smoking and Health*, is viewed as transformative report that widely used to initiate concerted efforts to reduce tobacco use in the United States [1]. Overall smoking rates, exposure to secondhand smoke (SHS), and tobacco-related mortality has been declined based on research and implementation of evidence-based measures. For example, smoking rates have declined from 42% in 1965 to 15.1% in 2015 [2]. Tobacco control efforts dating from 1964 are credited with preventing an estimated 8 million premature deaths by 2012 [3]. An analysis published in *The New England Journal of Medicine* in August 2016 found that the adult smoking rate in the U.S. fell more than twice since 2009, and the analysis made it clear that this progress is no accident: "The recent accelerated decrease in cigarette smoking has not occurred in a vacuum. The striking declines since 2009 are most likely due to the implementation of an array of tobacco-control interventions at the federal, state, non-profit, and private-sector levels [4]."

Although smoking prevalence has declined over time, more than 36 million adults still smoke, and there are large disparities in smoking rates, with higher rates among people who live below the poverty level; those with less education; American Indians/Alaska Natives; residents of the Midwest; lesbians, gays and bisexual people; people with mental illness; and adults who are uninsured or on Medicaid [3]. Smoking leads to disability, premature death and damages nearly every organ of the body, yet more than 16 million Americans still live with a smoking-related disease [2]. United States spends about \$170 billion per year on medical care to treat smoking-related illnesses in adults and more than \$156 billion in lost productivity due to premature death and second hand exposure [3,5]. Tobacco industry spent more than \$9 billion per year (nearly \$25 million every day) for product advertising and promotion, outspending tobacco prevention

funding nationwide by 18.5 to 1 [6]. To counteract the influence of tobacco industry, the Healthy People 2020 set its objective of reducing adult cigarette smoking prevalence to 12.0% from 20.6% [7]. In March 2012, the Centers for Disease Control and Prevention (CDC) launched the national tobacco education campaign – *Tips from former smokers*® (Tips®), in 2014, the Tips campaign motivated 1.83 million Americans to try to quit smoking cigarettes and 104,000 smokers quit smoking for good [8].

In 2015, an estimated 68% of adult smokers want to stop smoking, 55.4% made a past-quit-attempt, 7.4% recently quit smoking, 57.2% had been advised by a health professional to quit, and 31.2% used cessation counseling and/or medication when trying to quit [9]. Many smokers want to quit; pharmacists can play a pivotal role in fighting tobacco use as they interface between patients and other health providers. Pharmacists are well situated in a community practice where patients do not require an appointment or insurance to see them, as it opens the door for communication and intervention for underserved populations, where higher disparities and incidence of tobacco-related illnesses [2,10,11]. When initiating a conversation about quitting tobacco use, pharmacists can utilize the Tips® campaign as a conversation starter, as this program offers resources for both pharmacists and patients [10].

In the state of California, SB 493 legislation has expanded the role of pharmacists and designed pharmacists as "healthcare providers", which allowed pharmacists to furnish prescription nicotine replacement products and devices for smoking cessation without a prescription. California Board of Pharmacy allowed this regulation to be effective as of January 25, 2016, for pharmacists to furnish nicotine replacement therapy (NRT) to assist patients in smoking cessation. To provide these services pharmacists must complete two hours of approved continuing education and ongoing biennial training and follow procedures set forth by California Board of Pharmacy

Table 1: DSM-5 Tobacco Use Disorder: There are 11 possible criteria, of which at least 2 must be present in the last 12 months [16].

1. Tobacco taken in larger amount or over longer periods of time
2. Persistent desire or unsuccessful efforts to cut down or control use
3. A great deal of time is spent on activities necessary to obtain or use tobacco
4. Craving or a strong desire or urge to use tobacco
5. Recurrent tobacco use resulting in a failure to fulfill major role obligations at work, school or home
6. Continued tobacco use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by effects of tobacco (e.g., arguments with others about tobacco use)
7. Important social, occupational, or recreational activities are given up or reduced because of tobacco use
8. Recurrent tobacco use in situations in which it is physically hazardous (e.g. smoking in bed)
9. Tobacco use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by tobacco
10. Tolerance, as defined by either the need for markedly increased amounts of tobacco to achieve the desired effect or a markedly diminished effect with continued use of the same amount of tobacco
11. Withdrawal, as manifested by either the characteristic withdrawal syndrome or the use of tobacco to relieve or avoid withdrawal symptoms

Table 2: CAGE Questionnaire Modified for Smoking Behavior [17].

1. Have you ever felt a need to <u>C</u> ut down or control your smoking, but had difficulty doing so?
2. Do you ever get <u>A</u> nnoyed or angry with people who criticize you smoking or tell you that you ought to quit smoking?
3. Have you ever felt <u>G</u> uilty about your smoking or about something you did while smoking?
4. Do you every smoke within half an hour of waking up (Eye-opener)?

Table 3: Modified Fagerstrom Test for Nicotine Dependence (FTND) [18].

Items and scoring for FTND		
Questions	Answers	Points
1. How soon after you wake up do you smoke your first cigarette?	Within 5 minutes	3
	6-30 minutes	2
	31-60 minutes	1
	After 60 minutes	0
2. Do you find it difficult not to smoke in places where you shouldn't, such as church or school, in a movie, at the library, on a bus, in court or in a hospital?	Yes	1
	No	0
3. Which cigarette would you most hate to give up; which cigarette do you treasure the most?	The first one in the morning	1
	All others	0
4. How many cigarettes do you smoke each day?	10 or less	0
	20-30	1
	21-30	2
	31 or more	3
5. Do you smoke more during the first few hours after waking up than during the rest of the day?	Yes	1
	No	0
6. Do you still smoke if you are so sick that you are in bed most of the day, or if you have a cold or the flu and have trouble breathing?	Yes	1
	No	0

Scoring: 7-10 points = highly dependent; 4-6 points = moderately dependent; less than 4 points = minimally dependent.

for pharmacists furnishing nicotine replacement products [12,13] (Appendix 1). Majority of pharmacy practitioners are interested in providing assistance for patients to quit smoking, the most commonly cited barriers to provide counseling include time constraints and lack of knowledge and skills to provide these services [14,15]. There are various training programs and Web-based educational resources available for pharmacy students and pharmacists to enhance their knowledge in tobacco dependence treatment. This article provides a simple overview of tobacco use disorder, screening patients for tobacco dependence, nicotine addiction, counseling, pharmacotherapies, monitoring nicotine withdrawal symptoms, relapse prevention, special populations, role of electronic cigarettes and future directions.

Tobacco Use Disorder

The Diagnostic and Statistical Manual of Mental Disorders fifth edition (DSM-5) replaced the terms nicotine abuse and dependence with an overarching category called “*tobacco use disorder*” (Table 1) to

avoid confusion between dependence and addiction [16]. Pharmacists can assess *tobacco use disorder* by either using the CAGE questionnaire for smoking (modified from the familiar CAGE questionnaire for alcohol), or the Fagerstrom test and the calculation of pack year history whichever fits their style of practice. The CAGE questionnaire is a simple, accurate tool that has been utilized for many years to screen patients for addictive disorders such as alcohol, opioid, etc. The CAGE questions have been revised to apply to smoking behavior (Table 2) and can be included in a pharmacist interview [17]. Patients who quit smoking and relapse within two to three weeks usually do so to relieve withdrawal symptoms secondary to physical dependence on nicotine. The Fagerstrom Test for Nicotine dependence is a standard instrument (Table 3) for assessing the intensity of the physical addiction. The Fagerstrom score ranges from 1-10 points and the higher the scoring system the higher the dependence on nicotine [18]. The calculation of pack year history assigns a numerical value to lifetime tobacco exposure, this is calculated based on this formula:

Table 4: FDA Approved Pharmacotherapies.

First-line therapies			
Nicotine replacement therapies (NRTs)	Dose	Instructions for use	Availability
Nicotine patch	21 mg, 14 mg, 7 mg	<ul style="list-style-type: none"> One patch per day If ≥ 10 cigs/day 21 mg Post-quit: up to 12 weeks Optional pre-quit up to 6 months prior to quit dates with smoking reduction 	OTC or prescription Generic Nicoderm CQ Nicotrol
Nicotine gum	2 mg and 4 mg	<ul style="list-style-type: none"> 1 piece every 1 to 2 hours 6-15 pieces per day If smoke > 30 minutes after waking 2 mg If smokes ≤ 30 minutes after waking 4 mg Post-quit: up to 12 weeks Optional pre-quit up to 6 months prior to quit dates with smoking reduction 	OTC only Generic Nicorette
Nicotine lozenge	2 mg and 4 mg	<ul style="list-style-type: none"> If smoke > 30 minutes after waking 2 mg If smokes ≤ 30 minutes after waking 4 mg Weeks 1-6: 1 every 1-2 hours Weeks 7-9: 1 every 2 hours Weeks 10-12: 1 every 4-8 hours 3-6 months 	OTC only Generic Commit
Nicotine inhaler	10 mg cartridge	<ul style="list-style-type: none"> 6-16 cartridges/day Inhale 80 times/cartridge May save partially used cartridge for next day Post-quit: up to 6 months; taper at end Optional Pre-quit: up to 6 months before quit date with smoking reduction 	Prescription only Nicotrol inhaler
Nicotine nasal spray	0.5 mg in each nostril	<ul style="list-style-type: none"> 1 "dose" = 1 squirt per nostril 1 to 2 doses per hour 8 to 40 doses per day DO NOT inhale 3-6 months; taper at end 	Prescription only Nicotrol NS
Non-nicotine products			
Bupropion SR	150 mg two times a day	<ul style="list-style-type: none"> Days 1-3: 150 mg each morning Days 4-end: 150 mg twice a day Start 1-2 weeks before quit date Use 2 to 6 months 	Prescription only Generic Zyban Wellbutrin SR
Varenicline	1 mg two times a day	<ul style="list-style-type: none"> Days 1-3: 0.5 mg every morning Days 4-7: 0.5 mg twice a day Day 8 –end: 1 mg twice a day Start 1 week before quit date and use 3-6 months 	Prescription only Chantix
Second-line therapies			
	Dose	Instructions for use	Availability
Clonidine	Oral 0.15-0.74 mg/day Patch 0.1-0.2 mg/day	<ul style="list-style-type: none"> Initiate on quit date or up to 3 days before quit date Initial dose 0.1 mg two times a day orally or 0.1 mg/day Transdermal, increase by 0.1 mg/day per week 3-10 weeks of treatment Titrate dose down over 2-4 days 	Prescription only Generic Catapres-TTS-1 Catapres-TTS-2
Nortriptyline	75-150 mg/day	<ul style="list-style-type: none"> Initial dose 25 mg/day and titrate up to 75-150 mg/day 10-28 days prior to quit date 12 weeks of treatment 	Prescription only Generic Aventyl Pamelor

number of cigarettes per day times number of years smoked divided by 20 equals pack years. For example, a patient smoked 40 cigarettes per day for 40 years, then $40 \text{ cigarettes} \times 40 \text{ years} / 20 = 80$ pack years. The time to first cigarette and total cigarettes per day are the two strongest predictors of nicotine addiction, most smokers addicted to nicotine and research suggests that nicotine may be as addictive as heroin, cocaine, or alcohol [2,19,20].

Nicotine Addiction

Nicotine addiction is multifactorial which includes nicotine delivery, nicotine effect on the brain, clearance of nicotine, physiological dependence, genetics, and social and environmental factors all of which play a significant role in the initiation and

maintenance of nicotine addiction. *Nicotine delivery* is dependent on the amount of nicotine, route of administration, and the alkalinity of the product. Nicotine, 3-(1-methyl-2-pyrrolidiny) pyridine, is a volatile alkaloid ($pK_a=8.5$) and its absorption and renal excretion are highly dependent on pH. At a high (alkaline) pH, nicotine is in the non-ionized state and rapidly absorbed into the cell membranes compared to its ionized state [21]. Nicotine when inhaled through cigarette smoking, is rapidly absorbed in the lungs due to large surface area of the alveoli and small airways and undergoes dissolution in pulmonary fluid at high pH [22]. From there, it enters the arterial circulation and eventually moves quickly into the brain, nicotine reaches the brain within eleven seconds [23,24].

Nicotine by diffusing and targeting the neuronal nicotine

Table 5: Precautions/warnings and adverse effects with NRTs.

NRTs	Precautions/Warnings	Most frequent adverse effects
All NRTs	<ul style="list-style-type: none"> Cardiac disease, myocardial infarction, irregular heartbeat Peptic ulcers Insulin-dependent diabetes Uncontrolled hypertension Drug therapy for depression or asthma Pregnancy Category D Hyperthyroidism, pheochromocytoma or type 1 diabetes mellitus 	
Nicotine patch	<ul style="list-style-type: none"> Do not use if patient has severe eczema or psoriasis 	Local skin irritation, and insomnia
Nicotine gum	<ul style="list-style-type: none"> Caution with dentures Caution with history of esophageal oral or pharyngeal inflammation Do not eat or drink 15 minutes before or during use 	Jaw ache, mouth soreness, dyspepsia, hiccups
Nicotine lozenge	<ul style="list-style-type: none"> One lozenge at a time Limit 20 in 24 hours Do not eat or drink 15 minutes before or during use 	Hiccups, mouth or throat irritation, cough, heartburn or dyspepsia
Nicotine inhaler	<ul style="list-style-type: none"> Bronchospastic disease 	Local irritation of mouth and throat, coughing and rhinitis
Nicotine nasal spray	<ul style="list-style-type: none"> Chronic nasal disorder Severe reactive airway disease 	Nasal and airway irritation

Table 6: Precautions, contraindications and potential adverse effects with bupropion and varenicline.

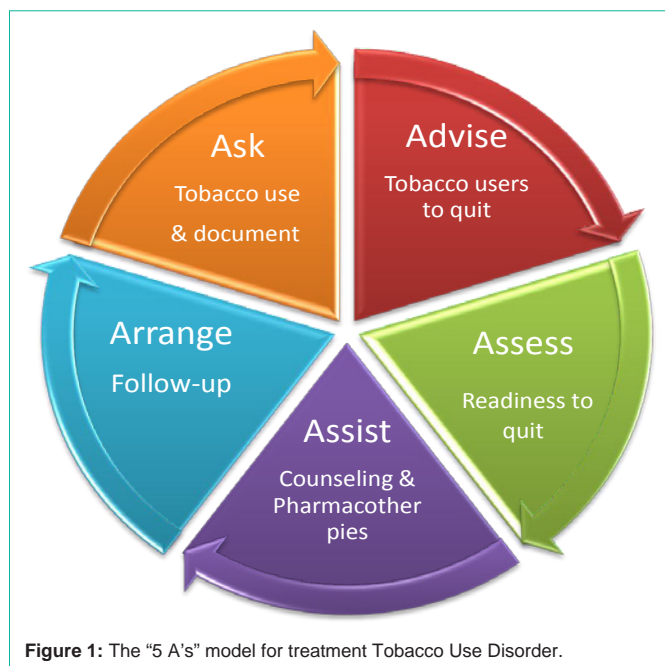
Medication	Precautions	Contraindications	Potential adverse events
Bupropion SR	<ul style="list-style-type: none"> Pregnancy Category C 	<ul style="list-style-type: none"> MAO inhibitor in past 14 days 	<ul style="list-style-type: none"> Insomnia, dry mouth, headaches, pruritus, pharyngitis, tachycardia, seizures, neuropsychiatric effects and suicide risk
(Zyban®, Wellbutrin®)	<ul style="list-style-type: none"> Uncontrolled hypertension Severe cirrhosis – dose adjustment required Mild-moderate hepatic & moderate-severe renal impairment – consider dose adjustment 	<ul style="list-style-type: none"> Seizure disorder, bulimia/anorexia Abrupt discontinuation of ethanol or sedatives 	<ul style="list-style-type: none"> As of December 16, 2016, the FDA removed the Boxed Warning for this medication. https://www.fda.gov/Drugs/DrugSafety/ucm532221.htm
Varenicline (Chantix®)	<ul style="list-style-type: none"> Pregnancy category C Seizure disorder CrCl < 30 or dialysis – dose adjustment required May increase risk of Cardiovascular events in patients with cardiovascular disease Operate heavy machinery May lower alcohol tolerance 	<ul style="list-style-type: none"> Known history of serious hypersensitivity or skin reactions to varenicline 	<ul style="list-style-type: none"> Nausea, insomnia, abnormal dreams, constipation, neuropsychiatric effects, seizures, suicide risk and cardiovascular events As of December 16, 2016, the FDA removed the Boxed Warning for this medication. https://www.fda.gov/Drugs/DrugSafety/ucm532221.htm

acetylcholine receptor (nAChRs) subtypes, located in the central nervous system causing a ligand-gated ion channel to open, allowing entry of cations such as sodium and calcium, thereby depolarizing each cell. This response in turn leads to the release of an array of neurotransmitters in the brain, with the most significant one being dopamine. Nicotine also causes the release of norepinephrine, acetylcholine, glutamate, serotonin, opioids and gamma-amino butyric acid (GABA), leading to a mixture of responses, such as pleasure, appetite suppression, arousal, cognitive enhancement, memory enhancement, mood modulation, and reduction of anxiety and tension [24]. Repeated exposure of nicotine leads to tolerance, which therefore leads to a decrease in brain reward function. Along with tolerance, there is also an increase in the number of nAChR binding sites in the brain. The increase in the number of binding sites in the brain is believed to represent up regulation in response to the nicotine-mediated desensitization of receptors. This desensitization may play a key factor in nicotine tolerance and dependence [22]. With the decrease in reward due to nicotine tolerance, smokers need to increase the number of cigarettes per day to achieve the desired effects

they crave and minimize the symptoms of nicotine withdrawal [24]. Besides the mechanism of action of nicotine, the pharmacokinetics of nicotine also plays a key role in nicotine addiction.

Clearance of nicotine is through the liver, primarily by C-oxidation via CYP2A6 metabolizing enzymes, which metabolize nicotine to cotinine. Cotinine is used as a diagnostic test for the use of tobacco and can be used as a measure of compliance with treatments for smoking cessation. Since nicotine's half-life is around 2 hours, nicotine eventually accumulates in the body over six to nine hours of regular smoking [22]. Nicotine is also metabolized through glucuronidation and N-oxidation via uridine diphosphate-glucuronosyl transferase (UGT) and flavin-containing monooxygenase (FMO) isoenzymes and plays a functional role in circulating levels of nicotine and the amount of nicotine reaches the brain [25].

Physiological dependence includes nicotine tolerance and withdrawal. Increased nAChR receptor sites and increased neurotransmitters are associated with chronic or acute administration of nicotine [22,24]. One potential mechanism leading to the



development of nicotine tolerance in chronic nicotine use is associated with the upregulation and desensitization or inactivation of nAChR subtypes [26]. In a chronic tobacco user, abstaining from smoking for more than a few hours leads to nicotine withdrawal symptoms. Withdrawal symptoms associated with negative affect are irritability and anger, anxiety and depressed mood; cognitive symptoms are restlessness, sleep disturbance, an increased appetite, and difficulty concentrating. Other possible symptoms may include constipation, cough, dizziness, increased dreaming and mouth sores [27,28]. Emergence of withdrawal symptoms occurs within few hours of after the last cigarette, peaks within a few days to one week and returns to baseline within two to four weeks [27-29]. Withdrawal symptoms are major risk factors that impair the ability to remain abstinent from smoking in an individual smoker. The management of withdrawal and craving symptoms (e.g., urge to smoke) is a primary treatment goal for tobacco dependence treatment [29-31].

Along the nicotine effects on the brain, clearance of nicotine and physiological dependence, other factors play a significant role in tobacco initiation or persistent utilization. These factors include characteristics of the individual (e.g., genes, co-morbid psychiatric conditions, etc.), environmental aspects (access and availability of tobacco products, tobacco use bans, cost, social acceptability, etc.). *Genetics* play a contributory role in the initiation of smoking behavior and transition to dependence or in the need of medication to improve the chances of quitting tobacco use. The specific candidate gene variants include a cluster of cholinergic nicotinic receptor genes such as CHRNA5 ($\alpha 5$ nicotinic receptor subunit), CHRNA3 ($\alpha 3$ nicotinic receptor subunit), CHRNB4 ($\beta 4$ nicotinic receptor subunit) have shown contribute to nicotine dependence and heavy smoking. Other genes studied in the literature includes: dopamine pathway and transport genes; serotonin pathway and transporter genes; monoamine oxidase (MAO-A) and dopamine beta hydroxylase genes; genes involved in metabolism of nicotine such as P450 CYP2A6 [32-35]. Furthermore, co-morbid psychiatric conditions

or substance use disorders may predispose smokers to begin or persist in smoking, and these consume almost 40% of all cigarettes smoked by adults in the U.S [36]. Studies have demonstrated a higher prevalence of alcohol and drug dependence, depression and anxiety disorders among dependent smokers compared to non-smokers or non-dependent smokers [37]. Nicotine has mood-altering effects that can temporarily mask the negative symptoms and placing mental illness people at increased use of smoking and nicotine addiction [38-41]. People with mental illness or substance use disorders die at least five years earlier than those without these disorders, and the most common causes of death among these individuals are heart disease, cancer, and lung disease, which can all be caused by smoking [38-41].

Due to the multifactorial effects of nicotine addiction, far few smokers have been successful in quitting and only about 4-6% of the population succeeds annually. The lapsing pattern of tobacco use among smokers led to the characterization of tobacco use disorder as a chronic and relapsing brain disease and thus health care providers should treat this public health issue similar to that of other chronic conditions.

Treatments

Treatment should be targeted towards the physical addiction of nicotine, the psychological effects of nicotine and the behavioral aspects of tobacco use disorder. Pharmacists and pharmacy students are recommended to refer to the Cochrane Collaboration Tobacco Addiction Group key review summaries and the United States Public Health Service (U.S. PHS) Clinical Practice Guideline Treating Tobacco Use and Dependence [42] for more specific recommendations. The U.S. PHS Clinical Practice Guideline recommends providing brief counseling and pharmacotherapies (if not contraindicated) for all smokers and also recommends identifying tobacco users and documenting tobacco use status at each patient visit. Pharmacists can implement 5 As (Figure 1) individually or with the other healthcare providers to assist patients in achieving tobacco abstinence [1,2].

Counseling

Pharmacists counseling encompasses educating patients about the health benefits of tobacco cessation, motivating tobacco users to quit, coping skills to deal with high risk situations, managing withdrawal symptoms, obtaining support from others, and preventing relapses for cessation efforts. In the event that pharmacists are unable to provide tobacco dependence treatments, tobacco users should be referred to tobacco treatment providers or telephone quit lines (1-800-QUITNOW) or TIPS. Quit lines are effective in providing counseling and easy accessibility to reach large population of diverse tobacco users [1,2,8,9,43-45].

Pharmacotherapies

According to U.S. PHS guidelines, all tobacco users should receive pharmacotherapies, unless contraindicated, for tobacco use disorder similar to that of other chronic medical conditions. Special considerations should be taken in smokers with certain medical conditions such as pregnant/breast feeding women, smokeless tobacco users, light smokers and adolescents. The first-line pharmacotherapies are those that have been approved by the Food and

Drug Administration (FDA) and included all nicotine replacement therapies (NRTs), and non-nicotine replacement therapies such as bupropion and varenicline. Second line pharmacotherapies are clonidine and nortriptyline, both of which demonstrated efficacy but have not been approved by the FDA [42]. Table 4 describes all available treatment options for tobacco use disorder.

Nicotine replacement pharmacotherapies

In California under SB 493 pharmacists can furnish both over-the-counter (OTC) and prescription NRTs when a patient requests or pharmacists feel necessary for patient's betterment of health. The first effective treatment available for tobacco use disorder was nicotine gum which received approval from the FDA in 1984, since then there are several formulations approved by the FDA. Currently the available NRTs in the market as [1] oral formulations, such as nicotine gum, lozenge and inhaler, [2] nasal formulation as a nicotine nasal spray and [3] transdermal formulation as a nicotine patch. The principle mechanism of action for all NRTs is to replace nicotine that tobacco users used to and reduces withdrawal symptoms and cravings while reducing toxicities associated with tobacco use. According to one study the authors found nicotine patches reduced reinforcement of cigarette smoking by desensitizing nicotinic receptors in the brain [46]. In a randomized head to head study comparison of nicotine gum, patch, nasal spray and inhaler found that no significant differences were observed in the effects of these products on withdrawals, urge to smoke or rates of abstinence (12 week abstinence rates were 20% gum, 21% patch, 24% for spray and inhaler) [47]. The Cochrane meta-analysis found that all forms of NRTs helps a person's attempt successful in quit smoking and the chances of quitting were increased by 50% to 70% [47]. The authors also found that NRTs work with or without additional counseling and the use of NRT patches shortly before the planned quit date may increase the chance of success [48]. The meta-analysis included 117 trails and the risk ratio (RR) of abstinence for any form of NRT vs. control was 1.60 (95% confidence interval [CI] 1.53 to 1.68) and the pooled RRs for each NRT were 1.49 (95% CI 1.40 to 1.60) for nicotine gum; 1.64 (95% CI 1.52 to 1.78) for nicotine patch; 1.95 (95% CI 1.61 to 2.36) for lozenges; 1.90 (95% CI 1.36 to 2.37) for nicotine inhaler; and 2.02 (95% CI 1.49 to 2.73) for nicotine nasal spray. In addition, the authors found that combination of nicotine patches with rapid acting form of NRT is more effective than a single type of NRT (RR 1.34, 95% CI 1.18 to 1.51) [48]. Specific warnings and most common adverse effects associated with the NRTs are listed in Table 5.

Pharmacists should assess patient readiness and offer appropriate therapy, based on the above literature patients' can use NRT patches shortly before the planned quit date which might increase their success rate. If patient is ready to quit tobacco, pharmacists should assess patient's nicotine intake and recommend appropriate therapy. Majority of patients require dual therapy, such as a long acting nicotine agent (nicotine patch) for continuous nicotine suppression and a short acting nicotine agent (gum, lozenge, inhaler, nasal spray) for cravings. Pharmacists should follow-up with these patients regularly to monitor the nicotine withdrawal symptoms and possible adverse effects associated with the NRT therapies.

Non-nicotine pharmacotherapies

First-line agents (bupropion, varenicline): *Bupropion* was

initially introduced in the U.S. as an antidepressant drug but was subsequently found that it reduces the desire to smoke cigarettes and shown in the clinical trials as an effective agent in tobacco use disorder. Bupropion's mechanism of action for antismoking activity is not fully understood, but it inhibits reuptake of dopamine, noradrenaline, and serotonin in the central nervous system and therefore increasing their levels in the synapse. It is also a non-competitive nicotine receptor antagonist, and at high concentrations it inhibits the firing of noradrenergic neurons. The cessation effects of bupropion seems to be independent of its anti-depressant properties as bupropion is equally effective in smokers with and without depression [49]. In a comparative trial of sustained release (SR) bupropion vs. placebo, the drug yielded similar abstinence rates to that of NRT and achieved long term abstinence in 19% of smokers [50]. In a head-to-head double-blind, placebo-controlled study, the authors found that the abstinence rates at 12 months with bupropion was 30.3% and 35.5% in bupropion plus NRT compared to placebo (15.6%) or nicotine patch alone (16.4%) [51].

Varenicline, a partial agonist of $\alpha_4\beta_2$ nicotinic acetylcholine receptors, through its agonist action relieves withdrawal symptoms, and its antagonist action blocks the reinforcing effects of nicotine. In Phase 2 and Phase 3 clinical trials varenicline has higher abstinence rates than placebo and the alternative active treatments [52]. The Cochrane meta-analysis on nicotine receptor partial agonists for smoking cessation found 39 trails that tested varenicline covered 25,290 participants, 11,801 of them used varenicline. The pooled RR for continuous abstinence for tobacco use disorder at six months or longer for varenicline at standard dosage vs. placebo was 2.24 (95% CI 2.06 to 2.43), low or variables doses of varenicline were also shown to be effective with a RR of 2.08 (95% CI 1.56 to 2.78), RR of varenicline vs. placebo at 6 months was 1.39 (95% CI 1.14 to 1.37). Based on the weighted mean control rate, the number needed to treat with varenicline is 11 (95% CI 9 to 13) for additional beneficial outcome [53]. Due to concerns about possible association between varenicline and depressed mood, agitation, and suicidal behavior or ideation led to the addition of a Block Box Warning (BBW) about the neuropsychiatric disorders in package insert in 2008 [54]. EAGLES trial did not find a link between varenicline use and neuropsychiatric disorders, including suicidal ideation and suicidal behavior, with this FDA modified the package insert and removed BBW and added this information in to the warnings and precautions section [55,56]. Using varenicline in the treatment of tobacco use disorder increases long-term cessation rates between two-and three-fold compared with unassisted quit rates.

Precautions, cautions and most common adverse events associated with bupropion and varenicline are listed in Table 6.

Pharmacists can leverage collaborative practice agreements to prescribe and dispense non-nicotine pharmacotherapies for patients who are unable to quit tobacco with the NRT therapies or unable to tolerate NRT therapies.

Second-line agents (clonidine, nortriptyline): *Clonidine* and *nortriptyline* have been proposed as a second-line pharmacotherapies by the US Clinical Practice Guidelines for treating tobacco use disorder [1,2].

Clonidine is an α_2 -adrenergic agonist and is used as an antihypertensive medication, which decreases sympathetic outflow and acts on the central nervous system may reduce withdrawal symptoms associated with tobacco use disorder. Clonidine appears to be more effective in women, as an aid in tobacco cessation. The dose-dependent, unfavorable adverse effect profile (sedation and dry mouth) and limited efficacy of clonidine preclude its widespread use [57]. Nortriptyline is a tricyclic antidepressant and its proposed mechanism of action is to block the re-uptake of norepinephrine and serotonin. It may reduce withdrawal symptoms. However, its unfavorable adverse effect profile limited its clinical use [58]. Refer to Table 4 for instructions for use and available forms clonidine and nortriptyline in U.S.

Combination Therapies

Each of the first- and second-line pharmacotherapies has indication for treating tobacco use disorder. Combination therapy offers synergistic effects with distinct mechanism of action or therapeutic properties (bupropion combines with nicotine patch). Combining different forms of NRT offers a persistent nicotine level (nicotine patch) and for intermittent increase in nicotine level from immediate-release NRT (nicotine gum, lozenge, inhaler or nasal spray) to deal with the craving and withdrawal symptoms [59]. There are two types of pharmacotherapy combination that has been studied in the literature to enhance abstinence rates: 1) combination of nicotine patch and the use of ad libitum nicotine (which can help to deal with cravings or high stress situations); or 2) combination of nicotine and non-nicotine medications (bupropion SR plus nicotine patch). In a systematic review of NRT for stopping smoking, the authors found that combination of nicotine patch with rapid acting form of NRT is more effective than a single type of NRT (RR 1.34, 95% CI 1.18 to 1.51) [49]. The US Department of Health and Human Services guideline meta-analysis suggests that bupropion SR plus nicotine patch increase long term tobacco abstinence rates compared with nicotine patch alone with odds ratio (OR) 1.3 (95% CI 1 to 1.8) [42]. There was one study that evaluated the combination of varenicline plus bupropion SR (single-arm, open-label pilot study) for 12 weeks along with behavioral therapy. Abstinence rates were reported 71% (95% CI 54-85%) at 3 months and 58% (95% CI 41-74%) at 6 months, larger randomized trials are currently underway [60]. Pharmacists may recommend combination therapy in patients with heavy tobacco use or tobacco users who have relapsed multiple times or severe withdrawal symptoms.

Relapse Prevention

Pharmacotherapies and counseling are all effective treatment strategies for tobacco use disorder, many tobacco users stop after using these methods and subsequently return to smoking within 6 to 12 months following a quit attempt [61]. Interventions that can reduce relapse rates among tobacco abstinence users could have substantial long term abstinence [62]. The Cochrane review concluded that there is insufficient evidence to support the use of specific behavioral interventions to assist tobacco users who have successfully quit for short time to avoid relapse. Pharmacological studies with extended bupropion treatment failed to detect a significant effect with RR 1.15 (95% CI 0.98 to 1.35). On the other hand pharmacological interventions with varenicline significantly reduced relapse in one trial with RR

1.18 (95% CI 1.03 to 1.36) [63]. There were two recent meta-analyses published in the literature that concluded differently for relapse prevention treatment. The Cochrane review concludes that extended treatment with nicotine studies are needed, extended treatment with bupropion has little to no clinical benefit and that only extended treatment with bupropion is effective. In contrast to Cochrane review, the review by Agboola et al concluded that all available pharmacotherapies NRT, bupropion, and varenicline are effective in preventing relapse following tobacco abstinence [62].

Special Populations

Psychiatric comorbidity

Tobacco use among individuals with mental illness is higher than the general population. The U.S. 2009-2011 national survey of substance use and health, estimated tobacco use prevalence at 36.1% in those with behavioral disorder [41]. Data from the National Comorbidity Survey found that tobacco use in those with lifetime mental illness is about 55.3% [37]. Smoking prevalence increases with severity of mental illness, in one sample of 991 serious mental illness patients, the prevalence was 64% in schizophrenia and 44% in bipolar disorder patients [64,65]. Smoking-related mortality is high in mental illness patients and the most common causes of death are heart disease, cancer, and lung disease [39]. Tobacco use increases cardiovascular morbidity and mortality among individuals with mental illness in association with atypical antipsychotic-induced weight gain and the subsequent incidence of type 2 diabetes mellitus [66]. People with mental illness are as motivated to quit tobacco as the general public and quit rates are usually lower in this population [67,68]. Cochrane review of a total 101,804 participants showed that NRT, bupropion and varenicline are superior to placebo, all forms of NRT are effective and varenicline is superior to bupropion with odds ratio OR 1.59 (95% CI 1.29 to 1.96) and to single type of NRT with OR 1.57 (95% CI 1.22 to 1.87) but not combination of NRT with OR 1.06 (95% CI 0.75 to 1.48) [69]. Cochrane review for patients with schizophrenia showed significantly high abstinence rates with varenicline RR 4.74 (95% CI 1.34 to 16.71) and bupropion RR 3.03 (95% CI 1.69 to 5.42) compared to placebo [70]. The U.S. PHS Clinical Practice Guideline Treating Tobacco Use and Dependence recommends that smokers with psychiatric or addictive conditions can use any medication proven to be effective in the general public, except when the medication is contra indicated [42].

Pregnancy

Smoking reduces a woman's chance of getting pregnant. Smoking cigarettes throughout pregnancy causes adverse pregnancy outcomes and results in both short- and long-term negative effects for the mother and unborn child [71,72]. There is consistent evidence in the literature about negative effects of fetal and postnatal exposure to parental tobacco use: preterm birth, fetal growth reduction, low birth weight, sudden infant death syndrome, neurodevelopmental and behavioral problems, obesity, type 2 diabetes mellitus, tobacco addiction, and psychiatric disorders in the offspring [71-73]. A review of clinical outcomes for pregnant women who quit smoking revealed a 20% reduction in the number of low-birth-weight babies, a 17% decrease in preterm births, and average increase in birth weight of 28 grams [74-76]. Pharmacological aids such as NRT, bupropion, and varenicline have not been sufficiently tested for efficacy and safety

in pregnant women and should not be used as first-line agents in pregnant patients [77,78]. Pharmacists should refer pregnant patients to obstetricians and gynecologists for further assessment.

Adolescents

Tobacco use is initiated and consolidated primarily during adolescence and more than 80% of adult smokers begin smoking by 18 years of age with 99% of first used tobacco by age 26 [2]. In addition, adolescents who use multiple tobacco products are at high risk for developing nicotine dependence and might be more likely to continue to use tobacco into adulthood [79]. Flavorings in tobacco products can make it more appealing to youth. In 2014, 73% of high school students and 56% of middle school students reported using flavored tobacco products in the past 30 days [80]. All tobacco product use in youth has been declined from 2013 to 2016, 7 out of every 100 middle school students (17.7% in 2013 to 7.2% in 2016) and 20 out of every 100 high school students (46% in 2013 to 20.2% in 2016) used some types of tobacco product [81]. The reduction in tobacco use among youth has been associated with multiple factors such as national, state and local policies (increasing taxes on tobacco products, prohibiting smoking indoor areas, etc.) and social and environmental factors (religious participation, racial/ethnic pride, higher academic achievement and aspirations) [82]. The U.S. PHS Clinical Practice Guideline recommends that counseling interventions should be provided to adolescent smokers to assist them in quitting tobacco use [42]. A meta-analysis of smoking cessation for teens found that the following treatments such as cognitive behavioral, motivational and social influence strategies have significant effects [83]. Asking adolescents about tobacco use and advising them to quit are the first steps, in a sample of 11th graders, more than 79% reported they would acknowledge their smoking if they asked about it [84]. Pharmacists should ask pediatric and adolescent patients about their tobacco use and clearly communicate the importance of abstaining from using these products.

Role of Electronic Cigarettes

Electronic cigarettes (ECs) are also called e-cigarettes or electronic nicotine delivery systems are battery operated devices that people use to inhale an aerosol, which typically contains nicotine, flavorings and other chemicals. Since 2006 ECs introduced in the market, there have been more than 460 different brands currently available in the market [85]. Although, ECs are aggressively promoted as smoking cessation aids, studies of their effectiveness for abstinence have been implausible. Smokers report using ECs to reduce risks of smoking, but healthcare providers, tobacco control advocacy groups, and policy makers have been reluctant to encourage smokers to use ECs due to lack of evidence [86,87]. A randomized trial comparing ECs with and without nicotine, and nicotine patch found no differences in 6-month quit rates [87]. Among US quit line callers, ECs were less likely to quit at seven months than non-users [88]. Cochrane review on ECs concluded that current evidence for ECs is low and more studies are needed [89]. Electronic cigarettes may reduce the risk of pulmonary diseases induced by tars and other products present in regular cigarettes. However, long term studies using these products needs to be conducted to ensure that this is the case.

Future Direction

Currently available pharmacotherapies have been shown to

improve success rates, the absolute cessation rate remain relatively low. Several other medications have been registered in clinical trials. gov and the following would be of interest for pharmacists in the future: Exenatide once weekly for smoking cessation (ClinicalTrials.gov Identifier: NCT02975297), Guanfacine clinical trial for smoking cessation (ClinicalTrials.gov Identifier: NCT02051309), Test of novel drug for smoking cessation (ClinicalTrials.gov Identifier: NCT02217527), Trial to evaluate the efficacy of simvastatin for smoking cessation (ClinicalTrials.gov Identifier: NCT02399709). Cytisine an $\alpha_4\beta_2$ nicotine acetylcholine receptor partial agonist has been shown to be safe and effective for tobacco use disorder in European countries but not approved in the U.S. at this time. Tobacco use is associated with inhibition of both monoamine oxidase (MAO) A and B subtypes has led to development of MAO selective inhibitors for tobacco use disorder. Although, initial trials were promising and subsequent trials did not yield significant results in randomized, placebo controlled trials [90-93].

Nicotine vaccine is designed to stimulate to the production of antibodies by the immune system that bind to nicotine in the bloodstream and prevent nicotine from crossing blood-brain barrier and binding to its receptors at the central nervous system, leading to decreases in its reinforcing effects thereby increasing chances for quitting tobacco. One of the vaccines called Nic VAX failed in phase III trials that the vaccine did not increase abstinence rates. There is another nicotine vaccine study underway in the clinical trials.gov (ClinicalTrials.gov Identifier: NCT03148925).

Other possible mechanisms that have been considered useful for pharmacological treatments of tobacco addiction are Topiramate and bupropion [94]. Topiramate inhibits glutamatergic neurotransmission while increase GABAergic tone. In a randomized, double-blind, placebo-controlled study topiramate has shown gender-specific effects, men were approximately four times more likely to quit smoking when treated with topiramate as compared to placebo [95]. Topiramate has also shown to be effective in reducing smoking in alcoholic patients [96]. The other agents has been studied in the literature are bupropion, gabapentin, cycloserine, N-acetylcysteine, and modafinil. None of these agents are promising in treating tobacco dependence at this time, more studies underway and pharmacists need to keep up with the literature on possible treatment options for tobacco use disorder.

Conclusion

Healthcare providers play an important role in war against tobacco use, the number one cause of preventable death and disease in the United States. Many patients approach pharmacists to inquire about prescription and OTC medications and other simple ailments. Some of these patients may be tobacco users and want to quit. The first and foremost step is simply asking patients about their tobacco use and documenting this in patient's medical record is one way to identify patients with tobacco use disorder. Once identified, using remaining 4A's to assist patients to quitting tobacco use. There are seven FDA approved medications and out of those seven five of them are NRTs. Majority of the studies concluded that the NRT combinations have optimal patient outcomes with brief counseling. Despite effective treatment strategies and successful short term quits, many smokers relapse, long-term pharmacotherapies may be needed to increase

continuous abstinence and to prevent relapses.

Pharmacists should treat tobacco use disorder like any other chronic medical conditions which necessitate long term pharmacological treatment not only to induce but also to maintain abstinence. SB493 allowed pharmacists to furnish NRT without a prescription; pharmacist should carefully assess patient's withdrawal symptoms and optimize therapy. Treatments that maintain long term abstinence would significantly reduce tobacco-related morbidity and mortality. However, pharmacists should keep up with their knowledge about effective treatment strategies that are currently available and also new treatments that are being studied to assist patients in quitting tobacco use.

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