



City and County of San
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**APPROACHES TO TOBACCO USE DISORDER MEDICATION-ASSISTED TREATMENT
GUIDELINE**

SCOPE: This Approaches to Tobacco Use Disorder Medication-Assisted Treatment (TUD MAT) Guideline is intended to offer prescribing assistance for providers, clients and the interested general public to increase the effectiveness and utilization of TUD MAT in the ambulatory care setting. It is not intended to be comprehensive in scope. These recommendations are not a substitute for clinical judgment, and decisions about care must carefully consider and incorporate the clinical characteristics and circumstances of each individual client.

INTRODUCTION: Tobacco Use Disorder is a chronic and relapsing disease characterized by the compulsive use of tobacco products despite known negative health effects and/or negative financial consequences. Although smoking cigarettes represents the most common form of tobacco use, other forms of tobacco ingestion include; smokeless tobacco, compressed dissolvable tobacco, cigars, tobacco pipes and water pipes (hookahs) and electronic nicotine delivery system (ENDS: vaporizers and electronic cigarettes). There is currently no form of tobacco that is considered without health risks. Despite heavy debate about recommending ENDS as a form of harm reduction to replace smoking tobacco, they are currently not a recommended treatment. ENDS are not FDA regulated and products being advertised as containing no nicotine have been found to contain varying levels of nicotine. ENDS contain cancer causing chemicals and heavy metals.

In the past 50 years smoking rates have significantly declined from approximately 40% prevalence in 1965 to 16.8% in 2014. Despite the substantial decrease in prevalence in the overall population, tobacco use has not declined in persons with mental health (MH) and/or substance use disorders (SUD). In fact, it is estimated that 75% of those with either a SUD or MH disorder use tobacco products. Nearly half of all deaths occurring in those being treated for a SUD or MH disorder are due to a tobacco related illness. Tobacco related deaths also occur decades earlier than in the general population. A staggering 200,000 of the 435,000 annual deaths from smoking are in people with a SUD or MH disorder. The lack of progress within these groups is not due to lack of desire as the majority of persons with a SUD or a MH disorder want to quit using tobacco products and want information about the resources to aid in doing so. Of clients residing in substance use facilities, 50-70% are interested in quitting. Of hospitalized psychiatric clients with TUD, approximately 80% are interested in smoking cessation. Therefore, SUD and MH disorder clients are in many cases willing and ready to attempt to stop using tobacco products.

Barriers that contribute to inadequate TUD treatment in the SUD and MH populations include lack of adequate staff training, lack of knowledge about treatment resources, time constraints, providers and clients alike may share concerns about MH or SUD symptom relapse/exacerbation and may expect failure to quit as the rule not the exception. On the contrary, persons who abstain from tobacco use during SUD treatment are less likely to relapse to drugs or alcohol. Although it is not uncommon for people to believe that smoking helps improve or control MH symptoms research suggests that tobacco use is associated with greater depressive symptoms, anxiety and an increase in suicidal behavior. People

with depression, schizophrenia and post-traumatic stress disorder can quit without impairing their mental health recovery. Despite some misconceptions this population can stop smoking at rates comparable to those in the general population. Tobacco use and dependence should routinely and aggressively be treated within the behavioral health system. Treatment should include both counseling and medication interventions. Having a psychiatric disorder can make this population more susceptible to relapse related to stress and negative feelings. In fact, a psychiatric diagnosis in itself is a risk factor for relapse even for those who haven't smoked in more than 1 year. Treatment should include relapse support and be offered well past the point of cessation.

A further barrier is the historical relationship of tobacco used as a therapeutic tool in the SUD and MH treatment facility setting. Long term relationships with tobacco by providers and clients alike have made TUD more accepted in MH and SUD than in comparable primary care settings. Research has revealed that ignoring TUD in MH and SUD treatment is tantamount to causing harm. This has resulted in policy changes in some residential programs requiring smoke free campuses. Smoke free campus requirements have significantly decreased smoking prevalence in treatment facility staff and have resulted in meaningful decreases in cigarettes per day for clients. Currently the Department of Health Care Services will reimburse residential treatment programs for their smoking cessation efforts, including groups. To decrease program absences medical staff is encouraged to write prescriptions for nicotine replace therapy (NRT) for TUD clients attending residential smoke-free programs.

ASSESSMENT AND INTERVENTION PLANNING: A comprehensive approach to addressing quitting is summarized in Table 1. See Appendix 1 for resources available to clients and providers.

Table 1: “5 A’s” Algorithm

ASK	
Ask about tobacco use at every encounter	Identify all tobacco users and determine nicotine product used, quantity and current tobacco use status Suggested Dialogue: “Benazepril is used to treat hypertension which is often made worse by smoking tobacco products. Do you, or does someone in your household smoke?” “Anxiety is made worse by tobacco smoke. Do you, or does someone in your household smoke?”
ADVISE	
In a clear, personalized, non-judgmental message advise every smoker to quit	Suggested Dialogue: “As your medical provider I want to encourage you to consider cutting down or quitting smoking.” “I’m concerned about your smoking and how that is affecting your goal to stop drinking alcohol. Did you know that some research has shown when you stop drinking and using tobacco products at the same time you can improve your chances of sobriety?”
ASSESS	
Assess willingness to make a quit attempt in the next month Discuss client specific benefits Identify client’s position on readiness to change model	Preparation: Ready to make a quit attempt in the next 30 days → Proceed to Assist Contemplation: Ready to quit in the next 6 months → Schedule a follow up “what is getting in the way of you quitting now?” Pre-Contemplation: Not ready to quit in the next 6 months → Offer empathy and autonomy support. Offer to set a date

	<p>in the future to check-in and provide motivational intervention.</p> <p>Maintenance: Quit for longer than 6 months → Relapse prevention</p>
ASSIST	
Aid client in quitting	<p>See Appendix 2 Smoking Cessation Client Interview</p> <ol style="list-style-type: none"> 1) Assess tobacco use history 2) Set a quit date “have you thought about a quit date?” <ol style="list-style-type: none"> a. Alternative: recommended practicing not smoking for 24 hours and seeing how it goes → then setting a quit date 3) Develop a quit plan which may include: <ol style="list-style-type: none"> a. Referral to local resources (see Appendix 1) b. Identifying social support/resources c. Identifying pattern of use/triggers d. Planning coping skills and routine changes e. Exploring past attempts and identifying what worked well and what didn’t work well f. Determining preferred method of cessation (medication-assisted, cold turkey, reduction)
ARRANGE	
Schedule follow-up contact	<p>Highest risk of drop-out is within the first 7 days. Some evidence suggests more contact with mental health clients leads to more success.</p> <p>Actions during follow-up:</p> <ol style="list-style-type: none"> 1) Congratulate any successes 2) Review wins and challenges 3) Assess pharmacotherapy <p>Minimum follow-up frequency:</p> <ol style="list-style-type: none"> 1) First contact within first week after the quit date 2) Second contact within the first month after quit date 3) Further contact as needed

NICOTINE WITHDRAWAL: Nicotine causes physical dependence and tolerance to the user. When quitting, nicotine withdrawal symptoms can peak in the first 3 days. Symptoms typically subside over the next 3 weeks but may continue for months. Symptoms include negative mood, urges to use, difficulty concentrating, increased appetite/weight gain, insomnia, irritability, anxiety, and restlessness. About half of nicotine users experience at least four of these symptoms when they quit. Any of the first-line pharmacologic agents described below are efficacious in reducing withdrawal symptoms. Clients that report prolonged cravings and withdrawal may be candidates for extended treatment or a combination of pharmacotherapy agents to target symptoms. See Appendix I for client resources regarding nicotine withdrawal and behavioral strategies to treat nicotine withdrawal symptoms and cravings.

TOBACCO USE DISORDER PHARMACOTHERAPY: The use of pharmacotherapy improves the rate of abstinence by 100%-200% compared to “cold-turkey.” Three pharmacologic modalities are approved by the US Food and Drug Administration (FDA) for the treatment of TUD and include: nicotine replacement therapy (NRT), varenicline, and bupropion. These agents have different mechanisms of action and should be used with the consideration of client specific factors and preferences. The goal of treatment is complete abstinence from smoking. Clients that fail to quit, but

reduce the number of cigarettes per day, still incur the negative health risks associated with smoking. The health benefits of smoking reduction are not well studied, however clients that are able to reduce their smoking are more likely to quit in the future. Pharmacotherapy is generally not recommended in clients who smoke less than 10 cigarettes a day. Best outcomes are obtained when pharmacotherapy is used with behavioral counseling. See Appendix 3 for a summary of pharmacotherapy options.

NICOTINE REPLACEMENT THERAPY (NRT): See Appendix 3 for a summary of the nicotine products available, common side effects, and dosing recommendations. NRT relieves nicotine withdrawal symptoms and is used to treat nicotine cravings. The combination of long-acting nicotine (transdermal patch) plus short-acting nicotine as needed (gum or lozenge) is more effective than either alone, however the choice is based largely on client preference and cost. Alternatively, nicotine replacement therapy can safely be added to bupropion to improve abstinence rates. NRT should gradually be reduced as the client abstains from smoking.

Side effects: Treatment side effects are listed in Appendix 3 and differ depending on route of administration. Thorough education of how to use each product is necessary to maximize benefit and limit side effects. For clients that experience vivid dreams with the nicotine transdermal patch, it is suggested to remove the patch at bedtime. Clients that complain of gastrointestinal symptoms with nicotine gum products should be educated on proper gum chewing technique to minimize oral ingestion of nicotine. Those with temporomandibular joint disease, poor dentition, or dental appliances may find nicotine lozenges easier to use compared to the gum.

Drug interactions: There are no clinically meaningful drug interactions with nicotine in any of the routes of administration described. Some clients may experience increased side effects (i.e. nausea, headache, indigestion) to NRT when used in combination with varenicline, however the mechanism to this interaction is unknown.

VARENICLINE: Varenicline is an oral medication that works by blocking nicotine from binding to the receptors that mediate nicotine dependence to reduce withdrawal symptoms and decrease cravings. Randomized controlled trials with varenicline suggest a more robust quit rate in the general population when compared to other monotherapy treatment modalities. When compared to combination NRT, varenicline did not show superior efficacy and produced similar quit rates. It has yet to be studied in a prospective manner in clients with unstable psychiatric symptoms and therefore is not recommended as first-line treatment in clients with unstable psychiatric symptoms. Varenicline allows for an alternative gradual approach to quitting for clients who are not able or not willing to quit abruptly. See Appendix 3 for dosing recommendations and client considerations.

Side effects: Varenicline carried a boxed warning regarding potential neuropsychiatric side effects that was removed in 2016 after more recent studies demonstrated no difference in neuropsychiatric side effects compared with nicotine or bupropion. Neuropsychiatric effects include behavioral changes, hostility, agitation, depressed mood, and suicidal thoughts and attempts. Systematic reviews of varenicline in clients with mental health disorders reveal no significant difference in neuropsychiatric events compared to placebo, however the included studies have smaller sample sizes and exclude clients with unstable psychiatric symptoms (see special populations below). Despite the removal of the warning, clients should be counseled on the potential exacerbation of psychiatric symptoms and report any changes in mood or behavior. In the event of new or worsening suicidal thoughts, varenicline should be stopped immediately.

Drug interactions: There are no clinically meaningful pharmacokinetic drug interactions with varenicline. Some clients may experience increased side effects (i.e. nausea, headache, indigestion) to NRT when used in combination with varenicline, however the mechanism to this interaction is unknown.

BUPROPION: Bupropion is an oral antidepressant medication that enhances norepinephrine and dopamine release in the brain. Its exact mechanism to aid in smoking cessation is not known. It can be considered for those with underlying depression but is also effective in those that are not diagnosed with depression. Bupropion can potentially reduce the amount of weight gain associated with smoking cessation and can be considered in clients for which this would be a concern. When used as monotherapy for the treatment of TUD, bupropion demonstrates slightly lower abstinence rates than other first-line therapies. See Appendix 3 for dosing recommendations and client considerations.

Side effects: Bupropion reduces the seizure threshold in a dose-dependent manner and should be avoided in clients with a known seizure disorder or predisposition to seizure (e.g. alcohol withdrawal, bulimia nervosa). Common side effects are listed in Appendix 3.

Drug Interactions: The major metabolic pathway for bupropion is via CYP2B6 and acts as a moderate inhibitor of CYP2D6. See Table 2 for more information about drug interactions.

Table 2: Bupropion Drug Interactions

Interaction	Clinical Concern
CYP2D6 substrates (ex: fluoxetine, tamoxifen, risperidone, beta-blockers, tramadol)	Increased concentrations of 2D6 substrates when co-administered with bupropion.
CYP2B6 inducers (ex: phenytoin, carbamazepine, rifampin)	Decrease in bupropion exposure when co-administered. Efficacy may be reduced.
MAO inhibitors in preceding 14 days or concurrent use of reversible MAO inhibitors	Increased risk of hypertensive reaction. Combination is contraindicated.

DURATION OF TREATMENT WITH TUD MAT: All clients who initiate pharmacotherapy should have initial follow-up via an office visit or phone call within one to two weeks to assess for positive responses, side effects, and medication optimization. The optimal duration of TUD MAT has not been established.

NRT manufacturers recommend treatment for two to three months, however BHS recommends continuing NRT until the client feels they are no longer at risk for relapse as continued pharmacotherapy can help prevent relapse. When treated with NRT for two months relapse rates are up to 80% during the first year following NRT cessation. It is estimated that approximately 50% of relapses could be averted with extended NRT use past the recommended guidelines. Long-term treatment with NRT (> 6 months) has not been associated with additional major health risks or adverse effects and is preferable in clients who are at high risk of relapsing to cigarette use. Clients with prolonged use may be at higher risk of nicotine withdrawal when stopping their NRT and should be tapered using a lower dose patch, gum, or lozenge. Insurance companies may not cover smoking cessation medications beyond three months and may require additional authorizations for continued use.

Clients may benefit from continuing varenicline after the recommended 12 weeks to prevent relapse. Safety and efficacy have been established up to 6 months of continued use.

The duration of treatment with bupropion may be influenced by other indications outside of TUD (i.e. depression, ADHD) that would require longer term treatment. The recommended duration of treatment with bupropion for TUD is 7-12 weeks, however safety and efficacy has been established up to 12 months of continued use.

MEDICATION SELECTION FOR TUD MAT: Appendix 5 provides decision guidance in selecting pharmacologic therapy. Recommendations are based on randomized-controlled trials, cost, availability,

and other practical considerations. Client preference and co-morbid conditions should be considered when choosing an initial agent as the three different treatment modalities have relatively comparable abstinence rates ranging from 20-35%. Clients with no response to the initial agent at four weeks should have a re-assessment of their treatment to determine if a change in medication is indicated. Medication dosing and administration should be reviewed to ensure adherence and proper use. Those with a partial response to the initial treatment may benefit from the addition of a second agent based residual symptoms such as ongoing withdrawal or cravings. For clients who successfully quit then relapse, the medication that previously worked should be considered.

OFF-LABEL AGENTS WITH INSUFFICIENT EVIDENCE TO RECOMMEND AS FIRST-LINE THERAPY

Nortriptyline: Nortriptyline is a tricyclic antidepressant medication with modest evidence for use in TUD. It can be considered for clients who require adjunctive treatment to a first-line therapy. It may be poorly tolerated in many clients due to sedation, dry mouth, constipation, and dizziness. Nortriptyline should be avoided in clients at risk of arrhythmias, bipolar disorder, and those at risk of overdose. See Appendix 3 for dosing recommendations and client considerations.

Clonidine: Clonidine has limited evidence to support its use in smoking cessation with conflicting efficacy study results. Side effects such as drowsiness, fatigue, and dry mouth may further limit its use. See Appendix 3 for dosing recommendations and client considerations.

Electronic Cigarettes: The role of electronic cigarettes (also known as e-cigarettes) in the treatment of TUD is still unknown. They do not burn tobacco like in conventional cigarettes and have fewer traditional toxins, however information regarding their safety is still uncertain. The use of e-cigarettes to aid in smoking cessation is not currently recommended.

CO-OCCURRING DISORDERS AND SPECIAL POPULATIONS

Cardiovascular disease: In those with stable cardiovascular disease (CVD) the same treatments can safely be used as the general population. Caution should be used with NRT in the first two weeks immediately following a myocardial infarction because of its potential to increase cardiac demand.

Pregnancy: Smoking during pregnancy is the most important modifiable risk factor associated with adverse pregnancy outcomes. Smoking cessation early in pregnancy is most beneficial for the mother and fetus, however quitting at any time in pregnancy can provide benefit. The U.S. Clinical Practice Guideline states that pregnant smokers should be encouraged to quit without medication based on insufficient evidence of effectiveness and theoretical concerns with safety. It is reasonable to consider pharmacotherapy in women who are unable to quit and are at high risk for continued smoking throughout pregnancy. Women that are unable to quit smoking should be referred to a specialist in high risk obstetrics. American College of Obstetricians and Gynecologists recommends the use of NRT with close supervision after discussing the risks of continued smoking against possible risks of pharmacotherapy. There is no strong evidence that pregnant smokers who use NRT are at higher risk of adverse events than pregnant smokers not using NRT. Bupropion can also be considered in this population after discussing the risks and benefits of treatment. Bupropion is known to cross the placenta, however is associated with a low risk of teratogenicity. There is no information regarding the safety of varenicline in pregnancy and thus should be avoided in this population.

Lactation: The Committee on Drugs of the American Academy of Pediatrics recommends NRT as the preferred pharmacotherapy in breastfeeding women. Although nicotine passes into breast milk, the risks associated with smoking are deemed to be of greater harm. Nicotine may have adverse effects on the infant, such as interfering with lung development and increasing the risk of sudden infant death syndrome. Bupropion and its active metabolites are present at low concentrations in breast milk. It may be used in breastfeeding women after discussion of the potential risks of exposure that include vomiting,

jitteriness, sedation, and potential seizures. Data on varenicline in humans is not available and thus should be avoided in breastfeeding women.

Co-occurring mental illness: Those with mental illness are often more nicotine dependent than the general population and may need higher doses, longer duration of treatment, and combined medications to optimize therapy. Clients on medications for the treatment of their mental illness may incur changes in medication blood levels depending on their smoking status. This drug interaction is due to the induction of CYP 1A2 secondary to the hydrocarbons found in smoke that is inhaled from cigarettes, therefore nicotine replacement therapy would not have the same effect. See Appendix 4 for a summary of psychotropic medications susceptible to this interaction. Monitoring medication side effects and symptoms of illness are necessary as a client quits smoking or relapses to determine if a change in dose is required.

Depression: Consider using bupropion for clients with a diagnosis of depression although bupropion's efficacy has been shown independent of depressive symptoms. Varenicline has limited evidence in clients with unstable depressive symptoms or active suicidal ideation. Existing prospective studies have only included patients currently in remission or those on a stable dose of antidepressant for at least 2 months. These studies have not demonstrated an increase in suicidality or worsening depression. Clients with comorbid depression with unstable symptoms should be monitored closely if started on varenicline due to potential for worsening suicidality and other neuropsychiatric symptoms.

Schizophrenia: The combination of bupropion and NRT has been shown to be more effective in clients with schizophrenia than NRT alone and may be considered as a first-line option. Conflicting evidence exists regarding varenicline exacerbating psychotic symptoms in schizophrenia. Generally, varenicline should be avoided in this population, particularly in the setting of unstable symptoms as this has not been evaluated in a prospective manner. Studies that have not demonstrated a worsening in neuropsychiatric symptoms have included participants without hospitalization or acute exacerbation for at least 6 months prior to enrollment and stable dose of treatment.

Bipolar disorder: There are relatively fewer data specific to smokers with bipolar disorder. It is reasonable to avoid bupropion in the setting of bipolar disorder as antidepressant therapy may lead to resurgence of manic symptoms. Clients with unstable symptoms of bipolar disorder should be monitored closely if started on varenicline due to potential for worsening neuropsychiatric symptoms.

Anxiety disorders: Bupropion has the potential to worsen anxiety symptoms upon initiation, however has been effectively used in clients with comorbid anxiety. Bupropion has also demonstrated efficacy in the treatment of TUD in clients with PTSD. Clients with uncontrolled symptoms or unstable comorbid mental illnesses should be monitored closely if started on varenicline due to potential for worsening neuropsychiatric symptoms.

Substance use disorders: Clients with a co-occurring substance use disorder have the highest prevalence of smoking among people with mental illness reaching as high as 98%. Recent evidence supports treating TUD improves treatment of other substance use disorders. Clients with comorbid substance use disorders have a lower abstinence rate than the general population and may benefit from more intensive behavioral interventions. Active substance abuse precludes clients from enrollment into most prospective studies, therefore other patient factors should be considered in treatment selection.

Adolescents: The safety and efficacy of TUD MAT in adolescents is less known as compared with adults. NRT can be used safely in this population and may be considered in addition to behavioral interventions. Lower doses of nicotine patches and gum should be used in those with body weight less than 45 kilograms. Of note, over the counter (OTC) sales of NRT products are restricted to those ≥ 18

years of age. Bupropion and varenicline should be used at the discretion of the clinician as evidence in this age group is limited.

Older adults: There are no meaningful differences in safety or efficacy in older adults.

Hepatic impairment: NRT can safely be used in hepatic impairment although clearance may be reduced. Bupropion should be used with caution in clients with hepatic impairment. Dose reductions are recommended in for those with moderate-severe impairment. No dosage adjustment is necessary for varenicline.

Renal impairment: No dosage adjustment is necessary for NRT. Bupropion side effects should be monitored in those with reduced renal clearance. Varenicline requires dose reduction for clients with creatinine clearance less than 30 ml/min. See Appendix 3 for recommendations.

REFERENCES AND FURTHER READING

INTRODUCTION, ASSESSMENT, AND INTERVENTION PLANNING

U.S. Department of Health and Human Services. (2014). Reducing the health consequences of smoking: 50 years of progress: a report of the surgeon general. US Department of Health and Human Services, Rockville, MD. Available online at: <https://www.surgeongeneral.gov/library/reports/50-years-of-progress/full-report.pdf>

Grant BF, Hasin DS, Chou P, et al. Nicotine dependence and psychiatric disorders in the United States; results from the national epidemiologic survey on alcohol and related conditions. *Arch Gen Psychiatry*. 2004;61:1107-1115.

Bandiera FC, Anteneh B, Le T, et al. Tobacco-related mortality among persons with mental health and substance abuse problems. *PloS One*. 2015;10 e0120581.

Royal College of Physicians, Royal College of Psychiatrist. (2013). Smoking and mental health. London RCP. Available online at: <https://www.rcplondon.ac.uk/file/3583/download?token=bAgvRKDO>

Morris CD, Giese AA, Turnbull JJ, et al. Predictors of tobacco use among persons with mental illness in a statewide population. *Psychiatric Serv*. 2006;57:1035-1038.

Tulloch HE, Pipe AL, Clyde MJ, et al. The quit experience and concerns of smokers with psychiatric illness. *AM J of Prev Med*. 2016;50:709-718.

Han B, Compton, M, Blanco C. Tobacco use and 12-month suicidality amount adults in the United States. *Nicotine Tob Res*. 2017;19:39-48.

Weinberger AH, Platt J, Esan H, et al. Cigarette smoking is associated with increased risk of substance use disorder relapse. A nationally representative, prospective longitudinal investigation. *J Clin Psych*. 2017; 78:e152-e160.

Weir K. Smoking and mental illness. People with behavioral health conditions are more likely to smoke. Psychologists are among those working to understand why and helping them quit. *Monitor on Psychology*. 2013;44:36.

Alvarez Gutierrez FJ, Ferrer Galvan M, Ruiz Bernal AP, et al. Predictors of 10-year smoking abstinence in smokers abstinent for 1 year after treatment. *Addiction*. 2016;111:545-551.

McKelvey K, Thrul J, Ramo D. Impact of quitting smoking and smoking cessation treatment on substance use outcomes; An updated and narrative review. *Addict Behav*. 2017;65:161-170.

Knudsen HK, Studts JL, Boyd S, et al. Structural and cultural barriers to the adoption of smoking cessation services in addiction treatment organizations. *J of Addict Dis*. 2010;29:294-305.

U.S. Department of Health and Human Services. (2016). E-cigarette use among youth and young adults: a report of the surgeon general. US Department of Health and Human Services, Rockville, MD. Available online at: https://e-cigarettes.surgeongeneral.gov/documents/2016_sgr_full_report_non-508.pdf

National Association of State Mental Health Program Directors. (2007). Tobacco-free living in psychiatric settings: a best-practices toolkit promoting wellness and recovery. Available online at: https://www.nasmhpd.org/sites/default/files/April142011TCIP_tk_FINAL_electronic0414.pdf

PHARMACOTHERAPY

University of California San Francisco School of Pharmacy. (2018). The Rx for change: clinician-assisted tobacco cessation curriculum. Available online at: <http://rxforchange.ucsf.edu>

Fiore MC, Jaén CR, Baker TB, et al. (2008). Treating tobacco use and dependence: 2008 update. US Department of Health and Human Services, Rockville, MD. Public Health Service. Available online at: https://www.ahrq.gov/sites/default/files/wysiwyg/professionals/clinicians-providers/guidelines-recommendations/tobacco/clinicians/update/treating_tobacco_use08.pdf

National Institute for Clinical Excellence (NICE). (2013). Smoking: acute, maternity and mental health services. NICE Public Health Guidance 48. Available online at: <https://www.nice.org.uk/guidance/ph48/resources/smoking-acute-maternity-and-mental-health-services-pdf-1996364658373>

Stead LF, Koilpillai P, Fanshawe TR, et al. Combined pharmacotherapy and behavioral interventions for smoking cessation. *Cochrane Database Syst Rev.* 2016;24:3:CD008286.

Cahill K, Stevens S, Perera R, Lancaster T. Pharmacological interventions for smoking cessation: an overview and network meta-analysis. *Cochrane Database Syst Rev.* 2013;5:CD009329.

Hajek P, West R, Foulds J, et al. Randomized comparative trial of nicotine polacrilex, a transdermal patch, nasal spray, and an inhaler. *Arch Intern Med.* 1999;159:2033–2038.

Wennike, P, et al. Smoking reduction promotes smoking cessation: results from a double blind, randomized, placebo-controlled trial of nicotine gum with 2-year follow-up. *Addiction.* 2003;98:1395–402.

Ziedonis D, Hitsman B, Beckham JC, et al. Tobacco use and cessation in psychiatric disorders: national institute of mental health report. *Nicotine Tob Res.* 2008;10:1691–1715.

Williams JM, Hughes JR. Pharmacotherapy treatments for tobacco dependence among smokers with mental illness or addiction. *Psychiatric Annals.* 2003;33:457- 466.

Morris CD, Morris CW, Matrin LF, et al. (2009). Tobacco cessation toolkit for mental health providers. University of Colorado Denver, Department of Psychiatry, Behavioral Health and Wellness Program. Available online at: https://www.integration.samhsa.gov/Smoking_Cessation_for_Persons_with_MI.pdf

Kleber HD, et al. (2006). Treatment of patients with substance use disorders, second edition. American Psychiatric Association. Available online at: http://www.psych.org/psych_pract/treatg/pg/SUD2ePG_04-28-06.pdf

Wu Q, Gilbody S, Peckham E, et al. Varenicline for smoking cessation and reduction in people with severe mental illness: systematic review and meta-analysis. *Addiction.* 2016 Sep;111:1554-67.

Kroon LA. Drug interactions with smoking. *Am J Health-Syst Pharm.* 2007;64:1917-21.

APPENDIX 1: LOCAL RESOURCES

Program Name	Overview
Free Smoking Cessation Groups	
<p>San Francisco Tobacco Free Project Zuckerberg San Francisco General Hospital and Trauma Center 2550 23rd St, Building 40, on the 5th floor San Francisco, CA 94110 Phone: (628) 206-6074 http://sanfranciscotobaccofreeproject.org/you/</p>	<p>A free program to assist residents of San Francisco to quit smoking or cut back located at the Zuckerberg San Francisco General Hospital. This program consists of a series of classes aimed at assisting those that wish to quit smoking achieve this goal.</p>
<p>The Last Drag 290 Dolores Street San Francisco, CA 94103 Phone: 415-339-7867 Hours: Wednesdays 6:30-8:00 pm www.lastdrag.org</p>	<p>A group cessation program for lesbian, gay, bisexual, transgender, and HIV positive individuals.</p>
<p>Northern California Intergroup of Nicotine Anonymous 1748 Market St, Suite #202 San Francisco, CA 94102 Phone: 415-775-7171 Hours: Wednesdays 6:30 pm</p> <p>2118 Greenwich St San Francisco, CA 94123 Phone: 415-308-1886 Hours: Saturdays 10:00 am http://www.nica-norcal.org/index.shtml</p>	<p>A 12-step help program for men and women.</p>
Free Phone and Online Programs	
<p>California Smokers' Helpline English: 1-800-NO-BUTTS (1-800-662-8887) Spanish: 1-800-456-6386 Mandarin & Cantonese: 1-800-400-0866 Vietnamese: 1-800-778-8440 Korean: 1-800-556-5564 Deaf/Hearing Impaired: 1-800-933-4TDD https://www.nobutts.org/</p>	<p>Free telephone counseling, self-help materials, and online help in six languages to help clients quit smoking.</p>
<p>quitSTART smartphone app http://tinyurl.com/freequitstart</p>	<p>A free smartphone app created by the Tobacco Control Research Branch at the National Cancer Institute in collaboration with the FDA. The app takes personal information about a person's smoking history and gives tips, inspiration, and challenges to assist in becoming smokefree.</p>
<p>QuitGuide smartphone app https://www.cdc.gov/tobacco/campaign/tips/quit-smoking/mobile-quit-guide/index.html</p>	<p>A free smartphone app developed by the Tobacco Control Research Branch at the National Cancer Institute. The app helps an individual understand smoking patterns and build the skills needed to become and stay smokefree.</p>
<p>Smokefree.gov</p>	<p>An online website created by the Tobacco Control Research Branch at the National Cancer Institute that provides free, accurate, evidence-based information and professional assistance to help support the immediate and long-term needs of people trying to quit smoking.</p>

Program Name	Overview
Resources for Providers	
<p>Rx for Change http://rxforchange.ucsf.edu/</p>	<p>Clinician-Assisted Tobacco Cessation is a comprehensive tobacco cessation training program that equips health professional students and practicing clinicians, of all disciplines, with evidence-based knowledge and skills for assisting clients with quitting.</p> <p>UCSF openly shares the Rx for Change materials with others at no cost; however, all persons who receive any component of the Rx for Change program must complete an online registration process. Rx for Change can be used only for non-commercial teaching and research purposes and cannot be used for profit.</p>
<p>Smoking Cessation Leadership Center https://smokingcessationleadership.ucsf.edu/</p>	<p>A national program office of the Robert Wood Johnson Foundation at the University of California, San Francisco with a mission to raise the number of health professionals and health care institutions that successfully help their clients to quit smoking. It provides clinicians with research and information, and smokers with resources to quit. The Center creates partnerships for results with a variety of groups and institutions to develop and implement action plans around smoking cessation.</p>
<p>1800-NO-BUTTS https://www.nobutts.org/free-training</p>	<p>The Center for Tobacco Cessation (CTC) provides training for the California Smokers' Helpline. CTC helps organizations with professional training, structure and provides the following free services:</p> <ol style="list-style-type: none"> 1) Free continuing education credits through online courses designed to provide the knowledge necessary to treat tobacco dependence. Smoking cessation behavioral health CE's include: substance use disorder, anxiety, depression and behavioral health 2) Provider Toolkits complete with webinars and client educational materials 3) Customized Training- CTC staff can come onsite upon request and put together customized training for health professionals upon request. 4) Provider Support-CTC offers phone and email consultation in areas such as, developing a comprehensive cessation strategy, cessation in special populations, evidence-based behavioral treatments, pharmacological treatments and preventing relapse <p>For assistance, please contact Lesley C. Phillips at (858) 300-1051 or lcopeland@ucsd.edu.</p>

APPENDIX 2: SMOKING CESSATION INTERVIEW



Smoking Cessation Interview

1. Smoking Status

- a. How many cigarettes do you smoke each day? _____
- b. How soon do you smoke after you wake up? _____

2. Readiness

- a. On a scale from 0-10, (where “0” is not ready to quit smoking and “10” is ready to quit smoking), what score would you give yourself?

- b. If not 0, you gave yourself a score of __. Why did you think __ and not a lower number?
- c. If 0, is there anything that would help raise your score to a 1 or 2?

3. Confidence

- a. On the same scale (from 0-10), how confident are you that you would be able to quit smoking?

- b. If score is < 6, what would help you feel more confident?

3. Motivation

- a. What would you say are the good things about smoking? (What do you like about smoking)?

- b. What are the not so good things about smoking? (What is your main reason to quit)?

4. Smoking History

- a. How old were you when you first started smoking regularly? _____
- b. Have you ever quit before? Yes No
- c. If yes. Last time? _____ Longest time? _____

5. Quitting Method

- a. What method(s) would you like to use to quit smoking?
 - Nicotine replacement therapy (e.g., patches, gum, lozenges)
 - Medication (e.g., Zyban, Chantix)
 - Cold Turkey
 - Cutting down..... toward a Quit Date.

6. Planning

- a. When you quit smoking what will be your 3 most difficult triggers?
- b. What can you do instead of smoking in those situations? (Cognitive & behavioral strategies, pharmacotherapy & referral)

Triggers	Strategies

7. Setting a Quit Date

- a. When would you like to set your quit date?

8. If planning on using Nicotine Replacement Products Please complete the following questions:

Questions to be asked by pharmacist:

- a. Could you be pregnant or do plan to become pregnant? *If yes-defer to health care provider*
 - YES NO

Heart History: *If yes to any of the below furnish with caution and defer to provider*

- a. Have you had a heart attack within the last two weeks?
 YES NO

- b. Do you have a history of heart palpitations/irregular beats/arrhythmia?
 YES NO

- c. Do you currently experience frequent chest pain or do you have unstable angina?
 YES NO

Other History:

- a. Do you have serious dental problems or have you been diagnosed with TMJ (pain or popping of the jaw)? *If yes-avoid nicotine gum*
 YES NO

- b. Do you have a history of severe acid reflux or stomach upset? *If yes-monitor for exacerbation from gum or lozenge*
 YES NO

APPENDIX 3: FDA-APPROVED MEDICATIONS FOR TOBACCO USE DISORDER

Product	Dosage^	Common Side Effects	Availability	Counseling Points	Advantages	Disadvantages
Short-Acting Products						
Nicotine Gum 2 mg, 4 mg	For the following weeks, use gum as needed for cravings or urges to smoke: Wks 1-6 every 1-2 hrs Wks 7-9 every 2-4 hrs Wks 10-21 every 4-8 hrs <i>If 1-24 cigs/day: use 2 mg</i> <i>If 25+ cigs/day*: use 4 mg</i> NTE: 24 pcs/day *for combination NRT, start with 2 mg dose	Mouth/jaw soreness, indigestion, hiccups	OTC Only Relative Cost: \$	<ul style="list-style-type: none"> Chew each piece slowly Park between cheek and gum when peppery or tingling sensation appears (~15–30 chews) Resume chewing when tingle fades Repeat chew/park steps until most of the nicotine is gone (tingle does not return; generally 30 min) Park in different areas of mouth No food or beverages 15 minutes before or during use 	<ul style="list-style-type: none"> Might serve as an oral substitute for tobacco Can be titrated to manage withdrawal symptoms Can be used in combination with other agents to manage situational urges Relatively inexpensive 	<ul style="list-style-type: none"> Frequent dosing can be problematic with significant dental work Proper chewing technique is required for effectiveness
Nicotine Lozenge 2 mg, 4 mg	For the following weeks, take one lozenge* as needed for cravings or urges to smoke: Wks 1-6 every 1-2 hrs Wks 7-9 every 2-4 hrs Wks 10-21 every 4-8 hrs NTE: 20 pcs/day <i>If 1st cig within 30 mins of waking: use 4 mg</i> <i>If 1st cig after 30 mins of waking: use 2 mg</i> *for combination NRT, start with 2 mg dose	Mouth and throat soreness, indigestion, hiccups	OTC Only Relative Cost: \$	<ul style="list-style-type: none"> Allow to dissolve slowly (20–30 minutes for standard; 10 minutes for mini lozenge) Nicotine release may cause a warm, tingling sensation Do not chew or swallow Occasionally rotate to different areas of the mouth No food or beverages 15 minutes before or during use 	<ul style="list-style-type: none"> Might serve as an oral substitute for tobacco Can be titrated to manage withdrawal symptoms Can be used in combination with other agents to manage situational urges Relatively inexpensive 	<ul style="list-style-type: none"> Frequent dosing Gastrointestinal side effects can compromise use of lozenge

^NRT dosing is based on recommendations from package inserts. Clients can safely smoke and continue to use NRT beyond package instructions. We recommend using NRT until the client feels ready to step down therapy or stop treatment.

Product	Dosage [^]	Common Side Effects	Availability	Counseling Points	Advantages	Disadvantages
Short Acting Products						
Nicotine Nasal Spray 10 mg/ml metered spray	Spray 1-2 sprays in each nostril every hour as needed for nicotine cravings. <i>One dose= 1 spray in each nostril, each spray delivers 0.5 mg.</i> NTE: 5 doses/hr or 40 doses/day	Nasal irritation, change in sense of smell/taste, cough, tearing, headache	Prescription Only Relative Cost: \$\$\$	<ul style="list-style-type: none"> Avoid with underlying chronic nasal disorders (rhinitis, nasal polyps, sinusitis) or severe reactive airway disease Do not sniff or inhale the spray when administering 	<ul style="list-style-type: none"> Can be titrated to rapidly manage withdrawal Can be used in combination with other agents to manage situational urges Shown to be more efficacious than other short-acting NRT 	<ul style="list-style-type: none"> Frequent dosing Nasal irritation can be problematic Relatively expensive
Nicotine Inhaler 10 mg cartridges	Puff or deeply inhale 1 cartridge every 1-2 hrs; Titrate to level of nicotine desired to diminish cravings. Each cartridge delivers 4 mg of nicotine NTE: 16 cartridges/day	Local irritation of mouth and throat, cough, indigestion	Prescription Only Relative Cost: \$\$\$	<ul style="list-style-type: none"> Avoid in clients with bronchospastic disease Inhale into back of throat or puff in short breaths Highest chance of success when at least 6 cartridges/day are used at start of treatment Best effects with continuous puffing for 20 minutes Nicotine in cartridge is depleted after 20 minutes of active puffing Open cartridge retains potency for 24 hours No food or beverages 15 minutes before or during use 	<ul style="list-style-type: none"> Might serve as an oral substitute for tobacco Can be titrated to rapidly manage withdrawal Can be used in combination with other agents to manage situational urges 	<ul style="list-style-type: none"> Frequent dosing Relatively expensive

[^]NRT dosing is based on recommendations from package inserts. Clients can safely smoke and continue to use NRT beyond package instructions. We recommend using NRT until the client feels ready to step down therapy or stop treatment.

Product	Dosage [^]	Common Side Effects	Availability	Counseling Points	Advantages	Disadvantages
Long-Acting Products						
Nicotine Transdermal Patch 7 mg, 14 mg, 21 mg (24-hr release) patches	Place one patch on dry skin every 24 hours as directed*: 21 mg/24 hrs x 4 wks, 14 mg/24 hrs x 2 wks, 7 mg/24 hrs x 2 wks Start with 21 mg patch if smoking > 10 cigs/day and 14 mg patch is ≤ 10 cigs NTE: 21 mg/day (Higher doses may be considered on an individual basis for those that smoke >20 cigs or continue to smoke while using the patch)	Local skin reaction, insomnia, vivid dreams	OTC and Prescription Relative Cost: \$	<ul style="list-style-type: none"> • Rotate patch application site daily; do not apply a new patch to the same skin site for at least one week • May wear patch for 16 hours if client experiences sleep disturbances (remove at bedtime) • Not recommended for use by clients with dermatologic conditions (i.e. psoriasis, eczema, atopic dermatitis) 	<ul style="list-style-type: none"> • Once-daily dosing • Discreet appearance • Can be used in combination with other agents • Delivers consistent nicotine levels over 24 hours • Relatively inexpensive • Most efficacious product on BHS formulary as NRT monotherapy 	<ul style="list-style-type: none"> • When used as monotherapy, cannot be titrated to acutely manage withdrawal symptoms

[^]NRT dosing is based on recommendations from package inserts. Clients can safely smoke and continue to use NRT beyond package instructions. We recommend using NRT until the client feels ready to step down therapy or stop treatment.

Product	Dosage [^]	Common Side Effects	Availability	Counseling Points	Advantages	Disadvantages
Oral Medications						
Bupropion Sustained Release (SR) 150 mg tablet	Begin therapy 1–2 weeks prior to quit date: Take 150 mg PO qAM x 3 days, then 150 mg PO BID Contraindications: <ul style="list-style-type: none"> Seizure disorder Current or prior diagnosis of bulimia or anorexia nervosa Simultaneous abrupt discontinuation of alcohol or sedatives/benzodiazepines MAO inhibitors in preceding 14 days; concurrent use of reversible MAO inhibitors 	Insomnia, dry mouth, nervousness/difficulty concentrating, nausea, dizziness, constipation, seizures	Prescription Only Relative Cost: \$\$	<ul style="list-style-type: none"> Allow at least 8 hours between doses Avoid bedtime dosing to minimize insomnia Use with caution in clients with concomitant therapy with medications/conditions known to lower the seizure threshold 	<ul style="list-style-type: none"> May reduce weight gain associated with quitting May be beneficial in clients with co-morbid depression Once daily bupropion extended-release (XL) may be used in place of the SR formulation to enhance adherence Can be used in combination with NRT Dose tapering is not necessary 	<ul style="list-style-type: none"> Seizure risk is increased Several contraindication and precautions preclude use in some clients (see below) No emergent relief
Varenicline 0.5 mg, 1 mg tablets	Start 1 week before quit date: On days 1-3, take 0.5 mg PO qAM On days 4-7, take 0.5 mg PO BID On weeks 2-12, take 1 mg PO BID Dosing adjustment is necessary for clients with severe renal impairment (< 30 ml/min) to a maximum of 0.5 mg BID	Nausea, vomiting, sleep disturbances (insomnia, abnormal/vivid dreams), constipation, flatulence, neuropsychiatric symptoms	Prescription Only Relative Cost: \$\$\$	<ul style="list-style-type: none"> Take dose after eating and with a full glass of water Clients that incur sleep disturbances can be instructed to take the evening dose earlier in the day or may require skipping the evening dose Avoid alcohol while taking Gradual approach with no defined quit date or if clients continue to smoke past quit date: Titrate dose as above to 1 mg PO BID. 	<ul style="list-style-type: none"> Offers a different mechanism of action for clients who failed other agents Dose tapering is not necessary May provide greater efficacy in the general population compared to other monotherapy 	<ul style="list-style-type: none"> Cost of treatment No emergent relief Clients should be monitored for potential neuropsychiatric symptoms

[^]NRT dosing is based on recommendations from package inserts. Clients can safely smoke and continue to use NRT beyond package instructions. We recommend using NRT until the client feels ready to step down therapy or stop treatment.

Product	Dosage [^]	Common Side Effects	Availability	Counseling Points	Advantages	Disadvantages
				<p>Clients should reduce smoking by 50% in first 4 weeks, then additional 50% in following 4 weeks, continued until abstinence in 12-24 weeks</p> <ul style="list-style-type: none"> • 		
Off-Label Agents						
<p>Nortriptyline 10 mg, 25 mg, 50 mg, 75 mg capsules</p>	<p>Take 25 mg PO at bedtime. Increase dose as tolerated by 25 mg/week up to 75-100 mg</p> <p>Contraindications MAO inhibitors in preceding 14 days; concurrent use of reversible MAO inhibitors</p>	<p>Dry mouth, orthostatic hypotension, cardiac arrhythmia, constipation, urinary retention, sexual dysfunction, sedation</p>	<p>Prescription Only</p> <p>Relative Cost: \$</p>	<ul style="list-style-type: none"> • Begin therapy 4 weeks prior to quit date • Take at bedtime to avoid daytime sedation • Should be used with caution in clients with a history of cardiovascular disease 	<ul style="list-style-type: none"> • May be beneficial in clients with co-morbid depression, anxiety, insomnia, or chronic pain • Relatively inexpensive • Can be used in combination with NRT 	<ul style="list-style-type: none"> • High side effect burden • Dangerous in overdose • May require blood level monitoring
<p>Clonidine 0.1 mg, 0.2 mg, 0.3 mg tablets</p> <p>0.1 mg/24hr, 0.2 mg/24 hr, 0.3 mg/24 hr patches</p>	<p>Oral: Can be started at 0.1 mg PO BID and titrated to 0.4 mg divided TID</p> <p>Patch: Apply 0.1 mg/24 hr patch to dry skin every 7 days. Can be titrate based on effect and tolerability.</p>	<p>Decreased heart rate, sedation, orthostatic hypotension, dizziness, dry mouth</p>	<p>Prescription Only</p> <p>Relative Cost: \$</p>	<ul style="list-style-type: none"> • Begin therapy 48-72 hours before quit attempt • Do not discontinue abruptly, dose must be gradually reduced • Start medication at bedtime as it can cause drowsiness and dizziness 	<ul style="list-style-type: none"> • May be beneficial in clients with co-morbid ADHD or insomnia • Weekly patch may improve adherence • Relatively expensive 	<ul style="list-style-type: none"> • Can be poorly tolerated due to side effects • Drug interaction and disease states may limit use

[^]NRT dosing is based on recommendations from package inserts. Clients can safely smoke and continue to use NRT beyond package instructions. We recommend using NRT until the client feels ready to step down therapy or stop treatment.

APPENDIX 4: TOBACCO USE DISORDER MEDICATION PHARMACOTHERAPY SELECTION

Level of Recommendation	Medication(s)	Pertinent Treatment Considerations (Not exhaustive, see Appendix 3 for additional details)
Strongest	NRT combination: nicotine patch + gum or lozenge	<ul style="list-style-type: none"> • Produces relatively constant levels of nicotine and allows for acute dose titration as needed • Cost-effective, on BHS formulary • Demonstrates superior efficacy over other monotherapy pharmacologic treatments • Minimal risk of exacerbating psychiatric symptoms
Moderate	NRT monotherapy: nicotine patch, gum, or lozenge	<ul style="list-style-type: none"> • NRT monotherapy results in significantly lower quit rates than combination NRT • If a single NRT agent is preferred, the patch has been shown to be most efficacious and on BHS formulary
	Bupropion	<ul style="list-style-type: none"> • Least robust effects compared to other pharmacologic treatments • Treatment for co-morbid depression • Drug interactions, precautions, and contraindications may preclude use in clients with mental health disorders
	Varenicline	<ul style="list-style-type: none"> • Shown to be most efficacious in general population compared to other monotherapy pharmacologic treatments • Limited prospective evidence in clients with unstable psychiatric symptoms • Not on BHS formulary
Lowest	Nortriptyline	<ul style="list-style-type: none"> • Moderate efficacy in clients who cannot use a first-line agent or who need an adjunct to first-line therapy • Treatment of co-morbid depression, chronic pain, insomnia, and anxiety • High side effect burden • Dangerous in overdose
	Clonidine	<ul style="list-style-type: none"> • Treatment of comorbid ADHD • Limited evidence of benefit over placebo

APPENDIX 4: NOTABLE DRUG INTERACTIONS OF PSYCHIATRIC MEDICATIONS WITH HYDROCARBONS FROM TOBACCO SMOKE

Drug/Class	Mechanism of interaction and effects
Alprazolam	<ul style="list-style-type: none"> • Conflicting data on significance, but possible ↓ plasma concentrations (up to 50%); ↓ half-life (35%).
Caffeine	<ul style="list-style-type: none"> • Metabolism (induction of CYP1A2); ↑ clearance (56%). Caffeine levels likely ↑ after cessation
Chlorpromazine	<ul style="list-style-type: none"> • ↓ AUC (36%) and serum concentrations (24%). • ↓ Sedation and hypotension possible in smokers; smokers may require ↑ dosages.
Clozapine	<ul style="list-style-type: none"> • ↑ Metabolism (induction of CYP1A2); ↓ plasma concentrations (by 18%). • ↑ Levels upon cessation may occur; closely monitor drug levels and reduce dose as required to avoid toxicity.
Fluvoxamine	<ul style="list-style-type: none"> • ↑ Metabolism (induction of CYP1A2); ↑ clearance (24%); ↓ AUC (31%); ↓ C_{max} (32%) and C_{ss} (39%). • Dosage modifications not routinely recommended but smokers may need ↑ dosages.
Haloperidol	<ul style="list-style-type: none"> • ↑ Clearance (44%); ↓ serum concentrations (70%); data are inconsistent therefore clinical significance is not established
Methadone	<ul style="list-style-type: none"> • Possible ↑ metabolism (induction of CYP1A2, a minor pathway for methadone). • Carefully monitor response upon cessation.
Olanzapine	<ul style="list-style-type: none"> • ↑ Metabolism (induction of CYP1A2); ↑ clearance (98%); ↓ serum concentrations (2%). • Dosage modifications not routinely recommended but smokers may need ↑ dosages.
Propranolol	<ul style="list-style-type: none"> • ↑ Clearance (77%; via side-chain oxidation and glucuronidation).
Ropinirole	<ul style="list-style-type: none"> • ↓ C_{max} (30%) and AUC (38%) in study with clients with restless legs syndrome. • Smokers may need ↑ dosages.
Tizanidine	<ul style="list-style-type: none"> • ↓ AUC (30–40%) and ↓ half-life (10%) observed in male smokers.
Tricyclic antidepressants (e.g. imipramine, nortriptyline)	<ul style="list-style-type: none"> • Possible interaction with tricyclic antidepressants in the direction of ↓ blood levels, but the clinical significance is not established.

Not a comprehensive list, for additional interactions see:

<https://smokingcessationleadership.ucsf.edu/sites/smokingcessationleadership.ucsf.edu/files/A4%20DI%20TABLE.pdf>