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Smoking Cessation Pharmacotherapy: Special Populations Pearls

Cardiovascular Disease

Smoking cessation in patients with established cardiovascular disease (CVD) has been shown to reduce the risk of recurrent heart attack[1] and stroke[2]. It also reduces the progression and improves symptoms of heart failure[3] and peripheral arterial disease[4]. The first line smoking cessation agents [nicotine replacement therapy (NRT), bupropion and varenicline] appear to be safe for patients with stable CVD.[5-10] Information on the safety of these agents in patients with unstable CVD is limited; however any potential increase in risk must be weighed against the large reduction in CVD risk that is known to follow smoking cessation.

Smoking Cessation Pharmacotherapy in Patients with Cardiovascular Disease	
NRT (Nicotine Replacement Therapy)	(i) Considered safe for patients with stable cardiovascular disease .[11] (ii) Use with caution if patients have coronary heart disease, serious arrhythmias or vasospastic diseases such as Buerger's disease or Prinzmetal's angina.[11] However, recently published studies suggest NRT use after acute coronary syndromes (ACS) does not increase the risk of major adverse cardiovascular events.[12,13] (iii) Monographs contraindicate use if life-threatening arrhythmias, severe or worsening angina pectoris, recent stroke, and for 2 weeks following myocardial infarction.[5,7]
Bupropion	(i) Safe and effective in patients with stable CVD.[6] (ii) Safety in unstable heart disease and immediately after a myocardial infarction is unknown.[6] (iii) Combination with NRT has been associated with a trend towards increased blood pressure, especially in patients with pre-existing hypertension. Blood pressure should be monitored if combination is used.[14] (Note a recent study found no increase in smoking cessation rates with combination compared with bupropion or NRT alone.[15])
Varenicline	(i) Conflicting information on safety for patients with stable CVD[16,17,18] but more recent studies report no significant increase in CVD events [8.9.10]. (ii) In the study commissioned by the FDA a higher number of CV events was observed in the treatment group but the difference was not statistically significant. CV events were uncommon in both the treatment and placebo group.[19] (iii) Known benefits of varenicline in smoking cessation must be weighed against the small potential risk in smokers with CVD. [13] Advise patients to monitor for and report new or worsening symptoms of CVD while taking varenicline.[19]

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The third line smoking cessation agents, clonidine and nortriptyline, should be used cautiously in patients with CVD. Clonidine lowers blood pressure and heart rate.[20] Tricyclic antidepressants as a class have been associated with cardiac arrhythmias.[21] Both agents are contraindicated in the two week period immediately after a myocardial infarction and in patients with heart failure.[20,21]

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Mental Health Population:

Smoking is problematic in mental health patients due to its potential to reduce the efficacy of antipsychotic medications.[1] Smoking is associated with increased CYP1A1/ 1A2 and 2E1 activity.[2,3] Substrates of these enzymes include several antidepressants (e.g. fluvoxamine), antipsychotics (e.g., haloperidol, olanzapine), anxiolytics (e.g., lorazepam, alprazolam), and other medications (e.g., caffeine).[2,3] Upon smoking cessation, enzyme induction will abate quickly so there is potential for a period of dangerously high blood levels if dosage adjustments are not made.[2,3]

Smoking Cessation Pharmacotherapy in Mental Health Population:	
NRT	(i) Good choice for bipolar disorder and depression.[4] (ii) Nicotine patch can be used for steady state replacement with nicotine gum or lozenges to manage acute urges to smoke (monitor regularly).[5] (iii) Lack of evidence for efficacy in patients with schizophrenia.[6] Monograph-recommended NRT doses may not control withdrawal symptoms in heavy smokers with *schizophrenia.*[7]
Bupropion	(i) In cases of mild, untreated depression bupropion can be recommended as it treats both depression and smoking.[4] (ii) Bupropion can be used cautiously for smoking cessation in patients currently stabilized on an SSRI antidepressant.[8] (iii) Avoid in *bipolar* patients as antidepressant use may trigger mania.[4] (iv) In a recent Cochrane meta-analysis (2013), bupropion reduced the number of cigarettes smoked and increased complete smoking cessation in patients with schizophrenia without harming mental status.[6] (v) It may also be useful in substance abuse disorders.[3,4]
Varenicline	(i) Effective and safe option in stable depression.[4] (ii) Appears to improve smoking cessation rates in patients with schizophrenia but psychiatric adverse effects have been reported.[6] May consider using with caution in stable patients.[3,4,6] (iii) Avoid if patient has a history of suicidal ideation/current unstable psychiatric status.[4,9] (iv) Monitor carefully for emerging or worsening psychiatric symptoms especially during first week of treatment and first week of smoking cessation.[10]

	(v) Instruct patients to stop taking immediately and contact physician if they experience, (or others observe) new/worsened psychiatric symptoms; in many post-marketing reports, symptoms usually resolved upon discontinuation – but in some cases symptoms persisted.[9] (vi) Maintenance treatment for one year with varenicline may decrease the risk of relapse in patients with schizophrenia and bipolar disorder (limitation - small sample size study).[10,11]

Smoking cessation pharmacotherapy works to curb symptoms of nicotine withdrawal; however mental health patients may experience an exacerbation in psychiatric symptoms. Nicotine withdrawal symptoms can mimic or aggravate anxiety disorders so it is imperative to monitor and treat symptoms accordingly.[12]

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Pregnant & Breastfeeding Women:

Adverse outcomes in pregnancy can result due to cigarette smoking such as: spontaneous pregnancy loss, placental abruption, preterm premature rupture of membranes, preterm labor and delivery, low birth weight, and ectopic pregnancy.[1] As for the post-partum period of lactation, smoking is associated with a decreased likelihood and duration of breast feeding.[2] Additionally, there is an increased risk of sudden infant death syndrome (SIDS) in newborns due to second-hand smoke exposure in the home.[3] Therefore, facilitation of smoking cessation for pregnancy and breastfeeding should be maintained until completion of the breastfeeding phase. The following interventions are recommended[1,2,4]:

(i) **Offer psychosocial intervention**. Smoking cessation counselling has been proven to be effective and is recommended as first line treatment for women during pregnancy and lactation.

(ii) **Offer intervention throughout pregnancy and lactation**. Quitting early in pregnancy is most beneficial, albeit quitting at any point within the pregnancy still has value. Reduction in number of cigarettes smoked alone does not improve fetal health outcomes whereas sustained abstinence does.[5]

(iii) **Consider pharmacotherapy** when a pregnant woman is: (a) otherwise unable to quit via non-pharmacological therapy (b) when the likelihood of quitting, with its potential benefits, outweighs the risks of the pharmacotherapy and potential continued smoking.[1] Although there is limited data to inform this choice, particularly for bupropion and varenicline, the benefits of smoking cessation during pregnancy and lactation are well documented. For this reason, some experts suggest that these agents should not be withheld from women unable to stop smoking with nonpharmacologic interventions.[6]

	Smoking Cessation Pharmacotherapy in Pregnant/Breastfeeding Women:
NRT	(i) Although considered the pharmacologic therapy of choice if nonpharmacologic measures fail, there is no clear evidence that NRT is efficacious in smoking cessation in pregnant women.[7,8] Use should be *evaluated case by case*.* (ii) Nicotine crosses the placenta but fetal exposure is less with NRT than with moderate to heavy smoking.[8] Intermittent forms of NRT such as gum, lozenge, or inhaler may limit nicotine exposure compared to the transdermal form. If the transdermal patch is used, recommend removing at night, tapering as directed and discontinuing after 8 to 10 weeks.[1,4,8] (iii) Nicotine may pass into breast milk.[9,10] Rapid release/as needed forms, such as nicotine gum, lozenges or inhaler may be preferred for breastfeeding women.[8,9] These products will produce variable nicotine blood levels similar to smoking; therefore breastfeeding mothers can be advised to nurse before using and / or refrain from using for 2 to 3 hours after nursing to minimize infant exposure.[1,10] However, choice of product should be based on the individual mother's smoking and breastfeeding patterns. Co-ordinate dose to suit the smoker's needs. (iv) Nicotine patch is shown to have no significant influence on the milk intake by the infant; the patch provides a sustained but lower nicotine plasma level.[9]

	(v) A nicotine inhaler will produce plasma levels too low to affect a breastfeeding infant.[10]
Bupropion	(i) Recommendations vary amongst health professionals; limited data on the safety of bupropion in human pregnancies[1,8]; may pass into breast milk although plasma levels in breastfed infants are undetectable[9,10]. (ii) Advantages - No nicotine exposure to the fetus in pregnancy and patient may experience fewer nicotine withdrawal symptoms.[11] (iii) If concomitant depression, bupropion may be considered to treat both smoking and depression in a pregnant woman as long as she does not have an eating or a seizure disorder.[4,11,12] (iii) *Zyban®* post marketing surveillance indicates some neonates exposed to bupropion SR SSRIs, or other new antidepressants during the 3rd trimester have developed complications involving hospitalization (similar symptoms to those caused by SSRIs, or other new antidepressants); if a pregnant woman is treated with bupropion SR, consider tapering in the third trimester[12]. If being used to treat concomitant depression, tapering would not be appropriate.[11]
Varenicline	(i) Varenicline has not been well studied in pregnancy or lactation.[6,9,10] (ii) Until more data become available, reserve varenicline for pregnant mothers who are heavy smokers and have not responded to other smoking cessation interventions.[13] (iii) Varenicline may pass into breast milk. Given its long half-life, caution is advised if used by lactating mothers. Advise mothers to monitor the infant for vomiting, constipation, excess flatulence and change in sleep patterns.[9,10]

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Adolescents:

Teenagers who begin smoking in their adolescent years are likely to continue smoking as adults; therefore management of early nicotine dependence is key.[1,2] Behavioral and motivational interventions should always be employed.[1,2,3] The majority of smoking cessation studies focus on the adult population. The few studies that have investigated pharmacotherapies involved the nicotine patch, nicotine gum and bupropion.[1] In general, none of these interventions demonstrated efficacy in adolescents.[1]

Smoking Cessation Pharmacotherapy in Adolescents:	
NRT	(i) 1st line pharmacotherapy in adolescents with nicotine dependence[1,2,3] i.e. not indicated for intermittent smoking.[3] (II) Both the patch and gum have demonstrated safety. [1,2,3] (ii) Low starting doses for patient <45kg OR smokes less than ½ pack a day.[4]
Bupropion	(i) Can try as 2nd line agent; lower abstinence rates and rapid relapse upon discontinuation.[3]
Varenicline	(i) Not recommended; lack of evidence and safety concerns raised in adult post-marketing reports.[1,3,4]

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Hospital Based Populations:

The reason for admission may serve as an eye-opener to the patient of the dangers of smoking and can motivate smoking cessation.[1] Being in a smoke-free environment removed from the smoking cues associated with everyday life provides an opportunity for the patient to actively pursue quitting. Data to date supports offering hospital-based interventions to all smokers. [2]

For the preoperative hospital population, evidence shows that smoking cessation interventions may decrease postoperative morbidity. Generally, if interventions were implemented 4 to 8 weeks prior to the surgery (NRT and weekly counseling) this would be more likely to result in long-term smoking cessation.[3]

Pharmacotherapy during hospitalization is provided for two purposes: 1) to treat withdrawal symptoms during hospitalization and 2) to promote long term smoking cessation.[4]
attempts.

	Smoking Cessation Pharmacotherapy in Hospital Based Populations:
NRT	(i) Useful to curb nicotine withdrawal symptoms in smokers forced to abstain from smoking temporarily while in hospital.[1] (ii) Use with caution in following patients: ≤2 weeks post myocardial infarction, patients with arrhythmias of concern, and patients with serious or deteriorating angina pectoris.[5] In these patients, recommend oral rather than transdermal NRT.[3] (iii) Cautious initiation of nicotine replacement may be an option during hospitalization for patients with ACS if benefits appear to outweigh the risks.[6] For these patients, recommend oral rather than transdermal NRT.[3] (iv) Nicotine patch most studied for in-hospital use; effective; ideal for bed-ridden patients.[7] (v) Adding NRT to intensive counseling begun during hospitalization increases cessation rates over counseling alone.[1]
Bupropion	(i) Limited evidence to support use of bupropion in hospital setting.[1,2,8] (ii) Bupropion improved abstinence over placebo at the end of the treatment period but not at 12 months in a study of patients hospitalized with CVD.[8]
Varenicline	(i) The addition of varenicline to smoking cessation counselling in the hospital setting does not appear to increase the smoking cessation rate.[2]

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Aboriginal Peoples:

In respect to the rest of the Canadian population, the smoking rate within the Aboriginal community is more than double for adults and youth.[1-3] This is particularly worrisome because smoking is a chief source of morbidity and mortality for this population.[3] There is limited research on this issue but available data suggests that cessation strategies which are effective in the general population are likely to be effective if tailored to aboriginal peoples' culture and traditions.[4] Potential barriers to the use of pharmacotherapy include lack of awareness of these strategies, lack of trust in conventional medicine, accessibility issues, cost, and noncompliance with treatment regimens.[4] Note it is important to distinguish between use of tobacco for traditional ceremonies and substance use disorders involving commercial tobacco.[4] Within Saskatchewan, the TAR program (Tobacco Addiction Recovery) is a culturally relevant tobacco cessation program developed specifically for Aboriginal communities.[5]

	Smoking Cessation Pharmacotherapy for Aboriginal People
NRT	Systematic review of smoking cessation programs indicated that NRT in combination with counselling may be effective.[6,7]
Bupropion	One study reported significant short-term effectiveness.[8]
Varenicline	No published studies.

It has been noted that lack of awareness of coverage options is associated with less compliance to use drug therapy available for smoking cessation.[2] Therefore, as a healthcare practitioner, it is helpful to discuss applicable drug coverage available to Aboriginal patients as that can help motivate cessation. ***Under FNIHB the following drugs are covered for approximately 3 months of therapy per year*: varenicline, bupropion, nicotine gum, lozenges, patch and inhaler.**[9]

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Effects of Smoking/Quitting on Medications:

Pharmacokinetic drug interactions:
Polycyclic aromatic hydrocarbons (PAH's) are in the tar of tobacco smoke and they can interfere with medications by increasing the metabolism of certain drugs, thereby leading to diminished pharmacologic response.[1] PAHs are potent inducers of the hepatic CYP P-450 isoenzymes 1A1/1A2, and 2E1. CYP1A2 accounts for 15% of the total cytochromes present in the liver and there can be significant individual variation in its metabolic activity.[2] After a person quits smoking, an important consideration is how quickly the induction of the affected enzymes dissipates.[1] Upon cessation of smoking, with or without NRT, there may be reduced clearance of medications that are metabolized by these enzymes.[1,2] Clozapine, olanzapine, clomipramine, imipramine, and fluvoxamine are examples of drugs that could be affected.[1,2] The degree of the interaction will vary depending on the importance of the enzyme(s) for clearance and the range of the therapeutic window for the involved drugs.[1,2] Caffeine levels can increase 2- to 3-fold after patients *stop* smoking. The irritability and insomnia that patients think is due to nicotine withdrawal may be from caffeine toxicity.[4] See the table below for all known pharmacokinetic drug interactions associated with smoking.

Drug	Effect of Smoking	Management after smoking cessation
Caffeine	↑ metabolism	↓ caffeine intake by half; Monitor for caffeine toxicity
Clozapine	↑ metabolism (↓ plasma concentrations by 18%)	Monitor for clozapine toxicity; dose ↓ may be needed
Flecainide	↑ metabolism (~17% higher dose requirement)	Dose ↓ may be needed
Fluvoxamine	↑ metabolism (↓ AUC by 30%)	Dose ↓ not usually needed; monitor for side-effects
Insulin	↑ insulin requirements	Monitor for episodes of hypoglycemia
Mexiletine	↑ metabolism	Dose ↓ may be needed; monitor for adverse effects
Olanzapine	↑ metabolism (minimal decrease in plasma concentration)	Dose ↓ may be needed; monitor for adverse effects
Propranolol	↑ metabolism	Dose ↓ may be needed; monitor for adverse effects
Theophylline	↑ metabolism	Monitor levels and ↓ dose accordingly; decrease often needed
Warfarin	INR increases reported	Monitor INR 3-5 days after cessation and adjust dose if needed

Adapted from: https://www.health.gov.bc.ca/pharmacare/pdf/sc-interact.pdf

Pharmacodynamic drug interactions:
A clinically significant interaction can occur with smoking and *combined hormonal contraceptives*. Oral contraceptive use itself can increase the risk of cardiovascular adverse effects and smoking increases the risk of arterial events associated with oral contraceptives.[1] The efficacy of *inhaled or oral corticosteroids* can be reduced in those individuals who smoke.[1,5] Insulin dependent diabetics may experience decreased subcutaneous absorption of insulin, leading to greater dosing requirements.[6,7] This connection has a dose-response relationship which can be noted between the number of cigarettes smoked and degree of insulin sensitivity.[6,7]

General management guidelines:

i. For most drugs the clinician can monitor for an increase in adverse effects of the affected medication post smoking cessation***. Dose adjustments should be guided by monitoring the clinical status of the patient*** [8]

ii. For narrow therapeutic index drugs, decrease dose of affected drugs by 10% for each day for 4 days after quitting.[9] Monitoring serum drug level (if feasible) is also an option, before stopping smoking, and up to two weeks post smoking cessation.[8,9]

iii. If the patient lapses and begins smoking again then adjustment needs to be again considered as sub therapeutic drug levels may result.[9]

iv. Pharmacotherapy cost coverage can positively influence likelihood of use and success rates.[10]

v. For the general population, cost analysis studies demonstrate bupropion and varenicline are more cost-effective than NRT.[10]

vi. Since smoking can affect drug levels, it is important to note smoking status on patient profiles.

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