

Drug InterACTIONS with Tobacco Smoke

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Speaker disclosures

Presenter's Name: Ron Pohar, BScPharm

I have received Honoraria and Speaker/Consulting Fees from:

- Lundbeck, Johnson & Johnson, AA Pharma, HLS Pharma, Indivior

I have no commercial interest in the Drug InterACTIONS with Tobacco Smoke tool which is freely available for download and use.

Learning objectives

After completion of today's session, the participant will:

1. Have increased awareness and understand the importance of identifying drug interactions with tobacco smoke in individuals who are attempting to quit.
2. Identify key drug interactions with tobacco smoke using a tools-based approach.
3. Identify the clinical significance of drug interactions with tobacco smoke and the appropriate action to take by applying a tools-based approach.
4. Apply the Drug InterACTIONS with Tobacco Smoke tool through case-based examples.

Tobacco Use

Tobacco is the number one cause of preventable disease in Canada.

An estimated 48,000 Canadians die each year as a result of smoking.

Approximately 1 in 10 Canadians report smoking cigarettes on a regular basis

- Canadians aged ≥ 25 more likely to report being a current smoker (11%) than those aged 15 to 19 (3%)

Canadians want to quit smoking

- About 64% of Canadians who smoke want to quit
- Over 40% will make one quit attempt over the course of a year
- Almost one third attempt to quit two or more times in a year

Individuals who Smoke Want and Need Help

Patients expect their healthcare providers to ask them about smoking and encourage them to quit.

Patient satisfaction with their healthcare providers is higher when tobacco use is assessed, and treatment is offered.

Asking about tobacco use is not intrusive

- 85% of patients indicate that they would appreciate being asked about smoking behaviour.

Without healthcare professional intervention, individuals who use tobacco may not attempt to quit.

- Studies show that if patients are not asked about tobacco use, they are less likely to quit over a five-year period.

Individuals who Smoke Want and Need Help

Quitting smoking and remaining smoke free can be extremely difficult to achieve.

Without assistance or support, less than 2 to 5% of individuals who smoke manage to stop smoking and remain smoke-free.

Advice to quit smoking from a health care provider can increase the chances of an individual who smokes engaging in a quit attempt

- Community pharmacist interventions have been shown to increase abstinence rates in individuals who smoke approximately two-fold.

Key Message

Pharmacists should not feel uncomfortable asking about tobacco use.

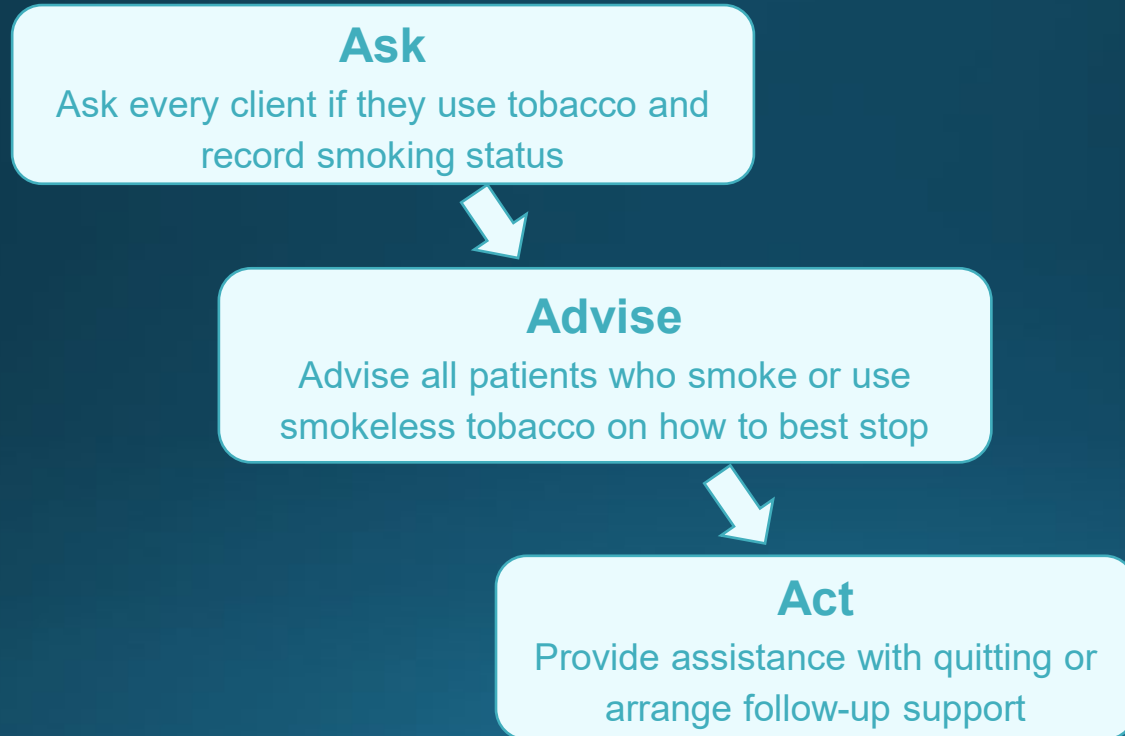
The majority of patients who currently smoke want to quit smoking.

Patients expect healthcare providers to ASK them about smoking.

Quitting is extremely difficult.

- Without support, quitting is even more difficult.

The 3A's Approach



3A's: ASK, ADVISE, ACT

Ask: It is important not just to ASK but to record smoking status

Advise: Advise that best results typically are achieved with pharmacotherapy and support

Act: offer action

How to Ask

- Do you currently or have you ever used tobacco?

How **not** to Ask

- Don't you want to stop smoking?
- How much do you smoke?
- Why are you still smoking?
- What do you smoke?

How to Advise

- Did you know the most effective way to stop smoking is with a combination of support and medication? Both are available to you, and this combination makes you much more likely to succeed in quitting.

How **not** to Advise

- You need/have to stop smoking!
- If you don't stop it will kill you!
- Other people quit without assistance, so you should be able to do it if you have the willpower.

How to Act

Act on patient response

- Build confidence
- Give information
- Refer
- Prescribe if in your scope of practice

Pharmacotherapy

CAN-ADAPTT guidelines:

- ***Combining counselling and smoking cessation medication is more effective than either alone, therefore both should be provided to patients/clients trying to stop smoking where feasible.***

Choose pharmacotherapy based on

- Evidence/Efficacy
- Clinical suitability (medical conditions, contraindications, addiction level)
- Potential drug interactions
- Patient preferences, history, needs (dexterity, coverage)

Drug Interactions and Smoking Cessation

Tailoring of pharmacotherapy for smoking cessation should consider potential drug interactions with a patient's current medications.

But what about the effect of tobacco smoke?

Often the potential for interactions between tobacco smoke and a patient's medication are not considered

- Depending on the pathway through which the medication is metabolized, changes in efficacy of the medication and potential adverse effects can occur.

Metabolic Changes with Smoking: Pharmacokinetic Drug Interactions

Polycyclic aromatic hydrocarbons (PAHs)

Carcinogens found in tobacco smoke

- Inducers of cytochrome P450 enzymes found in the liver
 - CYP1A1
 - CYP1A2
 - CYP2E1

↑metabolism and ↓pharmacological effect of substrate drugs

Can result in pharmacokinetic drug interactions

The effect on drug metabolism is not due to nicotine

Pharmacokinetic Drug Interactions

There is a risk of drug toxicity with smoking cessation due to dissipation of CYP450 induction.

Risk will vary according to patient and drug-related factors

- Number of cigarettes smoked each day
- Inter-individual variation in CYP450 function
- Therapeutic index of the drug
- Extent to which drug is metabolized by CYP450

Pharmacodynamic Interactions with Smoking

Some drugs have pharmacodynamic interactions with tobacco smoke
These effects are thought to be mediated by the nicotine component of tobacco smoke

Nicotine activates the sympathetic nervous system:

- Stimulant effects
- Vasoconstriction

Examples of medications affected by pharmacodynamic interactions due to smoking include beta-blockers and benzodiazepines

Drug Interactions with Tobacco Smoke

How can clinically relevant drug interactions with tobacco smoke be quickly identified?

How should these interactions be managed?

Drug InterACTIONS with Tobacco Smoke Tool

Tool for use by health professionals that identifies

- Key drugs that have PK and PD interactions with tobacco smoke
- The effects of smoking and smoking cessation on those key drugs
- Action to take to manage a potential drug interaction during a quit attempt or period of abstinence from smoking

Tool is based on previously developed evidence-based guidance documents that were developed for use in other jurisdictions (e.g., the United States, Australia, and the United Kingdom)

Drug InterACTIONS with Tobacco Smoke Tool

A large volume of literature has reported on drug interactions, but the tool is focused on those interactions that are most clinically relevant.

The ratings of clinical significance were taken from the literature sources, which potentially varied in definition and severity.

For a particular drug, the tool may include a range of ratings if there was disagreement across the cited literature with respect to the clinical significance.

One-page, double-sided; quick and easy to keep on hand

Available free for download and use from:

<https://www2.gov.bc.ca/assets/gov/health/health-drug-coverage/pharmacare/drug-data/drug-interactions-with-tobacco-smoke-dec-2021.pdf>

Drug InterACTIONS with Tobacco Smoke

The polycyclic aromatic hydrocarbons (PAHs) found in tobacco smoke induce liver enzymes responsible for the metabolism of drugs (IA2, 2B6, 2E1) resulting in pharmacokinetic drug interactions. Pharmacodynamic drug interactions with the components of tobacco smoke may also occur. When supporting quit attempts, it is important to be familiar with the drugs which are affected by tobacco smoke and may require dose adjustment or increased monitoring when smoking status changes. Narrow therapeutic index drugs should be monitored closely.^{1,2,3}

Drug	Effect of smoking	Change with Smoking Cessation	Clinical Significance*	Action
Benzodiazepines ^{1,2,5} (e.g., Alprazolam, diazepam, clonazepam)	Stimulation from nicotine may reduce sedative effects Increased metabolism may result in lower serum levels	Potential increase in levels with smoking cessation Possible increase in sedation	Low to Moderate	Monitor - may require dosage reductions
Betablockers ^{1,2,5}	Increased clearance which may lower serum levels Pharmacodynamic interactions may result in less effective antihypertensive and heart rate control	Potential increase in levels with smoking cessation Effectiveness may be enhanced Possible bradycardia and hypotension	Moderate	Monitor - may require dosage reductions
Bendamustine ¹	Smoking may decrease bendamustine concentrations, with an increase in concentrations of its two active metabolites	Theoretical change in concentration of both bendamustine and its active metabolites	Moderate	Manufacturer recommends caution should be used, or alternative treatments considered in individuals who smoke
Caffeine ^{1,2}	Smoking increases the clearance of caffeine by about 50%	Potential increase in levels with smoking cessation	Moderate	Increased risk of caffeine related side effects (tremor, nausea) Advise patients to reduce caffeine consumption prior to a quit attempt (eg., reduce to half)
Chlorpromazine ^{1,2}	Smoking can reduce serum levels	Potential increase in levels with smoking cessation	Moderate	Monitor for adverse effects (e.g., hypotension, sedation) May require dosage reductions
Clopidogrel ^{1,3}	Smoking-related enzyme induction may increase the metabolism of clopidogrel to its active metabolite Effect of clopidogrel is enhanced in individuals who smoke ≥10 cigarettes/day	Effect of clopidogrel may be diminished by smoking cessation	Low to Moderate	Tobacco cessation should still be recommended in at-risk populations needing clopidogrel
Clozapine ^{1,2,3}	Smoking can increase metabolism and reduce serum levels	Potential increase in levels with smoking cessation	Moderate to High	Closely monitor drug levels and for symptoms of toxicity (e.g., drowsiness, confusion, rapid heart rate) Reduce dose as required to avoid toxicity An average 50% dosage reduction may be required ³
Duloxetine ²	Smoking may lower plasma levels	Potential increase in levels with smoking cessation	Low	May need to decrease dose with smoking cessation Monitor for possible increase in side effects (e.g., nausea, vomiting, and tachycardia)
Erlotinib ^{2,4}	Smoking increases clearance Individuals who smoke may require higher dosages	Potential increase in levels with smoking cessation	Moderate	Individuals who smoke should be advised to quit (according to the manufacturers recommendations) Dosage adjustment may be required
Flecainide ^{1,5}	Smoking increases clearance Individuals who smoke may require higher dosages	Potential increase in levels with smoking cessation	Low to Moderate	Monitor for adverse effects (e.g., dizziness and visual disturbances) Assess need for dose reduction
Fluphenazine ²	Smoking may lower plasma levels	Potential increase in levels with smoking cessation	Moderate	Monitor for increased drowsiness, extrapyramidal side effects, hypotension
Fluvoxamine ^{1,2}	Smoking may lower plasma levels	Potential increase in levels with smoking cessation	Moderate	Routine dosage adjustment not recommended, but dosage reduction may be required
Haloperidol ^{1,2}	Smoking may lower plasma levels Individuals who smoke may require higher dosages	Potential increase in levels with smoking cessation	Moderate	Dosage adjustments may be required Monitor for increased drowsiness, hypotension, and extrapyramidal side effects
Heparin ^{1,2}	Due to pharmacokinetic and pharmacodynamic drug interactions, individuals who smoke may require increased dosages	Prothrombin time may increase with smoking cessation which can increase the risk of bleeding	Moderate	Close monitoring is required along with potential dosage adjustment according to prothrombin time
Insulin, subcutaneous ^{1,2,3}	Individuals who smoke may have increased insulin resistance and may require higher dosages	Insulin resistance may decrease with smoking cessation	Moderate	Potential for hypoglycemia - more frequent blood glucose monitoring is recommended Dosage decreases may be required
Irinotecan ¹	Due to multiple pharmacokinetic mechanisms, systemic exposure and efficacy may be reduced with smoking	Potential increase in levels with smoking cessation; however, dosages are not usually adjusted in presence of smoking	Low	Generally no adjustment is required with smoking cessation

Drug	Effect of smoking	Change with Smoking Cessation	Clinical Significance*	Action
Lithium ²	Smoking increases clearance of caffeine, which indirectly affects lithium levels	Changes in amount of caffeine may affect serum lithium levels (caffeine increases lithium excretion) Theoretically, smoking cessation could indirectly change lithium excretion in the absence of a reduction in caffeine intake	Low	Lithium levels should be checked in patients who have a clinical deterioration
Methadone ^{1,3}	Methadone is metabolized by multiple enzymes Smoking may increase methadone metabolism	Potential reduction in metabolism with smoking cessation	Moderate	Monitor for signs of methadone toxicity (sedation and respiratory depression) and make dose adjustments accordingly
Mexiletine ¹	Smoking may increase clearance	Potential increase in levels with smoking cessation	Low to Moderate	Monitor for adverse effects
Mirtazepine ²	Smoking lowers levels	Potential increase in levels with smoking cessation	Low	Monitor for adverse effects and the need for dosage adjustment
Nintedanib ¹	Exposure is reduced by smoking but dosage adjustment is not recommended	Potential increase in level with smoking cessation; however, dosages are not usually adjusted in presence of smoking	Uncategorized	Patients should be advised not to smoke while using nintedanib
Olanzapine ^{1,2}	Metabolism and clearance increased by smoking Dosage modifications are not routinely recommended but individuals who smoke may require higher dosages	Potential increase in levels with smoking cessation	Moderate to High	Monitor for adverse effects (e.g., dizziness, sedation, hypotension) Dosage reductions may be required
Opioids ¹ (pentazocine, dextropropoxyphene)	Smoking may increase the metabolism of some opioids (i.e. propoxyphene and pentazocine) Smoking may decrease the analgesic effect of opioids	Adequate pain control may be experienced with lower opioid doses	Low	Monitor for adverse effects
Pirfenidone ¹	Metabolism increased by smoking	Decreased exposure in individuals who smoke might alter efficacy profile	More Clinically Significant ¹	Patients should be encouraged to stop smoking before and during treatment with pirfenidone
Propranolol ^{1,3}	Clearance is increased by smoking	Serum levels may rise and effects enhanced	Low to Moderate	May need lower dose
Quinine ²	Clearance is increased by smoking	Plasma levels may rise with smoking cessation	Low	Monitor for signs of quinine toxicity (e.g. nausea, tremor, tinnitus, visual disturbance) If toxicity occurs, stop the drug and monitor the patient closely
Riociguat ¹	Smoking may reduce exposure to riociguat	Potential for increase in levels with smoking cessation	High	Patients should be advised to quit smoking
Ropinrole ^{1,2}	Smoking may increase metabolism	Potential for increase in levels with smoking cessation	Low	Monitor for increased adverse effects of ropinrole (e.g. nausea, dizziness) Dosage reduction may be required
Tacrine ^{1,2}	Smoking may increase metabolism Individuals who smoke may require higher dosages	Potential for increase in levels with smoking cessation	Low	Monitor for adverse effects of tacrine (e.g. gastrointestinal effects, hepatotoxicity) Dosage reduction may be required
Theophylline ^{1,2}	Smoking increases metabolism Maintenance doses are considerably higher in individuals who smoke	Plasma levels rise with smoking cessation	High	Levels should be monitored if smoking is initiated, discontinued, or changed Dosage adjustment required according to levels
Tricyclic Antidepressants ¹ (e.g., imipramine, nortriptyline)	Smoking may decrease blood levels	Serum levels may increase	High	Monitor for side effects and consider dose adjustment if appropriate
Tizanidine ¹	Males who smoke may have lower blood levels	Plasma levels may rise with smoking cessation	Uncategorized	Monitor for adverse effects with smoking cessation
Warfarin ^{1,2}	Smoking may decrease the serum concentration of warfarin	INR may increase with smoking cessation	Moderate	Monitor the INR more closely and monitor for signs of increased warfarin effect (e.g., bleeding) Advise primary care provider or individual monitoring warfarin of the quit attempt
Zolpidem ²	Smoking may lower plasma levels and reduce hypnotic effect Individuals who smoke heavily may need higher dosages	Plasma levels may rise with smoking cessation	Moderate	Monitor for increased sedation Dose reduction may be required

*The ratings of clinical significance were taken from the cited sources, which varied in definition and severity. A range of ratings have been presented when there was disagreement across citations. The content of this document was current at the time of the review. It may not represent a comprehensive list of all potential drug interactions with tobacco smoke, however, given the volume of drug interactions. Assessment and dosage adjustment must be individualized to the specific patient. Professional judgment must be used in applying the information contained in this document. This material is intended for personal, non-commercial use only provided that the content is not modified in any way. The content is intended for educational and informational purposes and to be used only with permission.

1. Drug Interactions with Tobacco Smoke. Rx for Change, 2019. <https://smokingcessationleadership.ucsf.edu/factsheets/drug-interactions-tobacco-smoke-rx-change-2019>.
2. Medication interactions with smoking and smoking cessation. New South Wales Government Health. <https://www.health.nsw.gov.au/tobacco/publications/fool-14-medication-intera.pdf>
3. Quick guide to drug interactions with smoking cessation. New South Wales Government Health. <https://www.health.nsw.gov.au/tobacco/factsheets/fool-7-guide-drug-interactions.pdf>
4. Roche Canada. Tarceva Product Monograph. https://www.rochecanada.com/PMs/Tarceva/Tarceva_PMI_E.pdf
5. NHS. What are the clinically significant drug interactions with tobacco smoking? https://www.nhs.uk/wp-content/uploads/2020/05/UKNIW_Q4_interactions-with-tobacco_update_jul-2020.pdf

Drug InterACTIONS with Tobacco Smoke Tool

Provides a reasonable action to take based on the anticipated clinical significance of an interaction.

Monitoring parameters are provided to assist health care professionals determine when a dosage adjustment may be required based on the individual patient experience.

Can be used in clinical practice to help plan quit attempts with any existing program or documentation.

Applicable to clinical situations aside from planned quit attempts

- E.g. hospitalized patients who are not smoking while in hospital and upon discharge may return to smoking.
- Drug InterACTIONS with Tobacco Smoke Tool can help navigate these clinical situations.

Example: Caffeine

Drug InterACTIONS with Tobacco Smoke

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Drug	Effect of smoking	Change with Smoking Cessation	Clinical Significance*	Action
Caffeine ^{1,2}	Smoking increases the clearance of caffeine by about 50%	Potential increase in levels with smoking cessation	Moderate	Increased risk of caffeine related side effects (tremor, nausea) Advise patients to reduce caffeine consumption prior to a quit attempt (eg., reduce to half)



Case Study Example: Clozapine

AG is a 45-year old male

- Resides in an inner-city supportive living facility
 - Controlled environment
 - Monitored by staff

30-year history of smoking

- Smokes 2 to 2.5 packs of cigarettes per day

Medical conditions

- Schizophrenia
- Insomnia
- Anxiety
- Hypercholesterolemia

Medications

- Clozapine 600mg at bedtime
- Lorazepam SL 1mg three times daily as needed
- Zopiclone 7.5mg at bedtime
- Atorvastatin 20mg once daily

Case Study Example: Andy

During an onsite follow-up, Andy was ASKED about smoking, and he expressed interest in quitting/reducing smoking.

Assessment

Fagerstrom test of nicotine dependence

- Score: 9 (very high level of nicotine dependence)

After some discussion, AG states the following are his goals:

- By the end of the month, reduce the amount of cigarettes smoked to half a pack daily
- To quit smoking in the next two months
- To be able to participate in the rec program at the facility

	Score
1. How soon after you wake do you smoke your first cigarette?	
<input checked="" type="checkbox"/> Within 5 minutes	3
<input type="checkbox"/> 6-30 minutes	2
<input type="checkbox"/> 31-60 minutes	1
<input type="checkbox"/> After 60 minutes	0

2. Do you find it difficult to refrain from smoking in places where it is forbidden? e.g. library, cinema, workplace, etc.	
<input checked="" type="checkbox"/> Yes	1
<input type="checkbox"/> No	0

3. Which cigarette would you hate most to give up?	
<input checked="" type="checkbox"/> The first one in the morning	1
<input type="checkbox"/> All others	0

4. How many cigarettes per day do you smoke?	
<input type="checkbox"/> 10 or less	0
<input type="checkbox"/> 1-20	1
<input type="checkbox"/> 21-30	2
<input checked="" type="checkbox"/> 31 or more	3

5. Do you smoke more frequently during the first hours after waking than during the rest of the day?	
<input checked="" type="checkbox"/> Yes	1
<input type="checkbox"/> No	0

6. Do you smoke even if you are so ill that you are in bed most of the day?	
<input type="checkbox"/> Yes	1
<input checked="" type="checkbox"/> No	0

Add up your responses to all the questions to get your **TOTAL SCORE:** 9

Dependence scores: 0-2: very low 3-4: low 5: medium 6-7: high 8-10: very high

Reference

Heatherton TF *et al.* The Fagerstrom Test for Nicotine Dependence: a revision of the Fagerstrom Tolerance Questionnaire. *Br J Addict* 1991; 86:1119-27.

NOTE: patients who smoke more than 3 cigarettes per day and have their first cigarette within 5 minutes of waking are considered to be highly dependent (score = 6).

Case Study Example: Andy

Developed a quit plan:

- Consultation with addictions psychiatrist to initiate NRT (nicotine replacement therapy)
- Reviewed:
 - Behavioural strategies for smoking cessation
 - Triggers and tips for avoiding
 - Management of nicotine withdrawal symptoms should they arise
- Weekly follow-up to monitor progress
- Recommend use of a diary to record triggers, ongoing smoking



Case Study Example: Andy

- Pharmacotherapy
 - NRT (nicotine replacement therapy)
 - Initiated 42 mg nicotine patch daily (2 x 21mg)
 - Nicotine inhaler (6 to 12 cartridges daily)
- Continued to have nicotine withdrawal symptoms and cravings
- Began titrating dose of nicotine patch by 7mg to control symptoms
- Achieved a final dose of 63 mg (3 x 21mg) patch plus inhaler for breakthrough
- Reduced smoking to $\frac{1}{4}$ to $\frac{1}{2}$ pack per day
- Staff at the facility observed changes in AG during his quit attempt
 - Hypersalivation at meals
 - Stumbling when getting up from chair or out of bed
- Drug screen is ordered given AG's history of substance abuse
 - Negative



Case Study Example: Andy

Assessment

- Symptoms and change in clozapine level are suggestive of clozapine toxicity
- What is the cause of clozapine toxicity?
 - Overdose?
 - Unlikely as staff administer medications
 - Drug-drug Interaction?
 - No changes to medication regimen
 - No OTC or herbal medications added
 - Reduction in smoking?

Drug InterACTIONS with Tobacco Smoke

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Drug	Effect of smoking	Change with Smoking Cessation	Clinical Significance*	Action
Clozapine ^{1,2,3}	Smoking can increase metabolism and reduce serum levels	Potential increase in levels with smoking cessation	Moderate to High	Closely monitor drug levels and for symptoms of toxicity (e.g., drowsiness, confusion, rapid heart rate) Reduce dose as required to avoid toxicity An average 50% dosage reduction may be required ³

Clozapine and Tobacco Smoke Interaction

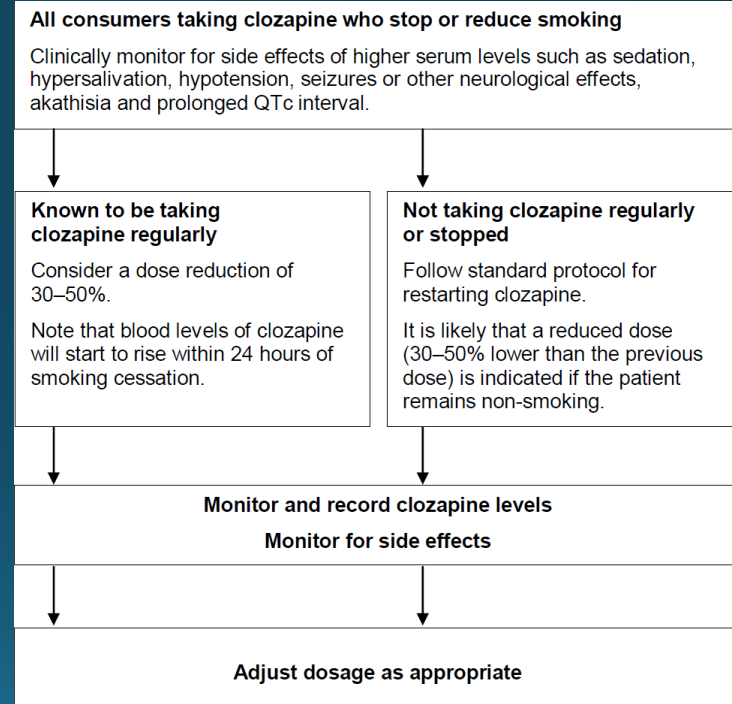
Clozapine is metabolized primarily by CYP1A2
Smokers achieve lower clozapine levels than nonsmokers

- Effect may be greater in males than females

Levels will start to rise within 24 hours of stopping smoking

Consider a dose reduction of 30 to 50% upon smoking cessation

- This can be either an immediate reduction or decrease by 10% per day for 4 days



Case Study Example: Andy

Management plan:

- Hold clozapine for 24 to 48 hours (until symptoms of toxicity resolve)
- Re-initiate clozapine at half of previous dose
- Monitor for symptoms of clozapine toxicity and emergent psychiatric symptoms
- Repeat clozapine level after one week at reduced dose
- Continue to monitor smoking
 - Assess potential impact on clozapine levels with increase or decrease in smoking



Considerations when using the Drug InterACTIONS with Tobacco Smoke Tool

Pharmacists should

- Be aware of pharmacokinetic and pharmacodynamic drug interactions with tobacco smoke
- Be prepared to identify key medications that have clinically relevant interactions and the action to take
- Consider patient and drug-related factors when assessing the potential severity of an interaction for their individual patient
 - e.g., Amount smoked, therapeutic index of the drug
- Be confident in managing these interactions
- Most require monitoring to determine if a dosage change is warranted
- Be prepared to educate patients on monitoring relevant parameters
- Incorporate monitoring and follow-up into the standard quit plan

Considerations when using the Drug InterACTIONS with Tobacco Smoke Tool

Pharmacokinetic and pharmacodynamic drug interactions can be highly variable.

Assessment and dosage adjustment must be individualized to the specific patient.

Professional judgment must still be used in applying the information contained in the tool.

The content of this document was current at the time of the review.

It may not represent a comprehensive list of all potential drug interactions with tobacco smoke, however, given the volume of drug interactions.

Key Messages

The majority of patients want their healthcare providers to ASK about tobacco use and ACT accordingly by supporting quit attempts.

The chances of success in a quit attempt are low without pharmacotherapy and behavioural support.

A well-planned quit attempt will also consider the potential for drug interactions with tobacco smoke.

The Drug InterACTIONS with Tobacco Smoke Tool can help simplify the process for identifying clinically relevant drug interactions with tobacco smoke and the appropriate action to take to manage those interactions.

