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**Tobacco smoking and its drug interactions with comedications involving CYP and UGT enzymes and nicotine**

Maideen NMP. Smoking**:** Drug interactions

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**Abstract**

Tobacco smoking is a global public health threat causing several illnesses including cardiovascular disease (Myocardial infarction), cerebrovascular disease (Stroke), peripheral vascular disease (Claudication), chronic obstructive pulmonary disease, asthma, reduced female infertility, sexual dysfunction in men, different types of cancer and many other diseases. It has been estimated in 2015 that approximately 1.3 billion people smoke, around the globe. Use of medications among smokers is more common, nowadays. This review is aimed to identify the medications affected by smoking, involving Cytochrome P450 (CYP) and uridine diphosphate-glucuronosyltransferases (UGTs) enzymes and Nicotine. Polycyclic aromatic hydrocarbons (PAHs) of tobacco smoke have been associated with the induction of CYP enzymes such as CYP1A1, CYP1A2 and possibly CYP2E1 and UGT enzymes. The drugs metabolized by CYP1A1, CYP1A2, CYP2E1 and UGT enzymes might be affected by tobacco smoking and the smokers taking medications metabolized by those enzymes, may need higher doses due to decreased plasma concentrations through enhanced induction by PAHs of tobacco smoke. The prescribers and the pharmacists are required to be aware of medications affected by tobacco smoking to prevent the toxicity-associated complications during smoking cessation.

**Key words**: Drug Interactions; Tobacco smoking; Cytochrome P450 enzymes; Uridine diphosphate-glucuronosyltransferases enzymes; Nicotine

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**Core tip:** Use of medications among smokers is more common, nowadays. This review is aimed to identify the medications affected by smoking, involving cytochrome P450 (CYP) and uridine diphosphate-glucuronosyltransferases (UGTs) enzymes and Nicotine. The drugs metabolized by CYP1A1, CYP1A2, CYP2E1 and UGT enzymes might be affected by tobacco smoking and the smokers taking medications metabolized by those enzymes, may need higher doses due to decreased plasma concentrations through accelerated metabolism by Polycyclic aromatic hydrocarbons of tobacco smoke. The prescribers and the pharmacists are required to be aware of medications affected by tobacco smoking to prevent the toxicity-associated complications during smoking cessation.

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**INTRODUCTION**

Tobacco use is a global public health threat causing several illnesses including coronary heart disease, cancers of organs such as lungs, mouth, throat, esophagus, pancreas, *etc.*, chronic obstructive pulmonary disease, asthma and premature deaths. The World Health Organization (WHO) estimated that over 7 million people die of tobacco related diseases, annually and it has been projected to kill 10 million users of tobacco a year, by 2030[[1](#_ENREF_1)]. Tobacco products are categorized majorly as smokeless tobacco and smoked tobacco. Various forms of smokeless tobacco include chewing tobacco, snus, moist snuff, dry snuff, gutka, loose leaf, twist and plug[2] while the smoked tobacco products include who did not use such products.cigarettes, cigars, bidis, kreteks, pipe tobaccos and water pipe tobaccos[3].

In 2015, it has been estimated that approximately 1.3 billion people smoke, around the globe, and almost 80 percent of smokers live in Low or middle income countries (LMICs) such as Bangladesh, India, Indonesia, *etc*[4]. In addition, over 8 million smokers are expected to be killed due to tobacco smoking every year globally, by the year 2030. Generally, tobacco smokers are expected to die 10 years earlier than non-smokers do.

Tobacco smoking is associated with various conditions such as cardiovascular disease [Myocardial infarction (MI)], cerebrovascular disease (Stroke), peripheral vascular disease (Claudication), chronic obstructive pulmonary disease, asthma, reduced female infertility, sexual dysfunction in men, different types of cancer and many other diseases[5]. Maternal smoking during pregnancy affect the offspring in many ways including low birth weight, premature birth, still birth, fetal death, infant death, congenital heart defects, CNS effects, and respiratory complications[6] while smoking related negative outcomes in mothers include placental abruption, placenta previa, premature rupture of membranes and ectopic pregnancy[7].

Smoking can affect non-smokers through second hand smoke (SHS) and third hand smoke which can induce many health complications as the voluntary smoking does. SHS is the mixture of sidestream smoke (SSS) (-85%) and exhaled mainstream smoke (MSS) (-15%). SHS is also known as passive smoking, involuntary smoking or environmental tobacco smoke and SHS is reported to be associated with negative health effects such as increased incidence of cancers, asthma, respiratory infections, reduced lung growth in children, and many others[8]. Thirdhand smoke (THS) is the residue of chemicals emitted from SHS, adhered to indoor surfaces like walls, furniture, carpet, blankets, and toys, and reemitted into the air[9].

It has been estimated that tobacco smoke may contain 7357 chemical constituents[10] including hazardous chemicals like polycyclic aromatic hydrocarbons (PAHs), ammonia, aromatic amines, phenols, carbonyls, hydrocyanic acid, and N-nitrosamines[11] as a complex mixture of gases and particulate matter. The gaseous part of smoke contains the constituents such as Carbon monoxide, Hydrogen cyanide, and Aldehydes while the particulate matter containing Nicotine, PAHs, tars, pigments, trace elements, nitrosamines and insecticides[12].

Interference of effects of one drug by the comedications or tobacco smoke is termed “Drug interaction”. Increased incidence of adverse effects or decreased therapeutic efficacy of a drug resulting from a drug interaction is called “Adverse drug interaction”[13,14].As the number of comedications increases, the rate of drug interactions also increases[15].

The cytochrome P450 (CYP) enzymes are hemoproteins, which are responsible for the metabolism of drugs and detoxification of xenobiotics. These enzymes are involved in the metabolism of drugs occurring through phase I (Oxidation) reactions. The drugs or other substances (herbs, nutients, supplements or tobacco smoke) inhibiting or inducing CYP enzymes, determine drug interactions[16].PAHs of tobacco smoke have been associated with the induction of CYP enzymes such as CYP1A1, CYP1A2 and possibly CYP2E1[17].

Uridine 5’-diphospho-glucuronosyltransferases [Uridine diphosphate (UDP)-glucuronosyltransferases, UGTs] are the family of enzymes catalyzing glucuronidation (Phase II (conjugative) reactions[18]. PAHs of tobacco smoke have also been associated with the possible induction of UDP glucuronyltransferase (UGT) enzyme[19].

The databases such as Medline/PMC/PubMed, Google Scholar, Science Direct, Cochrane Library, Directory of open access journals (DOAJ) and reference lists were searched to identify related articles using the keywords such as Drug interactions, Tobacco Smoke, CYP enzymes, UGT enzymes and Nicotine.

Pharmacokinetic drug interactions associated with tobacco smoking are mediated through the stimulation of CYP and UGT enzymes while the pharmacodynamic interactions are mediated by Nicotine.

***Pharmacokinetic interactions***

The drugs metabolized by CYP1A1, CYP1A2, CYP2E1 and UGT enzymes might be affected by tobacco smoking and the smokers taking medications metabolized by those enzymes, may need higher doses due to decreased plasma concentrations through enhanced induction by PAHs of tobacco smoke (Figure 1).

***Antipsychotics***

The second-generation antipsychotics or atypical antipsychotics such as clozapine and olanzapine are very much useful in the treatment of schizophrenia compared to typical antipsychotics[20]. Clozapine[21] and olanzapine[22] are primarily metabolized by CYP1A2 enzyme. It has also been reported that clozapine is metabolized by UDP‐glucuronosyltransferase 1A1 (UGT1A1) and UGT1A4[23] while olanzapine is metabolized by UGT1A4[24].

Approximately 70%-80% of patients with schizophrenia smoke[25] and the plasma concentrations of clozapine[26] and olanzapine[27] could be lowered in smokers as the PAHs of tobacco smoke enhancing their metabolism mediated by CYP1A2 and UGT enzymes.Smoking cessation may elevate the risk of toxicity in patients taking clozapine[28,29] and olanzapine[30].The habitual smokers taking clozapine or olanzapine, should be monitored after smoking cessation for symptoms related to their toxicity.The symptoms of clozapine toxicity[31] include confusion, tachycardia, miosis, hyperthermia and leukocytosisand olanzapine toxicity[28] include extrapyramidal symptoms.The patients stopped smoking may need dosage reduction of clozapine and olanzapine[32].

The plasma concentrations of haloperidol found decreased in smokers and it is recommended to monitor the patients taking haloperidol while starting or stopping smoking[33].

The clearance of Chlorpromazine has been increased by Cigarette smoking[34] and the abrupt cessation of smoking resulted in worsening of adverse effects of chlorpromazine[35].

***Antidepressants***

Tobacco smoking affects the bioavailability of antidepressants metabolized by CYP1A2 enzyme including Fluvoxamine, Duloxetine, Mirtazapine and Imipramine.

Fluvoxamine is an antidepressant, which belongs to Selective Serotonin Reuptake Inhibitor (SSRI) category. It has been reported to be metabolized by CYP enzymes like CYP1A2 and CYP2D6[36].Tobacco smoking may decrease the serum concentrations of fluvoxamine through the induction of CYP1A2-mediated metabolism[37].

Duloxetine is categorized as a selective serotonin and norepinephrine reuptake inhibitor (SNRI) antidepressant. The CYP enzymes such as CYP1A2 and CYP2D6 are involved in the metabolism of duloxetine[38].PAHs of tobacco smoke decreases bioavailability of duloxetine by increasing the expression of CYP1A2 and metabolism of duloxetine[39].

Mirtazapine is an atypical antidepressant and it is categorized as Tetracyclic antidepressant. The metabolism of mirtazapine is known to be mediated by CYP enzymes like CYP1A2, CYP2D6, and CYP3A4[40]. In addition, UGT enzymes also found to be involved in the metabolism of mirtazapine to some extent[41].The serum levels of mirtazapine could be reduced in smokers due to the induction of metabolism mediated by CYP1A2 and UGT enzymes.

Imipramine is a tricyclic antidepressant and it is known to be metabolized primarily by CYP2C19 enzyme and by CYP1A2 enzyme to a smaller extent[42].Required doses of Imipramine might be increased in Smokers due to the induction CYP1A2-mediated metabolism[43].

***Theophylline and aminophylline***

Theophylline is used to treat patients with airway diseases such as asthma and chronic obstructive pulmonary disease (COPD) that are poorly controlled by bronchodilators, as an add-on therapy[44].Theophylline is effective as oral therapy and Aminophylline (Ethylenediamine salt of theophylline) is suitable for intravenous route.

CYP1A2 is known to be the major enzyme involved in the metabolism of theophylline and aminophylline[45]. The plasma levels of theophylline was lesser in smokers[46] as the PAHs of tobacco smoke accelerate the CYP1A2-mediated metabolism of theophylline. It has been reported that the plasma concentrations of theophylline was also decreased by secondhand smoke in adults[47] and in children[48] as the PAHs of sidestream smoke may induce the CYP1A2-mediated metabolism of theophylline.

The smokers may need higher doses of theophylline to compensate higher rate of clearance and smoking cessation in patients taking theophylline may result in theophylline toxicity as it has a narrow therapeutic index. The patients should be advised to seek medical attention if they develop the symptoms of theophylline toxicity such as seizures, hypotension, palpitations, nausea, vomiting, diarrhea, and others[49].

***Caffeine***

Caffeine is metabolized predominantly by CYP1A2 enzyme[50].The CYP1A2-mediated metabolism of caffeine is enhanced in smokers[51] and the regular smokers may consume more coffee or other caffeinated drinks due to increased clearance of caffeine[52].

***Riociguat***

Riociguat is the first-in-class soluble guanylate cyclase (sGC) stimulator and it is useful to treat the patients with pulmonary hypertension[53].Riociguat is metabolized mainly by CYP enzymes including CYP1A1, CYP3A4, CYP3A5, CYP2C8, and CYP2J2[54].

The plasma concentrations of riociguat was reduced in smokers[55,56], as the PAHs content of tobacco smoke can induce CYP1A1-mediated metabolism of riociguat.The smokers may need higher doses of riociguat and it is recommended to do dosage adjustment of riociguat in patients stopped smoking.

***Erlotinib***

Erlotinib is an inhibitor of tyrosine kinase activity of Epidermal Growth Factor (EGF) receptor and it is approved to treat non-small-cell lung cancer[57].The metabolism of Erlotinib is mediated by CYP3A4 and CYP1A2 enzymes[58].

The plasma concentrations of Erlotinib have been decreased significantly in smokers which might have occurred due to enhanced CYP1A2-mediated metabolism of Erlotinib by tobacco smoke[59].

***Tacrine***

Tacrine isa centrally acting cholinesterase inhibitor and it is approved for the treatment of Alzheimer’s disease[60,61].Tacrine is known to be metabolized by CYP1A2 enzyme[62].The serum conentrations of Tacrine might be decreased in smokers due to CYP1A2-mediated metabolism[63].

***Warfarin***

Warfarin is an anticoagulant drug used widely to prevent thromboembolic events. It is a racemic mixture of two enantiomers including R-Warfarin and S-Warfarin. The R-warfarin is metabolized primarily by CYP1A2[64].

Tobacco smoke may induce CYP1A2-mediated metabolism of R-Warfarin and decrease its efficacy. Smoking cessation may require close monitoring of International Normalised Ratio (INR) of patients taking warfarin[65].

***Propranolol***

Propranolol is an antagonist of adrenergic beta receptors and it may be useful to treat various conditions including hypertension, angina pectoris, migraine, essential tremor, and many others. Propranolol has been identified as a substrate of CYP1A2 and CYP2D6 enzymes[66].

The plasma concentrations of propranolol was diminished by smoking[67] and it was noted higher in patients stopped smoking[68].

***Ropinirole***

Ropinirole is a dopamine agonist and it is approved for the treatment of Parkinson's disease and restless legs syndrome[69].Ropinirole is metabolised principally by CYP1A2 enzyme[70] and the plasma concentrations of Ropinirole may be decreased in smokers due to enhanced CYP1A2-mediated metabolism.

Smoking cessation in a patient taking Ropinirole resulted in increased rate of adverse effects such as excessive sweating at night, disturbed sleep with increased awakenings for several nights in a row[71].The dosage adjustments of Ropinirole may be required during smoking cessation.

***Mexiletine***

Mexiletine is a class 1B antiarrhythmic drug and it is a substrate of CYP1A2 enzyme[72].PAHs of tobacco smoke may induce the CYP1A2-mediated metabolism of mexiletine and it has been reported that the oral clearance of mexiletine was enhanced by tobacco smoking[73].

***Frovatriptan***

Frovatriptan is an agonist of 5-hydroxytryptamine (5-HT) receptors and it is effectively used in the acute management of migraine and the prevention of menstrual migraines[74].Frovatriptan is principally metabolized by the CYP1A2 isoenzyme[75]. The plasma concentrations of Frovatriptan was slightly decreased in tobacco smokers[76].

***Zolmitriptan***

Zolmitriptan helps the patients with migraine by exhibiting agonistic activity on 5-HT receptors[77].It is primarily metabolised by CYP1A2 enzyme[78].PAHs of tobacco smoke may decrease plasma concentrations of Zolmitriptan by inducing the CYP1A2-mediated metabolism.

***Alosetron***

Alosetron is a potent and selective blocker of 5-HT3 receptors and it is approved to treat the women with irritable bowel syndrome (IBS) having diarrhea as predominant bowel symptom[79].Alosetron is metabolised by various CYP enzymes including CYP1A2[80].Tobacco smoke may induce the CYP1A2-mediated metabolism of alosetron.

***Flutamide***

Flutamide is a nonsteroidal antiandrogen drug and it is used widely to treat carcinoma of prostate[81].CYP1A2 enzyme is involved principally in the metabolism of flutamide[82].CYP1A2-mediated metabolism of flutamide might be induced by PAHs of tobacco smoke.

***Melatonin***

Melatonin is a hormone, which regulates sleep-wake cycle and it is produced by the pineal gland. Exogenous melatonin is used as a dietary supplement to manage sleep disorders[83].The CYP enzymes including CYP1A2 and CYP1A1 are involved in the metabolism of exogenous melatonin[84].The plasma concentrations of exogenous melatonin was decreased in smokers[85].

***Ramelteon***

Ramelteon is an agonist of melatonin receptors and it is approved to treat insomnia[86].Ramelteon is metabolised primarily by CYP1A2 enzyme[87]. It has been postulated that smoking may decrease the levels of ramelteon by inducing CYP1A2-mediated metabolism.

***Tasimelteon***

Tasimelteon is an agonist of melatonin receptors (MT1 and MT2) and it is approved to treat non-24-hour sleep-wake disorder (N24HSWD). It is metabolised extensively by CYP1A2 and CYP3A4 enzymes[88].The exposure of tasimelteon was 40% decreased in cigarette smokers[89].

***Rasagiline***

Rasagiline is a potent monoamine oxidase-B (MAO-B) inhibitor and it is indicated in the treatment of Parkinson’s disease**.** It is metabolised mainly by CYP1A2 enzyme[90]. The plasma concentrations of Rasagiline could be decreased in heavy smokers due to PAHs of tobacco smoke induced CYP1A2-mediated metabolism[91]. heavy smokers, there is also a risk that rasagiline, AUC could be decreased due to induction of CYP1A2.

***Tizanidine***

Tizanidine is a centrally acting α2 adrenergic receptor agonist and it is widely used as a skeletal muscle relaxant, to treat painful muscle spasms and spasticity[92].Tizanidine is substantially metabolised by CYP1A2 enzyme[93,94].The plasma concentrations and effects of Tizanidine could be decreased by smoking and the male smokers may require higher than average doses[95].

***Triamterene***

Triamterene is a potassium-sparing diuretic and it is approved to treat hypertension and edema. Triamterene is exclusively metabolised by CYP1A2 enzyme[96]. Cigarette smoking may induce the CYP1A2-mediated metabolism of triamterene and decrease its plasma concentrations.

***Ropivacaine***

Ropivacaine is an effective local anaesthetic which can be administered through epidural, intrathecal and other routes[97].Ropivacaine is metabolised extensively by CYP1A2 enzyme[98] and it was noted that tobacco smoking increased the CYP1A2-mediated metabolism of ropivacaine[99].

***Methadone***

Methadone is a synthetic opioid drug used to treat chronic pain. It is metabolized mainly by CYP3A4 and also by CYP1A2 and CYP2D6 enzymes in lesser extent[100].PAHs of tobacco can induce the CYP1A2-mediated metabolism of methadone and decrease its plasma concentrations.

Methadone toxicity (Decreased respirations and altered mental status) has been reported in a patient stopped smoking while being on methadone maintenance dose to treat chronic back pain[101].The prevalence of smoking is higher (85%-98%) in patients taking methadone as a maintenance therapy[102].Monitor the symptoms of methadone toxicity when the patients stopped smoking and the dose of methadone may need to be adjusted.

***Hormonal replacement therapy***

Tobacco smoke can increase the hepatic clearance of orally administered estrogens and reduce the therapeutic efficacy of hormonal replacement therapy (HRT) such as reduction of hot flashes, osteoporosis, urogenital symptoms and cholesterol. The smoking women should be recommended to use transdermal HRT that bypasses hepatic metabolism[103].

***Pharmacodynamic interactions***

The pharmacodynamic drug interactions of cigarette smoking are mediated mainly by nicotine, which is a major active constituent of tobacco smoke. Nicotine comprises approximately 1.5% of tobacco weight in each cigarette[104].

***Combined hormonal contraceptives***

Combined hormonal contraceptives (CHCs) contain both an estrogen and a progestin. CHCs are available as oral pills, injectables, patches and vaginal rings. The use of CHCs is associated with elevated risk of venous thromboembolism (VTE) including deep vein thrombosis (DVT) and pulmonary embolism (PE), and arterial diseases including MI and stroke[105]. The women using CHCs containing levonorgestrel or norgestimate are at lowered risk of VTE compared to their peers using CHCs containing desogestrel, cyproterone, gestodene or drospirenone[106].The hypertensive women using CHCs may be at heightened risk of arterial diseases[107].

Cigarette smoking is also associated with increased risk of arterial diseases and VTE[108].Smoking may cause VTE through nicotine-induced generation of platelet-dependent thrombin[109] and smoking-related cardiovascular diseases[110].Tobacco smoking can induce the atherosclerotic changes and hypercoagulability resulting in adverse cardiovascular events[111].

The risk of VTE[112] and ischemic stroke and MI[113] is elevated in women smokers using CHCs.Administration of CHCs in women older than 35 years and smoking more than 15 cigarettes a day, is contraindicated due to heightened risk of arterial adverse events[114].

It has been estimated that approximately 27% of smoking women of reproductive age in the United States, use oral contraceptives concurrently[115].The women smokers using CHCs should be advised to quit smoking or to use progestin-only pills or other contraceptive methods.

***Inhaled corticosteroids***

Nicotine content of cigarette smoke can induce small airway inflammation[116] and decrease the sensitivity of inhaled corticosteroids in asthmatic patients[117,118].The patients with chronic asthma and with the habit of regular smoking should be advised to quit smoking or be recommended to use antiasthmatic drugs other than inhaled corticosteroids[119].

***Benzodiazepines***

Benzodiazepines (BZDs) are effective sedative, hypnotic and anxiolytic drugs and they include alprazolam, chlordiazepoxide, diazepam, lorazepam, temazepam, triazolam, and oxazepam[120].Nicotine induces the release of various neurotransmitters including acetylcholine, dopamine, serotonin, glutamate, and others through the binding to presynaptic nicotinic acetylcholine receptors (nAChRs) in the brain[121].

Attenuated sedation has been observed in patients taking BZDs and smoking concurrently[122].Excessive central nervous system depression may occur when the patients stop smoking while taking BZDs.

***Opioids***

Opioids are the drugs used to treat moderate to severe pain and they act on opioid receptors. Smoking is associated with hyperalgesia due to desensitization of nAChR[123] and it was noticed that the pain relief provided by opioid analgesics was less in smokers[124].

The smokers needed to be administered with higher doses of morphine, pethidine (meperidine) and propoxyphene[125] and the smokers requiring opioid analgesics should be advised to quit smoking[126].

***Antihypertensives***

Nicotine content of cigarette smoke increases the sympathetic activity and rises the blood pressure acutely[127] and it was reported that the blood pressure elevated persistently due to heavy smoking[128]. Cigarette smoking is associated with higher arterial stiffness leading to cardiovascular diseases[129,130].Pulse wave velocity (PWV) helps to measure the arterial stiffness and the stiffer arteries have higher values of PWV[131].The beneficial effects of amlodipine on PWV was delayed by long-term cigarette smoking[132].

***Antihyperlipidemics***

Smoking increases the risk of vascular diseases through various mechanisms including elevated levels of oxidized low-density lipoprotein, triglycerides (TG), packed cell volume (PCV) and fibrinogen, reduced high-density lipoprotein (HDL) levels, increased carotid artery intima-media thickness (IMT), enhanced arterial stiffness, increased insulin resistance and intensified endothelial damage. It has been reported that smoking decreased the beneficial effects of statins on the reduction of morbidity and mortality associated with ischemic heart disease[133].

***Alcohol***

Alcohol use in smokers can increase the smoking satisfaction, calmness, etc. of rewarding effects of nicotine[134].The alcoholics tend to be heavy smokers and the smokers seem to be heavy alcohol drinkers[135,136].

**CONCLUSION**

Tobacco smoking is very common around the globe and most of the smokers are living in LMICs. Tobacco smoking including SHS and third hand smoke is associated with various health hazards. Tobacco smoke contains many chemicals including PAHs which involves in majority of pharmacokinetic interactions of smoking. PAHs of tobacco smoke have been associated with the induction of CYP enzymes such as CYP1A1, CYP1A2 and possibly CYP2E1.

The smokers may need higher doses of drugs such as clozapine, olanzapine, haloperidol, chlorpromazine, fluvoxamine, duloxetine, mirtazapine, imipramine, theophylline, aminophylline, caffeine, riociguat, erlotinib, tacrine, warfarin, propranolol, Ropinirole, mexiletine, Frovatriptan, zolmitriptan, alosetron, flutamide, melatonin, Ramelteon, Tasimelteon, Rasagiline, Tizanidine, triamterene, ropivacaine, methadone and oral estrogens (Hormonal replacent therapy) due to enhanced CYP1A-mediated metabolism and upon smoking cessation they need to be monitored for toxicity of drugs and the dosage adjustments to be done if needed.

Smoking can also interact pharmacodynamically with the drugs including CHCs, inhaled corticosteroids, BZDs, opioids, antihypetensives, antihyperlipidemics and alcohol. The clinicians should be aware of the drugs affected by smoking, to prevent adverse effects especially at the time of smoking cessation.

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**Figure 1 Pharmacokinetic drug interactions of smoking.** Main mechanisms contributing to hyperkalemia with angiotensin converting enzyme inhibitors (ACEi)/angiotensin receptor blocker (ARB) include decreased aldosterone concentrations, decreased delivery of sodium to the distal nephron, abnormal collecting tubule function, and excessive potassium intake Main mechanisms contributing to hyperkalemia with ACEi/ARB include decreased aldosterone concentrations, decreased delivery of sodium to the distal nephron, abnormal collecting tubule function, and excessive potassium intake Main mechanisms contributing to hyperkalemia with ACEi/ARB include decreased aldosterone concentrations, decreased delivery of sodium to the distal nephron, abnormal collecting tubule function, and excessive potassium intake.