

Smoking in Patients Receiving Psychotropic Medications

A Pharmacokinetic Perspective

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Contents

Abstract	470
1. Overview of Drug Metabolism and Smoking	471
1.1 Cytochrome P450 (CYP) 1A2/1A1	471
1.2 CYP2E1	471
1.3 Other Constituents	472
1.4 Mechanism of Induction	472
2. Cigarette Smoking and Psychiatry	473
3. Impact on Psychotropic Drugs	473
4. Antidepressants	473
4.1 Tricyclic Antidepressants	473
4.1.1 Amitriptyline and Nortriptyline	473
4.1.2 Imipramine	475
4.1.3 Clomipramine	477
4.2 Selective Serotonin Reuptake Inhibitors (SSRIs)	478
4.2.1 Fluvoxamine	478
4.2.2 Other SSRIs	478
4.3 Other Antidepressants	478
4.3.1 Trazodone	478
4.3.2 Amfebutamone (Bupropion)	478
4.3.3 Venlafaxine	479
5. Antipsychotics	479
5.1 Typical Antipsychotics	480
5.1.1 Chlorpromazine	480
5.1.2 Trifluoperazine	480
5.1.3 Tiotixene	482
5.1.4 Fluphenazine	482
5.1.5 Haloperidol	483
5.2 Atypical Antipsychotics	484
5.2.1 Clozapine	484
5.2.2 Olanzapine	485
5.2.3 Zolopine	486
5.2.4 Risperidone	486
6. Anxiolytics	486
6.1 Triazolam and Alprazolam	486

6.2	Lorazepam	489
6.3	Diazepam and Chlordiazepoxide	489
7.	Mood Stabilisers	490
7.1	Carbamazepine	490
7.2	Other Agents	490
8.	Pharmacodynamic Effects of Nicotine on the Dopaminergic System	490
9.	Conclusion	491

Abstract

Many psychiatric patients smoke, and are believed to be heavier smokers than those without psychiatric disorders. Cigarette smoking is one of the environmental factors that contributes to interindividual variations in response to an administered drug. Polycyclic aromatic hydrocarbons (PAHs) present in cigarette smoke induce hepatic aryl hydrocarbon hydroxylases, thereby increasing metabolic clearance of drugs that are substrates for these enzymes. PAHs have been shown to induce 3 hepatic cytochrome P450 (CYP) isozymes, primarily CYP1A1, 1A2 and 2E1. Drug therapy can also be affected pharmacodynamically by nicotine.

The most common effect of smoking on drug disposition in humans is an increase in biotransformation rate, consistent with induction of drug-metabolising enzymes. Induction of hepatic enzymes has been shown to increase the metabolism and to decrease the plasma concentrations of imipramine, clomipramine, fluvoxamine and trazodone. The effect of smoking on the plasma concentrations of amitriptyline and nortriptyline is variable. Amfebutamone (bupropion) does not appear to be affected by cigarette smoking.

Smoking is associated with increased clearance of tiotixene, fluphenazine, haloperidol and olanzapine. Plasma concentrations of chlorpromazine and clozapine are reduced by cigarette smoking. Clinically, reduced drowsiness in smokers receiving chlorpromazine, and benzodiazepines, compared with non-smokers has been reported. Increased clearance of the benzodiazepines alprazolam, lorazepam, oxazepam, diazepam and demethyl-diazepam is found in cigarette smokers, whereas chlordiazepoxide does not appear to be affected by smoking. Carbamazepine appears to be minimally affected by cigarette smoke, perhaps because hepatic enzymes are already stimulated by its own autoinductive properties.

Cigarette smoking can affect the pharmacokinetic and pharmacodynamic properties of many psychotropic drugs. Clinicians should consider smoking as an important factor in the disposition of these drugs.

Cigarette smoking is the most preventable cause of illness and death, yet it remains highly prevalent in most countries. It is estimated that 45 million Americans smoke (about 25%) and 1 of every 6 deaths in the US can be related to smoking.^[1] There are 4000 chemical compounds found in cigarette smoke and 43 have been identified to be carcinogenic. Nicotine is not carcinogenic, but it has a variety of effects on the body.

In addition to all the long term health consequences of smoking, it also has a profound effect on drug metabolism. Cigarette smoke constituents have been shown to stimulate or induce hepatic cytochrome P450 (CYP) isozymes, which play a central role in drug metabolism. Polycyclic aromatic hydrocarbons (PAHs) from cigarette smoke are responsible for the induction of CYP isozymes. The enhancement of metabolic activity increases

the risk of cancer as a result of the activation of carcinogens.^[2] PAHs have been shown to induce primarily 3 isozymes, CYP1A1, CYP1A2 and CYP2E1. Not only are the PAHs involved in enzyme induction, but nicotine, carbon monoxide and cadmium may also play a role.

Cigarette smoking can affect the clinical management of patients with psychiatric disorders because of the pharmacokinetic and pharmacodynamic changes it can cause to various psychotropic drugs. This article reviews the impact of smoking on psychotropic medications with an emphasis on the pharmacokinetic perspective.

1. Overview of Drug Metabolism and Smoking

The human liver is the primary CYP-containing site for xenobiotic metabolism. However, some of these isozymes are located in other areas of the body, such as in the gastrointestinal tract, brain and lung. Most medications undergo biotransformation via phase I and phase II metabolic reactions in the liver. CYP isozymes are involved with phase I metabolism, an oxidative process that metabolises both endogenous and exogenous substances to more hydrophilic compounds for elimination.

1.1 Cytochrome P450 (CYP) 1A2/1A1

CYP1A2/1A1 accounts for approximately 13 to 17% of the total liver CYP content.^[3-5] CYP1A2 is primarily found hepatically but it has been found in the brain and lung, and in the placentas of mothers who smoke.^[6] CYP1A2/1A1 substrates include imipramine, clozapine, olanzapine, theophylline, paracetamol (acetaminophen), tacrine, propranolol, (*R*)-warfarin and caffeine.^[3] It has also been associated with the activation of some procarcinogens such as aryl and heterocyclic amines.^[6] CYP1A2/1A1 are susceptible to induction by PAHs, various indoles and omeprazole.^[4]

Caffeine has been established as a reliable metabolic probe to evaluate the activity of CYP1A2 in an individual.^[7] The activity is determined by the extent of demethylation of caffeine in the blood

and urine.^[6] Phenacetin has also been used as a marker for CYP1A2 activity.

Human liver microsomes contain relatively low levels of CYP1A1 in comparison to CYP1A2. However, it is readily detectable in the human lung, intestine, skin, lymphocytes and placenta, particularly from cigarette smokers.^[4] Risk of lung cancer and high levels of activity of CYP1A1 are strongly associated.^[6] In a Japanese population, squamous cell lung carcinoma was associated with an allele of the CYP1A1 gene.^[8] Smokers (both women and men) had a significantly lower ($p < 0.01$) incidence of adverse events than nonsmokers given an oral test dose of caffeine 300mg.^[9] Caffeine metabolic ratios (N^1 -, N^3 - and N^7 -demethylation) were significantly lower in nonsmokers, indicating that smoking induces CYP1A2. Higher serum caffeine concentrations were found in nonsmoking women receiving the drug which accounted for increased adverse events, such as tremors and nervousness.

Significant differences were not found in CYP1A2 metabolic activity between genotypes in nonsmokers; however, smokers who were homozygous for the A allele had a 1.6-fold higher activity, as measured by CYP1A2 induction, compared with nonsmokers and smokers with the homozygous mutant allele.^[10] A single base change C \rightarrow A was identified to have a significant effect upon caffeine ratios, indicating increased activity of CYP1A2 due to induction by smoking.

1.2 CYP2E1

CYP2E1 accounts for approximately 7 to 10% of the total CYP content in the human liver.^[3-5] The lung, kidney, lymphocytes and placenta are also additional locations for this enzyme. Paracetamol, alcohol, chlorzoxazone, dapsone, disulfiram and enflurane are common substrates. CYP2E1 is also associated with the activation of procarcinogens. Genetic polymorphism, alcohol and isoniazid are associated with induction of CYP2E1.^[3] The level of enzyme activity for CYP2E1 has been shown to be different between the genders. It appears that women have lower CYP2E1 enzyme activity levels compared with men.^[6] Chlorzoxazone is used as

the metabolic probe for CYP2E1 activity by measuring the plasma ratio of 6-hydroxychlorzoxane to chlorzoxazone.^[4]

1.3 Other Constituents

Other constituents in cigarettes have been shown to have an effect on the CYP system in animal models. Carbon monoxide and cadmium were shown to inhibit drug metabolism in animals. The inhibitory effect of carbon monoxide is dose dependent.^[6] Cadmium was associated with specific inhibition of CYP2E1 in rat liver. Induction of CYP2E1, CYP2A1/2A2 and CYP2B1/2B2 were seen with nicotine in rat brains, but not all regions were affected.^[6] The relevance of these data from animal models to human drug metabolism has not been established.

Smoking was shown not to significantly affect other CYP isozymes, such as 2C19, 2C9 and 2D6.^[11]

1.4 Mechanism of Induction

Induction is an increase in the amount and/or activity of an enzyme. The time delay often observed in enzyme induction may be due to the time needed for transcription, translation or stabilisation of the enzyme prior to its actions on other compounds.^[7]

The mechanism of induction of CYP isozymes by aromatic hydrocarbons involves the binding of the hydrocarbon to a specific intracellular receptor called the Ah (aryl hydrocarbon) receptor. The hydrocarbon-Ah receptor complex then migrates into the cell nucleus and interacts with the Ah responsive element (ARE), a specific enhancer region of the gene. The result is an increase in messenger ribonucleic acid (mRNA) from transcriptional activation of the CYP gene. The mRNA directs the assembly of amino acids into protein on the rough endoplasmic reticulum. With addition of haem to the protein, the production of new CYP is completed. It is believed that the inducer itself or its by-products also slows down the degradation of CYP proteins, and therefore enhances the metabolic effects of the enzymes.^[3]

The onset of induction varies based on the chemical inducer. The time interval for complete

induction is about 2 days for rifampicin (rifampin), 7 days for phenobarbital (phenobarbitone) and 2 weeks for carbamazepine.^[3,12] The mechanism of induction by rifampin and phenobarbital may occur via a variety of mechanisms including via the Ah, and also the pregnane X (CYP3) and constitutive androstane (CYP2) receptors.

The information on the time or magnitude of change in the CYP system at the initiation or cessation of smoking is not clear. The hepatic effects of PAHs can occur within 3 to 6 hours and the time to maximum effect is within 24 hours.^[13] Smoking has no effect on liver size or hepatic blood flow.^[13,14] The extent of induction can be reduced with increased age.^[14,15] This was demonstrated by comparing antipyrine clearance in smokers and non-smokers >40 or <40 years of age. In the younger group, antipyrine clearance was significantly greater in smokers ($p < 0.02$), whereas in the older group there was no difference between smokers and non-smokers.^[14]

The inducing effects of cigarettes vary depending on the bioavailability of the cigarette smoke components and the extent of inhalation. The PAHs include 3,4-benzpyrene, 3,4-benzofluorene, anthracene, fluoranthene, chrysene and pyrene. It is estimated that 0.4 μ g of 3,4-benzpyrene is available by smoking 20 filtered cigarettes compared with 0.7 μ g from 20 unfiltered cigarettes.^[14] The quantity of cigarettes has been shown to affect drug clearance. Heavier smokers had the greatest increase in drug clearance.^[13]

Pharmacokinetic changes in psychotropic drugs when patients cease smoking have not yet been reported. Theoretically, when the inducer is stopped, plasma drug concentrations will rise.^[16] For example, several case reports have shown that plasma concentrations of antipsychotics increase by 2- to 5-fold over a 4-week time period when carbamazepine (an agent that produces induction) is discontinued.^[17] Patients experienced either sedation or extrapyramidal adverse effects during this time. There is a case report of a patient who stopped smoking (1.5 packs/day for 5 years) while on clozapine and 3 weeks after smoking cessation experienced a

grand mal seizure.^[18] Clozapine plasma concentrations were not obtained; however, this clinical profile fits into the general scheme of induction where it could take several weeks for hepatic enzymes to re-equilibrate after the inducer has been discontinued.

2. Cigarette Smoking and Psychiatry

It is estimated that up to 80% of patients with schizophrenia or with alcohol or cocaine addiction smoke cigarettes.^[19] Patients with psychiatric disorders are believed to be heavier smokers than individuals without psychiatric disorders due to the quantity of cigarettes that they smoke and how deeply they inhale.^[19] Proposed reasons for the high incidence of smoking among these patients include that smoking has anxiolytic effects and reduces therapeutic drug-related adverse effects, use with over-the-counter and herbal products, genetic vulnerability and increased opportunities for socialisation.

Since 1993, the US Joint Commission on Accreditation of Healthcare Organization has required smoke-free hospitals in the US.^[20] This regulation has changed the management of inpatients with psychiatric disorders. Special areas in the hospital have been designated for smoking. Patients who temporarily stop smoking in the hospital usually resume smoking after discharge. The long term smoking cessation rate is estimated to be 15% in psychiatric patients compared with 30% in the general population.^[19]

3. Impact on Psychotropic Drugs

A summary of the psychotropic drugs that are substrates for the CYP isozymes is shown in table I. It is commonly found that multiple isozymes influence the metabolism of many individual psychotropic drugs. For example, the antipsychotic clozapine is mainly metabolised by CYP1A2 and 3A4, with minor effects by CYP2D6 and 2C19.

The following sections review the impact of smoking on the disposition of psychotropic drugs. Studies with pharmacokinetic data, drug concentrations or population analysis (i.e. logistic regres-

sion) with psychotropic drugs were selected to be reviewed in this article.

4. Antidepressants

The most recent study supports previous investigations that the rate of smoking in patients with depression is higher than in the general population.^[22] Among depressed patients who are still actively smoking or patients attempting to quit smoking, what impact does smoking have on the pharmacokinetics of antidepressants and on clinical management of depression? Table II summarises the studies comparing antidepressant pharmacokinetics in smokers and nonsmokers; it includes only studies that provided the number of participants, dosages and plasma (or serum) drug concentrations.

4.1 Tricyclic Antidepressants

The metabolic profiles of the tricyclic antidepressants (TCAs) have revealed complex CYP isozyme involvement. As a basic model, the parent drug can be metabolised to an active metabolite by multiple CYP isozymes and the metabolite in turn is converted by another CYP isozyme. For example, amitriptyline is converted to nortriptyline via CYP1A2, 3A4 and 2C19, and nortriptyline is metabolised to its hydroxy metabolites by CYP2D6 (see table I).

4.1.1 Amitriptyline and Nortriptyline

Most studies have not found significant correlations between cigarette smoking and the plasma concentrations of amitriptyline or nortriptyline.^[23-25]

The effect of cigarette smoking on the steady-state plasma concentrations of amitriptyline and nortriptyline in 65 patients with depression was evaluated.^[23] 35 patients (18 smokers) received amitriptyline and 30 (19 smokers) received nortriptyline in a dosage range of 50 to 200 mg/day. Smokers were defined as those who smoked at least 10 cigarettes per day, while nonsmokers had denied any use of tobacco. There was no significant difference in steady-state TCA concentrations or in the rates of demethylation of amitriptyline to

Table I. Psychotropic substrates of cytochrome P450 (CYP) isozymes based upon *in vitro* and *in vivo* studies^[21]

	CYP1A1/1A2 ^a	CYP2B6	CYP2C9	CYP2C19	CYP2D6	CYP3A4
Antidepressants						
Amitriptyline	✓		✓	✓	✓	✓
Clomipramine	✓			✓	✓	✓
Desipramine					✓	
Imipramine	✓			✓	✓	✓
Nortriptyline					✓	
Demethyl-citalopram					✓	
Citalopram				✓		
Fluoxetine					✓	✓
Fluvoxamine	✓				✓	✓
Paroxetine					✓	
Sertraline					✓	✓
Amfebutamone (bupropion)		✓				
Maprotiline						
Moclobemide				✓		
Nefazodone						✓
Trazodone						✓
Venlafaxine					✓	✓
Antipsychotics						
Chlorpromazine	✓					
Haloperidol	✓				✓	✓
Perphenazine					✓	
Reduced haloperidol					✓	
Thioridazine					✓	
Trifluoperazine	✓					
Clozapine	✓			✓	✓	✓
Olanzapine	✓			✓	✓	
Risperidone					✓	✓
Sertindole					✓	✓
Zuclophenthixol					✓	
Anticonvulsants						
Carbamazepine						✓
Hexobarbital (hexobarbitone)				✓		
Mephénytoin				✓		
Phenytoin			✓	✓		
Miscellaneous						
Alprazolam						✓
Clonazepam						✓
Diazepam				✓		✓
Midazolam						✓
Triazolam						✓
Buspirone						✓
Caffeine	✓					
Tacrine	✓					
Zolpidem						✓
Zopiclone	✓		✓			

a Smoking induces CYP1A1/1A2, and CYP2E1.

nortriptyline between smokers and nonsmokers (table II).

Studies by Rickels et al.,^[24] in 74 patients with depression treated with 150 mg/day amitriptyline for 2 to 6 weeks, and Norman et al.,^[25] in 22 smokers and 31 nonsmokers who received nortriptyline 150 mg/day for at least 2 weeks, also found no significant correlation between cigarette smoking and the plasma concentrations of these TCAs. Additionally, the authors of the latter study showed that the number of cigarettes smoked per day (at least 10 cigarettes per day) did not have a significant effect on plasma concentrations.^[25]

However, the findings of the study by Linnoila et al.^[26] contradict the above studies. This study evaluated the effect of cigarette smoking in 88 patients with depression receiving either nortriptyline alone (23 smokers) or combined amitriptyline and nortriptyline (17 smokers) for a minimum of 7 days. Smokers had significantly lower ($p < 0.05$) mean nortriptyline and mean combined amitriptyline and nortriptyline concentrations than did nonsmokers. Smoking was associated with low plasma amitriptyline and/or nortriptyline concentrations. The mean plasma ratios of amitriptyline to nortriptyline in the smokers and nonsmokers receiving amitriptyline were 1.61 and 1.11, respectively (non-significant difference). It is important to note that of the smokers, 16 were also consuming more than the equivalent of a 12 ounce (336ml) can of beer a day, and the use of benzodiazepines and antipyretic analgesics (not specified) was also allowed in this study. However, moderate drinking of alcoholic beverages was not associated with an increased capability to metabolise amitriptyline and/or nortriptyline, due to the relationship between free serum concentrations and total (bound plus free) serum concentrations. The lack of interaction can be explained by the fact that alcohol was acting upon CYP2E1 rather than on the CYP isozymes involved in the metabolism of amitriptyline/nortriptyline.

Perry et al.^[27] determined nortriptyline half-life, volume of distribution (Vd) and steady-state plasma concentration normalised to a 100 mg/day maintenance dosage in 9 smokers and 15 nonsmokers with

depression. The smokers smoked an average of 1.8 ± 0.6 packs of cigarettes per day. The mean total nortriptyline concentration in the smokers was significantly lower than in the nonsmokers. Smokers had a slightly higher percentage of free nortriptyline compared with the nonsmokers ($p = 0.08$). However, the mean free plasma concentration in the smokers did not differ from that in the nonsmokers.

Based on the available data, dosage adjustments for amitriptyline and nortriptyline do not appear to be warranted when the drugs are administered to smokers.

4.1.2 Imipramine

Steady-state plasma concentrations of imipramine and its active metabolite desipramine were compared in 22 smoking and nonsmoking patients with depression receiving 3.5 mg/kg/day.^[28,33] Patients who had smoked at least 15 cigarettes or 6 cigars per day were included as smokers, and nonsmokers were patients who had not smoked at all during the preceding 4 months. Plasma concentrations in smokers were significantly lower than in nonsmokers (table II), and it was suggested that smokers might require dosages above those normally recommended in order to receive optimal therapeutic benefit. Smoking was shown not to affect protein binding of imipramine.^[34]

The different findings of the effect of cigarette smoking on the biotransformation of nortriptyline and imipramine suggest that smoking may preferentially affect demethylation rather than hydroxylation, but investigators have not yet examined this possibility. However, the conversion of amitriptyline to nortriptyline mediated by *N*-demethylation was shown to be unaffected by cigarette smoking (see section 4.1.1). Therefore, it appears that the effect of smoking on drugs which undergo *N*-demethylation is highly selective. These findings suggest that the enhanced biotransformation of drugs in smokers is a selective process, with various microsomal pathways being both induced and unaffected by tobacco smoke.^[13]

Table II. Effect of cigarette smoking on the disposition of antidepressants. Values are means \pm SD

Drug	Pharmacokinetic changes	Significance (percentage change in pharmacokinetics in smokers)	Reference
Amitriptyline, nortriptyline	C _p (amitriptyline) [μ g/L]: NS = 77.9 S = 68.1 C _p (nortriptyline) [μ g/L]: NS = 86.3 S = 95.7	p-Values were not provided	23
Amitriptyline, nortriptyline	Correlation of C _p with tobacco intake at 2 weeks and at 6 weeks, respectively: amitriptyline = -0.035, -0.174 nortriptyline = 0.104, -0.187 amitriptyline + nortriptyline = 0.035, -0.197	Differences were not significant; p-values were not provided	24
Nortriptyline	C _p (μ g/L): NS = 169.3 \pm 92.4 S = 191.2 \pm 141.3	p > 0.1; difference was not significant	25
Amitriptyline, nortriptyline	C _p (nortriptyline) [μ g/L]: NS = 69.4 \pm 18.0 S = 39.9 \pm 18.5 C _p (amitriptyline + nortriptyline) [μ g/L]: NS = 107.3 \pm 31.5 S = 73.4 \pm 13.7	p < 0.05 (43% decrease) p < 0.05 (32% decrease)	26
Nortriptyline	Normalised C _p (μ g/L): NS = 158 \pm 35 S = 118 \pm 33 Normalised free C _p (μ g/L): NS = 11.5 \pm 2.6 S = 11.4 \pm 3.5 Free nortriptyline (%): NS = 7.4 \pm 1.5 S = 10.2 \pm 4.0	p \leq 0.01 (25% decrease) Differences were reported as nonsignificant; p-values not provided p = 0.08 (38% increase)	27
Imipramine	C _p (μ g/L): NS = 290 S = 160	p < 0.05 (45% decrease)	28
Clomipramine	C _p (clomipramine) [μ g/L]: NS = 60.6 \pm 15.3 S = 29.0 \pm 3.0 C _p (demethyl-clomipramine) [μ g/L]: NS = 62.8 \pm 12.41 S = 54.9 \pm 5.9	p-values were not provided (52% decrease) Differences were not significant; p-values were not provided	29
Fluvoxamine	C _{max} (nmol/L): NS = 57.7 \pm 21.5 S = 39.1 \pm 17.3 AUC (nmol \cdot h/L): NS = 1110 \pm 511 S = 771 \pm 346 t _{1/2} (h): NS = 10.7 \pm 2.3 S = 10.1 \pm 1.9 CL (L/min): NS = 3.3 \pm 2.7 S = 4.1 \pm 1.9	p = 0.012 (32% decrease) p = 0.012 (31% decrease) p > 0.2; difference was not significant p = 0.12; difference was not significant	30
Trazodone	C _p (trazodone) [μ g/L]: NS = 661 \pm 204 S = 508 \pm 192	p < 0.05 (23% decrease)	31

Continued over page

Table II. Contd

Drug	Pharmacokinetic changes	Significance (percentage change in pharmacokinetics in smokers)	Reference
Amfebutamone (bupropion)	C_p (mCPP) [$\mu\text{g/L}$]: NS = 57 ± 19 S = 56 ± 23	Difference was not significant; p-value was not provided	32
	C_p (mCPP/trazodone ratio): NS = 0.091 ± 0.030 S = 0.117 ± 0.040	$p < 0.05$ (29% increase)	
	AUC ($\mu\text{g} \cdot \text{h/L}$): NS = 1161 ± 292 S = 1164 ± 220	$p > 0.05$; none of these pharmacokinetic parameters were significantly different between smokers and nonsmokers	
	C_{max} ($\mu\text{g/L}$): NS = 143 ± 39 S = 144 ± 28		
	t_{max} (h): NS = 2.88 ± 0.49 S = 3.00 ± 0.50		
	$t_{1/2}$ (h): NS = 18 ± 3 S = 19 ± 5		

AUC = area under the plasma concentration-time curve; **CL** = clearance; **C_{max}** = maximum plasma drug concentration; **C_p** = plasma concentration; **mCPP** = *m*-chlorophenylpiperazine; **NS** = nonsmoker; **S** = smoker; **SD** = standard deviation; $t_{1/2}$ = elimination half-life; t_{max} = time to C_{max} .

4.1.3 Clomipramine

The influence of cigarette smoking, in addition to age and oral contraceptive use, on the plasma concentrations and safety of clomipramine and its pharmacologically active demethyl metabolite was studied in 58 patients with depression (36 smokers; >15 cigarettes per day).^[35] Patients smoking 15 or more cigarettes per day were found to have fewer adverse effects with daily doses of clomipramine 75mg than nonsmokers in the same age group, although a significant difference in plasma concentrations of clomipramine or its metabolite between smokers and nonsmokers was not found. This lack of significant differences between groups may have been caused by the high drop-out rate amongst nonsmokers, which may have biased these data. Only 8% of smokers were forced to withdraw from treatment prematurely because of adverse effects compared with 36% of nonsmokers, and only 8% of smokers had to have their dosage reduced to minimise adverse effects, as compared with 22% of nonsmokers.

Similar findings were seen in a study by John et al.,^[29] which included 67 patients with depression (38 smokers, 29 nonsmokers). Clomipramine was far better tolerated in smokers, with 90% of smokers and 68% of nonsmokers successfully completed the study. The mean plasma concentration of clomipramine was significantly lower in smokers compared with nonsmokers, but there was no difference in the mean demethyl metabolite concentrations (table II). Smoking, therefore, appeared to either induce specifically the enzymes responsible for producing ring hydroxylated metabolites, but not those for producing the demethyl metabolite, or alternatively induce both the rates of production and removal of the demethyl metabolite, thus maintaining the same overall concentration. Interestingly, these findings for the demethyl metabolite of clomipramine are similar to those for nortriptyline,^[25] a structurally related secondary amine antidepressant.

The observations from an analysis of interindividual variability in clomipramine (dosage 25 to 200 mg/day) metabolism in 147 depressed patients

(50 smokers)^[36] was in contrast with the findings of the study by John et al.^[29] This study showed increased demethylation for smokers but no alteration of hydroxylation capacity. Tobacco smoke significantly altered the apparent demethylation clearance without affecting other processes (i.e. hydroxylation). The average oral clearances were 17.1 ± 7.9 L/h for hydroxylation, 22.5 ± 11.1 L/h for demethylation and 39.9 ± 19.8 L/h for elimination. Smoking induced demethylation, leading to a 34% increase in oral clearance in smokers (+4.4 L/h) compared with nonsmokers (-2.3 L/h; $p < 0.005$).^[36] A recent similar study of the metabolism of clomipramine conducted in 108 Japanese patients with psychiatric disorders showed that smoking had significant effects on the metabolic ratio of clomipramine hydroxylation ($p = 0.03$) and demethylation ($p = 0.047$), but not glucuronidation ($p = 0.325$).^[37]

In summary, studies of the effects of smoking on TCA disposition have shown considerable variation. Several factors could account for these inconsistent findings, including unknown information at the time regarding the relationship between CYP isozymes and TCA metabolic pathways, lack of established criteria for smoking status, analytical accuracy and technology, and the limitation of the effects of smoking to specific CYP isozymes, mainly CYP1A2.

4.2 Selective Serotonin Reuptake Inhibitors (SSRIs)

4.2.1 Fluvoxamine

The selective serotonin (5-hydroxytryptamine; 5-HT) reuptake inhibitor (SSRI) fluvoxamine is metabolised by CYP1A2, and smoking induces this isozyme. Spigset et al.^[30] investigated the pharmacokinetics of a single dose of fluvoxamine 50mg in 12 smokers (≥ 10 cigarettes per day) and 12 nonsmokers. Although smokers had significantly lower areas under the plasma concentration-time curve (AUC) and maximum plasma concentrations (C_{max}) than nonsmokers (table II), terminal half-life and oral clearance did not differ significantly because of the wide interpatient variability. Smokers had a lower serum concentration of fluvoxamine

than nonsmokers after a single oral dose. The authors suggested that there may be a need for higher dosages of fluvoxamine in smokers than in nonsmokers.

4.2.2 Other SSRIs

The effects of smoking on the disposition of other SSRIs (fluoxetine, sertraline, paroxetine and citalopram) have not been extensively evaluated. Based upon the CYP isozyme information in table I, smoking would not be expected to significantly affect their pharmacokinetic disposition.

4.3 Other Antidepressants

4.3.1 Trazodone

Effects of smoking on the steady-state plasma concentration of trazodone and its active metabolite *m*-chlorophenylpiperazine (mCPP) were studied in 43 Japanese patients with depression (16 smokers; ≥ 10 cigarettes/day) receiving 150 mg/day for 1 to 3 weeks.^[31] Smokers had significantly lower plasma concentrations of trazodone and higher mCPP : trazodone ratios than nonsmokers (table II). The plasma concentration of mCPP did not differ significantly between the groups.

This result suggests that either smoking enhances hydroxylation and/or *N*-oxidation of trazodone, or that it enhances both the formation and metabolism of mCPP. The significantly higher mCPP : trazodone ratios in smokers also suggest there could be a difference in clinical response to trazodone treatment between smokers and nonsmokers. Smokers may require higher dosages of trazodone to obtain an optimal clinical response.

4.3.2 Amfebutamone (Bupropion)

Amfebutamone (bupropion) is approved by various regulatory agencies for smoking cessation. There are a number of reports that patients with depression taking amfebutamone decreased the number of cigarettes smoked or stopped smoking after the initiation of the drug. Smokers who quit smoking while using amfebutamone are likely to experience the reversal of any metabolic changes induced by smoking. The efficacy and safety of amfebutamone may change significantly during the transition period. Therefore it is important to

determine the effect of smoking on its pharmacokinetics and metabolism. *In vitro* studies with human liver microsomes indicated that CYP2B6 is the major isozyme that converts amfebutamone to its hydroxy metabolites.^[32] Minor contributions occur with CYP1A2, 3A4, 2A6, 2C9 and 2E1.

A single 150mg tablet of sustained-release amfebutamone hydrochloride was administered to 17 smokers (≥ 10 cigarettes/day) and 17 nonsmokers and pharmacokinetic parameters were calculated for amfebutamone and its 3 major metabolites.^[32] None of the pharmacokinetic parameters of amfebutamone and its metabolites were significantly different between smokers and nonsmokers (table II). This result suggests that smoking did not significantly affect the metabolism of amfebutamone and its metabolites. Because smokers handle amfebutamone and its metabolites in a manner similar to that of nonsmokers, this reduces the safety concerns. Based on these results, there is no reason to adjust the administration regimen of amfebutamone on the basis of smoking status.

4.3.3 Venlafaxine

The effect of steady-state venlafaxine (37.5 to 75mg every 12 hours) on the CYP1A2-dependent pharmacokinetics and metabolism of caffeine 200mg in 16 healthy nonsmokers was evaluated in a non-blind study.^[38] This *in vivo* study demonstrated that venlafaxine did not significantly alter the pharmacokinetic profile of caffeine, and confirmed *in vitro* data that venlafaxine does not inhibit CYP1A2 metabolism. Based upon these results, one would expect that there would be a very low potential for pharmacokinetic changes to venlafaxine in smokers.

5. Antipsychotics

Smoking prevalence is highest in schizophrenia compared with that in other psychiatric diagnoses.^[39] The incidence of smoking among patients with schizophrenia is approximately 80%.^[40] Institutionalised patients with chronic schizophrenia are the heaviest smokers, and it appears that patients with schizophrenia who smoke have an earlier age of

onset of psychiatric illness compared with nonsmokers.^[22,40]

The proposed reasons for this high incidence include genetic vulnerability, and that smoking reduces drug-induced adverse effects, alleviates positive and negative symptoms of schizophrenia and improves cognitive deficits.^[22,39] A study on negative symptoms of schizophrenia and the number of cigarettes smoked showed no significant correlation, but the heaviest smokers tended to have the least negative symptoms.^[40]

Nicotine interacts with the dopaminergic system. It increases the release of dopamine from the nucleus accumbens and prefrontal cortex, which in turn activates the reward system in the brain.^[22] Negative symptoms may be associated with a diminished reward system activity.

Drugs of abuse are known to activate this reward pathway. Nicotine also stimulates the presynaptic nicotinic receptors on glutaminergic neurons, increasing prefrontal cortex levels of glutamate and enhancing the glutaminergic input to the midbrain. Dysfunction of the prefrontal cortex is associated with negative symptoms.^[40]

The most frequent reason for smoking reported by patients with schizophrenia is to help facilitate relaxation. Among all smokers, most report that smoking produces arousal, improves their concentration, and enhances their mood and pleasure. It has been proposed that smoking cessation can exacerbate psychiatric symptoms. Dalack and Meador-Woodruff^[40] reported 3 cases of symptom exacerbation with smoking cessation or reduction in cigarettes. All 3 patients had a long history of schizophrenia and smoking. These patients were fairly stable with minimal hospitalisations. In all 3 incidents, reduction or alleviation of the acute symptoms occurred once smoking was resumed.

The reduction in drug-induced adverse effects associated with smoking is believed to be caused by induction of antipsychotic metabolism resulting in reduced plasma blood concentrations. The influence of cigarette smoking on tardive dyskinesia is controversial. A study by Nilsson et al.^[41] concluded that chronic cigarette smoking predicts dyskinetic

movements independent of exposure to antipsychotics. There is indirect evidence to support the suggestion that smoking reduces antipsychotic concentrations and adverse effects. Vinarová et al.^[42] calculated the average dosage of antipsychotics for smokers and nonsmokers. The dosage in nonsmokers was 25% less than in smokers ($p < 0.01$).

It also appears that smokers with schizophrenia undergo more hospitalisations than nonsmokers.^[40] Several cross-sectional studies have postulated that smoking may be a marker for more severe symptoms of schizophrenia, which require higher drug dosages.^[40] It will be difficult to determine whether or not smoking produces a pharmacokinetic alteration and/or a pharmacodynamic impact upon the dopaminergic system in patients with schizophrenia that contributes toward symptom severity.

Salokangas et al.^[43] compared the effects of age, gender and smoking habits on the daily dosage of antipsychotics. Gender alone was not significant, but the interaction with gender, age and smoking was significant. In female nonsmokers, the daily dose requirements were reduced with age, whereas the dose in smokers increased. In both male and female nonsmokers >50 years of age, the plasma concentration : daily dose ratios were higher than in nonsmokers.

5.1 Typical Antipsychotics

5.1.1 Chlorpromazine

The frequency of drowsiness attributed to orally administered chlorpromazine was compared among 130 nonsmokers and 201 'light' (<20 cigarettes/day) and 72 'heavy' (>20 cigarettes/day) smokers. Drowsiness was highest in nonsmokers (16%), intermediate in light smokers (11%) and lowest in heavy smokers (3%).^[44] It was hypothesised that these findings were a result of induction of liver microsomal enzymes and more rapid metabolism of chlorpromazine in smokers. Another possibility is that nicotine (see section 8) could produce 'activation' effects, thereby partially accounting for the less sedation found in the heavy use group.

Smoking has been shown to be related to altered serum chlorpromazine concentration. A case report

of a 25-year-old patient with schizophrenia controlled on chlorpromazine described more severe adverse effects following abrupt cessation of cigarette smoking, which was correlated with an increase in plasma chlorpromazine concentration.^[45] The patient's serum chlorpromazine concentration was 10 µg/L during her smoking history of 40 cigarettes/day and 106 µg/L within 1 week after smoking cessation.

The effect of cigarette smoking on disposition of a single dose of chlorpromazine was investigated.^[46] The mean C_{max} and AUC of chlorpromazine were 24 and 36% lower, respectively, in 8 smokers than in 9 nonsmokers. These differences were not statistically significant, probably because of the small number of patients involved in the study. Additionally, there was no correlation between the plasma exposure parameters and the degree of either sleepiness or orthostatic hypotension in these individuals. Based on these findings, it is unlikely that cigarette smoking influences the effects of chlorpromazine by enhancing its overall metabolism, and thereby decreasing its concentration. However, these findings with single doses may not reflect clinical situations with steady-state conditions.

A recent study by Chetty et al.^[47] showed that the average clearance of chlorpromazine measured in the population of patients with chronic schizophrenia was 127 L/h in the absence of other drugs and 175 L/h in cigarette smokers (table III). The combination of cannabis and cigarette smoking increased the clearance of chlorpromazine further to 263 L/h. The authors postulated that heavy smoking was associated with a decrease in the plasma concentrations of chlorpromazine due to enzyme induction, and that a higher dosage may be required in patients who are smokers of cannabis or cigarettes.

5.1.2 Trifluoperazine

The single dose pharmacokinetics of trifluoperazine 5mg were investigated in 13 smoking and 44 nonsmoking men.^[53] Smokers consumed less than 1 pack of cigarettes per day. For all pharmacokinetic parameters examined (C_{max} , AUC and clearance), significant differences were not detected between smokers and nonsmokers. The authors attributed

Table III. Effect of cigarette smoking on the disposition of conventional antipsychotics. Values are means \pm SD

Drug	Pharmacokinetic changes	Significance (percentage change in pharmacokinetics in smokers)	Reference
Chlorpromazine	Mean C_{max} and AUC were 24% and 36% lower in smokers than in nonsmokers	C_{max} and AUC values were not provided; differences were not significant	46
Chlorpromazine	CL (L/h): NS = 127 S = 175 (263 when cigarette smoking was combined with cannabis)	p-Value was not provided	47
Tiotixene	C_p (all patients) [μ g/L]: NS = 1.24 ± 1.63 S = 1.33 ± 1.40	p = 0.83; difference was not significant	48
	CL (all patients) [L/min]: NS = 37.0 ± 34.0 S = 45.6 ± 36.2	p = 0.43; difference was not significant	
	C_p (patients with no other concurrent drugs) [μ g/L]: NS = 1.22 ± 1.32 S = 1.19 ± 0.48	p = 0.95; difference was not significant	
	CL (patients with no other concurrent drugs) [L/min]: NS = 27.5 ± 9.2 S = 37.4 ± 14.4	p = 0.05 (36% increase)	
	CL (patients with concurrent enzyme/CL inhibitor) [L/min]: NS = 8.1 ± 2.7 S = 13.7 ± 2.1	p = 0.041 (69% increase in presence of concurrent inhibitor)	
Fluphenazine (hydrochloride and decanoate)	C_p (hydrochloride) [μ g/L]: NS = 1.83 ± 0.94 S = 0.89 ± 0.43	p < 0.05 (51% decrease)	49
	CL (hydrochloride) [L/min]: NS = 9.99 ± 2.82 S = 16.2 ± 5.20	p < 0.005 (62% increase)	
	CL (decanoate) [L/min]: NS = 3.6 ± 0.78 S = 7.37 ± 3.28	p < 0.005 (105% increase)	
	Dosage to achieve equivalent C_p (decanoate) [mg/week]: NS = 28.34 ± 14.39 S = 48.28 ± 20.95	p < 0.02 (70% increase)	
Haloperidol	C_p (haloperidol) [μ g/L]: NS = 28.80 ± 18.42 S = 16.83 ± 9.25	p < 0.01 (71% increase)	50
	CL (haloperidol) [L/min]: NS = 1.10 ± 0.36 S = 1.58 ± 0.78	p = 0.0052 (44% increase)	
	C_p (reduced haloperidol) [μ g/L]: NS = 34.23 ± 29.91 S = 16.76 ± 18.81	p < 0.05 (51% decrease)	
Haloperidol	$t_{1/2}$ (h): NS = 22.5 ± 9.6 S = 14.3 ± 5.7	p < 0.05 (36% decrease)	51
	CL (ml/min): NS = 17.0 ± 6.4 S = 27.4 ± 12.7	p < 0.05 (61% increase)	
	C_p (μ g/L): NS = 21.2 ± 15.0 S = 11.4 ± 4.8	p > 0.05; difference was not significant	

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Table III. Contd

Drug	Pharmacokinetic changes	Significance (percentage change in pharmacokinetics in smokers)	Reference
Haloperidol	$t_{1/2}$ (h): NS = 14.5 ± 6.2 S = 21.7 ± 13.9	p = 0.06; difference was not significant	52
	CL (ml/min): NS = 16.3 ± 7.1 S = 19.9 ± 9.3	p = 0.2; difference was not significant	
	C_p ($\mu\text{g/L}$): NS = 22.2 ± 11.2 S = 21.2 ± 12.9	p = 0.79; difference was not significant	
	C_p (haloperidol dosage <0.5 mg/kg/day) [$\mu\text{g/L}$]: NS = 18.1 ± 8.3 S = 10.5 ± 7.0	p = 0.046 (42% decrease)	
	C_p (haloperidol dosage >0.5 mg/kg/day) [$\mu\text{g/L}$]: NS = 27.5 ± 12.9 S = 28.8 ± 10.5	p = 0.81; different was not significant	
	C_p (reduced haloperidol) [$\mu\text{g/L}$]: NS = 7.5 ± 5.7 S = 10.7 ± 11.1	p = 0.36; difference was not significant	

AUC = area under the plasma concentration-time curve; **CL** = clearance; **C_p** = plasma concentration; **C_{max}** = maximum plasma drug concentration; **N** = nonsmoker; **S** = smoker; **SD** = standard deviation; **$t_{1/2}$** = elimination half-life.

the inability of statistical tests to uncover significant differences between smokers and nonsmokers to the effects of smoking superimposed on a far greater interindividual variation caused by the combined effects of all other factors. Further, the small number of smokers may have been insufficient to provide any reliable findings. However, the results could also indicate that smoking has no effect on the metabolism of trifluoperazine.

5.1.3 Tiotixene

A retrospective analysis of the pharmacokinetic drug interactions of tiotixene (mean dosage 26.9 ± 21.3 mg/day; range 0 to 100 mg/day) with hepatic enzyme/clearance inducers or inhibitors and with smoking status and demographic variables was performed in 42 patients with schizophrenia.^[48] Groups of patients were categorised by concomitant medications (i.e. no interacting drugs, enzyme/clearance inducers and enzyme/clearance inhibitors). Smokers smoked 5 to 40 cigarettes per day. Clearance differences produced by drug interactions were analysed for the effects of smoking. Tobacco smoking significantly increased the hepatic clearance of tiotixene within the no interactions and inhibitor groups, but not in the inducer group

(table III). Smoking had a significant effect on the oral clearance of tiotixene in that plasma concentrations of tiotixene were detectable only in those patients who did not have concomitant enzyme-inducing drugs. Significantly more patients in the inducer group had nondetectable plasma concentrations of tiotixene than in the other groups.

5.1.4 Fluphenazine

The effect of smoking on drug clearance in psychiatric inpatients maintained on oral fluphenazine hydrochloride ($n = 22$) and fluphenazine decanoate ($n = 39$) was described in a retrospective longitudinal drug utilisation review.^[49] 18 patients receiving fluphenazine hydrochloride (7 smokers) and 22 patients receiving fluphenazine decanoate (10 smokers) were selected for analysis. Smokers and nonsmokers in the fluphenazine hydrochloride group had no significant difference in dosage. However, in the smoking group, plasma concentrations were significantly lower and clearance was significantly higher than in the nonsmoking group (table III). In the fluphenazine decanoate group, plasma concentrations were not significantly different between smokers and nonsmokers. However, in the smoking group, clearance and dosage to

achieve equivalent plasma concentrations were significantly higher than in the nonsmoking group. The calculated clearance ratios for smokers : non-smokers were 1.67 and 2.33 for fluphenazine hydrochloride and fluphenazine decanoate recipients, respectively.

5.1.5 Haloperidol

Steady-state plasma concentrations of haloperidol and its reduced metabolite (reduced haloperidol) were investigated in 50 patients with schizophrenia (23 smokers, 27 nonsmokers) in a retrospective, longitudinal drug utilisation review.^[50] Smokers were defined as patients who consumed more than 1 pack of cigarettes per day. In smokers, plasma concentrations of haloperidol and reduced haloperidol were significantly lower than in nonsmokers. The clearance of haloperidol was significantly greater in smokers compared with nonsmokers (table III). The calculated clearance ratio of haloperidol for smokers : nonsmokers was 1.44. Clinical assessment with the Clinical Global Impression Scale (CGIS) did not show significant differences between the 2 groups. The authors suggested that plasma concentrations of haloperidol should be carefully monitored when patients either start or stop smoking.

The influence of cigarette smoking on the pharmacokinetics of a single 20mg test dose of haloperidol in 20 patients (10 smokers, >1 pack of cigarettes/day for >1 month) was prospectively studied.^[51] The elimination half-life in smokers was significantly shorter than in nonsmokers (table III). After the single dose study, patients were then placed on haloperidol dosages calculated to achieve plasma concentrations between 8 and 18 µg/L (from a previous study) for the next 2 weeks. Blood samples were collected at the end of weeks 1 and 2. There was a trend toward smokers having lower plasma concentrations at steady state than nonsmokers, but this was not statistically significant. However, total plasma clearance at steady state was significantly higher in the smoking than in the nonsmoking group. These findings and those of Jann et al.^[50] suggest, 'at least mathematically', that smokers may require slightly higher dosages

of haloperidol to achieve similar plasma concentrations.

Perry et al.^[52] investigated the effect of smoking on haloperidol dosage requirements in 43 patients with schizophrenia (26 smokers, 17 nonsmokers). Smoking status and dosage of the drug independently did not affect the average haloperidol concentration. Their combined effects showed that haloperidol concentrations were dependent on smoking status at specific dosages. An interaction between smoking status and the haloperidol dosage significantly affected the prediction of steady-state plasma haloperidol concentration on the basis of the haloperidol dosage. The nonsmokers had higher steady-state haloperidol concentrations than did smokers at dosages lower than 0.5 mg/kg/day (table III). At haloperidol dosages greater than 0.5 mg/kg/day, there was no longer any difference between the steady-state concentration of the smokers and the nonsmokers. The reason for this finding may be that high serum concentrations of reduced haloperidol saturate its back conversion to haloperidol. Smokers receiving lower dosages might convert reduced haloperidol to haloperidol faster, and thereby serum haloperidol concentrations would become undistinguishable from those in nonsmokers. This finding could imply that other CYP isozymes not induced by smoking may be involved in haloperidol disposition.

In contrast to the above findings, 2 studies have not found any differences in the pharmacokinetics of haloperidol in smokers and nonsmokers. A study by Midha et al.,^[54] which was designed to determine the interindividual variation in the pharmacokinetics of haloperidol and reduced haloperidol after a single dose of haloperidol 5mg, did not find any significant differences in the C_{max} , AUC or clearance of haloperidol between 19 smokers (who smoked more than 1 pack per day) and 9 nonsmokers. The results of this study might have been influenced by the uneven number of smokers and nonsmokers, the small sample size and the use of a single dose of haloperidol. Additionally, there was a 5-fold variation in AUC values among the nonsmokers, which sug-

gested that the effects of smoking were probably superimposed on a naturally wide interindividual variation in haloperidol kinetics.

Another study investigated the pharmacokinetics of haloperidol decanoate in red blood cells and plasma of 9 patients (6 smokers; one-fifth to 2 packs of cigarettes/day).^[55] Monthly haloperidol decanoate doses ranged from 50 to 200mg. Red blood cell and plasma

concentrations of haloperidol and reduced haloperidol did not correlate significantly with smoking.

5.2 Atypical Antipsychotics

5.2.1 Clozapine

Clozapine is metabolised by various CYP isozymes, including 1A2, 3A4 and 2D6 (table I).

Table IV. Effect of cigarette smoking on the disposition of atypical antipsychotics. Values are means \pm SD

Drug	Pharmacokinetic changes	Significance (percentage change in pharmacokinetics in smokers)	Reference			
Olanzapine	C_{max} ($\mu\text{g/L}$): NS = 12.9 ± 7.5 S = 13.2 ± 7.4	Differences were not significant except for CL; p values were not provided	57			
	t_{max} (h): NS = 6.1 ± 1.9 S = 5.5 ± 1.4					
	AUC ($\mu\text{g} \cdot \text{h/L}$): NS = 492 ± 294 S = 419 ± 220					
	$t_{1/2}$ (h): NS = 32.5 ± 7.2 S = 29.3 ± 4.0					
	CL (L/h): NS = 22.3 ± 7.9 S = 27.5 ± 7.7			p = 0.03 (23% increase)		
	Zotepine			C_{max} ($\mu\text{g/L}$): NS = 7.9 ± 3.2 S = 4.4 ± 1.5	Differences were not significant; p values were not provided	58
				t_{max} (h): NS = 3.9 ± 1.6 S = 3.6 ± 0.5		
	$t_{1/2}$ (h): NS = 16.9 ± 7.2 S = 24.0 ± 8.8					
	CL (L/h): NS = 4.1 ± 2.6 S = 5.0 ± 5.0					
Clozapine	C_p ($\mu\text{g/L}$): NS = 183.2 ± 15.5 S = 141.0 ± 114.2	p = 0.02 (24% decrease)	59			
Clozapine	C_p (clozapine) [$\mu\text{g/L}$]: NS = 436.6 ± 298.7 S = 347.7 ± 243.6	p = 0.24; difference was not significant	60			
	C_p (norclozapine) [$\mu\text{g/L}$]: NS = 346.4 ± 221.2 S = 244.6 ± 175.9	p = 0.07; difference was not significant				
Clozapine	C_p (clozapine) [$\mu\text{g/L}$]: NS = 205.9 ± 78.9 S = 140.7 ± 48.7	p < 0.05 (32% decrease)	61			
	C_p (norclozapine) [$\mu\text{g/L}$]: NS = 110.1 ± 74.4 S = 98.1 ± 35.5	p value was not reported; difference was not significant				

AUC = area under the plasma concentration-time curve; **CL** = clearance; **C_p** = plasma concentration; **C_{max}** = maximum plasma drug concentration; **NS** = nonsmoker; **S** = smoker; **SD** = standard deviation; **t_{1/2}** = elimination half-life; **t_{max}** = time to reach C_{max}.

These *in vitro* findings differ from *in vivo* results where CYP1A2 and 3A4 were found to be the most important isozymes influencing clozapine disposition.^[56] Since CYP1A2 significantly influences clozapine disposition, smoking can be presumed to affect the pharmacokinetic disposition of the drug, as shown by various studies summarised in table IV.

Plasma clozapine concentrations were measured in 148 patients with schizophrenia treated with dosages between 12.5 and 700 mg/day for at least 8 days.^[59] Smokers had significantly lower mean plasma clozapine concentrations than nonsmokers. Interestingly, when the data were analysed with gender as an additional factor, significantly lower plasma clozapine concentrations (average 67% lower) were found only in male smokers ($p < 0.01$), whereas female nonsmokers and smokers did not differ.^[55] This lack of difference in females may be related to the overall lower CYP1A2 activity found in women.^[59] In another study, plasma clozapine and norclozapine (demethyl-clozapine) concentrations were found to be lower in smokers than in nonsmokers, although the difference was not statistically significant.^[60] Similar results were reported by Wetzel et al.,^[61] although in this study the difference between smokers and nonsmokers was statistically significant for clozapine but not for norclozapine.

These studies indicate that plasma clozapine concentrations are generally lower in smokers compared with nonsmokers. As the therapeutic 'threshold' of clozapine was found to be about 350 µg/L, or 450 µg/L for clozapine plus norclozapine,^[62] smokers may need higher drug dosages to achieve this threshold. Interestingly, both parent and metabolite concentrations were decreased in smokers compared with nonsmokers. A precise pharmacological mechanism for both parent and metabolite concentrations to decrease in smokers has not been elucidated, although one can speculate that isozyme induction could occur for both compounds. While it is easily understood that induction of metabolism of the parent drug can occur, conversion of the metabolite either by CYP1A2 or possibly by induction of glucuronidation (this mechanism has not been

observed) could explain lower metabolite concentrations. Another explanation for a lower, but not statistically significantly different, metabolite concentration is the large interpatient variability observed with psychotropic drug concentrations, suggesting that a significant induction effect on metabolite metabolism is unlikely to occur.

5.2.2 Olanzapine

Olanzapine is primarily metabolised to its 10- and 4'-*N*-glucuronides, to 4'-*N*-demethyl-olanzapine by CYP1A2 and to olanzapine *N*-oxide by flavin mono-oxygenase 3. Metabolism to 2-hydroxymethyl-olanzapine via CYP2D6 is a minor pathway. The 10-*N*-glucuronide is the most abundant metabolite, but formation of 4'-*N*-demethyl-olanzapine is correlated with the clearance of olanzapine.^[57] Fluvoxamine, an inhibitor of CYP1A2, increases plasma concentrations of olanzapine, and inducers of CYP1A2, such as tobacco smoke and carbamazepine, decrease olanzapine concentrations. Dosage modification should be considered for patients with factors that are associated with decreased oxidative metabolism.^[57]

In a dose-proportionality and bioequivalency trial of 5, 10 and 15mg capsules and tablets, the pharmacokinetics of olanzapine in 19 smokers and 30 nonsmokers were evaluated.^[57] In smokers, the C_{\max} of olanzapine was slightly greater but the time to reach C_{\max} (t_{\max}) was shorter compared with nonsmokers (table IV). The oral clearance of olanzapine in smokers was 23.3% higher than in nonsmokers ($p = 0.03$) secondary to induction of the CYP1A2 metabolic pathway by cigarette smoking. In a composite analysis of healthy participants in all studies, the pharmacokinetic difference between smokers and nonsmokers was evident for the relationship between olanzapine AUC and dose. Population pharmacokinetic analysis confirmed the effect of smoking on olanzapine clearance. Olanzapine clearance was determined to be 37 to 48% lower than the clearance for smokers. The difference in the pharmacokinetic profile of olanzapine among smokers is consistent with CYP1A2 induction by smoking.^[57,63]

5.2.3 Zotepine

Recently, it was reported that the mean steady-state serum concentration of zotepine was lower in 37 smokers than in 22 nonsmokers (table IV), suggesting the enhanced metabolism of zotepine by smoking.^[64] To confirm these pharmacokinetic findings and the possibility of an effect of smoking, the effect of CYP2C19 inhibition on the single dose kinetics of zotepine 25mg in 14 healthy men (8 smokers; ≥ 10 cigarettes/day) was re-examined.^[58] However, in this study, there was no significant difference in any pharmacokinetic parameters between the 8 smokers and 6 nonsmokers. The authors suggested that this discrepancy might be partly explained by the small number of participants in this study and a large interindividual variation in the pharmacokinetics and metabolism of zotepine.

5.2.4 Risperidone

Studies directly linking smoking and alterations in risperidone pharmacokinetics have not yet been reported. One retrospective study (92 patients, 32 smokers) reported that women and nonsmokers received significantly lower daily doses ($p < 0.05$) than men and smokers.^[65] However, serum risperidone concentrations were not reported in any of these groups. Further studies are warranted to determine if smoking significantly affects risperidone disposition.

6. Anxiolytics

There appears to be an association between anxiety disorders and cigarette smoking, but the evidence is less consistent than for other psychiatric diagnoses.^[22] Smokers report that nicotine reduces their symptoms of anxiety. However, nicotine has been shown to have stimulant properties in animals and humans.^[22] The pharmacotherapy of anxiety disorders includes benzodiazepines, buspirone and antidepressants. The pharmacokinetic effect of smoking has not been fully established with benzodiazepines; this section briefly describes the studies that have been published. These agents are grouped together based upon their metabolic profiles.

6.1 Triazolam and Alprazolam

As shown in table I, both triazolam and alprazolam are substrates of CYP3A4.

The influence of cigarette smoking on the pharmacokinetics of a single dose of triazolam 0.5mg was evaluated in 12 nonsmoking and 12 smoking men who smoked an average of 24 cigarettes per day (range 15 to 30).^[66] Both groups were matched for age, height and bodyweight. Significant differences between nonsmoking controls and smokers in triazolam C_{max} or t_{max} were not found. Compared with nonsmoking controls, the half-life of triazolam was shorter, total AUC was smaller, and clearance was higher in cigarette smokers, as shown in table V. However, these differences did not approach statistical significance. Further analysis indicated that the nonsignificance of the difference was attributable mainly to the interindividual variability in each group and the small sample size.

A comparison of the pharmacokinetics of single doses of triazolam 0.5mg and alprazolam 0.8mg was performed in 10 healthy Japanese men (5 smokers; > 10 cigarettes/day).^[67] The only significant finding was that the mean elimination half-life of alprazolam was significantly ($p < 0.01$) shorter in the smokers than in the nonsmokers. Significant differences in the pharmacokinetic parameters of triazolam between the 2 groups were not found. These findings suggested that CYP1A2 might be involved in the metabolism of alprazolam, but not triazolam.

In contrast, a study of 17 healthy volunteers (8 smokers) who completed a bioavailability study of the immediate-release and controlled-release forms of alprazolam showed that cigarette smoking was associated with a 100% increase in clearance of alprazolam compared with nonsmokers (table V).^[68] A population analysis with the nonlinear mixed effects model (NONMEM) programme found that smoking was a significant variable in alprazolam clearance. Since alprazolam has been suggested to be mainly metabolised by the CYP3A4 isozyme, this finding suggests that smoking might be an inducer of CYP3A4 and/or that alprazolam might be metabolised by other isozyme(s)

Table V. Effect of cigarette smoking on the disposition of anxiolytics. Values are means \pm SD

Drug	Pharmacokinetic changes	Significance (percentage change in pharmacokinetics in smokers)	Reference
Triazolam	C_{\max} ($\mu\text{g/L}$): NS = 4.64 ± 0.54 S = 4.73 ± 0.65 t_{\max} (h): NS = 0.98 ± 0.19 S = 1.0 ± 0.17 $t_{1/2}$ (h): NS = 2.84 ± 0.21 S = 2.49 ± 0.16 AUC ($\mu\text{g} \cdot \text{h/L}$): NS = 19.8 ± 2.3 S = 15.8 ± 1.9 CL (ml/min/kg): NS = 6.64 ± 0.86 S = 8.92 ± 1.10	t = 1.0; difference was not significant t = 0.08; difference was not significant t = 1.28; difference was not significant t = 1.34; difference was not significant t = 1.62; difference was not significant	66
Triazolam	C_{\max} ($\mu\text{g/L}$): NS = 3.5 ± 1.2 S = 2.9 ± 0.9 t_{\max} (h): NS = 0.9 ± 0.3 S = 0.9 ± 0.2 AUC ($\mu\text{g} \cdot \text{h/L}$): NS = 14.3 ± 6.7 S = 9.2 ± 0.7 $t_{1/2}$ (h): NS = 2.7 ± 1.4 S = 2.3 ± 0.6	Differences between smokers and nonsmokers were not significant	67
Alprazolam	C_{\max} ($\mu\text{g/L}$): NS = 11.0 ± 2.8 S = 11.7 ± 3.7 t_{\max} (h): NS = 1.3 ± 0.7 S = 1.7 ± 1.0 AUC ($\mu\text{g} \cdot \text{h/L}$): NS = 237.2 ± 53.9 S = 227.6 ± 70.1 $t_{1/2}$ (h): NS = 20.0 ± 2.7 S = 13.0 ± 3.1	Differences between smokers and nonsmokers were not significant except for $t_{1/2}$ p < 0.01 (35% decrease)	67
Alprazolam	CL/F (L/h): NS = 3.77 S = 7.5	p < 0.05 (99% increase)	68
Lorazepam (intravenous)	CL (smokers included) [ml/min/kg]: elderly = 0.77 ± 0.06 young = 0.99 ± 0.08	p < 0.05 (29% increase in young)	69
	CL (smokers excluded) [ml/min/kg]: elderly = 0.78 young = 0.96	p > 0.1; difference was not significant	
Lorazepam (intravenous)	$t_{1/2}$ (h): NS = 16.4 ± 1.2 S = 13.3 ± 0.7 CL (ml/min/kg): NS = 0.96 ± 0.09 S = 1.08 ± 0.05	p < 0.05 (19% decrease) t = 1.13; difference was not significant	70

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Table V. Contd

Drug	Pharmacokinetic changes	Significance (percentage change in pharmacokinetics in smokers)	Reference
	AUC (mg • h/L): NS = 0.58 ± 0.07 S = 0.47 ± 0.02	t = 1.61; difference was not significant	
Diazepam (intravenous) ^a	CL (ml/min/kg): elderly = 0.24 young = 0.39	p < 0.01 (63% increase in young smokers due to heavy smoking)	71
Demethyl-diazepam	t _{1/2} (h): NS = 54.7 ± 17.7 S = 29.8 ± 9.9	p < 0.05 (46% decrease)	72
	C _{max} (µg/L): NS = 413 ± 106 S = 245 ± 50	p < 0.05 (40% decrease)	
	CL (L/kg/h): NS = 0.016 ± 0.0041 S = 0.044 ± 0.025	p < 0.05 (175% increase)	
Diazepam (intravenous)	t _{1/2} (h): NS = 33.5 ± 2.9 S = 31.3 ± 3.5	t = 0.49, p = not significant	70
	AUC (mg • h/L): NS = 4.73 ± 0.58 S = 3.83 ± 0.34	t = 1.32, p = not significant	
	CL (ml/min/kg): NS = 0.44 ± 0.05 S = 0.47 ± 0.04	t = 0.42, p = not significant	
Demethyl-diazepam	t _{1/2} (h): NS = 59 S = 55	p-Values were not reported; differences were not significant	73
	CL (L/kg/h): NS = 0.016 S = 0.017		
Chlordiazepoxide (intravenous)	t _{1/2} (h): NS = 13.7 ± 7.3 S = 13.3 ± 5.7	p-Value was not reported; difference was not significant	74

a 1 of 11 elderly and 4 of 11 young smokers smoked >10 cigarettes/day.

AUC = area under the plasma concentration-time curve; **CL** = clearance; **CL/F** = apparent (oral) clearance; **C_{max}** = maximum plasma concentration; **NS** = nonsmoker; **S** = smoker; **SD** = standard deviation; **t** = Student's t-test value; **t_{1/2}** = elimination half-life; **t_{max}** = time to reach C_{max}.

(specifically CYP1A1/1A2) that are induced by cigarette smoke.

Elimination half-life is not the only parameter that influences steady-state plasma concentrations and is affected by smoking. V_d is another important factor, especially for lipid-soluble drugs such as benzodiazepines. Smokers generally tend to weigh less than nonsmokers, which could also explain differences in steady-state drug concentrations in situations where V_d plays a significant role in drug disposition. However, when these 2

factors are considered and the result is minimal differences in plasma drug concentrations, dosage adjustments between smokers and nonsmokers would not be necessary.

6.2 Lorazepam

Lorazepam disposition does not involve phase I oxidation metabolism but phase II glucuronidation. The kinetic properties of single 1.5 to 3mg intravenous doses of lorazepam were assessed in 15 elderly (aged 60 to 84 years) and 15 young (aged 19 to 38

years) healthy volunteers.^[69] Of the 12 elderly and 9 young participants who were smokers, only 1 in the elderly group and 4 in the young group were defined as moderate to heavy smokers (≥ 15 cigarettes/day). Multiple regression analysis was performed to identify possible confounding influences on the kinetics of lorazepam, and smoking accounted for 8% of variability in total clearance and age accounted for 17% (table V). Total lorazepam clearance in the elderly was 22% lower than in the younger group ($p < 0.05$). These age differences in lorazepam clearance were attributed partly to more frequent cigarette smoking in the younger group. When all smokers and/or moderate to heavy smokers were excluded from both groups, the mean lorazepam clearance did not differ significantly between the elderly and the young groups ($p > 0.1$). These findings suggest enhanced lorazepam clearance due to cigarette smoking.

In another study, 10 healthy cigarette smokers (mean 31 cigarettes/day) and 10 nonsmoking control volunteers matched for age, bodyweight and gender received a single intravenous dose of lorazepam 2mg.^[70] Elimination half-life was significantly shorter in smokers compared with controls ($p < 0.05$). In smokers, there was a slight increase in total lorazepam clearance compared with nonsmokers, but this difference did not reach significance. V_d did not differ significantly between the groups.

6.3 Diazepam and Chlordiazepoxide

Diazepam and chlordiazepoxide are long-acting benzodiazepines because of their metabolic conversion to the active metabolite demethyl-diazepam. The Boston Collaborative Drug Surveillance Program indicated that tobacco smoke stimulated hepatic enzymes and accelerated the metabolism of diazepam and chlordiazepoxide, and therefore that heavy smokers experienced less drowsiness when administered these drugs than nonsmokers.^[75,76] Drowsiness was reported in 7.9% of 644 nonsmokers, 7.7% of 289 light smokers and 2.8% of 181 heavy smokers taking diazepam; in chlordiazepoxide recipients, 9.7% of 216 nonsmokers, 6.1% of 314 light smokers and 3.5% of 258 heavy smokers

experienced drowsiness. The differences among the comparison groups were statistically significant for both diazepam ($p < 0.05$) and chlordiazepoxide ($p < 0.02$) irrespective of the dosages. The relationship between cigarette smoking and the benzodiazepine was evident at all dosage levels. Plasma drug concentrations were not measured in this early study and may be lower in the heavy smoking group. An additional factor to consider is that the increased nicotine consumption may counteract the sedative effects from the benzodiazepines.

Factors influencing the kinetics of single doses of intravenous diazepam 5 to 10mg were assessed in 22 elderly (11 smokers) and 22 young (11 smokers) individuals by Greenblatt et al.^[71] Of the 11 elderly smokers and 11 young smokers, only 1 elderly and 4 young individuals smoked more than 10 cigarettes per day. The clearance of diazepam in elderly men was significantly less than in young men (table V). Cigarette smoking appeared to influence diazepam clearance in the young group, and higher values were associated with heavier cigarette smoking. These findings^[71] for diazepam were similar to the previous observations of Greenblatt and colleagues^[69] for lorazepam, for which higher clearance was also associated with heavy cigarette smoking.

In a study of the pharmacokinetics of demethyl-diazepam following administration of clorazepate 20mg to 12 healthy male volunteers (6 smokers; 5 to 30 cigarettes/day), the half-life was significantly shorter and C_{max} was lower in smokers than in nonsmokers ($p < 0.05$) [table V].^[72] The sedative effect of clorazepate was less severe in smokers than in nonsmokers.

In contrast to these studies,^[71,72] some studies have reported no influence of cigarette smoking on diazepam or demethyl-diazepam kinetics. In one of these studies, 10 healthy cigarette smokers (mean, 31 cigarettes/day) and 10 nonsmoking control volunteers matched for age, bodyweight and gender received single intravenous doses of diazepam 5 to 10mg.^[70] There was no significant difference in V_d , elimination half-life, total AUC, total clearance, and free fraction between the groups (table V). Mean

AUC for demethyl-diazepam was lower in smokers ($3.51 \mu\text{g} \cdot \text{h/L}$) than in controls ($4.54 \mu\text{g} \cdot \text{h/L}$, $p < 0.05$), although this difference was not significant when AUC was normalised for bodyweight (246 vs $298 \mu\text{g} \cdot \text{h/L}$). Similarly, in 8 cigarette smokers (mean, 19 cigarettes/day) and 11 nonsmokers, there were no significant differences in the Vd, clearance, free fraction in serum or elimination half-life for demethyl-diazepam (table V).^[73] Klotz et al.^[77] also reported no influence of smoking on the plasma half-life or clearance of intravenous diazepam 10mg in 33 patients (13 smokers; >20 cigarettes/day).

Smoking has been reported not to influence the disposition of chlordiazepoxide. 28 nonsmokers and 17 smokers (>20 cigarettes/day) were administered intravenous chlordiazepoxide 0.6 mg/kg. A statistically significant difference in terminal elimination half-life between smokers and nonsmokers was not found (table V).^[74] Furthermore, no statistically significant differences in systemic plasma clearance or Vd were noted. Changes in pharmacokinetic parameters, therefore, do not account for the decreased incidence of sedation in smokers.

Existing data thus conflict, and increased metabolism may not account entirely for the observed differences in the CNS adverse effect profile or the pharmacokinetics of benzodiazepines in smokers versus nonsmokers. Diminished end-organ responsiveness following cigarette smoking may attenuate the drowsiness associated with benzodiazepines.^[78]

7. Mood Stabilisers

7.1 Carbamazepine

Carbamazepine is metabolised by liver microsomal enzymes, mainly CYP3A4 with a minor effect of CYP1A2,^[79] and thus may be susceptible to interaction with smoking. When 15 men who smoked were compared with 16 nonsmoking men, the mean serum carbamazepine concentration was not appreciably different (3.83 ± 0.89 and $4.85 \pm 1.35 \text{ mg/L}$, respectively), although a downward trend in concentrations was noted in smokers.^[80] Similarly, mean carbamazepine concentrations did not differ

in women who were smokers or nonsmokers (4.56 ± 1.30 and $4.58 \pm 1.66 \text{ mg/L}$, respectively).^[80]

The effect of smoking on the pharmacokinetics of carbamazepine was also evaluated by Martin et al.^[81] in 45 patients (33 smokers), and smoking had no effect on post-induction carbamazepine clearance. As carbamazepine possesses hepatic enzyme induction properties, these enzymes may be refractory or minimally sensitive to further stimulation by tobacco. It therefore appears that adjustments in carbamazepine dosage are not required in patients who smoke.^[81]

7.2 Other Agents

Other anticonvulsant agents used as mood stabilisers in psychiatry include valproic acid (sodium valproate), lamotrigine and gabapentin.^[79] These agents are mainly metabolised by phase II glucuronidation or renally eliminated. Lithium is the classic agent used for bipolar disorders and it is also renally eliminated from the body.^[82] This information tends to support that smoking (at least through CYP1A2 induction) would not significantly effect the disposition of these agents.

8. Pharmacodynamic Effects of Nicotine on the Dopaminergic System

This article has mainly focused upon the pharmacokinetic interactions of smoking with psychotropic drugs. It would be incomplete if the impact of smoking upon pharmacodynamic parameters was not discussed. This section briefly describes the pharmacodynamic interactions when smoking occurs in conjunction with other psychotropic drugs. A more complete description of tobacco dependence can be found elsewhere.^[83]

Although many other substances are found in cigarettes and other smoking substrates, nicotine remains the most important pharmacological agonist (and most studied compound) arising from tobacco use. In addition to its actions on nicotinic receptors, thus modulating cholinergic activity, nicotine has been extensively evaluated for its effects upon the dopaminergic system.^[84] Autoradiographic studies in animal and human *in vitro* models

show that nicotine has high affinity agonist binding for the nicotinic receptors on dopaminergic neurons. These neurons are located in the mesolimbic, substantia nigra and ventral tegmental areas. Interestingly, in addition to many CNS functions, these neurons could be involved in the basic reward mechanism found in drug dependence. This agonistic effect results in a variety of pharmacological activities, including stimulation of dopamine release in a dose-dependent manner, development of acute and chronic tolerance and increased dopamine utilisation.^[84]

The pharmacokinetics and pharmacodynamics of nicotine have been extensively evaluated in smokers and nonsmokers.^[85-87] The average elimination half-life of nicotine has been estimated to be about 30 minutes in both groups, which explains the multiple drug intakes needed by nicotine consumers to maintain steady-state conditions during the day.^[87] However, despite its short elimination half-life in the body, nicotine could have additional pharmacodynamic effects when taken concomitantly with psychotropic drugs. Preclinical models have shown that nicotine potentiates the actions of haloperidol in terms of catalepsy and locomotor hypoactivity.^[88] The use of nicotine and haloperidol and its clinical significance remains unclear, but in a small nonblind trial of nicotine gum combined with low dosage haloperidol (mean 2.8 mg/day) in patients with Tourette's syndrome, the frequency of tic movements was significantly reduced during 30 minutes of, and 1 hour after, gum chewing.^[89] Although nicotine cannot be recommended for routine use, other nicotine agonists could perhaps be developed as therapeutic agents.

In patients with psychiatric disorders treated with antipsychotic drugs, epidemiological studies have reported a higher incidence of tardive dyskinesia among smokers.^[90] This interaction between antipsychotics and smoking forms a complex pattern, as smoking increases drug clearance through hepatic enzymatic stimulation, but nicotinic actions may potentiate dopaminergic and other pharmacological mechanisms, thereby increasing the overall risk of tardive dyskinesia.^[91] Besides tardive dys-

kinesia, it was reported that female smokers treated with antipsychotics also experienced increased subjective and objective symptoms of akathisia compared with female nonsmokers.^[92] In another study, smokers were genotyped for the CYP1A2 C→A polymorphism, which was found to be significantly associated with antipsychotic-induced tardive dyskinesia compared with the homozygous group ($p < 0.007$). The C/C group had higher mean scores from the Abnormal Involuntary Movements Scale (AIMS) than the heterozygote and A/A homozygous groups ($p < 0.008$).^[93] Therefore, patients with a CYP1A2 C→A genotype could be more prone to developing tardive dyskinesia, and induction by smoking may promote movement disorders.

The interaction between antipsychotics and nicotine exposure from smoking is very complex, involving both pharmacokinetic and pharmacodynamic mechanisms, and the details remain to be elucidated. Clinicians need to be aware that smoking is a major factor that can affect antipsychotic pharmacodynamics.

9. Conclusion

Smoking has a tremendous impact upon the healthcare delivery system in our society. This review indicates that smoking can stimulate hepatic CYP isozymes, particularly CYP1A2. It remains to be elucidated whether smoking can influence other hepatic isozymes that significantly contribute to enzyme induction. Psychotropic drugs that are major substrates of CYP1A2 appear to be significantly affected by smoking. Many studies that did not report significant differences between smokers and nonsmokers lacked statistical power because of the small sample sizes evaluated. Smoking could have a minor impact on, or inconsistently affect, psychotropic agents that are substrates of other CYP isozymes. Studies that evaluate the impact of smoking upon psychotropic drug disposition have not consistently over the years defined what amount of daily cigarette consumption constitutes smoking behaviour (i.e. 10 versus 20 cigarettes per day or more). It remains to be determined whether or not the metabolism of com-

pounds that undergo significant phase II glucuronidation is influenced by smoking. Factors such as age, ethnicity, gender, concurrent use of other substances commonly abused with tobacco dependence and amount of smoking (light vs heavy) can also contribute towards the wide inter-patient variability found between smoking and drug disposition. Finally, one of the main ingredients of tobacco – nicotine – could have additional pharmacodynamic effects. Therefore, smoking creates complex interactions with psychotropic drugs.

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References

- DeSimone EM, Scott DM. Nicotine and caffeine abuse. In: Koda-Kimble MA, Young LY, editors. Applied therapeutics: the clinical use of drugs. 5th ed. Vancouver: Applied Therapeutics, Inc; 1992: 85-113
- Pantuck EJ, Kuntzman R, Conney AH. Decreased concentration of phenacetin in plasma of cigarette smokers. *Science* 1972; 175: 1248-50
- Chan L, Horn JR. Management of metabolic drug interactions. In: Carter B, Lake K, Raebel M, et al., editors. Pharmacotherapy self-assessment program, 3rd Ed. gastroenterology module. Kansas City, MO: American College of Clinical Pharmacy 1999: 85-108
- Parkinson A. Biotransformation of xenobiotics. In: Klaassen CD, Doull J, Amdur MO, editors. Toxicology: the basic science of poisons. 5th ed. New York: McGraw-Hill; 1996: 113-86
- Shimada T, Yamazaki H, Mimura M, et al. Interindividual variations in human liver cytochrome P-450 enzymes involved in the oxidation of drugs, carcinogens and toxic chemicals: studies with liver microsomes of 30 Japanese and 30 Caucasians. *J Pharmacol Exp Ther* 1994; 270: 414-23
- Zevin S, Benowitz NL. Drug interactions with tobacco smoking. *Clin Pharmacokinet* 1999; 36 (6): 425-38
- Pelkonen O, Mäenpää J, Taavitsainen P, et al. Inhibition and induction of human cytochrome P450 (CYP) enzymes. *Xenobiotica* 1998; 28 (12): 1203-53
- Gonzalez FJ. Human cytochromes P450: problems and prospects. *Trends Pharmacol Sci* 1992; 13: 346-52
- Carrillo JA, Benitez J. CYP 1A2 activity, gender, smoking as variables influencing the toxicity of caffeine. *Br J Clin Pharmacol* 1996; 41: 605-8
- Sachse C, Brockmoller J, Baurer S, et al. Functional significance of a C → A polymorphism in intron I of the cytochrome P 450 1A2 gene tested with caffeine. *Br J Clin Pharmacol* 1999; 47: 445-9
- Okey AB. Enzyme induction in the cytochrome P450 system. *Pharmacol Ther* 1990; 45: 241-98
- Ereshfsky L, Tran-Johnson T, Davis CM, et al. Pharmacokinetic factors affecting antidepressant drug clearance and clinical effect: evaluation of doxepin and imipramine – new data and review. *Clin Chem* 1988; 34 (5): 863-80
- Jusko WJ. Influence of cigarette smoking on drug metabolism in man. *Drug Metab Rev* 1979; 9 (2): 221-36
- Luczynska C, Wilson K. The significance of the effects of cigarette smoking on drug disposition. *Methods Find Exp Clin Pharmacol* 1983; 5 (7): 479-87
- Özdemir V, Fourie J, Busto U, et al. Pharmacokinetic changes in the elderly: do they contribute to drug abuse and dependence? *Clin Pharmacokinet* 1996; 31 (5): 372-85
- Jann MW, Fidone GS, Hernandez JM, et al. Clinical implications of increased antipsychotic plasma concentrations upon anticonvulsant cessation. *Psychiatry Res* 1989; 28: 153-9
- Edge SC, Markowitz JS, DeVane CL. Clozapine drug-drug interactions: a review of the literature. *Hum Psychopharmacol* 1997; 12: 5-20
- McCarthy R. Seizure following smoking cessation in a clozapine responder. *Pharmacopsychiatry* 1994; 27: 210-1
- Hughes JR, Frances RJ. How to help psychiatric patients stop smoking. *Psychiatr Serv* 1995; 46 (5): 435-6, 45
- Wong E. Collaborative drug therapy management and smoking cessation. *Hosp Pharm* 1999; 34 (11): 1295-303
- Aitchinson KJ, Jordan BD, Sharma T. The relevance of ethnic influences on pharmacogenetics to the treatment of psychosis. *Drug Metab Drug Interact* 2000; 16 (1): 15-38
- Lasser K, Boyd JW, Woolhandler S, et al. Smoking and mental illness. *JAMA* 2000; 284: 2606-10
- Ziegler VE, Biggs JT. Tricyclic plasma levels effects of age, race, sex, and smoking. *JAMA* 1977; 238 (20): 2167-9
- Rickels K, Weise C, Case G, et al. Tricyclic plasma levels in depressed outpatients treated with amitriptyline. *Psychopharmacology* 1983; 80: 14-8
- Norman TR, Burrows GD, Maguire KP, et al. Cigarette smoking and plasma nortriptyline levels. *Clin Pharmacol Therapeutics* 1976; 21 (4): 453-6
- Linnoila M, George L, Guthrie S, et al. Effect of alcohol consumption and cigarette smoking on antidepressant levels of depressed patients. *Am J Psychiatry* 1981; 138 (6): 841-2
- Perry PJ, Browne JL, Prince RA, et al. Effects of smoking on nortriptyline plasma concentrations in depressed patients. *Ther Drug Monit* 1986; 8 (3): 279-84
- Perel JM, Mendlewicz J, Shostak M, et al. Plasma levels of imipramine in depression. *Neuropsychobiology* 1976; 2: 193-202
- John VA, Luscombe DK, Kemp H. Effects of age, cigarette smoking and the oral contraceptive on the pharmacokinetics of clomipramine and its desmethyl metabolite during chronic dosing. *J Int Med Res* 1980; 8 Suppl. 3: 88-95
- Spigset O, Carlborg L, Hedenmalm K, et al. Effect of cigarette smoking on fluvoxamine pharmacokinetics in humans. *Clin Pharmacol Ther* 1995; 58 (4): 399-403
- Ishida M, Otani K, Kaneko S, et al. Effects of various factors on steady-state plasma concentrations of trazodone and its active metabolite *m*-chlorphenylpiperazine. *Int Clin Psychopharmacol* 1995; 10: 143-6
- Hsyu P, Singh A, Giargiari TD, et al. Pharmacokinetics of bupropion and its metabolites in cigarette smokers versus nonsmokers. *J Clin Pharmacol* 1997; 37: 737-43
- Rigal JG, Albin H, Cuchier AR, et al. Imipramine blood levels and clinical outcome. *J Clin Psychopharmacol* 1987; 7: 222-9
- Miller LG. Cigarettes and drug therapy: pharmacokinetic and pharmacodynamic considerations. *Clin Pharm* 1990; 9: 125-35

35. Luscombe DK, John V. Influence of age, cigarette smoking and oral contraceptive on plasma concentrations of clomipramine. *Postgrad Med J* 1980; 56 Suppl. 1: 99-102
36. Gex-Fabry M, Balant-Gorgia AE, Balant LP, et al. Clomipramine metabolism model-based analysis of variability factors from drug monitoring data. *Clin Pharmacokinet* 1990; 19 (3): 241-55
37. Shimoda K, Noguchi T, Ozeki Y, et al. Metabolism of clomipramine in a Japanese psychiatric population: hydroxylation, demethylation, and glucuronidation. *Neuropsychopharmacology* 1995; 12 (4): 323-33
38. Amchin J, Zarycranski W, Taylor KP, et al. Effect of venlafaxine on CYP1A2-dependent pharmacokinetics and metabolism of caffeine. *J Clin Pharmacol* 1999; 39: 252-9
39. Diwan A, Castine M, Pomerleau CS, et al. Differential prevalence of cigarette smoking in patients with schizophrenic vs mood disorders. *Schizophr Res* 1998; 33: 113-8
40. Dalack GW, Meador-Woodruff JH. Smoking, smoking withdrawal and schizophrenia: case reports and a review of the literature. *Schizophr Res* 1996; 22: 133-41
41. Nilsson A, Waller L, Rosengren A, et al. Cigarette smoking is associated with abnormal involuntary movements in the general male population – a study of men born in 1933. *Biol Psychiatry* 1997; 41: 717-23
42. Vinarová E, Vinar O, Kalvach Z. Smoker need higher doses of neuroleptic drugs. *Biol Psychiatry* 1984; 19 (8): 1265-8
43. Salokangas R, Saarijärvi S, Taiminen T, et al. Effect of smoking on neuroleptics in schizophrenia. *Schizophr Res* 1997; 23: 55-60
44. Swett Jr C. Drowsiness due to chlorpromazine in relation to cigarette smoking. *Arch Gen Psychiatry* 1974; 31: 211-3
45. Stimmel GL, Fallon I. Chlorpromazine plasma levels, adverse effects, and tobacco smoking: Case report. *J Clin Psychiatry* 1983; 44 (11): 420-2
46. Pantuck EJ, Pantuck CB, Anderson KE, et al. Cigarette smoking and chlorpromazine disposition and actions. *Clin Pharmacol Ther* 1982; 31: 533-8
47. Chetty M, Miller R, Moodley SV. Smoking and body weight influence the clearance of chlorpromazine. *Eur J Clin Pharmacol* 1994; 46: 523-6
48. Ereshefsky L, Saklad SR, Watanabe MD, et al. Thiothixene pharmacokinetics interactions: a study of hepatic enzyme inducers, clearance inhibitors, and demographic variables. *J Clin Psychopharmacol* 1991; 11 (5): 296-301
49. Ereshefsky L, Jann MW, Saklad SR, et al. Effects of smoking on fluphenazine clearance in psychiatric inpatients. *Biol Psychiatry* 1985; 20: 329-52
50. Jann MW, Saklad SR, Ereshefsky L, et al. Effects of smoking on haloperidol and reduced haloperidol plasma concentrations and haloperidol clearance. *Psychopharmacology* 1986; 90: 468-70
51. Miller DD, Kelly MW, Perry PJ, et al. The influence of cigarette smoking on haloperidol pharmacokinetics. *Biol Psychiatry* 1990; 28: 529-31
52. Perry PJ, Miller DD, Arndt SV, et al. Haloperidol dosing requirements: the contribution of smoking and nonlinear pharmacokinetics. *J Clin Psychopharmacol* 1993; 13 (1): 46-51
53. Midha KK, Hawes EM, Hubbard JW, et al. A pharmacokinetic study of trifluoperazine in two ethnic populations. *Psychopharmacology* 1988; 95: 333-8
54. Midha KK, Chakraborty BS, Ganes DA, et al. Intersubject variation in the pharmacokinetics of haloperidol and reduced haloperidol. *J Clin Psychopharmacol* 1989; 9 (2): 98-104
55. Dysken MW, Kim SW, Vatassery G, et al. Haloperidol decanoate pharmacokinetics in red blood cells and plasma. *J Clin Psychopharmacol* 1992; 12 (2): 128-32
56. Dahl ML, Llerena A, Bondesson U, et al. Disposition of clozapine in man: lack of association with debrisoquine and S-mephenytoin hydroxylation polymorphism. *Br J Clin Pharmacol* 1994; 37: 71-4
57. Callaghan JT, Bergstrom RF, Ptak LR, et al. Olanzapine pharmacokinetic and pharmacodynamic profile. *Clin Pharmacokinet* 1999; 37 (3): 177-93
58. Kondo T, Tanaka O, Otani K, et al. Possible inhibitory effect of diazepam on the metabolism of zotepine, an antipsychotic drug. *Psychopharmacology* 1996; 127: 311-4
59. Haring C, Fleischhacker WW, Schett P, et al. Influence of patient-related variables on clozapine plasma levels. *Am J Psychiatry* 1990; 147 (11): 1471-5
60. Hasegawa M, Gutierrez-Esteinou R, Way L, et al. Relationship between clinical efficacy and clozapine concentrations in plasma in schizophrenia: effect of smoking. *J Clin Psychopharmacol* 1993; 13 (6): 383-90
61. Wetzel H, Anghelescu I, Szegei A, et al. Pharmacokinetic interaction of clozapine with selective serotonin reuptake inhibitors: differential effects of fluvoxamine and paroxetine in a prospective study. *J Clin Psychopharmacol* 1998; 18 (1): 2-9
62. Jann MW, Grimsley SR, Gray EC, et al. Pharmacokinetics and pharmacodynamics of clozapine. *Clin Pharmacokinet* 1993; 24: 161-76
63. Kisicki JC, Bergstrom RF, Cerimele BJ, et al. Olanzapine: bioequivalence of capsule and tablet formulations. Lilly Laboratory for Clinical Research. Eli Lilly and Co., 1995 (Data on file)
64. Otani K, Kondo T, Kaneko S, et al. Steady-state serum kinetics of zotepine. *Hum Psychopharmacol* 1993; 7: 331-6
65. Balant-Geogria AE, Gex-Fabry M, Genet C, et al. Therapeutic drug monitoring of risperidone using a new rapid HPLC method: reappraisal of interindividual variability factors. *Ther Drug Monitor* 1999; 21: 105-15
66. Ochs HR, Greenblatt DJ, Burstein ES. Lack of influence of cigarette smoking on triazolam pharmacokinetics. *Br J Clin Pharmacol* 1987; 23: 759-63
67. Otani K, Yasui N, Furukori H, et al. Relationship between single oral dose pharmacokinetics of alprazolam and triazolam. *Int Clin Psychopharmacol* 1997; 12: 153-7
68. Hossain M, Wright E, Baweja R, et al. Nonlinear mixed effects modeling of single dose and multiple dose data for an immediate release (IR) and a controlled released (CR) dosage form of alprazolam. *Pharm Res* 1997; 14 (3): 309-15
69. Greenblatt DJ, Allen MD, Locniskar A, et al. Lorazepam kinetics in the elderly. *Clin Pharmacol Ther* 1979; 26 (1): 103-13
70. Ochs HR, Greenblatt DJ, Knüchel M. Kinetics of diazepam, midazolam, and lorazepam in cigarette smokers. *Chest* 1985; 87 (2): 223-6
71. Greenblatt DJ, Allen MD, Locniskar A, et al. Diazepam disposition determinants. *Clin Pharmacol Ther* 1980; 27 (3): 301-12
72. Norman TR, Fulton A, Burrows GD, et al. Pharmacokinetics of N-desmethyldiazepam after a single oral dose of clorazepate: the effect of smoking. *Clin Pharmacol* 1981; 229-33
73. Ochs HR, Greenblatt DJ, Locniskar A, et al. Influence of propranolol coadministration on cigarette smoking on the kinetics of desmethyldiazepam following intravenous clorazepate. *Klin Wochenschr* 1986; 64: 1217-21

74. Desmond PV, Roberts PK, Wilkinson GR, et al. No effect of smoking on the metabolism of chlordiazepoxide. *N Engl J Med* 1979; 300: 199-200
75. Jick H, Slone D, Shapiro S, et al. Clinical depression of the central nervous system due to diazepam and chlordiazepoxide in the relation to cigarette smoking and age. *N Engl J Med* 1973; 288 (6): 277-80
76. Miller RR. Effects of smoking on drug action. *Clin Pharmacol Ther* 1977; 22 (5): 749-56
77. Klotz U, Avant GR, Hoyumpa A, et al. The effects of age and liver disease on the disposition and elimination of diazepam in adult man. *J Clin Invest* 1975; 55: 347-59
78. Miller LG. Recent developments in the study of the effects of cigarette smoking on clinical pharmacokinetics and clinical pharmacodynamics. *Clin Pharmacokinet* 1989; 17 (2): 90-108
79. Cloyd JC, Remmel RP. Antiepileptic drug pharmacokinetics and interactions: impact on treatment of epilepsy. *Pharmacotherapy* 2000; 20 (8 Pt 2): 139S-51S
80. Benetello P, Furlanut M, Pasqui L, et al. Absence of effect of cigarette smoking on serum concentrations of some anticonvulsants in epileptic patients. *Clin Pharmacokinet* 1987; 12 (4): 302-4
81. Martin ES, Crismon ML, Godley PJ. Postinduction carbamazepine clearance in an adult psychiatric population. *Pharmacotherapy* 1991; 11 (4): 296-302
82. Ereshefsky L, Jann MW. Lithium. In: Mungall D, editor. *Applied Clinical Pharmacokinetics*. New York: Raven Press, 1983: 245-70
83. Henningfeld JE, Schuh LM, Jarvik ME. Pathophysiology of tobacco dependence. In: Bloom FE, Kupfer DJ, editors. *Psychopharmacology: the fourth generation of progress*. New York: Raven Press, 1995: 1715-29
84. Clarke PBS. Dopaminergic mechanisms in the locomotor stimulant effects of nicotine. *Biochem Pharmacol* 1990; 40: 1427-32
85. Porchet HC, Benowitz NL, Sheiner LB, et al. Apparent tolerance to the acute effect of nicotine results in part from distribution kinetics. *J Clin Invest* 1987; 80: 1466-71
86. Robinson DE, Balter NJ, Schwartz SL. A physiologically based pharmacokinetic model for nicotine and cotinine in man. *J Pharmacokinet Biopharm* 1992; 20: 591-609
87. Benowitz NL, Jacob P. Nicotine and cotinine elimination pharmacokinetics in smokers and nonsmokers. *Clin Pharmacol Ther* 1993; 53: 316-23
88. Emerich DF, Zanol MD, Norman AB, et al. Nicotine potentiates haloperidol induced catalepsy and locomotor hypoactivity. *Pharmacol Biochem Behav* 1991; 38: 875-80
89. McConville BJ, Folgelson MH, Norman AB, et al. Nicotine potentiation of haloperidol in reducing tic frequency in Tourette's disorder. *Am J Psychiatry* 1991; 148: 793-4
90. Binder RL, Kazamatsuri H, Nishimura T, et al. Smoking and tardive dyskinesia. *Biol Psychiatry* 1987; 22: 1280-2
91. Kirch DG, Alho AM, Wyatt RJ. Hypothesis: a nicotine-dopamine interaction linking smoking with Parkinson's disease and tardive dyskinesia. *Cell Mol Neurobiol* 1988; 8: 285-91
92. Menza MA, Grossman N, VanHorn M, et al. Smoking and movement disorders in psychiatric patients. *Biol Psychiatry* 1991; 30: 109-15
93. Basile VS, Ozdemir V, Masellis M, et al. A functional polymorphism of the cytochrome P450 1A2 gene: association with tardive dyskinesia in schizophrenia. *Mol Psychiatry* 2000; 5: 410-7

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