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REVIEW ARTICLE

Drugs and Diseases Interacting with Cigarette Smoking in US Prescription Drug Labelling

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Abstract The US Food and Drug Administration (FDA) draft guidance for industry on drug interaction studies recommends, but does not mandate, that both cigarette smokers and non-smokers can be used to study drug metabolism in clinical trials, and that important results related to smoking should be included in drug labelling to guide medication usage. This study aimed to provide a comprehensive review of drugs or diseases interacting with smoking, as presented in all US drug labelling. The 62,857 drug labels deposited in the FDA Online Label Repository were searched using the keywords 'smoke', 'smoker(s)', 'smoking', 'tobacco' and 'cigarette(s)' on 19 June 2014. The resultant records were refined to include only human prescription drug labelling, for manual examination. For 188 single-active-ingredient drugs and 36 multiple-active-ingredient drugs, the labelling was found to contain smoking-related information. The pharmacokinetics of 29 and 21 single-active-ingredient drugs were affected and unaffected, respectively, by smoking. For the remaining drugs, the provided information related to smoking affecting efficacy, safety or diseases but not pharmacokinetics. Depending on the nature of specific drugs, the perturbation in pharmacokinetic parameters in smokers ranged from 13 to 500 %, in comparison with non-smokers. Dosage modifications in smokers are necessary for four drugs and may be necessary for six drugs, but are unnecessary for seven drugs although the pharmacokinetic parameters of four of them are affected by smoking. Cigarette smoking is a risk factor for 16 types of diseases or adverse drug reactions. For one single-active-ingredient contraceptive drug and 10 multiple-active-ingredient contraceptive drugs, a black box warning (the FDA's strongest safety warning) is included in the labelling for increased risks of heart attacks and strokes in female smokers, and "women are strongly advised not to smoke" when using these drugs. This study presents the first comprehensive overview of cigarette smoking interacting with drugs and/or diseases, as presented in US drug labelling.

Key Points

Information on drugs and diseases interacting with cigarette smoking is present in some US Food and Drug Administration (FDA)-approved drug labelling.

Dosage adjustments on the basis of cigarette smoking are recommended by the FDA for ten drugs.

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1 Introduction

Cigarette smoking poses significant health risks [1]. Its interactions with drugs and diseases have been extensively studied, and numerous literature reviews have been published [2–7]. However, the relevant information in US Food and Drug Administration (FDA)-approved drug labelling has not been analysed.

In an FDA document for new drug development [8], it is suggested that "a clinical study can be conducted in smokers as compared to non-smokers (in lieu of an interaction study with an inducer), when appropriate". In the FDA draft guidance for industry on drug interaction studies, published in 2006 [9] and 2012 [10], it is recommended that "for a drug that is a substrate of CYP1A2, the evaluation of the effect of induction of CYP1A2 can be carried out by comparative pharmacokinetics (PK) studies in smokers vs. non-smokers". Furthermore, these draft guidance documents recommend that important drug interaction information, including information on smoking–drug interactions, should be included in different sections of a drug label [9, 10].

We therefore carried out a comprehensive analysis of all FDA-approved drug labelling, aiming to assess if and how much information related to cigarette smoking is present in US drug labelling.

2 Search Strategy

The FDA Online Label Repository (at http://labels.fda.gov), the content of which is also deposited in DailyMed (at http://dailymed.nlm.nih.gov/dailymed/about-dailymed.cfm) as an alternative interface, was chosen as the source of US drug labelling. These websites provide the most comprehensive coverage (>85 %) of FDA-approved product labelling in the public domain [11].

The FDALabel database, which allows a user to search the full text of all labels deposited in DailyMed (at http://www.fda.gov/ScienceResearch/BioinformaticsTools/ucm289739.htm), was used to collect relevant information. Though the FDALabel database is publically available (at https://rm2.scinet.fda.gov/druglabel/#simsearch-0), we used the FDA intranet version (at http://ncsvmweb01.nctr.fda.gov/druglabel/#simsearch-0) because the latter is updated more frequently. Nevertheless, our preliminary results show that the final results were the same regardless of which version was used.

The keywords 'smoke', 'smoker(s)', 'smoking', 'tobacco' and 'cigarette(s)' were used to search the FDALabel database in the full text of all labels, using the 'simple search' function. Any words in the label that match the submitted query are recorded and the corresponding label is extracted. This strategy provides the most comprehensive coverage of relevant information. The resulting records were downloaded and combined, and then duplicates were removed. Labels for over-the-counter (OTC) medications, unapproved drugs and animal drugs were excluded.

The remaining labels were then downloaded directly from DailyMed and manually examined to collect all information related to cigarette smoking. Though this study was initiated to analyse smoking–drug interactions, it was noted that a lot of information regarding smoking–disease interactions was also present in the labelling. We therefore decided to scrutinize all of the information related to cigarette smoking. The permanent link to each examined label in DailyMed and the original statement relevant to cigarette smoking were recorded in an Excel table.

3 Number and Percentage of Labels Providing Smoking-Related Information

As of 19 June 2014, a total of 62,857 labels were deposited in the FDALabel database. A complete list of all of these labels is provided online in Supplementary Table 1 in the Electronic Supplementary Material. Using the keywords 'tobacco', 'cigarette(s)' and 'smoke(r)(s)/smoking' to query the database, 745, 1,245 and 6,695 labels were obtained, respectively. Among these 8,685 labels, there were 1,726 duplicates. The remaining 6,959 unique labels represent 11 % of all 62,677 labels, and they are also presented in Supplementary Table 1.

Among the 6,959 unique labels, 3,207 are for OTC drugs, 215 are for unapproved products, 28 are for animal drugs, 14 are for dietary supplements/vaccines/medical devices and the remaining 3,495 are for human prescription drugs.

Non-human prescription drug labels were excluded for either of two reasons: (1) they were not reviewed or approved by the FDA; or (2) the information was not relevant, as most of them are for safe handling or storage of the products.

The 3,495 human prescription drug labels are for 371 unique drugs, as a specific drug may have multiple labels from different manufacturers. Further excluded were those providing information that was not relevant, such as those dealing with safe handling or storage of flammable drugs (such as oxybutynin chloride). A list of 188 single-active-ingredient drugs and 36 multiple-active-ingredient drugs was finally chosen for detailed analysis, and the original statement regarding cigarette smoking and the link to each label in DailyMed are presented in Supplementary Table 1.

4 Drugs with a Single Active Ingredient

The summarized results for the 188 single-active-ingredient drugs are presented in Tables 1 and 2.

Table 1 Effects of cigarette smoking on drug pharmacokinetics, efficacy and dosage modifications

Drug	Effects of cigarette smoking[a]	Dosage modification according to smoking status	Labelling sections
Alosetron hydrochloride	Clearance ↑	NA	CP
Alprazolam	(Blood) alprazolam concentrations ↓ 50 %	NA	CP
Aminophylline dihydrate	Clearance ↑ 50–80 %	May be necessary	CP; W; P; D&A
Aripiprazole	No effects anticipated	NA	DI
Asenapine maleate	No effects observed	NA	DI
Bendamustine hydrochloride	Has "potential to ↓ plasma concentrations of bendamustine and ↑ plasma concentrations of its active metabolites"	NA	DI
Bupropion hydrochloride	No effects on "C_{max}, half-life, T_{max}, AUC, or clearance of bupropion or its active metabolites"	NA	CP
Chlorhexidine gluconate	Efficacy ↓	NA	CP
Cilostazol	(Blood) cilostazol concentrations ↓ ~20 %	NA	CP
Cimetidine	Efficacy ↓	May be necessary	D&A
Cimetidine hydrochloride	Efficacy ↓	May be necessary	D&A
Clozapine	"[M]ay ↓ clozapine plasma level"	NA	DI
Desipramine hydrochloride	Plasma levels ↓	NA	CP
Diazepam	No effects observed	NA	CP
Duloxetine hydrochloride	AUC ↓ ~33 %	Not necessary	UISP
Dyphylline	No effects anticipated	NA	CP
Erlotinib hydrochloride	Clearance ↑ 24 %, AUC_{∞} ↓ 50–67 %, steady-state trough plasma concentrations ↓ 50 %	Necessary	CP; DI; D&A
Estazolam	Clearance ↑, $t_{½}$ ↓	NA	CP; DI
Fluoxetine hydrochloride	NA	May be necessary	D&A
Fluvoxamine maleate	Metabolism ↑ 25 %	NA	DI
Gefitinib	Efficacy ↓	NA	CS
Iloperidone	No effects anticipated	NA	DI; UISP
Insulin	Systemic insulin exposure ↑ 2- to 5-fold; efficacy ↑	Necessary	CP; D&A
Leflunomide	Clearance ↑ 38 %; no effects on efficacy	NA	CP
Lorazepam	No effects observed	NA	UISP
Loxapine	No effects observed	Not necessary	CP; UISP
Lurasidone hydrochloride	No effects anticipated	NA	CP
Methysergide maleate	May "result in enhanced vasoconstriction"	NA	DI
Naratriptan hydrochloride	Clearance ↑ 30 %	NA	CP
Olanzapine	Clearance ↑ 40 % or even ↑ 300 %	Not routinely recommended but may be necessary when multiple factors are present	CP; DI; UISP
Olanzapine pamoate	Clearance ↑	Not routinely recommended but may be necessary when multiple factors are present	CP; DI; UISP
Paliperidone	No effects anticipated	Not necessary	CP
Paliperidone palmitate	No effects anticipated	Not necessary	CP
Pemetrexed disodium	No effects observed	NA	CP
Pomalidomide	May ↓ pomalidomide exposure and ↓ efficacy	NA	DI
Prasugrel hydrochloride	No effects observed	NA	CP
Propafenone hydrochloride	May ↑ plasma propafenone levels	NA	W&P
Propranolol hydrochloride	May ↓ propranolol exposure and ↓ efficacy	NA	DI
Quetiapine fumarate	No effects on clearance	NA	CP

Table 1 continued

Drug	Effects of cigarette smoking[a]	Dosage modification according to smoking status	Labelling sections
Quinidine gluconate	No effects observed	NA	P
Quinidine sulfate	No effects observed	NA	P
Quinine sulfate	AUC ↓ 44 %, C_{max} ↓ 18 %, $t_{½}$ ↓ from 12 to 7.5 h in healthy subjects; AUC ↓ 25 %, C_{max} ↓ 16.5 % in malaria patients; efficacy not affected	Not necessary in malaria patients	DI
Riluzole	Elimination ↑ 20 %	Not necessary	CP; DI
Riociguat	Plasma concentrations ↓ 50–60 %	Necessary	CP
Rivastigmine tartrate	Clearance ↑ 23 %	NA	CP; DI; D&A
Roflumilast	AUC of roflumilast ↓ 13 %, AUC of roflumilast metabolite ↑ 17 %; C_{max} not affected	NA	CP
Ropinirole hydrochloride	Clearance ↑, C_{max} ↓ 30 %, AUC ↓ 38 %	NA	CP; DI
Rosiglitazone maleate	No effects observed	NA	CP
Tasimelteon	Tasimelteon exposure ↓ ~40 %; efficacy may ↓	NA	CP; UISP
Temozolomide	No effects on clearance	NA	CP
Theophylline	Clearance ↑ 50–80 %	Necessary	W; CP; D&A
Tiagabine hydrochloride	No effects on clearance	NA	CP
Ticagrelor	Clearance ↑ ~22 %	Not necessary	CP
Varenicline tartrate	No effects observed	NA	CP
Warfarin sodium	Warfarin exposure ↓; efficacy ↓	NA	DI
Ziprasidone hydrochloride	No effects observed	NA	UISP

↑ increase(d), ↓ decrease(d), *AUC* area under the plasma concentration–time curve, AUC_{∞} AUC from time zero to infinity, C_{max} maximum plasma drug concentration, *CP* clinical pharmacology, *CS* clinical studies, *D&A* dosage and administration, *DI* drug interactions, *NA* not available, *P* precautions, $t_{½}$ half-life, T_{max} time to reach C_{max}, *UISP* use in specific populations, *W* warnings, *W&P* warnings and precautions

[a] Wording in quotation marks is copied directly from the labelling

As shown in Table 1, smoking may affect the pharmacokinetics and/or efficacy of 34 drugs but shows no effect for 21 other drugs. For 18 drugs, the quantitative effects of smoking on drug pharmacokinetics are specified. Depending on the nature of the specific drugs, smoking could increase or decrease exposure levels, and the perturbations in pharmacokinetic parameters range from 13 to 500 %. Dosage modifications in smokers are necessary for four drugs, including erlotinib hydrochloride, riociguat, theophylline and insulin. For six drugs, including cimetidine and olanzapine, dosage modifications in smokers are necessary only when multiple factors that may affect safety or efficacy are present. For seven drugs, dosage modifications in smokers are not necessary, although the pharmacokinetic parameters of four of them are affected by smoking. This information is presented mainly in the 'Clinical Pharmacology' and 'Drug Interactions' sections of the label.

Table 2 shows that smoking is a risk factor for 16 types of diseases or adverse drug reactions. One notable example concerns nonsteroidal anti-inflammatory drugs (NSAIDs). All 22 NSAIDs may cause gastrointestinal bleeding, and smoking is a risk factor for this type of adverse reaction. The labelling clearly states that gastrointestinal bleeding is more likely to occur in smokers receiving this class of drugs. Another example concerns antihypertensive drugs. As smoking is a well-established risk factor for cardiovascular disease, it is suggested that usage of any of the 22 antihypertensives "should be part of comprehensive cardiovascular risk management, including … smoking cessation".

Several drugs in Table 2 warrant discussion in detail. For the drug norethindrone, a black box warning (BBW), the strongest warning about adverse drug reactions issued by the FDA [12], is included in the labelling to highlight the significantly increased risks of heart attacks and strokes in female smokers using oral contraceptives, and "women who use oral contraceptives are strongly advised not to smoke". This is the only BBW for a single-active-ingredient drug regarding smoking–drug interactions in all labelling. In contrast, for two drugs, doxycycline hyclate and calcitonin salmon, smoking appeared to have no effects on adverse reactions.

Table 2 Effects of cigarette smoking on diseases or adverse drug reactions

Diseases or adverse drug reaction	Drug name	Labelling sections	Effects of cigarette smoking[a]
CAD	Abacavir sulfate	W&P	Smoking is a risk factor for CAD; these drugs (except for atorvastatin calcium, cholestyramine, colestipol hydrochloride and fenofibrate) may also cause CAD, and they should be prescribed with caution in smokers
	Almotriptan malate	W&P	
	Atorvastatin calcium	I&U	
	Cholestyramine	I&U	
	Colestipol hydrochloride	I&U	
	Dihydroergotamine mesylate	W	
	Eletriptan hydrobromide	W&P	
	Fenofibrate	I&U	
	Frovatriptan succinate	W&P	
	Methylergonovine maleate	W	
	Naratriptan hydrochloride	W&P; UISP	
AVD	Esterified estrogens	W	Smoking is a risk factor for AVD; these drugs (except for norethindrone acetate) may also cause AVD, and they should be prescribed with caution in smokers
	Estradiol	W	
	Estradiol acetate	W&P	
	Estradiol cypionate	W	
	Estradiol hemihydrate	W	
	Estradiol transdermal system	W	
	Estradiol valerate	W	
	Estrogens, conjugated	W	
	Norethindrone acetate	W	
	Ospemifene	W&P	
	Progesterone	W	
CVD	Rizatriptan benzoate	W&P	Smoking is a risk factor for CVD; these drugs (except for rosuvastatin calcium) may also cause CVD, and they should be prescribed with caution in smokers
	Rosuvastatin calcium	I&U	
	Sumatriptan	W&P	
	Sumatriptan succinate	W&P	
	Varenicline tartrate	W&P	
	Zolmitriptan	W&P	
High blood pressure	Aliskiren hemifumarate	I&U	Smoking is among the cardiovascular risks; usage of these drugs "should be part of comprehensive cardiovascular risk management, including … smoking cessation"
	Amlodipine besylate	I&U	
	Atenolol	I&U	
	Azilsartan kamedoxomil	I&U	
	Doxazosin mesylate	I&U	
	Enalapril maleate	I&U	
	Eplerenone	I&U	
	Felodipine	I&U	
	Lisinopril	I&U	
	Metoprolol succinate	I&U	
	Nadolol	I&U	
	Nebivolol hydrochloride	I&U	
	Nifedipine	I&U	
	Olmesartan medoxomil	I&U	
	Prazosin hydrochloride	I&U	
	Propranolol hydrochloride	I&U	
	Quinapril hydrochloride	I&U	
	Ramipril	I&U	
	Spironolactone	I&U	
	Telmisartan	I&U	
	Valsartan	I&U	
	Verapamil hydrochloride	I&U	

Table 2 continued

Diseases or adverse drug reaction	Drug name	Labelling sections	Effects of cigarette smoking[a]
Gastrointestinal bleeding	Celecoxib	W&P	These drugs may cause gastrointestinal bleeding, and such a risk is higher in smokers
	Diclofenac epolamine	W&P	
	Diclofenac potassium	W&P	
	Diclofenac sodium	W&P	
	Diflunisal	W	
	Etodolac	W	
	Fenoprofen calcium	W	
	Flurbiprofen	W	
	Ibuprofen	W	
	Indomethacin	W	
	Ketoprofen	W	
	Ketorolac tromethamine	W	
	Meclofenamate sodium	W	
	Mefenamic acid	W	
	Meloxicam	P	
	Nabumetone	W	
	Naproxen sodium	W	
	Oxaprozin	W	
	Piroxicam	W	
	Sulindac	W	
	Tolmetin sodium	W	
	Valdecoxib	W	
Serious blood clots	Etonogestrel	PI	This drug may cause serious blood clots, and such a risk is higher in smokers
Decreased bone mineral density/ osteoporosis	Budesonide	PI	Smoking is a risk factor for decreased bone mineral density/osteoporosis; these drugs (except for estropipate and ibandronate sodium) may also cause decreased bone mineral density/ osteoporosis, and they should be prescribed with caution in smokers
	Desonide	W&P	
	Estropipate	I&U	
	Flunisolide	W&P	
	Goserelin acetate	PI	
	Ibandronate sodium	PI	
	Leuprolide acetate	P	
	Medroxyprogesterone acetate	W	
	Nafarelin acetate	P	
	Prednisone	P	
Bacterial pneumonia	Enfuvirtide	W&P	This drug may cause bacterial pneumonia, and such a risk is higher in smokers
NAION	Sildenafil citrate	W&P	These drugs may cause NAION, and such a risk is higher in smokers
	Tadalafil	W&P	
Periodontal diseases	Chlorhexidine gluconate	CS	Smoking is a risk factor for periodontal diseases; smokers appear to show decreased efficacy of chlorhexidine gluconate
Malignancies	Adalimumab	W&P	Smoking is a risk factor for malignancies
	Omalizumab	W&P	
	Procarbazine hydrochloride	AR	"The risks of secondary lung cancer from [procarbazine hydrochloride] treatment appear to be multiplied by tobacco use"
Asthma	Cromolyn sodium	PI	Smoking is a "trigger" of asthma
COPD	Tiotropium bromide	PI	"Most COPD is caused by smoking"
Stroke	Raloxifene hydrochloride	W&P	Smoking is a risk factor for stoke
	Thyrotropin alfa	W&P	
	Norethindrone	BBW	"Cigarette smoking greatly increases the possibility of suffering heart attacks and strokes. Women who use oral contraceptives are strongly advised not to smoke"

Table 2 continued

Diseases or adverse drug reaction	Drug name	Labelling sections	Effects of cigarette smoking[a]
Erectile dysfunction	Alprostadil	PI	"Excessive smoking" is a cause of erectile dysfunction
Emphysema in patients with Alpha1-PI deficiency	Alpha1-PI	CP	"Smoking is an important risk factor for the development of emphysema in patients with Alpha1-PI deficiency"
Adverse events	Doxycycline hyclate	AR	"[S]moking status did not appear to be correlated with adverse events"
	Calcitonin salmon	AR	"Smoking did not have a contributory effect on the occurrence of nasal adverse reactions"

Alpha1-PI alpha-1-proteinase inhibitor (human), *AR* adverse reactions, *AVD* arteriovascular disease, *BBW* black box warning, *CAD* coronary artery disease, *COPD* chronic obstructive pulmonary disease, *CP* clinical pharmacology, *CS* clinical studies, *CVD* cardiovascular disease, *I&U* indications and usage, *NAION* non-arteritic anterior ischaemic optic neuropathy, *P* precautions, *PI* patient information, *UISP* use in specific populations, *W* warnings, *W&P* warnings and precautions

[a] Wording in quotation marks is copied directly from the labelling

5 Drugs with Multiple Active Ingredients

As for the 36 multiple-active-ingredient drugs, none of their labels include information regarding smoking affecting pharmacokinetics. For 27 drugs, the smoking-relevant information is the same as that for the individual active ingredients (see Supplementary Table 1). Of note, the combination drug norethindrone and mestranol has the same BBW for smoking–drug interactions as does the single-active-ingredient drug norethindrone. The remaining nine multiple-active-ingredient drugs are for contraceptive use, and all of them have a BBW stating that "smoking increases the risk of serious cardiovascular side effects from oral contraceptive use" and that "this risk increases with age and with the extent of smoking (in epidemiologic studies, 15 or more cigarettes per day was associated with a significantly increased risk) and is quite marked in women over 35 years of age". The BBW concludes that "women who use oral contraceptives should be strongly advised not to smoke". These nine drugs are a combination of ethinylestradiol with either desogestrel, drospirenone, levonorgestrel, ethynodioldiacetate, etonogestrel, levonorgestrel, norelgestromin, norethindrone or norgestimate (see Supplementary Table 1).

6 Discussion and Perspectives

This is the first study to explore information regarding cigarette smoking in FDA-approved drug labelling. By using the FDALabel database, we were able to address this issue in a comprehensive and systematic manner. Specifically, the enormous number of readily available drug labels (62,857 labels as of 19 June 2014; and the number is growing on a daily basis in DailyMed) and the rich and diverse content in the labelling (averaging 20 pages per label; each label includes about ten sections for different types of information) poses a significant challenge for manual review of all of the documents. The FDALabel database provides the unique capability to search the full text of all labels deposited in the FDA Online Label Repository and allows the user to download the search results without limitations. To our knowledge, the FDALabel database is the only publically available tool that provides these functionalities. This database is particularly suitable for the present study, as the three keywords 'cigarette(s)', 'smoke(r)(s)/smoking' and 'tobacco' effectively cover all of the relevant information. In other words, as there are no alternative ways to describe the relevant information, these three keywords are sufficient to extract all of the target information. This is in contrast to more complicated applications, such as a previous study of drug-induced liver injury, for which a significant amount of unwanted information was retrieved because of the lack of specific keywords, and extensive manual annotation was therefore required [13]. For the current study, the use of three keywords enabled us to quickly extract the relevant information with no false negatives and only a minimal number of false positives. For example, we manually double-checked the labelling of 100 drugs that were not picked up by keyword searching, and we found no false negatives. We believe our data present the most comprehensive and accurate picture of cigarette smoking interacting with drugs and/or diseases in US prescription drug labelling.

Only a small number of drug labels were found to carry information related to cigarette smoking. This is not necessarily unexpected, for four possible reasons. First, inclusion is advised by the FDA but is not mandatory. The FDA draft guidance clearly states that it is "for comment purposes only" [9, 10], and no specific inclusion criteria are provided that define what types of interactions involving cigarette smoking are to be included in drug

labelling. It is therefore possible that relevant studies were performed in clinical trials during the drug development process, but the results were somehow not analysed or included in the labelling. Second, the first FDA draft guidance that recommended inclusion of smokers as subjects in clinical trials and drug labelling was issued in 2006 [9]. It is therefore likely that drug labelling approved before 2006 does not contain sufficient information regarding cigarette smoking. Third, the FDA draft guidance recommended inclusion of smokers as subjects only in cytochrome P450 (CYP) 1A2-related studies [9, 10]. The effects of smoking on other drug-metabolizing enzymes, such as CYP1B1, CYP2A6, CYP2E1 and uridine 5′-diphosphate-glucuronosyltransferases (UGT) enzymes [14, 15], are currently not included in FDA labelling documents. Lastly, drug labelling usually does not include animal-based data regarding smoking–drug interactions. All of these are important reasons why, in comparison with literature reports [2, 3], only a small number of drugs were identified in this study.

A significant difference between the literature reports and the FDA drug labelling is that the latter does not tend to be exhaustive. Specifically, "only information that would be useful to" clinical decisions should be included in drug labelling [9, 10]. While a recent analysis concluded that FDA drug labelling contains excessive information that may "reduce physician comprehension of important safety warning" [11], another report argued that the FDA is not updating drug labelling consistently when new research findings become available [16]. Currently, the FDA is using its Adverse Event Reporting System (FAERS) to monitor potential signals of serious adverse drug reactions, and the results may lead to a change in drug labelling [17] (see http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/ucm082196.htm). Analysis of the FAERS database may help identify potential smoking–drug reactions for regulatory considerations. This may be particularly important for drugs that were approved before the first FDA draft guidance recommending inclusion of smokers as subjects in drug development trials was issued in 2006. As the FAERS database contains mainly postmarketing information, the data would also be useful to validate some findings already presented in the labelling, which are largely from clinical trials. In addition, the newly established FDA Center for Tobacco Products (CTP) aims to reduce the adverse health impact for those who use tobacco products, and is collecting safety reports involving tobacco products (at https://www.safetyreporting.hhs.gov/fpsr/WorkflowLoginIO.aspx?metinstance=0E1F229876AB85975D41F4FF60E512B19FF9C2BC). It can be expected that data accumulated by the FDA CTP will help improve drug labelling regarding cigarette smoking in the future. However, the limitations of the FAERS database, such as under-reporting [18], should be taken into consideration for these future endeavours.

The inclusion of smoking–drug interactions in drug labelling appears not to be well recognized by many researchers. Several elegant review articles [2–4, 14] and research papers [19, 20] on smoking–drug interactions have been published, but none of them mentioned the possible inclusion of relevant information in drug labelling. There is an urgent need to increase the awareness of this issue in the research community.

7 Conclusion

Though the current study may represent an underestimate of all smoking–drug interaction investigations in the drug development process, it presents an overview of this issue with regard to drug labelling. This information may be useful to both regulatory agencies and the pharmaceutical industry for future action, such as revising or finalizing the FDA draft guidance [10]. The drug lists presented here may also help basic researchers to design future investigations, and may serve as a good reference source for physicians to better assess the risks of cigarette smoking in patient management.

It should be pointed out that the content of FDA-approved drug labelling, despite being "the official description of a drug product" (see http://www.fda.gov/Drugs/InformationOnDrugs/ucm079436.htm) and "the primary source for drug safety information for physicians" [11], is not perfect or static [13, 16]. Some authors even argue that the content in the BBW section needs to be improved [21]. Part of the statement in the drug labelling, particularly that related to pharmacokinetics, is based on limited sets of clinical trials and may not reflect the most recent findings in the literature [16]. The information presented here may serve as a useful reference but not definitive guidance. It is likely that future studies will reveal additional important smoking–drug interactions that may warrant a change in the labelling.

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