SUPPLEMENTARY MATERIALS

P-glycoprotein-mediated drug interactions in pregnancy and the changes in the risk of congenital anomalies: A case-reference study

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Supplementary Table 1: Drugs associated with P-gp transport and the number of users in cases and the reference population.

Drugs	Number of users	
	Cases (N=4,634)	Reference population (N=25,126)
P-gp substrates		
Drugs for acid related disorders, A02		
Cimetidine, A02BA01	2	20
Ranitidine, A02BA02	6	142
Drugs for functional gastrointestinal disorders, A03		
Domperidone, A03FA03	8	182
Antidiarrheals, intestinal anti-inflammatory/anti-infective agents, A07		
Loperamide, A07DA03 (OTC)	5	40
Antithrombotic agents, B01		
Clopidogrel, B01AC04	0	0
Cardiac therapy agents, C01		
Digoxin, C01AA05	0	0
Beta-blocking agents, C07		
Propranolol, C07AA05	11	92
Talinolol, C07AB13	0	0
Celiprolol, C07AB08	0	0
Drugs acting on the renin-angiotensin system, C09		
Losartan, C09CA01	0	4
Lipid modifying agents, C10		
Lovastatin, C10AA02	0	0
Corticosteroids for systemic use, H02		
Aldosterone, H02AA01	0	0
Betamethasone, H02AB01	1	7
Methylprednisolone, H02AB04	0	4
Hydrocortisone, H02AB09	3	25
Triamcinolone, H02AB08	7	34
Antibacterials for systemic use, J01		
Doxycycline, J01AA02	102	566
Tetracycline, J01AA07	4	27
Sparfloxacin, J01MA09	0	0
Levofloxacin, J01MA12	0	5
Antineoplastic agents, L01		
Melphalan, L01AA03	0	0
Paclitaxel, L01CD01	0	0
Docetaxel, L01CD02	0	0
Epirubicin, L01DB03	0	0
Mitomycin C, L01DC03	0	0
Teniposide, L01CB02	0	0
Imatinib, L01XE01	0	0
Topotecan, L01XX17	0	0
Irinotecan, L01XX19	0	0
Actinomycin D, L01DA01	0	0
Muscle relaxants, M03		
Vecuronium, M03AC03	0	0
Analgesics, N02		
Paracetamol, N02BE01 (OTC)	361	458
Sumatriptan, N02CC01	18	180
Antiepileptics, N03		
Phenobarbital, N03AA02	0	2
Lamotrigine, N03AX09	3	17
Topiramate, N03AX11	0	2

Gabapentin, N03AX12	0	4
Levetiracetam, N03AX14	1	4
Psycholeptics, N05		
Levomepromazine, N05AA02	0	1
Perphenazine, N05AB03	0	1
Bromperidol, N05AD06	0	0
Clozapine, N05AH02	0	1
Olanzapine, N05AH03	0	21
Risperidone, N05AX08	2	14
Aripiprazole, N05AX12	0	3
Psychoanaleptics, N06		
Imipramine, N06AA02	0	4
Clomipramine, N06AA04	6	42
Trimipramine, N06AA06	0	1
Nortriptyline, N06AA10	2	4
Citalopram, N06AB04	17	101
Escitalopram, N06AB10	0	9
Venlafaxine, N06AX16	8	74
Desvenlafaxine, N06AX23	0	0
Antihelmintics, P02		
Ivermectin, P02CF01	0	0
Antihistamines for systemic use, R06		
Fexofenadine, R06AX26	5	81
Cetirizine, R06AE07 (OTC)	15	221
P-gp inhibitor		
Antineoplastic agents, L01		
Gefitinib, L01XE02	0	0
Erlotinib, L01XE03	0	0
Antithrombotic agents, B01		
Dipyridamole, B01AC07	0	5
Cardiac therapy agents, C01		
Propafenone, C01BC03	0	0
Ranolazine, C01EB18	0	0
Dronedarone, C01BD07	0	0
Beta-blocking agents, C07		
Carvedilol, C07AG02	0	0
Calcium channel blockers, C08		
Gallopamil, C08DA02	0	0
Nicardipine, C08CA04	0	0
Felodipine, C08CA02	0	0
Nitrendipine, C08CA08	0	0
Bepridil, C08EA02	0	0
Agents acting on the renin-angiotensin system, C09		
Captopril, C09AA01	0	0
Sex hormones and modulators of the genital system, G03		
Progesterone, G03DA04	58	273
Mifepristone, G03XB01	0	0
Psychoanaleptics, N06		
Desipramine, N06AA01	0	0
Maprotiline, N06AA21	0	2
Duloxetine, N06AX21	1	4
Antiprotozoals, P01		
Mepacrine/Quinacrine, P01AX05	0	0
Quinine, P01BC01	0	0
Mefloquine, P01BC02	1	5
Ectoparasiticides, incl. scabicides, insecticides and repellents, P03		
Disulfiram, P03AA04	0	0

P-gp substrate/inhibitor		
Drugs for acid related disorders, A02		
Omeprazole, A02BC01	41	295
Pantoprazole, A02BC02	12	36
Lansoprazole, A02BC03	0	6
Cardiac therapy agents, C01		
Quinidine, C01BA01	0	0
Diuretics, C03		
Spironolactone, C03DA01	0	1
Conivaptan, C03XA02	0	0
Lipid modifying agents, C10		
Simvastatin, C10AA01	2	18
Atorvastatin, C10AA05	2	12
Antibacterials for systemic use, J01		
Clarithromycin, J01FA09	30	125
Azithromycin, J01FA10	16	161
Antimycotics for systemic use, J02		
Ketoconazole, J02AB02	1	5
Itraconazole, J02AC02	6	56
Immunosuppressants, L04		
Sirolimus, L04AA10	0	0
Cyclosporine A, L04AD01	1	4
Analgesics, N02		
Pentazocine, N02AD01	0	0
Psycholeptics, N05		
Chlorpromazine, N05AA01	0	0
Fluphenazine, N05AB02	0	1
Haloperidol, N05AD01	4	25
Quetiapine, N05AH04	3	21
Psychoanaleptics, N06		
Amitriptyline, N06AA09	8	101
Fluoxetine, N06AB03	17	110
Paroxetine, N06AB05	44	294
Sertraline, N06AB06	5	35
Fluvoxamine, N06AB08	3	55
Antihistamines for systemic use, R06		
Terfenadine, R06AX12	7	67
P-gp substrate/inhibitor/inducer		
Calcium channel blockers, C08		
Verapamil, C08DA01	0	9
Diltiazem, C08DB01	1	2
Antibacterials for systemic use, J01		
Erythromycin, J01FA01	13	80
Antivirals for systemic use, J05		
Saquinavir, J05AE01	0	0
Ritonavir, J05AE03	0	0
Nelfinavir, J05AE04	0	1
Indinavir, J05AE02	0	0
Lopinavir, J05AR10 (with ritonavir)	0	1
Amprenavir, J05AE05	0	0
Antineoplastic agents, L01		
Vinblastine, L01CA01	0	0
Endocrine therapy, L02		
Tamoxifen, L02BA01	0	0
Other gynecologicals, G02		
Bromocriptine, G02CB01	3	0
Immunosuppressants, L04		

Tacrolimus, L04AD02	0	3
P-gp inducer		
Drugs used in diabetes, A10		
Insulins and analogues, A10A	28	110
Cardiac therapy agents, C01		
Nicardipine, C08CA04	0	0
Calcium channel blockers, C08		
Nifedipine, C08CA05	0	12
Antineoplastic agents, L01		
Chlorambucil, L01AA02	0	0
Methotrexate, L01BA01	0	0
Fluorouracil, L01BC02	0	3
Cisplatin, L01XA01	0	0
Hydroxyurea/ hydroxycarbamide, L01XX05	0	0
Endocrine therapy, L02		
Tamoxifen, L02BA01	0	0
Antigout agents, M04		
Probenecid, M04AB01	0	0
P-gp substrate/inducer		
Antimycobacterials, J04		
Rifampicin, J04AB02	0	2
Corticosteroids for systemic use, H02		
Dexamethasone, H02AB02	1	11
Antineoplastic agents, L01		
Vincristine, L01CA02	0	0
Doxorubicin, L01DB01	0	0
Daunorubicin, L01DB02	0	0
Mitoxantrone, L01DB07	0	0
Etoposide, L01CB01	0	0
Antigout agents, M04		
Colchicine, M04AC01	0	0
Analgesics, N02		
Morphine, N02AA01	1	3
Antiepileptics, N03		
Phenytoin, N03AB02	1	2
Carbamazepine, N03AF01	8	56
P-gp inducer/inhibitor		
Psycholeptics, N05		
Midazolam, N05CD08	2	18
Cardiac therapy agents, C01		
Amiodarone, C01BD01	0	0
Antihypertensives, C02		
Reserpine, C02AA02	0	0

This list of P-gp substrates, inhibitors and inducers were obtained from various review articles and original articles, which reports the results from *in vitro* and *in vivo* studies. The references are as follows:

a) Review articles:

1. Unadkat JD, Dahlin A, Vijay S. Placental drug transporters. Curr. Drug Metab. 2004;5:125–31.
2. Schinkel AH, Jonker JW. Mammalian drug efflux transporters of the ATP binding cassette (ABC) family: an overview. Adv. Drug Deliv. Rev. 2003;55:3–29.
3. Endres CJ, Hsiao P, Chung FS, Unadkat JD. The role of transporters in drug interactions. Eur. J. Pharm. Sci. 2006;27:501–17.
4. Hutson JR, Koren G, Matthews SG. Placental P-glycoprotein and breast cancer resistance protein: influence of polymorphisms on fetal drug exposure and physiology. Placenta. Elsevier Ltd; 2010;31:351–7.
5. Hodges LM, Markova SM, Chinn LW, Gow JM, Kroetz DL, Klein TE, et al. Very important pharmacogene summary: ABCB1 (MDR1, P-glycoprotein). Pharmacogenet. Genomics. 2011;21:152–61.
6. Kim RB. Drugs as P-glycoprotein substrates, inhibitors, and inducers. Drug Metab. Rev. 2002;34:47–54.
7. Zhou S-FF. Structure, function and regulation of P-glycoprotein and its clinical relevance in drug disposition. Xenobiotica. 2008;38:802–32.

b) Original research articles:

1. Wang J-S, Zhu H-J, Gibson BB, Markowitz JS, Donovan JL, DeVane CL. Sertraline and its metabolite desmethylsertraline, but not bupropion or its three major metabolites, have high affinity for P-glycoprotein. Biol. Pharm. Bull. 2008;31:231–4.
2. Weiss J, Dormann SG, Martin-facklam M, Kerpen CJ. Inhibition of P-Glycoprotein by Newer Antidepressants. J. Pharmacol. Exp. Ther. 2003;305:197–204.
3. Akamine Y, Yasui-Furukori N, Ieiri I, Uno T. Psychotropic drug-drug interactions involving P-glycoprotein. CNS Drugs. 2012;26:959–73.
4. Choo EF, Leake B, Wandel C, Imamura H, Wood a J, Wilkinson GR, et al. Pharmacological inhibition of P-glycoprotein transport enhances the distribution of HIV-1 protease inhibitors into brain and testes. Drug Metab. Dispos. 2000;28:655–60.
5. Holtzman CW, Wiggins BS, Spinler S a. Role of P-glycoprotein in statin drug interactions. Pharmacotherapy. 2006;26:1601–7.
6. Harmsen S, Meijerman I, Febus CL, Maas-Bakker RF, Beijnen JH, Schellens JHM. PXR-mediated induction of P-glycoprotein by anticancer drugs in a human colon adenocarcinoma-derived cell line. Cancer Chemother. Pharmacol. 2010;66:765–71.
7. Shimizu M, Uno T, Sugawara K, Tateishi T. Effects of itraconazole and diltiazem on the pharmacokinetics of fexofenadine, a substrate of P-glycoprotein. Br. J. Clin. Pharmacol. 2006;61:538–44.

Supplementary Table 2: The risk of specific anomalies among cases of individual drug with association and the risk determination from the comparison with the reference population

Types of specific anomalies	Drugs with associations	Number of users, n (%)		OR (95% CI)	*p* value†
		Case of specific anomalies (N_s)	Reference population (N=25,126)		
Heart anomalies (N_s=1244)	Cimetidine	2 (0.2)	20 (0.08)	2.02 (0.47-8.66)	0.28
	Ranitidine	3 (0.2)	142 (0.6)	0.43 (0.14-1.34)	0.17
Genital (N_s=406)	Omeprazole	8 (2)	295 (1.2)	1.69 (0.83-3.44)	0.16
	Pantoprazole	1 (0.2)	36 (0.1)	1.72 (0.24-12.58)	0.45
Respiratory (N_s=84)	Morphine	1 (1.2)	3 (0.01)	**100.9 (10.39-979.94)**	**0.013**
Musculoskeletal (N_s=1,054)	Haloperidol	3 (0.3)	25 (0.1)	2.87 (0.86-9.51)	0.1
	Quetiapine	1 (0.1)	21 (0.1)	1.14 (0.15-8.45)	0.6
	Risperidone	1 (0.1)	14 (0.1)	1.70 (0.22-12.97)	0.46
Nervous system (N_s=347)	Fluoxetine	1 (0.3)	110 (0.4)	0.66 (0.092-4.72)	1.0
	Citalopram	4 (1.2)	101 (0.4)	2.89 (1.06-7.9)	0.056
	Paroxetine	4 (1.2)	294 (1.2)	0.99 (0.37-2.66)	1.0
	Sertraline	1 (0.3)	35 (0.1)	2.07 (0.28-15.17)	0.39
	Fluvoxamine	1 (0.3)	55 (0.2)	1.32 (0.18-9.55)	0.54

†Fisher's exact test

Supplementary Table 3: The risk estimation of overall and specific congenital anomalies with P-gp-mediated drug interaction patterns, excluding SSRIs as drugs with associations

Drug interaction patterns		Users, n (%)		Odds ratios (95% CI)	*p* value†
		Case (N=4,634)	Reference population (N=25,126)		
A	Use of P-gp substrates alone	174 (3.8)	1292 (5.1)	1.0	-
	Use of P-gp substrates + any inhibitor/inducer*	25 (0.5)	228 (0.9)	0.81 (0.52-1.27)	0.4
B	Drugs with assoc. alone	9 (0.2)	384 (1.5)	1.0	-
	Drugs with assoc. + substrate	5 (0.06)	69 (0.3)	3.09 (1.0-9.5)	0.055
	Drugs with assoc. + substrate + inhibitor**	3 (0.06)	14 (0.06)	**9.14 (2.22-37.5)**	**0.01**
C	Drugs (S) with assoc. alone	1 (0.02)	129 (0.5)	1.0	-
	Drugs (S) with assoc. + substrate	2 (0.04)	16 (0.06)	**16.13 (1.38-187.99)**	**0.039**
	Drugs (S) with assoc. + substrate + inhibitor**	1 (0.02)	7 (0.03)	18.43 (1.04-326.42)	0.11
D	Drugs (S/I) with assoc. alone	8 (0.2)	259 (1.0)	1.0	-
	Drugs (S/I) with assoc. + substrate	3 (0.06)	56 (0.2)	1.73 (0.45-6.7)	0.43
	Drugs (S/I) with assoc. + substrate + inhibitor**	2 (0.04)	11 (0.04)	5.89 (1.12-31.05)	0.073

The reference for the odds ratio calculation is the use of drug substrates alone for each subgroup.
A) showed the risk of overall anomalies associated with drug interactions in all P-gp substrates;
B) showed the risk for specific anomalies (heart, genital, respiratory, musculoskeletal) in drugs previously associated with these anomalies (cimetidine, ranitidine, omeprazole, pantoprazole, morphine, haloperidol, risperidone, quetiapine);
C) showed the risk for specific anomalies (heart, musculoskeletal) in P-gp substrates (S) previously associated with these anomalies (cimetidine, ranitidine, risperidone);
D) showed the risk for specific anomalies (genital, musculoskeletal) in P-gp substrates/inhibitors (S/I) previously associated with these anomalies (omeprazole, pantoprazole, haloperidol, quetiapine);
* substrate/inhibitor, inhibitor, inducer, substrate/inducer, and substrate/inducer/inhibitor;
** substrate/inhibitor, inhibitor, inhibitor/inducer, substrate/ inhibitor/inducer;
†Fisher's exact test