7èmes Journées Nationales du réseau PIC

Pharmacie Clinique et Innovation en Santé mentale

Interactions médicamenteuses pharmacocinétiques en psychiatrie : du mécanisme à la clinique

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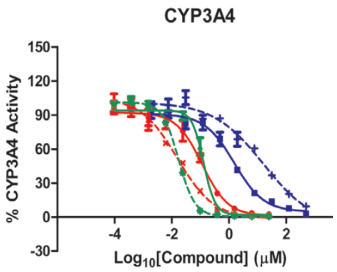
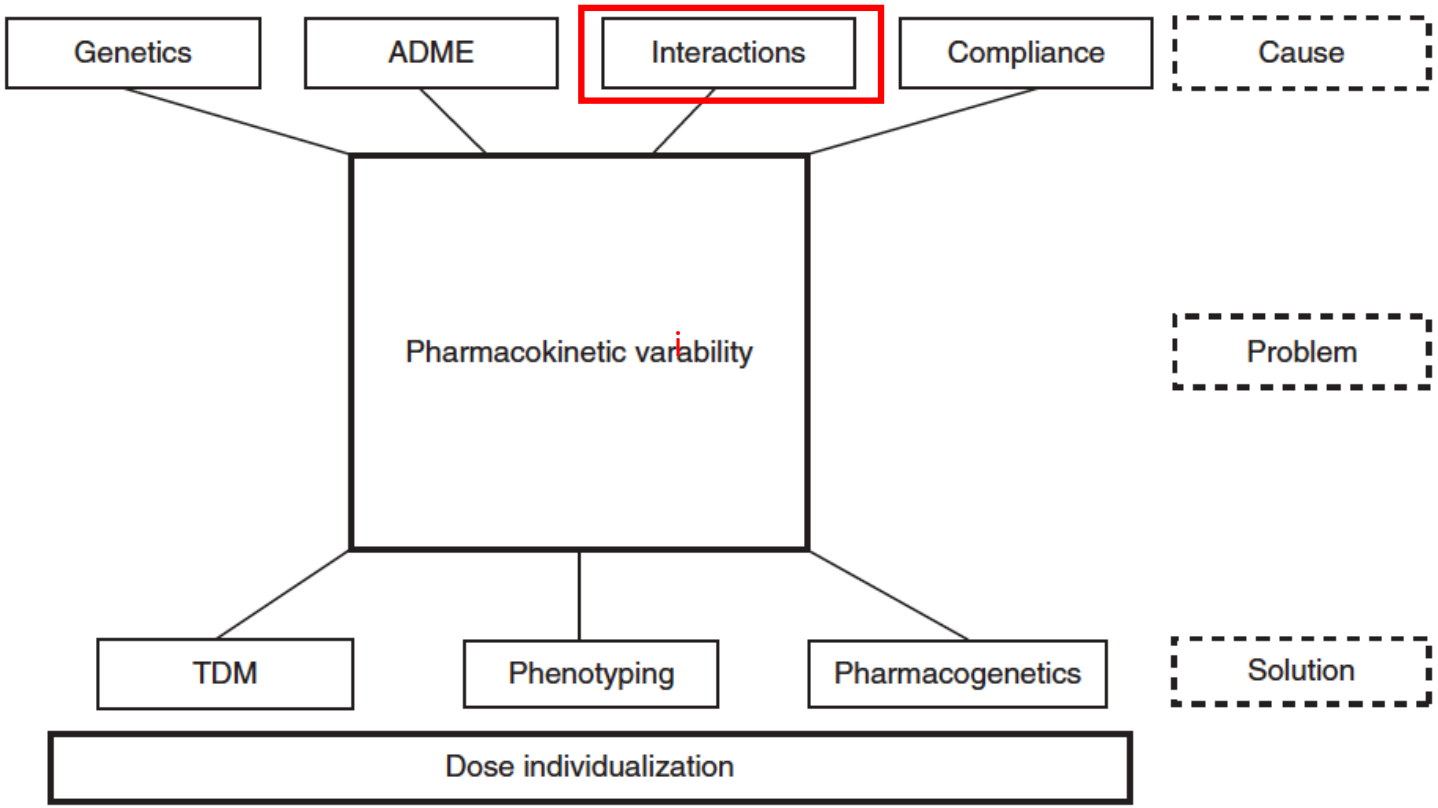
INSERM IRSET U1085

Liens d’intérêt

Amgen SAS, Astellas, Biogaran, Boeringer-Ingelheim, Celgene, LFB-Biomédicaments, Merck Serono, Novartis.

Interactions médicamenteuses du mécanisme ……. à la clinique





Drug Discovery Today

Sites d'interactions pharmacocinétiques

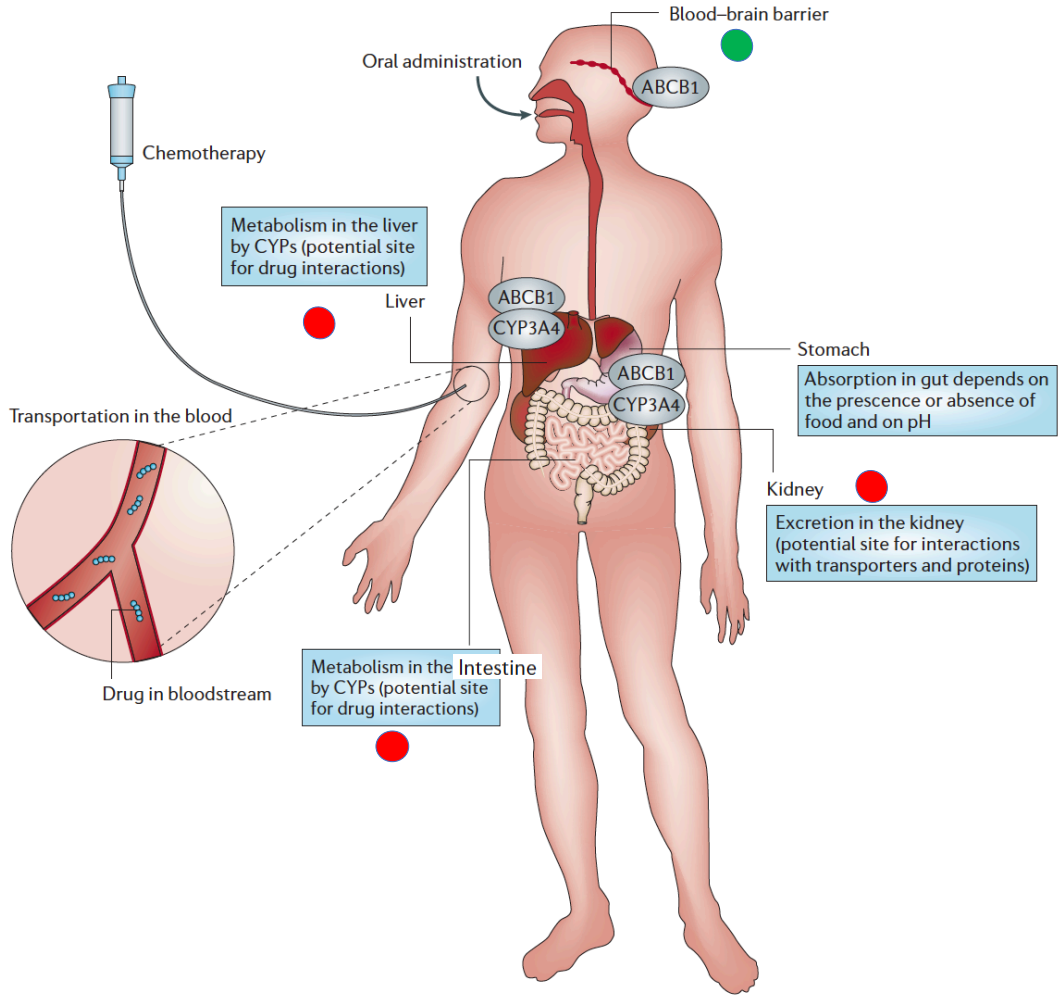
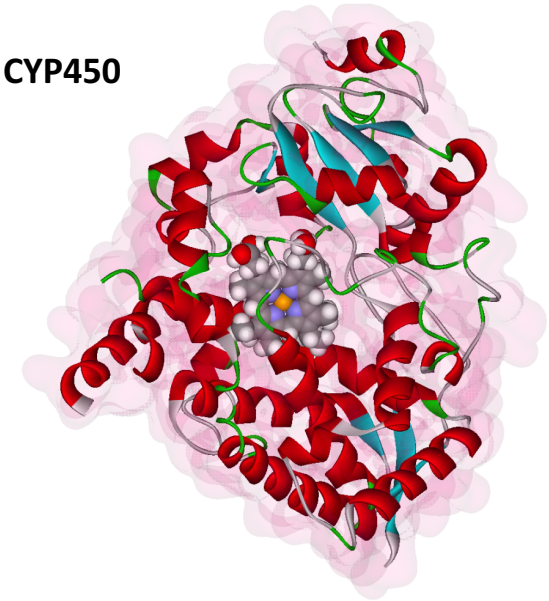
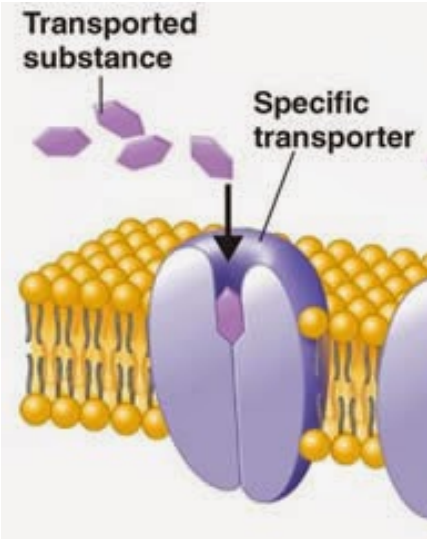


Figure 1 | **Sites of drug disposition.** The process of drug disposition can be divided into four parts — absorption, distribution, metabolism and excretion. Drug interactions can occur throughout the process of disposition as a result of endogenous and exogenous factors. The sites at which interactions can occur, and the sites of action of important mediators of interactions, ATP-binding cassette transporter B1 (ABCB1) and cytochrome P450 3A4 isoform (CYP3A4), are shown. CYP, cytochrome P450 enzymes.

Mécanismes : induction ou inhibition d'enzymes ou de transporteurs

CYP450





EFFLUX

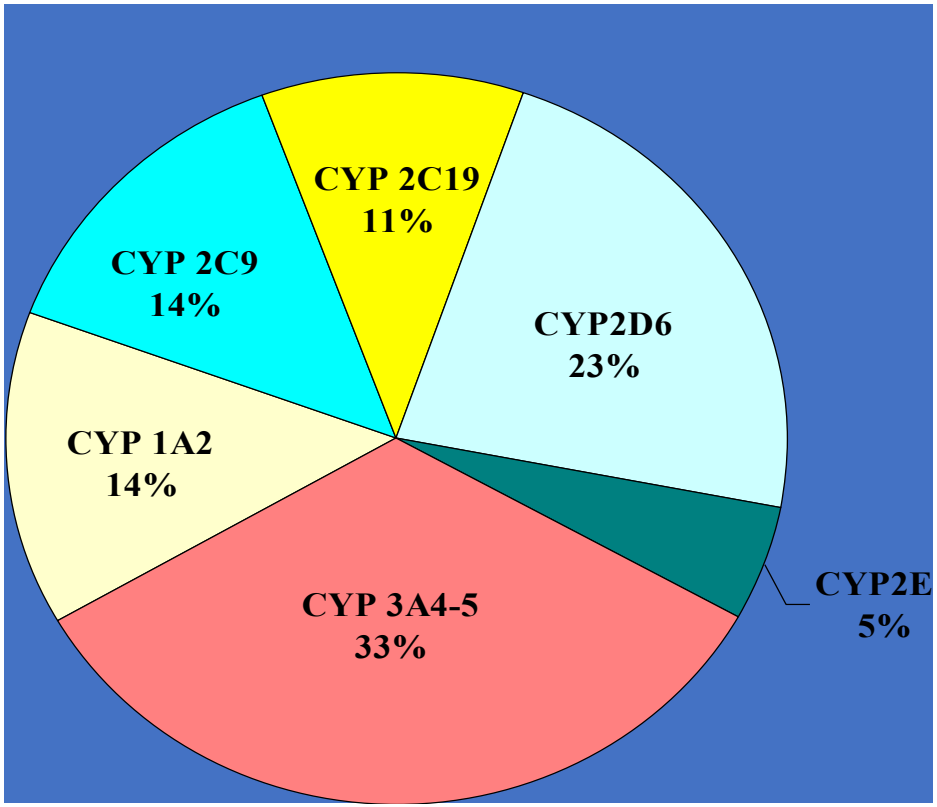
INFLUX

induction : délai environ 72 h (synthèse de protéines)

Inhibition : effet immédiat (compétitif)

CYP ENZYMES IN HEPATIC DRUG METABOLISM

% DRUGS METABOLIZED BY CYP ENZYMES



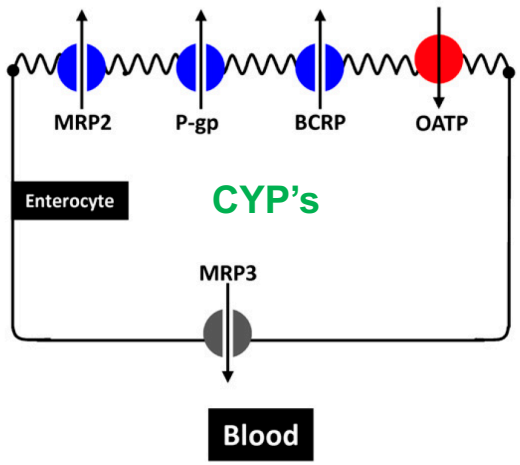


Fig. 1. Transporters expressed in enterocytes of the human intestinal epithelium. Uptake transporters discussed in this review are colored in red, export pumps in blue.

= transporteur d'influx

= transporteur d'efflux

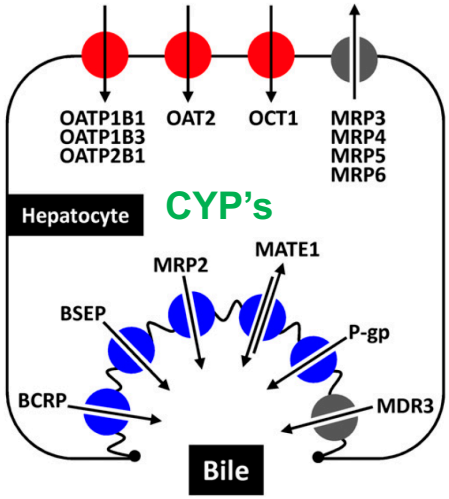


Fig. 2. Transporters expressed in human hepatocytes. Uptake transporters discussed in this review are colored in red, export proteins in blue.

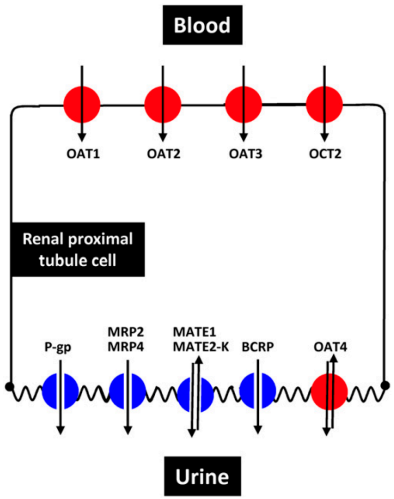


Fig. 3. Transporters expressed in human renal proximal tubule epithelial cells. Uptake transporters discussed in this review are colored in red, export proteins in blue.

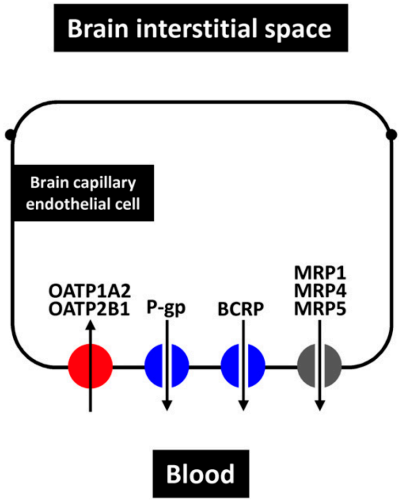


Fig. 4. Transporters expressed in human brain capillary endothelial cells. Uptake transporters discussed in this review are colored in red, export proteins in blue.

Pharmacol Rev 65:944–966, July 2013

Métabolisme des anti-psychotiques de 2nd génération (SGA)

Table 1 Summary of the pharmacokinetic parameters of second-generation antipsychotics

Drug	t_{max} (h)	$t_{½}$ (h)	V_d	CL	Protein binding	Primary metabolic pathways
Lurasidone [43, 44]	1–3	29–37	6,173 L	3.902 L/min	99 %	CYP3A4
Iloperidone [45, 46]	2–4	14	2,527 L	47–102 L/h	93 %	CYP3A4, CYP2D6, CYP1A2 (minor/partial)
Asenapine (sublingual) [49]	1	24	1,700 L	0.867 L/min	95 %	CYP1A2, UGT
Ziprasidone [11, 53]	4	4–10	1.03 L/kg	5.08 mL/min/kg	99 %	Aldehyde oxidase, CYP3A4 (minor/partial), CYP1A2 (minor/partial)
Aripiprazole [51, 52]	3–5	75	4.9 L/kg	3.4 L/h	99 %	CYP3A4, CYP2D6
Paliperidone (extended-release) [46, 54]	24	24	70–192 L	1.4–8.2 L/h	74 %	UGT, CYP3A4 (minor/partial), CYP2D6 (minor/partial)
Risperidone [58, 61, 67]	1	22	1.0 L/kg	5.0 mL/min/kg	89 %, 77 % (9-hydroxrisperidone)	CYP2D6, CYP3A4 (minor/partial) 9-hydroxyrisperidone
Olanzapine [12, 59]	6	33	16 L	26 L/h	93 %	UGT, CYP1A2, CYP2D6 (minor/partial)
Quetiapine (immediate-release) [33, 69]	1.5	6	513–710 L	55–87 L/h	83 %	CYP3A4, CYP2D6 (minor/partial)
Clozapine [60]	1–4	9–17	2–7 L/kg	9–53 L/h	95 %	CYP3A4, CYP1A2, CYP2C19 (minor/partial), CYP2D6 (minor/partial)

CL clearance, *CYP* cytochrome P450, $t_{½}$ elimination half-life, t_{max} time to reach the peak serum drug concentration, *UGT* uridine diphosphate-glucuronosyltransferase, V_d volume of distribution

Plusieurs voies métaboliques

P-gp et anti-psychotiques de 2nd génération

Substrats de P-gp (à concentrations thérapeutiques) :

amisulpride,
aripiprazole,
olanzapine,
paliperidone,
perospirone,
risperidone

Non-substrats de P-gp :

clozapine,
quetiapine

Peu ou pas d'information :

sertindole,
ziprasidone,
zotepine

La plupart sont inhibiteurs de P-gp ➔ impact sur d'autres molécules (Moons T et al Pharmacogenomics 2011)

Métabolisme des anti- dépresseurs

Table 1. Pharmacokinetic parameters of newer antidepressants.

	Bioavailability (%)	Protein binding (%)	Half-life (h)	Metabolism	Active metabolites	Inhibitory effect on CYP isoenzymes
SSRI						
Citalopram	95	82	23 – 45	CYP3A4, CYP2C19, CYP2D6		CYP2D6 (weak)
Escitalopram	80	56	27	CYP3A4, CYP2C19, CYP2D6		CYP2D6 (weak)
Fluoxetine	80	95	2 – 4 days	CYP2D6, CYP2C9, CYP2C19, CYP3A4	Norfluoxetine	CYP2D6 (potent) CYP2C9 (moderate) CYP2C19 and CYP3A4 (weak to moderate) CYP1A2 (weak)
Fluvoxamine	< 53	77	15 – 22	CYP1A2, CYP2D6		CYP1A2 and CYP2C19 (potent) CYP2C9 and CYP3A4 (moderate) CYP2D6 (weak)
Paroxetine	> 64	93	10 – 21	CYP2D6 (major), CYP3A4		CYP2D6 (potent) CYP1A2, CYP2C9, CYP2C19, CYP3A4 (weak)
Sertraline	> 44	98	22 – 36	CYP2C9, CYP2C19, CYP2D6, CYP3A4		CYP2D6 (weak to moderate) CYP1A2, CYP2C9, CYP2C19 and CYP3A4 (weak)

(Spina E & de Leon J, Exp Opin Drug Metab Toxicol 2014)

Table 1. Pharmacokinetic parameters of newer antidepressants.

	Bioavailability (%)	Protein binding (%)	Half-life (h)	Metabolism	Active metabolites	Inhibitory effect on CYP isoenzymes
SNRI						
Desvenlafaxine	80	30	9 – 15	UGT, CYP3A4 Excreted unchanged (45%)		
Duloxetine	50	> 90	10 – 12	CYP1A2 (major), CYP2D6		CYP2D6 (moderate)
Levomilnacipran	92	22	12	CYP3A4 (18%), other CYP and UGTs Excreted unchanged (58%)		
Milnacipran	85	13	8 – 10	Glucuronidation (20 – 30%) CYP3A4 (10%) Excreted unchanged (50 – 60%)		CYP3A4 (weak)
Venlafaxine	92	27	5	CYP2D6 (major), CYP3A4	Desvenlafaxine	
Other newer antidepressants						
Agomelatine	< 5	95	1 – 2	CYP1A2 (90%), CYP2C9 (10%)		
Bupropion	90	84	20	CYP2B6	Hydroxybupropion Threohydrobupropion Erythrohydrobupropion	CYP2D6 (moderate)
Mirtazapine	50	85	20 – 40	CYP2D6, CYP3A4, CYP1A2		
Reboxetine	> 60	97	12 – 16	CYP3A4		
Vilazodone	72*	96 – 99	20 – 24	CYP3A4 (major), CYP2C19, CYP2D6, Carboxylesterase		CYP2C8 (?)
Vortioxetine	75	98	57 – 66	CYP2D6 (major), CYP3A4, CYP2C19, CYP2C9, CYP2A6, CYP2C8, CYP2B6		

(Spina E & de Leon J, Exp Opin Drug Metab Toxicol 2014)

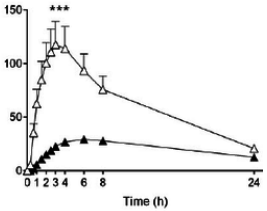
WEAK

MODERATE

POTENT

INHIBITEUR = AUGMENTATION de SSC

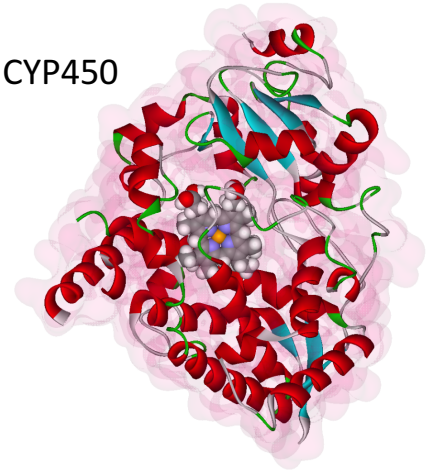
Puissant	**> x 5**
Modéré	**x 2 à 5**
Faible	**x 1,25 à 2**

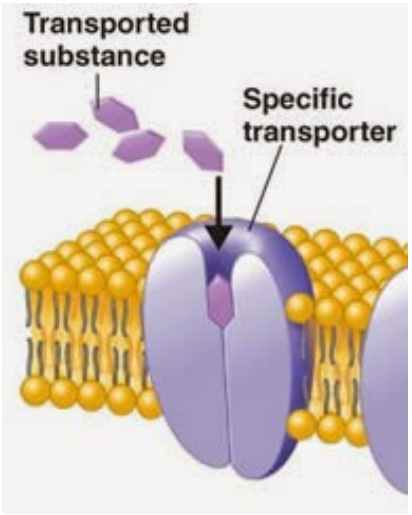


INDUCTEUR = DIMINUTION de SSC

Puissant	**> 80 %**
Modéré	**50 à 80 %**
Faible	**20 à 50 %**

CYP450





FDA

TABLE 1

Inhibition DDIs with AUC ratios ≥5, NME as substrate

Drugs were orally administered unless specified.

Victim Drug	Inhibitor	Main Enzymes/Transporters Possibly Involved	AUC Ratio	Reference
Paritaprevir	Ritonavir	CYP3A, P-gp, BCRP, OATP1B1/3	47.43	FDA (2014m)
Eliglustat	Ketoconazole/paroxetine	CYP3A, CYP2D6[a]	37.85 (PBPK in EMs)	FDA (2014c)
Eliglustat	Paroxetine	CYP2D6	28.40 (UMs)	FDA (2014c)
Ibrutinib	Ketoconazole	CYP3A	23.90	FDA (2013g)
Eliglustat	Fluconazole/terbinafine	CYP3A, CYP2D6	19.31 ($AUC_{0-24\ h}$, PBPK in EMs)	FDA (2014c)
Grazoprevir	Cyclosporine	OATP1B1/3[b]	15.25 ($AUC_{0-24\ h}$)	FDA (2016d)
Grazoprevir	Lopinavir/ritonavir	CYP3A, OATP1B1/3[b]	12.87	FDA (2016d)
Naloxegol	Ketoconazole	CYP3A[a]	12.42	FDA (2014h)
Grazoprevir	Atazanavir/ritonavir	CYP3A, OATP1B1/3[b]	10.56	FDA (2016d)
Grazoprevir	Rifampin (i.v.)	OATP1B1/3	10.22	FDA (2016d)
Eliglustat	Paroxetine	CYP2D6	10.00 (EMs)	FDA (2014c)
Dasabuvir	Gemfibrozil	CYP2C8	9.90	FDA (2014m)
Eliglustat	Ketoconazole/paroxetine	CYP3A, CYP2D6[a]	9.81 (PBPK in IMs)	FDA (2014c)
Ibrutinib	Erythromycin	CYP3A	8.60 (PBPK)	FDA (2013g)
Grazoprevir	Rifampin	OATP1B1/3[b]	8.37	FDA (2016d)
Ivabradine	Josamycin	CYP3A[a]	7.70	FDA (2015c)
Ivabradine	Ketoconazole	CYP3A[a]	7.70	FDA (2015c)
Eliglustat	Fluconazole	CYP3A	7.54 (PBPK in PMs)	FDA (2014c)
Grazoprevir	Darunavir/ritonavir	CYP3A, OATP1B1/3[b]	7.49	FDA (2016d)
Simeprevir	Ritonavir	CYP3A[a]	7.18	FDA (2013i)
Tasimelteon	Fluvoxamine	CYP1A2[c]	6.87	FDA (2014f)
Pirfenidone	Fluvoxamine	CYP1A2	6.81 (smokers), 3.97 (nonsmokers)	FDA (2014d)
Cobimetinib	Itraconazole	CYP3A[a]	6.62	FDA (2015d)
Simeprevir	Erythromycin	CYP3A[a]	6.54	FDA (2013i)
Flibanserin	Fluconazole	CYP3A, CYP2C19	6.41	FDA (2015a)
Venetoclax	Ketoconazole	CYP3A, P-gp	6.40	FDA (2016e)
Eliglustat	Ketoconazole	CYP3A[a]	6.22 (PBPK in PMs)	FDA (2014c)
Ibrutinib	Diltiazem	CYP3A	5.50 (PBPK)	FDA (2013g)
Isavuconazonium sulfate (prodrug)	Ketoconazole	CYP3A, butyrylcholinesterase	5.22	FDA (2015e)
Eliglustat	Paroxetine	CYP2D6	5.20 (IMs)	FDA (2014c)

EM, CYP2D6 extensive metabolizer; IM, CYP2D6 intermediate metabolizer; PM, CYP2D6 poor metabolizer; UM, CYP2D6 ultrarapid metabolizer; i.v., intravenously.

[a]Also a substrate of P-gp based on in vitro results; inhibition of P-gp might contribute to the observed interaction.

[b]Also a substrate of P-gp and BCRP based on in vitro results.

[c]Also metabolized by CYP3A, CYP2C9, and CYP2C19; fluvoxamine inhibits these P450s.

Inhibiteurs du CYP3A4

Azolés

Anti-viraux HIV-VHC

Macrolides

Jus pamplemousse

Table 3-2: Examples of clinical inhibitors for P450-mediated metabolisms (for concomitant use clinical DDI studies and/or drug labeling) (9/26/2016)

	Strong inhibitors	Moderate inhibitors	Weak inhibitors
	conivaptan[(h)], danoprevir and ritonavir[(j)], elvitegravir and ritonavir[(j)], grapefruit juice[(k)], indinavir and ritonavir[(j)], itraconazole[(h)], ketoconazole, lopinavir and ritonavir[(h,j)], paritaprevir and ritonavir and (ombitasvir and/or dasabuvir)[(j)], posaconazole, ritonavir(h,j), saquinavir and ritonavir[(h,j)], telaprevir[(h)], tipranavir and ritonavir[(h,j)], troleandomycin, voriconazole	ciprofloxacin, clotrimazole, crizotinib, cyclosporine, dronedarone[(h)], erythromycin, fluconazole[(f)], fluvoxamine[(a)], imatinib, tofisopam, verapamil[(h)]	fosaprepitant, istradefylline, ivacaftor[(h)], lomitapide, ranitidine, ranolazine[(h)], tacrolimus, ticagrelor[(h)]
	clarithromycin[(h)], diltiazem[(h)], idelalisib, nefazodone, nelfinavir[(h)]		

Table 3-3: Examples of clinical inducers for P450-mediated metabolisms (for concomitant use clinical DDI studies and/or drug labeling) (9/26/2016)

	Strong inducers	Moderate inducers	Weak inducers
CYP1A2		phenytoin[a] rifampin(b), ritonavir[c], smoking, teriflunomide	-
CYP2B6	carbamazepine[d]	efavirenz[e], rifampin[a], ritonavir[c]	nevirapine
CYP2C8	-	rifampin[a]	-
CYP2C9	-	aprepitant, carbamazepine[d], enzalutamide(f), rifampin[a], ritonavir[c]	-
CYP2C19	rifampin[a], ritonavir[c]	efavirenz[e], enzalutamide[f], phenytoin[b]	-
CYP3A	carbamazepine[d], enzalutamide[f], mitotane, phenytoin[b], rifampin[a], St. John's wort(g)	bosentan, efavirenz, etravirine, modafinil	armodafinil, rufinamide

Table 5-2: Examples of clinical inhibitors for transporters (for use in clinical DDI studies and drug labeling) (9/26/2016)

Transporter	Gene	Inhibitor
P-gp[a]	*ABCB1*	amiodarone, carvedilol, clarithromycin, dronedarone, itraconazole, lapatinib, lopinavir and ritonavir, propafenone, quinidine, ranolazine, ritonavir, saquinavir and ritonavir, telaprevir, tipranavir and ritonavir, verapamil
BCRP	*ABCG2*	curcumin, cyclosporine A, eltrombopag
OATP1B1, OATP1B3	*SLCO1B1*, *SLCO1B3*	atazanavir and ritonavir, clarithromycin, cyclosporine, erythromycin, gemfibrozil, lopinavir and ritonavir, rifampin (single dose), simeprevir
OAT1, OAT3	*SLC22A6*, *SLC22A8*	p-aminohippuric acid (PAH)[b], probenecid, teriflunomide
MATE1, MATE2-K	*SLC47A1*, *SLC47A2*	cimetidine, dolutegravir, isavuconazole, ranolazine, trimethoprim, vandetanib

Anti-psychotiques & Anti-dépresseurs

Plusieurs enzymes impliquée dans le métabolisme

➔ moindre risque d'interaction majeure

- sauf si blocage de plusieurs enzymes
- sauf si blocage d'une enzyme principale

Marge thérapeutique assez large

➔ interaction <u>modérée à importante</u> peut avoir des conséquences cliniques

Quel impact des interactions au niveau de la BHE

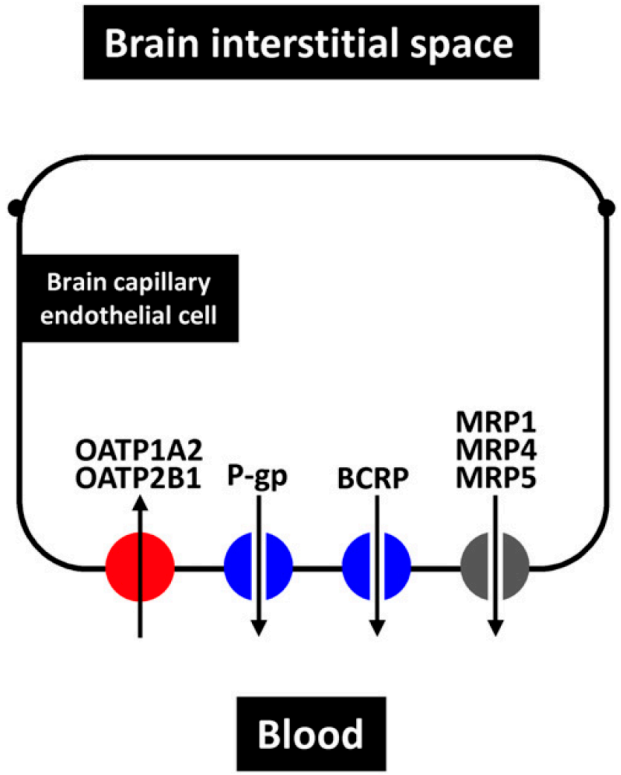


Fig. 4. Transporters expressed in human brain capillary endothelial cells. Uptake transporters discussed in this review are colored in red, export proteins in blue.

Anti-psychotiques & antidépresseurs substrats de P-gp :

- Polymorphisme (mutations)

- Interactions médicamenteuses

Mutation 1199G>A (**augmentation d'activité de P-gp**, Wang R et al DNA & Cell Biol 2018) :

- *réduirait l'accumulation intra-cérébrale*

- *démontré in vitro (cellules transfectées)*

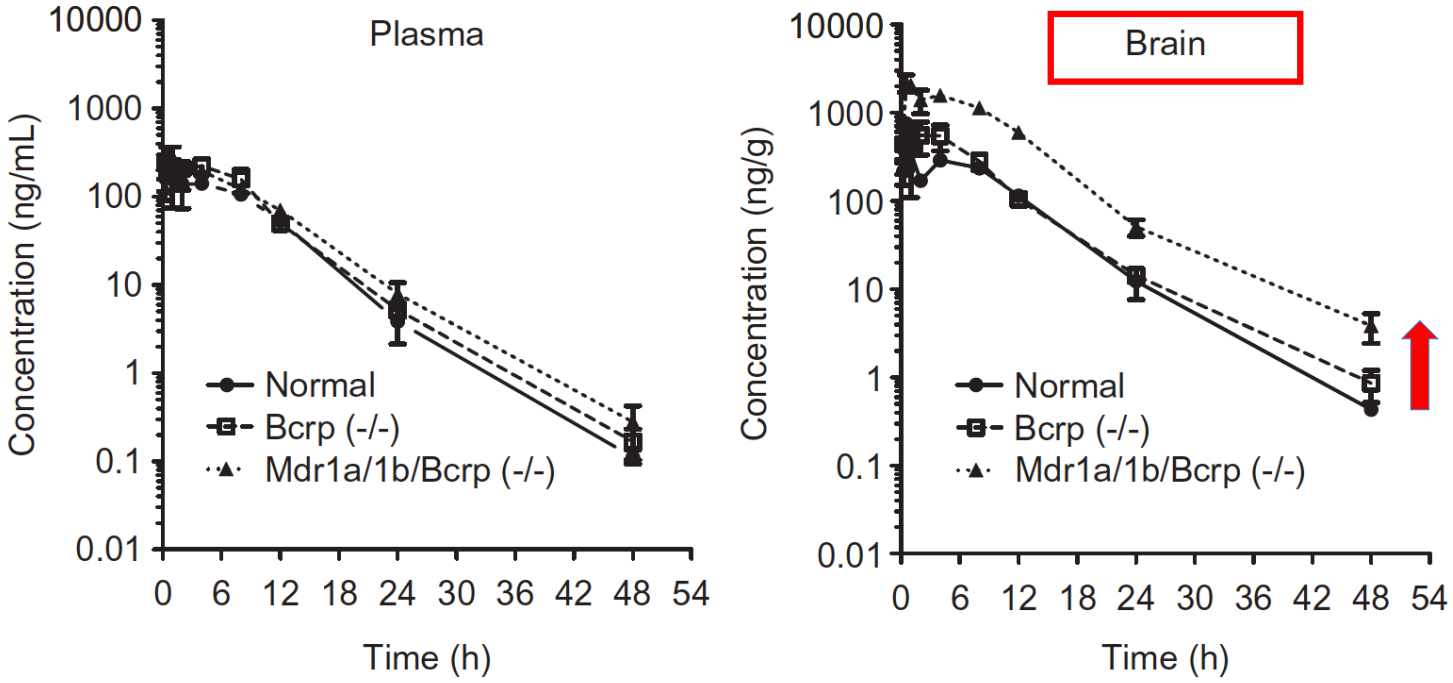
  - *Olanzapine, Aripiprazole, Amisulpride et Risperidone*
  - *pas pour Paliperidone (?)*

Mutations déficientes (**baisse d'activité de P-gp**, Nagasaka Y et al Xenobiotica 2014) :

- *augmenterait l'accumulation intra-cérébrale*

- *démontré in vivo (animal)*

  - *Aripiprazole*



Concentrations d'aripiprazole (plasma et cerveau) chez des souris normales et des souris mutantes (P-gp et BCRP), Nagasaka Y et al Xenobiotica 2014)

Pas d'effet au niveau du plasma
Effet au niveau du cerveau mais concentration globale (broyat) … . Pas les concentrations libres

Et chez l'homme ??

Sujets schizophrènes (de Klerk OL et al, Psychiatry Research 2010)

Baisse de distribution cérébrale de substrat de la P-gp par augmentation locale d'expression de P-gp

Pourrait expliquer la résistance à certains anti-psychotiques

Utiliser plutôt clozapine ou haldol que risperidone

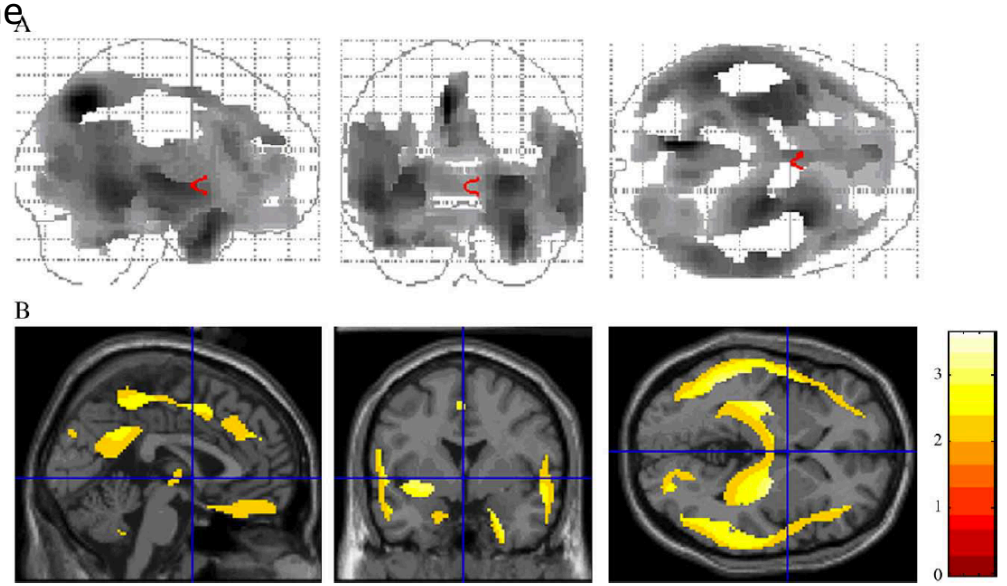


Fig. 1. *T*-map showing a diminished a trend towards a decreased Distribution Volume of [^{11}C]verapamil in 10 patients with schizophrenia compared with 10 healthy controls in sagittal, coronal and axial directions. The clusters of voxels at $P_{FDR}=0.09$ (in SPM2) are shown. (A): projections on a glass brain. (B) MRI-overlay: clusters located in (fronto) temporal and parietal lobes, as well as subcortical nuclei are shown.

Et chez l'homme ??

Sujets dépressifs majeurs (de Klerk OL et al, Int J Neuropsychiatry 2009)

Baisse de distribution cérébrale de substrat de la P-gp par augmentation locale d'expression de P-gp (frontal et temporal)

Résistance à certains antidépresseurs (origine ?? : polymorphisme, pas une induction de P-gp)

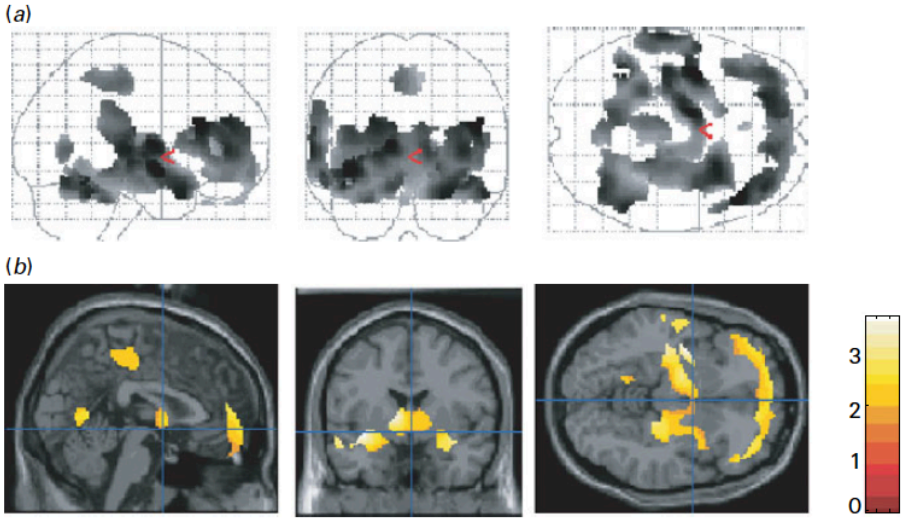
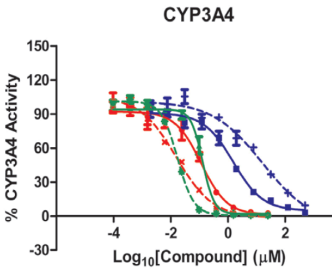


Fig. 2. T-map showing a diminished distribution volume of [^{11}C]verapamil in 13 patients with a depressive episode compared to the healthy control group ($n=13$). The clusters that reached statistical significance in a voxel-wise t test ($p_{FDR}<0.05$) (in SPM2) are shown. (*a*) Significant projections on a glass brain. (*b*) MRI overlay : a large cluster located in frontal cortex, left and right temporal lobes, and subcortical nuclei is shown.

Interactions médicamenteuses
du mécanisme ……. à la clinique



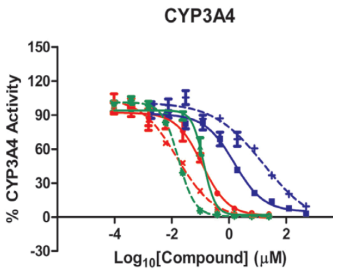
Surtout CYP450 ou P-gp (induction ou inhibition)

Intensité modérée (le plus souvent)

marge thérapeutique assez large (anti-psychotiques 2nd génération)

distribution cérébrale pas toujours reflétée par les concentrations plasmatiques

Interactions médicamenteuses
du mécanisme ……. à la clinique



Ostermann *et al. BMC Health Services Research* (2016) 16:482
DOI 10.1186/s12913-016-1724-8

BMC Health Services Research

RESEARCH ARTICLE Open Access

Frequency and clinical relevance of potential cytochrome P450 drug interactions in a psychiatric patient population – an analysis based on German insurance claims data

Julia K. Ostermann[1*], Anne Berghöfer[1], Frank Andersohn[1] and Felix Fischer[1,2]

Conclusions: The number of patients with DDEs was not alarmingly high in our sample. Nevertheless, prescription information showed that some prescribed drug combinations could result in serious adverse consequences that are known to weaken or strengthen the effect of the drugs and should therefore be avoided.

Table 1 Baseline characteristics of all patients ($n = 1221$)

	All patients ($n = 1221$)
Female, n (%)	846 (69.3)
Age, mean (SD)	47.9 (16.2)
Younger than 35 years, n (%)	269 (22.0)
35–55 years old, n (%)	592 (48.5)
Older than 55 years, n (%)	360 (29.5)
Most common psychiatric diagnosis, n (%)	
F32 – Major depressive disorder	338 (27.7)
F33 – Major depressive disorder, recurrent	304 (24.9)
F20 – Schizophrenia	163 (13.4)
F41 – Anxiety disorders	96 (7.9)
F31 – Bipolar disorder	66 (5.4)

15 % des patients avec InterX

5 % des patients interX avec inhibiteur enzymatique puissant

Table 5 Most frequent drug-drug exposures with a strong inhibitor in all patients ($n = 1221$). Classification of the potential drug-drug exposure was determined by the content of the prescribing information associated with the brand-name drug

Potential drug-drug exposure (bold = strong inhibitor)	Frequency	Events per 100 person-years (95%CI)	Number of patients with at least one DDE (%)	Clinical relevance of a potential interaction (as per prescribing information)
amitriptyline & paroxetine	29	0.56 (0.37–0.80)	9 (0.74)	Patients taking SSRIs should only be treated with amitriptyline with particular caution [35] [reason not given]
paroxetine & risperidone	21	0.40 (0.25–0.62)	6 (0.49)	Paroxetine increases the plasma-concentration of risperidone [36]
codeine & fluoxetine	8	0.15 (0.07–0.30)	5 (0.41)	not mentioned [37, 38]
amitriptyline & fluoxetine	16	0.31 (0.18–0.50)	5 (0.41)	Taking fluoxetine and amitriptyline in parallel might result in an increased plasma-concentration of amitriptyline Dose-reduction might be necessary [33]
fluoxetine & tramadol	42	0.81 (0.58–1.09)	5 (0.41)	Taking tramadol and fluoxetine in parallel can induce serotonin syndrome [32]
amlodipine & clarithromycin	5	0.10 (0.03–0.22)	4 (0.33)	Taking clarithromycin and amlodipine parallel might result in an increased plasma concentration of amlodipine [39]
clomipramine & paroxetine	76	1.46 (1.15–1.82)	4 (0.33)	Paroxetine can increase the plasma concentration of clomipramine [40]
paroxetine & tramadol	6	0.12 (0.04–0.25)	4 (0.33)	Taking tramadol and SSRIs [i.e., paroxetine] in parallel can induce serotonin syndrome [32]. Patients taking tramadol and paroxetine must be monitored closely [35]
…				
Sum	380	7.29 (6.57–8.06)	90	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Hiemke C et al. Handb Exp Pharmacol. (2012)
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The Differential Binding of Antipsychotic Drugs

Table 3. Summary of pharmacokinetic drug interactions between newer antidepressants and second-generation antipsychotics.

Antidepressant	Antipsychotic	Effect	Proposed mechanism	Ref.
Fluoxetine	Clozapine	Increase in plasma clozapine concentrations (40 – 70%)	Inhibition of various CYP isoforms (CYP2D6, CYP2C19 and CYP3A4)	[37-40]
	Risperidone	Increase in plasma concentrations of the active moiety of risperidone by 75%	Inhibition of CYP2D6 and, to a lesser extent, CYP3A4	[41,42]
	Olanzapine	No change or minimal increase in plasma olanzapine concentrations	Inhibition of CYP2D6	[43]
	Aripiprazole	Increase by 45% in plasma concentrations of aripiprazole	Inhibition of CYP2D6 and CYP3A4	[46]
	Iloperidone	Increase (up to twofold) in plasma iloperidone concentrations	Inhibition of CYP2D6	[25,26]
Paroxetine	Clozapine	Increase in plasma clozapine concentrations (20 – 40%)	Inhibition of CYP2D6	[38,50,51]
	Risperidone	Increase in plasma concentrations of the active moiety of risperidone by 40 – 50%	Inhibition of CYP2D6	[48,49]
	Aripiprazole	Increase in plasma concentrations of aripiprazole by 40 – 50%	Inhibition of CYP2D6	[52,53]
	Iloperidone	Increase (up to twofold) in plasma iloperidone concentrations	Inhibition of CYP2D6	[25,26]
Fluvoxamine	Clozapine	Increase (up to 5 – 10-fold) in plasma clozapine concentrations	Inhibition of CYP1A2 and, to a lesser extent, CYP2C19 and CYP3A4	[51,54-58]
	Olanzapine	Increase (up to twofold) in plasma olanzapine concentrations	Inhibition of CYP1A2	[63-66]
	Risperidone	No significant changes in plasma risperidone concentrations at fluvoxamine dosage of 100 mg/day, increase by 26% at fluvoxamine dose of 200 mg/day	Inhibition of CYP2D6 and CYP3A4	[68]
	Quetiapine	Increase in plasma concentrations of quetiapine by 159%	Inhibition of CYP3A4	[45]
	Aripiprazole	Decrease by 40% in systemic clearance of aripiprazole	Inhibition of CYP3A4	[53]
	Asenapine	Increase by 29% in the AUC of asenapine at fluvoxamine dosage of 50 mg/day	Inhibition of CYP1A2	[25,26]
Sertraline	Risperidone	Increased plasma concentrations of risperidone (36 – 52%) only at high doses of sertraline (150 mg/day)	Inhibition of CYP2D6	[69]
Citalopram/ escitalopram	Aripiprazole	Minimal increase (by 20%) in plasma concentrations of aripiprazole and dehydroaripiprazole	Inhibition of CYP2D6	[46]
Duloxetine	Risperidone	Minimal increase (by 26%) in plasma concentrations of the active moiety of risperidone	Inhibition of CYP2D6	[83]
	Olanzapine	No change or minimal increase in plasma olanzapine concentrations		

Expert Opin. Drug Metab. Toxicol. (2014)

Table 3 Summary of drug–drug interaction studies of second-generation antipsychotics (SGAs) conducted during drug development

Drug	Inhibitor	Inducer	Pharmacokinetic effects on SGA
Lurasidone	Ketoconazole, diltiazem	Rifampicin	Lurasidone C_{max} ↑ 6.9-fold and AUC ↑ 9-fold with ketoconazole; lurasidone should not be co-administered with ketoconazole. Lurasidone C_{max} and AUC ↑ 2-fold with diltiazem; lurasidone dose limit 40 mg/day. Lurasidone C_{max} and AUC ↓ 80 % with rifampicin; lurasidone should not be co-administered with rifampicin [43, 44]
Iloperidone	Ketoconazole, paroxetine	[Not done]	Iloperidone AUC ↑ 57 % with ketoconazole and ↑ 2- to 3-fold with paroxetine; ↓ iloperidone dose by 50 % [45–47]
Asenapine	Fluvoxamine, cimetidine, paroxetine, valproic acid	Carbamazepine	Asenapine AUC ↑ 29 % with fluvoxamine; co-administer fluvoxamine with caution; no dose adjustments needed with other drugs [48–50]
Aripiprazole	Ketoconazole, quinidine	Carbamazepine	Aripiprazole AUC ↑ 63 % with ketoconazole, AUC ↑ 112 % with quinidine, C_{max} and AUC ↓ 70 % with carbamazepine; adjust dose by 50 % [51, 52, 112]
Ziprasidone	Ketoconazole	Carbamazepine	Ziprasidone AUC ↓ or ↑ by 35–40 %; no dosage adjustment suggested [53]
Paliperidone	Paroxetine, valproic acid	Carbamazepine	Paliperidone AUC ↑ 16 % with paroxetine, C_{max} and AUC ↑ 50 % with valproic acid, C_{max} and AUC ↓ 50 % with carbamazepine [54, 63]
Risperidone	Fluoxetine, paroxetine	Carbamazepine	Risperidone Cpss ↑ 2.5- to 9-fold with inhibitors, Cpss ↓ 50 % with inducers; adjust doses accordingly [58, 67, 81, 101]
Quetiapine	Ketoconazole	Phenytoin	Quetiapine CL ↓ 84 % with ketoconazole, CL ↑ 5-fold with phenytoin; adjust doses [69, 121]
Olanzapine	Fluvoxamine	Carbamazepine	Olanzapine AUC ↑ 54 % in nonsmokers, AUC ↑ 108 % in smokers with fluvoxamine, CL ↑ 50 % with carbamazepine; adjust doses [89–91, 107, 108]
Clozapine	Fluvoxamine, paroxetine, cimetidine	Phenytoin	Required clozapine dose adjustments included in manufacturer's prescribing information [60, 85–89, 100, 153]

AUC area under the plasma concentration–time curve, *CL* drug clearance, C_{max} peak serum drug concentration, *Cpss* serum drug concentration, ↑ increase(d), ↓ decrease(d)

Kennedy WK et al CNS Drugs 2013

Table 4 Summary of the effects of selective serotonin-reuptake inhibitors (SSRIs) on second-generation antipsychotics (SGAs)

SSRI	SGA	Comments
Fluoxetine	Clozapine	40–70 % ↑ in plasma clozapine concentrations [79, 80]
	Risperidone	↑ plasma risperidone and active moiety concentrations, Parkinson's side effects noted in a few patients [81]
Fluvoxamine	Clozapine	5- to 10-fold ↑ in plasma clozapine concentrations in patients with dose-dependent fluvoxamine effects [85–88]
	Olanzapine	1- to 2-fold ↑ in serum olanzapine concentrations and dose-dependent effects [89–91]
	Quetiapine	159 % ↑ in quetiapine *C/D* ratio noted, most likely due to CYP3A4 inhibition [64, 66, 69]
Paroxetine	Clozapine	↑ plasma clozapine levels similar to fluoxetine [80]
	Risperidone	↑ total active moiety concentrations with dose-dependent effects
		↑ extrapyramidal side effects and Parkinson's side effects in some patients [94]
Sertraline	Clozapine	↑ plasma clozapine levels similar to fluoxetine [80]
	Risperidone	Sertraline 50 and 100 mg doses had no changes in total drug Cpss, but 150 mg/day was reported to ↑ total drug Cpss by 36 % in 1 patient and by 52 % in another [96]

C/D concentration/dose ratio, *Cpss* serum drug concentration, *CYP* cytochrome P450, ↑ increase(d), ↓ decrease(d)

Kennedy WK et al CNS Drugs 2013

Table 5 Summary of drug–drug interactions between mood stabilizers and second-generation antipsychotics (SGAs)

Drug	SGA	Pharmacokinetic effects of mood stabilizer on SGA
Carbamazepine	Clozapine	Plasma clozapine concentrations ↓ 50 % [99, 100]
	Risperidone	Total active moiety concentrations ↓ 50 %, risperidone CL ↑ 2-fold [61, 101]
	Olanzapine	Median serum concentration ↓ by about 59 % and *C/D* ratio ↓ 71 % [104, 105]
	Quetiapine	*C/D* ratio dramatically ↓ 9-fold, CL ↑ 7.49-fold [109]
	Ziprasidone	AUC ↓ 36 % with modest induction [111]
	Aripiprazole	Mean AUC ↓ 71 % and CL ↑ 4-fold [112]
Lamotrigine	Clozapine	No significant changes [114]
	Risperidone	No significant changes [114]
	Olanzapine	No significant changes detected in 2 in-depth pharmacokinetic studies [115, 116]
Phenobarbital	Clozapine	Significantly ↓ plasma concentrations; when phenobarbital was discontinued, a 56 % ↑ in the plasma clozapine concentration was seen [119, 120]
Phenytoin	Quetiapine	CL ↑ 5-fold [121]
Valproic acid	Clozapine	Variable results reported (↑ and ↓) [79, 124–126]
	Risperidone	No significant changes [101]
	Olanzapine	Plasma concentrations ↓ 53 % with ↑ psychosis in 3/4 patients, another study reported a 20 % ↓ in plasma concentrations [127, 128]
	Aripiprazole	AUC ↓ 26 % with CL ↑ 24 % [129]

AUC area under the plasma concentration–time curve, *C/D* concentration/dose ratio, *CL* clearance, ↑ increase(d), ↓ decrease(d)

Kennedy WK et al CNS Drugs 2013

Table 4. Practical summary of newer antidepressants and SGA drug interactions.

Antidepressants	SGAs	Outcome	Actions
PK DI. Fluoxetine		↑ level several weeks* after adding fluoxetine	In the absence of TDM use dose correction factor:‡
	Aripiprazole, iloperidone, risperidone,	↓ level several weeks* after D/C fluoxetine	0.5
	Clozapine, olanzapine		0.75
	Lurasidone, quetiapine		Unknown in clinical conditions
	Asenapine, amisulpride, paliperidone, ziprasidone		Possibly no clinically relevant changes
PK DI. Paroxetine		↑ level 1 week after adding paroxetine	In the absence of TDM use dose correction factor:‡
	Aripiprazole, risperidone, iloperidone	↓ level 1 week after D/C paroxetine	0.5
	Clozapine		0.8
	Asenapine, amisulpride, lurasidone, olanzapine paliperidone, quetiapine, ziprasidone		Possibly no clinically relevant changes
PK DI. Fluvoxamine		↑ level 1 week after adding fluvoxamine	In the absence of TDM use dose correction factor:‡
	Clozapine	↓ level 1 week after D/C fluvoxamine	0.1 – 0.2. Use TDM; varies according to individual
	Olanzapine		0.5
	Asenapine, aripiprazole, iloperidone, lurasidone, quetiapine, risperidone		Caution (not well studied, current approximation 0.5 – 0.75)
	Amisulpride, paliperidone, ziprasidone		Possibly no clinically relevant changes

Table 4. Practical summary of newer antidepressants and SGA drug interactions.

Antidepressants	SGAs	Outcome	Actions
PK DI. Sertraline. It may be relevant only in high doses	Aripiprazole, clozapine, iloperidone, risperidone	↑ level 1 week after adding sertraline ↓ level 1 week after D/C sertraline	Be aware Monitor for ADRs (after adding) and lack of efficacy (after D/C) Consider TDM
	Asenapine, amisulpride, lurasidone, olanzapine paliperidone, quetiapine, ziprasidone		Possibly no clinically relevant changes
PD DI. Bupropion and duloxetine	Aripiprazole, risperidone, iloperidone	↑ level 1 week after adding bupropion or duloxetine ↓ level 1 week after D/C bupropion or duloxetine	Be aware Monitor for ADRs (after adding) and lack of efficacy (after D/C) Consider TDM
	Asenapine, amisulpride, clozapine, lurasidone, olanzapine paliperidone, quetiapine ziprasidone		Possibly no clinically relevant changes
PK DI. Paroxetine or venlafaxine	Asenapine may be an inhibitor of paroxetine or venlafaxine	↑ level 1 week after adding asenapine ↓ level 1 week after D/C asenapine	Be aware Monitor for ADRs (after adding) and lack of efficacy (after D/C)
PD DI. Bupropion	All SGAs	Weight loss	Be aware

Table 4. Practical summary of newer antidepressants and SGA drug interactions (continued).

Antidepressants	SGAs	Outcome	Actions
PD DI. Bupropion	All SGAs (clozapine>olanzapine, quetiapine >other)[§]	↑ risk for seizures	Be aware
PD DI. Bupropion	All SGAs when used in psychosis	May rarely cause psychotic exacerbations	Be aware
PD DI. Mirtazapine	All SGAs	Weight gain and increased metabolic ADRs ↑ sedation risk from most SGAs	Be aware Monitor for ADRs
PD DI. Mirtazapine, paroxetine and reboxetine	Clozapine, olanzapine, high quetiapine doses	↑ risk for antimuscarinic ADRs	Be aware Monitor for ADRs
PD DI. Desvenlafaxine, duloxetine, levominalcipran, milnacipran and venlafaxine	Clozapine	↑ risk for tachycardia and/or hypertension	Be aware Monitor for ADRs
PD DI. Most newer antidepressants	Aripiprazole, lurasidone, ziprasidone	Possible additive risk for nausea and vomiting	Monitor closely
PD DI. SSRIs	SGAs	Possible additive risk for ↑ QTc	Be vigilant (can be lethal) Consider need for ECG

Interactions entre SSRI et anti-psychotiques de 2nd génération sont souvent cliniquement significatives

TDM peut être utile mais concentrations pas toujours corrélées à l'effet clinique

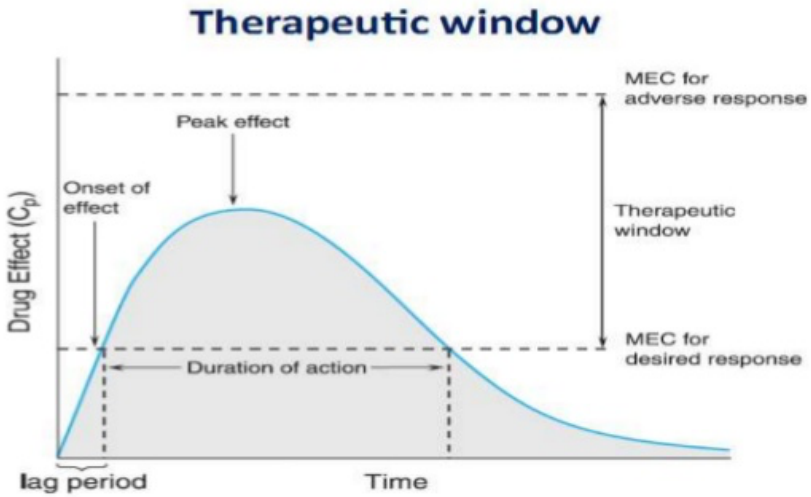

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Table 2 Suggested therapeutic plasma concentration ranges of second-generation antipsychotics [39–41]

Drug	Plasma concentration (ng/mL or µg/L)	Level of recommendation
Clozapine	350–600 [39]	1 (strong)
Risperidone (+ 9-hydroxyrisperidone)	20–60 [39]	2 (recommended)
Paliperidone	20–52 [40]	2 (recommended)
Olanzapine	20–80 [39]	1 (strong)
Quetiapine	70–170 [39]	3 (useful)
Ziprasidone	50–120 [39]	4 (probably useful)
Aripiprazole	150–300 [41]	5 (not recommended)
Iloperidone	None recommended	
Asenapine	None recommended	
Lurasidone	None recommended	

➔ Nécessité d'études PKIN et de publications de cas cliniques


case reports

Gee *et al. BMC Psychiatry* (2015) 15:195
DOI 10.1186/s12888-015-0536-4

BMC Psychiatry

CASE REPORT Open Access

Optimising plasma levels of clozapine during metabolic interactions: a review and case report with adjunct rifampicin treatment

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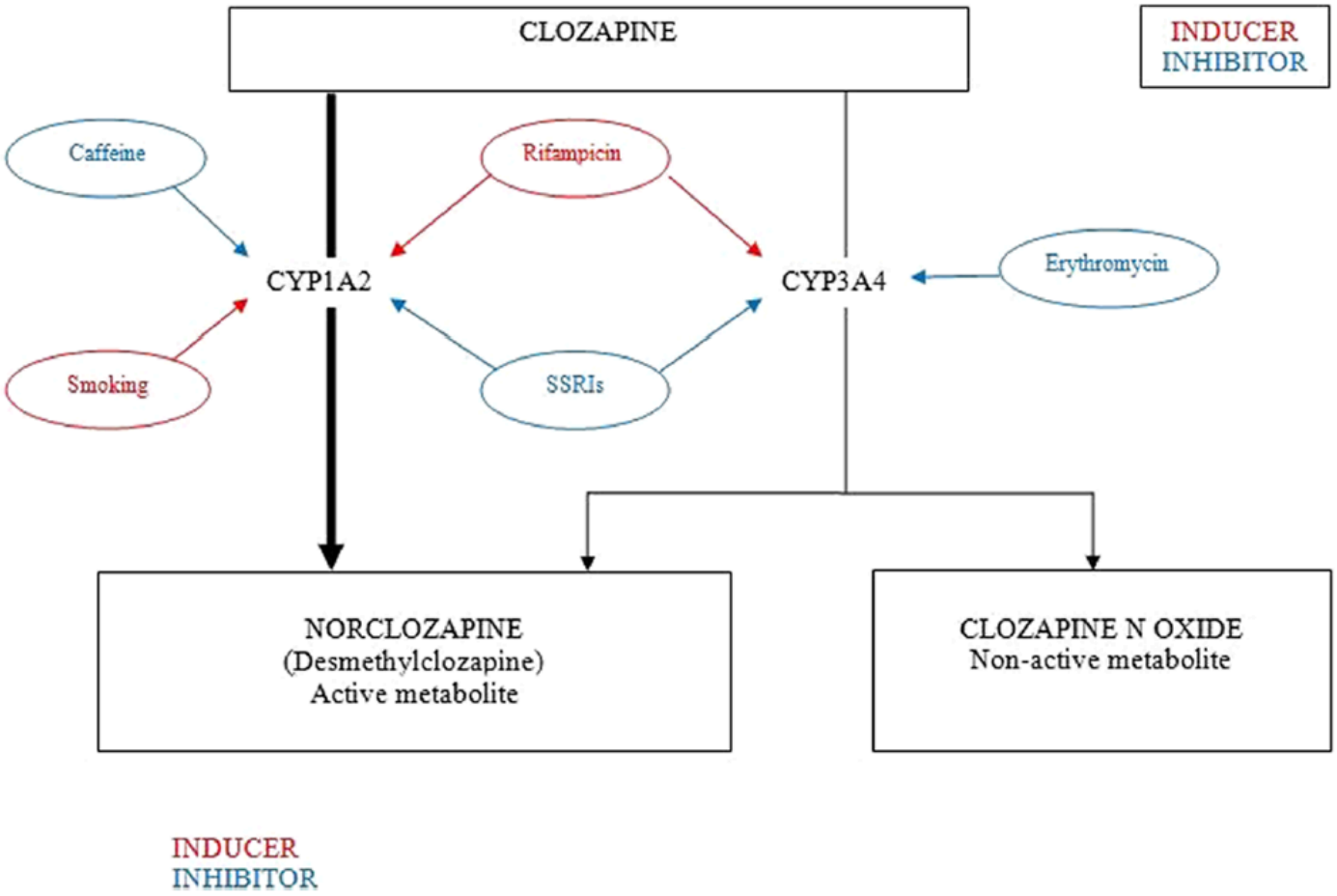

Fig. 1 The main clozapine metabolic pathways and pharmacokinetic interactions

Arrêt de Fluoxetine
Perte de inhibition 1A2-3A4
Faible-modéré

Début de traitement antituberculeux Anticipation de induction avec rifampicine (forte de 3A4 et modérée de 1A2)

Arrêt de rifampicine
Perte d'induction de 3A4 et de 1A2

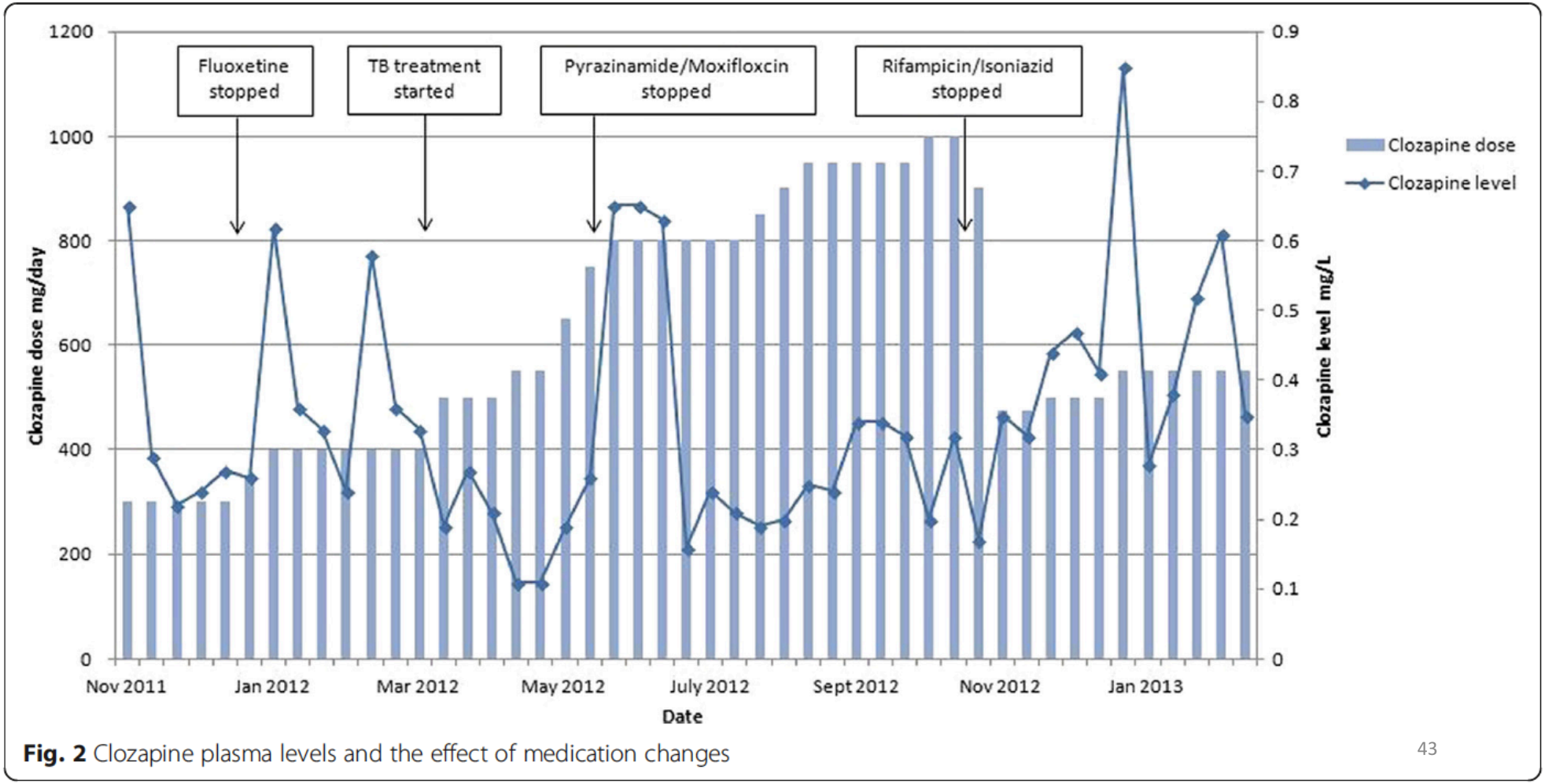

Fig. 2 Clozapine plasma levels and the effect of medication changes

*CYP2D6 *6/*6* genotype and drug interactions as cause of haloperidol-induced extrapyramidal symptoms

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[3]Clinical Unit of Clinical Pharmacology & Toxicology, Department of Medicine, University Hospital Centre Sisters of Charity, Zagreb, Croatia

Pharmacogenomics 2016

- Ciprofloxacine (5 jours, après plusieurs TTMT anti-infectieux inefficaces)

  Inhibiteur puissant de 1A2 et modéré de 3A4

- Traitement par Haldol 1 mg bid

  Métabolisé par CYP2D6 et secondairement par CYP3A4 et UGT2B7

- Syndrôme Extra-Pyramidal rapide et sevère …..
- Génotypage *6/*6 ➔ métaboliseur lent de 2D6

  ➔ CYP3A4 est devenue voie majeure de métabolisme

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Review

Interactions between valproic acid and quetiapine/olanzapine in the treatment of bipolar disorder and the role of therapeutic drug monitoring

Thomas Vella and Janet Mifsud

Department of Clinical Pharmacology and Therapeutics, University of Malta, Msida, Malta.

Journal of Pharmacy and Pharmacology, **66**, pp. 747–759

Combinaison Acide Valproique + Olanzapine ou Quetiapine : bien tolérée

Etudes d'interactions peu conclusives (effectif, pas d'essai croisé …)

Interaction complexe et intérêt du suivi thérapeutique

Diminution des concentrations d'olanzapine

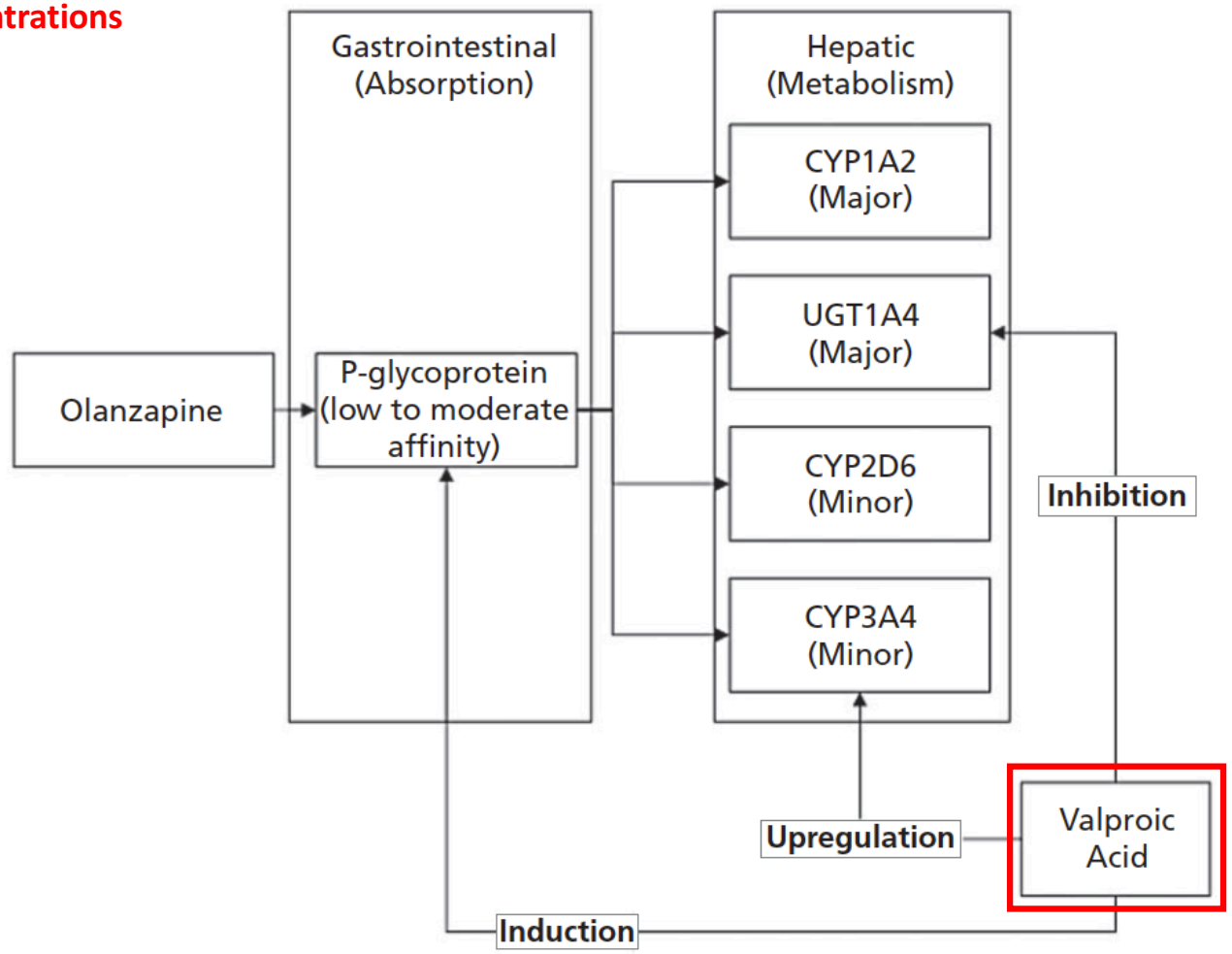

Figure 1 Possible sites of interaction between valproic acid and olanzapine accounting for the decrease in plasma concentration of olanzapine.

Augmentation des concentrations de quetiapine

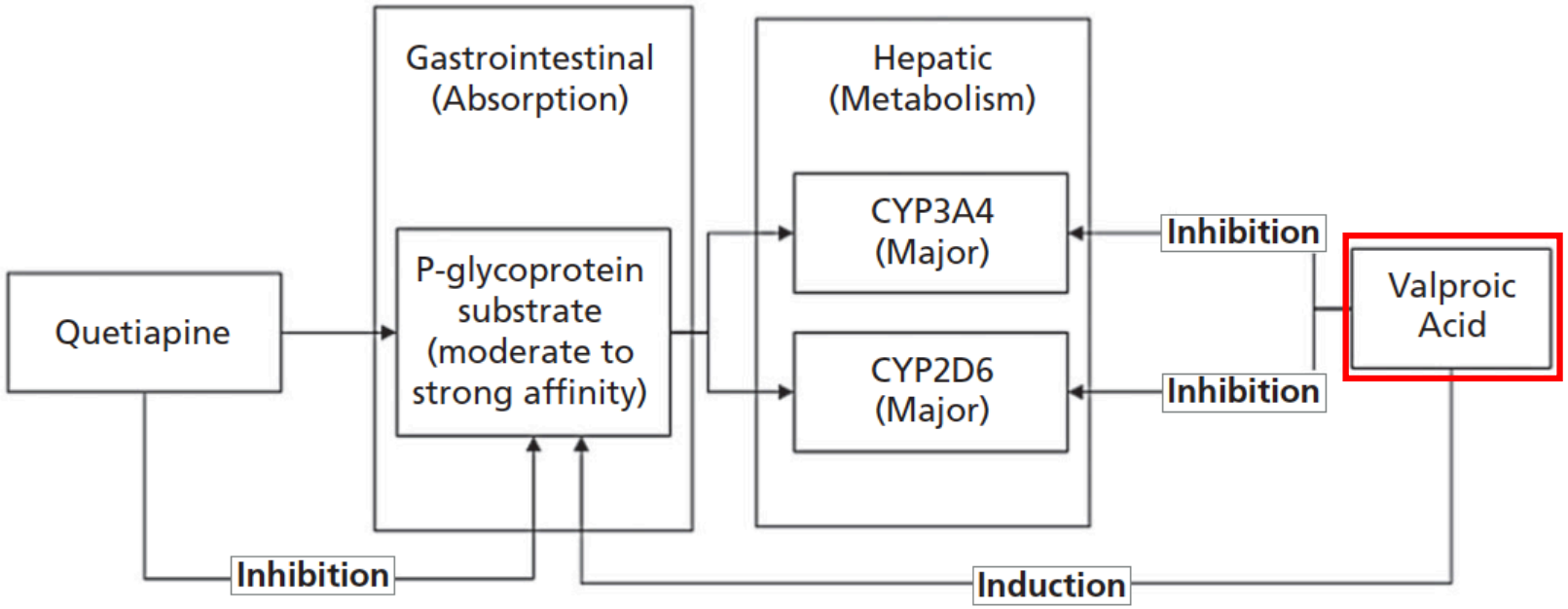

Figure 2 Possible sites of interaction between valproic acid and quetiapine accounting for the increase in plasma concentration of quetiapine.

Pharmacokinetic Drug-Drug Interactions of Mood Stabilizers and Risperidone in Patients Under Combined Treatment

Georgios Schoretsanitis, MD,† Ekkehard Haen, MD, PhD,‡ Gerhard Gründer, MD,* Benedikt Stegmann, PhD,‡ Koen R. J. Schruers, MD, PhD,§ Christoph Hiemke, PhD,|| Sarah E. Lammertz, PhD,* and Michael Paulzen, MD**

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Journal of Clinical Psychopharmacology • Volume 36, Number 6, December 2016

TABLE 2. Median (and Range) Plasma Concentrations and Metabolic Ratios of Risperidone in the Study Groups

Group	RIS, ng/mL	9-OH-RIS, ng/mL	RIS + 9-OH-RIS, ng/mL	RIS/9-OH-RIS
Valproate (R_{VPA})	7.0*(0.1–252.0)	16.0 (1.2–147.0)	27.0 (1.7–255.7)	0.363*(0.009–68.1)
Lamotrigine (R_{LMT})	6.4† (0.2–60.9)	15.5 (2.0–83.5)	23.5 (8.0–144.4)	0.525† (0.008–27.0)
Carbamazepine (R_{CBZ})	4.0 (0.2–42.0)	9.6‡ (1.9–55.0)	14.8‡ (3.3–57.9)	0.333 (0.052–5.25)
Control (R_0)	4.4 (0.1–224.0)	17.0 (0.3–196.5)	24.0 (1.8–264.0)	0.262 (0.003–23.68)

Drug-Drug Interaction Studies of Paliperidone and Divalproex Sodium Extended-Release Tablets in Healthy Participants and Patients with Psychiatric Disorders

The Journal of Clinical Pharmacology
2016, 56(6) 683–692

DOI: 10.1002/jcph.648

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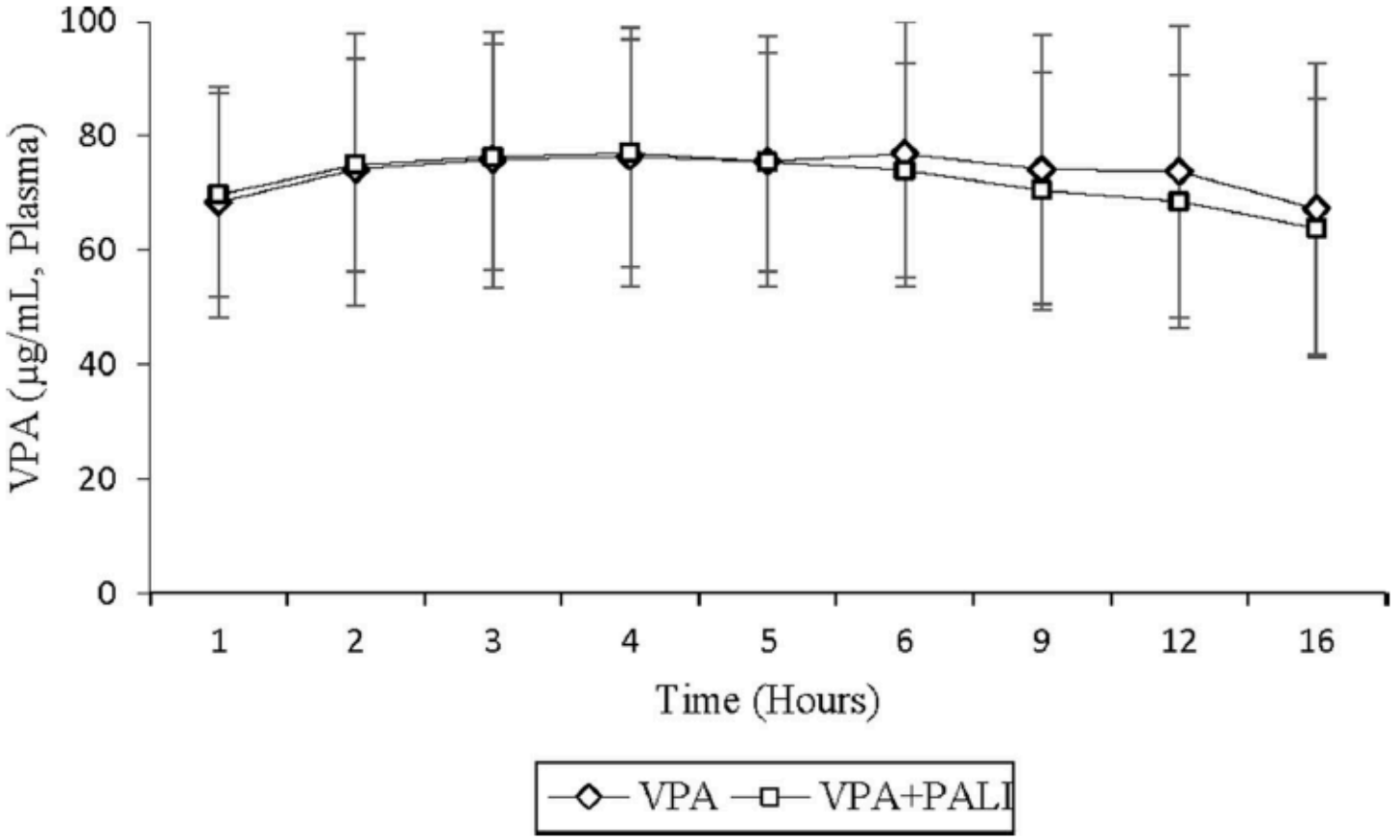

Figure 2. Mean plasma concentration-time profile of VPA. Pali, Paliperidone ER; VPA, valproic acid; SD, standard deviation.

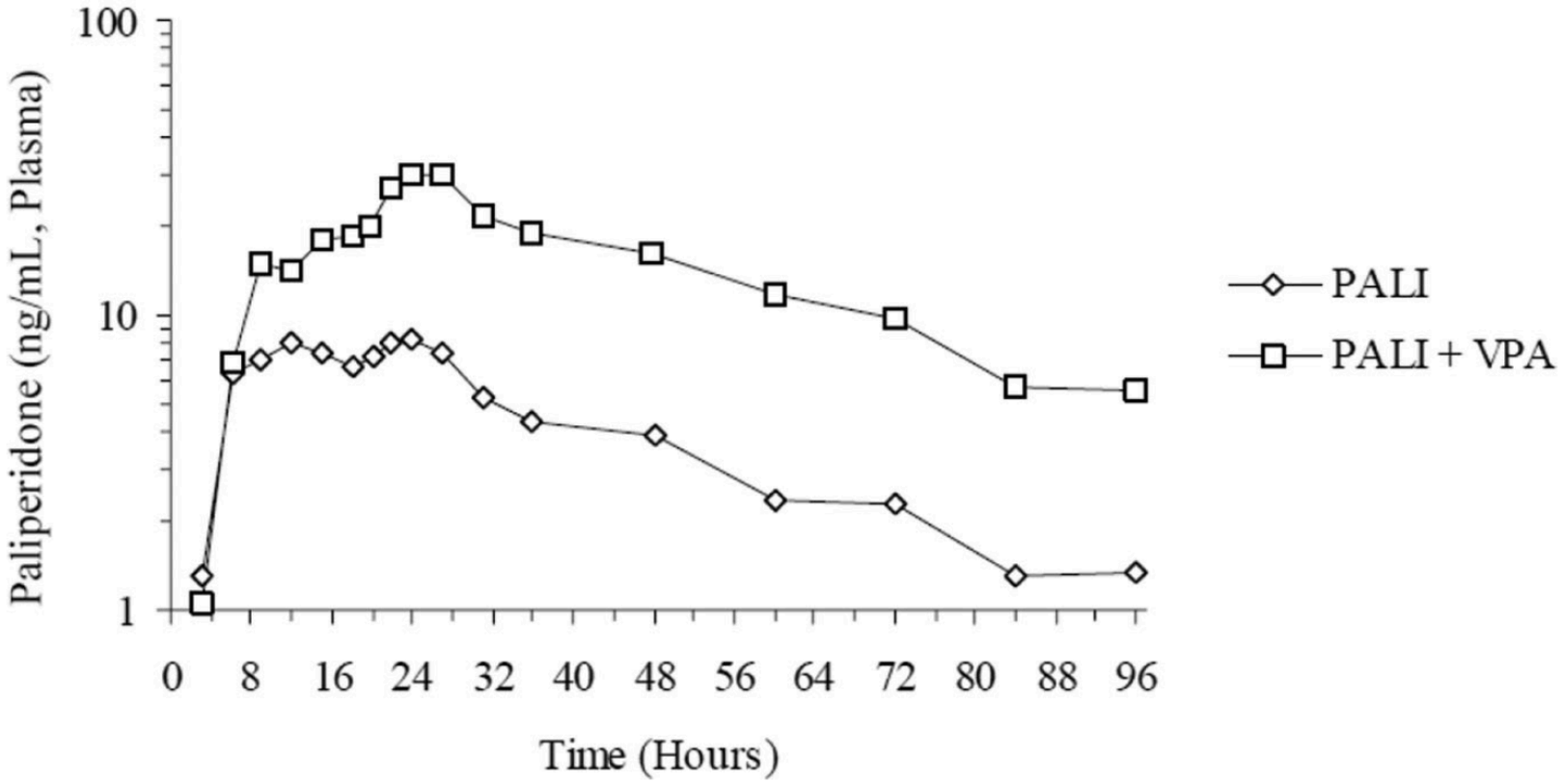

Figure 3. Linear and semilogarithmic individual plasma concentration-time profiles of paliperidone (of a typical participant with high geometric mean ratio). Pali, paliperidone ER; VPA, valproic acid.

Paliperidone

- Excrétion rénale à 50 %

- Métabolisme

    - CYP3A4, 2D6 et 2 voies métaboliques NON-CYP
    - chaque voie < 5 %

- Substrat de P-gp

Acide valproique

- Inhibiteur modéré de CYP 3A4 et 2D6
- inducteur de P-gp

Hypothèse : Interaction par augmentation de la durée de vidange gastrique …. Observé également en prise avec repas « high Fat-High Cal »

PHRC_National – lettre d'intention 2018

Etude PROMISE - Olivier BLIN APHM

Comment le recours à une médecine personnalisée via la pharmacogénétique associée au suivi thérapeutique pharmacologique peut diminuer le taux de rechute chez des patients atteints de schizophrénie: une étude comparative prospective, contrôlée, multicentrique, en aveugle.

Directions pour le futur :

1 - Modélisation PBPK pour

- extrapolation de dose ou entre Adulte et enfant,

- estimation de l'intensité de l'interaction

2 - Optimisation du moment de prise

Adultes

Enfants

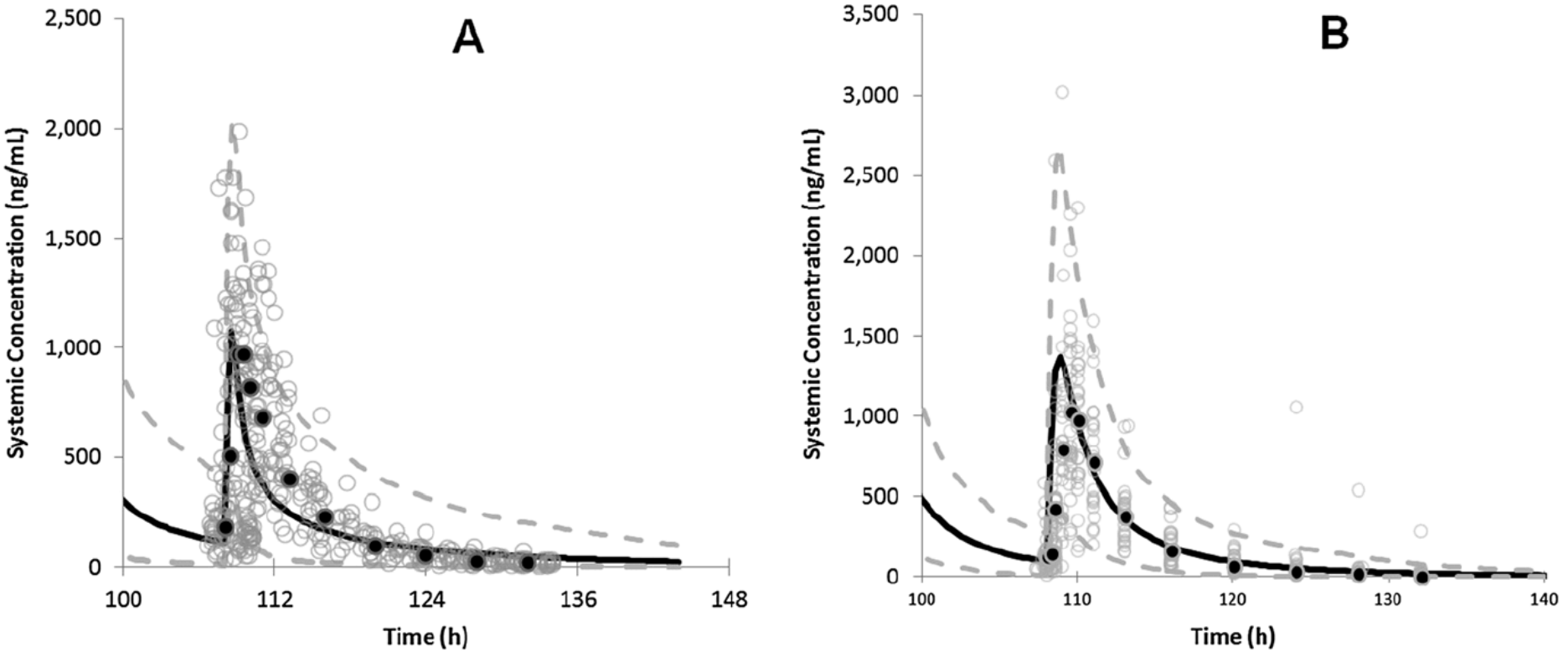

Figure 3. Simulated mean plasma drug concentration–time profile (solid black line) during dosing of 400 mg quetiapine b.i.d.

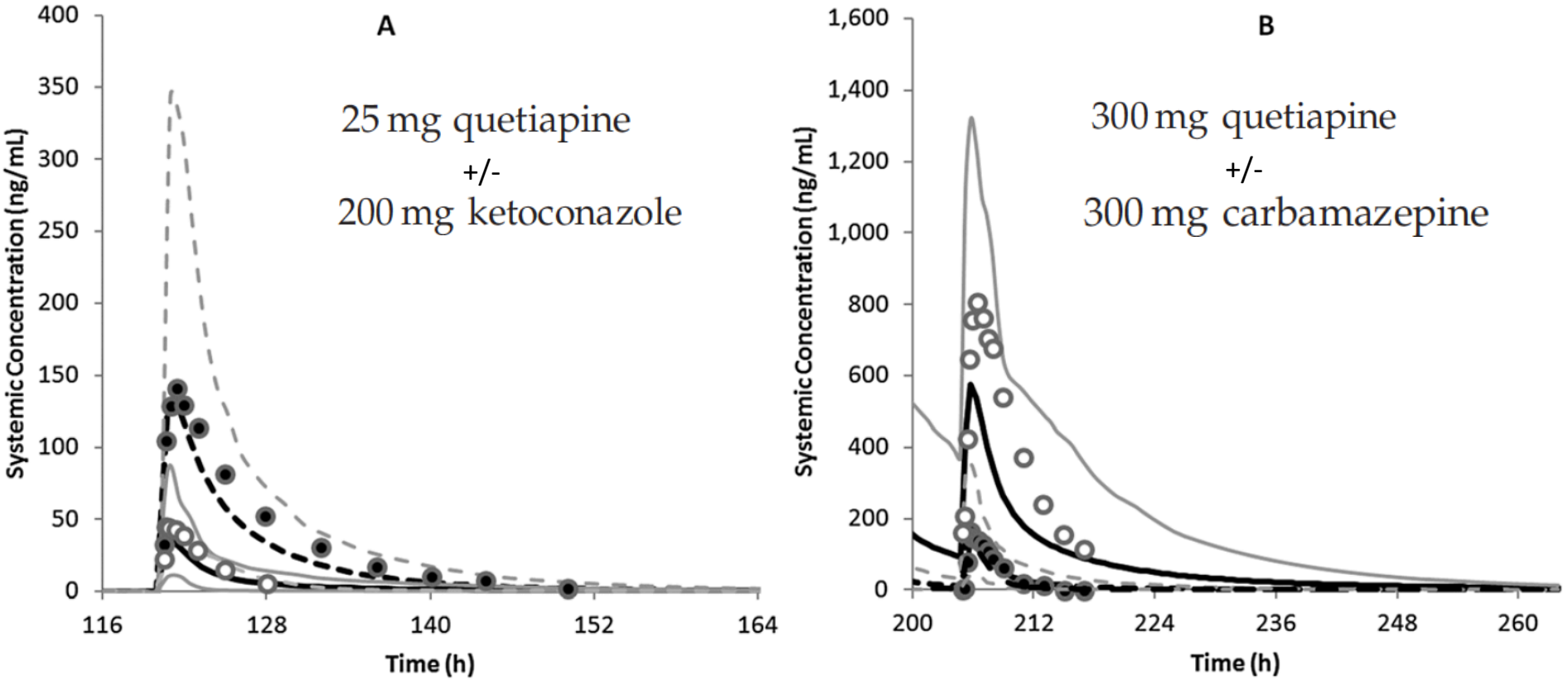

Figure 2. Simulated mean plasma drug concentration–time profile of quetiapine

Johnson TN et al Biopharm Drug Dispos 2014

Directions pour le futur :

1 - Modélisation PBPK pour

2 - Optimisation du moment de prise

Début du sommeil | sommeil tardif | **début d'activité** | activité tardive

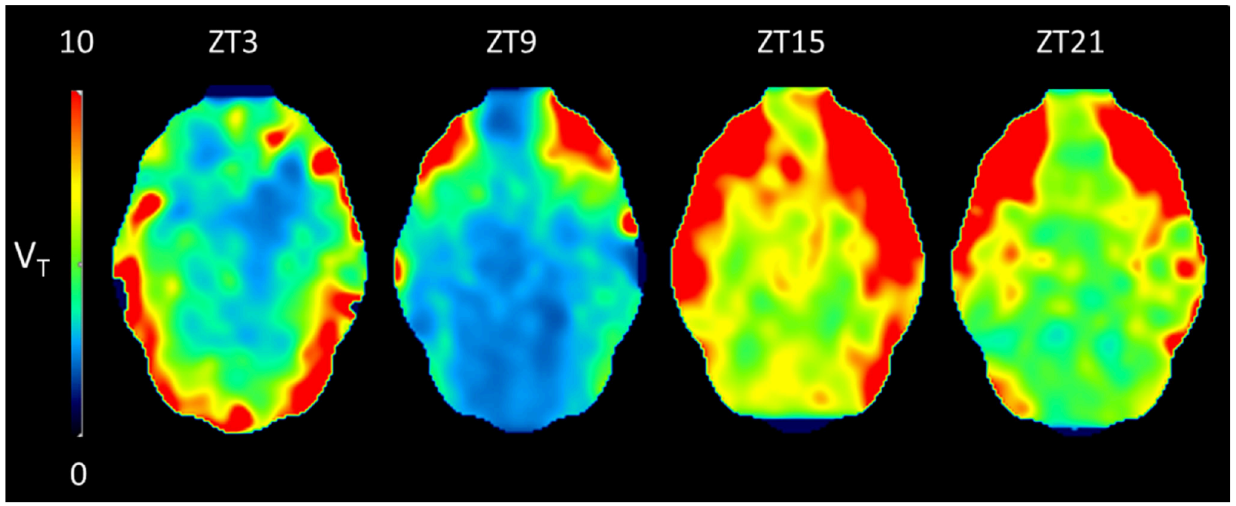

Fig. 4. Examples of parametric V_T-images in each group of the daily rhythm study (ZT3, ZT9, ZT15, and ZT21). Images were generated using a 1TCM (Alpert) fit in the PXMOD module of the PMOD software

Savolainen H et al AAPS J 2016

Directions pour le futur :

2 - Optimisation du moment de prise

- rythme circadien de fonctionnement de P-gp cérébrale (chez l'animal ….)

- transposition à l'homme ???

➔ prise matinal optimale pour médicaments substrats de P-gp (activité réduite de P-gp)

- interX nombreuses
- mécanismes complexes (CYP450’s et transporteurs)
- intensité variable, certaines significatives
- assez peu de recommandations de prescription
- choix pertinent de sources d’informations validées
- Nécessité de d’études prospectives et de publier des cas cliniques
- Place importante du pharmacien clinicien

OK le pharmacien vérifie les interX !!!!

Merci de votre attention