Drug-drug interactions about antipsychotics

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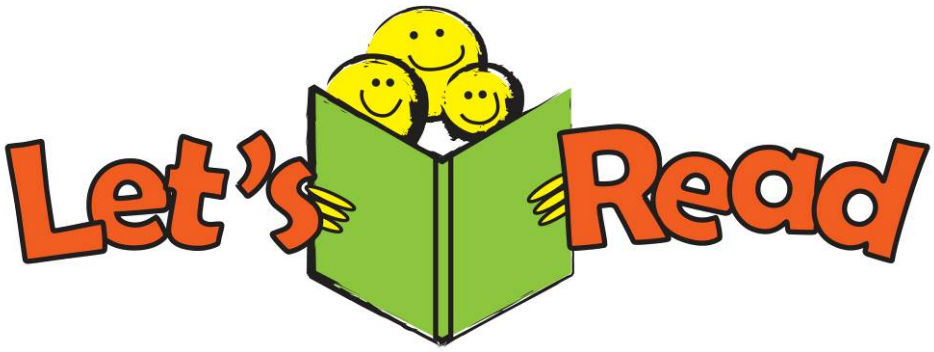
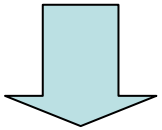


Introduction

- Drug-related morbidity and mortality are major medical issues with significant costs.

- Each year an estimated $177.4 billion is spent to address the treatment failures and new medical problems that are generated by adverse drug events.

- Such events occur in up to 40% of patients on five or more medications. It has been estimated that 6% to 10% of adverse events are drug-drug interactions and that 50% to 84% of adverse events are preventable through proper identification and surveillance.



A growing and sobering evidence base implicates drug-drug interactions as a major contributor to hospital admissions, treatment failures, avoidable medical complications, and subsequent health care costs.

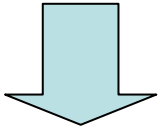
Psychiatric Services 63:1080–1088, 2012.

Introduction

- Patients with schizophrenia commonly receive multiple medications. 53% of patients with schizophrenia who used antipsychotic medication also received drug therapy for a comorbid chronic condition, such as HTN, DM, CAD.

- The risk of these events occurring from the use of antipsychotics may be heightened by concomitant drug therapy and exposure to potentially harmful drug-drug-interactions of medication pairs.

- Most antipsychotics are metabolized by the hepatic cytochrome P450 (CYP450) system. CYP450 enzymes CYP1A2, CYP2D6, and CYP3A4 are of particular importance to the metabolism of antipsychotics.



Drug-drug interactions are actually quite commonplace and are responsible for considerable patient morbidity and mortality.

Psychiatric Services 63:1080–1088, 2012.

Definition of drug-drug interaction

- The phenomenon that occurs when the effects or pharmacokinetics of a drug are altered by prior administration or coadministration of a second drug.

- 27 to 37% of potential DDIs in general prescriptions.

- The results of a drug interaction can be complex and unpredictable.

- Drug-drug interactions are a common problem during drug treatment and give rise to a large number of hospital admissions as a result of medically important, sometimes serious or even fatal adverse events.

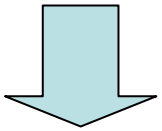
- The potential for drug-drug interactions is considered in the benefit-risk evaluation of a medicinal product and can negatively impact on this balance either through increased incidence of adverse events or reduced efficacy.

Types of drug-drug interaction

- Drug interactions are usually classified as pharmaceutical, pharmacodynamic and pharmacokinetic.

Pharmaceutical interactions

- Pharmaceutical interactions occur when drugs are mixed outside the body prior to administration.
- Mixing chemically incompatible drugs before intravenous infusion can result in precipitation or inactivation.
- An example is the incompatibility of phenobarbital with chlorpromazine or opioid analgesics when mixed in the same syringe.

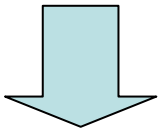


Least likely to cause problems in clinical practice, and there are no potentially hazardous interactions of this type with psychotropic drugs.

Types of drug-drug interaction

Pharmacodynamic interactions

- The most common interactions encountered in clinical practice.
- Ooccur when drugs compete for the same receptor or produce antagonistic or synergistic effects on the same target organ or system.
- Many instances of antagonism are beneficial: for example, naloxone is a specific antagonist that reverses the action of morphine.
- Synergistic interactions may be used therapeutically, for example in augmentation treatment of resistant depression with lithium and an antidepressant.



1. Should be notice whether the adverse reaction occur.
2. A common result is toxicity of the central nervous system (CNS) and hypertension or hypotension.

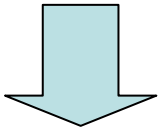
Types of drug-drug interaction

Pharmacokinetic interactions

- Occur when one compound alters the absorption, distribution, metabolism or excretion of another.

Absorption

- Usually result from the binding of two drugs in the gut, preventing their absorption.
- Decreased absorption of phenothiazines or sulpiride when they are taken with antacids, leading to a reduced antipsychotic effect.
- This property is used therapeutically when activated charcoal is given following an overdose of tricyclic antidepressants.



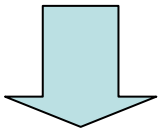
Important clinical effects caused by changes in drug absorption are rarely seen in general medical or psychiatric practice.

Types of drug-drug interaction

Pharmacokinetic interactions

Distribution -- Protein binding

- The most frequently recognised, because many psychotropic drugs are bound to plasma proteins.
- Reduced protein binding increases the free drug fraction and therefore the effect of the drug.
- Drugs that are highly protein bound (>90%), such as phenytoin, are most prone to interactions mediated by this mechanism.
- Although the plasma level of the free drug rises briefly, the increased metabolism rapidly restores the level to the previous steady state.



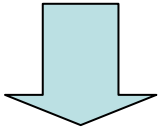
The effects of protein displacement are usually not of clinical significance in either general medical or psychiatric practice

Types of drug-drug interaction

Pharmacokinetic interactions

Metabolism

- Induction / inhibition of enzymes involved in drug metabolism results in reduced / increased plasma concentrations of drugs.
- The most important enzymes involved in drug interactions are members of the cytochrome P450 (CYP) system.
- Many psychotropic drugs have a high affinity for one or more of the enzymes in the CYP or UGT systems, which play a major role in their metabolism.



Induction and inhibition of the activity of drug-metabolising enzymes, maybe the potential reason to precipitate hazardous drug interactions.

UGTs = uridine diphosphate glucuronosyltransferases

Types of drug-drug interaction

Pharmacokinetic interactions

Metabolism

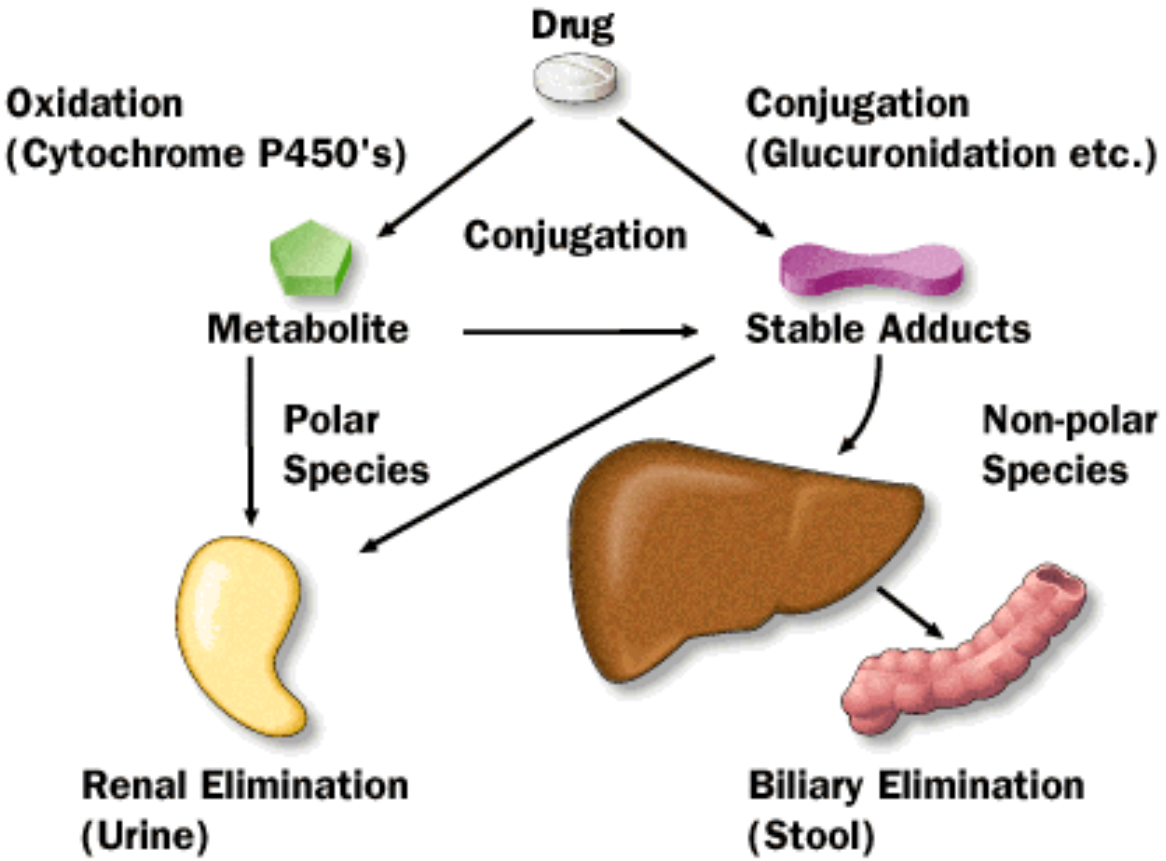
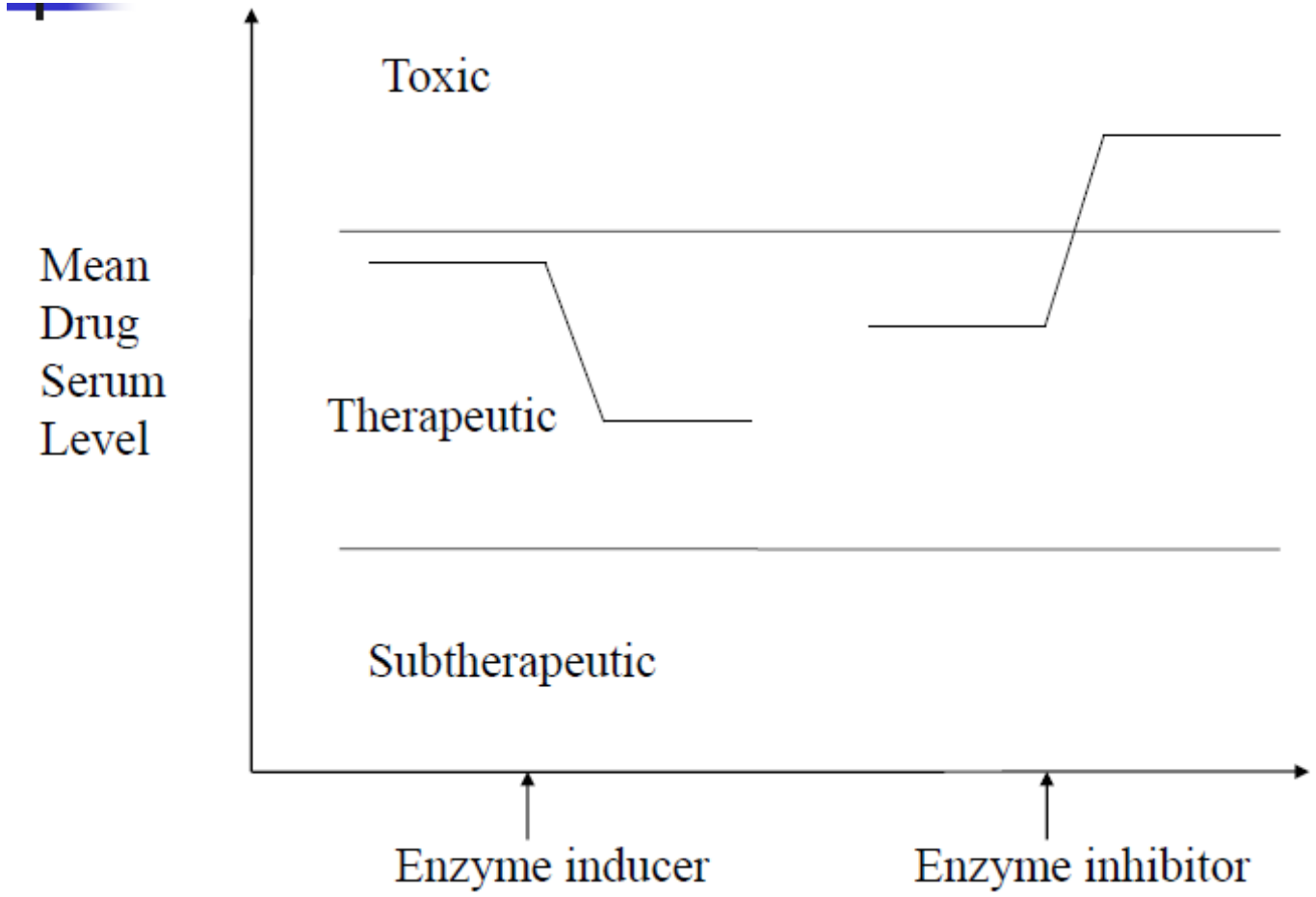


Table 2. Inhibitors and Inducers of Antipsychotic-Metabolizing Cytochrome P450 Enzymes

Cytochrome P450 (CYP) Enzyme Subtype	Inhibitor	Inducer
CYP1A2 Involved in metabolism of clozapine, olanzapine	Fluvoxamine Grapefruit juice in large quantities	Cigarette smoking
CYP2D6 Involved in metabolism of clozapine, olanzapine, risperidone	SSRIs (especially fluoxetine, paroxetine, high-dose sertraline)	
CYP3A4 Involved in metabolism of clozapine, quetiapine, ziprasidone	Erythromycin and other macrolide antibiotics Ketoconazole and other antifungal drugs Protease inhibitors	Barbiturates Carbamazepine Phenytoin Rifampin Glucocorticoids

Abbreviation: SSRI = selective serotonin reuptake inhibitor.

Mean drug blood level response to an enzyme inducer or enzyme inhibitor

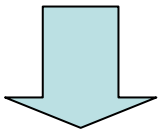


Types of drug-drug interaction

Pharmacokinetic interactions

Excretion

- Most clinically significant drug interactions involving excretion relate to the kidneys.
- The most important of these in psychiatric practice are interactions with lithium.
- Lithium is filtered by the kidney and reabsorbed by the proximal renal tubule in parallel with sodium.
- A sustained increase in urinary sodium excretion such as that produced by thiazide diuretics promotes a compensatory reabsorption of sodium by the proximal renal tubule.



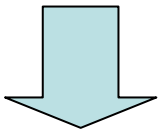
Lithium reabsorption is similarly enhanced, and because it has a narrow therapeutic index this can increase the plasma lithium concentration to potentially toxic levels.

Types of drug-drug interaction

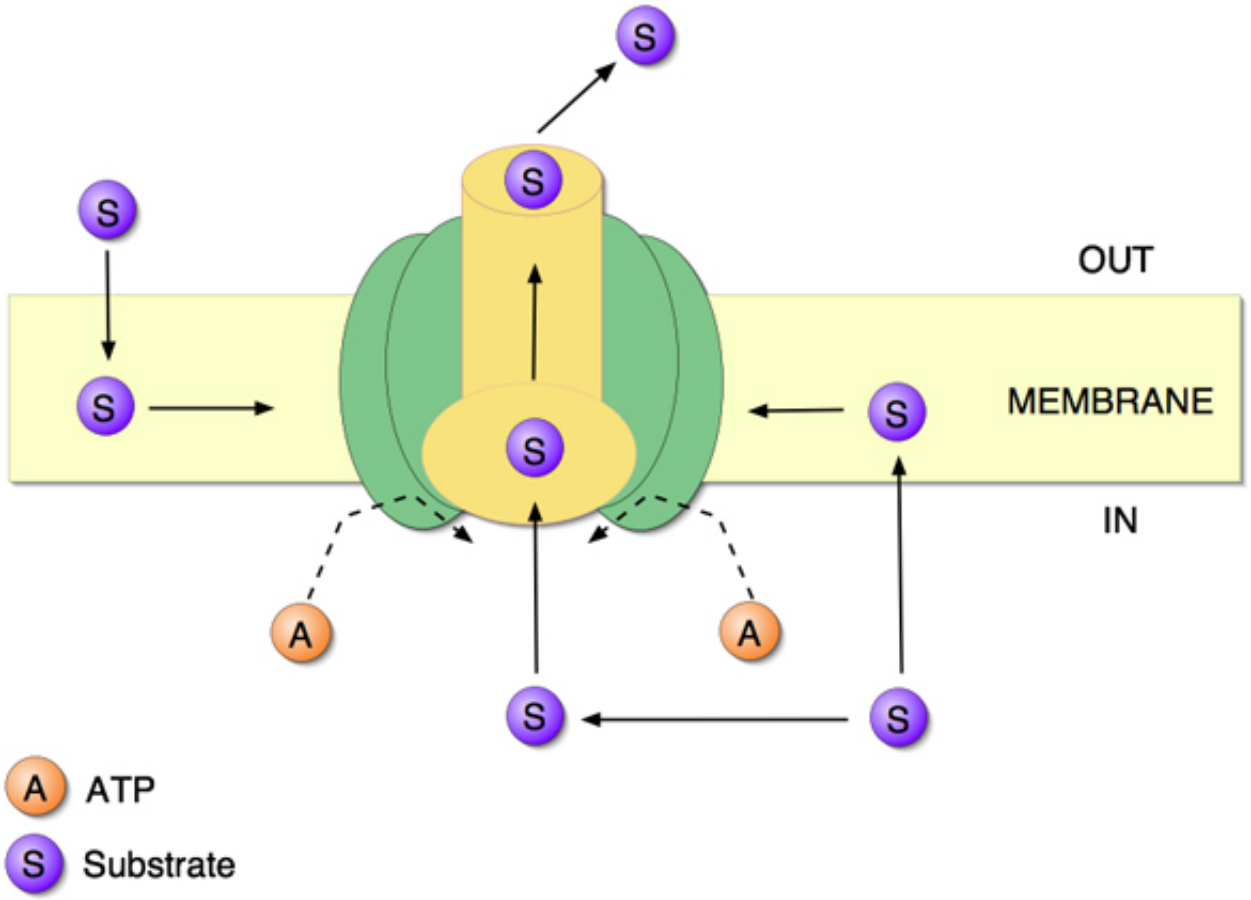
Pharmacokinetic interactions

P-glycoprotein

- A specific cell membrane transport protein known as P-glycoprotein (P-gp).
- P-glycoprotein is involved in drug absorption, distribution and excretion.
- It is a multidrug efflux transporter highly expressed in the small intestine, brain, liver and kidney.
- It acts as a natural defense mechanism against several drugs by limiting their absorption from the gut and penetration into the brain and promoting their elimination in the bile and urine.



Fluoxetine, fluvoxamine, paroxetine and sertraline, as well as many SGAs, such as risperidone, paliperidone, olanzapine, aripiprazole and ziprasidone, are substrates of P-gp. (inhibitors)



The P-glycoprotein molecule spans the cell membrane and in this way is in contact not only with the membrane but also the inside and the outside of the cell. The central portion of the molecule is a channel or pore through which toxic chemicals are pumped back out into the environment. The toxic chemicals can enter the transport pore either from the interior of the cell or from its membrane as shown. Molecules of ATP power the pumping action.

Types of drug-drug interaction

Table 1 Types and examples of drug interactions

Interaction type	*Example*
Pharmacodynamic	
Direct	Tricyclic antidepressant + monoamine oxidase inhibitor → CNS toxicity
Indirect	Selective serotonin reuptake inhibitor + aspirin → increased risk of gastrointestinal bleeding
Pharmacokinetic	
Absorption	Beneficial: charcoal adsorbs tricyclic antidepressant → decreased absorption of tricyclic overdose → decreased plasma concentration → less toxicity Undesirable: antacids → decreased absorption of phenothiazines → decreased plasma concentration and therapeutic effect of phenothiazines
Distribution	Diazepam displaces phenytoin from plasma proteins → increased plasma concentration → increased side-effects of phenytoin
Metabolism	Carbamazepine → induction of CYP3A4 → increased metabolism → decreased plasma concentration of risperidone → decreased therapeutic effect of risperidone
	Protease-inhibiting antiviral drugs → inhibition of CYP3A4 → increased plasma concentration of thioridazine → ventricular arrhythmias

Review

Clinically relevant interactions between newer antidepressants and second-generation antipsychotics

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Expert Opin. Drug Metab. Toxicol. 10 (5) : 721-746, 2014

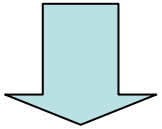
Background

- Antipsychotic (AP) drugs can be similarly divided into traditional or first-generation antipsychotics (FGAs) and atypical or second-generation APs (SGAs).

- SGAs have become the mainstream treatment intervention for patients with schizophrenia and bipolar disorder due to a lower risk for acute and chronic extrapyramidal symptoms and prolactin elevation as compared to traditional APs.

- In view of the frequent co-prescription of newer antidepressants and SGAs, information on potential drug interactions (DIs) between these compounds is important for safe prescribing.

- The aim of the present article is to provide an updated review of clinically significant DIs between newer antidepressants and SGAs.



Articles for this review were obtained from PubMed search with no time limit. Only articles published in peer-reviewed journals were included, while meeting abstracts were excluded.

成分及商品名對照表

藥理分類	成分名	商品名
SSRI	Citalopram	Citao® 20mg
	Escitalopram	Lexapro® 10mg
	Fluoxetine	Prozac® 20mg　Sinzac® 20mg
	Fluvoxamine	Genbou® 50mg　Lote® 100mg
	Paroxetine	Setine® 20mg
	Sertraline	Kinloft® 50mg　You-Jet® 50mg
SNRI	Duloxetine	Cymbalta® 30mg
	Milnacipran	Milpran® 50mg
	Venlafaxine	Rafax XR® 75mg
Other newer	Agomelatine	Valdoxan® 25mg
	Bupropion	Wellbutrin SR® 150mg　Funnix® 75mg
	Mirtazapine	Mirtazapine® 30mg　Remeron® 30mg

成分及商品名對照表

藥理分類	成分名	商品名
SGAs	Amisulpride	Ribelite® 200mg Solian® 200mg Cospirit® 400mg
	Aripiprazole	Abilify® 10mg Ariple® 10mg
	Clozapine	Clopine® 100mg / 25 mg Clozaril® 100mg
	Olanzapine	Nodoff® 5mg Olandus® 10mg Olan OD® 5mg Zyprexa OD® 5mg
	Paliperidone	Invega® 6mg Invega® 3mg
	Quetiapine	Queropin® 300mg Seroquel® 300mg Seroquel XR® 50mg Utapine® 200mg / 100mg / 25mg
	Risperidone	Apa-risdol® 2mg / 3mg Spiterin® 2mg Apo-risperidone sol 1mg/ml Risperidal Consta® ing 37.5mg / 25mg
	Ziprasidone	Geodon® 40mg

PK parameters of newer antidepressants

	Bioavailability (%)	Protein binding (%)	Half-life (h)	Metabolism	Active metabolites	Inhibitory effect or 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)

	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 (wea
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		

PK parameters of SGAs

	Bioavailability (%)	Protein binding (%)	Half-life (h)	Metabolism	Active metabolites
Amisulpride	43 - 48	17	12	Unchanged renal excretion	
Aripiprazole	87	99	48 - 68	CYP2D6, CYP3A4	Dehydroaripiprazole
Asenapine	35*	95	1 - 2	UGT 1A4, CYP1A2	
Clozapine	12 - 81	95	6 - 33	CYP1A2 (major), CYP2C19, CYP3A4, CYP2D6	Norclozapine§
Iloperidone	96	93	20 - 24	CYP2D6 (major), CYP3A4	P88¶ P95
Lurasidone	9 - 19‡	99	18	CYP3A4	ID-14823
Olanzapine	60 - 80	93	20 - 70	CYP1A2 (major), UGT1A4, CYP2D6, FMO	
Paliperidone	28	30	24	Minimal hepatic metabolism	
Quetiapine	NA	83	5 - 8	CYP3A4	Norquetiapine
Risperidone	68	90	3 - 24	CYP2D6 (major), CYP3A4	9-hydroxyrisperidone
Ziprasidone	60‡	99	4 - 10	CYP3A4, Aldehyde oxidase	

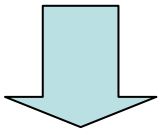
Fluoxetine's interaction

- Fluoxetine and its metabolite norfluoxetine are potent inhibitors of CYP2D6 and moderate inhibitors of CYP2C9, while they mildly to moderately affect the activity of CYP2C19 and CYP3A4.

With Clozapine

- Fluoxetine may impair the elimination of clozapine resulting in an increase of approximately 40~70% of its plasma concentrations in patients concomitantly treated with fluoxetine 20 mg/day.

- During fluoxetine administration, mean plasma concentrations of clozapine and norclozapine increased significantly ($p < 0.01$) by 58 and 36%, respectively.



A study controlling other variables estimated that fluoxetine increases plasma clozapine concentration by 36% on average, which requires multiplying the clozapine dose by 0.73 to compensate.

Fluoxetine's interaction

With Risperidone

- In 10 schizophrenic patients stabilized on risperidone (4~6 mg/day), coadministration of fluoxetine (20 mg/day) for 4 weeks caused a significant elevation (by 75%; $p < 0.01$) of plasma concentration of the active fraction of risperidone.

- This interaction is presumably due to inhibition of CYP2D6.

- A reduction in risperidone dosage is advisable in case of concomitant administration of fluoxetine.

With Aripiprazole

- In patients co-medicated with CYP2D6 inhibitors (including 9 subjects on fluoxetine) dose-normalized serum concentrations of aripiprazole were 45% higher compared with controls ($p < 0.05$).

Paroxetine's interaction

- Paroxetine is a potent inhibitor of CYP2D6, while it only minimally affects other CYPs.

With Risperidone

- 10 schizophrenic patients stabilized on risperidone therapy (4 -- 8 mg/day), coadministration of paroxetine (20 mg/day) for 4 weeks resulted in a mean, statistically significant increase by 45% ($p < 0.05$) in plasma concentrations of the active fraction of risperidone.

- Paroxetine resulted in a dose-dependent increase in risperidone and active moiety plasma concentrations.

- An initial low dose of paroxetine (10 or 20 mg/day) may be safe whenever paroxetine is coadministered with risperidone.

Paroxetine's interaction

With Clozapine

- A moderate elevation of plasma clozapine concentrations (by approximately 20 ~40%), presumably not associated with clinically relevant effects, following administration of therapeutic doses of paroxetine, 20 mg/day.

- A study controlling other variables estimated that paroxetine increased plasma clozapine concentration on average by 30%, which requires multiplying the clozapine dose by 0.77 to compensate.

With Aripiprazole

- Plasma concentrations of the sum of aripiprazole and its active metabolite during coadministration of paroxetine 10 and 20 mg/day were also significantly higher (1.4- and 1.5-fold) than those before paroxetine coadministration.

- In a study of healthy subjects, coadministration of paroxetine (20 mg/day) decreased systemic clearance of aripiprazole by 23~58%.

Fluvoxamine's interaction

- It is a potent inhibitor of CYP1A2 and CYP2C19 and a moderate inhibitor of CYP2C9 and CYP3A4, while it affects CYP2D6 activity only slightly.

With Clozapine

- Concomitant administration of fluvoxamine (50 ~100 mg/day) may cause a 5~10-fold increase in plasma concentrations of clozapine, along with signs of toxicity (nausea, dizziness, extrapyramidal symptoms).

- Clinicians should be aware of a DI between clozapine and fluvoxamine.

- Downward dosage adjustments of clozapine may be necessary.

Fluvoxamine's interaction

With Olanzapine

- Fluvoxamine (50~100mg/day) may also elevate plasma levels of olanzapine approximately 2-fold, presumably through inhibition of CYP1A2, with possible ADR occurrence.

- The magnitude of the effect of fluvoxamine on plasma levels of olanzapine is lower than observed with clozapine, as olanzapine is metabolized by multiple enzyme systems, namely UGT.

- Low dose of fluvoxamine (25 mg/day) has been proposed as an adjunct to reduce olanzapine dose requirements as a cost-saving measure.

Fluvoxamine's interaction

With Risperidone

- On a chronic treatment with risperidone (3 ~ 6 mg/day), when patients receiving adjunctive treatment with fluvoxamine 200 mg/day, the concentration of risperidone increased slightly but significantly (by a mean of 26% over pretreatment) .

With Quetiapine

- In a large routine TDM program for quetiapine, concomitant administration with fluvoxamine was associated with a significant increase in quetiapine serum concentration--dose ratio.

With Aripiprazole

- In healthy subjects, coadministration of fluvoxamine (100 mg/day) resulted in a 40% decrease in the systemic clearance of a single 3 mg dose of aripiprazole.

- Inhibition of CYP3A4-mediated biotransformation of aripiprazole by fluvoxamine.

Sertraline's interaction

- It is a mild to moderate *in vitro* inhibitor of CYP2D6 and a weak inhibitor of the other CYP isoenzymes.

With Risperidone

- Risperidone (4~6 mg/day), co-medication with sertraline, 50~100 mg/day, for 8 weeks did not significantly change risperidone's concentration.

- The highest dose of sertraline, 150 mg/day, at week 8 total plasma risperidone concentrations were increased 36~52%, as compared to baseline values. (dose-dependent inhibition)

With other antipsychotics

- Sertraline 50~100 mg/day, add to AP monotherapy caused minimal but not clinically significant changes in serum levels of various SGAs, including risperidone, olanzapine, quetiapine and aripiprazole.

Citalopram/Escitalopram's interaction

- Citalopram and its active S-enantiomer, escitalopram, are weak inhibitors of CYP2D6 and are negligible inhibitors of CYP1A2, CYP2C9, CYP2C19 and CYP3A4.

- Due to their minimal effect on drug-metabolizing enzymes, citalopram and escitalopram are not expected to cause clinically relevant DIs with SGAs.

- A large routine TDM service, dose-corrected quetiapine serum concentrations were slightly (by 16%), but significantly higher in patients co-medicated with citalopram/escitalopram.

- Due to the limited increase in quetiapine concentrations and its wide therapeutic index, quetiapine dose adjustment is not necessary.

Venlafaxine/desvenlafaxine's interaction

- Venlafaxine is a weaker CYP2D6 inhibitor and has minimal or no effect on the activity of CYP1A2, CYP2C9 and CYP3A4.

- Desvenlafaxine, venlafaxine-active metabolite, has no inhibitory effect on the activity of the major CYP isoforms.

- In 30 healthy volunteers, treatment with venlafaxine, 150 mg/day for 9 days, caused minimal, presumably not clinically relevant, changes in the PKs of a single 1-mg oral dose of risperidone, a CYP2D6 substrate.

- Low-to-moderate doses of venlafaxine did not significantly affect plasma clozapine levels.

- TDM studies documented that concomitant administration with venlafaxine was associated with no changes in dose-normalized serum concentrations of quetiapine nor in those of aripiprazole and its active metabolite.

Duloxetine's interaction

- Duloxetine is a moderate inhibitor of CYP2D6, while it has minimal or no effect on the activity of other enzymes.

- Administration of duloxetine, 60 mg/day for up to 6 weeks, to 20 outpatients stabilized on clozapine (n = 6), olanzapine (n = 8) or risperidone (n = 7), did not modify the plasma concentrations of clozapine and olanzapine, but potentially clinically significant, increase in the plasma concentration of the active moiety of risperidone (by a mean 26%).

- In a study based on a TDM database, coadministration of duloxetine, 30~120 mg/day, was not associated with significant effects on the serum concentrations of both risperidone and aripiprazole.

Mirtazapine's interaction

- Mirtazapine has minimal inhibitory effects on the various CYP isoforms and appears to carry a low risk for DIs.

- Adjunctive mirtazapine resulted in minimal and statistically insignificant changes in the mean plasma concentrations of risperidone (3~8 mg/day), clozapine (200~650 mg/day), olanzapine (10~20 mg/day), and their major metabolites.

- Lack of PK DIs between mirtazapine and these SGAs.

- Data from a routine TDM service, concomitant intake of mirtazapine did not significantly affect serum concentrations of aripiprazole or dehydroaripiprazole.

Basic mechanisms of DIs between newer antidepressants and SGAs

Pharmacodynamic drug interactions

- The majority of the SGAs are dopamine 2 receptor (D2) antagonists, while aripiprazole is a D2 partial agonist.

- The PD DIs take place directly at the site of action of a drug or indirectly by interfering with another physiological mechanism.

- They result in a modification of the pharmacological action of a drug without any change in the plasma concentration and are more difficult to identify and measure than PK DIs.

Pharmacodynamic interactions

PD DIs increasing efficacy

- SGAs may have a synergistic effect and increase the antidepressant response in patients taking antidepressants for major depressive disorder.
- RCTs suggested a synergistic effect between AP and antidepressant co-treatment since the combination appeared superior to monotherapy of either drug class.
- Combining fluoxetine and olanzapine in pill form would suggest that they have additive or synergistic effects in bipolar depression. A meta-analysis indicates some increase of efficacy, but ADRs were frequent.
- A SGA meta-analysis of OCD studies suggested some evidence that adding quetiapine or risperidone to antidepressants increases efficacy.
- α 2 antagonist properties of some newer antidepressants such as mirtazapine may explain the improvement of negative symptoms.

.

Pharmacodynamic interactions

PD DIs decreasing efficacy

- Some antidepressants may increase the switch to mania, whereas bupropion and SSRIs may have fewer risks than TCAs and SNRIs.

- Future studies will need to verify whether antidepressants decrease the mood-stabilizing properties of SGAs by increasing mania-switching or not.

PD DIs increasing safety

- As bupropion treatment can be associated with weight loss, one can propose that adding it to SGAs may decrease the risk of weight gain from SGAs.

Basic mechanisms of DIs between SGAs and newer antidepressants

Pharmacodynamic drug interactions

Antidepressants

DEPRESSION*
Inhibitors of noradrenaline and serotonin transporter‡
Desvenlafaxine, duloxetine, levominalcipran, milnacipran (not approved in the US) and venlafaxine
Selective inhibitors of the serotonin transporter‡
All SSRIs
Selective inhibitors of the serotonin transporter and serotonin receptor antagonists§
Vilazodone and vortioxetine
Inhibitor of the noradrenaline and dopamine transporter‡
Bupropion
Selective inhibitor of the noradrenaline transporter
Reboxetine (not approved in the US)
Other
Mirtazapine¶ and agomelatine# (not approved in the US)
OCD
Inhibitors of the serotonin transporter
SSRIs (not all are approved in the US**)
ANXIETY
Probably the same mechanism as antidepressant action‡‡
Different compounds are approved for different disorders§§ but specificity is doubtful
PAIN
Inhibition of the noradrenaline transporter¶¶
Duloxetine and milnacipran are approved in the US for fibromyalgia
Duloxetine is approved in the US for diabetic peripheral neuropathic and chronic musculoskeletal pain

WEIGHT LOSS
Inhibition of the dopamine transporter
Bupropion (not approved in the US)##
SMOKING CESSATION
Inhibition of the dopamine transporter
Bupropion***
ATTENTION-DEFICIT HYPERACTVITY DISORDER
Inhibition of the noradrenaline and dopamine transporter
Bupropion (not approved in the US)‡‡‡
INSOMNIA
Antagonism of brain H_1 receptors
Mirtazapine (not approved in the US; daily sedation can be a problem)
Agonism of brain MT_2 receptors
Agomelatine (not approved in the US)
STRESS URINARY INCONTINENCE
Not well understood, noradrenergic mechanisms are probably important
Duloxetine (not approved in the US)§§§

Basic mechanisms of DIs between newer antidepressants and SGAs

Pharmacodynamic drug interactions

SGAs	**ANTAGONISM OF D_2 RECEPTORS AT BASAL GANGLIA AND CORTEX***
	Explains antipsychotic efficacy in schizophrenia
	All SGAs are approved in the US except amisulpride‡
	Explains antipsychotic efficacy in other psychoses
	None are approved in the US§
	Possibly explains anti-manic properties
	Aripiprazole, asenapine, olanzapine, quetiapine, risperidone and ziprasidone are approved in the US as monotherapy¶
	Possibly explains postulated mood-stabilizing properties (maintenance in bipolar disorder)
	Aripiprazole and olanzapine are approved in the US as monotherapy#
	Possibly explains anti-irritability action in autism
	Aripiprazole and risperidone are approved in the US
	Possibly explains postulated anti-OCD properties when added to serotonergic antidepressants
	None are approved in the US but reasonable data exist on risperidone and quetiapine
	DEPRESSION
	Treatment of bipolar depression
	Lurasidone and quetiapine are approved in the US as monotherapy**
	Adjunctive therapy of treatment-resistant depression
	Aripiprazole, quetiapine, olanzapine are approved in the US‡‡
	Different theories on mechanism of action§§

ORIGINAL ARTICLE

Interaction Between Paliperidone and Carbamazepine

Norio Yasui-Furukori, MD, PhD, Kazutoshi Kubo, MD, Masamichi Ishioka, MD, Shoko Tsuchimine, PhD, and Yoshimasa Inoue, BS

Ther Drug Monit. 35: 649–652, 2013.

Introduction

- Paliperidone is an atypical antipsychotic drug that is a potent antagonist of the serotonin 5-HT2 and dopamine D2 receptors.

- Paliperidone has pharmacologic properties similar to those of risperidone.

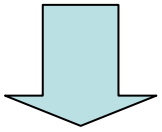
- Paliperidone's metabolic pathway remains unclear, is primarily removed through renal excretion.

- The absolute bioavailability of the instant-release formulation of paliperidone is 106%. These data also suggest that the metabolism of paliperidone is limited.

- Risperidone and paliperidone are both P-glycoprotein substrates.

Introduction

- Carbamazepine induces metabolism catalyzed by CYP3A4, so it induces the metabolism of many drugs, including itself.
- Carbamazepine has little effect on the activity of CYP2D6, CYP1A2, CYP2C19.
- The transcriptions of numerous CYPs genes and several transporter genes were altered by carbamazepine administration.
- Coadministration of paliperidone with 200 mg of carbamazepine BID causes a decrease of 37% in the mean steady-state peak concentration and area under the curve of paliperidone.
- Several *in vitro* and *in vivo* studies related to drug–drug interactions have shown that carbamazepine is also a P-glycoprotein inducer.



Confirm the possible effects of carbamazepine on the pharmacokinetics of paliperidone in patients with schizophrenia

Methods

- The subjects were outpatients with schizophrenia (5 women and 1 man) who fulfilled the criteria for schizophrenia (paranoid type, 4 cases; undifferentiated type, 2 cases).

- Before the coadministration of carbamazepine, the subjects had received 6–12 mg of paliperidone QD at 8:00 AM for 8–24 weeks.

- The coadministered drugs were flunitrazepam (2–4 mg/d) for 3 patients, biperiden (4–6 mg/d) for 2 patients, and sennoside (12–48 mg/d) for 2 patients.

- Carbamazepine (100 mg) was coadministered BID (8:00 AM and 8:00 PM) to all subjects for 2–4 weeks, and the dose was thereafter increased to 200 mg BID and finally to 300 mg BID for 2–4 weeks.

- Blood samples were taken between 9:00 AM and 11:00 AM.

Results

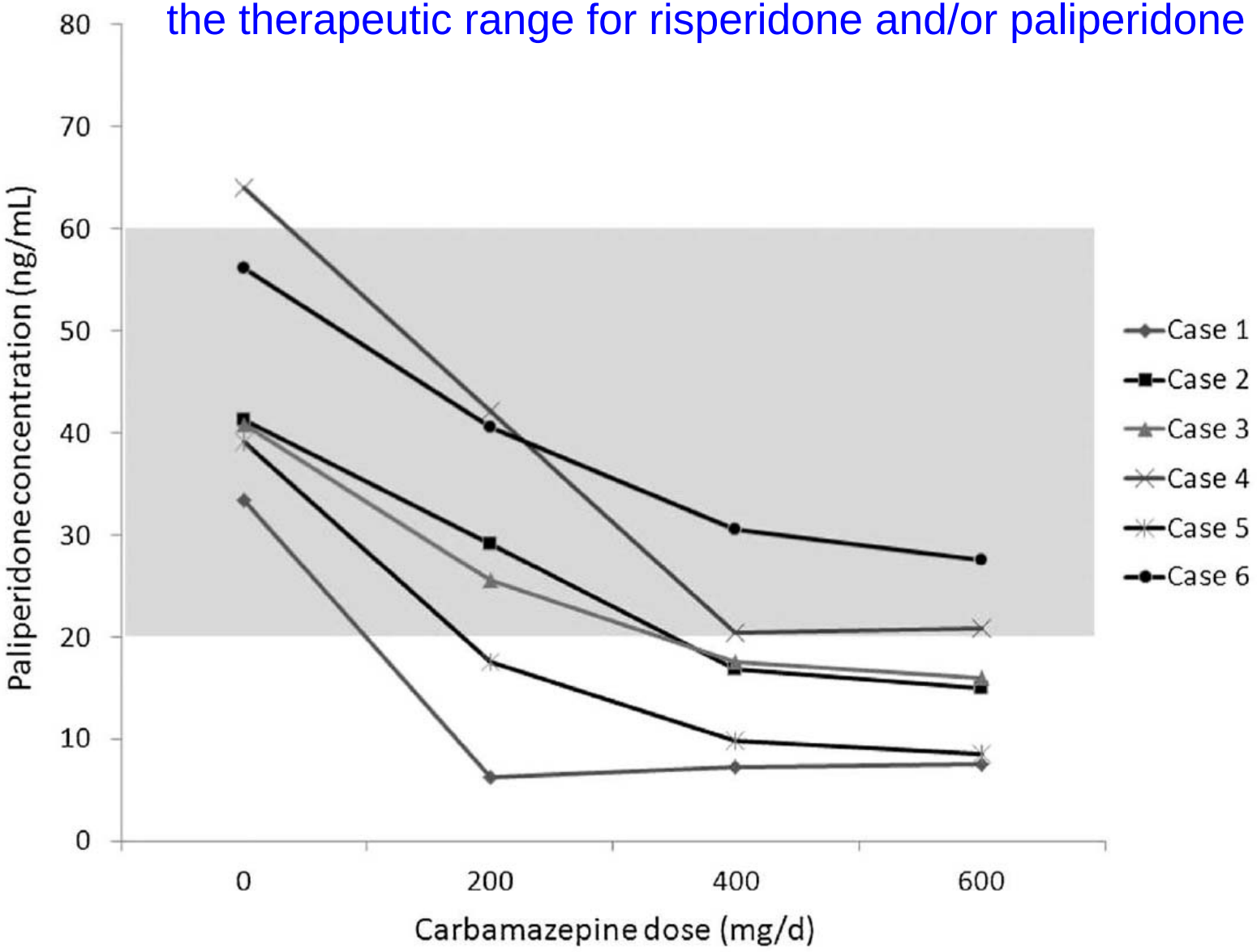
TABLE 1. Patient Characteristics and Plasma Concentrations of Paliperidone (ng/mL) and Clinical Outcomes

	Age, y	Sex	Body Weight	Paliperidone Dose, mg/d	Carbamazepine Dose, mg/d				Final Outcome	Measurements
					Pre	200	400	600		
Case 1	42	F	56	6	33.4	6.2	7.3	7.5	Poor impulse control	Increase to 12 mg and withdraw
Case 2	45	F	58	6	41.3	29.1	16.8	15.0	Grandiosity, hyperactivity	Increase to 12 mg and withdraw
Case 3	50	F	58	6	40.9	25.5	17.5	16.0	Persecutional delusions	Increase to 12 mg and withdraw
Case 4	48	F	52	12	64.0	42.2	20.4	20.9	No change	Withdraw due to ethical reason
Case 5	65	F	53	6	39.2	17.6	9.8	8.6	Insomnia	Adding hypnotics
Case 6	36	M	86	12	56.1	40.5	30.5	27.6	Hyperactivity, hostility	Adding valproate and withdraw
Mean	47.7	—	60.5	8.0	45.8	26.9*	17.1*	15.9*	—	—
SD	9.8	—	12.7	3.1	11.7	13.7	8.2	7.6	—	—

*$P < 0.001$compared with pretreatment of carbamazepine.

5 of the 6 patients deteriorated approximately 2–3 months after the start of the carbamazepine coadministration.

A systematic review suggests that 20–60 ng/mL is the therapeutic range for risperidone and/or paliperidone



Discussion

- Adjunctive treatment with carbamazepine in patients receiving paliperidone results in a significant reduction in the plasma concentration of paliperidone.

- Even a low dose of carbamazepine, that is 200 mg/d, significantly decreased the plasma concentration of paliperidone.

- Because paliperidone has a lower affinity for CYP3A4 than does risperidone, this finding was surprising when considering the roles of CYPs.

- Paliperidone is primarily removed through renal excretion and is a P-glycoprotein substrate.

- P-glycoprotein plays an important role in the renal excretion of paliperidone.

Discussion

- In addition to being a potent CYP3A inducer, several *in vitro* and *in vivo* studies related to drug–drug interactions have shown that carbamazepine is also a P-glycoprotein inducer.

- The effect occurred even at a dose of 200 mg/d of carbamazepine and reached a plateau at doses higher than 400 mg/d.

- Carbamazepine reduces the concentration of paliperidone in a dose-dependent manner, most likely because of the induction of several drug-metabolizing enzymes and several drug transporters.

- Carbamazepine might decrease the brain concentration of paliperidone more than the plasma concentration of paliperidone because of P-glycoprotein induction.

JPP
Journal of Pharmacy
And Pharmacology

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.

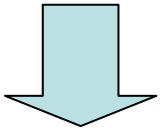
Journal of Pharmacy and Pharmacology. 66: 747 - 759, 2014.

Background

- By the mid-1990s, valproic acid had replaced lithium as the mood stabiliser of choice, because it is has an efficacy comparable to lithium but is easier to utilise, safer and has TDM requirements which are less stringent.

- Study revealed a bidirectional relationship between schizophrenia and epilepsy and thus it could be possible that the rate of incidence of epilepsy in patients suffering from schizoaffective disorder is higher.

- Valproic acid would have a dual role – as an anticonvulsant and as a mood stabiliser, whereas lithium has no anticonvulsant activity.



Valproic acid combined with an atypical antipsychotic provides synergistic mood-stabilising and antidepressant activity, suitable for controlling the extreme changes in mood characteristic of these diseases, as well as antipsychotic activity in patients with schizoaffective disorder.

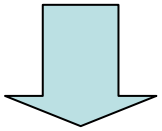
Background

- Such a combination is generally well tolerated, with the increase in adverse effects such as weight gain, dry mouth and somnolence being relatively minor compared with the benefits of combination therapy.

- Recent cases of rare but serious (sometimes lethal) side effects occurring with the use of valproic acid with olanzapine or quetiapine have been reported.

- Researchers hypothesising that a pharmacokinetic interaction results in plasma concentrations of olanzapine or quetiapine are altered than result in toxicity.

- Pharmacodynamic interactions are also known to occur, an example of this is the potential for neutropenia when valproic acid and olanzapine are combined.



A thorough literature search was carried out using the PubMed search engine

ADRs possibly caused by DDI between valproic acid and olanzapine or quetiapine

- Combination of olanzapine plus valproic acid significantly increases glycosylated haemoglobin, body mass index, weight (up to three times more), triglycerides, and triglyceride-to-HDL cholesterol ratio.

- Olanzapine has been associated with glucose disregulation and weight gain, and valproic acid has been known to cause hyperinsulinaemia and insulin resistance.

- Increased incidence of neutropenia while being treated with high doses of valproic acid (3000 mg daily) and olanzapine (30 mg).

- Significantly higher mean and peak hepatic enzyme levels when combination of olanzapine and valproic acid in adolescents.

- Hypersalivation was also described as treatment for bipolar disorder.

ADRs possibly caused by DDI between valproic acid and olanzapine or quetiapine

- 44% of patients taking valproic acid and quetiapine together developed neutropenia or leukopenia as opposed to 26% and 6% with valproic acid and quetiapine monotherapy, respectively.

- Thrombocytopenia also be reported.

- Two mild renal insufficiency patients presenting with delirium on starting combination. (renal insufficiency can decrease quetiapine clearance)

- Cervical dystonia and pedal oedema have also been attributed to DDIs between quetiapine and valproic acid.

- Two cases of patients taking valproic acid and quetiapine developing pancreatitis.

Occurrence and rate of incidence of ADRs with valproic acid, compared with olanzapine and quetiapine monotherapy

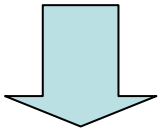
Valproic acid		Olanzapine	Quetiapine
Valproic acid side effects	Frequency of occurrence	Frequency in olanzapine	Frequency in quetiapine
Hepatobiliary disorders	Rare	Very rare	Rare
Severe liver damage	Rare	Very rare	Rare
Increased liver enzymes, normally transient	Common	Common	Common
GI disorders (nausea, diarrhoea)	Common	/	Common
Pancreatitis, can be lethal	Very rare	Very rare	/
Sedation (usually transient)	Occasional	Very common	Very common
Lethargy	Rare	Very common	Very common
Reversible parkinsonism	Very rare	Common	/
Fine postural tremor	Rare	Common	/
Thrombocytopenia	Common	Very rare	/
Anaemia	Rare	/	/
Leukopenia	Rare	Uncommon	Common
Pancytopenia	Rare	Unknown	Unknown
Neutropenia	Occasional	Uncommon	Unknown
Agranulocytosis	Rare	Very rare	Unknown
Rash	Rare	Common	Unknown
Stevens–Johnson syndrome	Very rare	/	Very Rare
Alopecia (transient)	Common	Uncommon	/
Enuresis	Very rare	Uncommon	/
Angioedema/allergic reactions	Rare	Rare	Very rare
Nonsevere peripheral oedema	Very rare	Common	Common
Weight Gain	Common	Very common	Common

Existing evidence of PK interaction between valproic acid and olanzapine

- A number of studies have identified a possible pharmacokinetic interaction in which valproic acid was found to lower the plasma concentration of olanzapine.

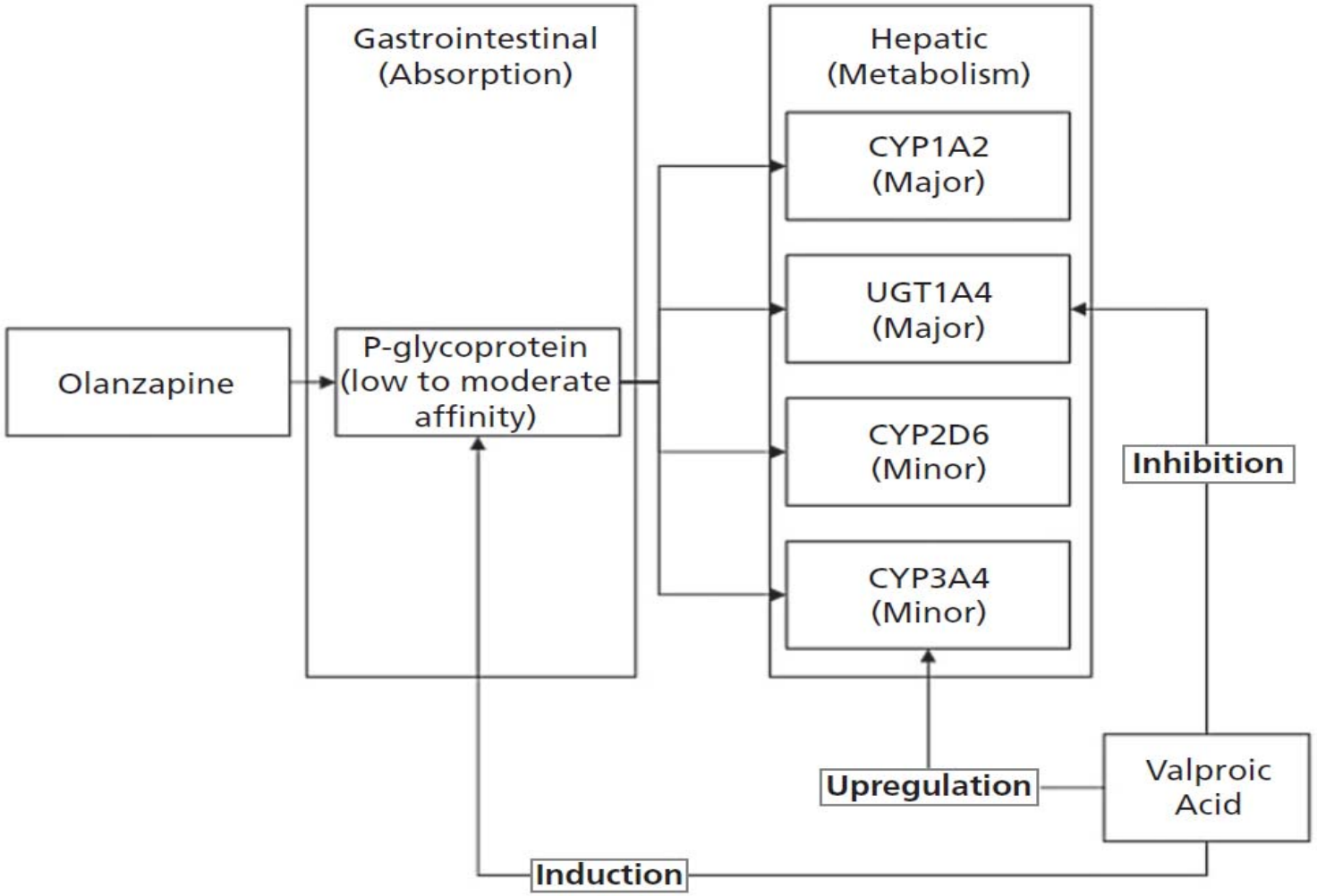
- Addition of valproic acid resulted in a mean decrease of 53.6% (from 9.78 ng/ml to 4.62 ng/ml) in the dose-corrected plasma olanzapine concentration.

- Another study show that after 4 weeks the valproic acid addition, cause average a small but significant 18% decrease in plasma olanzapine concentrations.



Valproic acid was associated with an average decrease in olanzapine concentration possibly because of induction of olanzapine metabolism.

Mechanism of PK interaction between valproic acid and olanzapine



Valproic acid plasma concentrations range within 500 to 1000 μm, could cause DDIs with co-administered drugs that are metabolized by CYP3A4.

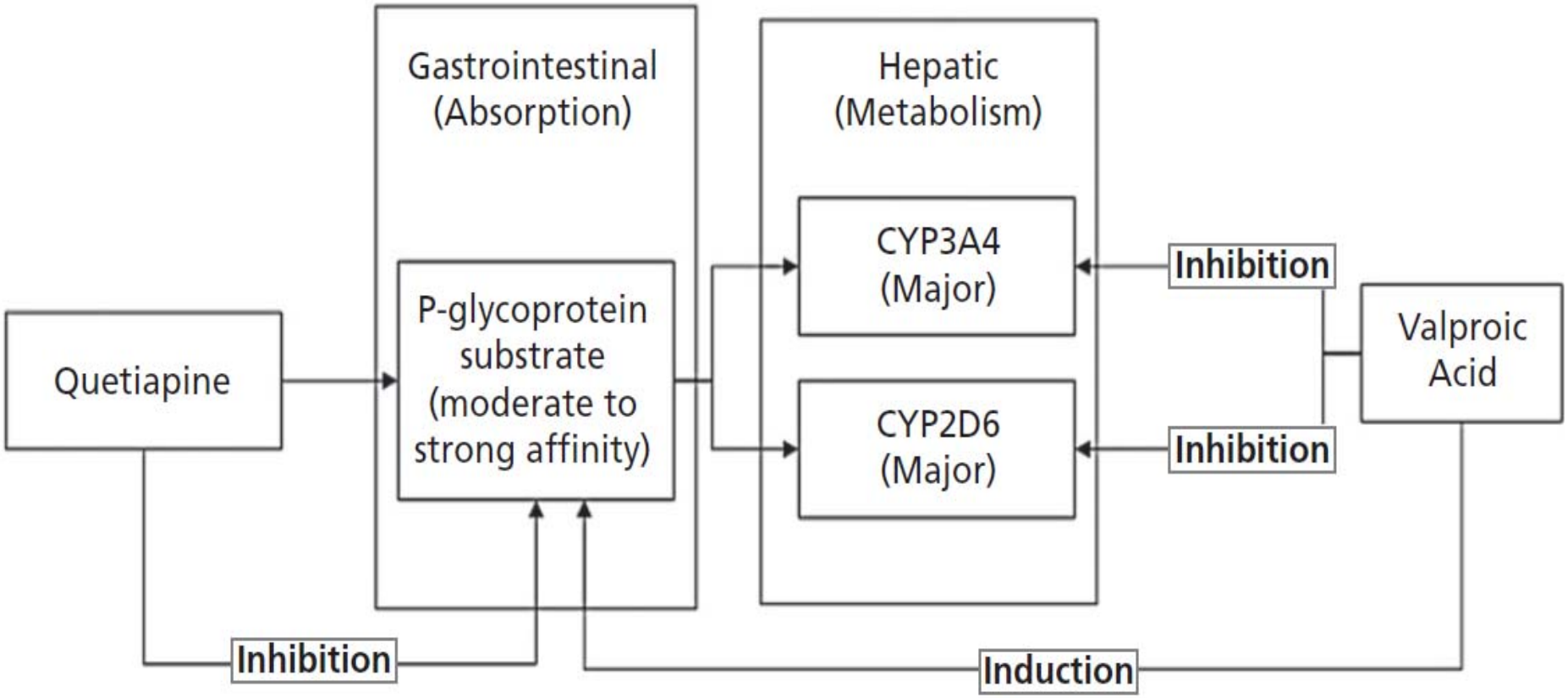
Existing evidence of PK interaction between valproic acid and quetiapine

- Valproic acid was found to increase the plasma concentrations of quetiapine which could in theory translate to an increased risk of adverse effects occurring.

- Valproic acid co-administration has an appreciable influence on quetiapine plasma concentrations, resulting in a 77% increase in quetiapine levels.

- Another similar study was concluded that the use of valproic acid as an adjunct in patients being treated with quetiapine did not result in any significant change in the serum concentrations of quetiapine.

Mechanism of PK interaction between valproic acid and quetiapine



The use of TDM to monitor for DDIs and decreasing the incidence of DDI-induced adverse drug reactions

- TDM in general is recommended for use in cases of suspected toxicity, lack of clinical response, suspected nonadherence, potential drug interactions, and to assess therapy following a change in dosage regimen or a change in the clinical state of a patient.

- The main reason that TDM has been found to be useful in patients on olanzapine therapy is that plasma concentration has been linked with both efficacy and toxicity. (**Not available in Taiwan**)

- Several factors can alter the plasma concentrations of olanzapine, including age, gender and smoking. (males required a higher dose of olanzapine to reach threshold concentration)

Other interactions to consider

Smoking

- Tobacco smoke contains polycyclic aromatic hydrocarbons, which are potent inducers of CYP 1A2.
- Smokers taking clozapine consistently show up to 50% lower plasma levels than non-smokers.
- Smoking as few as 7-12 cigarettes per day may be sufficient to cause the maximum enzyme induction.
- Giving up smoking can cause an increase in clozapine levels between 50-72%, which can lead to severe adverse effects such as seizure and postural hypotension.

Other interactions to consider

Smoking

- Other antipsychotics affected include olanzapine (plasma levels may reduce by up to 50%), haloperidol (around 20% reduction in plasma levels) and possibly fluphenazine, chlorpromazine and zuclopenthixol.

- The interaction usually occurs gradually between two to four weeks.

- It would prudent to monitor clozapine and olanzapine levels before stopping smoking, reduce the dose gradually by approximately 25% and recheck levels four weeks after stopping.

- Smoking marijuana would be expected to have the same effect.

Other interactions to consider

Caffeine

- Excessive caffeine consumption, ie above 250mg/day, or four to five cups of coffee per day, can cause multiple psychotropic effects such as restlessness, excitement, insomnia and possible worsening of psychosis.

- Clozapine and caffeine compete for the same metabolic pathway (CYP 1A2), which may result in an increase in clozapine levels.

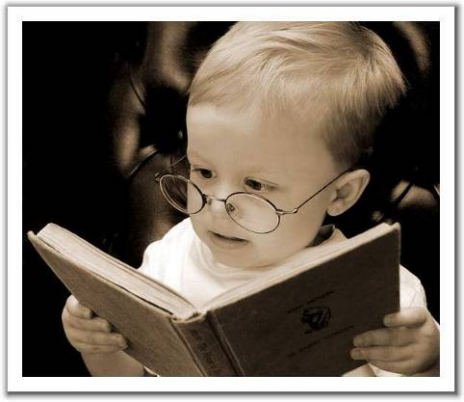
- The effect is subject to much patient variability but increases of between 14-47%have been reported.

- Olanzapine may also be affected by caffeine in this way.

Drug-Drug Interactions Between Warfarin and Psychotropics: Updated Review of the Literature

Ashwini Nadkarni, M.D., Mark A. Oldham, M.D., Mark Howard, M.D., and Isidore Berenbaum, M.D.

Pharmacotherapy 2012;32(10):932-942



Introduction

★ The use of psychotropics in the management of mental illness is becoming increasingly prevalent as the literature on their efficacy expands.

★ Patients with mental illness are at risk of developing thromboemboli, including deep vein thromboses, pulmonary emboli, and thromboembolic complications of atrial fibrillation or cardiac valve replacement.

→ Warfarin is used for the prophylaxis and treatment of thromboemboli in the outpatient.

★ Interactions between warfarin and psychotropics are myriad.

★ The primary concern of such interactions is the resultant effect on the international normalized ratio (INR).

→ Subtherapeutic or supratherapeutic values can result in increased risk for thromboemboli or hemorrhagic complications.

Introduction

★ Clinicians should be wary of interactions when introducing agents that may affect warfarin metabolism as well as when discontinuing certain agents.

★ This updated literature review on interactions between warfarin and psychotropic drugs, with a primary emphasis on interactions mediated through the CYP system, and consider potential interactions mediated through protein binding as well as interactions with drugs that have independent effects on hemostasis.

➡ Articles were identified by performing a search of the MEDLINE database using the search terms.

Mechanisms of Interactions Between Warfarin and Psychotropics

Cytochrome P450 System and Protein Binding

★ Warfarin is a racemate composed of a potent S-enantiomer and less potent R-enantiomer.

★ The S-enantiomer is metabolized primarily by the CYP2C9, whereas the R-enantiomer is metabolized primarily by the CYP1A2 and through minor pathways by the CYP2C19 and CYP3A4.

★ Warfarin is more than 95% protein bound at therapeutic concentrations.

1. Interactions between warfarin and psychotropics mediated by the CYP system are of significant clinical concern given warfarin's narrow therapeutic window.

2. Protein displacement has also been considered as a potential means of interaction.

Mechanisms of Interactions Between Warfarin and Psychotropics

Independent Effects on Hemostasis

★ Blockade of serotonin reuptake into platelets leads to serotonin depletion in platelets and, consequently, diminished serotonin-mediated platelet aggregation.

1. SSRIs impair platelet aggregation; case reports have noted increased bleeding events such as ecchymoses, epistaxis, and prolonged bleeding time.
2. Such bleeding events occur rarely, and clotting parameters have not been demonstrated to be altered drastically.

★ Valproic acid causes thrombocytopenia in a dose-dependent fashion and also impairs platelet aggregation.

The prevalence of valproic acid effects on platelet count in a psychiatric population, only 12% of patients met criteria for thrombocytopenia, and none experienced hemorrhagic complications.

Ecchymoses: 瘀斑
Epistaxis: 鼻出血

Specific DDIs by Psychotropic Class

Antidepressants -- SSRIs

★ The SSRIs are among the most commonly prescribed drug classes.

Table 1. Reported and Theoretical Interactions of Psychotropic Drugs with Warfarin

Interacting Drug with Warfarin	Most Likely Effect	Proposed Mechanism of Interaction	Supporting Evidence
Antidepressants			
Fluvoxamine[a,12, 13]	↑ INR	CYP1A2, CYP2C9, CYP2C19, and CYP3A4 inhibition	Published case reports: ↑ INR
Fluoxetine[a,14–16]	↑ INR	CYP2C9, CYP2C19, and CYP3A4 inhibition	Volunteer study: no change in PT Published case reports: ↑ INR
Citalopram[17, 18]	↑ INR	CYP2C19 and CYP3A4 substrate	Volunteer study: minor ↑ PT, not judged clinically significant
Escitalopram	↑ INR (?)	CYP2C19 and CYP3A4 substrate	No published case reports or studies
Sertraline[19, 20]	↑ INR	CYP2C19 inhibition	Volunteer study: minor ↑ PT, not judged clinically significant Published case report: ↑ INR
Paroxetine[3, 21]	↑ INR	CYP2C9 inhibition	Study: mild ↑ bleeding risk, but no change in PT Case reports to FDA: ↑ INR

★ 院內商品對照表

成分名	商品名
Fluvoxamine	Lote® 50 mg
Fluoxetine	Fluxen® 20 mg
Citalopram	Citao® 20 mg、Sitalo® 20 mg
Escitalopram	Leeyo® 10 mg
Sertraline	Kinloft® 50 mg
Paroxetine	Setine® 50 mg

Antidepressants -- SSRIs

★ Fluvoxamine and fluoxetine are the two SSRIs most likely to inhibit warfarin metabolism, which is supported by several case reports.

-- In two reports of a fluvoxamine interaction with warfarin, the INR was elevated without hemorrhagic complications.

-- One report of a fluoxetine-warfarin interaction, an elderly man experienced a fatal intracerebral hemorrhage.

→ Inhibition of warfarin metabolism is thought to be mediated by CYP2C9.

★ Citalopram and sertraline harbor the lowest risk of interactions with warfarin.

★ No studies or case reports suggesting an interaction between warfarin and escitalopram, which is the isolated S-enantiomer of citalopram.

★ One study examining coadministration of paroxetine with warfarin found increased bleeding tendency after several days.

→ The risk of hemorrhagic complication was thought to be moderate compared with fluvoxamine.

Specific DDIs by Psychotropic Class

Antidepressants -- SNRIs

Interacting Drug with Warfarin	Most Likely Effect	Proposed Mechanism of Interaction	Supporting Evidence
Venlafaxine	↑ INR	Unclear	Unpublished reports: ↑ INR
Desvenlafaxine	↑ INR (?)	Unclear	No published case reports or studies
Duloxetine[22–25]	Unclear	Weak CYP1A2 inhibition	Study: no clinically significant interaction Two published case reports: one with ↑ INR, one with ↓ INR

★院內商品對照表

成分名	商品名
Venlafaxine	Venfaxime® 75 mg

★ In view of their low protein binding and their lack of effects on the CYP system, venlafaxine and desvenlafaxine are unlikely to have clinically significant interactions with warfarin.

★ Duloxetine had no clinically or statistically significant interactions with warfarin.

Specific DDIs by Psychotropic Class

Antidepressants

Interacting Drug with Warfarin	Most Likely Effect	Proposed Mechanism of Interaction	Supporting Evidence
Mirtazapine[26]	Unclear	Unclear	No published case reports
Bupropion	No change	None known	No published case reports or studies
Trazodone[b,27–29]	↓ INR	CYP3A4 substrate	Published case reports: ↓ INR
Nefazodone[30]	↑ INR	CYP3A4 inhibition	Study: no clinically significant interaction

★ 院內商品對照表

成分名	藥理分類	商品名
Mirtazapine	Nonselective SSRI	Mirtine® 30 mg
Bupropion	Dopamine-norepinephrine reuptake inhibitor	Funnix® 150 mg
Trazodone	Atypical antidepressants	Mesyrel® 20 mg

★ Mirtazapine does not exhibit significant effects on the CYP system.

★ Bupropion is not known to affect the CYP isoenzymes involved in warfarin's metabolism.

Atypical antidepressants

★ Trazodone is metabolized by CYP3A4, one of the minor metabolic pathways for R-warfarin, to its primary metabolite m-chlorophenylpiperazine and is 80–90% protein bound.

★ Five clinically significant cases of suspected trazodone-warfarin interactions have been identified, but the mechanism is somewhat unclear.

-- In a case report and a three-patient case series, the introduction of trazodone to patients receiving stable doses of warfarin led to a decreased prothrombin time (PT) and INR.

-- In one case, a patient receiving stable doses of warfarin began both trazodone and omega-3 fatty acids, which caused a considerable elevation of INR to 8.06.

-- In no case did any patient experience adverse effects due to the marked changes in PT and INR.

★ Nefazodone, a potent inhibitor of CYP3A4, has been found to be safe and well tolerated during coadministration with warfarin in a randomized, double-blind, controlled trial.

Specific DDIs by Psychotropic Class

Antidepressants

Interacting Drug with Warfarin	Most Likely Effect	Proposed Mechanism of Interaction	Supporting Evidence
Tricyclics[31–33]	↑ INR	Amitriptyline and imipramine: CYP1A2 inhibition	Study (in humans): no change in PT Study (amitriptyline and nortriptyline in rats): ↑ PT
MAO inhibitors	↑ INR	Tranylcypromine: CYP2C19 inhibition	No published case reports or studies
Reboxetine	Unclear	CYP3A4 substrate	No published case reports or studies
Moclobemide	↑ INR	CYP1A2 and CYP2C19 inhibition	No published case reports or studies
St. John's wort[b,34–36]	↓ INR	CYP1A2, CYP2C9, and CYP3A4 induction	Study: increased clearance of S-warfarin (expect ↓ INR)

★ Data regarding interactions between specific tricyclic antidepressants (TCAs) and warfarin are limited.

Specific DDIs by Psychotropic Class

Antipsychotics

Interacting Drug with Warfarin	Most Likely Effect	Proposed Mechanism of Interaction	Supporting Evidence
Antipsychotics			
Chlorpromazine	Unclear	CYP1A2 substrate	No published case reports or studies
Haloperidol	Unclear	CYP1A2 and CYP3A4 substrate	No published case reports or studies
Clozapine	Unclear	CYP1A2 and CYP3A4 substrate	No published case reports or studies
Olanzapine	Unclear	CYP1A2 substrate	No published case reports or studies
Quetiapine[a,37, 38]	↑ INR	CYP3A4 substrate	Published case reports: ↑ INR
Asenapine	Unclear	CYP1A2 substrate	No published case reports or studies

★ 院內商品對照表

成分名	商品名
Chlorpromazine	Morefine® 100 mg
Haloperidol	Haldomin oral solution® 2 mg/ml
Clozapine	Mezapin® 100 mg
Olanzapine	Olandus® 10 mg
Quetiapine	Hiloca® 200 mg、Seroquel® 25mg

Antipsychotics

★ The CYP1A2 is involved in the primary metabolism of chlorpromazine, haloperidol, clozapine, olanzapine, and asenapine; haloperidol and clozapine are also metabolized by CYP3A4 through minor routes of metabolism.

★ Although these enzymes are involved in the less active of the two warfarin enantiomers, R-warfarin, we cannot entirely rule out the potential of an interaction.

-- One case report detailed the substantial elevation of a patient's INR after the addition of quetiapine to warfarin therapy.

-- In another case report, the addition of quetiapine to a patient's stable warfarin regimen resulted in an INR of 3.54 and was associated with several intracerebral hemorrhages.

1. CYP3A4 is the isoenzyme that metabolizes quetiapine to the major inactive sulfoxide metabolite.
2. CYP2D6 may contribute to the 7-hydroxylation pathway of quetiapine, and CYP2C9 may be an enzymatic pathway for a quetiapine metabolite.

★ Quetiapine's high degree of protein binding (83%) may have played a lesser role in the interaction.

★ Olanzapine is more protein bound than quetiapine (93%), yet we found no case reports of an interaction between olanzapine and warfarin.

Specific DDIs by Psychotropic Class

Sedatives, Hypnotics, and Anxiolytics

Interacting Drug with Warfarin	Most Likely Effect	Proposed Mechanism of Interaction	Supporting Evidence
Sedatives, hypnotics, and anxiolytics			
Chloral hydrate[39, 40]	↑ INR	Protein binding displacement	Study: minor ↑ PT, not judged to be clinically significant
Diazepam[40]	No change	CYP2C19 and 3A4 substrate	Study: no change in anticoagulant activity
Chlordiazepoxide[40]	No change	Unknown	Study: no change in anticoagulant activity
Buspirone[41]	No change	CYP3A4 substrate	Study: does not displace warfarin from plasma proteins

★ 院內商品對照表

成分名	商品名
Fludiazepam	ERA® 0.25 mg、Erispan® 0.25mg
Buspirone	Busp® 10 mg

Sedatives, Hypnotics, and Anxiolytics

★ Benzodiazepines have been shown to have little to no effect on warfarin metabolism.

★ A theoretical interaction is possible given diazepam is a substrate of CYP2C19 and CYP3A4, which represent the minor routes of R-warfarin metabolism.

★ A study examining coadministration of nitrazepam, diazepam, and chlordiazepoxide with warfarin demonstrated no effect on steady-state warfarin plasma concentrations, plasma half-life of warfarin, or anticoagulant control in patients.

→ It is safe to prescribe BZDs to patients receiving long-term oral anticoagulants.

★ Buspirone, also a substrate of CYP3A4, has not been noted to have clinically significant interactions with warfarin.

★ An additional mechanism of interaction is possible, as buspirone is highly protein bound (> 95%), interacting with both albumin and α 1-acid glycoprotein.

-- One study demonstrated that buspirone does not displace warfarin from plasma proteins.

Specific DDIs by Psychotropic Class

Mood Stabilizers

Interacting Drug with Warfarin	Most Likely Effect	Proposed Mechanism of Interaction	Supporting Evidence
Mood stabilizers			
Lithium[3]	No change	None known	Thought to be no interaction
Carbamazepine[b,42–48]	↓ INR	CYP1A2 and CYP3A4 induction	Study: increased clearance of S- and R-warfarin (↓ INR) Published case reports: ↓ INR
Oxcarbazepine[49, 50]	No change	CYP2C19 inhibition, CYP3A4 induction	Study: no significant effects on warfarin anticoagulant activity No published case reports
Valproic acid[a,4, 5, 51–56]	↑ INR	CYP2C9 and CYP2C19 inhibition, protein binding displacement	Studies: ↑ S- and R-warfarin levels Published case reports: ↑ INR

★ 院內商品對照表

成分名	商品名
Lithium	Ligilin® 300 mg
Carbamazepine	Tegol® 200 mg
Valproic acid	Convulex® 300 mg、Depakine® 145mg

Mood Stabilizers

★ Lithium is a simple element and is excreted by the kidneys, it does not produce interactions with warfarin through the CYP system.

★ Carbamazepine is a potent inducer of the CYP system, notably CYP1A2 and CYP3A4.

★ The tendency of carbamazepine to induce the metabolism of warfarin, leading to subtherapeutic anticoagulation.

-- More hemorrhagic complications, such as widespread dermal ecchymoses and intramural hematoma of the small intestines, appear to be published.

-- In one instance, the introduction of carbamazepine in a patient receiving a stable dose of warfarin led to a subtherapeutic INR within 2 weeks.

-- In another case, the PT was found to increase to 5 times the upper limit of normal 1 month after discontinuation of carbamazepine.

Carbamazepine discontinuation should be undertaken cautiously while monitoring the INR frequently, as warfarin doses will almost certainly need to be reduced.

Mood Stabilizers

★ Three case reports suggest a potential for an interaction between valproic acid and warfarin.

-- The addition of warfarin to a 42-year-old woman who was receiving stable doses of valproic acid drug regimen was followed by a rapid rise in her INR to 6.54.

-- An initial dose of valproic acid given to a 68-year-old woman with steady-state levels of warfarin caused an elevation of her INR to 3.9.

-- A 71-year-old woman who was receiving warfarin for previous DVT. After IV loading with valproic acid was administered, a rapid increase in INR to 7.6.

★ The interaction between warfarin and valproic acid could be attributed to both pharmacokinetic and pharmacodynamic explanations.

-- Valproic acid is a competitive inhibitor of CYP2C9 but also affects CYP2C19, altering levels of both the S- and R-warfarin enantiomers.

-- Valproic acid can displace ligands from the warfarin binding site, leading to an increased warfarin plasma level and elevation of INR.

→ There were no cases of bleeding complications or bruising, suggesting that these effects are not likely to be clinically relevant.

Specific DDIs by Psychotropic Class

Stimulants & β-Blockers

Interacting Drug with Warfarin	Most Likely Effect	Proposed Mechanism of Interaction	Supporting Evidence
Stimulants			
Modafinil[57, 58]	Unclear	CYP1A2 and CYP3A4 induction, CYP2C9 and CYP2C19 inhibition	Study: no changes in warfarin levels No published case reports
Armodafinil	Unclear	Weak CYP1A2 and CYP3A induction, CYP2C19 inhibition	No published case reports or studies
Methylphenidate	↑ INR	Unclear	Case reports to FDA: ↑ coumarin anticoagulant levels
Mixed amphetamine salts	No change	Weak CYP1A2 and CYP3A4 inhibition	No published case reports or studies
β-Blockers			
Propranolol[59]	↑ INR	CYP1A2 and 2C19 substrate	Study: no change in PT, 14.7% ↑ in warfarin plasma concentration

★ 院內商品對照表

成分名	商品名
Methylphenidate	Concerta® 18 mg、Ritalin® 10mg
Propranolol	Inderal® 10 mg

★ Modafinil, a novel stimulant used to treat excessive daytime sleepiness.

Stimulants & β-Blockers

★ No published case reports have documented the interactions between warfarin and methylphenidate.

★ The package insert for methylphenidate cites the drug's "inhibition of metabolism of coumarin anticoagulants, anticonvulsants, and some antidepressants."

★ β-blockers may be used off-label for performance anxiety and drug induced akathisia.

-- The effect of β-blockers on hemorrhagic risk in patients with congestive heart failure concurrently treated with warfarin, bleeding events were found to occur in 15.3% of patients.

-- An interaction between propranolol and warfarin in healthy volunteers revealed that coadministration of the two drugs produced a 14.7% elevation of the warfarin concentration, but no statistically significant change in PT was observed.

★ Bisopropolol has been reported to be well tolerated when coadministered with warfarin.

★ No case reports suggesting clinically significant interactions between atenolol and warfarin.

Specific DDIs by Psychotropic Class

Psychotropics Indicated for Management of Substance Use Disorders & Cognitive Enhancers

Interacting Drug with Warfarin	Most Likely Effect	Proposed Mechanism of Interaction	Supporting Evidence
Agents for substance use disorders			
Tobacco cigarettes[b,60–62]	↓ INR	CYP1A2 induction	Meta-analysis: decreased anticoagulant effect
Nicotine replacement	No change	None known	No published case reports or studies
Varenicline	No change	None known	No published case reports or studies
Buprenorphine[63]	↑ INR	CYP3A4 inhibition	No published case reports or studies
Methadone	No change	None known	No published case reports or studies
Disulfiram[64–66]	↑ INR	CYP2C9 inhibition	Published case reports: ↑ INR
Naltrexone	No change	None known	No published case reports or studies
Acamprosate	No change	None known	No published case reports or studies
Cannabis[67]	↑ INR	CYP3A4 inhibition	Case report: weak CYP2C9 inhibition
Cognitive enhancers			
Donepezil[68]	No change	Protein binding displacement (?)	Study: no changes in warfarin levels
Tacrine[69]	No change	CYP1A2 substrate	Study: no changes on anticoagulant effect of warfarin

★ 院內商品對照表

成分名	商品名
Donepezil	Rewise® 10 mg

Psychotropics Indicated for Management of Substance Use Disorders & Cognitive Enhancers

★ A systematic meta-analysis on interactions between warfarin and smoking revealed several cases of increased warfarin requirements in patients who smoked.

★ The polycyclic aromatic carbons inhaled while smoking induce CYP1A2, enhancing warfarin metabolism and reducing its efficacy.

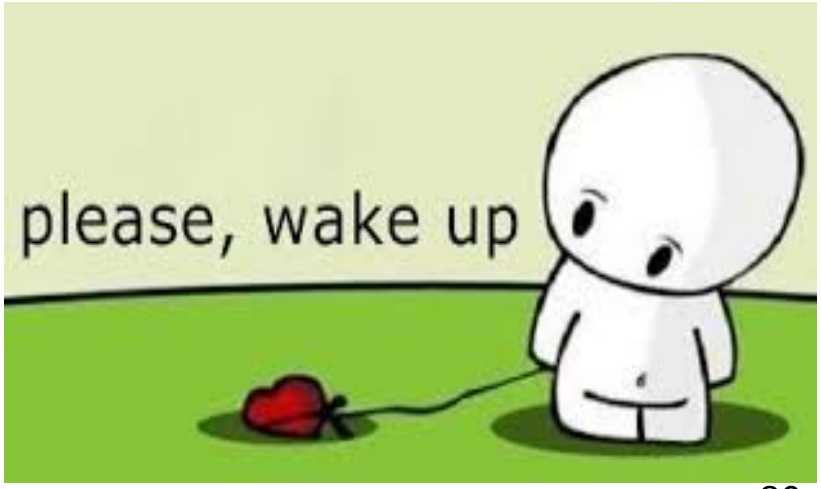
-- A study involving adults who abruptly stopped smoking suggested that reversal of CYP1A2 induction occurred over several days.

-- The authors advised clinicians to decrease the doses of CYP1A2 substrates immediately, with the doses decreased by 10%/day for 4 days.

★ Concurrent administration of anticholinesterase inhibitors such as donepezil and tacrine have not been shown to alter the PK or PD profile of warfarin in healthy volunteers.

➡ Donepezil and tacrine may be safely coadministered with warfarin without the need for dose modification.

Conclusion



Summary

★ Interactions between warfarin and psychotropic drugs are important and likely underrecognized.

★ Clinicians must note the potential for psychotropics to act as either inhibitors or inducers of warfarin metabolism.

★ Psychotropics that pose particular risk of increasing the INR include the antidepressants fluoxetine and fluvoxamine, the antipsychotic quetiapine, and the mood stabilizer valproic acid.

★ Those that may significantly decrease the INR include the antidepressants trazodone and the mood stabilizer carbamazepine, and tobacco products (but not nicotine replacement therapies).

1. The need for anticoagulation in patients receiving above psychotropics may necessitate switching to a different psychotropic.

2. Patients should be monitored closely and frequently to ensure that the INR remains in the therapeutic range.

Summary

- There are a few simple questions that can help highlight potential antipsychotic drug interactions.

- Do any drugs being added to the antipsychotic cause similar adverse effects or alter the way the antipsychotic works (pharmacodynamic interactions)?

  -- If an adverse effect becomes a problem, reducing the dose or switching to an antipsychotic with a lower risk of this effect may be possible.

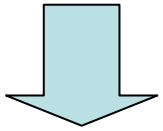
- Does the potential combination of drugs (or other substances) affect the way the antipsychotic is handled by the body (pharmacokinetic interactions)?

  -- One factor that contributes to the complexity of predicting pharmacokinetic interactions is genetic polymorphism.

- Does the patient's physical state or comorbidity increase the risks associated with prescribing the antipsychotic?

Summary

- It would be almost impossible to avoid all drugs, substances or disease states potentially interacting with antipsychotics.
- What is important is to be aware of the potential interactions, inform the patient and monitor closely for any increased adverse reactions.
- Altering the dose of the antipsychotic or choosing a drug that is less likely to interact may also be an option.



Having a working knowledge of potential drug interactions and the ability to predict problems are essential skills for all mental health clinicians.

Common pharmacodynamic interactions to consider with antipsychotic drugs

Potential additive side-effects	Most problematic antipsychotic(s)	Drug or class combined with antipsychotic
QT prolongation	haloperidol pimozide sertindole high-dose antipsychotic prescribing	escitalopram citalopram high-dose methadone erythromycin clarithromycin co-trimoxazole mefloquine sotalol amiodarone ciclosporin hydroxyzine tamoxifen
Increased risk of neutropenia / agranulocytosis	***clozapine***	***carbamazepine*** ***carbimazole*** ***chloramphenicol*** ***cytotoxics*** ***long-acting depot antipsychotics*** ***penicillamine*** ***phenylbutazone*** ***sulfonamides, eg co-trimoxazole***
Increased sedation	chlorpromazine clozapine olanzapine quetiapine pericyazine zuclopenthixol	alcohol antihistamines benzodiazepines mirtazapine opioid analgesics trazodone tricyclic antidepressants

particularly hazardous interactions and should be avoided

Common pharmacodynamic interactions to consider with antipsychotic drugs

Increased risk of anticholinergic side-effects, *eg* constipation, urinary retention, blurred vision, confusion	chlorpromazine clozapine pimozide trifluoperazine zuclopenthixol	anticholinergic drugs, *eg* procyclidine, hyoscine tricyclic antidepressants
Decreased blood pressure or falls	chlorpromazine clozapine pericyazine pimozide risperidone sertindole	ACE inhibitors alcohol antihypertensives tricyclic antidepressants
Increased risk of seizures	chlorpromazine clozapine most phenothiazines zotepine	sudden benzodiazepine withdrawal tricyclic antidepressants
Increased weight gain / metabolic changes	chlorpromazine clozapine olanzapine perphenazine sertindole zotepine	lithium mirtazapine other antipsychotics tricyclic antidepressants valproate

Potential metabolic pharmacokinetic interactions associated with antipsychotic drugs

Metabolising (cytochrome P450) enzyme	Inhibitor	Inducer	Antipsychotic substrate
1A2	caffeine cimetidine ciprofloxacin fluvoxamine	barbiturates phenytoin tobacco smoke	asenapine clozapine† olanzapine
2D6	amiodarone bupropion cimetidine duloxetine fluoxetine paroxetine sertraline* terbinafine	rifampicin	aripiprazole chlorpromazine clozapine†† fluphenazine haloperidol perphenazine risperidone sertindole thioridazine zuclopenthixol
3A4	cimetidine diltiazem grapefruit juice** itraconazole ketoconazole clarithromycin erythromycin protease inhibitors verapamil	carbamazepine efavirenz phenytoin rifampicin St John's wort	aripiprazole chlorpromazine clozapine†† haloperidol quetiapine risperidone sertindole ziprasidone

* at higher doses; ** unclear significance; † major; †† minor
NB. Sulpiride, amisulpride and paliperidone are not extensively metabolised and are largely excreted unchanged

Antiepileptic and psychotropic drugs as substrates, inhibitors, or inducers of CYP enzymes

	CYP1A2	CYP2C9	CYP2C19	CYP2D6		
Substrates	Tricyclic antidepressants (demethylation) Fluvoxamine	Phenytoin Phenobarbital	Tricyclic antidepressants (demethylation) Citalopram	Tricyclic antidepressants (hydroxylation) Fluoxetine Paroxetine	Thioridazine Perphenazine Haloperidol Clozapine Olanzapine	Tricyclic antidep (demethylatio Sertraline Nefazodone
	Clozapine Olanzapine		Phenytoin Diazepam	Venlafaxine Mianserin	Risperidone Sertindole	Reboxetine Diazepam Alprazolam Midazolam Triazolam
Inhibitors	Fluvoxamine	Fluoxetine Valproate	Felbamate	Thioridazine Fluoxetine Paroxetine		Fluoxetine Fluvoxamine Nefazodone
Inducers	Carbamazepine Phenytoin Phenobarbital Primidone					Carbamazepine Phenytoin Phenobarbital Primidone Oxcarbazepine[a] Topiramate[a] Felbamate[a]

[a] Oxcarbazepine, topiramate and felbamate are much weaker enzyme inducers compared with carbamazepine, phenytoin, and barbiturates.

Summary of PK DIs between newer antidepressants and SGAs

Antidepressant	Antipsychotic	Effect	Proposed mechanism
Fluoxetine	Clozapine	Increase in plasma clozapine concentrations (40 – 70%)	Inhibition of various CYP isoforms (CYP2D6, CYP2C19 and CYP3A4)
	Risperidone	Increase in plasma concentrations of the active moiety of risperidone by 75%	Inhibition of CYP2D6 and, to a lesser extent, CYP3A4
	Olanzapine	No change or minimal increase in plasma olanzapine concentrations	Inhibition of CYP2D6
	Aripiprazole	Increase by 45% in plasma concentrations of aripiprazole	Inhibition of CYP2D6 and CYP3A4
	Iloperidone	Increase (up to twofold) in plasma iloperidone concentrations	Inhibition of CYP2D6
Paroxetine	Clozapine	Increase in plasma clozapine concentrations (20 – 40%)	Inhibition of CYP2D6
	Risperidone	Increase in plasma concentrations of the active moiety of risperidone by 40 – 50%	Inhibition of CYP2D6
	Aripiprazole	Increase in plasma concentrations of aripiprazole by 40 – 50%	Inhibition of CYP2D6
	Iloperidone	Increase (up to twofold) in plasma iloperidone concentrations	Inhibition of CYP2D6
Duloxetine	Risperidone	Minimal increase (by 26%) in plasma concentrations of the active moiety of risperidone	Inhibition of CYP2D6
	Olanzapine	No change or minimal increase in plasma olanzapine concentrations	Inhibition of CYP2D6 (?)

Summary of PK DIs between newer antidepressants and SGAs

Antidepressant	Antipsychotic	Effect	Proposed mechanism
Fluvoxamine	Clozapine	Increase (up to 5 – 10-fold) in plasma clozapine concentrations	Inhibition of CYP1A2 and, to a lesser extent, CYP2C19 and CYP3A4
	Olanzapine	Increase (up to twofold) in plasma olanzapine concentrations	Inhibition of CYP1A2
	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
	Quetiapine	Increase in plasma concentrations of quetiapine by 159%	Inhibition of CYP3A4
	Aripiprazole	Decrease by 40% in systemic clearance of aripiprazole	Inhibition of CYP3A4
	Asenapine	Increase by 29% in the AUC of asenapine at fluvoxamine dosage of 50 mg/day	Inhibition of CYP1A2
Sertraline	Risperidone	Increased plasma concentrations of risperidone (36 – 52%) only at high doses of sertraline (150 mg/day)	Inhibition of CYP2D6
Citalopram/ escitalopram	Aripiprazole	Minimal increase (by 20%) in plasma concentrations of aripiprazole and dehydroaripiprazole	Inhibition of CYP2D6

Pharmacodynamic interactions

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. Bupropion	All SGAs	Weight loss	Be aware

Pharmacodynamic interactions

Antidepressants	SGAs	Outcome	Actions
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 Torsades de pointes is very rare but additive risk factors are family history of sudden death; personal history of syncopes, arrhythmias or heart conditions; hypokalemia, hypomagnesemia and co-prescription of other medications that ↑ QTc. Cases are more frequent in females aged > 65 years. In the US, consider legal risk. Some SGAs (iloperidone and ziprasidone) have been approved with warnings after particular concern for QTc prolongation and FDA asked for more studies. The FDA requires a QTc warning for the use of high doses of citalopram. Consider these warnings when co-prescribing.

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Questions ?