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Psychotropic drugs and ART

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There is an increased risk for depression in individuals infected with HIV. Goal of this paper is to inform of potential drug interactions between various psychotropic drug classes and antiretroviral therapy and to discuss how these may be co-administered. Clinically relevant interactions with altered concentrations of psychotropic agents are seen mostly with boosted ART-regimes as well as those containing the non-nucleoside reductase inhibitors (NNRTIs) efavirenz and nevirapine. The effect of psychotropic medications on ART is minimal. Exceptions are the inducing effect of St. John's wort on protease inhibitors (PIs) and NNRTIs, and the CYP3A4 inhibition of fluvoxamine. [1]

Tricyclic antidepressants (TCAs)

TCAs have a narrow therapeutic window. TCA concentrations can easily reach toxic levels, potentially causing arrhythmias, anticholinergic reactions, sedation and confusion. Both ritonavir and cobicistat can increase TCA concentrations, requiring careful monitoring for adverse reactions. Efavirenz and nevirapine on the other hand reduce TCA levels and hence its therapeutic efficacy. These interaction phenomena are especially relevant for those TCAs, which are primarily metabolized via the isoenzyme CYP3A4, eg. amitryptyline, clomipramine, imipramine and trimipramine. Theoretically the interaction potential is lower with desipramine, nortriptyline, maprotiline and doxepin, since these are primarily metabolized via CYP2D6. [1, 2]

Selective serotonin re-uptake inhibitors (SSRIs)

SSRIs have a broad therapeutic window. Fluctuations in concentrations are therefore less problematic as seen with TCAs. They are less cardiotoxic and have fewer anticholinergic side effects. Within the SSRI class, agents are comparable with respect to their efficacy, but differ in side effect and interaction profiles. Up to 30% of patients on SSRIs report sexual dysfunction (citalopram 3%) and 20% suffer from gastrointestinal problems (especially after therapy initiation). Further side effects are restlessness, sleep disturbance, dry mouth, headache, hyperprolactinemia, hypoglycemia and mania. SSRI concentrations may be elevated by co-administration of ritonavir or cobicistat, and may be reduced by NNRTIs. Fluvoxamine also has an inhibiting effect. Its use should therefore be avoided if possible, or if co-administered, one should monitor for elevated PI- and NNRTI-levels. SSRIs are eliminated by various pathways, requiring individual evaluation for potential interactions. Citalopram's potential for interacting is very low. It is currently being discussed, if sertraline and paroxetine have sufficient efficacy when combined with a boosted ART-regime. More frequent side effects are reported when fluoxetine is combined with ritonavir, hence a boosting agent should be avoided if possible. A patient's genetic polymorphism generally plays an additional role, as seen in the following case. [1, 2]

Case 1: drug interaction with escitalopram despite its low interactive potential

A 46-year old HIV-infected female is being treated for depression with escitalopram 10mg. On April 25th, her ART was changed to emtricitabine/tenofovir 200/245 mg qd with darunavir/ritonavir 600/100 mg bid. Three days later, esomeprazole is added to treat gastroesophageal reflux. On April 29th, the patient presents with nausea and

confusion. Upon examination, likely diagnosis is serotonin syndrome based on the following symptoms: sweating, mydriasis, myoclonus, hyperactive reflex of deep tendons and stiffness. These symptoms disappeared after discontinuation of escitalopram.
The fact that an interaction occurred despite escitalopram's low interactive potential, can be explained by darunavir/ritonavir and esomeprazole blocking its elimination pathways. The enzymes involved in the metabolism of escitalopram, including CYP3A4, CYP2D6 and CYP2C19, additionally manifested an innate reduced activity. Hence the inhibitory effect of medications in addition to the genetic polymorphism lead to an escitalopram level that was 12-times higher (619nmol/l vs. 52nmol/l). Its half-life increased 2-3-fold. [3]
In order to prevent such interaction in slow metabolizers, pantoprazole should be considered as a drug of choice if a proton pump inhibitor is indicated. [4]

Miscellaneous antidepressants

These are mostly substrates of CYP3A4 enzymes; concentrations can be elevated by co-administration with ritonavir or cobicistat and reduced by NNRTI-containing regimens. With these substances, doses of antidepressants should be individually titrated to response. St. John's wort is an inducer of both the isoenzyme CYP3A4 and p-glycoprotein. With it, PI and NNRTI levels can fall below the therapeutic range, resulting in a loss in ART efficacy. Patients should be informed to watch for St. John's wort in numerous commercially available products, eg. Remifemin plus ®, as well as in certain herbal sleep remedies. [1, 2]

Antipsychotics

Since aripiprazole and quetiapine are intensively metabolized by CYP3A4, numerous drug interactions are expected with boosted ART regimens. A reduced dose is required as seen in case 2 below. Risperidone is mainly metabolized via CYP2D6 and has a low interactive potential unless the patient is a slow metabolizer for this enzyme. [2, 5]
Olanzapine exhibits another elimination profile, being metabolized also by CYP1A1, which is induced by ritonavir. A 50% dose increase of olanzapine is indicated, as shown in pharmacokinetic study. This phenomenon is not expected with cobicistat. [6, 7]

Case 2: regular quetiapine dose is not tolerated when combined with boosted ART

A 57-year old HIV-infected patient, on emtricitabine, tenofovir, atazanavir/ritonavir, commences treatment with quetiapine for depression. He experiences rapid weight gain, fatigue and confusion. After the discontinuation of quetiapine, he loses weight, the other symptoms subside. Quetiapine is extensively metabolized by CYP3A4, which in turn is inhibited by ritonavir and cobicistat. If treatment with quetiapine is indicated, it is recommended to reduce its dose to 1/6th when also on ritonavir. [2, 8]

Case 3: aripiprazole over-dose symptoms intensified through CYP3A4-inhibition

A 43-year old HIV-infected Spanish patient on darunavir/ritonavir is being treated with aripiprazole and duloxetine for depression and anxiety. After one month, the aripiprazole dose is increased to 50 mg, and the patient suffers from confusion and loss in coordination. Weeks later he presents at the emergency department with fever, cough, headache, stiff neck, back ache, blurred vision; meningitis is suspected. Because symptoms are relieved only temporarily with analgesics and fluids, all medications are discontinued. An aripiprazole concentration of 1100ng/ml is measured (therapeutic range 100-200ng/ml). It is recommended that the aripiprazole dose be reduced to ¼ when co-administered with CYP3A4 and CYP2D6 inhibitors. [9]

Miscellaneous agents

The drug interaction potential with pregabalin and valproate are low, since these agents are not metabolized via the isoenzyme CYP3A4. A case reports of an interaction between valproate and ritonavir due to an induction of glucuronyl transferase. [2]

Case 4: reduced efficacy of valproate when co-administered with lopinavir/ritonavir

An HIV-infected patient with bipolar disorder takes paroxetine and valproate 250 mg tid. Three weeks after initiating ART with lopinavir/ritonavir, lamivudine and zidovudine, his manic symptoms worsen. A 48% reduction in valproic acid levels is documented. After an increase in the daily dose to 1500 mg and the addition of olanzapine, valproic acid concentrations return to normal. Since this is a ritonavir-specific interaction,

Major enzymes involved in the metabolism of atypical antipsychotics

Enzyme	Psychotropic agent					
	quetiapine	olanzapine	clozapine	risperidone	ziprasidone	aripiprazole
CYP1A2		++	++			
CYP2C19			+			
CYP2D6		+	+	++		++
CYP3A4	++	+	+	+	+	++
UGT1A4		++				
aldehyde oxidase					++	
recommendation with ritonavir	1/6 dose	1 1/2 dose	Increased dose?			1/4 dose

valproate doses need to be adjusted only with ritonavir, and not likely with cobicistat. [2]

Benzodiazepines

Many benzodiazepines are metabolized via CYP3A4 and should therefore not be combined with boosted ART if possible. Midazolam, alprazolam and triazolam use is contraindicated with ritonavir or cobicistat due to a drastic increase in plasma concentrations and half-life. [2] The half-life of triazolam, for example, increases from four to 50 hours. Concurrent use with other benzodiazepines requires a low initial dose with careful titration. Diazepam is also metabolized via CYP2C19. Increased light-headedness and confusion may occur when combined with a boosted regimen and omeprazole, since all enzymes involved would be blocked. Pantoprazole may be used instead. Oxazepam, lorazepam and tetrazepam do not interact significantly and may be combined with all antiretrovirals. [2, 4]

Overview of interactions between ART and psychotropics

Medication	Interactions with protease inhibitors	Interactions with NNRTIs	Comments
Antidepressants			
Tricyclic antidepressants	TCA ↑	EFV, NVP: TCA ↓	Agents of choice: desipramine, nortriptyline, maprotiline, doxepine
SSRIs			
Citalopram **Escitalopram** [11]	study: escitalopram 20mg QD + RTV 600mg (single dose) in 18 healthy subjects: no significant interactions	citalopram ↓ possible escitalopram ↓ possible	escitalopram is metabolized via numerous enzymes reducing the potential for interactions
Fluoxetine [12, 13]	in theory: fluoxetine ↑, PIs ↓; reports of cardiac and neurologic events; case study: serotonin syndrome with RTV-containing ART (100-600mg BID) and fluoxetine; symptoms: mental changes, convulsions, fever, diarrhea, vomiting; symptoms disappeared with discontinuation or dose reduction of RTV or fluoxetine; fluoxetine 50%, RTV 100mg BID	EFV: no interaction NVP ↑ possible	PIs/NNRTIs: higher potential for drug interactions; long half-life: 4 days; monitor for toxicity
Fluvoxamine [2]	in theory: PIs ↑	in theory: NVP ↑	monitor for PI-/NNRTI-toxicity
Paroxetine [14]	study: paroxetine 20mg QD + FPV/r 700/100mg BID for 10 days in healthy subjects: paroxetine; AUC ↓ 58%; DRV/r: paroxetine ↓ 30-40%	EFV: no interaction	Mechanism unclear; With PIs monitor for paroxetine efficacy and titrate dose accordingly
Sertraline [15]	DRV/r: sertraline (50mg): 49% ↓	EFV: sertraline ↓ 39%	with PIs/RTV monitor for sertraline efficacy and adjust dose accordingly
Other antidepressants			
St. John's wort [17, 18]	St. John's wort: IDV/r AUC ↓ 57%, CYP-3A4-Substrate ↓	St. John's wort: NVP 35% ↓	use with PIs and NNRTIs is contraindicated
Trazodone [19, 20]	DRV/r: trazodone ↑ study: trazodone 50mg + RTV 4x200mg in 10 healthy subjects: trazodone: C_{max} 34% ↑, t½ 122% ↑, cl 52% ↓, fatigue, nausea, dizziness, hypertension, loss of consciousness reported	trazodone ↓	with PIs/RTV monitor for trazodone toxicity and adjust dose accordingly
Venlafaxine [21]	in theory: venlafaxine ↑ study (single dose): indinavir 800mg – no change in venlafaxine levels	in theory: venlafaxine ↓	study performed without RTV boosting
Antipsychotics			
Aripiprazole [2]	reduce oral aripiprazole dose to ¼	efavirenz/rilpivirine: monitor, titrate dose individually; nevirapine/etavirine: p.o.: double dose, upon discontinuation decrease dose to 10-15mg i.m./extended release: avoid co-administration	caution: QT-prolongation with RTV, EFV, RPV
Risperidone [2]	risperidone ↑	risperidone ↓	caution: QT-prolongation with RTV, EFV, RPV

Olanzapine [2, 6, 7]	RTV: olanzapine 50% ↓ cobicistat: olanzapine ↑ (clinical relevance unclear)	?	caution: QT-prolongation with RTV, EFV, RPV
Quetiapine [2, 15]	avoid co-administration or reduce quetiapine dose to 1/6th	EFV: quetiapine ↓	caution: QT-prolongation with RTV, EFV, RPV
Amisulpride [2, 15]	no interaction	no interaction	caution: QT-prolongation with RTV, EFV, RPV
Miscellaneous			
Pregabalin [2, 15]	no interaction	no interaction	easy to combine
Valproate [2, 15]	RTV: valproate ↓	no interaction	easy to combine
Benzodiazepine sedatives			
Lorazepam (2,15)	no interaction	no interaction	easy to combine
Oxazepam (2,15)	no interaction	no interaction	easy to combine
Diazepam (2,15)	diazepam ↑	EFV: diazepam ↓↑	reduce interactive potential by adding pantoprazole with boosted regimens
Triazolam [19]	contraindicated	triazolam ↓	Avoid co-administration

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