Treating psychosis in patients with HIV/AIDS

Michael N. Diduch, PharmD, Rebecca H. Campbell, PharmD, Mary Borovicka, PharmD, BCPS, BCPP, Elizabeth A. Cunningham, DO, FAPA, and Christopher J. Thomas, PharmD, BCPS, BCPP

Mr. S, age 56, has human immunodeficiency virus (HIV) and schizoaffective disorder. He presents to your clinic with increased auditory hallucinations, disorganized behavior, and worsened tremors that have begun to seriously disrupt his daily life. Mr. S is prescribed risperidone; however, he reports that he has not been taking it lately due to the tremor despite being controlled on his medication regimen for nearly 1 year. His Abnormal Involuntary Movement Scale (AIMS) score reveals an increased wrist rigidity compared with previous clinic visits. Mr. S has a 40 pack-year history of smoking and history of IV drug use. Furthermore, he has a medical history of type 2 diabetes mellitus, hypertension, and hyperlipidemia.

His medication regimen includes atazanavir sulfate, 200 mg/d, ritonavir, 100 mg/d, efavirenz/emtricitabine/tenofovir disoproxil fumarate, 600/200/300 mg/d, risperidone, 6 mg/d, bupropion extended-release, 300 mg/d, gabapentin, 600 mg/d, amlodipine, 5 mg/d, pravastatin, 40 mg/d, metformin, 1000 mg twice daily, and glipizide, 10 mg twice daily. Today, his laboratory findings show that his CD4 count is 405 cell/mm^3, and his viral load is <40 copies/mL, indicating his HIV is well managed. A hepatitis C virus antibody test result is negative and serum creatinine level is 1.0 mg/dL. Total cholesterol is 212 mg/dL, high-density lipoprotein cholesterol is 43 mg/dL, low-density lipoprotein cholesterol is 121 mg/dL, and triglycerides level is 238 mg/dL. Electrocardiography reveals a QTc interval of 426 ms. Mr. S's blood pressure is 105/65 mm Hg. Based on this clinic visit, the treatment team decides to change Mr. S's antipsychotic.

Drs. Diduch and Campbell are PGY-1 Pharmacy Practice Residents, Chillicothe Veterans Affairs Medical Center, Chillicothe, Ohio. Dr. Borovicka is Associate Professor, University of Toledo College of Pharmacy and Pharmaceutical Sciences, Toledo, Ohio. Dr. Cunningham is Psychiatrist, Community Health Network, Indianapolis, Indiana. Dr. Thomas is Director, PGY-1 and PGY-2 Residency Programs, Clinical Pharmacy Specialist in Psychiatry, Chillicothe Veterans Affairs Medical Center, Clinical Associate Professor of Pharmacology, Ohio University College of Osteopathic Medicine, Chillicothe, Ohio.

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Psychiatric illness and HIV/AIDS

There is a strong link between mental illness and HIV/AIDS; 50% or more of patients with HIV/AIDS have a comorbid psychiatric disorder.[1] The prevalence of mental illness

Practice Points

- **Many cytochrome P450 (CYP) enzyme interactions exist between antiretrovirals and antipsychotics.** The degree to which an antiretroviral induces or inhibits CYP enzymes affects the metabolism of antipsychotics.
- Patients diagnosed with HIV/AIDS may be at a higher risk of experiencing extrapyramidal symptoms (EPS); therefore, **selection of antipsychotic agents less likely to cause EPS is an important consideration**.
- Both antiretrovirals and antipsychotics carry the risk of metabolic syndrome. **When selecting an antipsychotic agent, consider the associated likelihood of metabolic disturbances**, especially in patients with comorbidities that increase their risk of developing metabolic syndrome.

Vicki L. Ellingrod, PharmD, FCCP
Department Editor

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Table 1

Interactions between first-generation antipsychotics and protease inhibitors

		Protease inhibitors								
		Atazanavir	Darunavir	Fosamprenavir	Indinavir	Lopinavir/ Ritonavir	Nelfinavir	Ritonavir	Saquinavir	Tipranavir
First-generation antipsychotics	Chlorpromazine	+	+	+	+	+++	+	+	+++	++
	Fluphenazine		+			+		+	+++[a]	++
	Haloperidol	++	++	+	++	+++	++	++	+++[a]	++
	Loxapine[b]									
	Molindone					+		+		+
	Perphenazine					+		+	+++[a]	++
	Pimozide	+++	+++	+++	+++	+++	+++	+++	+++	+++
	Thioridazine	++[a]	+++			+++	++[a]	++	+++[a]	+++
	Thiothixene					++		+		
	Trifluoperazine					+		+	+++[a]	

Source: References 6-14,19-28

\+ Interaction exists
++ Interaction exists; consider alternative therapy
+++ Interaction exists; avoid therapy

[a]Interaction based primarily on prolonged QTc associated with adding both agents
[b]While loxapine does not have CYP interactions, its metabolite amoxapine is a major CYP2D6 substrate

Note: For combination products, please refer to individual medications

Clinical Point

Patients with HIV/AIDs with primary psychosis may have poor medication adherence rates due to illness-related confusion or paranoia about medications

in patients with HIV/AIDS is reported to be 8 times higher than in those without HIV/AIDS.[2] Depression, bipolar disorder, anxiety disorders, delirium, substance abuse, and schizophrenia have all been identified in persons receiving highly active antiretroviral therapy (HAART). Patients with HIV/AIDS and psychiatric illness have a decreased quality of life, poor adherence to medications, faster disease progression, and increased mortality. Care of these individuals is complicated by the stigma of HIV/AIDS and the prevalence of the illness in underserved populations, as well as the need for complex medication regimens and the possibility of drug–drug interactions (DDIs).[1,2] If left untreated, psychiatric illness in patients with HIV/AIDS may lead to further transmission of HIV as a result of patients engaging in high-risk behaviors, along with poor adherence to HAART.[3]

Individuals diagnosed with schizophrenia, schizoaffective disorder, and bipolar disorder are at greater risk for HIV infection.[3] Patients with HIV/AIDS with primary psychosis may have poor medication adherence rates due to illness-related confusion or paranoia about medications. Furthermore, they may lack the resources to manage the complications and stress related to living with HIV/AIDS.

New-onset, or secondary psychosis, has been reported in individuals with late-stage HIV/AIDS with CD4 counts <200 who have not been diagnosed with a psychotic disorder previously.[3] These patients may experience more persecutory and grandiose delusions rather than hallucinations. Neuropsychiatric symptoms in patients with HIV/AIDS may be due to the presence of HIV or other infections

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Table 2

Interactions between second-generation antipsychotics and protease inhibitors

		Protease inhibitors								
		Atazanavir	Darunavir	Fosamprenavir	Indinavir	Lopinavir/ Ritonavir	Nelfinavir	Ritonavir	Saquinavir	Tipranavir
Second-generation antipsychotics	Aripiprazole	++	++	+	++	++	++	++	++	++
	Asenapine					+		+		
	Brexpiprazole	+	+	+	+	+	+	+	+	+
	Cariprazine	+	+	+	+	+	+	+	+	+
	Clozapine	+	+	+	+	+++	+	+	+++	+
	Iloperidone	+	+	+	+	+	+	+	+	+
	Lurasidone	++	+++	++	+++	+++	+++	+++	+++	+
	Olanzapine		+			++		+		+
	Paliperidone	++[a]				+++[a]	++[a]	++[a]	+++[a]	
	Quetiapine	++	++	+	++	+++	++	++	+++	+
	Risperidone	+	+	+	+	++	+	+	+	++
	Ziprasidone	++	+	+	+	+++	++	++	+++	+

Source: References 15-28

\+ Interaction exists
++ Interaction exists; consider alternative therapy
+++ Interaction exists; avoid therapy

[a]Interaction based primarily on prolonged QTc associated with adding both agents
[b]While loxapine does not have CYP interactions, its metabolite amoxapine is a major CYP2D6 substrate

Note: For combination products, please refer to individual medications

in the CNS, tumors, or other inflammatory illnesses. Medications that have been implicated in neuropsychiatric symptoms include efavirenz, rilpivirine, and other HAART regimens; interferon; metoclopramide; corticosteroids; muscle relaxants; and clonidine. It is possible that symptoms may continue even after the medications are discontinued.[3]

Antipsychotics remain the treatment of choice for psychosis in HIV/AIDS, regardless of the cause of the symptoms. Many factors must be taken into consideration when choosing an antipsychotic, such as DDIs, adverse effect profiles, patient history of antipsychotic use, cost, and patient preference. Here we focus primarily on DDIs and adverse effect profiles.

Drug–drug interactions

When treating psychosis in patients with HIV/AIDS, it is crucial to consider potential DDIs. Many antipsychotics and antiretroviral medications utilize cytochrome P450 (CYP) enzymes for their metabolism. The CYP enzyme system is responsible for the oxidative reactions that constitute the phase I reactions necessary for the metabolism of most drugs. Inhibition and induction of CYP enzymes are among the most common causes of pharmacokinetic DDIs. Antipsychotics are predominately metabolized by CYP3A4, CYP1A2, and CYP2D6.[4]

The DDIs arise because many antiretroviral medications inhibit, or in some cases, induce, these CYP enzymes, thereby altering substrate-drug metabolism. Inhibiting

Clinical Point

Many antiretrovirals inhibit or induce CYP enzymes used in the metabolism of antipsychotics

Clinical Point

Non-nucleoside reverse transcriptase inhibitors and PIs are the antiretrovirals most likely to cause DDIs with antipsychotics

Table 3

Interactions between first-generation antipsychotics and non-nucleoside reverse transcriptase inhibitors

		Non-nucleoside reverse transcriptase inhibitors			
		Delavirdine	Efavirenz	Nevirapine	Etravirine
First-generation antipsychotics	Chlorpromazine	+	++	+	+
	Fluphenazine				
	Haloperidol	+	++	+	+
	Loxapine[b]				
	Molindone				
	Perphenazine				
	Pimozide	+++	+++	+	+
	Thioridazine		+++[a]		
	Thiothixene				
	Trifluoperazine				

Source: References 6-14,19-28

\+ Interaction exists
++ Interaction exists; consider alternative therapy
+++ Interaction exists; avoid therapy

[a]Interaction based primarily on prolonged QTc associated with adding both agents
[b]While loxapine does not have CYP interactions, its metabolite amoxapine is a major CYP2D6 substrate

Note: For combination products, please refer to individual medications

a CYP enzyme pathway can decrease substrate-drug clearance and lead to increased levels of that drug. This, in turn, can cause an increased risk of adverse effects, such as extrapyramidal symptoms (EPS) or QTc prolongation, which are both types of pharmacodynamic DDIs.[4-28] However, because antipsychotics often have more than one pathway of metabolism, it can be challenging to understand the full effect of CYP-related DDIs. Furthermore, CYP enzyme inducers can decrease drug levels, and in the case of antipsychotics, lead to subtherapeutic responses.

Table 1[6-14,19-28] ***(page 36), Table 2***[15-28] ***(page 41), Table 3,***[6-14,19-28] and ***Table 4***[15-28] ***(page 43)*** list many of the known CYP enzyme-related DDIs that may occur with combination antipsychotic and antiretroviral medication therapy and aim to predict CYP induction or inhibition based on a particular combination. The following antiretroviral medications do not have any CYP-related interactions and therefore are not included in the ***Tables***: abacavir, didanosine, emtricitabine, lamivudine, stavudine, tenofovir disoproxil, zidovudine, enfuvirtide, maraviroc, and raltegravir.

These ***Tables*** include the risk ratings for all D-rated (consider alternative therapy) and X-rated (avoid therapy) combinations. The majority of D-rated interactions are caused by CYP inhibition or induction that could potentially lead to altered antipsychotic levels. The majority of X-rated interactions are caused by increased QTc prolongation that may or may not be due to CYP-related DDIs. For example, paliperidone is not believed to be affected by the CYP enzyme system, but it does present a high risk of QTc prolongation on its own. When combined with an antiretroviral that also has a high risk of QTc prolongation, such as lopinavir, then the risk further increases.

Non-nucleoside reverse transcriptase inhibitors and protease inhibitors (PIs) are the antiretroviral medications most likely to cause DDIs with antipsychotics. Other antiretroviral classes, such as nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs), fusion inhibitors, chemokine receptor 5 inhibitors, and integrase inhibitors, are not associated with CYP-related DDIs.[19-28] For the most part, the severity of the CYP-related DDIs have not been well studied; therefore, most recommendations call for closer patient monitoring when combining antiretroviral medications and antipsychotics.[6-18] The goal is to monitor for any changes in medication efficacy or adverse effects.

Consider adverse effect profiles

When selecting an antipsychotic agent for a patient receiving HIV therapy, also consider

adverse effect profiles. The emergence of adverse effects can greatly impact patients' quality of life, leading to consequences of medication nonadherence and exacerbation of mental illness.

Extrapyramidal symptoms. Patients with HIV have a higher sensitivity to treatment-emergent EPS from antipsychotics.[2] This sensitivity is generally thought to arise from the involvement of HIV on the basal ganglia. Historically, psychotic symptoms in HIV have been managed with second-generation antipsychotics (SGAs) at the lowest effective dose because these medications are less likely to cause EPS.[1,29] The antipsychotic with the lowest rate of EPS is clozapine, followed by quetiapine, olanzapine, ziprasidone, and aripiprazole. Conversely, high-potency first-generation antipsychotics (FGAs) have the highest rates of EPS, followed by intermediate-potency FGAs and risperidone.[30]

Metabolic disturbances are another concern with concomitant antipsychotic/antiretroviral therapy. Patients with HIV who are receiving NRTIs or PIs can present with drug-induced lipodystrophy syndrome, which is associated with hyperglycemia, hyperinsulinemia, hyperlipidemia, and hypertension, and ultimately may cause metabolic syndrome.[29] The prevalence of metabolic syndrome in patients receiving PI therapy has a vast range—2% to 84%—which can be attributed to inconsistent definitions, criteria, and assessment methodology.[29] Use of a PI is considered to be the most prominent risk factor for developing lipodystrophy.[29] Among the PIs, metabolic disturbances in regards to lipids are most often seen with lopinavir/ritonavir (LPV/r), saquinavir/ritonavir, tipranavir/ritonavir, and fosamprenavir/ritonavir.[31] In comparison with LPV/r, darunavir showed improvement in lipids.[32] Atazanavir (ATV) boosted with ritonavir has not shown clinically significant adverse effects on lipids.[31] Additionally, amprenavir, LPV/r, and ritonavir demonstrated more glucose uptake inhibition via blockade of the glucose transporter type 4 than ATV.[31] Of the NRTIs, lipodystrophy syndrome is most commonly seen with stavudine, which is used minimally in practice.[2]

The rates of metabolic disturbance with antipsychotic use range from 2% to 36%.[2] The American Psychiatric Association recommends selecting one of the SGAs least likely to affect metabolic parameters.[29] Aripiprazole and ziprasidone are associated with the lowest risk of weight gain, hyperglycemia, and hyperlipidemia. They are followed by risperidone and quetiapine, which are associated with moderate risk,

Table 4

Interactions between second-generation antipsychotics and non-nucleoside reverse transcriptase inhibitors

		Non-nucleoside reverse transcriptase inhibitors			
		Delavirdine	Efavirenz	Nevirapine	Etravirine
Second-generation antipsychotics	Aripiprazole	+	++	++	++
	Asenapine				
	Brexpiprazole	+	+	+	+
	Cariprazine	+	+	+	+
	Clozapine	+	++	+	+
	Iloperidone	+	+	+	+
	Lurasidone	+	+	+	+
	Olanzapine				
	Paliperidone		+++[a]		
	Quetiapine	+	+++	+	+
	Risperidone	+	+	+	+
	Ziprasidone	+	+++	+	+

Source: References 15-28

\+ Interaction exists
++ Interaction exists; consider alternative therapy
+++ Interaction exists; avoid therapy

[a]Interaction based primarily on prolonged QTc associated with adding both agents

Note: For combination products, please refer to individual medications

Clinical Point

Patients with HIV have a higher sensitivity to treatment-emergent EPS from antipsychotics

Clinical Point

Patients with HIV who are receiving NRTIs or PIs can present with drug-induced lipodystrophy syndrome

Related Resources

- Cohen MA. HIV: How to provide compassionate care. Current Psychiatry. 2013;12(6):19-23,A,B.
- Khan AY, Zaidi SN. Reducing morbidity and mortality from common medical conditions in schizophrenia. Current Psychiatry. 2016;15(3):30-32,34-38,40.

Drug Brand Names

Abacavir • Ziagen
Amlodipine • Norvasc
Amprenavir • Agenerase
Aripiprazole • Abilify
Asenapine • Saphris
Atazanavir • Reyataz
Brexpiprazole • Rexulti
Bupropion ER • Wellbutrin SR
Cariprazine • Vraylar
Chlorpromazine • Thorazine
Clonidine • Catapres
Clozapine • Clozaril
Darunavir • Prezista
Delavirdine • Rescriptor
Didanosine • Videx EC
Efavirenz • Sustiva
Efavirenz/emtricitabine/tenofovir disoproxil fumarate • Atripla
Enfuvirtide • Fuzeon
Emtricitabine • Emtriva
Etravirine • Intelence
Fluphenazine • Prolixin
Fosamprenavir • Lexiva
Gabapentin • Neurontin
Glipizide • Glucotrol
Haloperidol • Haldol
Iloperidone • Fanapt
Indinavir • Crixivan
Lamivudine • Epivir
Lopinavir/ritonavir • Kaletra
Loxapine • Loxitane
Lurasidone • Latuda
Maraviroc • Selzentry
Metformin • Glucophage
Metoclopramide • Reglan
Molindone • Moban
Nelfinavir • Viracept
Nevirapine • Viramune
Olanzapine • Zyprexa
Paliperidone • Invega
Perphenazine • Trilafon
Pimozide • Orap
Pravastatin • Pravachol
Quetiapine • Seroquel
Raltegravir • Isentress
Rilpivirine • Edurant
Risperidone • Risperdal
Ritonavir • Norvir
Saquinavir • Invirase
Stavudine • Zerit
Tenofovir disoproxil • Viread
Thioridazine • Mellaril
Thiothixene • Navane
Tipranavir • Aptivus
Trifluoperazine • Stelazine
Zidovudine • Retrovir
Ziprasidone • Geodon

and then clozapine and olanzapine, which are associated with high risk.[2,30,33]

Management of metabolic adverse effects involves switching the antiretroviral agent and/or antipsychotic agent to an alternative associated with lower metabolic risk. Antipsychotics with low metabolic risk include aripiprazole, lurasidone, and ziprasidone. Lifestyle modifications are encouraged. Additionally, medication interventions, such as metformin, are also recommended in patients meeting criteria for pre-diabetes or type 2 diabetes mellitus.[2] Lipid panels and metabolic parameters should be monitored periodically, according to guidelines.[25,34]

Bone marrow toxicity and blood dyscrasias. Lastly, consider the risk of bone marrow suppression. Patients receiving clozapine for treatment-resistant schizophrenia should be closely monitored for neutropenia and agranulocytosis. Although zidovudine is rarely used, its use is associated with adverse myelosuppressive effects, and the combination of clozapine and zidovudine could pose danger to the patient.[2,35,36]

CASE CONTINUED

Because Mr. S's diagnosis of HIV puts him at a higher risk of developing EPS, and because he is already experiencing increased wrist rigidity, the treatment team decides to switch his antipsychotic therapy to an agent with a lower risk of EPS. His comorbidities, including type 2 diabetes mellitus, hypertension, and hyperlipidemia, are taken into account, and an SGA with a benign metabolic profile is considered. Aripiprazole and ziprasidone are favorable options. However, because efavirenz, ATZ, and ritonavir may cause QTc prolongation, ziprasidone, the SGA with the highest rate of QTc prolongation, is not the preferred option.

Mr. S's SGA therapy is switched from risperidone to aripiprazole. Because potential CYP-related interactions between aripiprazole and Mr. S's current antiretroviral therapy could lead to increased aripiprazole levels. Mr. S is started on a low dose (5 mg/d) with the goal to titrate based on response and tolerability. Increased levels of aripiprazole may increase the risk of akathisia, drowsiness, headaches, and fatigue. Mr. S is monitored closely for improvement of EPS, adverse effects of medication, and metabolic parameters. Furthermore, if the treatment team believes there is a more preferred antipsychotic for the patient that it did not prescribe because of the risk of DDIs, it may be worthwhile to consider discussing the HAART regimen with the patient's infectious disease treatment team.

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Clinical Point

Although zidovudine is rarely used, its use is associated with adverse myelosuppressive effects

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