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# High Dose Haloperidol for Delirium in HIV-Associated Dementia

**Nicole M Bohm[1]*, Madelyne Ann C Bean[2], Ryan P Medved[3], Meghan May[4], Shannon Drayton[5] and M Sean Boger[6]**

[1]*Department of Clinical Pharmacy and Outcomes Sciences, Medical University of South Carolina College of Pharmacy, USA*
[2]*Department of Medicine, Division of Infectious Diseases, Medical University of South Carolina, USA*
[3]*South Carolina College of Pharmacy, USA*
[4]*Department of Pharmacy, Morton Plant Mease Bay Care Health System*
[5]*College of Pharmacy, Department of Clinical Pharmacy and Outcomes Sciences, Medical University of South Carolina, USA*
[6]*Department of Medicine, Division of Infectious Diseases, Medical University of South Carolina, USA*

***Corresponding author:** Nicole M Bohm, Department of Clinical Pharmacy and Outcomes Sciences, Medical University of South Carolina College of Pharmacy, 280 Calhoun St, QE205, Charleston, SC 29425, USA, **E-mail:** bohm@musc.edu

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## Abstract

The limited evidence available has suggested that patients with HIV–associated dementia respond clinically to low doses of antipsychotics and may be more prone to experience side effects at typically used doses. In this case, a 30-year-old female with untreated HIV/AIDS was admitted for aggressive behaviors refractory to low doses of multiple agents. However, she responded without adverse events to higher doses of haloperidol in conjunction with lorazepam in the setting of newly initiated combination antiretroviral therapy. A review of the relevant literature and discussion follows a description of this patient's hospital course.

**Keywords**: Antipsychotics; Delirium; HIV-Associated Neurologic Disorder (HAND); Dementia

## Background

HIV-associated neurocognitive disorder (HAND) describes a spectrum of neurocognitive deficits due to HIV infection including dementia [1]. HIV-associated dementia (HAD) is considered to be one of the most severe manifestations of HAND and may present as an end stage complication of HIV. Prior to the availability of combination antiretroviral therapy (cART), HAD affected 50-70% of individuals with CD4+ cell count<200 cell/mm$^3$ (AIDS) [2]. While the incidence has decreased about 50% since the early 1990s, the prevalence of HAD appears to be increasing as HIV has become a chronic medical illness with an improved life expectancy due to cART therapy [3].

The pathophysiology of HAND has not been fully elucidated, but because of its neurotropism, HIV can affect the central nervous system (CNS) directly, inducing a variety of neurological syndromes including depression, anxiety, dementia, delirium, and psychosis [1,3,4]. The primary mechanism involves infiltration of macrophages, direct infection of astrocytes, and upregulation of the inflammatory cascade [5,6]. Additionally, allelic variations in the apolipoprotein E (ApoE) gene also have been strongly associated with Alzheimer's disease in the HIV-uninfected population. In HIV-infected persons, possession of the ApoE4variant allele has been associated with several cognitive outcomes including dementia, peripheral neuropathy, and impairment in cognition and verbal memory [1].

Delirium is one of the most common psychiatric features associated with HAD, and may cause patients to experience visual and auditory hallucinations as well as delusions [7]. Delirium has been associated with increased risk of mortality, and if left untreated, it has been estimated to confer a 20% risk of mortality in hospitalized patients. Although patients with HAD are at greater risk for developing delirium, other general risk factors for delirium include older age, multiple medical co-morbidities, polypharmacy, impaired visual acuity, and previous episodes of delirium. Additional risk factors that have been reported in HIV patients include increased intracranial pressure due to CNS infection (e.g. toxoplasmosis, cytomegalovirus), hypoxia with Pneumocystis pneumonia (PJP), malnutrition, HIV nephropathy, substance intoxication and withdrawal, cART toxicity, and variations in hydration or electrolyte status [4,7].

Treating patients with HAD poses a major challenge to healthcare workers. The efficacy and safety of psychotropic drugs in the HIV patient population, especially those experiencing dementia with delirium, have yet to be fully evaluated. The antipsychotics specifically studied in this disease state include chlorpromazine, haloperidol, risperidone, and thioridazine which all demonstrate D2 dopamine receptor blockade [2,8,9]. It has been recommended that antipsychotics should be initiated at low doses and titrated up slowly based on the response and tolerability to the patient. Previous literature suggests that HIV patients may be more sensitive to antipsychotics due to damage of the basal ganglia causing alterations in the pharmacodynamics [2]. Given the paucity of evidence, these potential risks of therapy should be considered, but medication titration should be based on the response observed in the individual. In some situations, a more rapid titration or higher dose may be warranted.

## Case Report

A 30-year-old African American woman was brought to the emergency department by her family due to increasingly aggressive behaviors, including breaking dishes and setting curtains on fire, felt to be dangerous to herself and others. She had recently been admitted to another hospital for similar issues, at which time her family became aware of her HIV seropositivity. MRI at that time showed nonspecific

mild T2 flair hyperintense appearance adjacent to the posterior horns of lateral ventricles bilaterally. A lumbar puncture revealed normal opening pressure and no significant laboratory abnormalities other than protein of 51 mg/dL (reference range 15-45 mg/dL).

The patient had been diagnosed with HIV approximately two years ago, but long-standing infection was suspected. Her past medical history was significant for asthma and anemia in addition to HIV and dementia, but no other history was available. She took no medications prior to admission. Upon physical exam, the patient was cachectic, verbally and physically aggressive, and speaking nonsensically, impulsively, and tangentially. Auditory and/or visual hallucinations were suspected. She had no history of psychosis prior to the recent admission. Family reported several months of inattention, and more recently she had been calling out to dead people and pacing around the house. Although she previously smoked marijuana and crack cocaine, there was no known recent use and urine drug screen was negative. She did smoke approximately 1 pack per day of cigarettes according to her mother. Her family history was negative for psychotic illness.

In the emergency room, she required 4-point restraints and a sitter. Olanzapine 2.5 mg every 6 hours as needed (prn) was initiated, but no administration was documented. Consultations were obtained from infectious diseases, psychiatry, and neurology. Initially, it was felt that HAD was unlikely given the lack of atrophy on the previous MRI, so an infectious workup was pursued including cytomegalovirus, varicella zoster virus, herpes simplex virus, hepatitis, JC virus, syphilis, cryptococcal disease, toxoplasmosis, tuberculosis, and cerebrospinal fluid (CSF) and blood for bacterial, fungal, and acid fast bacilli stains and cultures. The infectious workup was negative, as was CSF cytology for malignancy. Repeat CT showed diffuse parenchymal volume loss in excess of what is expected for her age as well as hypoattenuation of the periventricular white matter. Subsequently, an MRI was suggestive of HIV encephalopathy (Figure 1). Pertinent HIV laboratory values include a CD4+ cell count of 26 cells/mm$^3$ (5%) and HIV RNA of 38,302 copies/mL.

Once admitted, olanzapine 2.5 mg every evening (qhs) was scheduled with prn doses available. During this treatment, the patient was intermittently sedated and agitated. During periods of wakefulness, she continued to be combative and aggressive physically and verbally. She was transitioned to several other regimens during her hospitalization, first haloperidol 2 mg orally (po) twice daily (BID) and 2 mg intravenously (IV) every 6 hours prn, then risperidone 0.5 mg BID plus 0.5 mg every 6 hours prn, and finally chlorpromazine 25 mg BID and 50 mg qhs with haloperidol 2 mg every 6 hours prn (Table 1). Due to concern for heightened sensitivity to antipsychotics based on previous reports in the literature, relatively low doses were used. If a lack of response was noted, a different agent was trialed with the rationale that response would be seen at a low dose and a different agent may be more effective without increasing the risk of side effects associated with higher doses. However, our patient remained aggressive despite medication adjustments. She would not participate in therapies, did not eat well, and often required physical restraints. Therefore, haloperidol was re-initiated at 2 mg three times daily (TID) and 2 mg every 8 hours prn in addition to lorazepam 1 mg every 6 hours prn. She demonstrated less consistent aggression and agitation. Adherence was initially intermittent, and administration required great perseverance by the staff. The patient continued to have a suboptimal response and displayed no adverse effects. Therefore, the haloperidol was titrated to 2.5 mg TID with the same prn regimen. After 5 additional days, it was again titrated to 5 mg TID, and after 9 days at that dose, to 5 mg BID with 7.5 mg qhs. Throughout this titration period, the patient seemed to improve somewhat, requiring physical restraints less often, eating more sufficiently, demonstrating less psychotic behavior, and showing overt improvement in adherence to medications. On hospital day 19, abacavir, lamivudine, and dolutegravir were initiated, both for a concerted effort to manage HIV infection and decrease the contribution of HAD/HAND but also to reduce viral load and, subsequently, the risk of HIV- transmission from her aggressive behaviors such as biting. After 1 month of cART, her HIV RNA was undetectable (<40 copies/mL). Eventually all physical restraints were discontinued. An attempt to remove the sitter was made, but the patient became agitated and fled her room. The patient continued to receive general medical care, and she was moved to a room nearby the unit clerk's desk with her door open. The sitter was removed from the room for increasing periods of time over the next 4 weeks and eventually discontinued. The patient remains resting through most of the day but is easily arousable and now participates with therapies. She now eats most of her meals, and her weight has increased from 38 kg on admission to 52 kg about 3 months later. Her CD4+ count increased to 181 cells/mm$^3$ approximately 2 months after antiretroviral initiation. Her behavior is appropriate, and no adverse events have been observed while receiving 17.5 mg daily of haloperidol and 4 mg daily of lorazepam.

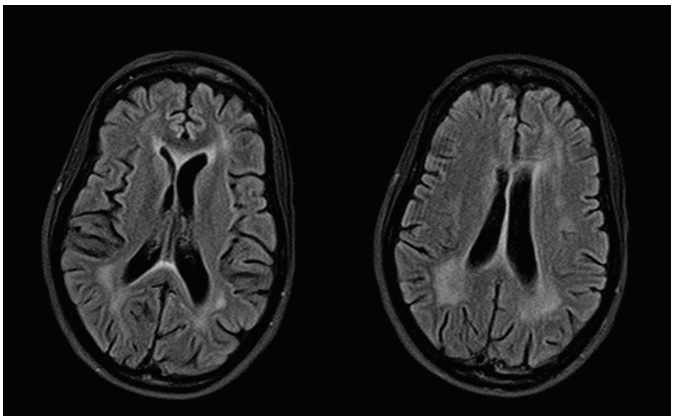

**Figure 1:** MRI showing patchy areas of periventricular T2 hyperintensity sparing the subcortical U fibers and associated parenchymal volume loss

## Discussion

This case illustrates an unexpectedly high requirement of neuroleptic medications to achieve control of neuropsychiatric symptoms. While HAD was not high on the differential initially, this diagnosis was later conferred. Unfortunately, the diagnosis of HAD is difficult and relies on exclusion of other pathology. The most common findings on brain CT include diffuse cortical atrophy out of proportion for the age of the patient, deep white matter hypoattenuation, and enlargement of the ventricles [10]. MRI findings include atrophy in the cortical and subcortical regions including the basal ganglia, [11] and T2 weighted hyperintensities may be seen in the basal ganglia,[12] periventricular white matter and centrum semiovale that don't typically enhance with IV contrast and are better visualized on FLAIR.

Prognosis may be dependent on clinical presentation and symptom severity and onset rather than on HIV-related markers (CD4+ count or HIV RNA) [4]. The severity of neurocognitive deficits is positively associated with mortality [5,13]. Following one episode of delirium, 6-month mortality may be as high as 25% in elderly patients with HIV.[5] While this patient is young, she had untreated and presumably long-standing HIV [5]. Her symptoms were severe but improved with a carefully titrated antipsychotic regimen in the setting of cART initiation. The role of cART is unclear but may have been important to achieving clinical stability. The pathophysiology of HIV-associated neurocognitive disorders

**Table 1:** Total daily dose (mg) of antipsychotic and sedative medications

| Hospital Day | Scheduled | Prn and 1× orders | Lorazepam |
|---|---|---|---|
| Evening admission; no documented administrations in Emergency Department | | | |
| 2 | 2.5 olanzapine | 12.5 olanzapine<br>5 haloperidol | 0.5 |
| 3 | 2.5 olanzapine | 5 olanzapine | 4 |
| 4 | 2.5 olanzapine | | 2 |
| 5 | 2.5 olanzapine | | 2.5 |
| 6 | 2.5 olanzapine | 7.5 olanzapine | |
| 7 | 2.5 olanzapine<br>2 haloperidol | 2.5 olanzapine | |
| 8 | 4 haloperidol | 4 haloperidol | |
| 9-10 | 4 haloperidol | 2 haloperidol | |
| 11 | 2 haloperidol<br>0.5 risperdone | 2 haloperidol | |
| 12 | 1 risperdone | | |
| 13 | 0.5 risperdone | 25 chlorpromazine<br>0.5 risperdone<br>2 haloperidol | |
| 14 | 50 chlorpromazine | 6 haloperidol | |
| 15 | 100 chlorpromazine | 4 haloperidol | |
| 16 | 100 chlorpromazine | 4 haloperidol | 2 |
| 17 | 25 chlorpromazine<br>2 haloperidol | 2 haloperidol | 3 |
| 18 | 8 haloperidol | | 2 |
| 19 | 6 haloperidol | | 1 |
| | Initiation of abacavir, lamivudine, dolutegravir | | |
| 20-26 | 6 haloperidol | | 3 |
| 27 | 8 mg haloperidol | | 2 |
| 28 | 6.5 mg haloperidol | | 3 |
| 29 | 8.5 mg haloperidol | | 3 |
| 30 | 6 haloperidol | | 3 |
| 31 | 6 haloperidol | | 2 |
| 32 | 6.5 haloperidol | | 2 |
| 33 | 6 haloperidol | 2 mg haloperidol | 2 |
| 34 | 7 haloperidol | | 3 |
| 35 | 7.5 haloperidol | | 5 |
| 36 | 9.5 haloperidol | | 2 |
| 37 | 7 haloperidol | | 2 |
| 38 | 12.5 haloperidol | | 3 |
| 39 | 15 haloperidol | | 3 |
| 40-46 | 15 haloperidol | | 4 |
| 47+ | 17.5 mg haloperidol | | 4[a] |

**a.** Occasionally 3 or 5 mg were received in a 24h period due to timing of administration.

likely involves HIV-infected monocytes crossing the blood-brain barrier (BBB), followed by virion release or replication following differentiation into macrophages [14-16]. The ensuing inflammatory response may cause neuronal damage [17]. Even in the setting of undetectable viral load, continued monocyte migration facilitated by tat protein may contribute to the progression of HAND [15]. Thus, it is possible but uncertain that cART initiation may have impacted this patient's outcome. The CNS penetration-effectiveness (CPE) ranking in combination with pharmacokinetic and dynamic studies can guide selection of cART when CNS sequelae of HIV are suspected [18,19]. The regimen utilized in this case, dolutegravir, lamivudine, and abacavir, distributes well into the CSF and may have potent CNS antiviral activity [20]. It remains controversial whether higher CPE improves HAND outcomes over generalized cART [19]. Additionally, some concerns remain about the risks of neurotoxicity of some cART agents [21,22]. Conflicting reports and the lack of consistent recommendations in guidelines leave clinicians without a clear basis for selecting cART.

The literature surrounding the use of antipsychotics in HAD also lacks robustness and mostly dates to the 1990s. In a prospective study conducted by Fernandez and colleagues, 38 AIDS patients with delirium, 50% of whom had comorbid organic mental disorder(OMD), were treated with 2 to 10 mg of IV haloperidol and 0.5 to 10 mg of IV lorazepam (total daily dose ranging from 12-132 mg and 4.5-37.5 mg, respectively) [23]. Half of the subjects experienced extrapyramidal symptoms (EPS), and patients with delirium and OMD experienced EPS more frequently (14/19 *vs* 3/19 patients), but doses administered to patients with versus without OMD are not reported. Sewell and colleagues performed a small prospective study evaluating 17 male patients with HIV infection aged 18 to 50 years old who were a part of the comprehensive study at the San Diego HIV Neurobehavioral Research Center [2]. The patients had prominent delusions and hallucinations without delirium or a history of psychosis. Ten were taking zidovudine. During the 6-week study period, patients were treated with haloperidol or thioridazine, and the doses were gradually increased, balancing the reduction of psychotic symptoms with side effects. Lower doses of the antipsychotics were used in this study compared to those used in other clinical situations. Eight of the 11 patients in the haloperidol group completed the study with a maximum dose of 2.9 mg and 5 of the 6 patients in the thioridazine completed the study with a maximum dose of 145 mg. The medications caused significant improvement as measured by the Brief Psychiatric Rating Scale (BPRS) and the BPRS disorganization subscale, for which total scores decreased by 32% and 62%, respectively. The improvement in disorganization occurred earlier in the thioridazine group and later in the haloperidol group. There was improvement in positive symptoms as demonstrated by the Scale for the Assessment for Positive Symptoms (SAPS) scores; however, no significant improvement was seen on the Scale for the Assessment of Negative Symptoms (SANS). The patients in the thioridazine group scored better on the BPRS hostility subscale. Although the patients received relatively low doses of antipsychotics, the majority experienced side effects. All patients in the haloperidol group required benztropine after experiencing EPS and one patient developed tardive dyskinesia (TD). Two of the 6 patients receiving thioridazine developed EPS treated with trihexyphenidyl, and one developed TD. This study suggested that low doses of antipsychotics may be appropriate for patients with HIV-associated psychosis, but it was limited by a small sample size, unblinded design, and lack of a placebo group.

An additional randomized, double blind trial compared haloperidol, chlorpromazine, and lorazepam in medically hospitalized AIDS patients with delirium [8]. Relevant exclusion criteria included schizophrenia, bipolar disorder, or schizoaffective disorder; presence of neuroleptic malignant syndrome; seizure disorder; withdrawal syndrome or anticholinergic delirium; or those who were experiencing delirium due to a terminal event (i.e., passing away in less than 24 hours). A total of 30 patients with an average age of 39 years, mostly men (77%), were included. Doses were titrated hourly until the patient was stabilized on a dose or scored a 12 or less on the Delirium Rating Scale (DRS). Subsequently, a maintenance dose was continued for up to 6 days. During the first 24 hours, the mean doses of chlorpromazine, haloperidol, and lorazepam were 50 mg, 2.8 mg, and 3 mg respectively, and the average maintenance doses were 36 mg, 1.4 mg, and 4.6 mg respectively. Delirium improved in both the haloperidol and chlorpromazine group on day 2, but not the lorazepam group. From day 2 to the end of treatment, there were no significant changes in any of the 3 groups on the DRS. Five patients died within 8 days of initiation. Patients in the chlorpromazine group did show significant improvement on the Mini-Mental State exam on day 2, but scores declined by the end of treatment. Patients only scored on the Parkinsonism subscale of the EPS Rating Scale, and these scores were not

significant at baseline or during maintenance treatment. As in Sewell's study, relatively low doses of antipsychotics were effective within the first 24 hours; however, the rate of EPS was minimal.

Risperidone was also studied in a cohort of 21 patients with HIV-associated psychosis and/or mania [9]. The mean age was 39 and 20 were male. Unlike the previous studies, 4 of the patients had psychiatric illness previously diagnosed and 12 of the patients had manic symptoms upon presentation. The risperidone mean maximum dose was 3.3 mg and the mean minimum dose was 1.6 mg. The one patient requiring 4 mg per day had preexisting psychiatric illness. The mean time to clinical response was 4.1 weeks. Thirteen patients became symptom-free and 1 patient had no improvement. Two of the patients had a history of EPS, but no serious adverse events occurred during the study period. Three patients experienced drowsiness, drooling, and a combination of these along with slight stiffness but all subsided when the risperidone dose was decreased.

Additional data are needed regarding the selection of antipsychotic agents, optimum dosing ranges, and strategies to mitigate adverse effects to guide clinicians and improve patient safety [5]. However, in patients with poor response and lack of adverse events, titrating to higher doses may be reasonable. The lack of evidence in patients with HAND for antipsychotics that confer a lower risk of EPS in the general population led to use of haloperidol for the patient reported above, but consideration could be given to alternative antipsychotics. Based upon our experience, an earlier titration could be considered to avoid prolonged symptoms for the patient and risk to staff. Additionally, the exact role of cART in improving symptoms remains unclear. For this patient, improvement coincided with both antipsychotic medication dose increases but also with improved HIV biomarkers. Therefore, we recommend considering early initiation of cART in patients with poor response to antipsychotic medications, and selecting agents with high CNS penetration seems prudent.

As opposed to the majority of patients in these studies, our patient was an African-American woman. When applying the aforementioned data to our patient, it is notable that most patients included in the studies were Caucasian. While our patient's genomic status was unknown, the prevalence of ultra-rapid metabolism is higher in certain ethnic groups, including those of African descent [24]. Patients with these alleles may require higher doses to achieve concentrations similar to those produced by lower doses in patients with less rapid metabolism.

She presented with aggressive and dangerous behaviors that persisted despite treatment with a variety of low dose antipsychotic regimens. Due to concern for heightened sensitivity due to HIV related factors that might have resulted in EPS, the haloperidol dose was not titrated up at a substantial pace for the first month of therapy. After that time, the dose was systematically increased every 1 to 2 days based on her response and the absence of adverse effects. This delayed titration may have decreased the risk of EPS. Once a therapeutic effect was attained at 17.5 mg the patient's symptoms stabilized without any notable adverse events other than mild sedation. The improvement in HIV biomarkers to cART was pronounced: undetectable viral load after 4 weeks and an increase from 26 to 181 CD4+ cells by 8 weeks. This was consistent with expected clinical response to cART initiation with viral suppression expected within 8-24 weeks and an average of 50-150 cells/$mm^3$ during the first year of cART [25]. It remains uncertain if her improvement was due solely to antipsychotic medication dose or duration, response to cART, or most likely, a combination of those factors.

## Conclusion

The patient described herein required higher doses of antipsychotic medications than described in the preponderance of available data, and she did not experience EPS. Therefore, in patients not responding to low doses, dose escalation with careful surveillance for adverse events may be reasonable to mitigate aggressive or dangerous symptoms of HAND. Depending on individual circumstances and co-infections, poor response to antipsychotic medications may prompt consideration for initiating cART, and selecting agents with high CNS penetration seems prudent.

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