Choice of Antipsychotic in HIV-Infected Patients

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Human immunodeficiency virus (HIV) infection is associated with a wide range of mental illnesses.[1–9] Some are due to HIV infection itself; others are higher in prevalence than among the general population due to a more frequent comorbidity associated with HIV risk factors. Psychosis is one that has been less frequently studied. Causes for psychotic symptoms in an HIV seropositive (HIV+) patient include delirium,[9,10] late stage HIV-associated dementia, mania (a subgroup of which is associated with HIV-1 infection itself), recurrence of premorbid psychotic illnesses (particularly in the severely mentally ill),[11] psychoactive substance intoxication, antiretroviral (ARV) medication toxicity,[12,13] and general medical conditions manifesting with psychotic symptoms (e.g., cryptococcal meningitis and neurosyphilis).[14,15]

Less is known about the specific forms of psychosis that occur in association with HIV infection. It is known that antipsychotic medications are effective in treating psychotic symptoms in this setting. With combination antiretroviral therapy (CART), also referred to as *highly active antiretroviral therapy* (HAART), HIV infection has become a chronic, manageable condition (akin to diabetes mellitus [DM]). Thus, the prevalence of psychotic disorders among HIV+ patients is expected to increase, and special issues are associated with choice of antipsychotic medication in the HIV infected.

Psychotic symptoms in HIV+ patients can be classified as due to a primary psychotic disorder (e.g., schizophrenia) or as secondary to other psychiatric disorders (e.g., delirium, dementia, mania, and alcohol and substance use disorders). This distinction is of limited clinical value, as psychotic symptoms most frequently occur as the manifestations of other psychiatric disorders in the HIV infected. For example, mania occurs in approximately 10% of patients with late-stage HIV infection and frequently manifests with psychotic symptoms.[16]

An alternate classification of perhaps greater utility in this setting is psychosis that postdates versus antedates (or is premorbid to) HIV infection, although variance may occur in this bifurcation related to the interval from infection to positive HIV antibody testing. The former category poses by far the greater challenge in establishing the etiology of the psychotic symptomatology. A medical work-up is necessary to exclude and treat secondary causes (particularly in delirium and dementia). Commonly, the psychotic symptoms occurring in HIV infection are associated with a general medical condition and require specific medical intervention beyond symptomatic control achieved with an antipsychotic. For example, manic symptoms associated with cryptococcal meningitis require treatment with fluconazole, itraconazole, or amphotericin B. Zidovudine may induce a mania requiring its discontinuation.[17] Neurosyphilis may present with mania and require treatment with IV aqueous penicillin G.[18]

With an otherwise negative medical work-up, HIV infection of the central nervous system (CNS) may present with mania, potentially indicating the use of a highly CNS-penetrating antiretroviral (ARV) regimen, although the specific utility of highly CNS-penetrating ARV regimens remains controversial. (See APA HIV/AIDS guidelines and the update.[6,7])

ARV Medication–Induced Psychosis

Psychosis postdating HIV infection may be a toxicity of CART.[13] As noted, zidovudine has been implicated.[17,19,20] Nevirapine,[21] efavirenz,[12,22] and abacavir[13] have also been ascribed to carry this toxicity, as have other categories of antiviral drugs such as ganciclovir[23] (used to treat cytomegalovirus infection). Psychoses occurring in the form of these toxicities have been transient, and they have responded to discontinuation of the offending agent together with substitution of a new drug (or CART regimen) and the use of low-dose haloperidol or risperidone.[13] As more patients are exposed to newly approved ARVs, a constant vigilance for psychosis (and other psychiatric symptoms) from psychoneurotoxicity will be necessary.

Typical or Atypical Antipsychotic Agent?

The quality and quantity of information on choice of antipsychotic for patients taking ARVs are limited.[24–30] No antipsychotic is specifically approved for HIV-associated psychosis—both typicals and atypicals have been used.

Bagchi et al.[31] reported on a case series of 350 schizophrenic, HIV+ patients enrolled in a managed health care system in New Jersey from 1992 to 1998, in which 282 (81%) had been given a prescription for an antipsychotic. Of those, 66.8% were prescribed typicals only, 3.2% were prescribed atypicals only, and 30% were treated with both atypical and typical agents during their treatment. A large percentage was switched from a typical to an atypical during their treatment. Patients prescribed an atypical were 4.25 times more likely to be maintained on their medication than patients who had been prescribed typical antipsychotic agents; however, the group taking atypical medications predominantly reflects the "switchers," limiting the generalizability of this study.

The rationale for switching to atypical antipsychotics and the higher frequency of treatment regimen maintenance with the atypicals are likely to be due to their lower side effect profile rather than any difference in efficacy. Specifically, the decreased rates of extrapyramidal reactions (particularly with the high-potency typical drugs) and of anticholinergic side effects (with the low-potency typical drugs) are a benefit of atypical antipsychotics. However, the long-term metabolic side effects of these agents, particularly clozapine and olanzapine, have become a greater concern[32] because the increased expected longevity of HIV+ patients is compromised by the potential for eventual development of DM as well as MI and CVA risk.

A rationale for the preference for atypical antipsychotic use in HIV-associated psychotic disorders has been suggested in a number of smaller case studies.[26,27,29,33] Risperidone (mean dose of 3.29 mg/day),[27] clozapine (mean dose of 27 mg/day),[25] and olanzapine (10–15 mg/day)[33] have each been reported to be effective. Clozapine was reported to be effective and reduced parkinsonian side effects[25]; however, the risk of agranulocytosis must be considered as a major precaution for use in the HIV infected due to the potential for a pharmacodynamic interaction with the neutropenia associated with the nucleoside reverse transcriptase inhibitors (an ARV group that constitutes the backbone of the predominant number of CART regimens).[26] One case report of an AIDS patient with cryptococcal meningitis showed that ziprasidone treatment reduced the Delirium Rating Scale score from 26 to 14; however, there were 2 episodes of premature ventricular contractions, mild-to-moderate prolongation of the QTc interval, hypokalemia, and hypomagnesemia concurrent with its use.[34] Ziprasidone was discontinued, and haloperidol was initiated and prescribed on discharge. We found no published reports to date on the use of ARVs with other atypical antipsychotic medications, i.e., aripiprazole and quetiapine or on the parenteral use of atypical medications in HIV+ patients with psychotic symptoms.

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Typical antipsychotics remain commonly prescribed.[31] Some consider low-dose haloperidol to be the preferred choice in this setting due to its established safety in the medically ill and low cardiac toxicity. Breitbart et al.[24] conducted a randomized controlled trial with delirious HIV-infected patients taking haloperidol or chlorpromazine (in low doses). Both were effective, whereas the benzodiazepine lorazepam was poorly tolerated. In fact, the lorazepam arm of the trial was discontinued as patients showed sedation, reduced level of consciousness, and decreased awareness of the environment or idiosyncratic agitation. In another study, the typical antipsychotic thioridazine (mean dose, 145 mg/day) was also effective in treating psychotic symptoms in HIV+ patients, and no extrapyramidal reactions were reported. Nevertheless, memory deficits due to anticholinergic side effects are a special concern for the HIV infected. Controlled empirical evidence supporting parenteral use of the antipsychotics is limited, although it is frequently used in clinical practice.[31]

While it is commonly accepted that atypical antipsychotics are preferred in the HIV infected, the empirical evidence specifically supporting their use over typical antipsychotics remains highly limited to date. The choice between first- and second-generation antipsychotics devolves to a choice of the specific antipsychotic medication indicated and must take into account side effect profile of the drug, clinical drug-drug interactions reported with CART regimens, cost, patient preference, and history of patient antipsychotic medication response. Consideration of the long-term metabolic effects of the atypical antipsychotics now carries a greater weight for use in this patient population. Although data are yet sparser for each specific atypical antipsychotic and the benefits are generally accorded to the entire group, variance on these side effects by agent should be carefully considered to attain optimal treatment outcomes.

Conclusions

Psychotic symptoms that occur in HIV+ patients may antedate or postdate HIV infection. The differential diagnosis is much more complex for the latter than the former. The added complexity of psychotic symptoms postdating HIV infection is due to CNS complications of HIV infection, other HIV-associated illnesses, and ARV toxicities that may cause psychotic symptoms. Antipsychotic medications are effective in treating psychotic symptoms in HIV+ patients. Clinicians should treat these patients aggressively.

The atypical drugs are generally preferred over the typical drugs in the setting of HIV infection due to their low propensity for extrapyramidal reactions and tardive dyskinesia, as well as their improvement of negative psychotic symptoms. However, they are now well described to carry the risk of metabolic syndrome, which is not shared by the typical drugs. This toxicity is of special concern to the HIV infected because the ARVs also cause metabolic syndrome (together with a potentially disfiguring lipodystrophy). While weight gain is not a significant issue for the HIV infected (who may be less than normal in total body weight), the associated DM and dyslipidemia risks of the atypical agents are a significant issue. The latter risks have now been clinically demonstrated to be associated with an increased risk for MI and CVA. The requisite use of ARVs for the HIV infected compounded by the concomitant use of the atypical antipsychotic medications places these patients at yet higher risk for metabolic syndrome and, therefore, for the potential for mortality associated with this syndrome over time.

While reports in the literature suggest that use of atypical antipsychotics may be preferred clinically for the HIV infected, this still remains to be proven in well-controlled clinical trials. Likewise, this preference must be justified against a risk:benefit ratio that has worsened for the atypical agents due to the metabolic syndrome. Unfortunately, the antipsychotics that are less likely to be associated with the metabolic syndrome (ziprasidone and aripiprazole) are not well studied to date in the HIV infected. Hence, an a priori rationale for use of the atypical antipsychotics in the HIV infected should not be adopted in lieu of the usual considerations for individually tailored psychopharmacologic treatment recommendations.

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