Psychopharmacologic Treatment Response of HIV-Infected Patients to Antipsychotic Medications

Dinesh Singh, M.B.Ch.B., M.Med. (Psych), F.C.Psych.; and Karl Goodkin, M.D., Ph.D., F.A.P.A.

As noted in last month's column, the atypical antipsychotics have generally been preferred to typical agents in the treatment of psychotic symptoms in patients infected with human immunodeficiency virus. However, these drugs also cause metabolic syndrome as a toxicity, which may exacerbate an existing metabolic syndrome toxicity (referred to as "lipodystrophy syndrome") commonly experienced by these patients and caused by long-term use of antiretroviral (ARV) medications. Hence, a more cautious deliberation over preference for the atypicals is warranted.

One relevant issue in evaluating the literature is that not all studies have quantified responses to therapy using reliable, validated psychometric scales. Singh et al.[1] described 12 manic patients treated with risperidone in a case series. The mean Young Mania Rating Scale score decreased from 28.4 to 3.9. Overall, psychotic symptoms remitted; however, not all patients respond to the first antipsychotic chosen, which necessitates switching.[1–3] The basal ganglia are an early site for HIV infection of brain, and parkinsonian symptoms (along with dopaminergic deficits) have specifically been attributed to HIV seropositive status (HIV+) in the absence of any neuroleptic exposure. Hence, the lower propensity for atypicals to cause EPS has contributed to a preference for them over typicals. With risperidone, few EPS and only mild sedation and sialorrhea were reported in this setting.[1] Olanzapine has been used successfully in an HIV infected patient who developed EPS with risperidone and other neuroleptics.[3] Clozapine-induced agranulocytosis has not yet been reported in an HIV+ patient but must be considered in this population, which is particularly disposed to ARV-associated neutropenia and is likely to be treated with filgrastim for this side effect.

Metabolic Syndrome and Lipodystrophy Syndrome

Metabolic syndrome and the associated lipodystrophy (predominantly characterized by lipoatrophy) described among the HIV infected has been largely attributed to protease inhibitors (PIs)[4]; however, the nucleoside reverse transcriptase inhibitor (NRTI) class has also been implicated.[4–7] The lipodystrophy syndrome predisposes HIV+ patients to an increased risk for insulin resistance, glucose intolerance, and diabetes mellitus; atherosclerosis; coronary artery disease; MI[8]; and CVA.[9] To the best of our knowledge, no study has yet examined the interaction of PIs (or NRTIs) with the atypical antipsychotics in terms of their potentially synergistic effects on the risk for and sequelae of the lipodystrophy syndrome. Patients treated with clozapine or olanzapine have higher risk of developing metabolic syndrome than do patients treated with risperidone or quetiapine, who, in turn, have higher risk than patients treated with aripiprazole or ziprasidone.[10] Therefore, we recommend using the atypical antipsychotics with the lowest propensity to cause metabolic syndrome, i.e., ziprasidone and aripiprazole. Still, new evidence suggests that treatment with medications to avert the metabolic syndrome toxicity of atypical antipsychotics, e.g., metformin, is effective in children and adolescents as well as adults.[11] Thus, if discontinuation of the offending agent proves to be an unviable option, concurrent treatment with other medications to reduce or eliminate this side effect may become a secondary therapeutic option. Metabolic side effects of atypical antipsychotics (increased insulin resistance, impaired glucose tolerance, and diabetes as well as dyslipidemia) need to be considered carefully in assessing the risk-benefit ratio among the HIV infected,[12,13] as these effects have still not been formally evaluated in this patient population but should be in the future.

As is true for the elderly and is generally true for the use of psychotropic medications in the HIV infected, the adage of "start low and go slow" applies. Since the beginning of the epidemic in the United States, there's a growing overlap between older age and HIV infection—11% of AIDS patients are over 50 years old. Lower doses of typical and atypical antipsychotics are preferred in HIV+ patients because they are more sensitive to EPS, lower doses avoid dose-sensitive toxicities generally, and most importantly, because response has been documented at doses lower than those used in a medically healthy population. HIV seropositive patients frequently have compromised liver function (which, for example, may be related to ARV toxicities, older age, or hepatitis C virus coinfection) and renal function (which may be related to older age or may occur in the setting of HIV nephropathy). Hence, liver and renal function should be screened routinely before prescribing to these patients. It should also be noted that higher doses (6 mg/day) of risperidone have been associated with EPS. It's currently unclear how long a patient should be treated with an antipsychotic once psychotic symptoms have resolved. With psychosis that postdates HIV infection, maintenance medication isn't necessarily required.[14] In patients with psychotic disorders that antedate HIV infection, e.g., chronic schizophrenia, long-term antipsychotic maintenance is recommended.[4,15] Combination ARV treatment (CART) for HIV infection is a long-term (possibly lifelong) treatment requiring 95% adherence to be ultimately successful in reducing plasma viral load of HIV to nondetectable levels (i.e., < 50 HIV-1 RNA copies/mL) in the peripheral blood. Importantly, patients with schizophrenia have been shown to be as adherent to their CART regimens as patients without a serious mental illness.[16] Adherence to atypical antipsychotics has been reported to be higher than that for typical antipsychotics among HIV+ schizophrenic patients.[2]

Drug-drug interactions are a major concern in the HIV infected. To date, 31 ARV or ARV combination drugs are approved by the U.S. FDA for use in the management of HIV infection. A new class of entry and fusion inhibitors has been approved (represented by enfuvirtide), and there are still other investigational drugs in process (e.g., the integrase inhibitors [e.g., MK-0518] and investigational non-NRTIs [NNRTIs], NRTIs, and PIs). In this field, there's a consistently rapid expansion of investigational drugs, and one must review the literature on a regular basis for usage guidelines. The use of ARVs sharing metabolism by the same cytochrome P450 (CYP) isoenzyme system is common in HIV/AIDS and, in fact, is used therapeutically as a "booster" strategy in combination formulations (e.g., ritonavir and lopinavir) based on their interaction on CYP3A4. Thus, some drug-drug interactions may be salutary, but one must be particularly aware of deleterious drug-drug interactions. Clinical reports of serious adverse events from ARV-psychotropic combinations have heightened awareness of the drug-drug interaction issue for psychiatrists treating the HIV+ patient.[4] The complexity arises from the pharmacokinetic variability in these patients, i.e., the same dose of drug does not produce the same steady-state plasma concentration in

all patients. For example, Marzolini et al.[17] reported a 10-fold variability in the concentration of efavirenz in patients taking a 600-mg dosage. Not only can drug-drug interactions accentuate this pharmacokinetic variability, but several others can as well: drug-food, drug–psychoactive substance use, and drug-disease (such as diseases affecting absorption, volume of distribution, metabolism, or excretion).

Most psychotropic medications are metabolized by the CYP isoenzymes, especially 3A4 and 2D6. Protease inhibitors and NNRTIs are primarily metabolized by the 3A4 microsomal enzyme isoform and by a secondary pathway to the 2D6 isoenzyme. Thus, when ARVs and psychotropic medications are used in combination, competition for metabolism by the same CYP isoenzyme system frequently occurs. Further, these drugs are substrates for the CYP system and may act as enzyme inducers or inhibitors. Significant inhibition of the 3A4 isoenzyme by the PIs, especially ritonavir, has resulted in reversible coma when combined with risperidone.[18] Use of clozapine, pimozide, and several benzodiazepines is contraindicated when ritonavir is concurrently prescribed. It should be noted that haloperidol, olanzapine, quetiapine, and risperidone are considered to be antipsychotics with little potential for interactions on the CYP hepatic microsomal oxidase system. Consideration of other concomitant medications is also important in making decisions about proper antipsychotic prescribing for the HIV infected. Medications commonly used concurrently with the ARVs for the HIV infected include antituberculous (e.g., rifampin and ethambutol) and antifungal (e.g., fluconazole, itraconazole, and ketoconazole) agents that also use the CYP isoenzyme system. Another potential source of drug-drug interactions is the altered plasma protein levels of HIV+ patients. For example, PIs and NNRTIs are highly protein bound and may displace other drugs in the setting of hypoalbuminemia, resulting in higher plasma concentrations of the displaced drug at the normally prescribed dosage.

Conclusions

As was clear from last month's column, low-dose treatment with the typical antipsychotic agents, e.g., haloperidol, is commensurately effective and may be as well tolerated as the atypical agents in HIV infected patients. Hence, enthusiasm for using atypical agents to treat psychotic symptoms in the HIV infected should be tempered for the present time. Likewise, when prescribing, it's important to understand both the interactions of the psychotropic medications with the ARVs in a CART regimen and the interactions that may occur with all of the other concomitant medications used (drugs used for opportunistic infections, over-the-counter medications, psychoactive substances, foods, nutritional supplements, and herbal remedies). Given the breadth that this area entails, it's wise to become well versed on the use of the most commonly prescribed medications and to understand the most common drug-drug interactions documented at the clinical (rather than the in vitro) level for psychotropic medications to be prescribed. We recommend that the psychiatrist consult updated resources on an ongoing basis, e.g., web-based databases for potential drug-drug interactions when initiating treatment or when adding new drugs for the HIV infected.*

The psychiatrist should maintain a high index of suspicion when HIV+ patients develop untoward side effects that are temporally related to starting new medications. Yet, many drugs have interactions in vitro that may not prove to be clinically significant. The relatively infrequent reports of severe adverse events, given the large number of psychotropic prescriptions in this patient population, bolster one's confidence that psychotropic medications (including the antipsychotics) are safe and sensible to use rather than sufficiently risky to justify withholding the benefits of psychopharmacotherapy. Whenever possible, it is recommended that psychiatrists use drugs that have a low potential for drug-drug interactions. Clinicians have more confidence using the typical antipsychotics; however, although the atypical agents are more deleterious regarding metabolic side effects and dyslipidemia, they have better safety profiles for EPS and anticholinergic side effects. Drugs with established safety profiles in this patient population should be chosen as the first line, which may explain, in part, why the typical antipsychotics remain commonly used with HIV+ patients. It's recommended that psychiatrists become specialized in treating this group of patients, that they attend multidisciplinary rounds with the infectious diseases physician, and that they participate in treatment decisions as a team member, to the greatest extent feasible.

*AIDS Education and Training Centers National Resource Center: http://www.aids-etc.org; AIDSInfo, the official repository for HIV/AIDS information from the U.S. Public Health Service: http://aidsinfo.nih.gov; AIDS drug info: www.pharminfo.com; American Foundation for AIDS Research (AmFAR): www.amfar.org; HIV/AIDS Treatment Information Service: www.hivatis.org; International Training and Education Center on HIV: http://go2itech.org.

Dr. Singh is Deputy Director, Consultant Psychiatrist, HIV Prevention Research Unit, South African Medical Research Council, Durban, South Africa. Dr. Goodkin is Professor, Departments of Psychiatry and Behavioral Sciences, Neurology, and Psychology, University of Miami School of Medicine, Miami, Fla.

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Corresponding author and reprints: Karl Goodkin, M.D., Department of Psychiatry and Behavioral Sciences and of Neurology (M836), University of Miami School of Medicine, 1400 NW 10th Ave., #803-A, Miami, FL 33136 (e-mail: KGoodkin@med.miami.edu).

References

1. Singh AN, Golledge H, Catalan J. J Psychosom Res 1997;42:489–493
2. Bagchi A, Sambamoorthi U, McSpiritt E, et al. Schizophr Res 2004;71:435–444
3. Meyer JM, Marsh J, Simpson G. Biol Psychiatry 1998;44:791–794
4. Forstein M, Cournos F, Douaihy A, et al. Arlington, Va: American Psychiatric Association; 2006: 1–17. Available at: http://www.psych.org/psych_pract/treatg/pg/HivAids.watch.pdf. Accessibility verified Feb 6, 2007
5. Dubé M, Zackin R, Parker R, et al. Program and Abstracts of the 11th Conference on Retroviruses and Opportunistic Infections; February 8–11, 2004; San Francisco, Calif. Abstract 74.
6. Dubé MP, Qian D, Edmondson-Melançon H, et al. Clin Infect Dis 2002;35:475–481
7. Gibert CL, Shlay JC, Bartsch G, et al. Program and Abstracts of the 16th International AIDS Conference; August 13–18, 2006; Toronto, Canada. Abstract WEPE0143
8. Henry K, Melroe H, Huebusch J, et al. Lancet 1998;351:1328
9. Maggi P, Fiorentino G, Epifani G, et al. AIDS 2002;16:947–948
10. Newcomer J, Nasrallah H. Adv Stud Med 2004;4:S1045–S1058
11. Klein DJ, Cottingham EM, Sorter M, et al. Am J Psychiatry 2006;163:2072–2079
12. Allison D, Mentore JL, Heo M, et al. Am J Psychiatry 1999;156:1686–1696
13. Henderson DC, Cagliero E, Copeland PM, et al. Arch Gen Psychiatry 2005;62:19–28
14. Halstead S, Riccio M, Harlow P, et al. Br J Psychiatry 1998;153:618–623
15. American Psychiatric Association. Am J Psychiatry 2000;157(11 Suppl):1–62
16. Walkup JT, Sambamoorthi U, Crystal S. J Clin Psychiatry 2004;65:1180–1190
17. Marzolini C, Telenti A, Decosterd LA, et al. AIDS 2001;15:71–75
18. Jover F, Cuadrado JM, Andreu L, et al. Clin Neuropharmacol 2002;25:251–253

