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# The concomitant use of second-generation antipsychotics and long-term antiretroviral therapy may be associated with increased cardiovascular risk

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ABSTRACT

To study the effect of concurrent use of second-generation antipsychotics (SGAs) on metabolic syndrome (MetS) components conferring increased cardiovascular risk in a sample of human immunodeficiency virus (HIV)-infected adults taking antiretroviral therapy (ART). A retrospective study of participants consecutively recruited at the UCSD HIV Neurobehavioral Research Program examined effects of combined ART and SGAs on body mass index (BMI), nonfasting serum lipids, diabetes mellitus (DM) incidence, and mean arterial pressure (MAP). Metabolic outcome variables and covariates were compared using *t*-tests, Chi-squared or Fisher's exact tests. Linear and logistic multivariable models explored metabolic outcomes for participants taking (SGA+) or not taking (SGA−) concomitant SGAs, after controlling for demographic and HIV disease- and ART-related covariates. Of 2229 HIV-infected participants, 12% ($N$=258) were treated with SGAs. In multivariable models adjusted for relevant covariates, the SGA+ group had significantly higher mean triglycerides, significantly higher odds of DM, significantly higher MAPs and marginally higher BMI. The use of SGAs in HIV-infected adults taking ART was independently associated with worse indicators of MetS and cardiovascular risk. Aggressive monitoring for the metabolic complications from concurrent SGA and ART is indicated in all patients receiving these medication combinations.



## 1. Introduction

Psychiatric disorders are more prevalent in human immunodeficiency virus (HIV) infected people than in the general population (Atkinson et al., 1988, 2008; Bing et al., 2001; Cournos and McKinnon, 1997; Gaynes et al., 2008; Rabkin, 2008). Prevalence of HIV infection among persons with serious mental illness (SMI) is estimated to be between 3% and 23%, or more than 10-fold higher than the 0.4% in the general United States population (Cournos and McKinnon, 1997; Lee et al., 2011; Meyer, 2003). Due to the high SMI prevalence in this population, psychotropic medications are commonly used by HIV-infected patients (Bing et al., 2001; Gaynes et al., 2008; Thompson et al., 2006; Vitiello et al., 2003; Walkup et al., 2004). Data from the US Medicaid population obtained from July 2002 through June 2003 showed that 89% of the HIV-infected people with SMI used psychotropic medications (Lee et al., 2011).

Antipsychotics are commonly employed for patients with SMI, in part due to the broad array of FDA-approved indications for antipsychotics in adults, including the acute and maintenance treatment of schizophrenia, acute mania, maintenance treatment in bipolar disorder and adjunctive therapy for major depressive disorder (MDD) (Meyer, 2010). While both the older "typical" and newer "atypical" medications (second-generation antipsychotics or SGAs) are widely used, SGAs have a therapeutic advantage due to a lower incidence of extrapyramidal symptoms (Meyer, 2010). Though SGA use has steadily increased due to this improved neurological tolerability and the availability of multiple generic drugs in this class, the enthusiasm for certain SGAs has been tempered by their association with metabolic abnormalities (e.g. hyperglycemia, weight gain, and hyperlipidemia) (Stahl et al., 2009) and an increased prevalence of metabolic syndrome (MetS)

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(Meyer and Stahl, 2009). MetS is a constellation of frequently concurrent conditions, including central obesity, atherogenic dyslipidemia, hypertension, glucose intolerance/diabetes mellitus (DM) and a prothrombotic/inflammatory state, that increase the risk of cardiovascular and cerebrovascular diseases (Girman et al., 2005; Wannamethee et al., 2005). Greater numbers of MetS components predict higher risk for myocardial infarction and stroke (Girman et al., 2005; Wannamethee et al., 2005). Whether due to treatment or inherent biological factors associated with SMI, MetS prevalence is 2–3 times greater in persons with schizophrenia or bipolar disorder compared to the general population (McEvoy et al., 2005), and thus represents an important source of increased cardiovascular risk.

In addition to possible biological variables related to the diagnosis of SMI itself, SMI patients also have a higher prevalence of behavioral factors (smoking tobacco, poor dietary habits, and inactivity) that amplify the risk of cardiovascular mortality compared to age-matched peers without SMI (Meyer, 2010), and higher rates of medical comorbidity noted at the time of diagnosis before exposure to antipsychotics (Meyer, 2010). Subsequent exposure to SGAs may therefore increase the risk of cardiovascular mortality for SMI patients as suggested by the increasing relative risk of cardiovascular mortality in SMI patients during the SGA era (Colton and Manderscheid, 2006; De Hert et al., 2009; Saha et al., 2007).

The development of metabolic adverse effects is not unique to SGAs, with an extensive literature documenting the impact of combination antiretroviral therapy (cART) for HIV on lipids, weight and cardiovascular risk. While cART markedly reduces mortality due to HIV infection, it is also associated specifically with increased prevalence of MetS (25–96%) (Carr, 2003; Falutz, 2007; Feeney and Mallon, 2011; Germinario, 2003). Despite the high rates of HIV and psychiatric comorbidity, and the known metabolic effects of SGAs and antiretrovirals, the metabolic consequences of SGA exposure in HIV-infected individuals have received virtually no coverage in the literature (Singh and Goodkin, 2007). This study attempts to address the gap in the clinical understanding of the metabolic impact of SGA use in HIV patients.

## 2. Methods

### 2.1. Study design

This retrospective, cross-sectional study examined metabolic outcomes in 2229 antiretroviral-treated, HIV-infected adults.

### 2.2. Subjects

Participants were HIV-infected volunteers consecutively recruited for clinical studies at the UCSD HIV Neurobehavioral Research Program (HNRP) in San Diego, CA, between January 1995 and September 2011. Participants were enrolled in various studies sponsored by the National Institute of Mental Health and the National Institute on Drug Abuse including 1097 from "The CNS HIV Anti-Retroviral Therapy Effects Research (CHARTER)" Study, 255 from "The California NeuroAIDS Tissue Network (CNTN)", 195 from "NeuroAIDS: Effects of Methamphetamine and Hepatitis C Virus", 179 from "Prospective Memory and HIV Infection (PROM)" and 509 from smaller HNRP studies.

Inclusion criteria were serologically documented HIV infection, age $\geq$ 18 years, current treatment with antiretroviral therapy (ART) and adequate documentation of concomitant medication use. Because the HNRP studies HIV-associated neurocognitive disorders, volunteers with conditions that prevented individuals from undergoing detailed neuropsychological testing (e.g., acute psychosis) or might confound assessment of specific HIV-related brain disorders were excluded (e.g., type I DM and schizophrenia, since the former can be associated with mircrovascular disease of the brain and neurocognitive impairment, and schizophrenia is a neurodevelopmental disorder with deficits in executive function, among other impairments). All subjects completed structured medical, psychiatric, and laboratory assessments. The duration of treatment with ARTs and SGAs was collected through standardized case report forms by trained research nurses. For the purpose of this study we selected data from the participant's most recent visit.

Protocols were approved by the Institutional Review Boards of participating institutions. Written informed consent was obtained from all study participants before enrollment.

### 2.3. Clinical evaluation and laboratory measures

Standardized general medical histories and physical examinations were performed, and blood pressure measurements obtained using automated calibrated mercury sphygmomanometers with appropriate cuff sizes. Systolic (SBP) and diastolic (DBP) measures were obtained from seated subjects to calculate mean arterial pressure (MAP). Height and weight for calculating body mass index (BMI) were measured. A diagnosis of DM was ascertained according to Expert Committee on the Classification of Diabetes Mellitus (2003) (Genuth et al., 2003). Venipuncture for nonfasting laboratory studies was performed at the time of the visit. After clotting, serum was assayed for total cholesterol (TC), high-density lipoprotein (HDL), low-density lipoprotein (LDL), serum triglycerides (TG) and glucose. TC was dichotomized as high ( $>$ 200 mg/dL) or normal, HDL-cholesterol values as low ( $<$ 40 mg/dL) or normal; the ratio of TC/HDL-cholesterol was also calculated (TC/HDL). Hepatitis C virus (HCV) serology (HCV Antibody essay: LabCorp, Burlington, NC) was examined because of the association of chronic HCV infection with DM (Mehta et al., 2000), insulin resistance (Romero-Gomez, 2006), impaired lipid metabolism (Lonardo et al., 2004; Negro and Sanyal, 2009) and MetS (Grigorescu et al., 2008).

### 2.4. Characterization of HIV infection

A detailed history of HIV illness and treatment was captured by a combination of questionnaires and standardized interview. Nadir CD4 cell count since HIV infection was self-reported. Past and current antiretroviral usage including usage dates, dose, and schedule for each drug was captured by self-report standardized questionnaires that were reviewed with clinicians. ART exposure was categorized as current use, past use, or never used. ART regimens were dichotomized as (1) protease inhibitor (PI) based vs. non-PI based (Nolan, 2003); and (2) Efavirenz (EFV) based vs. non-EFV based (Haubrich et al., 2009). Blood CD4 cell counts were measured by flow cytometry. HIV RNA levels were quantified in plasma and cerebrospinal fluid (CSF) by reverse transcriptase-polymerase chain reaction (Amplicor®, Roche Diagnostic Systems, Indianapolis, IN) using an ultrasensitive assay (lower quantification limit $<$ 50 copies/mL).

### 2.5. Psychiatric diagnoses and prescribed SGAs

Depending on the specific protocols, psychiatric diagnoses were assessed using either the Composite International Diagnostic Interview (CIDI) (Robins et al., 1988), the Psychiatric Research Interview for Substance and Mental Disorders (PRISM) (Hasin et al., 1996), or the Structured Clinical Interview for DSM-IV criteria (SCID IV) (Spitzer et al., 1992). Each of these assessments included modules for diagnosis of mood disorder, alcohol use disorders, and non-alcohol substance use disorders using DSM-IV criteria. Participants in the antipsychotic exposed group (SGA+) reported current use of one or more of the following SGAs: aripiprazole, clozapine, olanzapine, paliperidone, quetiapine, risperidone, or ziprasidone.

### 2.6. Statistical analysis

Two groups (SGA− and SGA+) were compared on demographic, HIV-associated, and psychiatric characteristics, using a two-sample $t$-test and Chi-square test for continuous and categorical variables, respectively. Two sample $t$-tests and Chi-square tests were also performed to analyze the effect of SGA use on eight metabolic variables: BMI, MAP, TC, HDL cholesterol, LDL cholesterol, TC/HDL ratio, triglycerides and DM. Additionally, TC and TG values were also analyzed on a dichotomized scale based on the most recent guidelines for risk ranges: TC $\geq$ 200 mg/dL, HDL $<$ 40 mg/dL, LDL $\geq$ 130 mg/dL, TC/HDL $\geq$ 5, and TG $\geq$ 150 mg/dL (Blackburn et al., 2008; Lemieux et al., 2000; Mannucci et al., 2008). Since each metabolic outcome was analyzed separately, we used all data available for each outcome to maximize the power of each analysis. Thus, sample sizes for regressions varied for each variable. HIV RNA levels were $\log_{10}$ transformed and analyzed both continuously and categorically, as undetectable vs. detectable.

Effects of individual SGAs on the metabolic outcomes were evaluated in a series of univariable analyses using the methods described above. In addition, outcomes were tested for an association with treatment duration of each SGA using Spearman correlation or logistic regression.

The use of individual ART medications in the SGA+ group was compared to that in SGA− group using the Chi-square test (or Fisher's exact test, if appropriate). The effects of PIs with known metabolic risks on the metabolic outcomes in this study were evaluated with $t$-tests (or Wilcoxon rank-sum test) and Chi-square test (or Fisher's exact test).

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