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Polypharmacy and risk of non-fatal overdose for patients with HIV infection and substance dependence

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ABSTRACT

Introduction: People living with HIV (PLWH) are at risk of both polypharmacy and unintentional overdose yet there are few data on whether polypharmacy increases risk of overdose. The study objective was to determine if the number and type of medication (e.g., sedating) were associated with non-fatal overdose (OD) among PLWH with past-year substance dependence or a lifetime history of injection drug use.
Materials and methods: This was a longitudinal study of adults recruited from two urban, safety-net HIV clinics. Outcomes were i) lifetime and ii) past-year non-fatal OD assessed at baseline and a 12-month follow-up. We used logistic regression to examine the association between each outcome and the number of medications (identified from the electronic medical record) in the following categories: i) overall medications, ii) non-antiretroviral (non-ARV), iii) sedating, iv) non-sedating, as well as any vs no opioid medication and any vs no non-opioid sedating medication. Covariates included demographics, medical comorbidities, depressive and anxiety symptoms, and substance use.
Results: Among 250 participants, 80% were prescribed a sedating medication, 50% were prescribed an opioid; 51% exceeded risky drinking limits. In the past month, 23% reported illicit opioid use and 9% illicit opioid sedative use; 37% reported lifetime non-fatal OD and 7% past-year non-fatal OD. The median number (interquartile range) of total medications was 10 (7, 14) and 2 (1, 3) sedating. The odds of lifetime non-fatal OD were significantly higher with each additional sedating medication (OR 1.26, 95% CI 1.08, 1.46) and any opioid medication (OR 2.31; 95% CI 1.37, 3.90), but not with each overall, non-ARV, or non-sedating medication. The odds of past year non-fatal OD were greater with each additional sedating medication (OR 1.18; 95% CI 1.00, 1.39, $p = 0.049$), each additional non-ARV medication (OR 1.07; 95% CI 1.00, 1.15, $p = 0.048$), and non-significantly for any opioid medication (OR 2.23; 95% CI 0.93, 5.35).
Conclusions: In this sample of PLWH with substance dependence and/or injection drug use, number of sedating medications and any opioid were associated with non-fatal overdose; sedating medications were prescribed to the majority of patients. Polypharmacy among PLWH and substance dependence warrants further research to determine whether reducing sedating medications, including opioids, lowers overdose risk.

1. Introduction

Treatment with effective antiretroviral medications has substantially extended the lives of people living with HIV (PLWH). Widespread use of single-tablet antiretroviral medications (ARV) with at least three active medications has led to prolonged viral suppression and management of HIV infection as a chronic disease (Deeks, Lewin, & Havlir, 2013; Greene, Justice, Lampiris, & Valcour, 2013). As a result, more than one-half of PLWH in the United States are over the age 50 (High et al., 2012). This epidemiologic shift has led to the accrual of age-related comorbidities such as cardiovascular disease, cancer, and neurocognitive disease in PLWH (Althoff et al., 2015; Greene et al., 2013; Robbins, Shiels, Pfeiffer, & Engels, 2014). In addition to older age, HIV-associated inflammation, frailty, and substance use (i.e. tobacco, alcohol, and other drugs) (Brothers & Rockwood, 2014; Crothers et al., 2005; Justice et al., 2016) contribute to a greater number of comorbidities complicating the management of HIV infection. Treatment guidelines, developed for

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people with one disease, but applied to people with multiple chronic conditions can lead to the prescription of multiple concomitant medications, often termed "polypharmacy," resulting in a significant daily medication burden (Edelman et al., 2013; Moore, Mao, & Oramasionwu, 2015). For PLWH, a greater number of medications raises the risk of medication interactions (Holtzman et al., 2013), medication nonadherence (Monroe, Rowe, Moore, & Chander, 2013), and discontinuation of ARV (Cantudo-Cuenca, Jiménez-Galán, Almeida-Gonzalez, & Morillo-Verdugo, 2014; Krentz & Gill, 2016).

Polypharmacy may also contribute to overdose, the leading cause of accidental injury death in the United States (Centers for Disease Control and Prevention, 2015). Examining overdose risks specifically among HIV populations is important because PLWH have twice the risk of overdose death as people without HIV infection (Green, McGowan, Yokell, Pouget, & Rich, 2012; Mathers et al., 2013). The proportion of deaths due to overdose among PLWH has increased as AIDS-related causes have declined (Schwarcz, Vu, Hsu, & Hessol, 2014). Why PLWH have greater overdose risk is not clear, but proposed reasons include co-morbid liver dysfunction, pulmonary dysfunction, more illicit drug and heavy alcohol use, and social isolation (Edelman et al., 2013; Green et al., 2012). Prescribed medications, particularly sedating medications like opioids and benzodiazepines, commonly contribute to polysubstance use-related overdose. PLWH are more likely to be prescribed high-dose opioid medications (Becker et al., 2016). Among patients prescribed opioid medications, the risk of overdose risk is greater for patients with depressive disorders (Turner & Liang, 2015), a common comorbidity of HIV infection. Despite the risk of overdose and increasing number of medications among a population with high incidence of substance use disorders, there are few data about whether the number of medications, or "polypharmacy" is associated with a greater risk of overdose for PLWH.

The objective of this study was to determine if the number of medications prescribed and/or type of medications prescribed is associated with non-fatal overdose in PLWH. Rather than using the conventional definition of polypharmacy (i.e., five or more medications) validated largely in elderly populations (Gnjidic et al., 2012), we also sought to determine an optimal discriminating number of medications associated with non-fatal overdose (both overall and for sedating medications specifically). We hypothesized that an association between the overall number of medications and non-fatal overdose would be driven by sedating medications, both from opioid and non-opioid sedating medications.

2. Material and methods

2.1. Study design

We used data from the Boston ARCH Cohort study, a longitudinal study of adults with HIV infection and substance dependence in the past year (as assessed by the Mini International Neuropsychiatric Interview Version 6.0 (MINI) (Sheehan et al., 1998) or ever injection drug use. Boston ARCH Cohort participants were recruited from the Center for Infectious Diseases at Boston Medical Center and the HIV program at Boston Healthcare for the Homeless Program.

Inclusion criteria were: documentation of HIV in any medical record, past 12-month substance dependence or ever injection drug use, ability to speak English, age 18 or older, and willingness to provide contact information for one other person to assist with follow up. Exclusion criteria were: pregnancy at time of enrollment, plans to leave the Boston area in the next year, or cognitive impairment such that the patient could not provide informed consent. Study enrollment occurred from December 2012 to November 2014. Past 12-month substance dependence or ever injection drug use will collectively be referred to as "substance dependence" given that PLWH with a lifetime history of injection drug use are likely to have a history of substance dependence).

Participants provided written informed consent and received compensation for each study assessment completed. The Boston University Medical Campus Institutional Review Board approved the study. The National Institute on Alcohol Abuse and Alcoholism (NIAAA) further protected participants with a Certificate of Confidentiality and the US Department of Health and Human Services approved the performance of follow-up assessments with participants who were incarcerated.

2.2. Data collection

Medication data were extracted from a clinical data warehouse that included the electronic medical record (EMR) of both recruitment sites. We abstracted the medication list corresponding to date of study entry for each participant. In order to obtain an accurate count of medications, duplicate medications were identified and removed by cross-referencing with both the National Drug Code (NDC) number and with the generic name as defined in the National Drug File (U.S. Department of Veterans Affairs) ("VA National Formulary - Pharmacy Benefits Management Services," 2016). Because multiple NDC numbers exist for the same medication, unique counts of the "generic name" were used as a proxy for total number of medications. Combination ARVs were recoded into their individual drug components. After a list of unique medications was determined for each study participant, we excluded medications that are not systemically active such as emollients, irrigation solutions, vitamins (except for vitamin D), peritoneal solutions, eye drops, rectal or vaginally administered medications, and complementary and alternative medications. We then further classified medications into the subcategories "sedating" and "non-sedating" (Fig. 1). Sedating medications were further subcategorized as opioid or non-opioid. The medication exclusion and categorization decisions were made by two of the study investigators (TK and AW) guided by U.S. Department of Veterans Affairs Drug Classification ("VA National Formulary - Pharmacy Benefits Management Services," 2016).

All other study data was collected by trained research associates who administered standardized in-person interviews at a study entry and a 12-month follow-up interview.

2.3. Measurements

2.3.1. Outcomes

Two separate outcomes were examined: 1) lifetime non-fatal overdose ("Have you ever overdosed?") assessed at study entry; and 2) past year non-fatal overdose assessed at study entry and 12-month study interview, defined as responding ≥1 to the question, "How many times have you overdosed in the past year?" The following

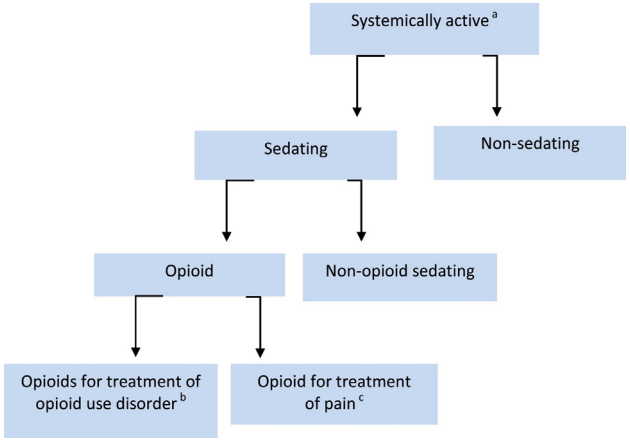

Fig. 1. Summary of medication categories used in analyses. [a]Medications not systemically active includes emollients, irrigation solutions, vitamins (except for vitamin D), peritoneal solutions, eye drops, rectal or vaginally administered medications, complementary and alternative medications. [b]Buprenorphine, methadone. [c]All other opioid medications.