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Adjusting Alcohol Quantity for Mean Consumption and Intoxication Threshold Improves Prediction of Nonadherence in HIV Patients and HIV-Negative Controls

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Abstract

Background—Screening for hazardous drinking may fail to detect a substantial proportion of individuals harmed by alcohol. We investigated whether considering an individual's usual drinking quantity or threshold for alcohol-induced cognitive impairment improves the prediction of nonadherence with prescribed medications.

Method—Cross-sectional analysis of participants in a large, multi-site cohort study. We used the timeline followback to reconstruct 30-day retrospective drinking histories and the timeline followback modified for adherence to reconstruct 30-day medication adherence histories among 3,152 individuals in the Veterans Aging Cohort Study, 1,529 HIV infected and 1,623 uninfected controls. We categorized daily alcohol consumption by using quantity alone, quantity after adjustment for the individual's mean daily alcohol consumption, and self-reported level of impairment corresponding to each quantity. A standard drink was defined as 14 g of ethanol. Nonadherence was defined as the proportion of days with ≥ 1 medication doses missed or taken ≥ 2 hours late, and clinically significant nonadherence was defined as $\geq 5\%$ absolute increase in the proportion of days with nonadherence.

Results—The mean adjusted- and impairment-based methods showed greater discrimination of nonadherence risk compared to the measure based on quantity alone (quantity-based categorization, 3.2-fold increase; quantity adjusted for mean daily consumption, 4.6-fold increase, impairment-based categorization, 3.6-fold increase). The individualized methods also detected greater numbers of days with clinically significant nonadherence associated with alcohol. Alcohol was associated with clinically significant nonadherence at a lower threshold for HIV infected versus uninfected patients (2 standard drinks vs. 4 standard drinks) using quantity-based categorization, but this difference was no longer apparent when individualized methods were used.

Conclusions—Tailoring screening questions to an individual's usual level of alcohol consumption or threshold for impairment improves the ability to predict alcohol-associated medication nonadherence.

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Keywords

Human Immunodeficiency Virus; Alcohol; Nonadherence

Screening populations for hazardous alcohol consumption has been widely advocated to reduce harmful consequences of alcohol (Conigliaro et al., 2000; Gordon et al., 2001; Reid et al., 1999). However, this strategy may need to be modified for HIV-infected individuals or for individuals with comorbidities or frailties that confer particular sensitivity to alcohol's effects. Alcohol leads to life-threatening nonadherence to HIV medications at quantities that do not meet criteria for hazardous drinking (Braithwaite et al., 2005, 2007a; Samet et al., 2004), and therefore, current screening strategies may fail to detect many individuals at risk for harm from alcohol.

One reason why current screening practice may miss at-risk persons is that screening strategies are population-based; yet, individual-patient characteristics may influence the effectiveness of screening. Susceptibility to alcohol-induced cognitive impairment may vary among individuals (Lange and Voas, 2001; Li et al., 2001; Moore et al., 1999; Perkins et al., 2001; Saunders and Lee, 2000; Suwaki et al., 2001) and may be an important determinate of whether a particular quantity of alcohol would induce nonadherence or other harmful consequences. Impaired decision-making may occur when individuals increase their alcohol consumption beyond usual levels of consumption, even if the magnitude of this increase may not be sufficiently high to satisfy the 1-day criterion for hazardous drinking. Conversely, usual levels of alcohol consumption may satisfy the 1-week criteria for hazardous drinking, yet may not impair decision-making or compromise adherence.

Because current, nonindividualized screening strategies may fail to detect drinking with harmful consequences, we sought to compare their performance with individualized strategies. We hypothesized that cognitive impairment is a likely mediator of alcohol's harmful effect on medication adherence. Consequently, we individualized screening based on an individual's self-reported tolerance to alcohol-induced cognitive impairment as well as based on an individual's usual level of alcohol consumption.

METHODS

We evaluated alcohol consumption by examining 30-day retrospective reported drinking history among 3,152 individuals. We performed 3 different categorizations of daily alcohol consumption, the first not individualized (*categorizing by quantity alone*), the second individualized based on usual level of alcohol consumption (*categorizing by comparing quantity to usual consumption*), and the third individualized based on susceptibility to alcohol-induced cognitive impairment (*categorizing by comparing quantity to impairment threshold*). We then compared how these categorization methods predicted medication nonadherence. Additionally, to determine whether their distinct drinking patterns predicted distinct likelihoods of medication nonadherence, we disaggregated the definition of hazardous or "at-risk" drinking (National Institute on Alcohol Abuse and Alcoholism (NIAAA) (1995) into its 2 components: binge—5 or more standard drinks in 1 day, and high cumulative exposure—more than 60 standard drinks in 30 days (based on the criterion of more than 14 standard drinks in 1 week).

Categorizing by Quantity Alone

We categorized alcohol consumption based on quantity alone by sorting it into 6 strata based solely on the daily quantity of alcohol consumed (no standard drinks, 1 standard drink, 2 standard drinks, 3 standard drinks, 4 or 5 standard drinks, and ≥ 6 standard drinks). Although

the timeline followback was designed to elicit alcohol consumption in multiples of 1 standard drink, a minority of individuals reported their drinking in fractions of standard drinks (e.g., half of a “beer”). We rounded these reports up to the next higher multiple of standard drinks to simplify the presentation of our results.

Categorizing by Comparing Quantity to Usual Consumption

We first individualized our categorization method based on how much drinking on a particular day exceeded each individual’s mean daily level of alcohol consumption. Each drinking day was again categorized into 6 levels (at or below mean alcohol consumption, more than mean alcohol consumption by 1 standard drink, more than mean alcohol consumption by 2 standard drinks, more than mean alcohol consumption by 3 standard drinks, more than mean alcohol consumption by 4 or 5 standard drinks, and more than mean alcohol consumption by ≥ 6 standard drinks). We also investigated analogous categorizations using mode and median daily alcohol consumption rather than mean daily alcohol consumption as reference measures for usual drinking.

Categorizing by Comparing Quantity to Impairment Threshold

We also individualized our categorization of alcohol consumption based on level of impairment. Each individual specified the quantity of alcohol consumption at which different levels of impairment occurred, and this specification was used to “map” that individual’s 30-day drinking history to these impairment levels. This method used colloquial terms for level of impairment that were easily understood by the target population (in order of increasing levels of impairment, “neither buzzed nor drunk,” “buzzed but not drunk,” “drunk”). Each individual was queried about their impairment thresholds at the time of the *Alcohol Timeline Follow Back* (TLFB) telephone survey.

Categorization Based on Components of Hazardous Drinking

Hazardous drinking is defined as drinking more than 14 drinks in a 7-day period or having 5 or more drinks at any one time. To further investigate the impact of usual drinking, we disaggregated the definition of hazardous or “at-risk” drinking (NIAAA, 1995) into its 2 components (≥ 5 standard drinks on any 1 day, which we term the *binge criterion* and >60 or more standard drinks during 30 days, which we term the *high cumulative exposure criterion*) because individuals who meet one but not both criteria may have differing likelihoods of cognitive impairment from alcohol consumption. In particular, individuals who meet the cumulative exposure criterion but not the binge criterion are likely to drink similar amounts every day, whereas individuals who meet the binge criterion but not the cumulative exposure criterion are likely to have widely fluctuating amounts of daily drinking. We then compared the extent to which individuals in each category increased their nonadherence on drinking days.

Definition of Nonadherence

We determined how well each method discriminated between the probability of medication nonadherence on a particular day by comparing the proportion of individuals who did not take ≥ 1 daily medication doses as directed (e.g., either missing a dose or taking it more than 2 hours late) across each of its stratifications. We included late doses in our definition of nonadherence because late medication doses are known to be particularly harmful for HIV-infected individuals, and have been included in other studies of nonadherence in HIV patients (Paterson et al., 2000). The distribution of antiretroviral therapies used by our sample is reported elsewhere (Braithwaite et al., 2007b). We defined a *clinically significant increase* as a 5% or greater absolute increase in the percentage of doses missed on a particular day, based on previous studies suggesting that $\geq 5\%$ missed doses was associated

with poorer virological outcomes (Paterson et al., 2000) and clinical outcomes (Braithwaite et al., 2007a). We rounded adherence increments to the nearest percentage point.

Data Sources

We surveyed patients enrolled in the Veterans Aging Cohort Study (VACS), a multi-site observational study of HIV-infected patients and matched uninfected controls that is collecting extensive information on patterns of alcohol consumption and adherence (Justice et al., 2006). Enrolled patients were considered eligible for the alcohol and adherence analyses if they reported consuming at least 1 alcohol beverage at any time in their lives, and if they were on at least 1 prescribed medication. This study was approved by the Institutional Review Board at each participating site. Patient characteristics are shown in Table 1.

VACS utilizes telephone surveys in a 50% sample of those enrolled. The TLFB (Skinner and Sheu, 1985; Sobell and Sobell, 1992; Sobell et al., 1988a,b) was administered by telephone, and was used to measure the quantity and pattern of alcohol consumption during a 30-day period immediately preceding the day of the phone call, and the *Timeline Followback modified for adherence* (TLFB-Adh), also administered by telephone, was used to measure the quantity and pattern of adherence to prescribed medications during the same period.

Interviewers were selected from a pool of experienced interviewers who were familiar with general interviewing practices and techniques. They were further qualified in the standards of best practices specific to this instrument by senior research investigators. Additional training included role playing, mock interviewing, and qualifying interviews to insure optimal interviewing skill and technique.

Measures of Alcohol Consumption

The TLFB, a drinking assessment method that obtains estimates of daily drinking, has been evaluated in clinical and nonclinical populations. Using a calendar, people provide retrospective estimates of their daily drinking over a 30-day period. This detailed information can provide a wide range of information about an individual's drinking (e.g., pattern, variability, and magnitude of drinking). The TLFB has been shown to have high test-retest reliability across multiple populations of drinkers, (Skinner and Sheu, 1985; Sobell et al., 1988a) good construct validity when measured against the Alcohol Dependence Scale and other instruments (Skinner and Sheu, 1985; Sobell et al., 1988a), and good criterion validity when measured against days jailed and hospitalized and collateral informants (Sobell and Sobell, 1992). We used the TLFB to assess the daily quantity of alcohol consumed by each study participant, as well as to assess characteristics of each participant's usual drinking pattern (mean, median, and mode).

Measures of Adherence

We previously modified the timeline follow back method to record deviations from perfect medication adherence over the same 30-day interval (TLFB-Adh) (Braithwaite et al., 2005). The telephone interviewer initially asked subjects how often during a typical day that they take prescription medications including pills, injections, inhalers, drops, liquids or patches on a regular basis. Then the interviewer, starting backward from the day of the call, asked the patient to recall on each of the preceding 30 days whether he took medications late (more than 2 hours) or missed medications. Holidays, weekends, and special events were used as memory cues for recording deviations in adherence. The modified instrument with instructions is available from the authors and on the VACS website

(<http://www.vacohort.org>). We used the TLFB-Adh to assess the medication nonadherence of each study participant.

Measures of Cognitive Impairment

We inquired about thresholds for cognitive impairment as part of a written survey that was administered separately from the telephone interview surveys. Participants were asked “How many drinks does it take for you to start to feel high or to start to get a buzz?”, and “How many drinks does it take for you to begin to lose control or get drunk?”

Statistical Analyses

The *patient-day* was our primary unit of analysis, and our outcome variable was the proportion of patient-days with nonadherence. Our criterion for a significant increase in nonadherence was based primarily on clinical rather than statistical significance, as the large power of this study would sometimes identify very small (i.e., clinically insignificant) increments in nonadherence (e.g., 1%) as statistically significant. However, we supplemented tests of clinical significance by statistically comparing (1) nonadherence in each drinking category to nonadherence on nondrinking days, (2) nonadherence in each mean-adjusted drinking category to nonadherence in the corresponding, unadjusted drinking category, and (3) nonadherence among HIV-infected patients to nonadherence among HIV-uninfected patients. To test statistical significance, we used the chi-square test for independent proportions.

RESULTS

Each of the categorization methods was able to discriminate between lower and higher probabilities of medication nonadherence; however, the individualized categorization methods showed greater discrimination than the nonindividualized categorization method.

Nonindividualized Categorization of Alcohol Consumption

We evaluated 1 nonindividualized categorization method, which was based solely on the quantity of alcohol consumed. Patient days on which greater quantities of alcohol were consumed showed progressively more nonadherence than patient days on which no alcohol was consumed ($p = 0.0062$, 1 drink per day compared to 0 drinks per day; $p < 0.0001$, other daily quantities compared to 0 drinks per day). At lower levels of alcohol consumption (from 0 to 3 drinks per day), the slope of the curve was shallow (Fig. 1) and the rise of the curve did not indicate a clinically significant increase in nonadherence. At higher levels of alcohol consumption (4 or more drinks per day), the slope of the curve was greater, and each level showed a clinically significant increase in nonadherence. The proportion of days with nonadherence in the highest alcohol stratum was 16%, an 11% absolute increase and 3.2-fold relative increase compared to nonadherence in the lowest alcohol stratum. This categorization method identified 3,703 drinking days as having clinically significant levels of alcohol-induced nonadherence.

Individualized Categorization of Alcohol Consumption

We evaluated 2 individualized categorization methods, *categorizing by comparing quantity to usual consumption*, and *categorizing by comparing quantity to impairment threshold*.

Categorizing by Comparing Quantity to Usual Consumption

When we adjusted each person's daily alcohol consumption to reflect its departure from his mean daily quantity of alcohol consumed, the curve demonstrated a steeper slope, and the amount of nonadherence in adjusted compared to unadjusted drinking categories was

statistically different ($p < 0.05$) for all categories except “2 drinks per day.” Patients who consumed 2 or more mean-adjusted standard drinks now had clinically significant increases in nonadherence (Fig. 1), a far lower threshold than when the quantity of consumption was not mean adjusted (4 or more standard drinks). The proportion of days with nonadherence in the highest alcohol stratum was 23%, an 18% absolute increase and 4.6-fold relative increase compared to the lowest alcohol stratum. The number of days identified with clinically significant levels of alcohol-induced nonadherence rose by 30%, from 3,073 to 4,003 days.

Categorizing by Comparing Quantity to Impairment Threshold

When we mapped each person’s daily alcohol consumption to his self-reported threshold for impairment (Fig. 2), the curve also showed a steep slope ($p < 0.0001$; nonadherence in each drinking category compared to nonadherence with no drinking). Drinking without impairment was not associated with a clinically significant increase in nonadherence, whereas drinking to “buzz” or “drunk” levels of impairment were associated with progressively greater and clinically significant increases in nonadherence. The proportion of days with nonadherence in the highest alcohol stratum was 18%, a 13% absolute increase and 3.6-fold relative increase compared to the lowest alcohol stratum, and an intermediate level of discrimination compared to the mean-adjusted categorization method (4.6-fold) and the categorization method based on quantity alone (3.2-fold). Similarly, the number of days identified with clinically significant levels of alcohol-induced nonadherence was 3,259, intermediate to the measure based on quantity alone (3,073 days) and the mean-adjusted measure (4,003 days).

Categorization Based on Components of Hazardous Drinking

High cumulative exposure drinkers did not have higher levels of nonadherence than nondrinkers, even on drinking days (Fig. 3). In contrast, binge drinkers had a 2.6-fold increase in nonadherence compared to nondrinkers, and the majority of that increase (2.1-fold) occurred only on drinking days. Drinkers who met both criteria for hazardous drinking (high cumulative exposure and binge) had the highest levels of nonadherence of all (3.4-fold higher than nondrinkers), but the component of that increase that occurred only on drinking days was similar to that for binge drinkers (2.1-fold). All of these increases were clinically significant, corresponding to at least a 5% absolute increase in the proportion of days with nonadherence. Nonhazardous drinkers showed an increase in the probability of nonadherence on drinking days (3% absolute increase) but this difference did not reach our threshold for clinical significance.

Subgroup Analyses by HIV Status

We also compared the threshold at which alcohol was first associated with clinically significant nonadherence for HIV infected versus uninfected patients. Using our non-individualized method, based on quantity alone (Fig. 4A), the HIV-infected patients first had a clinically significant increase in nonadherence at a threshold of 2 or more standard drinks per day, and their nonadherence was significantly higher than for uninfected patients ($p = 0.003$), who first had a clinically significant increase in nonadherence at a threshold of 4 or more standard drinks per day. At higher levels of alcohol consumption, there was no statistically significant difference between the nonadherence observed for HIV infected and uninfected patients.

When we individualized our categorization method using mean-adjusted quantity (Fig. 4B), there was no longer any difference in the threshold at which alcohol was associated with clinically significant nonadherence. It occurred at consumption levels of 2 or more standard drinks per day for both HIV infected and uninfected patients. When we individualized our

categorization method using self-reported impairment thresholds, alcohol consumption again was associated with a clinically significant increase in nonadherence at similar levels for both HIV infected and uninfected individuals, first occurring at the “buzz” level of impairment (data not shown).

DISCUSSION

Our results suggest that adjusting alcohol quantity for mean consumption and threshold for intoxication improves the prediction of alcohol-associated medication nonadherence in HIV-infected patients and HIV-negative controls. One possible explanation of this finding is that impaired judgment may be the causal mechanism linking alcohol consumption to nonadherence; i.e., a person who is impaired may forget to take his medication, or may underestimate its importance at that particular time. Because individuals may become habituated to varying quantities of alcohol consumption, individualized measures may offer a more reliable way of detecting levels of consumption that are associated with impairment.

We found that nonhazardous levels of daily alcohol consumption (i.e., <5 drinks per day) may confer substantially and clinically important increases in the risk of nonadherence, particularly for HIV-infected individuals. This is particularly notable because it suggests that nonhazardous drinking may sometimes induce harm yet is unlikely to be detected by current screening instruments, which are based on studies of general populations. Antiretroviral therapies have transformed HIV from a fatal condition to a chronic disease, yet their long-term effectiveness depends upon taking >95% of doses as directed (Paterson et al., 2000). Our results suggest that nonhazardous drinking may often induce levels of nonadherence in HIV-infected patients that are clinically significant, meeting or exceeding this threshold.

While screening for hazardous drinking may fail to detect drinking that induces nonadherence, it also may falsely identify drinking patterns that do not carry a higher risk of nonadherence. Hazardous drinkers with clinically significant increases in nonadherence were binge hazardous drinkers rather than cumulative exposure hazardous drinkers. This raises the possibility that a screening strategy could identify clinically important nonadherence using only 1 question to detect binge drinking, rather than using a multitude of questions designed to also detect cumulative exposure.

The importance of cognitive impairment may explain much of the variation in the impact of alcohol on HIV-infected patients compared to uninfected patients. Quantity-based measures suggested that alcohol is associated with nonadherence at lower levels of consumption for HIV-infected patients compared to uninfected patients. However, when measures are individualized based on usual levels of consumption, HIV infected and uninfected patients show very similar thresholds for alcohol-induced nonadherence. This suggests that HIV-infected patients may have lower usual levels of alcohol consumption than uninfected patients, but drink with more variability. The reasons for this are unclear and merit further research, but lower usual levels of consumption may stem from factors as diverse as mitochondrial and hepatic toxicity due to antiretroviral medications (Brinkman et al., 1998; Côté et al., 2002), comorbidities common in HIV-infected patients (e.g., Hepatitis C) (Rockstroh and Spengler, 2004), an accelerative effect of HIV on age-related frailty (Bortz, 2002; Fried et al., 2001), or history of prior alcohol dependence.

Our study has several important limitations. Our results are based on 1 single patient sample, albeit a large one that enrolled at 8 different sites across the country. Our analysis is based on observational data describing the relationship of alcohol consumption to adherence, and therefore causality cannot be proven. While the temporal design of this study allows us to control for known and unknown confounding variables that were stable over brief time

intervals (e.g., socioeconomic status, demographic factors, history of drug abuse, known psychiatric disorders), it does not allow us to control for confounders that may have varied from day to day in synchrony with alcohol consumption (e.g., stressors, mood fluctuations, active drug abuse). Perhaps the most important limitation of our study is it relies on self-report for daily alcohol and adherence measures. It is possible that these recollections were cued by particular events, leading to spurious associations. Nonetheless, the magnitude of the association (2.7-fold greater nonadherence on drinking vs. nondrinking days) was similar to results from studies that did not use temporal cues for recall (Samet et al., 2004), reducing the likelihood that this limitation critically undermined our results.

In conclusion, episodic drinking rather than high average drinking was associated with nonadherence, and the threshold at which cognitive impairment impacted adherence was moderate (“buzzed”) rather than high (“drunk”). Our results suggest that screening for hazardous drinking may fail to detect alcohol consumption that leads to harm, and raises the question of whether screening may falsely attribute harm when it is unlikely. Our conclusions may be particularly relevant to comorbid or frail populations, such as individuals with HIV.

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Fig. 1. Nonadherence stratified by alcohol consumption quantity, unadjusted and adjusted for each individual's mean daily alcohol consumption.

Fig. 2.
Nonadherence stratified by level of alcohol-induced impairment.

Proportion of days with medication nonadherence

Fig. 3. Nonadherence stratified by disaggregation of hazardous drinking definition. Drinking days are distinguished from nondrinking days.

Fig. 4. Nonadherence stratified by HIV status and alcohol consumption level, unadjusted (**A**) and adjusted (**B**) for mean alcohol consumption.

Table 1

Characteristics of Study Patients

Characteristic	Number (%)
Male	2,942 (94.0)
Race	
White, non-Hispanic	776 (24.8)
Black, non-Hispanic	1,961 (62.6)
Hispanic	276 (8.8)
Other	118 (3.8)
Homeless in past 4 weeks	268 (8.6)
Active smoker	1,637 (47.2)
Active illicit drug use	711 (23.3)
Education	
Less than high school	229 (7.4)
High school or equivalent	977 (31.4)
Some college or higher	1,907 (61.3)
Age (years)	
Below 40	364 (11.6)
40–49	1,274 (40.7)
50–59	1,127 (36.0)
60 or over	306 (11.7)