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The relationship of frequency of cocaine use to substance and psychiatric disorders in the U.S. general population

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Abstract

Background—In clinical trials of pharmacotherapy for substance use, abstinence is the primary endpoint accepted by regulatory agencies. However, this endpoint could be overly restrictive, impeding efforts to identify effective medications for cocaine use disorder. To examine non-abstinent gradations in cocaine use as potential indicators of improvement, we investigated the relationship of frequency of cocaine use to clinical correlates in national survey data.

Methods—Lifetime cocaine users (n=2,501) were interviewed in the National Epidemiological Survey on Alcohol and Related Conditions (NESARC) in 2001–2002 and re-interviewed in 2004–2005. Adjusted odds ratios (aORs) indicated associations between heaviest frequency of cocaine use and use of other substances, DSM-IV substance use disorders, psychiatric disorders, and change between 2001–2002 and 2004–2005. The reference category for all aORs was non-users.

Results: Greater lifetime cocaine use frequency was associated with lifetime cocaine, alcohol, and cannabis dependence (aOR for a linear trend=2.80, 1.22, 1.22, respectively) and past-year cocaine, alcohol, and cannabis dependence (aOR=1.78, 1.13, 1.16, respectively). Greater lifetime cocaine use frequency was associated with past-year depressive, panic, and generalized anxiety disorders (aOR=1.07, 1.09, 1.12, respectively). Among cocaine users in 2001–2002, compared to the reference group using less than monthly, use ≥1x/week and use 1–3 times a month was associated with cocaine use disorder in 2004–2005 (aOR=2.13 and aOR=1.67, respectively)

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Conclusion: Gradations in risk for dependence on cocaine, other substances and psychiatric disorders by frequency of cocaine use indicates a promising direction for more sensitive outcome measures of treatment effects on cocaine outcomes than binary indicators (e.g., any use vs. none). Study results add to findings suggesting that non-abstinent measures might be useful indicators of treatment efficacy in clinical trials.

Keywords

Cocaine use Disorder; Psychiatric Disorders; WHO risk Drinking categories; National survey; Abstinence endpoints; frequency of use

1.1 Introduction

Cocaine is a strong stimulant. Prolonged and continuous cocaine use is associated with transitioning to cocaine use disorder (Lopez-Quintero et al., 2011) (CoCUD). CoCUD is associated with disability and psychiatric comorbidity (Compton et al., 2007), including mood (Crits-Christoph et al., 2018; Hammond et al., 2016) and anxiety disorders (Conway et al., 2006), and psychotic disorders, both in clinical samples and in the general population (Araos et al., 2014; Martinez-Gras et al., 2016; Stinson et al., 2005). Cocaine use is also associated with elevated mortality risk (Degenhardt et al., 2011; Pavarin et al., 2020), including from suicide (Zhornitsky et al., 2020) and from medical causes, e.g., cardiovascular diseases(Havakuk et al., 2017; Kim and Park, 2019; Morentin et al., 2014; Santurtun et al., 2020), infectious diseases. Cocaine use is also increasingly linked to fatal drug overdoses (McCall Jones et al., 2017; Nolan et al., 2019; O'Donnell et al., 2020), with and without opioids (Hoots et al., 2020; Kariisa et al., 2019). For all of these reasons, identifying effective treatments for CoCUD is an urgent public health priority, as is improving clinical trial methods to better identify such treatments.

Unlike substance use disorders involving alcohol, nicotine, or opioids for which FDA-approved medications are available, no FDA-approved medications exist to treat CoCUD A factor that may have impeded efforts to identify effective medications is the outcome measure used in many trials, i.e., complete abstinence. Abstinence from cocaine is currently the only primary endpoint accepted by regulatory agencies in the United States and Europe for approval of new pharmacotherapies for CoCUD. However, if non-abstinent reductions in cocaine use improve how patients feel and function, and if such reductions can be sustained, complete abstinence may be an overly stringent outcome indicator, and thus an insensitive criterion to evaluate treatments for cocaine use disorders. Consistent with interest in non-abstinent reductions in alcohol use as an outcome indicator (Falk et al., 2019; Witkiewitz et al., 2019; Witkiewitz et al., 2017a), a recent call for research on alternative non-abstinent endpoints in clinical trials for drug use disorders has been put forward (Volkow et al., 2018).

In clinical trials to treat alcohol use disorders, non-abstinent outcomes as clinically meaningful efficacy indicators (van Amsterdam and van den Brink, 2013) have been examined in many recent studies, including samples in clinical samples (Falk et al., 2019; Witkiewitz et al., 2019; Witkiewitz et al., 2017a; Witkiewitz et al., 2020; Witkiewitz et al., 2018; Witkiewitz et al., 2017b) and in the general population (Hasin et al., 2017;

Knox et al., 2019a; Knox et al., 2020; Knox et al., 2018; Knox et al., 2019b). These studies used the WHO very high risk, high risk, moderate risk and low risk drinking categories to evaluate non-abstinent drinking reduction in clinical and national data, based on average grams of ethanol consumed per day (i.e., amount of alcohol in standard-sized drinks of beer, wine or liquor, with one standard drink=14 gr ethanol (National Institute on Alcohol Abuse and Alcoholism)). These studies began with cross-sectional evaluations of the relationship of different drinking levels to the risk of harms, particularly DSM-IV alcohol dependence. Having established these relationships, the studies then shifted to examining the relationship of reduction in drinking levels to reduced likelihood of harms. These studies consistently showed that non-abstinent reduction in the WHO drinking risk levels is associated with improvements in how individuals feel and function, and thus could serve as valid indicators of treatment outcome. A potential added benefit of non-abstinent drinking-reduction outcomes is that they better align with initial goals of many individuals considering treatment who are deterred because they are uninterested in total abstinence goals.

In contrast to alcohol, standardized measures for cocaine do not exist. Assessing quantity is particularly problematic since quantities are reported in various units (e.g., grams, lines, bags, rocks), and drug purity is unknown, making determination of categories of drug use patterns (e.g., heavy, medium, light) challenging. Also, routes of drug use vary, including oral (smoking), nasal (snorting) or intravenously (shooting up). Given these difficulties, studies have addressed cocaine use frequency, which can be reported in clearer metrics, i.e., the number of times used within a given timeframe, such as a week, month or year.

Identification of differential cocaine use frequency patterns is the first step towards investigating and determining whether a non-abstinent outcome measure of cocaine use could be a valid indicator of successful outcome in clinical trials. If research shows clinical benefit from reduction in frequency of use in non-abstaining cocaine users, then full abstinence may be an overly strict indicator of efficacy and clinical improvement. In order to identify clinically meaningful non-abstinent outcomes, associations between cocaine use outcomes and improvement across multiple domains must be empirically supported. In a growing effort to explore such outcomes, studies have examined the relationship of patterns of cocaine use during and after treatment to other outcomes.

In a clinical sample of 229 crack-cocaine users followed 18 months post-treatment, three groups were identified (Siegal et al., 2002): those with sustained abstinence (n=71, 31%), inconsistent ‘cycling’ abstinence (n=92, 40%) and lack of abstinence (n=66, 29%). No significant differences were found between the sustained and inconsistent abstainers on legal, family, or psychiatric status. Using pooled data across controlled trials for cocaine dependence (n=434), (Carroll et al., 2014) examined and compared widely-used outcome indicators in terms of sensitivity to treatment effects and relationship to cocaine use and general functioning during follow-up. Although no single outcome indicator demonstrated consistent superiority, analyses identified several outcomes that consistently performed poorly, including complete abstinence and retention, proposing to eliminate them in future research. A consensus panel of expert investigators, after reviewing available findings from

the literature, recommended additional studies to investigate operational definitions for reduction-based measures of cocaine use in terms of frequency (Kiluk et al., 2016).

In a subsequent study of 720 patients pooled across studies, the following frequencies were found: abstinence (10.6%); low-frequency (1–3 days/week, 66.3%) and persistent frequent use (≥4 days/week, 23.1%) (Roos et al., 2019b). At 6 months post-treatment, the low-frequency group had better functioning than the persistent frequent use group across multiple domains; at 12 months, the low-frequency and abstinent groups did not differ on any functioning domain, suggesting clinical benefit for reduction for reduction to low-frequency cocaine use. In a later study using the same pooled data (n=716) but slightly different definitions of cocaine use frequencies (abstinence: no use/past month; low frequency use: 1–4 day use/past month; and high frequency use: >5 days/past month, a binary indicator was created to examine a reduction in frequency level from baseline to end of treatment (EOT) (Roos et al., 2019a). Results showed that an indicator of at least one-level reduction in cocaine frequency level from baseline to EOT was significantly associated with better functioning up to one-year follow-up. Importantly, (Roos et al., 2019a) also found that those who reduced from high frequency level at baseline to low frequency had similar outcomes at follow-up as those who reduced to abstinence, suggesting that a one-level reduction in cocaine frequency level is a clinically meaningful endpoint up to one year of follow-up.

These studies of non-abstinent cocaine frequencies and outcome indicators in clinical samples provide important information. However, clinical samples are often highly selected (Blanco et al., 2017; Blanco et al., 2008) and may not provide generalizable information about whether reduced but non-abstinent cocaine use has clinical benefit. To address these issues using the same initial strategy used for non-abstinent drinking reduction, we investigated the relationship of varying frequencies of cocaine use to clinically salient conditions using data from the U.S. general population. We used national survey data to investigate the following questions:

1. Is lifetime heaviest (most frequent) use of cocaine associated with lifetime and past-year risk of cocaine dependence, dependence on other substances, depressive and anxiety disorders?
2. Is frequency of past-year cocaine use at one point in time associated with the risk for cocaine disorder and other disorders three years later?

2.1. METHODS

2.2. Sample and procedures

We used data from the US National Epidemiologic Survey on Alcohol and Related Conditions (NESARC), in which 43,093 participants were interviewed in 2001–02 (Wave 1) (Grant et al., 2004) and N=34,635 re-interviewed 3 years later (2004–05; Wave 2) (Grant et al., 2009; Hasin and Grant, 2015). Data were collected in face-to-face interviews conducted in participants' homes(Grant et al., 2003). Both surveys utilized similar rigorous filed procedures, e.g. structured interviewer training, on-going supervision, and quality control assurance. The NESARC target population was non-institutionalized civilians aged at least

18 years in households and group quarters (e.g., group homes and workers' dormitories). Black individuals, Hispanic individuals, and those aged 18–24 years were oversampled, and the data adjusted for oversampling and household-level and person-level nonresponse (Compton et al., 2007; Grant et al., 2009; Grant et al., 2004). All procedures, including written informed consent, were reviewed and approved by the US Census Bureau and US Office of Management and Budget.

The overall response rate in NESARC Wave 1 was 81.0% (Hasin et al., 2007). Excluding ineligible respondents (e.g., those who died before the follow-up interview), the overall response rate in Wave 2 among Wave 1 participants was 86.9% (Grant et al., 2009). Combined with the Wave 1 response rate, the weighted cumulative Wave 2 response rate (i.e, Wave 1 × Wave 2 rates) was 70.2% (Grant et al., 2009). Wave 2 data were weight-adjusted for non-response and demographic factors to ensure that the Wave 2 sample approximated the target population (Grant et al., 2009).

For analyses of lifetime heaviest (most frequent) cocaine use, the analyzed sample included 2,501 participants who ever used cocaine or crack in their lifetimes and had non-missing frequency of heaviest use, reported at Wave 1 (6.15%; weighted). Of these, 215 individuals used cocaine in the past 12 months at Wave 1, and 157 (73.0%) of these participated in the 3-year follow-up (Wave 2) with cocaine use data available. These 157 participants were analyzed to determine the relationship of frequency of Wave 1 cocaine use to the risk for Wave 2 outcomes.

2.3. Measures

2.3.1. AUDADIS-IV—The Alcohol Use Disorder and Associated Disabilities Interview Schedule-DSM-IV Version (AUDADIS-IV) of the US National Institute on Alcohol Abuse and Alcoholism is a structured interview administered by lay interviewers that is highly reliable in the general population (Grant et al., 2003; Ruan et al., 2008) and was used for NESARC Waves 1 and 2.

2.3.2. Cocaine frequency of use—At Wave 1, participants were asked if they ever used cocaine or crack and if yes, if they used in the past 12 months, prior to the past 12 months, or both. Lifetime 'ever' cocaine use was defined as positive for those who stated they ever used cocaine or crack. Among those who used in the past 12 months, participants indicated frequency of 12-month use by selecting a response from a flashcard showing ten categories (Every day; nearly every day; 3–4 times/week; 1–2 times/week; 2–3 times/month; once a month; 7–11 times/year; 3–6 times/year; 2 times/year; once a year). Participants who used cocaine in the past were then asked about frequency during the time they were "using cocaine the most" (therefore, period of lifetime heaviest use was self-defined by the participant). Frequency during the lifetime period of heaviest use was ascertained with the same flashcard showing the same ten categories. Among all lifetime cocaine ever users, to define lifetime heaviest (most frequent) use, the most frequent period was selected (for n's, see Supplementary Table 1). To provide categories that each had sufficient numbers of participants for analysis, the ten categories were collapsed into five mutually exclusive ordered categories. These five ordered categories included daily/near

daily use (5–7 times/week); weekly use (1–4 times/week); monthly use (1–3 times/month); sporadic use (3–11 times/year) and experimental use (1–2 times/year). In analyses of Wave 1 frequency predicting Wave 2 outcomes, given the smaller sample size, three mutually exclusive categories were used: at least once a week; at least once a month; and less often than once a month.

At Wave 2, participants were asked if they had used cocaine or crack since their previous interview. If yes, the same flashcard ascertained frequency of cocaine use during the prior 12 months (see Supplementary Tables 2 and 3 for n's within categories of frequency of use at Waves 1 and 2 for participants who were cocaine users at Wave 1 who participated in the Wave 2 interview). Participants were then asked if they used cocaine/crack since the last interview but prior to 12 months ago; if yes, frequency of use during that period was assessed with the same flashcard.

2.3.3. Other clinical conditions

DSM-IV substance use disorders.: Substances included cocaine, alcohol, cannabis, sedatives, tranquillizers, opioid painkillers, other stimulants, hallucinogens, inhalants, and heroin. DSM-IV dependence diagnoses for a given substance were considered positive if respondents met ≥3 of 7 dependence criteria within a one-year period; lifetime dependence was positive for a given substance if participants met ≥3 of 7 dependence criteria in the past year, or during a one-year period prior to the past year. Substance abuse was considered positive if participants met ≥1 of 4 abuse criteria within a one-year period. A substance use disorder was considered positive if substance abuse or dependence was present. The reliability and validity of AUDADIS DSM-IV substance use disorder diagnoses is good to excellent in general and clinical populations in the US and other countries (Chatterji et al., 1997; Grant et al., 1995; Hasin et al., 1997; Pull et al., 1997); reliability and validity of AUDADIS cocaine use and DSM-IV CoCUD diagnoses and associated criteria scales was fair to excellent in national and international clinical and general population studies (Chatterji et al., 1997; Grant et al., 1995; Hasin et al., 1997; Pull et al., 1997).

Depressive/anxiety disorders.: AUDADIS-IV provided diagnoses of DSM-IV major depression and dysthymia, categorized as any depressive disorder, and panic and generalized anxiety disorders, categorized as any anxiety disorder. These variables were available in Wave 1 (lifetime) and Wave 2 (past year). Reliability is moderate for anxiety disorders (kappa=0.40–0.52) and moderate to substantial for depressive disorders (kappa=0.50–0.73) (Hasin et al., 2007).

Sociodemographic covariates: These included gender; age (included as a continuous variable); race/ethnicity (Hispanic; non-Hispanic White, non-Hispanic Black, American Indian/Alaska Native, Asian/Native Hawaiian/Pacific Islander); education (less than high school, high school, some college, completed college); current cigarette smoking (yes, no); body mass index, and health insurance (any, none).

Statistical analysis: Observed weighted proportions of demographic characteristics and clinical outcomes were computed among all lifetime cocaine users and by frequency of

heaviest lifetime cocaine use. The clinical outcomes of interest included past year substance use, past year and lifetime diagnoses of DSM-IV substance dependence and psychiatric disorders and past-year cocaine use disorder at Wave 2. In order to examine the linear trend in frequency of heaviest lifetime use on clinical outcomes, logistic regression models were fit including a 5-level ordered categorical predictor for frequency of heaviest lifetime use (experimental, sporadic, monthly, weekly, daily/near-daily). The associated adjusted odds ratios (aOR) and 95% confidence intervals (CI) for the effect of frequency of use are interpreted as the multiplicative increase in odds of the clinical outcome for a one-level increase in frequency of use, where aOR>1.0 indicated a positive association between frequency of heaviest use, aOR=1.0 indicated no association, and aOR<1.0 indicated a negative association between frequency of cocaine use and the respective outcome.

To explore whether frequency of past year cocaine use at Wave 1 was associated with Wave 2 outcomes, a logistic regression model was fit among all Wave 1 past-year users with Wave 2 follow-up data available (n=157). Wave 2 outcomes included presence of past-year cocaine disorder, any substance dependence, or any psychiatric disorder (depressive disorder or anxiety disorder). From these models, adjusted odds ratios (aOR) and 95% confidence intervals (CI) were derived. Due to the smaller sample size of current cocaine users at Wave 1, the model evaluated the effect of frequency as a 3-level nominal categorical measure (less than monthly, monthly, or at least weekly), and corresponding aOR and CI were computed.

All models controlled for age, sex, education, ethnicity/race, insurance status, BMI, and current smoking status. Sensitivity analyses for analyses among lifetime cocaine ever-users additionally adjusted for time since heaviest cocaine use, defined as <1 year, 1–5 years, or >5 years. Moreover, supplemental analyses were run to examine the association between lifetime ever cocaine user versus non-users (n=43,066) on clinical outcomes utilizing logistic regression models. These models addressed the effect of ever using cocaine (yes vs no) and the clinical correlates.

All hypothesis tests were two-sided with a significance level of 5%. Logistic models were fit using PROC SURVEYLOGISTIC in SAS 9.4 to incorporate the complex survey designs of NESARC Waves 1 and 2.

3.1. Results

3.2. Sample characteristics (Table 1)

The majority of the sample were male (64%); White (77.8%) age 30–44 years old (51.9%); 38.0% had high school or more education. For most lifetime users, 79.4% had last used ≥5 years ago, and 34% reported heaviest lifetime cocaine use daily to 4x/week. Among the 30–44 age group, 55.3% reported heaviest lifetime cocaine use 1–3x/monthc

Compared to those who never used cocaine (Supplementary Table 4), significantly greater odds were found among lifetime cocaine users for alcohol, cannabis and other drug dependence (lifetime: aOR=5.57–15.52; past-year: aOR=3.98–6.67), and for lifetime and current depressive, anxiety, panic and generalized anxiety disorders (aOR=1.83–2.53).

3.3. Risk for lifetime and past-year DSM IV substance use and dependence by heaviest lifetime frequency of cocaine use.

Descriptively, those with greater frequency of heaviest lifetime cocaine use had higher prevalence of lifetime and past-year substance dependence and psychiatric disorders (Table 2). Greater lifetime frequency of cocaine use was associated with significantly greater odds of lifetime dependence on several substances (Table 3), including cocaine, aOR=2.80 (CI=2.60, 3.01); alcohol, aOR=1.22 (CI=1.19, 1.26); and cannabis, aOR=1.22 (CI=1.17, 1.27). In sensitivity analyses, additionally controlling for time since heaviest cocaine use did not make meaningful differences in any of these results.

In addition (Table 3), those with greater frequency of heaviest lifetime cocaine use had significantly greater adjusted odds of past-year cocaine use, aOR=1.15 (CI=1.09, 1.21) and significantly lower adjusted odds of alcohol use, aOR=0.80 (CI=0.77, 0.83). Greater lifetime frequency of heaviest cocaine use was also associated with greater odds of past-year dependence on cocaine, aOR=1.78 (CI=1.48, 2.15), cannabis, aOR=1.16 (CI=1.03, 1.31), and alcohol, aOR=1.13 (1.07, 1.19). Controlling for time since heaviest cocaine use (<1 year, 1–5 years, >5 years) did not lead to a clinically meaningful differences in the odds ratios.

3.4. Risk for lifetime and past-year DSM IV psychiatric disorders by heaviest lifetime frequency of cocaine use.

Those with greater frequency of heaviest lifetime cocaine use had greater odds of lifetime depressive disorder aOR=1.06 (CI=1.02, 1.10) and anxiety disorders (Table 3). Specifically, lifetime frequency of cocaine use was associated with increased odds of lifetime panic disorder, aOR=1.17 (CI=1.12, 1.23), generalized anxiety disorder, aOR=1.09 (CI=1.04, 1.14) and any depressive disorder, aOR=1.06 (CI=1.02, 1.10). In addition, those with greater frequency of heaviest lifetime cocaine use had greater odds of past-year depressive disorder, aOR=1.07 (CI=1.03, 1.10), and generalized anxiety disorder, aOR=1.12 (CI=1.05, 1.20). However, this association was not found for past-year anxiety disorder or panic disorder. Results were similar in the sensitivity analysis that additionally controlled for years since heaviest cocaine use.

3.5. Risk for Wave 2 outcomes by Wave 1 frequency of cocaine use

In Wave 2 (Table 4), the prevalence of cocaine disorder was greater in those who had been frequent cocaine users at Wave 1 (≥1x/week; 17.8%) than in the less frequent cocaine users (1–3x/month; 14.4%), with the odds of cocaine disorder greater for those using ≥1x/week, aOR=2.13 (CI=1.76, 2.59) and 1–3x/month, aOR=1.67 (CI=1.64, 1.69). Users of cocaine <1x/month at Wave 1 (n=91) had the lowest prevalence of cocaine disorder at Wave 2 (9.2%). The prevalence of other substance dependence at Wave 2 was lower for those who had been frequent cocaine users at Wave 1 (≥1x/week; 28.9%) than in the less frequent cocaine users (1–3x/month: 32.1% and <1x/month: 46.2%), with the odds of other substance dependence lower for those using ≥1x/week, aOR=0.47 (CI=0.45, 0.50) and 1–3x/month, aOR=0.55 (CI=0.50, 0.61). Similarly, the prevalence of any psychiatric diagnosis at Wave 2 was lower for those who had been frequent cocaine users at Wave 1 (≥1x/week; 18.5%) than in the less frequent cocaine users (1–3x/month: 23.8% and <1x/month: 41.7%), with

the odds of a psychiatric diagnosis lower for those using ≥1x/week, aOR=0.32 (CI=0.29, 0.34) and 1–3x/month, aOR=0.44(CI=0.41,0.47).

4. DISCUSSION

Interest is growing in outcomes of clinical trials that incorporate non-abstinent reductions in substance use as potentially more sensitive indicators of treatment efficacy than perfect abstinence. Considerable work has been done on this issue regarding alcohol outcomes, showing that non-abstinent reductions in heavy drinking are associated with significant and clinically meaningful improvements in how individuals feel and function. However, much less is known about the associations of graded, non-abstinent indicators of cocaine use frequency with how individuals feel and function. In this study of over 2,000 lifetime cocaine users in the general population, we examined whether gradations in the frequency of cocaine use were associated with differences in the odds of cocaine, alcohol, and cannabis dependence, and also psychiatric disorders. Results indicated significant differences in the odds of all these conditions by lifetime greatest frequency of cocaine use. These results were found controlling for numerous potentially confounding covariates. In addition, among the subset of participants who were cocaine users at Wave 1, Wave 1 frequency of cocaine use predicted greater odds of cocaine disorder three years later at Wave 2. These results were also found controlling for numerous potentially confounding covariates. However, unexpectedly, we found that greater frequencies of cocaine use at wave 1 predicted lower odds of other substance dependence, depressive or anxiety disorders. The divergent results for cocaine disorder with the other wave 2 outcomes may lie in the fact that of the 157 cocaine users at wave 1, 115 of them (weighted percent, 74.6%) had become abstainers by wave 2. While the remaining cocaine users almost certainly contributed to the continued higher odds for cocaine disorder at wave 2, the high proportion of wave 2 cocaine abstainers may have accounted for the decreased odds of the other conditions. Future studies of these relationships in different samples will be needed to better understand the divergent results across outcomes.

The present results are broadly consistent with studies that have been conducted in clinical samples showing graded relationships between initial frequency of cocaine use and outcomes such as functioning on the ASI (Roos et al., 2019b) and frequency of use during follow-up (Fitzmaurice et al., 2017, 2020). However, the present study moves this research forward by using a general population sample to show a relationship between cocaine frequency of use and increased risk for dependence on various substances, and for psychiatric disorders. These are clinically important outcomes and contribute to knowledge suggesting that reduced frequency of use may be a valuable aim, in addition to the goal of complete abstinence, which is likely to remain the gold standard for treatment efficacy but may not be attainable by many patients, particularly during the early stages of treatment and follow-up when most clinical trial data are collected.

In this study, frequency of cocaine use was determined with relatively straightforward survey items accompanied by flashcards allowing participants to quickly chose frequency categories. More complex, nuanced measures might certainly add valuable information, for example, the Timeline Follow-Back (TLFB) (Aharonovich et al., 2017; Sobell LC

and Sobell MB, 1992) that is used in many clinical studies, or technologically-assisted smartphone or other real-time frequency measures. However, our results based on the survey questions offer an indication of promise in the use of graded measures as an indicator of improvement in place of binary indicators of any cocaine use vs. none within a given period of time.

We used dependence on cocaine and other substances and psychiatric disorders as important indicators of how individuals feel or function, which are important considerations in whether a medication is judged as effective or not (Sullivan EJ). Studies of the relationship of cocaine frequency to additional outcome measures would be a valuable direction for future research.

Study limitations are noted. Results were based on self-report; biological substance use measures were not available in this national survey. The survey was conducted several years ago, although it remains the only data source known to us that combines the richness of variables with a prospective follow-up component. More recent surveys could be used to further develop the present results in cross-sectional designs. Also, while the ordered categories of cocaine frequency of use were designed to provide sufficient numbers of participants for analysis in each category while retaining meaning in terms of time units (days, weeks, months), other grouping could have potentially been used, or could have been determine through latent class analysis, which may have yielded different ordered categories. These alternative strategies could be valuable to pursue in future studies. In addition, the study did not have sufficient numbers of participants who were current users of cocaine at wave 1 to examine the effect of non-abstinent reduction in cocaine use frequency by wave 2 (Supplementary Tables 2 and 3). However, the study represents an important stage in the work on understanding the effects of non-abstinent cocaine reduction and closely follows the early stages of work on the benefits of non-abstinent drinking reduction that were also largely based on analyses of cross-sectional data. Additionally, in suitable data, future studies could address the nature of a non-abstinent reduction in cocaine use (linear, exponential, any reduction) to the study outcomes. Furthermore, while the NESARC is nationally representative of household residents, it does not include those in other types of dwellings or who are unstably housed, who may be more likely to use cocaine (Cano et al., 2020). Future studies of our research questions should examine them in samples with greater representations of participants from race/ethnic minority groups. Finally, NESARC respondents were not participants in a clinical trial, and findings from clinical trial data would also be important in determining the value of non-abstinent cocaine outcomes.

In conclusion, higher frequencies of cocaine use are associated with higher risk for clinically important conditions, and therefore, by inference, lower frequencies of cocaine use were associated with less risk for these conditions. These results contribute to a growing area of research interest, i.e., whether reductions in frequency of use that do not reach full abstinence could serve as indicators of improvement and benefit in clinical trials. Further work in this area is needed, particularly studies of reductions over time and their effects, since efforts to find a pharmacological treatment for cocaine use disorders have not yet been successful, and cocaine use disorders remain a significant clinical and public health problem.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- Greater lifetime frequency of cocaine use was associated with greater odds of past-year and lifetime dependence on cocaine.
- Lifetime greatest frequency of cocaine use was associated with greater odds of past-year cocaine, alcohol, and cannabis dependence, and also psychiatric disorders.
- Baseline frequency of cocaine use predicted greater odds of cocaine disorder three years later.
- Results suggest that non-abstinent cocaine use outcomes might be sensitive and useful indicators of treatment efficacy in clinical trials.
- This study moves research forward by using a general population sample to show the relationship between graded frequency of use and increased risk for dependence and psychiatric disorders.

Table 1.

Demographic characteristics of lifetime cocaine users (n=2,501), by frequency of lifetime heaviest use

		Frequency of heaviest lifetime cocaine use				
	Ever-users (n=2,501)	**Daily/Near Daily (n=345)**	**1–4x per week (n=513)**	**1–3x per month (n=488)**	**3–11x per year (n=354)**	**1–2x per year (n=801)**
Measure	**%**	**%**	**%**	**%**	**%**	**%**
Age (years)						
<30	19.3	19.8	17.5	15.0	17.4	23.7
30–44	51.9	48.8	56.1	55.3	54.6	47.4
45+	28.8	31.4	26.5	29.7	28.1	28.9
Gender						
Male	64.4	63.2	70.3	63.4	65.6	61.5
Female	35.6	36.8	29.7	36.6	34.4	38.5
Ethnicity/Race						
White (Not Hispanic)	77.8	70.7	71.7	77.9	82.0	82.1
Black (Not Hispanic)	7.7	15.5	11.6	7.5	4.4	4.0
American Indian/Alaska Native	3.7	5.5	3.1	5.7	3.0	2.5
Asian/Hawaiian/Pacific Islander	1.7	0.5	2.3	1.3	0.2	2.6
Hispanic or Latino	9.1	7.7	11.3	7.6	10.4	8.7
Education						
less than HS	1.8	2.4	2.2	1.4	1.3	1.7
HS or GED	38.0	51.8	47.8	41.2	28.8	29.4
Some College	25.1	26.9	26.6	25.6	27.3	22.3
College Graduate+	35.1	18.8	23.4	31.8	42.6	46.6
Current cigarette smoker						
No	41.6	29.2	38.5	41.9	45.4	46.3
Yes	58.4	70.8	61.5	58.1	54.6	53.7
BMI (kg/m2)						
underweight/normal	41.6	40.7	38.4	42.1	43.9	42.5
overweight/obese	58.4	59.3	61.6	57.9	56.1	57.5
Health Insurance						
No	24.0	34.5	26.8	22.8	20.7	20.4
Yes	76.0	65.5	73.2	77.2	79.3	79.6
Time since heaviest use (years)						
<1	7.2	9.3	6.3	6.4	8.8	6.6
1–5	13.4	22.3	13.2	12.6	11.4	11.5
5+	79.4	68.4	80.5	81.0	79.8	81.9

Table 2:

Prevalence of lifetime and past-year substance dependence, psychiatric disorder among lifetime cocaine users (n=2,501) by frequency of heaviest lifetime cocaine use

	Frequency of heaviest lifetime cocaine use				
	Daily/Near Daily n=345 %	**1–4x/week n=513 %**	**1–3x/month n=488 %**	**3–11x/year n=354 %**	**1–2x/year n=801 %**
Lifetime Dependence					
Cocaine	50.9	30.0	12.9	05.2	01.3
Alcohol	66.9	55.3	45.7	43.9	44.3
Cannabis	21.9	12.8	08.6	11.3	10.2
Other Drugs	30.9	21.3	15.0	15.3	16.0
Lifetime Disorder					
Any Depressive	41.8	38.9	37.1	35.0	34.6
Any Anxiety	33.3	30.9	30.5	25.3	30.4
Panic	19.8	13.7	14.8	09.2	10.5
Generalized Anxiety	13.4	10.4	07.6	07.8	08.9
Past-year Drug Use					
Cocaine	11.6	12.4	07.8	08.2	07.5
Alcohol	70.9	78.8	85.0	88.5	87.4
Cannabis	29.5	31.1	25.2	2 2.3	26.0
Other drugs	36.4	37.7	32.1	30.2	32.1
Past-year Dependence					
Cocaine	04.6	04.4	02.7	01.2	00.2
Alcohol	20.5	22.3	14.6	13.9	15.4
Cannabis	03.6	02.6	01.2	01.5	02.4
Other drugs	05.7	02.9	02.5	03.0	04.4
Past-year Disorder					
Any Depressive	21.8	22.2	18.1	13.3	16.6
Any Anxiety	23.6	20.3	16.5	14.3	20.9
Panic	07.9	07.8	05.0	03.1	05.5
Generalized Anxiety	08.4	06.1	05.1	03.9	04.5

Table 3:

Increase in risk for lifetime and past-year substance use, substance dependence or psychiatric disorders by lifetime heaviest frequency of cocaine use, odds ratios from logistic regression models[a] (n=2,501)

	aOR	95% CI	p
Lifetime Dependence			
Cocaine	**2.80**	**(2.60, 3.01)**	**<.001**
Alcohol	**1.22**	**(1.19, 1.26)**	**<.001**
Cannabis	**1.22**	**(1.17, 1.27)**	**<.001**
All Other Drug	**1.19**	**(1.15, 1.23)**	**<.001**
Lifetime Diagnoses			
Any Depressive	**1.06**	**(1.02, 1.10)**	**.001**
Any Anxiety	1.02	(0.99, 1.05)	ns
Panic	**1.17**	**(1.12, 1.23)**	**<.001**
Generalized Anxiety	**1.09**	**(1.04, 1.14)**	**<.001**
Past-year use			
Cocaine	**1.15**	**(1.09, 1.21)**	**<.001**
Alcohol	**0.80**	**(0.77, 0.83)**	**<.001**
Cannabis	**1.04**	**(1.00, 1.09)**	**.033**
All Other Drug	1.03	(0.99, 1.06)	ns
Past-year Dependence			
Cocaine	**1.78**	**(1.48, 2.15)**	**<.001**
Alcohol	**1.13**	**(1.07, 1.19)**	**<.001**
Cannabis	**1.16**	**(1.03, 1.31)**	**.011**
All Other Drug	0.97	(0.88, 1.07)	ns
Past-year Diagnoses			
Any Depressive	**1.07**	**(1.03, 1.10)**	**<.001**
Any Anxiety	1.00	(0.97, 1.03)	ns
Panic	**1.09**	**(1.02, 1.16)**	**.011**
Generalized Anxiety	**1.12**	**(1.05, 1.20)**	**<.001**

[a]Model controlled for sex, age, education, ethnicity/race, insurance, BMI, smoking status

[b]Models additionally controlling for time since heaviest use led to similar results, except that the effect of lifetime heaviest frequency of cocaine on any lifetime anxiety diagnosis became significant (aOR=1.03, 95% CI=(1.00, 1.06), p=.034)

Table 4:

Risk for Wave 2 outcomes (3-year follow-up), by Wave 1 frequency of cocaine use

Wave 2 Outcome				
Wave 1 frequency of past year cocaine use	**Adjusted Prevalence %**	**aOR** [a]	**95% CI**	**p**
Cocaine Use Disorder at Wave 2				
≥1x/week (n=40)	17.8	2.13	(1.76, 2.59)	<.001
1–3x/month (n=26)	14.4	1.67	(1.64, 1.69)	<.001
<1x/month (n=91)	09.2	reference	- -	
Other Substance Use Dependence at Wave 2 [b]				
≥1x/week (n=40)	28.9	0.47	(0.45, 0.50)	<.001
1–3x/month (n=26)	32.1	0.55	(0.50, 0.61)	<.001
<1x/month (n=91)	46.2	reference	- -	
Any Psychiatric Diagnosis at Wave 2 [c]				
≥1x/week (n=40)	18.5	0.32	(0.29, 0.34)	<.001
1–3x/month (n=26)	23.8	0.44	(0.41,0.47)	<.001
<1x/month (n=91)	41.7	reference	- -	

[a]Model adjusted for sex, age, insurance status, BMI, smoking, and respective outcome at Wave 1

[b]Substance use dependence with or without abuse at Wave 2 including alcohol, cannabis, sedatives, tranquillizers, opioid painkillers, other stimulants, hallucinogens, inhalants, and heroin

[c]Any psychiatric diagnosis at Wave 2 including major depression, dysthymia, panic, generalized anxiety, social or specific phobia

[c]Models additionally controlling for time since heaviest use led to similar results.