

Cocaine Use and the Occurrence of Panic Attacks in the Community: A Case-Crossover Approach

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The epidemiologic case-crossover method is a powerful tool for research on suspected hazards of illegal drug use, the advantage being a subject-as-own-control approach that constrains stable individual-level susceptibility traits. Here, we use the case-crossover method to estimate the magnitude of excess occurrence of panic attacks during months of cocaine use vs. months of no cocaine use, motivated by a prior estimate that cocaine users have three-fold excess risk of panic attack. The self-report data on cocaine and panic are from assessments of a nationally representative sample of 1071 recent panic cases age 18 years or older identified as part of the National Household Surveys on Drug Abuse conducted in the United States during 1994–1997. Based on case-crossover estimates, cocaine use is associated with a three- to four-fold excess occurrence of panic attack (estimated relative risk (RR) = 3.3, $p = 0.049$; 95% confidence interval: 1.0, 13.7). Year-by-year, the RR estimates from four independent yearly replicates (1994–1997) are 5.0, 2.0, 3.0, and 3.0. While there are several important limitations, this study adds new evidence about a previously reported suspected causal association linking cocaine use to occurrence of panic attacks, and illustrates advantages of the epidemiologic case-crossover approach and new directions in research on hazards of illegal drug use.

Keywords comorbidity; panic disorder; cocaine; case-crossover design; drug use; epidemiology; illegal drugs

Introduction

The purpose of this study is to estimate a suspected causal association between cocaine use and the occurrence of panic attacks. Drawing upon clinical experience with three psychiatric patients, Aronson and Craig (1986) hypothesized that cocaine use might precipitate panic attack and possibly panic disorder. In later case reports with samples of up to 10 patients, others have added new and generally consistent clinical observations (Pohl et al., 1987; Price and Giannini, 1987; Geraciotti and Post, 1991), as well as specifications for a treatment approach to address cocaine-induced panic disorder (Louie et al., 1989). Anthony and colleagues (1989) provided the first epidemiological estimates on this suspected causal association, finding cocaine users to have a three-fold excess risk of panic attack.

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Some theories and evidence on neurobiology of panic disorder and cocaine pharmacology can be used to lend plausibility to inferences that cocaine use might cause panic attacks (Louie et al., 1989; Hebert et al., 1999; Blanchard et al., 2000). Nevertheless, as with many hypotheses in psychiatric comorbidity research, the cocaine-panic linkage has not been tested in controlled laboratory experiments with human subjects, due to issues of feasibility and ethical concerns about administering cocaine to the point of inducing psychiatric disturbances.

In the cocaine-panic research described earlier, Anthony et al. (1989) created matched risk sets of first-time panic attack cases and noncases, based upon prospectively gathered data from almost 9000 young adult household residents who completed longitudinal Diagnostic Interview Schedule (DIS) assessments as part of the multisite collaborative Epidemiologic Catchment Area (ECA) Program. The conditional form of multiple logistic regression modeling then was used to estimate relative risks. As discussed by the authors in their report, this approach leaves open the possibility of confounding by unmeasured individual-level susceptibility traits that might give rise both to earlier cocaine use and then later occurrence of panic attacks.

For the present investigation, we returned to the suspected causal association linking cocaine use to panic attacks, but here we reestimate this association using the case-crossover design and, more recent nationally representative samples, in a manner that holds constant a broad array of hypothesized individual-level susceptibility traits (via the self-matching or "subject-as-own-control" feature of this design). These case-crossover estimates are based upon 1071 cases of recent panic attack, nested within a nationally representative household survey sample. Wu and Anthony (2000), previously introduced the details of the epidemiological case-crossover method to readers of *Substance Use and Misuse*, and explained how this design holds constant susceptibility traits. Here, we demonstrate this application of the case-crossover research design as an approach that might have a general utility in comorbidity studies and other psychiatric research on suspected hazards of drug use.

To our knowledge, the case-crossover method has not been used previously to test any general psychiatric comorbidity hypothesis nor our specific hypothesis about cocaine use and excess occurrence of panic. The only other epidemiological study on the possibility that cocaine use triggers panic attack is our own work (Anthony et al., 1989), published more than 10 years ago. We now offer an epidemiologic case-crossover approach to this research problem, hoping to shed some new light on the issue.

Methods

Study Sample

Data used in this study came from public use files of the 1994 through 1997 National Household Surveys on Drug Abuse (NHSDA). The NHSDA are ongoing surveys designed to provide national estimates on the use of illegal drugs, alcohol, and tobacco by the civilian non-institutionalized population of the United States. Youths age 12–17 years and adults aged 18 years and older are selected for participation in the survey based on a multistage area probability sampling. The sample design has changed over time, but the approach to sampling of adults has been to yield a sample that is representative of the U.S. household residents 18 years old and older.

Questions about panic attack were asked only in the assessment of respondents age 18 and older, not in assessment of 12–17 year olds. A total of 56,655 adults aged 18 and older

completed NHSDA in-home interviews between 1994 and 1997, years during which there was assessment of the calendar month of panic attacks. The interview response rates ranged from 78% to 81%. Other details of the survey design and data collection procedures were reported elsewhere (Office of Applied Studies, 1996, 1997, 1998a, 1998b).

For the purpose of testing the cocaine-panic association, we focused on 272 participants in 1994, 256 in 1995, 247 in 1996, and 296 in 1997, all reporting panic within the month of the assessment. These 1071 cases form the sample for our case-crossover analyses. These panic cases from the NHSDA nationally representative sample tended to be female (71%), aged less than 36 years (75%), white (73%), and not married at the time of the assessment (62%).

Definition of Variables

In this research we studied possible cocaine effects on risk of having a panic attack, which, by definition, is distinguished from formally defined panic disorder (see Glossary). In this context the concept of panic attack was made operational in terms of a study participant's answer to these two standardized survey questions: "During the past 12 months, did you ever have a spell or an attack when all of sudden you felt frightened, anxious, or very uneasy when most people would not be afraid or anxious?" This is essentially the same question asked in the National Institute of Mental Health (NIMH) Diagnostic Interview Schedule, as described in our prior report on the cocaine-panic association, but with a focus on the 12 months just before the interview (Anthony et al., 1989). In addition, the NHSDA questionnaire asked: "During the past 12 months, did you ever have a spell or attack when for no reason your heart suddenly began to race, you felt faint, or you couldn't catch your breath?" For this investigation, panic attacks were restricted to *recent panic attacks*, attacks that occurred in the same month as the assessment. To be conservative in our analysis, we treated the period of recall as a time interval of one month, though as noted in the Discussion section, in future research, standard life table conventions might be used to take into account the spread of interviews throughout the month (i.e., with a period of recall closer to the median of two weeks rather than one month).

Timing of panic attacks was assessed by the administrative survey record on the calendar month of the NHSDA interviews and by the panic-specific survey question: "In what month and year did you have (the last one/this attack)?" Respondents reporting their last panic attack in the same month as the interview were selected as cases; all others were excluded in order to focus attention on the most recently occurring panic attacks (e.g., in case passage of time might induce reporting errors). That is, individuals reporting the month of their last panic attack in a month other than the NHSDA month of assessment were excluded from the case-crossover analysis.

Cocaine use, defined to include crack smoking, was assessed via standardized NHSDA questions. Month-by-month assessment of cocaine or crack use was not available. We utilized standard NHSDA questions asking respondents about their cocaine or crack use in the past month and cocaine or crack use in the past 12 months to determine cocaine use in the hazard and control intervals. For example, the question "How long has it been since you last used any form of cocaine?" allows respondents to select from several answer choices, including within the past 30 days and more than 30 days ago but within the past 12 months. Responses to those items as well as responses to other questions such as, "On how many days in the past 12 months did you use cocaine?" and "Think specifically about the past 30 days. During the past 30 days, on how many days did you use cocaine?" were combined to create two variables: 1) cocaine use in the past 30 days and 2) cocaine use in the past

2–12 months (i.e., in the past year but not in the past 30 days). This allowed us to make an assessment of the panic case's use of cocaine in the 30 days encompassing the panic hazard interval only (but not in a prior control month), in the control interval only (but not in the 30 days encompassing the hazard interval), in neither interval, or in both.

Cocaine and panic assessments were embedded in the more general survey interview, and were separated by about 10 minutes of assessments on other topics. Neither interviewers nor subjects knew that this particular causal hypothesis about cocaine and panic was under investigation.

Statistical Analysis

The case-crossover data can be analyzed by using standard methods for matched pair case-control studies (Mittleman et al., 1995). Each case contributes a pair of hazard and control intervals. The hazard interval for each panic attack case has been defined as the same calendar month as the panic attack or within 30 days of assessment. We designated as our "control" interval the 11-month interval just prior to that calendar month. On a subject-by-subject basis, we checked which cases used cocaine only during the hazard interval (i.e., not during the control interval), and which cases used cocaine only during the control interval (i.e., not during the hazard interval). With a correction to address the shorter (30-day) duration of the hazard interval vs. the 11-month duration of the control interval, these discordant cells provide information for the standard matched-pair relative risk estimates of cocaine-associated excess occurrence of panic. *P*-values based on exact methods are used here as an aid to interpretation and as a measure of statistical uncertainty of the study evidence (StataCorp., 2001).

Based upon prior study findings, our significance testing is one-tailed because the weight of theory and prior evidence is balanced in favor of the thesis that cocaine use may increase risk of panic attack. To our knowledge, no one has suggested that cocaine protects against panic, and this seems an implausible outcome. More specifically, we expect that cocaine use will be associated with a moderately increased risk of panic attack (relative risk, $RR = 3.4$), which was the estimate reported by Anthony et al. (1989), based on ECA data from the early 1980s. Of course, some readers may wish to entertain the idea that cocaine use might protect against panic attack, or even that cocaine might be used to treat panic attack. For these readers, our preference for a one-tailed test can be ignored; our study's evidence will be somewhat less convincing to these readers.

Results

Of the 1071 individuals who experienced a panic attack during the same month or within 30 days of the assessment, 986 of these cases (92.1%) had no history of cocaine use during any of the 12 months prior to assessment (Table 1). Thirteen cases used cocaine only in the 30 days that encompassed occurrence of the panic attack (i.e., the "hazard" interval for the case-crossover design) but not in the 11-month period preceding the month of panic attack (i.e., the "control" interval for the case-crossover design). A total of 44 cases used cocaine during the period of 1–11 months before the month of panic attack but not during the hazard interval. A total of 28 panic attack cases used cocaine during both hazard and control intervals.

The informative cases are the 13 cases of panic attack who used cocaine in the hazard interval but not in the control interval, and the 44 panic cases who used cocaine in the

Table 1

Timing of cocaine use in relation to the hazard and control intervals: data from the United States National Household Survey on Drug Abuse (NHSDA), 1994–1997 (n = 1071)^a

Cocaine use during the 11-month control interval	Cocaine use during the one-month hazard interval ^b		Total 1071
	No	Yes	
No	N = 986 (91.5% of total)	N = 13 (1.3% of total)	999
Yes	N = 44 (4.2% of total)	N = 28 (3.0% of total)	72

^aEstimated Relative Risk = 3.3, 95% CI: 1.00, 13.68; one-tailed *p*-value = 0.049. The 95% confidence interval and the *p*-value are based on exact methods. This table should be read as one reads a corresponding table from a MZ co-twin study. That is, the informative cases are those with cocaine exposure in the hazard interval but not in the 1–11 months in the control interval (upper right-hand cell, n = 13) and also those with cocaine exposure in the control interval but not in the hazard interval (lower left-hand cell, n = 44). The relative risk estimate from this table is 13/1/44/11, where 44/11 is the expected number of panic attack cases during a one-month control interval. As in discordant MZ co-twin estimates, the values in the upper left-hand cell (n = 986) and lower right-hand cell (n = 28) do not contribute information to the point estimate.

^bThe hazard interval was the month prior to survey assessment, during which the index panic attack occurred. The control interval is the rest of the 12-month interval of the year prior to assessment such that the hazard interval is one month in duration and the control interval (before correction) is an 11-month interval.

control interval but not in the hazard interval. At first glance, the study results might appear to indicate a salubrious effect of cocaine use with respect to occurrence of panic attacks. That is, there were 13 cases using cocaine during the hazard interval (but not in the control interval) vs. 44 cases using cocaine within the control interval (but not in the hazard interval). However, the first glance is misleading because it makes no correction for the differences in duration of the hazard and control intervals (i.e., 30 days vs. 11 months). Correcting for the 11-month duration of the control interval, we would expect the one-month control interval to yield four cases of panic attack with a recent cocaine exposure (44 cases/11 months = 4 cases/month). In contrast, we observed 13 cases of panic attack to have recent cocaine exposure in the hazard period, about three times more than the expected value (i.e., 13/4 = 3.3; 95% confidence interval: 1.0, 13.7; *p* = 0.049). Year-by-year, the RR estimates from four independent yearly replicates (1994–1997) are 5.0, 2.0, 3.0, and 3.0. That is, all four of these survey years of the NHSDA give results consistent with a modestly increased cocaine-associated risk of panic attack.

Some of the participants had reexperienced panic attacks in the hazard interval after prior attacks in the control interval. By restricting the analysis to participants with panic solely occurring in the month prior to assessment (i.e., the hazard interval), the RR estimate is 11.0, a stronger association. However, due to the more limited number of panic attack cases for this estimate, the RR confidence interval is quite wide and traps the null value, 1.0.

Cases reporting cocaine use only in the hazard interval reported a mean of six panic attacks in the past year (range 1–30, median 3, mode 1); for all 1071 cases, the average number of panic attacks in the past year for the cases was 63 (range 1–365, median 5,

mode 1). The 85 cocaine users were generally male (53%), less than 36 years old (93%), white (66%), and not married at the time of the assessment (84%).

We explored the frequency of cocaine use among the 13 panic cases who used cocaine in the hazard interval but not in the prior 11 months. Ten of the 13 panic attack cases were novice users (i.e., nine of the 10 had used cocaine not more than two days in their lifetimes; only one had used cocaine more than this: between three and 11 days in his lifetime). The other three panic cases were more experienced users of cocaine, with two cases reporting cocaine use on 101 to 300 days in their lifetimes; one case reported having used more than 300 days in his lifetime. Similarly, nine of the 13 reported never having used crack, three reported lifetime use of not more than two days, and one reported having used crack more than 300 days in his lifetime.

We also examined whether this association between cocaine use and panic attack varied by type of panic symptoms. The simple, anxious type of panic is characterized by feeling frightened and/or anxious ($n = 728$) and the nonfearful, cardiovascular type is characterized by shortness of breath, faintness, or accelerated heart rate ($n = 390$). A total of 47 adults reported having both types of symptoms. The estimated relative risk of panic in association with cocaine use is 2.0 for the anxious type and 7.0 for the cardiovascular type.

To probe whether the association between cocaine use and panic might vary depending upon other drug use, separate analyses were conducted by stratifying panic attack cases in relation to use of tobacco cigarettes, alcohol, marijuana, stimulants, hallucinogens, inhalants, and sedatives or tranquilizers in the year prior to interview. Tobacco and alcohol did not distinguish the hazard period from the control period. Of the 1071 cases, 571 used tobacco cigarettes in the year prior to assessment, and all but three of the cocaine users used tobacco cigarettes in the year prior to assessment (i.e., tobacco use did not distinguish the hazard period from the control period). Similarly, 777 of the 1071 panic cases were alcohol users in the year prior to assessment, and all but one of the cocaine users used alcohol in the year prior to interview (i.e., alcohol use did not distinguish the hazard period from the control period). The estimated cocaine-panic relative risk (RR) did not vary appreciably between past-year marijuana users and nonusers (RR, 3.0 vs. 4.0). The estimated cocaine-panic association also did not vary markedly between past-year users and nonusers of sedatives and tranquilizer drugs (RR, 3.0 vs. 3.3). The cocaine-panic association was also very similar for users and nonusers of inhalants or stimulants. For inhalants, the RR estimates for past-year users vs. past-year nonusers are 4.0 and 3.7, respectively. For stimulants, the RR estimates for past-year users vs. past-year nonusers are 2.0 and 3.0, respectively. The point estimate for the cocaine-panic association was 5.0 for past-year users of hallucinogens and 3.0 for past-year nonusers of hallucinogens. However, these point estimates have large overlap in 95% confidence intervals; a larger study will be needed to yield more definitive evidence on this possible effect modification.

To put these case-crossover results from the early 1990s into a more recent perspective, we turned to the just-released data (February 2003) from the NHSDA assessments conducted during CY2001. Although the data on timing of panic attack no longer are collected, and hence, we are unable to replicate the case-crossover approach using these very recent data, we were able to make some pertinent estimates for adults age 18–29 years old, a period of life during which risk of having a panic attack and risk of starting cocaine use are rising to peak values (Eaton et al., 1989; Wagner and Anthony, 2002). Specifically, based on the CY2001 NHSDA data, among 17,664 18-to-29 year-olds who had never tried cocaine, an estimated 15% experienced at least one panic attack during the 12 months before assessment. In contrast, within the CY2001 sample, there are 93 18-to-29 year-olds who used cocaine for the first time during the year prior to assessment and who had used cocaine on just

one day of the year (i.e., qualified as a recent-onset cocaine user with few cocaine-taking experiences). Among these 93 recent-onset cocaine users, a total of 29 experienced at least one panic attack during the 12 months prior to assessment. This observed estimate of 31% among the recent-onset cocaine users can be compared to the population-expected value of 15% based on young adults who never had tried cocaine. The difference or ratio of these proportions (0.31 vs. 0.15) is consistent with the idea that panic attacks are occurring more frequently among recent onset cocaine users: young adult recent-onset cocaine users with no more than one day of cocaine use are experiencing panic attacks at an occurrence rate that is more than twice the panic attack occurrence rate expected for young adults who never have used cocaine. Repetition of these analyses with weighted data lead to the same conclusion of a cocaine-associated excess occurrence of panic attack.

Discussion

The main evidence of this study tends to support the idea that cocaine use is associated with increased occurrence of panic attacks. Cocaine use was associated with a 3.3-fold excess occurrence of panic attacks—very close to the relative risk estimate of 3.4 observed in the ECA study on this topic and consistent with previous case reports and studies (Aronson and Craig, 1986; Price and Giannini, 1987; Pohl et al., 1987; Geraciotti and Post, 1991; Anthony et al., 1989). What is new here is the use of a case-crossover method that holds constant long-standing individual-level vulnerabilities that might predispose the same individual to have a panic attack and also to use cocaine. Our observation that nine out of 13 informative users were very inexperienced users of cocaine helps localize a period of excess risk; only three of the panic attack cases had progressed beyond the stage of being a novice user of cocaine. If cocaine use is causing panic attacks, the period of excess risk may be during the first hours, days, or months after first use of cocaine; thereafter, there may be little or no cocaine-associated excess risk of panic attack.

There are some study limitations that merit attention. First, cross-sectional data based on self-reported retrospective recall leave issues of temporal sequencing unclear; our focus on recent panic attacks constrains potential memory bias to a large extent. A second limitation involves the small sample counts in the discordant cells, which prevented more detailed analyses. The only way to address this limitation is to gather more data in future NHSDA years; regrettably the NHSDA assessment of anxiety problems has changed and it was not possible to add new data and panic cases from 1998 forward. Third, because of the way cocaine use was assessed in the NHSDA, we were not able to test temporal sequencing of cocaine use and panic episodes, though the clinical reports make it plausible that cocaine use preceded rather than followed the occurrence of panic attack. Also, due to NHSDA assessments on cocaine use and panic attack, it was necessary to make assumptions about corrected values for the control interval (i.e., 44 cases divided by 11 months). Nevertheless, this particular limitation highlights the importance of securing fine-grained data on temporal sequencing in research on psychiatric comorbidity. Here, we have resolution to the level of month-by-month occurrence of panic attacks and cocaine use, and we still do not have sufficient resolving power with respect to the temporal sequencing issue. If we are to avoid all assumptions about temporal sequencing, our psychiatric comorbidity research must have resolution to the level of weeks or even days and hours. Indeed, if the reported panic attacks are occurring right after the initial exposure to cocaine, then a minute-by-minute resolution is required, such as might be gained by using experience-sampling methods now used in tobacco smoking research (e.g., see Anthony et al., 2000).

It might come as a surprise to some readers that in such a large epidemiological sample of adults ($n = 13,111$ in 1994; $n = 13,152$ in 1995; $n = 13,731$ in 1996; $n = 16,661$ in 1997), the estimated cocaine-panic association ends up resting upon a total of 57 informative subjects (the upper right-hand and lower left-hand cells in Table 1). For epidemiologists, this is a familiar situation, one that often arises in monozygotic twin studies on environmental causes of disease, when the point estimate for relative risk is based solely upon discordant twin pairs (i.e., pairs with twins who are discordant for disease and also for exposure). In a situation such as this one, the number of informative panic attack cases (or informatively discordant twin pairs) cannot be predetermined as it might be in a controlled experiment. Nonetheless, the investigator pays a price for studying a large sample with so few informative subjects—in the form of wider confidence intervals and larger p -values than would be seen with a greater number of informative subjects. The common rule for epidemiology applies here as it does in discordant monozygotic twin pair studies: for rare events, very large samples are needed.

Notwithstanding limitations such as these, this report illustrates how the case-crossover design may be used as an adjunct to current epidemiologic methods in drug use research. Findings from this study supplement clinical and laboratory research on cocaine use and the occurrence of panic attacks, and are congruent with the only other epidemiological study on the cocaine-panic association (Anthony et al., 1989). The use of a case-crossover design also highlights a need to develop standardized instruments with fine-grained assessment of the temporal sequencing of respondents' drug use and related problems. Despite the fact that the case-crossover design cannot control for potentially distorting influences that vary over time within each individual, we have tested for such potential bias by stratifying panic cases according to their antecedent use of other drugs. Most importantly, through the self-matching strategy, the case-crossover analysis is able to constrain potential bias in selection of controls, as well as bias resulting from other long-lasting individual characteristics, especially stable personality traits and inherited and/or acquired vulnerabilities. Maclure (1991) and Wu and Anthony (2000) provide additional details about the case-crossover method.

In light of the international readership of *Substance Use and Misuse*, we appreciate that some readers may question whether the reported cocaine-panic association is peculiar to the United States, and may wonder if these findings hold elsewhere. Regrettably, there seems to be an emerging global market for coca products, with coca paste, crack-cocaine, and cocaine hydrochloride powder use becoming more common outside the United States. We have been unable to locate published research investigating the cocaine-panic association in countries where other coca products such as coca paste and coca leaf are popular. We hope epidemiologists and clinicians in other countries will investigate the generality of the cocaine-panic association now observed in several studies with samples from the United States.

As a concluding note, we wish to stress that the epidemiologic case-crossover method sometimes will yield evidence that is more definitive than is evidence from studies of discordant monozygotic (MZ) twin pairs. For example, in comorbidity research using the discordant monozygotic co-twin method, we always are left with unanswered questions about how it happened that one of the MZ twins became a drug user and the co-twin did not. Factors or processes that led one MZ twin to use drugs when the other co-twin did not use drugs may represent confounding variables in the co-twin design. A great many, but not all, of these factors and processes are held constant in the case-crossover design, due to its status as a subject-as-own-control design. Nonetheless, even in the case-crossover design, we are left with a puzzle—namely, what accounts for the subject's use of the drug

in the hazard interval but not in the control interval? Questions of this type do not exist in randomized experiments where the experimenter has control over the exposure, but for many important research questions about psychiatric comorbidity, we will never have the luxury of investigator control via randomized exposure to illegal drugs.

One of the noteworthy features of this study is its use of the case-crossover subject-as-own-control design, which has the virtue of holding constant (via self-matching) any and all of the underlying psychiatric disturbances that might give rise to both cocaine use and panic attacks. As an example, mood disorders and especially major depressive disorder should be counted among the underlying suspected causal determinants, in that a mood disturbance might give rise to occurrence of cocaine use [e.g., consistent with Khantzian's (1997) self-medication hypothesis], and in that a mood disturbance can be primary, with panic attacks as a secondary consequence (e.g., consistent with the evidence presented by Anthony et al., 1989, in our research group's prior paper on the cocaine-panic association, and in more recent work by others such as Goodwin et al. (2002)). There also is reason to think that trait anxiety might be an important underlying marker of susceptibility to cocaine-induced psychiatric disturbances (Rosse et al., 1995). Here, with the subject-as-own-control design, we hold constant all of these long-standing underlying suspected causal determinants, whether they have been measured or not. This exceptional degree of almost total control over the subject's background of potentially confounding characteristics is one of the cardinal strengths of the epidemiological case-crossover design, which makes the design especially well-suited to the study of triggering hypotheses (Muller et al., 1996).

Another noteworthy feature of this study, which might be a limitation, is that the study evidence is relatively silent about the phenomenological character of the panic attacks as they might be triggered by cocaine use. Whereas we have been unable to find evidence based on human laboratory studies, there is preclinical evidence about panic-like flight responses, observed in a mouse model of anxiety disturbances (Blanchard et al., 2000; Hebert et al., 1999). In this large-scale epidemiological survey, there was no careful clinical psychiatric diagnosis such as might be possible in smaller scale clinical studies of human patients. As such, what we may have found is epidemiological evidence that even one or a few cocaine exposures can, in some individuals, precipitate something less akin to a full symptom panic attack as defined in psychiatry's diagnostic and statistical manuals, and more akin to a panic-like response (e.g., sudden concerns expressed by users that they might be having a heart attack, secondary to increased heart rate and other clinical manifestations of ingesting an effective dose of a psychostimulant drug). In this sense, the panic observed in this study may be a panic in the colloquial sense, rather than in a formal psychiatric diagnostic sense. Nonetheless, the epidemiological evidence from the field is important because cocaine self-administration laboratory studies of humans exposed to controlled doses of cocaine seem to be silent on this type of response to cocaine, whereas they are not silent on the topic of cocaine-induced suspiciousness or paranoia states (Sherer et al., 1988).

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Glossary

The following definitions are from the *American Psychiatric Association Diagnostic and Statistical Manual—Text Revision (DSM-IV-TRTM, 2000)*.

Panic Attack: A discrete period in which there is the sudden onset of intense apprehension, fearfulness, or terror, often associated with feelings of impending doom. During these attacks, symptoms such as shortness of breath, palpitations, chest pain or discomfort, choking or smothering sensations, and fear of "going crazy" or losing control are present. Panic Attack is not a codable disorder.

Panic Disorder: Recurrent unexpected Panic Attacks about which there is persistent concern (with or without Agoraphobia). In addition, the Panic Attacks are not due to the direct physiological effects of a substance (e.g., a drug of abuse, medication) or a general medical condition (e.g., hyperthyroidism), and the Panic Attacks are not better accounted for by another mental disorder (e.g., Social Phobia, Posttraumatic Stress Disorder).

RESUMEN

El método epidemiológico de cruces de casos es una poderosa herramienta para la investigación de riesgos atribuidos al uso de drogas ilícitas, siendo la ventaja el uso del sujeto como su mismo control lo que restringe las características estables de susceptibilidad individual. En esta investigación utilizamos el método de cruces de casos para estimar la magnitud excedente de ocurrencias de ataques de pánico durante los meses de uso de cocaína en comparación con los meses en los que no se usó esta droga, motivados por un estimado anterior en el cual el exceso de riesgo de padecer de ataques de pánico es tres veces mayor en los usuarios de cocaína. El auto reporte de datos acerca del uso de la cocaína y pánico provienen de evaluaciones de una muestra nacional representativa de casos recientes de ataques de pánico identificados como parte de la Encuesta Nacional de Hogares sobre el Abuso de Drogas, que se llevó a cabo en los Estados Unidos de 1994 a 1997. Basándose en los estimados de los cruces de casos, el uso de cocaína está asociado con una incidencia 3 a 4 veces mayor de ataques de pánico (riesgo estimado relativo, $RR = 3.3$, $p=0.049$; intervalo de confianza de 95% = 1.0,13.7). Año por año, los estimados de RR resultantes de nuestras cuatro réplicas anuales independientes (1994–1997) fueron: 5.0, 2.0, 3.0 y 3.0 respectivamente. A pesar de diversas limitaciones importantes, este estudio presenta nueva evidencia acerca de un reportaje previo atribuyendo una asociación causal relacionando el uso de cocaína con los ataques de pánico, e ilustra las ventajas del uso de cruces de casos en la epidemiología y nuevas trayectorias en la investigación de riesgos en el uso de drogas ilícitas.

Palabras Claves: Comorbilidad, trastorno de pánico, cocaína, diseño de cruces de casos, uso de drogas, epidemiología.

RÉSUMÉ

La méthode épidémiologique à cas-croisé (case cross-over) est un outil puissant pour la recherche de risques suspects d'usage de substances illicites, l'avantage étant une approche de sujet-comme-propre-contrôle qui contraint les traits de susceptibilités stables au niveau individuel.

Ici, nous employons la méthode de cas-croisé (case cross-over) pour estimer le niveau d'occurrence excessive des attaques de panique pendant des mois d'utilisation de cocaïne par rapport aux mois sans utilisation de cocaïne, motivés par une évaluation antérieure que les utilisateurs de cocaïne sont à triple risque d'attaque de panique.

Les données par rapport individuel sur la cocaïne et la panique sont des évaluations d'un échantillon nationalement représentatif de 1.071 cas de panique récent âgés de 18 ans ou plus identifiées par l'enquête de la National Household Surveys on Drug Abuse (enquêtes nationales de ménage sur l'abus de drogue) conduit aux Etats-Unis entre 1994–97. Se basant sur les évaluations de cas-croisé, l'utilisation de cocaïne est associée à une

occurrence d'attaque de panique 3 à 4 fois plus excessive (Risque Relatif estimé, $RR = 3.3$, $p = 0.049$; intervalle de confiance de 95% : 1.0–13.7). Année-par-année, les évaluations de RR de quatre répliques annuelles indépendantes (1994–1997) sont 5.0, 2.0, 3.0, et 3.0.

Bien qu'il y a plusieurs limitations importantes, cette étude ajoute nouvelle évidence à l'association causale suspecte, précédemment rapportée, liant l'utilisation de cocaïne à l'occurrence des attaques de panique, et illustre les avantages de l'approche épidémiologique de cas-croisé (case cross-over) ainsi que les nouvelles directions dans la recherche sur des risques d'usage de substances illicites

Mots-clés: Comorbidité, Désordre de Panique, Cocaïne, Conception de Cas-Croisement, Utilisation de Drogue, Épidémiologie, Drogues Illégales.

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