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Does Cannabis Onset Trigger Cocaine Onset? A Case-Crossover Approach

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Abstract

Psychiatric researchers tend to select the discordant co-twin design when they seek to hold constant genetic influence while estimating exposure-associated disease risk. The epidemiologic case-crossover research design developed for the past two decades represents a viable alternative, not often seen in psychiatric studies. Here, we turn to the epidemiologic case-crossover approach to examine the idea that cannabis onset is a proximal trigger for cocaine use, with the power of 'subject-as-own-control' research used to hold constant antecedent characteristics of the individual drug user, including genetic influence and other traits experienced up to the time of the observed hazard and control intervals. Data are from newly incident cocaine users identified in the 2002–2006 U.S. National Surveys on Drug Use and Health. Among these cocaine users, 48 had both cannabis onset and cocaine onset in the same month-long hazard interval; the expected value is 30 users, based on the control interval we had pre-specified for case-crossover estimation (estimated relative risk, RR = 1.6; exact mid-p = 0.042). Within the framework of a subject-as-own-control design, the evidence is consistent with the hypothesis that cannabis onset is a proximal trigger for cocaine use, with genetic influences (and many environmental conditions and processes) held constant. Limitations are noted and implications discussed.

Keywords

case-crossover design; gateway process; cannabis; cocaine; twin studies

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Introduction

Is there something about occasions of first cannabis use that trigger onset of first cocaine use? Perhaps starting to smoke cannabis promotes a more rapid contact with cocaine users and dealers in interpersonal or social developmental sequences that involve mixing of the cannabis and cocaine markets (O'Donnell & Clayton, 1982). Development of these sequences from first use of legal drugs (alcohol, tobacco) toward use of cannabis (marijuana) and onward toward drugs like cocaine and heroin sometimes has been called a 'stepping-stone' or 'gateway' process, with the 'steppingstone' idea cast as somewhat more deterministic than the more probabilistic 'gateway' idea (Anthony, 2002; Kandel, 1975; Morral, McCaffrey, & Paddock, 2002; O'Donnell & Clayton, 1982). A major conclusion from two prior studies of discordant co-twins has been that peer and social influences are at play in this process, over and above any genetic or other predispositions shared by twins (Lynskey, et al., 2003). For example, in monozygotic (MZ) twins discordant with respect to early onset of cannabis smoking, one sees excess occurrence of later use of drugs such as cocaine. This observation highlights the potential contribution of social conditions such as drug-using friends or drug markets where both cocaine and cannabis are made available, but it leaves us with a puzzling question. Namely, what accounts for one MZ twin becoming a cannabis smoker early on when the other one did not, even when shared genetic influence is held constant via the co-twin design?

Furthermore, as noted by Cleveland and Wiebe (2008), Lynskey and colleagues found little evidence that the cannabis-cocaine association differed in magnitude for dizygotic (DZ) versus MZ co-twins. Cleveland and Wiebe characterized the situation as follows: "…[their] genetic hypothesis was rejected because earlier marijuana differences predicted later hard drug use differences similarly across zygosities, as both DZ and MZ twin pairs demonstrated the gateway effect."

In their own twin research on this topic, Cleveland and Wiebe departed somewhat from the conventional discordant MZ co-twin research design that is used when the experimental plan is to hold constant shared genetic influences while estimating the relative risk of exposure-associated outcomes. They defined discordance in exposure as a between-twin difference in number of occasions of cannabis smoking, while discordance in outcome varied as a function of the Poisson count of the other drugs used. In their approach, within-pair differences in earlier marijuana use predicted later within-pair hard drug use differences for DZ twin pairs but not MZ twin pairs. These findings suggest that this sequence of drug use might be more appropriately conceptualized as a genetically influenced developmental trajectory rather than a sequence initiated when marijuana triggers later hard drug use – a conclusion that is not completely consistent with the gateway theory (Cleveland & Wiebe, 2008).

In addition to co-twin research, there is considerable supportive cross-sectional evidence on the cannabis-cocaine sequence, as well as a few contributions from longitudinal cohort studies, as summarized by van Ours (2003), and others (Fergusson, Boden, & Horwood, 2006; Fergusson & Horwood, 2000). Van Ours (2003) provides an especially thorough review of identification problems and uncertainties traced back to individual-level

heterogeneities in this evidence from between-subject study designs, which has helped motivate this application of a 'subject as own control' design.

We note that the observed within-twin discordance in early frequency of cannabis smoking resurrects the same type of puzzling question faced in the standard co-twin method. Namely, what is it that accounts for within-pair between-twin differences in the early frequency of cannabis smoking in the first place? Whereas Gillespie and colleagues (2009) recently reported novel co-twin research that begins to answer this question, we believe that other behavior genetics research approaches deserve consideration as well, when we seek to hold constant genetic influences as much as possible, as described below.

When the gateway process model has been given credence in the bench sciences, the perspective generally has invoked alternative underlying mechanisms – often, an exogenous set of cannabis-induced or more specifically Δ9-tetrahydrocannabinol (THC)-induced neurobiological changes that sub-serve the reinforcing functions of other drugs such as heroin and cocaine, which themselves might be subject to genetic influence (e.g., see Koob, et al., 2004). Recently, major progress in probing this system has been made by turning to animal models; specifically rat and squirrel monkey models (Justinova, et al., 2008; Panlilio, Solinas, Matthews, & Goldberg, 2007). Nonetheless, one suspects that these neurobiological processes take some time to develop, as well as multiple THC self-administrations. The process might not ordinarily be manifest over short spans of time, as would be implied by the idea that cannabis exposure 'triggers' or 'serves as a proximal trigger' for later self-administration of drugs such as cocaine.

This triggering hypothesis gives us some reason to suspect that some especially definitive evidence on the cannabis-cocaine linkage might be gained in future longitudinal studies on samples of monozygotic (MZ) twins discordant for cocaine use, with a substantially more fine-grained focus upon month to month temporal sequences that have not been investigated in prior twin research such as the studies cited above. In specific, if we were to turn to the month of first cocaine use for a MZ twin, we may consider where in the life of this cocaine-using 'index twin' we should see the cannabis-trigger, relative to onset of cannabis use in the life of the discordant co-twin who has not used cocaine by that same time. Unless cocaine use triggers onset of cannabis use (a 'reverse causation' hypothesis never advanced in the published literature), and if cannabis onset actually is serving as a proximal trigger for cocaine onset, we should see an excess odds of cannabis onset in the same month of the index twin's first cocaine use, relative to the odds of cannabis onset in the same month of life for the matched MZ co-twin who never used cocaine.

Several years ago, pondering this type of temporally fine-grained MZ twin research as a 'thought experiment,' we realized that the standard logic of epidemiological case-crossover research methods might be applicable in this context, in complement with the more standard co-twin designs of behavior genetics. In epidemiologic case-crossover research, as explained by MacClure & Mittleman, each subject serves as his or her own control and is genomically and experientially matched to himself or herself, which makes the case-crossover approach pertinent in behavior genetics (Maclure & Mittleman, 2000). As such, there is no need to turn to discordant MZ co-twins in order to look into the possibility that the month of

cannabis onset might be a month of excess risk for starting cocaine use as well, with genetic influences held constant. That is, when the goal is matching on a vector of background or antecedent characteristics that might function as confounding variables, including genetic and epigenetic influences, a subject-as-own-control research method can be as good as a discordant MZ co-twin design. In some respects, the case-crossover subject-as-own-control approach might prove to be an even better research approach. This might be especially true when twin-discordant gene expression or epigenetic processes are at play, or when there is a need for tight matching on prior experiences that lead up to the month of drug onsets, or when there is concern about the representativeness of MZ or other twins relative to the preponderance of non-twin human experience (e.g., see Madsen & Osler, 2009).

Back in 2002, when these thought experiments came to mind, Mittleman and colleagues had just published an example of epidemiologic case-crossover research on the hypothesis that acute myocardial infarction (MI) might be triggered by proximal cannabis smoking (Mittleman, Lewis, Maclure, Sherwood, & Muller, 2001). Whereas for that study the MI cases were interviewed about their cannabis smoking within four days after MI onset, we were unable to find any dataset with interviews of cocaine users within four days after onset of their cocaine use. Nonetheless, we were able to find a nationally representative survey sample in the United States (US) with audio-enhanced computer-assisted self-interviews (ACASI) conducted within 24 months after onset of cocaine use, and with assessment and recording of the month of first cocaine use and the month of first cannabis use when there had been recent onsets for use of these two drugs (i.e., with fine-grained month by month data on when cannabis smoking first occurred and when cocaine use first occurred) . Once access to the national sample survey data was granted, we developed a preliminary inquiry, adapting the Mittleman-Maclure epidemiologic case-crossover design, in order to investigate the possibility that cannabis onset might trigger a more rapid cocaine onset. That is, whereas Mittleman et al. (2001) had looked into the 60 minutes before the acute MI and had asked whether cannabis smoking had occurred with excess frequency in that 60 minute hazard interval, we looked at the month during which the cocaine onset had occurred, and asked whether cannabis smoking onset had occurred with excess frequency in that month-long interval. The results of the preliminary inquiry were promising. Now, by virtue of the release of additional data from the United States National Survey on Drug Use and Health (NSDUH), we now have been able to return to this facet of the cannabis-cocaine link, with an increased capacity and statistical power to estimate the relationship using the case-crossover approach.

We approached the research project with three goals in mind: (1) to investigate whether we might be able to harness the Maclure-Mittleman epidemiologic case-crossover research approach to extend prior behavior genetics research on the cannabis-cocaine sequence, in a fashion that would shed some new light on the cannabis-cocaine triggering possibility, given the subject-as-own-control features of this research method; (2) to draw attention to the unresolved puzzling within-pair between-twins question that must be faced when the MZ (or MZ/DZ) co-twin designs disclose evidence of cannabis-associated risk of later cocaine use and other serious drug involvement (i.e., what accounts for the co-twins being cannabis-discordant in the first place?), which is not pertinent in the subject-as-own-control design,

and (3) to derive a statistically precise estimate with respect to the cannabis-cocaine triggering process.

For context, readers of this research report might wish to know that according to the NSDUH data on community-dwelling United States residents age 12 years and older, by 2006, an estimated 35 million had tried cocaine (14%), and of these cocaine users, an estimated 34 million had smoked cannabis (97%). As for which drug tended to come first, it almost always was cannabis. For example, the NSDUH 2006 dataset included 239 individuals whose cocaine use had started in 2006. Almost all of them (n=216) had started smoking cannabis before 2006 (the year of onset of cocaine use); only 9 had never smoked cannabis. As for occurrence of cocaine use among cannabis smokers, again based on 2006 NSDUH data, an estimated 35 percent of the estimated 97 million lifetime cannabis smokers had tried cocaine at least once, with onset of cannabis smoking almost always preceding onset of cocaine use, and for those with no history of cannabis smoking, the corresponding estimate is 0.7 percent. That is, in this population, almost all of the risk of starting to use cocaine has been concentrated within the subgroup of individuals with a past or recent history of cannabis smoking.

Methods

Study Sample

Between 2002–2006, the NSDUH identified newly incident cocaine users in nationally representative samples of community-dwelling United States residents age 12 years and older, all of whom replied to standardized questions within a computerized confidential self-interview and disclosed recent-onset cocaine, other drug use, and related topics in the context of an IRB-approved research protocol for national sample survey research. As for validity and reliability of the computer-assisted self interview, the sponsoring federal agency has commissioned numerous methodological inquiries, especially with respect to the reliability of reports about onset of drug use, which for newly incident drug users tend to be quite high, especially for cocaine and cannabis (e.g., see Biemer & Witt, 1997; Kennet et al., 2005). In contrast to studies in which drug users are asked to describe the full lifetime history of drug use over a span of many years (e.g., Degenhardt, et al., 2008), for this research, all of the newly incident users started using cocaine within 24 months prior to the date of assessment, and for almost one-half, the first occasion of cocaine use had occurred during the past 12 months. This occasion, as well as the occasions of first cannabis use, were still relatively fresh in memory. Nonetheless, we return to the issue of measurement error in our discussion section.

Reliability and validity of the NSDUH has been extensively studied and are well documented (e.g., Biemer & Witt, 1997; Kennet, 2005). The number of NSDUH participants during each of those years was in the 65,000–70,000 range with survey participation levels between 75%–79% each year (SAMHSA, 2003, 2004, 2005, 2006, 2007).

In the aggregate study sample, the age range of the cocaine onset was 11 to 54 years, with an interquartile range from 16 to 20 years, and a median age of 18 years. Other characteristics

of the newly incident cocaine users in these NSDUH samples are published elsewhere in more detailed reports (e.g., O'Brien & Anthony, 2005), including survey reports readily available via the internet (e.g., http://www.oas.samhsa.gov/nsduh/2k6nsduh/2k6results.cfm#5.3 , last accessed 7 October 2010).

In this research, and as described elsewhere (O'Brien & Anthony, 2005), the newly incident recent-onset cocaine users (ROCU) are those for whom no more than 24 months had passed from the time of the first month of cocaine use to the time of the NSDUH computerized assessment; these ROCU are asked about the month and year of first cocaine use. The specific ACASI questions about that interval were of the following form: "In what month in <YEAR> did you first use cocaine in any form?" Only the recent-onset drug users are asked these ACASI questions about month of first use; they were not asked when drug use started in the more distant past.

In the context of this case-crossover research, the exact month of first onset of cocaine use offers a 'hazard interval' during which the outcome of interest has occurred in the subject's life, always no more than 24 months prior to assessment and sometimes as recently as the three months prior to assessment. An advantage of focus upon the newly incident recent-onset cocaine users is that there is no need for recollection of possibly unreliable and distorted age of onset of drug use over long spans of developmental time, as noted elsewhere (Cleveland & Wiebe, 2008; Degenhardt, et al., in press). All ROCU also were asked about age of onset of cannabis smoking, and all newly incident recent onset cannabis smokers were asked about month and year of first onset of cannabis smoking. The specific ACASI questions about cannabis were of the following form: "In what month in <YEAR> did you first use marijuana or hashish?" Here again measurement problems faced in research about events occurring many years ago are constrained by this focus on the most recent 24 months of experience, although perhaps not to the degree achieved when the assessments can be made within a few hours or days after the hazard interval of interest, as in the cannabis-heart attack research (Mittleman, et al., 2001).

Statistical Analysis

Case-crossover data can be analyzed by using standard methods for matched pair case control studies (Mittleman, Maclure, & Robins, 1995). Each case contributes a pair of hazard and control intervals. In our case-crossover approach to estimation of relative risk (RR), we specify the 'hazard' of interest to be onset of cocaine use. The 'hazard interval' is the month of first onset of cocaine use in the life of the participant. Evidence in favor of a very rapid cannabis triggering of cocaine onset is found in the number of cocaine initiates who also started cannabis use during the same hazard interval (i.e., in the same month). We pre-specified the 'control interval' for this case-crossover research to be the calendar month just prior to the month of onset of cocaine use. Evidence against a very rapid triggering of cocaine onset is found in the number of cocaine initiates for whom the onset of cannabis use occurs during this specified 'control interval' rather than during the specified 'hazard interval'. Consistent with case-crossover research generally, the RR is estimated by the ratio of the 'evidence favoring' number to the 'evidence against' number, as in a standard matched pairs or discordant MZ twin pair analysis (Gordis, 2008; M. S. O'Brien, Wu, &

Anthony, 2005). Because the size of the RR estimate may depend upon selection of the 'control interval,' via post-estimation exploratory analysis steps, we probed for variation in the size of the RR with alternative specifications for the control interval. Our preferred approach is to specify the control interval, t-1, as the month just prior to the hazard interval, t. Nonetheless, in our post hoc probing for RR variation, we considered alternative specifications for the control interval as the t-2 month, the t-3 month, and so on. These post hoc analysis results are presented below, in complement with what we found to be the RR estimates under our initial and primary specification for the research design.

Following statistical recommendations offered by Lydersen and colleagues (2009), we estimated p-values and 95% confidence intervals (CI) using the mid-p exact approach, implemented under Stata software, version 11 (StataCorp, 2009). Our own research team's preferred statistical approach in this context is one that favors one-tailed hypothesis-testing, because no one has suggested that cannabis smoking would protect against cocaine use. Nonetheless, some readers may prefer the two-tailed approach, as we have used here, representing an especially conservative approach in this context of hypothesis testing.

Results

Amongst the newly incident recent onset cocaine users, a total of 48 cocaine use initiates were found to have experienced a cannabis use onset in the same calendar month, *t*, as the cocaine onset. This is the 'evidence favoring' number that lends support to the idea that cannabis might serve to trigger cocaine onset quite rapidly. In contrast, only 30 cocaine initiates had experienced cannabis onset in the control interval (t-1 month relative to hazard interval month t). This is the 'evidence against' number that is not consistent with the idea that cannabis might serve to trigger a very rapid onset of cocaine use. Based upon standard case-crossover estimation procedures, the cannabis-associated excess risk of cocaine onset is the ratio of these numbers: 1.6 (exact mid-p = 0.042; 95% CI = 1.02, 2.55; see Table 1 for details).

We appreciate that some observers might question our pre-specification for the 'control interval' in this case-crossover research, which was month *t-1* relative to the 'hazard interval' month *t*. In advance of analysis, we chose *t-1* as the control month because our object of study involves the possibility of a very rapid "triggering" or precipitation process. In post hoc analyses, we re-specified the control interval to be months t-2 through t-12, prior to the 'hazard interval' in month t. The strongest relative risk estimate was observed with 't-8' as the control interval (RR = 2.7, 95% CI = 1.3, 6.0). The other RR estimates (for t-2, t-3…t-12) were in a range from slightly below the RR=1.6 value we found in the original contrast, upward to a substantially stronger association: i.e., all RR>1.4 (with month t-3 as the control interval) to RR=2.7 (with month t-8 as the control interval). Plotted in relation to an expected distribution, the t-8 RR estimate is not remarkable. For this reason, we surmise that there is nothing special about the t-8 control interval in these NSDUH data, but our discussion section mentions the t-8 month in the context of potential future lines of research on this topic.

Some readers may wish to know whether we have controlled for antecedent variables such as a within-subject 'common factor' propensity suggested by Morral and colleagues (2002), the 'developmental trajectory' trait suggested by Cleveland and Wiebe (2008), separately occurring discrete events such as onset of drinking alcohol or smoking tobacco, or levels of family or peer influence recently studied by Gillespie and colleagues in co-twin research (2009). The answer is in the affirmative, to the extent that the subject-as-own-control design holds constant all antecedents up to the time of the earliest interval of observation (here, specified as the t-1 through t-12 months for our control intervals, which always preceded the hazard interval). As a check on our assumption that alcohol and tobacco use would have pre-dated these control intervals, we interrogated the NSDUH datasets and found no instance in which the alcohol and tobacco onsets occurred during our specified control interval, t-1, or during the hazard interval month, t.

Readers also may be interested to know more about the distribution of lag times separating onset of cannabis use and onset of cocaine use for the 272 study participants who initiated both cannabis and also cocaine use with the 24 month interval prior to the date of survey assessment in this cross-sectional study. An estimated four percent started cocaine use in a month that preceded cannabis use; for 95% the cannabis use onset preceded onset of cocaine use. As for the details, Table 1 entries show that the estimated lag time from onset of cannabis use to onset of cocaine use was less than one month for 48 individuals and was an estimated one month for 30 individuals, but the sample included an additional 175 participants with onsets of cocaine following onsets of cannabis smoking during the same 24 month interval prior to assessment. For these others, the estimated interquartile range was 10 months; the estimated median lag time was 4 months, and the estimated mean lag time was just under five months.

Discussion

In this research, we were able to adapt the epidemiologic case-crossover design in order to produce a relative risk estimate pertinent to the possibility of a cannabis-cocaine triggering process, based on hazard and control intervals specified for the informative subset of newly incident cocaine users found in community samples from 2002–2006. Based on the case-crossover evidence, we conclude that at least in the United States the month of cannabis onset now represents a month of modestly but statistically robust excess risk of starting cocaine use, even if cannabis *per se* is not a cause of cocaine use. We cannot answer why that month should be a month of excess risk for initiation of cocaine use, but in the case-crossover context we do not face the unanswered question presented in the discordant twin design about why one co-twin started to use cannabis early on while the other co-twin of the pair did not. Observed excess risk may be due to cocaine-seeking once cannabis use starts, to differentially greater affiliation with drug users of all stripes during the month of cannabis onset, or to other circumstances or processes, such as the possibility that a street-level dealer of cannabis might be selling cocaine as well (Wagner & Anthony, 2002). Nonetheless, in this research, by using the epidemiological case-crossover design, we have constrained long-standing individual-level 'common factor' propensities, "developmental trajectory" or other susceptibility traits hypothesized by others to explain the cannabis-cocaine or "gateway" association, to the extent that this can be accomplished with a subject-as-own-control design

(Lynskey, et al., 2003; Morral, et al., 2002; van Ours, 2003). It is difficult for us to imagine any more thorough constraints on these propensities or traits than can be achieved in human research with a subject-as-own-control design. During the months leading up to and including the onset of cocaine use, one would expect much more variation in these propensities or traits across the two different twins in a co-twin pair and much less variation for any individual subject, from month to month. As such, there is some degree of methodological advantage of the epidemiologic case-crossover design when it can be applied in lieu of the alternative behavior genetics research approaches to hold constant genetic influences.

Of course, the case-crossover research design is not always applicable in psychiatric or behavior genetics research when genetic influence and related susceptibility traits must be constrained, as explained by Maclure and Mittleman (2000). For this reason, co-twin designs will continue to be methods of choice for many behavioral genetics researchers, unless the research question to be answered is suitable for the case-crossover design. Nonetheless, as noted above, for it to be complete, in co-twin research on biobehavioral processes such as the cannabis-cocaine sequence, there is need for attention to what has caused the twins to be discordant on the antecedent exposure found to be associated with disease – i.e., why one co-twin smoked cannabis early on, but the other co-twin did not. Gillespie and colleagues (2009) recently launched a line of twin research to study this type of cannabis exposure discordance. The incompleteness of evidence from the case-crossover design is somewhat more circumscribed, with boundary issues as outlined in the first paragraph of this discussion section.

Before more detailed discussion of this research, some limitations should be mentioned. With respect to the nature of the participants in large sample community survey research of this type, respect for the autonomy of the sampled participants means that sampled respondents must be given an opportunity to decline to participate, and in each year of this national survey, approximately 20%–30% have declined to participate. The resulting evidence is based upon community members who consented to participate. Nonetheless, the same constraints with respect to non-participation are faced in the co-twin design, and one might argue that with this type of community sampling, the newly incident cocaine users in a cross-sectional nationally representative sample are informative about human experience in general, and do not face questions of representativeness sometimes directed toward discordant twin pairs (e.g., see Madsen & Osler, 2009). It is worth mentioning that for this type of analysis, focused on 78 informative newly incident cocaine users found across a span of time from 2002 to 2006 within a probability sample of more than 300,000 participants, there is no need to produce an estimate for the nation as a whole or to use Taylor series linearization for variance estimation as might be the case in estimation of prevalence or correlates of recent or past drug use. These 78 informative newly incident cocaine users were distributed quite evenly across the survey years and across the neighborhood areas sampled for the survey. We found no evidence that they came from the same geographic areas. As such, they may be regarded as independent observations from the 'super-population' formed by combining each year's survey data in a single pool.

With respect to measurement, in such large sample research, it is not possible to take month-by-month toxicological assays as might be required to verify self-reported onsets of illegal drug-taking. Instead, the research depends upon the capacity of an individual to report accurately and completely with respect to the month of onset of each recent drug using experience during the year prior to assessment. Even though the questions on the month of first cocaine use were separated from the questions on the month of first cannabis use (with multiple intervening questions on topics such as frequency of cannabis smoking), we cannot rule out the possibility of shared methods co-variation in that each newly incident cocaine user had to assert which one of the past 24 months was the month of first cocaine use and which one of the past 24 months might have been a month of first cannabis smoking. In addition, based on available data about the cannabis-cocaine sequence, we made an assumption that cannabis use preceded cocaine use when both started in the same month; this is an assumption that can be tested more directly in future research.

With respect to sample size, the newly incident cocaine users who contributed information to test our hypothesis about a very rapid triggering of cocaine onset soon after onset of cannabis smoking constituted a very small number of individuals (n=78, with 48 recent-onset users contributing evidence in favor of the hypothesized cannabis-cocaine association and with 30 contributing evidence against that hypothesis. Some readers may regard this number as too small for any firm conclusion. Nonetheless, we note that this number was large enough to produce statistically robust relative risk estimates and respectably narrow 95% confidence intervals.

For readers who are concerned about these RR estimates being based upon no more than 78 newly incident ROCU with discordant hazard-control interval findings, we note that this situation is inherent in this experimental context and generally holds in the study of discordant MZ twin pairs as well. For example, Lynskey and colleagues studied 622 twins, but only 218 co-twins contributed to estimation of relative risk (via the odds ratio) in that research on the cannabis gateway. Lessem and colleagues (2006) studied 610 MZ twins, but their estimates were based only 82 co-twins in the 41 cannabis-discordant pairs.

Cleveland and Wiebe (2008), among others (e.g., Madsen and Osler (2009), have launched a line of criticism of the now-standard 'fixed effects' approach in co-twin research when the aim is to hold constant all genetic influences in order to shed light on exposure-associated risks of adverse outcomes, arguing that the discordant subsets might comprise a non-representative sample. Nonetheless, these critiques have not yet acknowledged that there must be variation in a bivariate exposure and variation in a bivariate phenotypic response in order to estimate the exposure-disease association, unless the advantage of the individual-level matching of a subject-as-own-control design or the twin pair-level matching of the MZ co-twin design is going to be broken up. There would seem to be nothing inherently non-representative about a sample focused on exposure-discordant individuals or twin-pairs if one specifies the population of interest in the etiological research to include only those informative elements that speak to estimation of the exposure-associated excess risk of the bivariate phenotype with otherwise unobserved genetic influences held constant (i.e., the discordant pairs in co-twin research, and the discordant subjects in case-crossover research of the type completed here). In the co-twin research, generalization to the roughly 98% of

humans who are not twins is uncertain. There may be somewhat greater external validity in the evidence from case-crossover subject-as-own-control research of the type conducted here, with the cases drawn as part of nationally representative sample surveys.

In summary, early drug epidemiologists set the stage for a productive line of research on processes leading from first use of legal drugs (alcohol, tobacco) toward use of cannabis (marijuana) and onward toward drugs like cocaine and heroin (e.g., Kandel, 1975; O'Donnell & Clayton, 1982). As mentioned, twins who had become seriously involved with illegal drugs were more likely to have had prior early-onset cannabis use as compared to their co-twins (Lynskey et al., 2003; Lessem et al., 2006). In their re-analysis of data from the sample studied by Lessem and colleagues, Cleveland and Wiebe (2008) did not find evidence in support of this cannabis-associated hazard, possibly due to their clever shift to the count-based phenotype for 'later hard drug use' and to a re-framing of the exposure variable in terms of the within-pair but between-twin difference in the number of occasions of cannabis smoking.

MZ co-twin designs can constrain temporally stable susceptibilities traced back to individual-level genomic profiles, which otherwise might confound and create spurious associations linking earlier cannabis use with later more serious drug involvement. Nonetheless, these co-twin designs fail to answer a puzzling question: "Why did one twin start using cannabis at an early age while the other twin did not do so?" Any uncontrolled explanation for this within-pair variation also is a plausible explanation for why one co-twin engaged in later serious drug involvement whereas the co-twin did not. Gillespie and colleagues are among the few twin researchers who have attempted to investigate sources of within-pair between-twin differences in the timing of early onset cannabis smoking and later cannabis involvement (Gillespie, et al., 2009).

Epidemiological case-crossover studies, using the subject-as-own-control design, are somewhat like the discordant MZ co-twin design used in psychiatric and behavior genetics research. The case-crossover design is fashioned so as to hold constant individual-level genetic influences. Nonetheless, in addition, more than MZ co-twin studies, case-crossover designs hold constant post-conception gene expression, social and interpersonal transactions, and the gene-environment interplay up to the months of the hazard and control intervals as specified in the research approach. In this study on a suspected causal linkage between earlier cannabis use and rapid triggering of later cocaine use, we used the epidemiological case-crossover design to constrain the influence of such 'background' conditions and processes that might be causing both cannabis use and cocaine use to co-occur. An advantage is that the cases were identified during the course of field surveys designed to achieve nationally representative samples of the source population under study.

Until evidence of this type can be replicated by others, we hesitate to mention any implications for primary or secondary prevention beyond those already discussed by van Ours (2003) and Fergusson et al. (2006). Of course, special vigilance may prove to be useful when a parent or primary care provider discovers that a young person has just started to smoke cannabis. Nonetheless, the great majority of young people starting to smoke cannabis never go on to try cocaine or other internationally regulated drugs (i.e., cannabis smoking, as

an experience, has quite limited positive predictive value with respect to subsequent illegal drug use).

There are some open questions that remain as future directions for research on these processes that link cannabis onsets with cocaine onsets. Does first cannabis use serve as a proximal trigger for cocaine onset in countries with less restrictive cannabis control regimes, where official government policy seeks to segregate cannabis markets from underground markets for cocaine and other drugs? For example, in the Netherlands, cannabis can be purchased without legal penalty. In Belgium, a partial prohibition policy allows cultivation and possession of small amounts of cannabis for personal use. Or, are the observed associations stronger or weaker in US states that allow access to medical marijuana (e.g., via clubs; MacCoun & Reuter, 2001). These would seem to be important questions for future drug control research with coordinated cross-national or cross-state studies, and with case-crossover and other subject-as-own-control analyses of month-by-month, week-by-week, or even day-by-day study data. In addition, results from our initial research specifications yielded RR estimates that were consistent with idea of a very rapid but modest triggering or precipitation process (i.e., RR=1.6; p=0.042). Our investigation of alternative 'control interval specifications' yielded RR estimates not appreciably different from this point estimate. As such, the main evidence of this study lends support to the idea that integration of cannabis and cocaine markets might foster co-occurrence of cannabis and cocaine onsets so rapidly that a neurobiological kindling process is not apt to have developed (by that point in time). But these data cannot rule out the possibility of a pharmacological response to cannabis intoxication in a neurobiological process that might give rise to cocaine-seeking over longer spans of time. This is perhaps an especially intriguing research issue raised by this observational epidemiological study, deserving of attention in future field studies. The hypothesized neurobiological processes might be illuminated via future laboratory research of an experimental character, in an application of pre-clinical animal models described as part of this paper's introduction, or in human brain imaging or gene expression studies of young people early in their stages of cannabis involvement. In future twin research on these issues, there is need for attention to questions about what accounts for one twin starting to smoke cannabis when the other co-twin of the pair never smokes cannabis, as well as the within-pair between-twin differences in subsequent cannabis involvement (see Gillespie and colleagues, 2009).

We are mindful that the specific cannabis-cocaine association might be a manifestation of a more general process of a rapid proximal escalation of illegal drug use in some individuals once the first occasion of illegal drug use has occurred (without respect to which drug comes first and which drug or drugs come next). More research is needed on the issue of whether there is specificity in this process of becoming an illegal drug user (as in the observed cannabis-cocaine association) versus an alternative more generalized process of becoming an illegal drug user (irrespective of the drugs involved).

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References

Anthony JC. Death of the 'stepping-stone' hypothesis and the 'gateway' model? Comments on Morral et al. Addiction. 2002; 97(12):1505–1507. [PubMed: 12472631]

Biemer, PP.; Witt, M. Repeated measures estimation of measurement bias for self-reported drug use with applications of the National Household Survey on Drug Abuse. In: Harrison, L.; Hughes, A., editors. The validity of self-reported drug use: Improving the accuracy of survey estimates. Rockville, MD: 1997. p. 439-476.

Cleveland HH, Wiebe RP. Understanding the association between adolescent marijuana use and later serious drug use: gateway effect or developmental trajectory? Dev Psychopathol. 2008; 20(2):615–632. [PubMed: 18423097]

Degenhardt L, Chiu WT, Sampson N, Kessler RC, Anthony JC, Angermeyer M, et al. Toward a global view of alcohol, tobacco, cannabis, and cocaine use: findings from the WHO World Mental Health Surveys. PLoS Med. 2008; 5(7):e141. [PubMed: 18597549]

Degenhardt L, Dierker L, Chiu WT, Medina-Mora ME, Neumark Y, Sampson N, et al. Evaluating the drug use "gateway" theory using cross-national data: Consistency and associations of the order of initiation of drug use among participants in the WHO World Mental Health Surveys. Drug Alcohol Depend. in press.

Fergusson DM, Boden JM, Horwood LJ. Cannabis use and other illicit drug use: testing the cannabis gateway hypothesis. Addiction. 2006; 101(4):556–569. [PubMed: 16548935]

Fergusson DM, Horwood LJ. Does cannabis use encourage other forms of illicit drug use? Addiction. 2000; 95(4):505–520. [PubMed: 10829327]

Gillespie NA, Neale MC, Kendler KS. Pathways to cannabis abuse: a multi-stage model from cannabis availability, cannabis initiation and progression to abuse. Addiction. 2009; 104(3):430–438. [PubMed: 19207351]

Gordis, L. Epidemiology. 4. Philadelphia: W.B. Saunders Company; 2008.

Justinova Z, Munzar P, Panlilio LV, Yasar S, Redhi GH, Tanda G, et al. Blockade of THC-Seeking Behavior and Relapse in Monkeys by the Cannabinoid CB(1)-Receptor Antagonist Rimonabant. Neuropsychopharmacology. 2008

Kandel DB. Stages in adolescent involvement in drug use. Science. 1975; 190:912–914. [PubMed: 1188374]

Kennet J. Assessing the reliability of key measures in the National Survey on Drug Use and Health using a test-retest methodology. 2005

Koob GF, Ahmed SH, Boutrel B, Chen SA, Kenny PJ, Markou A, et al. Neurobiological mechanisms in the transition from drug use to drug dependence. Neurosci Biobehav Rev. 2004; 27(8):739–749. [PubMed: 15019424]

Lessem JM, Hopfer CJ, Haberstick BC, Timberlake D, Ehringer MA, Smolen A, et al. Relationship between adolescent marijuana use and young adult illicit drug use. Behav Genet. 2006; 36(4):498–506. [PubMed: 16565887]

Lydersen S, Fagerland MW, Laake P. Recommended tests for association in 2 x 2 tables. Stat Med. 2009; 28(7):1159–1175. [PubMed: 19170020]

Lynskey MT, Heath AC, Bucholz KK, Slutske WS, Madden PA, Nelson EC, et al. Escalation of drug use in early-onset cannabis users vs co-twin controls. JAMA. 2003; 289(4):427–433. [PubMed: 12533121]

MacCoun R, Reuter P. Evaluating alternative cannabis regimes. Br J Psychiatry. 2001; 178:123–128. [PubMed: 11157425]

Maclure M, Mittleman MA. Should we use a case-crossover design? Annu Rev Public Health. 2000; 21:193–221. [PubMed: 10884952]

Madsen M, Osler M. Commentary: Strengths and limitations of the discordant twin-pair design in social epidemiology. Where do we go from here? Int J Epidemiol. 2009; 38(5):1322–1323. [PubMed: 19643735]

Mittleman MA, Lewis RA, Maclure M, Sherwood JB, Muller JE. Triggering myocardial infarction by marijuana. Circulation. 2001; 103(23):2805–2809. [PubMed: 11401936]

Mittleman MA, Maclure M, Robins JM. Control sampling strategies for case-crossover studies: an assessment of relative efficiency. Am J Epidemiol. 1995; 142(1):91–98. [PubMed: 7785679]

Morral AR, McCaffrey DF, Paddock SM. Reassessing the marijuana gateway effect. Addiction. 2002; 97(12):1493–1504. [PubMed: 12472629]

O'Brien MS, Anthony JC. Risk of becoming cocaine dependent: epidemiological estimates for the United States, 2000–2001. Neuropsychopharmacology. 2005; 30(5):1006–1018. [PubMed: 15785780]

O'Brien MS, Wu LT, Anthony JC. Cocaine use and the occurrence of panic attacks in the community: a case-crossover approach. Subst Use Misuse. 2005; 40(3):285–297. [PubMed: 15776977]

O'Donnell JA, Clayton RR. The stepping-stone hypothesis--marijuana, heroin, and causality. Chem Depend. 1982; 4(3):229–241. [PubMed: 6985447]

Panlilio LV, Solinas M, Matthews SA, Goldberg SR. Previous exposure to THC alters the reinforcing efficacy and anxiety-related effects of cocaine in rats. Neuropsychopharmacology. 2007; 32(3): 646–657. [PubMed: 16738542]

SAMHSA. Results from the 2002 National Survey on Drug Use and Health: National Findings. 2003.

SAMHSA. Results from the 2003 National Survey on Drug Use and Health: National Findings. 2004.

SAMHSA. Results from the 2004 National Survey on Drug Use and Health: National Findings. 2005

SAMHSA. Results from the 2005 National Survey on Drug Use and Health: National Findings. 2006

SAMHSA. Results from the 2006 National Survey on Drug Use and Health: National Findings. 2007

StataCorp. Stata Statistical Software: Release 11.0. College Station, TX: StataCorp; 2009.

van Ours JC. Is cannabis a stepping-stone for cocaine? J Health Econ. 2003; 22(4):539–554. [PubMed: 12842314]

Wagner FA, Anthony JC. Into the world of illegal drug use: exposure opportunity and other mechanisms linking the use of alcohol, tobacco, marijuana, and cocaine. Am J Epidemiol. 2002; 155(10):918–925. [PubMed: 11994231]

Table 1

Timing of cannabis onset relative to hazard and control intervals: Data from the NSDUH, 2001–2006

	Cannabis onset during the control interval (the month before cocaine onset)		Total
Cannabis onset during the one month hazard interval of first cocaine use	Yes	No	Row Total
Yes	Undefined*	n=48	48
No	n=30	n=3,412	3,442

Estimated Relative Risk = 1.6; Exact mid-p-value = 0.042.

Notes: This table should be read as one reads a corresponding table from research on discordant MZ co-twin pairs. That is, informative cases are those with cannabis onset in the hazard interval but not in the one-month control interval (upper right-hand cell, n = 30). The relative risk estimate from this table is 48 / 1 / 30 / 1. As in discordant MZ co-twin estimates, values in the upper left-hand cell and lower right-hand cell do not contribute information to point estimate calculations. Each hazard interval is the calendar month in which cocaine onset occurred. The control interval is specified to be the one month immediately prior to the hazard interval.