Does Marijuana Use Cause the Use of Other Drugs?

Denise B. Kandel, PhD

A DEVELOPMENTAL SEQUENCE OF INVOLVEMENT IN drugs is one of the best replicated findings in the epidemiology of drug use. Regular sequences and stages of progression in which the use of alcohol and cigarettes precedes the use of marijuana (cannabis), and, in turn, the use of marijuana precedes the use of other illicit drugs, has been observed in the United States as well as in other western societies. Very few individuals who have tried cocaine and heroin have not already used marijuana; the majority have previously used alcohol or tobacco. Such behavioral regularities are subsumed under the “gateway hypothesis.” The gateway hypothesis implies 3 interrelated propositions about sequencing, association of initiation, and causation. Sequencing implies that there is a fixed relationship between 2 substances, such that one substance is regularly initiated before the other. Association implies that initiation of one substance increases the likelihood of initiation of the second substance. Causation implies that use of the first substance actually causes use of the second substance. Causation, a controversial proposition, is the one most widely invoked in policy debates and is the proposition addressed in the article by Lynskey et al in this issue of THE JOURNAL.

Several strategies are available for determining the causal role of a lower-stage drug in the sequence on initiation of a higher-stage drug. In one strategy, epidemiologists attempt to specify the role of prior drug use on the subsequent use of other drug classes by controlling for theoretically relevant covariates and other confounding factors. Analyses based on this approach find that marijuana retains a significant association with the subsequent use of other illicit drugs even after control for risk and protective factors.

However, in naturalistic population studies, it is not possible to control for all potential relevant factors. Morral et al have attempted to overcome this limitation by developing a simulation model, which assumes that the use of marijuana and other illicit drugs is explained solely by a general propensity to use drugs and the ages at first opportunity to use and at first actual use of marijuana and other illicit drugs. This common-factor model replicates the empirical association between marijuana and other illicit drugs observed in a national sample without positing an effect of the use of marijuana itself. However, the fit of this model was not compared with one in which the causal effect of marijuana use on initiation of use of other illicit drugs would also explicitly be taken into account. The argument would be stronger if the 2 models had been tested and the common-factor model was found to provide as good a fit as the causal model. While the simulation model of Morral et al does not disprove the existence of a causal relationship between marijuana and other illicit drugs, it provides an alternative interpretation.

A second strategy is to evaluate the impact of prevention or intervention programs implemented among youths to prevent or reduce drug use. Such programs provide an imperfect substitution for an unrealizable social experiment in which adolescents would be randomly assigned to initiate the use of different drugs. However, programs designed to prevent or stop use of lower-stage drugs also seem to stop or reduce use of higher-stage drugs, as reported in Kandel.

Still a third strategy is the use of genetically informative samples. This approach has not previously been implemented to test the gateway hypothesis and represents a unique contribution of the work of Lynskey et al. In a previous report based on data from a large sample of Australian twins born in 1964 to 1971, Lynskey et al concluded that genetic risk factors are important determinants of the risk of marijuana dependence, at least among men. In the current report, based on a subsample of 311 same-sex twin pairs from the Australian cohort who were discordant for early marijuana use by age 17 years, Lynskey et al find that early marijuana use by itself, even after control for other covariates, increases significantly the use of other illicit drugs. As the authors emphasize, the strength of the twin design is that twins are assumed to share the same environment and family experiences, and monozygotic pairs share the same genetic risk. If these factors explained the association between early marijuana use and the use of other illicit drugs, the risk of using these drugs would be the same for early marijuana-using twins and their discordant co-twins. But it is not. Thus, Lynsey et al conclude that “The results . . . were consistent with early cannabis use having a causal role as a risk factor for other drug use and for any drug abuse or dependence.” But is the assumption of common environmental influences among twins too strong? An argument can be made that even identical twins do not share the same environment during adolescence and that envi-
ronmental differences can lead to learned differences in the brain, which in turn would lead to differences in behaviors. The effect attributed to early marijuana use could in part be due to nonshared environmental influences.

One of the best strategies to test the gateway hypothesis may be the use of animal models, such as rats or mice, in which animals can be assigned to a number of different drug use paradigms. Animal models provide a test of progression in which drug seeking can be observed in relation to well-defined prior experiences with specific drugs and independent of any social, legal, or moral definitions regarding the use of various substances. Such models may also help identify some of the critical biological processes involved in drug use behavior.

Prior exposure to one class of drug may sensitize the animal to the use of other drug classes and increase the consumption of these drugs.

While animal models cannot mimic the variety of cultural, social, and psychological factors that determine drug behavior in human populations, eg, norms, peer influences, personal meanings, personal traits, and so on, animal models can examine whether prior use of a drug per se increases the risk of the use of another drug class. This is the fundamental question that underlies the gateway hypothesis. But very few such animal experiments have been conducted, especially with marijuana, and most have focused on priming by one class of drug on the subsequent use of the same drug. Lynskey et al cite 2 recent studies. The work by Cardoni et al is of particular interest because it has documented not only cross-sensitization between repeated exposure to Δ9-tetrahydrocannabinol and opiates, but also reverse sensitization between morphine and cannabinoids. These experiments have important implications for human drug behavior and for the gateway hypothesis. With cross-sensitization, exposure to one class of drug increases consumption of other drug classes, consistent with the existence of a gateway effect. Reverse sensitization suggests that the particular sequence observed in any society may be determined by availability, cultural norms, or other factors.

Whether or not a true causal link exists between the use of marijuana and other drugs, the association between the 2 has been well established. It is important, however, to appreciate that the progression is not inevitable. Not all those who try marijuana will subsequently use cocaine or become heroin addicts. For policy makers, the gateway hypothesis raises 2 issues depending on whether the population of interest has or has not yet used marijuana. For a population of nonusers, the issue is: will preventing the use of marijuana prevent the use of other illicit drugs? Hopefully it will, for prevention efforts will presumably affect the underlying risk and protective factors related to the onset of marijuana use, whether or not these factors are shared with the onset of the use of other illicit drugs. For youths who have already used marijuana, the issue is: can and should intervention programs be developed to target this group at very high risk for progressing to other substances? It appears so. A marijuana user is at risk for using other illicit drugs, and measures to prevent subsequent use of these drugs are warranted. Interventions should focus on those factors that are associated with the use of illicit drugs, whether they are common to marijuana and the use of other illicit drugs or whether they are specific to illicit drugs other than marijuana. As noted by Lynskey et al, there are health risks associated with chronic marijuana use that also support intervention.

Finally, what inferences can be drawn about the use of marijuana for medicinal purposes? Will medical use increase the risk of using other illicit drugs? There are, unfortunately, no empirical data to guide policy. However, inferences can be made from appropriate medical use of morphine, which does not lead to addiction. This is a curious phenomenon that points out the complexity of drug behavior and the role of psychological and social conditions in shaping its development.

Thus, the central question remains: does marijuana use cause the use of other illicit drugs? The search for causes in the absence of direct experimental manipulation may be elusive. Nevertheless, the search for mechanisms is necessary if only to explain the association between the use of different drug classes. In particular, the progression from marijuana to other illicit drugs needs to be pursued. In this search, epidemiologists must collaborate with scientists who study drug behavior in animal models because each has much to contribute to the other’s quest. In this collaboration, epidemiologists can pose and specify the overall questions that need to be addressed, whereas animal researchers can use their models to test causation and provide insights into the neurobiological mechanisms underlying progression in drug use. But only in a human—as a model organism for the gods, as poetically defined by Sydney Brenner in his recent Nobel Prize lecture—can one explore the many other social, psychological, and contextual factors that are also important in drug use behavior.

Funding/Support: Work on this editorial was supported by Research Scientist Award DA00081 from the National Institute on Drug Abuse.

REFERENCES

©2003 American Medical Association. All rights reserved.