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COMMENTARIES: Comments on Fergusson et al's "Cannabis use and other illicit drug use: Testing the cannabis gateway hypothesis". *Addiction*, 2006; 101: 470-476.

**Testing the Cannabis Gateway Hypothesis: Replies to Hall, Kandel et al., and MacCoun**

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We would like to thank the contributors for their interesting and thoughtful comments on our research. These comments raise three major issues:

*1) Model Specification*

Kandel and associates [1] raise three major points regarding the model specification. First, they note that the analysis does not strictly test the Gateway hypothesis, but rather examines the more general issue of the effect of cannabis use on individual predisposition to use other illicit drugs. While this criticism is sound, we would note that the analysis does examine the major issue raised by the Gateway hypothesis: does using cannabis increase the likelihood that one will use other illicit drugs?

Second, Kandel et al. raise two important issues about the model specification we used. In particular, they suggest that the use of a lagged endogenous measure of other illicit drug use may lead to inconsistent parameter estimates. Further, they suggest that the model specification does not ensure that the use of cannabis preceded the use of illicit drugs within any given year of observation. To address these comments we have re-analysed the data, changing both fixed and random effects model specification by: (a) replacing the contemporaneous measure of cannabis use

by a lagged measure of cannabis use in the preceding year, ensuring that the assessment of cannabis use was temporally prior to the assessment of illicit drug use; and (b) by eliminating the lagged endogenous measure of previous illicit drug use. Eight model estimates resulted, ranging from our original model using a contemporaneous measure of cannabis exposure and a lagged measure of illicit drug use to a model using a lagged measure of cannabis use and excluding the lagged measure of previous illicit drug use.

Table 1 displays the estimates of the model parameters linking cannabis use to illicit drug use, the associated standard errors, and the Wald tests of statistical significance. The principal finding of the Table is that within each general model (fixed effects, random effects) variations in model specification have no effect on the general conclusions drawn in the study. In all cases, the analyses suggest that following covariate control, the use of cannabis remains related to increasing risks of the use of illicit drugs within a given year. The robust nature of the findings over a series of model specifications suggests that the concerns raised by Kandel and her associates about the role of temporal sequencing and the use of lagged endogenous variables do not pose a major threat to the validity of the conclusions drawn.

MacCoun [2] raises somewhat different issues about the model specification by suggesting that our results do not eliminate the common propensity account, but that we do show that any simple version is incorrect. In effect, MacCoun argues that there may be complex interactive relationships between confounders, use of cannabis and use of illicit drugs which are not adequately represented in our model. While these arguments are possible, they are not particularly plausible and there seem few, if any, reasons to postulate the models proposed by MacCoun. Further, the application of Occam's razor would imply that the simplest interpretation of the data (i.e. cannabis use increases risks of illicit drug use) is to be preferred to the untested and more complex counter models proposed by MacCoun.

MacCoun also suggests that twin study data may be more informative and points to the conflicting results found by Lynskey et al. [3] and Tsuang et al. [4]. Here two points should be

noted. First, the logic of the discordant twin design proves to be very similar to the logic of the fixed effects model. In the twin model we compare two individuals with the same genes and common environment but differing in exposure to cannabis. In the fixed effects model we compare the same individual with the same genes and common environment under differing exposure to cannabis. Both approaches control for the effects of common non-observed genes and environment. Furthermore, there is a good explanation of the inconsistent results reported by Lynskey et al. and Tsuang et al. In particular, both studies gathered only limited data on the use of cannabis and the use of illicit drugs in populations varying in age. Since the association depends on the extent of cannabis use and varies with age it is perhaps not surprising that the study findings were inconsistent. Our analysis highlights the importance of collecting comprehensive data on both cannabis use and illicit drug over the period from adolescence to adulthood.

## *2) Contributions of Animal Studies*

Kandel et al. [1] argue strongly for the use of animal studies to explore causation in this area, implying that the greater control available in animal studies makes them a better means of exploring causation than epidemiological studies where appropriate confounds cannot be controlled. While it is true that, all things being equal, laboratory research will provide firmer evidence than correlational research, in our view Kandel et al. overstate their case. It may indeed be possible to gain important insights into the ways in which cannabis may affect the brain and thence propensity to use drugs from animal studies; but, the extent to which processes observed in rats, mice, and flies in the laboratory are analagous to the processes involved with humans in the street is likely to be highly contentious. Rats, mice, and flies do not and cannot have the complex matrix of social and cultural experience of humans, and to assume that laboratory findings based on animals can be readily generalised to human experience in choosing to use and abuse cannabis and other illicit drugs is drawing a very long bow indeed.

### *3) The Political Context*

Both Hall [5] and MacCoun [2] discuss issues relating to the politics of cannabis use. In particular, in the past there has been a clear tendency to dismiss the gateway hypothesis as being a statistical artefact that can be explained away by postulating the presence of non-observed confounders. Our research makes such claims less plausible and as Hall points out "... it is no longer possible to regard the relationship as an artefact with little or no policy significance." The policy significance of these findings is, however, unclear. On the one hand, it may be argued that cannabis has a direct effect on the use of illicit drugs by altering individual susceptibility to use these drugs.

Alternatively, the association may arise because the use of cannabis encourages differential association with drug dealers, drug users, and a youth culture that encourages drug use. As we note, these explanations have opposite implications for drug policy, with the first tending to support a prohibitionist approach to cannabis, whereas the second suggests an approach of decriminalising cannabis to break the linkages between cannabis use and illicit drug markets. As both MacCoun and Hall point these perspectives coincide with the ways in which US and Dutch policy making has regarded the evidence on gateway effects, with US policy using gateway effects to justify prohibition and Dutch policy using this evidence to support liberalisation. The difficulty that arises is that neither approach (prohibition, liberalisation) has been shown clearly to break the linkages between cannabis use and illicit drug use (see for example Reinaman et al. [6]).

### *Future Directions*

It is our view that to further clarify the mechanisms that underlie gateway effects, two types of research are needed. First, as noted by Kandel et al. there is a clear place for laboratory-based studies to clarify the underlying neurophysiological and related mechanisms by which the use of cannabis may increase individual susceptibility to other forms of illicit drug use. These studies offer the hope of establishing the extent to which cannabis use may change individual susceptibility to illicit drug use by altering neurophysiological functioning. Second, there is a need for

sociological and social psychological research to examine the extent to which social climate (including legislation, youth culture, and association with drug dealers) may create circumstances in which using cannabis leads to an increased risk of using other illicit drugs. This approach offers perhaps the best hope of determining the extent to which gateway effects arise from social processes that increase the likelihood that cannabis users will experiment with and use other illicit drugs.

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Table 1. Parameter estimates for models linking cannabis use to other illicit drug use

Model	Model Type					
	Fixed effects			Random effects		
	B	SE	p <sup>1</sup>	B	SE	p <sup>1</sup>
1. Contemporaneous cannabis use; lagged other illicit drug use (original model)	.93	.07	<.0001	1.12	.07	<.0001
2. Lagged cannabis use; lagged other illicit drug use	1.27	.15	<.0001	1.11	.13	<.0001
3. Contemporaneous cannabis use; no lagged illicit drug use	.97	.08	<.0001	1.16	.07	<.0001
4. Lagged cannabis use; no lagged illicit drug use	1.11	.14	<.0001	1.16	.14	<.0001

<sup>1</sup> Wald  $\chi^2$  test of significance.