ADDICTION
SSA SOCIETY FOR THE STUDY OF ADDICTION
ADDICTION CLASSICS
doi:10.1111/add.14190

Denise Kandel's classic work on the gateway sequence of drug acquisition

Michael T. Lynskey[1] & **Arpana Agrawal**[2]

Addictions Department, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK[1] and Psychiatry Department, Washington University School of Medicine, St Louis, MO, USA[2]

ABSTRACT

During the early 1970s Denise Kandel and her colleagues documented an 'invariant sequence' in initiation of drug use: starting with alcohol and tobacco, progressing to cannabis and then to other illicit, or 'harder' drugs. This observation, which became known as the 'gateway sequence' of drug use, has been influential in policy debates but remains highly contentious, with the area of greatest controversy focusing upon whether cannabis use increases risk causally for initiation of other illicit drugs. While numerous studies have replicated Kandel's initial findings (sequence of onset) and reported that associations between cannabis use and the use of other illicit drugs remain after controlling for potentially confounding factors, the mechanisms underlying these observed associations remain hotly debated. In particular, it is possible that the observed associations are non-causal but reflect the influence of confounding factors which influence both early-onset drug use and subsequent progressions. However, research employing a range of techniques to address this issue has been unable to discount the possibility that associations between earlier and subsequent drug use reflect causal processes. This paper reviews Kandel's ongoing contributions to this field, which span 45 years, and discusses both the influence of her work and the controversy that it has aroused.

Keywords Adolescence, cannabis, Denise Kandel, gateway theory, longitudinal, transition.

Correspondence to: Michael T. Lynskey, Addictions Department, Institute of Psychiatry, Psychology and Neuroscience, King's College London, 4 Windsor Walk, London SE5 8BB, UK. E-mail: michael.lynskey@kcl.ac.uk
Submitted 27 November 2017; initial review completed 19 January 2018; final version accepted 5 February 2018

INTRODUCTION

Denise Kandel and her colleagues documented an 'invariant sequence' in progression of drug use among adolescents and youth. They observed that individuals typically start their drug use careers with alcohol and tobacco, progressing to cannabis and then to other illicit, or 'harder' drugs [1,2]. They noted that users of 'harder' drugs almost invariably reported prior use of licit drugs (sequence) and that the use of licit drugs increased the likelihood of progression to 'harder' drugs (association). This work has had a considerable impact, but has also attracted considerable controversy. Notably, there are misconceptions surrounding the interpretation of the often-replicated finding of stages in adolescent drug use, which are interpreted primarily to reflect causal processes. In this paper, we provide a brief overview of Kandel's original work and discuss its importance in light of subsequent findings.

THE CLASSIC PAPER

Kandel & Faust [3] reported the results of a longitudinal study of students from 18 public secondary schools in New York State. These students provided information on their patterns of drug use in two surveys conducted 6 months apart, with further follow-up of a subset of students conducted 5–9 months after the second survey. The final samples included 5468 students studied from waves 1 to 2 and 985 studied from waves 2 to 3.

Results identified an invariant sequence in drug use initiation, with students transitioning from no substance use to: (a) use of beer or wine, (b) followed by tobacco and/ or hard liquor, (c) then cannabis and (d) other illicit drugs. Kandel & Faust noted that nearly all students who had used a drug at one stage had previously used drugs at earlier stages. In her initial writings, Kandel was explicit about the limitations of this research, noting that her findings:

> '…do not prove that the use of a particular drug infallibly leads to the use of other drugs higher up in the sequence. Many youths stop at a particular stage without progressing any further. Nor can the findings be interpreted to show that there is something inherent in the pharmacological properties of the drugs themselves that leads inexorably from one to another' (Kandel & Faust, 1975, p. 931).

She distanced her findings from the controversial and largely discredited 'stepping-stone' hypothesis that posited that use of cannabis would lead inevitably to heroin use. Other aspects of her initial formulation are worth noting. First, Kandel distinguished between the use of beer/wine and the use of hard liquor, a distinction that has largely been lost from subsequent research. Secondly, she did not distinguish between different types of 'hard drugs', but considered the use of these different drugs as representing a single (final) stage in drug use. This convention appears to have been largely followed by subsequent researchers, although there have been some elaborations of the model to consider other potential stages of progression, including prescription drug use [4], regular use of tobacco or alcohol [5] and inhalants [6].

LONGER-TERM FOLLOW-UPS, REPLICATIONS AND EXTENSIONS

Kandel re-interviewed a subset of the sample during 1980–81, at average age 24.7 years (n = 1325) [1,2,7], and a further follow-up was conducted in 1990, at age 34–35 years (n = 1160) [8]. While the results of these studies largely confirmed her previous findings, several observations are noteworthy. First, they reported gender differences in progression pathways, with men demonstrating use of alcohol, cigarettes and cannabis prior to use of prescribed drugs, but for women, use of alcohol and either cigarettes or cannabis was sufficient. Further, onset of cannabis prior to age 16 was pivotal in use of other illicit drugs, particularly in males. Similarly, age of onset of alcohol use predicted cannabis use. In this later work, Kandel also noted that current use of alcohol and cigarettes was related more strongly to initiation of cannabis use than prior use of these substances. Her later work also emphasized the role of cannabis use in the use of other illicit drugs, showing the persistence of the association over and above related features, such as delinquency and peer drug use. In addition, she emphasized the importance of frequency of use, showing that other illicit and prescription drug use was often preceded by cannabis use on more than 10 occasions [8].

In contrast to her earlier work, these studies embraced a stronger causal interpretation of the mechanisms underlying these associations with Yamaguchi & Kandel [2], arguing that:

> '…prevention of early involvement in legal drugs would reduce the use of marijuana, and that prevention of early involvement in marijuana use would reduce involvement in other illicit drugs' (p. 680).

While these reports analysed US samples, Kandel reported a very similar sequence of drug onset in cross-sectional surveys in France and Israel [9].

CAVEATS

Even though the trajectories identified by Kandel have been broadly replicated, there are exceptions. For instance, in a US cohort Degenhardt *et al.* [10] identified rare violations of the gateway sequence. These violations were related to earlier history of internalizing disorders, but were unrelated to future risks for drug dependence. In further work, they extended this analysis to 17 countries and concluded that violations of the sequence were also related closely to cultural factors [11]. In countries in which cannabis use is rare (e.g. Japan and Nigeria), illicit drug use did not appear to be contingent upon prior cannabis use. Other replicated violations in sequence include the use of cannabis prior to tobacco use ('reverse gateways'), due potentially to higher taxation and tighter control policies related to tobacco products [12,13]. In the United States, studies also suggest that African American youth are more likely to begin their substance use trajectories with cannabis rather than alcohol [14].

Together, the suggestion that the traditional gateway sequence may be country-, culture- or context-specific argues against the hypothesis that specific drugs may influence progression causally to other drug use. Instead, it suggests that contextual factors, including access and availability, determine both sequence of initiation and risks of progression.

POTENTIAL MECHANISMS

The most contentious issue surrounding this research concerns the extent to which the observed sequence implicates tobacco, alcohol and cannabis as causing the use of other drugs, and the potential implications of different interpretations of the mechanism underlying these observed associations for both policy and prevention.

This controversy is most pronounced with reference to cannabis and whether or not early initiation of cannabis is a risk factor for or 'gateway' to other illicit drug use. Morral *et al.* [15,16] have shown that sequencing in the onsets of different drug classes is consistent with a model assuming a shared liability to drug use, which is also well supported by

numerous twin studies of shared genetic and environmental influence of general drug use propensity [17,18]. While Morral's analyses indicate that it is not necessary to invoke gateway processes to explain the sequence of drug onsets, or associations across them, they do not, in themselves, discount the possibility of gateway processes.

Indeed, research that has attempted to control for potential confounding through a variety of methods has largely failed to disprove the possibility that use—and particularly early-onset use—may influence risks causally for progression to other drug use. In a subsequent follow-up of New York high school students, Kandel again made a significant contribution to this debate [2]. Using event history analysis she reported that, even after control for adolescent behaviour, mental health and peer affiliations, cannabis use strongly predicted progression to the use of other drugs, even suggesting that it was a necessary condition for the use of other illicit drugs.

More recently, Fergusson & Horwood [19] reported that frequency of cannabis use was associated with risks for other drug use, even after adjustment for both a wide array of potentially confounding covariates and for time-varying measures (peer affiliations, licit drug use and other life-style factors) that may have mediated the association between cannabis and other drug use. Controlling for this array of factors, those using cannabis on 50 or more occasions at age 21 had hazards for other illicit drug use which were more than 50 times higher than those for individuals who had not used cannabis. Fergusson *et al.* [20] further reported strong associations between frequency of cannabis use and other illicit drug use after control for non-observed and time-dynamic sources of confounding using random- and fixed-effects regression models. However, the strength of the association between cannabis and other illicit drug use declined with increasing age.

Similarly, Taylor *et al.* [21] reported that late-onset occasional, early-onset occasional and regular cannabis users had dramatically elevated odds of other illicit drug use [odds ratio (OR) =15.9–47.9] [21]. Swift *et al.* also reported that never users of cannabis were at the lowest risk for uptake of other illicit drugs. Further, individuals who had used other illicit drugs but who had never used cannabis were significantly more likely to cease illicit drug use, while daily cannabis use was associated with significantly lower rates of cessation [22].

Genetically informative research designs have also been unable to discount the possibility that early-onset cannabis use may influence risks for the onset of and progression in use of other illicit drugs [23–27]. Lynskey *et al.* reported that within pairs of identical and fraternal twins, the twin who used cannabis prior to age 17 was at 2.4–3.9 odds of using other illicit drugs compared to their co-twin, who initiated cannabis use at a later age [23]. Critics of the discordant twin approach argue that, despite providing rigorous control of familial factors, the approach does not account adequately for the origins of the discordance (i.e. why one twin is an early user but the other is not). Nonetheless, alternative case–cross-over approaches (self as control) also suggested that onset of cannabis use was a 'proximal trigger' for cocaine initiation [relative risk (RR) = 1.6], and that the mechanisms underlying the temporal association may include aspects of the drug market or methods used to obtain drugs [28].

A further approach to evaluating the potential causal impact of specific environmental exposures involves Mendelian randomization, which relies upon the identification of genetic variants that strongly predict risk of exposure (e.g. cannabis use). Any such variants (or a polygenic composite) can be used as substitutes (i.e. genetic instruments) for that exposure, and an association with the specific outcome (e.g. other illicit drug use) can be interpreted as evidence of a causal association [29]. For instance, a recent study used this approach and did not find evidence for causal effects of using one substance (as indexed by genomic instruments derived from the best-powered genome-wide association studies of each substance) on use of others [30], but it did not explore whether or not cannabis use led to use of other illicit drugs. The use of this approach to examine associations between cannabis and other illicit drug use may be hampered by the limited number of gene variants associated replicably with cannabis initiation [31] and also by the high likelihood of pleiotrophic effects of any identified loci [32,33] (i.e. a locus directly influences both cannabis initiation and later outcomes), although several modern methods allow for adjustments for pleiotrophy [34].

More recently, Kandel has employed a further novel approach to test gateway hypotheses in the general population. She examined cohort differences in rates of tobacco use during 8th grade and subsequent rates of cannabis and cocaine use in the same cohorts (but not the same individuals) assessed in 12th grade [35]. Cross-sectional data from the US Monitoring the Future School survey included repeated samples of approximately 45 000 school students assessed annually from 1992 to 2012. Results indicated that a 1% change in the prevalence of tobacco use was associated with an 8% change in cannabis use and a 14–23% change in cocaine use. The authors attributed these associations to the potential priming effects of nicotine on later drug use, including those observed in pre-clinical models [36]. However, it is not necessary to invoke causal interpretations of gateway mechanisms to explain these associations. Indeed, it is likely that they may reflect the influence of broad macro-sociological factors (e.g. availability, social norms) which influence patterns of drug use between cohorts, with these effects expressed as tobacco use among younger students and cannabis or cocaine use among older students. A notable finding from the study

was the absence of any elevation in cannabis and cocaine use as a function of nicotine exposure in black youth. The authors were able to adjust statistically for general perceptions of the harmfulness of drug use; there are other potential factors that were not controlled for (see e.g. [37]).

PHARMACOLOGICAL STUDIES OF DRUG SEQUENCE AND GATEWAY EFFECTS

Pre-clinical research has demonstrated associations between cannabis exposure and subsequent patterns of opioid use in rats. For example, Ellgren *et al.* [38] reported that intraperitoneal exposure to tetrahydrocannabinol (THC) during the peri-pubertal period in Long–Evan male rats was associated with greater use of opioids and apparently more reinforcing effects of opioids in learning tasks. However, it has been suggested that such effects may be strain-dependent, highlighting the potential role of genetic differences in susceptibility to addiction and in moderating associations between cannabis exposure and subsequent behaviours [39].

In her recent contributions, Kandel also used animal models to examine potential mechanisms underlying drug progression [40]. She found that mice primed with nicotine showed a substantial increase in both cocaine-induced locomotor activity and chamber preference when administered nicotine and cocaine. They also reported that priming with nicotine led to reduced synaptic plasticity in the nucleus accumbens, the brain's hub for reward response. Epigenetic alterations were also noted. Kandel & Kandel [40] posited that the results provided a 'biological basis and a molecular mechanism for the sequence of drug use observed in people'. Extrapolating to humans, they noted parallel decreases in tobacco smoking and cocaine prevalence in 18–25-year-olds from the National Survey on Drug Use and Health, and argued provocatively that recent increases in e-cigarette use may place individuals at heightened risks for cocaine dependence [35]. Interestingly, they also (re)defined a gateway drug as 'a drug that lowers the threshold for addiction to other agents' (p. 932), a definition that deviates from earlier definitions but which is more consilient with pre-clinical findings.

While such pharmacological experiments can provide controlled evidence of molecular pathways they do not address issues surrounding choice, which are central to supposed gateway effects. Many studies that have reported on gateway sequences in drug use have employed a very low level of exposure, including single episodes of use, which are substantially lower than those used in pre-clinical research. Hence, the utility of pharmacological explanations for causality appears limited. However, the possibility that repeated exposure to one drug might result in cross-tolerance or lasting changes in the dynamic genome, especially during co-administration of subsequent drugs with the priming drug, is plausible.

NON-PHARMACOLOGICAL CAUSATION

We believe that if causal pathways undergird drug sequences, they are more likely to be of a social nature. Use of one drug is likely to result in exposure to a social milieu that might encourage use of and access to other drugs. Fergusson & Horwood [19] noted that associations between cannabis and other illicit drug use were mediated partially by peer affiliations and other risk-taking or non-normative behaviours. Similarly, the use of one drug (e.g. alcohol) influences the opportunity to use another drug (e.g. cannabis) [41], while weekly tobacco use was associated with an earlier onset of first opportunity to use cannabis [42]. This is consistent with Yamaguchi & Kandel's [2] claim that:

> 'experience with a particular drug… may remove the fear and perceived risk associated with the use of other drugs… and may facilitate further escalation' (p. 679).

Studies of initial subjective reactions to drugs also support this. For instance, initial experiences with cannabis are rated typically as pleasurable, and these apparently positive experiences may both negate drug prevention efforts and encourage further experimentation [43]. Similarly, Baggio *et al.* reported that escalation to the use of other illicit drugs was higher in those reporting greater response (both positive and negative) to initial cannabis use [44]. However, null findings of such cross-drug effects exist, and the extant literature on initial subjective reactions is clouded by concerns regarding recall bias. Hall & Lynskey [45] provide a provocative avenue for tests of social causation—the study of alterations in patterns of illicit drug use as a function of changing legislation.

CONCLUSIONS

Despite these caveats, it is clear that the use of tobacco, alcohol and cannabis is initiated frequently prior to the onset of other illicit drug use. Additionally, it has not been possible to fully discount the possibility that the early use of these drugs may influence risks causally for other drug use (albeit at a far lower escalation in risk that is typically assumed). The implications of these findings rest critically upon the interpretation of any (potentially causal) association. While much policy debate has focused upon the legal status of cannabis, very similar associations exist between early-onset licit drug use and increased rates of illicit drug use. For consistency, calls to retain the illegal status of cannabis motivated by the role of cannabis in the gateway

sequence of drug use should be matched by calls for legal prohibitions against both tobacco and alcohol.

In summary, Kandel's landmark studies made many important contributions, highlighting both the superiority and feasibility of conducting longitudinal research on patterns of drug use. She also highlighted the importance of examining risk factors for specific stages of drug use, a recommendation often overlooked. Her findings have been confirmed largely by additional research, but interpretation remains controversial. At least some of this controversy may stem from a misrepresentation of her initial work, as Kandel was careful both to distance her own theory from the 'stepping-stone' hypothesis and to note explicitly that an invariant sequence does not imply causality. Initial findings have been open to multiple interpretations and, intriguingly, it appears that Kandel's own beliefs about the nature of these associations have changed over time: recent work has adopted a more causal tone, particularly in reference to potential links between nicotine (including e-cigarette) use and subsequent risks for cocaine dependence.

Declaration of interests

None.

Acknowledgement

A.A. acknowledges support from National Institute on Drug Abuse grants R01DA23668 and K02DA32573.

References

1. Yamaguchi K., Kandel D. B. Patterns of drug-use from adolescence to young adulthood. 2. Sequences of progression. *Am J Public Health* 1984; **74**: 668–72.
2. Yamaguchi K., Kandel D. B. Patterns of drug-use from adolescence to young adulthood. 3. Predictors of progression. *Am J Public Health* 1984; **74**: 673–81.
3. Kandel D., Faust R. Sequence and stages in patterns of adolescent drug-use. *Arch Gen Psychiatry* 1975; **32**: 923–32.
4. Fiellin L. E., Tetrault J. M., Becker W. C., Fiellin D. A., Hoff R. A. Previous use of alcohol, cigarettes, and marijuana and subsequent abuse of prescription opioids in young adults. *J Adolesc Health* 2013; **52**: 158–63.
5. Ellickson P. L., Hays R. D., Bell R. M. Stepping through the drug-use sequence—longitudinal scalogram analysis of initiation and regular use. *J Abnorm Psychol* 1992; **101**: 441–51.
6. Castaldelli-Maia J. M., Nicastri S., De Oliveira L. G., De Andrade A. G., Martins S. S. The role of first use of inhalants within sequencing pattern of first use of drugs among brazilian university students. *Exp Clin Psychopharmacol* 2014; **22**: 530–40.
7. Kandel D. B., Logan J. A. Patterns of drug-use from adolescence to young adulthood. 1. Periods of risk for initiation, continued use, and discontinuation. *Am J Public Health* 1984; **74**: 660–6.
8. Kandel D. B., Yamaguchi K., Chen K. Stages of progression in drug involvement from adolescence to adulthood—further evidence for the gateway theory. *J Stud Alcohol* 1992; **53**: 447–57.
9. Adler I., Kandel D. B. Cross-cultural perspectives on developmental stages in adolescent drug-use. *J Stud Alcohol* 1981; **42**: 701–15.
10. Degenhardt L., Chiu W. T., Conway K., Dierker L., Glantz M., Kalaydjian A. *et al*. Does the 'gateway' matter? Associations between the order of drug use initiation and the development of drug dependence in the National Comorbidity Study Replication. *Psychol Med* 2009; **39**: 157–67.
11. Degenhardt L., Dierker L., Chiu W. T., Medina-Mora M. E., 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* 2010; **108**: 84–97.
12. Patton G. C., Coffey C., Carlin J. B., Sawyer S. M., Lynskey M. Reverse gateways? Frequent cannabis use as a predictor of tobacco initiation and nicotine dependence. *Addiction* 2005; **100**: 1518–25.
13. Agrawal A., Silberg J. L., Lynskey M. T., Maes H. H., Eaves L. J. Mechanisms underlying the lifetime co-occurrence of tobacco and cannabis use in adolescent and young adult twins. *Drug Alcohol Depend* 2010; **108**: 49–55.
14. Sartor C. E., Agrawal A., Lynskey M. T., Duncan A. E., Grant J. D., Nelson E. C. *et al*. Cannabis or alcohol first? Differences by ethnicity and in risk for rapid progression to cannabis-related problems in women. *Psychol Med* 2013; **43**: 813–23.
15. Morral A. R., McCaffrey D. F., Paddock S. M. Evidence does not favor marijuana gateway effects over a common-factor interpretation of drug use initiation: responses to Anthony, Kenkel & Mathios and Lynskey. *Addiction* 2002; **97**: 1509–10.
16. Morral A. R., McCaffrey D. F., Paddock S. M. Reassessing the marijuana gateway effect. *Addiction* 2002; **97**: 1493–504.
17. Tsuang M. T., Lyons M. J., Meyer J. M., Doyle T., Eisen S. A., Goldberg J. *et al*. Co-occurrence of abuse of different drugs in men—the role of drug-specific and shared vulnerabilities. *Arch Gen Psychiatry* 1998; **55**: 967–72.
18. Kendler K. S., Chen X. N., Dick D., Maes H., Gillespie N., Neale M. C. *et al*. Recent advances in the genetic epidemiology and molecular genetics of substance use disorders. *Nat Neurosci* 2012; **15**: 181–9.
19. Fergusson D. M., Horwood L. J. Does cannabis use encourage other forms of illicit drug use? *Addiction* 2000; **95**: 505–20.
20. Fergusson D. M., Boden J. M., Horwood L. J. Cannabis use and other illicit drug use: testing the cannabis gateway hypothesis. *Addiction* 2006; **101**: 556–69.
21. Taylor M., Collin S. M., Munafo M. R., MacLeod J., Hickman M., Heron J. Patterns of cannabis use during adolescence and their association with harmful substance use behaviour: findings from a UK birth cohort. *J Epidemiol Community Health* 2017; **71**: 764–70.
22. Swift W., Coffey C., Degenhardt L., Carlin J. B., Romaniuk H., Patton G. C. Cannabis and progression to other substance use in young adults: findings from a 13-year prospective population-based study. *J Epidemiol Community Health* 2012; **66**: e26.
23. Lynskey M. T., Heath A. C., Bucholz K. K., Slutske W. S., Madden P. A., Nelson E. C. *et al*. Escalation of drug use in early-onset cannabis users vs co-twin controls. *JAMA* 2003; **289**: 427–33.
24. Lynskey M. T., Vink J. M., Boomsma D. I. Early onset cannabis use and progression to other drug use in a sample of Dutch twins. *Behav Genet* 2006; **36**: 195–200.
25. Grant J. D., Lynskey M. T., Scherrer J. F., Agrawal A., Heath A. C., Bucholz K. K. A cotwin-control analysis of drug use and

abuse/dependence risk associated with early-onset cannabis use. *Addict Behav* 2010; **35**: 35–41.
26. Agrawal A., Neale M. C., Prescott C. A., Kendler K. S. A twin study of early cannabis use and subsequent use and abuse/dependence of other illicit drugs. *Psychol Med* 2004; **34**: 1227–37.
27. Lessem J. M., Hopfer C. J., Haberstick B. C., Timberlake D., Ehringer M. A., Smolen A. *et al*. Relationship between adolescent marijuana use and young adult illicit drug use. *Behav Genet* 2006; **36**: 498–506.
28. O'Brien M. S., Comment L. A., Liang K. Y., Anthony J. C. Does cannabis onset trigger cocaine onset? A case–crossover approach. *Int J Methods Psychiatr Res* 2012; **21**: 66–75.
29. Byrne E. M., Yang J., Wray N. R. Inference in psychiatry via 2-sample Mendelian randomization—from association to causal pathway? *JAMA Psychiatry* 2017; **74**: 1191–2.
30. Verweij K. J. H., Treur J. L., Vink J. M. Investigating causal associations between use of nicotine, alcohol, caffeine, and cannabis: a two-sample bidirectional Mendelian randomization study. *Addiction* 2018; https://doi.org/10.1111/add.14154.
31. Verweij K. J. H., Vinkhuyzen A. A. E., Benyamin B., Lynskey M. T., Quaye L., Agrawal A. *et al*. The genetic aetiology of cannabis use initiation: a meta-analysis of genome-wide association studies and a SNP-based heritability estimation. *Addict Biol* 2013; **18**: 846–50.
32. Kendler K. S., Jacobson K. C., Prescott C. A., Neale M. C. Specificity of genetic and environmental risk factors for use and abuse/dependence of cannabis, cocaine, hallucinogens, sedatives, stimulants, and opiates in male twins. *Am J Psychiatry* 2003; **160**: 687–95.
33. Lynskey M. T., Grant J. D., Li L., Nelson E. C., Bucholz K. K., Madden P. A. *et al*. Stimulant use and symptoms of abuse/dependence: Epidemiology and associations with cannabis use—a twin study. *Drug Alcohol Depend* 2007; **86**: 147–53.
34. Bowden J., Davey Smith G., Burgess S. Mendelian randomization with invalid instruments: effect estimation and bias detection through Egger regression. *Int J Epidemiol* 2015; **44**: 512–25.
35. Keyes K. M., Hamilton A., Kandel D. B. Birth cohorts analysis of adolescent cigarette smoking and subsequent marijuana and cocaine use. *Am J Public Health* 2016; **106**: 1143–9.
36. Levine A., Huang Y. Y., Drisaldi B., Griffin E. A. Jr, Pollak D. D., Xu S. *et al*. Molecular mechanism for a gateway drug: epigenetic changes initiated by nicotine prime gene expression by cocaine. *Sci Transl Med* 2011; **3**: 107ra109.
37. Degenhardt L., Stockings E., Patton G., Hall W. D., Lynskey M. The increasing global health priority of substance use in young people. *Lancet Psychiatry* 2016; **3**: 251–64.
38. Ellgren M., Spano S. M., Hurd Y. L. Adolescent cannabis exposure alters opiate intake and opioid limbic neuronal populations in adult rats. *Neuropsychopharmacology* 2007; **32**: 607–15.
39. Cadoni C., Simola N., Espa E., Fenu S., Di Chiara G. Strain dependence of adolescent cannabis influence on heroin reward and mesolimbic dopamine transmission in adult Lewis and Fischer 344 rats. *Addict Biol* 2015; **20**: 132–42.
40. Kandel E. R., Kandel D. B. A molecular basis for nicotine as a gateway drug. *N Engl J Med* 2014; **371**: 932–43.
41. Wagner F. A., Anthony J. C. 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**: 918–25.
42. Hines L. A., Morley K. I., Strang J., Agrawal A., Nelson E. C., Statham D. *et al*. Onset of opportunity to use cannabis and progression from opportunity to dependence: are influences consistent across transitions? *Drug Alcohol Depend* 2016; **160**: 57–64.
43. Fergusson D. M., Horwood L. J., Lynskey M. T., Madden P. A. F. Early reactions to cannabis predict later dependence. *Arch Gen Psychiatry* 2003; **60**: 1033–9.
44. Baggio S., Henchoz Y., Studer J., Deline S., N'Goran A., Mohler-Kuo M. *et al*. Cannabis use and other illicit drug use: do subjective experiences during first cannabis use increase the probability of using illicit drug? *J Subst Use* 2015; **20**: 234–8.
45. Hall W. D., Lynskey M. Is cannabis a gateway drug? Testing hypotheses about the relationship between cannabis use and the use of other illicit drugs. *Drug Alcohol Rev* 2005; **24**: 39–48.