

EDITORIAL

The link between cannabis use and psychosis: furthering the debate¹

The issue of whether an association exists between cannabis and psychosis exists, and why, has received considerable attention in recent years (Hall, 1998; Mueser *et al.* 1998; Blanchard *et al.* 2000; Degenhardt & Hall, 2002). There are probably a number of reasons for the sustained interest. First, psychotic disorders such as schizophrenia are often chronic or recurring (Mason *et al.* 1996), are associated with significant disability (Keith *et al.* 1991) and they place a considerable burden upon the community at large (Hall *et al.* 1985; Knapp, 1997). Secondly, over the past few decades, high rates of cannabis use and use disorders have been observed among persons with schizophrenia and other psychoses (Barbee *et al.* 1989; Fowler *et al.* 1998), suggesting the possibility that cannabis use may be causally related to psychotic disorders. Thirdly, given what is known about the psychotomimetic effects of cannabis (Hall *et al.* 2001), it is plausible that high doses of cannabis may produce psychotic symptoms. Finally, clinical research with persons with psychotic disorders has found that problematical substance use is correlated with a range of negative outcomes including relapse, re-hospitalization, poor medication compliance, poorer social functioning and increased treatment costs (Salyers & Mueser, 2001), suggesting drug use may be related to worsened clinical outcomes.

Although this evidence suggests cause for concern, there has been controversy over: (a) the existence (and size) of an association between cannabis use and psychosis; (b) the cause of such an association; (c) the effects of such an association; and (d) the clinical implications of the association. However, much of the debate has been based cross-sectional research, clinical samples and case reports. This research is limited in its ability to disentangle the effects of selection biases, confounding factors, and temporal factors involved.

Two articles in this issue of *Psychological Medicine* examine the link between cannabis use and psychotic symptoms, and have added important evidence regarding the nature of the association between cannabis use and psychosis (Fergusson *et al.* 2003, pp. 15–21; Verdoux *et al.* 2003, pp. 23–32). Fergusson and colleagues have used data from their cohort study in Christchurch, New Zealand, to examine prospective relationships between cannabis use in late adolescence and the development of significant psychotic symptoms in young adulthood, considering the effects of vulnerability to psychosis. Verdoux and colleagues have used a method whereby participants reported their cannabis use and psychotic symptoms over several hour periods to examine links between vulnerability to psychosis, cannabis use and the experience of psychotic-type symptoms after cannabis use. Both studies represent much needed advances in the literature on this topic. This editorial examines how these papers add further pieces to the puzzle concerning mechanisms underlying the association between cannabis use and psychosis, and considers the way forward for research in this area.

DOES AN ASSOCIATION BETWEEN CANNABIS USE AND PSYCHOSIS EXIST?

There has been a series of case reports of psychosis occurring among persons who had recently used cannabis (Bernardson & Gunne, 1972; Chopra & Smith, 1974; Solomons *et al.* 1990; Wylie *et al.* 1995). A number of controlled studies have also been conducted over the past 20 years (Rolfe *et al.* 1993; McGuire *et al.* 1995). Some have compared persons with 'cannabis-induced' psychoses with persons who have schizophrenia, while others have compared psychoses occurring in persons who do and do not have evidence of cannabis use prior to presenting for treatment. Perhaps because of small

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sample sizes and varied research methods, results have differed: associations in some studies have not been replicated in others.

Some commentators have criticized these studies for the poor quality of information on cannabis use and its relationship to the onset of psychosis, and of information on the person's pre-morbid adjustment and their family history of psychosis (Thornicroft, 1992; Gruber & Pope, 1994). They also emphasize the wide variety of clinical pictures of psychoses reported by different observers, which reduces confidence that there is a specific clinical disorder caused by cannabis use.

There has been a small amount of epidemiological research on the co-morbidity between psychosis and cannabis use, which is free of the biases inherent in clinical research on co-morbidity (Berkson, 1946). This research has identified an association between regular or dependent cannabis use and reported psychotic symptoms (Tien & Anthony, 1990; Degenhardt & Hall, 2001), which has remained after adjusting for demographics, mental health and other substance use. Interestingly, both studies found that cannabis use remained associated with a doubling of risk for psychotic symptoms.

WHAT EXPLAINS THE ASSOCIATION?

Cross-sectional evidence is limited in its ability to distinguish between competing explanations for any observed association. Possible explanations include the following: that there are common causes of psychosis and heavy cannabis use, such as shared genetic vulnerabilities; that cannabis use is a form of self-medication for persons with psychosis; that psychosis is caused by cannabis use; and that substance use exacerbates or precipitates psychotic symptoms among individuals vulnerable to psychotic illness (Hall, 1998; Blanchard *et al.* 2000; Hall & Degenhardt, 2000; McKay & Tennant, 2000; Degenhardt & Hall, 2002).

While experimental designs (such as those conducted in the 1960s to examine the effects of amphetamines upon psychotic symptoms) would provide the strongest evidence regarding causality, the ethics of such research are questionable. Longitudinal research provides an opportunity to observe temporal relationships between variables in a non-experimental design.

PROSPECTIVE STUDIES OF PERSONS WITH PSYCHOSIS

There has been some suggestion from a limited number of prospective studies that persons with psychosis who use cannabis may be at higher risk of relapse to psychotic symptoms (Jablensky *et al.* 1991; Linszen *et al.* 1994; Martinez-Arevalo *et al.* 1994). In the study by Jablensky and colleagues (1991), 'street drug' use was associated with: a poorer clinical course, greater length of time experiencing psychotic episodes, and poorer social functioning over a 2-year follow-up period. This relationship existed after adjusting for age, gender, marital status, pre-morbid adjustment, and a number of indicators of social adjustment and social support (Jablensky *et al.* 1991). However, there was no adjustment for other mental health problems or drug use. Such adjustments were made in a prospective study of 93 persons with first-episode psychosis followed up over one year (Linszen *et al.* 1994). An association was found between cannabis use and relapse to psychotic symptoms after adjusting for age at admission, gender and alcohol use.

PROSPECTIVE GENERAL POPULATION STUDIES

A study of Swedish army conscripts found that the use of cannabis by age 18 years was associated with having received a diagnosis of schizophrenia 15 years later (Andreasson *et al.* 1987). There was also a dose-response relationship between cannabis use and diagnosis. The adjusted relative risk of a diagnosis of schizophrenia was just over twice as high for those who had used more than 10 times compared to those who had never used it (Andreasson *et al.* 1987).

More recently, Van Os and colleagues (1992) found that cannabis use was associated with both a higher risk of incidence of psychosis, particularly among those with an established vulnerability to psychosis, and a poorer prognosis of those with psychosis, in a general population sample followed over 3 years. This association remained after adjustment for some demographic variables.

In this issue, Fergusson and colleagues have gone further, in that they were able to adjust for a very wide range of demographic, individual, and social variables due to the extensive dataset established on their birth cohort of New Zealand children (Fergusson *et al.* 2003). In this way, they have been able to examine whether: (a) the association between cannabis use and psychosis is mediated in some way by a vulnerability to psychosis; and (b) whether ‘common causes’ explain the association. They were able to demonstrate that vulnerability to psychosis does explain some of the association; and that common causes do account for some of the association. Nevertheless, a significant association remained between cannabis dependence and later development of psychotic symptoms – an approximate doubling of risk.

While these studies provide evidence regarding the nature of temporal associations, one of the limitations of longitudinal studies is the relative lack of exactitude in the timing of the variables of interest. In most of the studies, cannabis use is measured in the past year, as are psychotic symptoms. The paper by Verdoux and colleagues provides a unique piece of evidence in that the time periods measured were several hours, and the association between cannabis use and psychotic symptoms could be assessed in a fairly exact manner. They also found that: cannabis use and psychotic symptoms were associated; that this association remained after adjusting for other drug use, age and gender; and that the risk was higher among those who were vulnerable to psychosis (Verdoux *et al.* 2003).

WHERE DO WE GO FROM HERE?

Further longitudinal studies are desirable to examine the associations between cannabis use and psychosis among cohorts followed up over considerable periods of time, and for whom there are considerable data on the social and environmental factors. There is also a need to examine whether genetic factors explain the association; behavioural genetic research could examine this possibility.

Given that it increasingly appears that cannabis use may worsen the clinical outcome for persons with psychosis, future research is required to examine this issue, especially prospective studies that examine the effect of changes in cannabis use upon the outcome of psychosis. The effect of treatment for cannabis use upon outcome for psychosis also needs to be evaluated.

Regardless of the effect of cannabis upon psychosis, there is a need for effective treatments for problematic substance use among persons with psychosis. There is currently a lack of well-controlled evaluations of treatments for problematical substance use in this population (Bellack & Gearon, 1998; Drake *et al.* 1998a; Kavanagh *et al.* 1998). Reviews have suggested that simply treating persons with psychosis in existing substance abuse treatment services was not effective (Drake *et al.* 1998b). However, there has been encouraging evidence for the effectiveness of skills training and intensive case management (Drake *et al.* 1998b; Bennett *et al.* 2001). Further controlled evaluations are needed to see if behavioural interventions are effective for this group. In general, it may be wise to consider a combination of integrated interventions, as opposed to discrete components.

CONCLUSIONS

The research in this issue of *Psychological Medicine* is consistent with evidence that is increasingly suggesting that cannabis use may place persons who are vulnerable to developing psychotic symptoms at particular risk of developing such symptoms, and perhaps of developing lasting psychotic disorders. Future work could aim to characterize the nature of such vulnerabilities. It must be noted that given the increases in cannabis use that have occurred over the past few decades, and the lack of a corresponding increase in rates of psychosis, a strong causal relationship (in which cannabis use caused cases of psychosis that would not otherwise have occurred) does not appear to exist (Degenhardt *et al.* 2001). Regardless of the reasons for the association, research into treatment approaches for persons with both problematical cannabis use and psychosis would be of great use.

REFERENCES

- Andreasson, S., Allebeck, P. & Rydberg, U. (1987). Cannabis and schizophrenia: a longitudinal study of Swedish conscripts. *Lancet* **2**, 1483–1486.
- Barbee, J. G., Clark, P. D., Crapanzo, M. S., Heintz, G. C. & Kehoe, C. E. (1989). Alcohol and substance abuse among schizophrenic patients presenting to an emergency psychiatry service. *Journal of Nervous and Mental Disease* **177**, 400–417.
- Bellack, A. S. & Gearon, J. S. (1998). Substance abuse treatment for people with schizophrenia. *Addictive Behaviors* **23**, 749–766.
- Bennett, M., Bellack, A. & Gearon, J. (2001). Treating substance abuse in schizophrenia: an initial report. *Journal of Substance Abuse Treatment* **20**, 163–175.
- Berkson, J. (1946). Limitations of the application of fourfold table analysis to hospital data. *Biometrics Bulletin* **2**, 47–53.
- Bernardson, G. & Gunne, L. M. (1972). Forty-six cases of psychosis in cannabis abusers. *International Journal of Addictions* **7**, 9–16.
- Blanchard, J., Brown, S., Horan, W. & Sherwood, A. (2000). Substance use disorders in schizophrenia: review, integration, and a proposed model. *Clinical Psychology Review* **20**, 207–234.
- Chopra, G. S. & Smith, J. W. (1974). Psychotic reactions following cannabis use in East Indians. *Archives of General Psychiatry* **30**, 24–27.
- Degenhardt, L. & Hall, W. (2001). The association between psychosis and problematic drug use among Australian adults: findings from the National Survey of Mental Health and Well-Being. *Psychological Medicine* **31**, 659–668.
- Degenhardt, L. & Hall, W. (2002). Cannabis and psychosis. *Current Psychiatry Reports* **4**, 191–196.
- Degenhardt, L., Hall, W. & Lynskey, M. (2001). *Modelling some Possible Relationships between Cannabis Use and Psychosis*. NDARC Technical Report No. 121. National Drug and Alcohol Research Centre, University of NSW: Sydney.
- Drake, R., Mercer-McFadden, C., Mueser, K., McHugo, G. & Bond, G. (1998a). Review of integrated mental health and substance abuse treatment for patients with dual disorders. *Schizophrenia Bulletin* **24**, 589–608.
- Drake, R., Mercer-McFadden, C., Mueser, K., McHugo, G. & Bond, G. (1998b). Review of integrated mental health and substance abuse treatment for patients with dual disorders. *Schizophrenia Bulletin* **24**, 589–608.
- Fergusson, D., Horwood, J. & Swain-Campbell, N. (2003). Cannabis dependence and psychotic symptoms in young people. *Psychological Medicine* **33**, 15–21.
- Fowler, I., Carr, V., Carter, N. & Lewin, T. (1998). Patterns of current and lifetime substance use in schizophrenia. *Schizophrenia Bulletin* **24**, 443–455.
- Gruber, A. J. & Pope, H. G. (1994). Cannabis psychotic disorder: does it exist? *American Journal of the Addictions* **3**, 72–83.
- Hall, W. (1998). Cannabis use and psychosis. *Drug and Alcohol Review* **17**, 433–444.
- Hall, W. & Degenhardt, L. (2000). Cannabis use and psychosis: a review of clinical and epidemiological evidence. *Australian and New Zealand Journal of Psychiatry* **34**, 26–34.
- Hall, W., Goldstein, G., Andrews, G., Lapsley, H., Bartels, R. & Silove, D. (1985). Estimating the economic costs of schizophrenia. *Schizophrenia Bulletin* **11**, 598–611.
- Hall, W., Degenhardt, L. & Lynskey, M. (2001). *The Health and Psychological Effects of Cannabis Use*, 2nd edn. (National Drug Strategy Monograph No. 44). Australian Publishing Service: Canberra.
- Jablensky, A., Sartorius, N. & Ernberg, G. (1991). *Schizophrenia: Manifestations, Incidence and Course in Different Cultures. A World Health Organization Ten-Country Study*. Psychological Medicine Supplement No. 20. Cambridge University Press: Cambridge.
- Kavanagh, D., Young, R., Boyce, L. & Clair, A. (1998). Substance abuse options in psychosis (STOP): a new intervention for dual diagnosis. *Journal of Mental Health* **7**, 135–143.
- Keith, S., Regier, D. & Rae, D. (1991). Schizophrenic disorders. In *Psychiatric Disorders in America: The Epidemiological Catchment Area Study* (ed. L. Robins and D. Regier), pp. 33–52. Macmillan, Inc.: New York.
- Knapp, M. (1997). Costs of schizophrenia. *British Journal of Psychiatry* **171**, 509–518.
- Linszen, D. H., Dingemans, P. M. & Lenior, M. E. (1994). Cannabis abuse and the course of recent-onset schizophrenic disorders. *Archives of General Psychiatry* **51**, 273–279.
- McGuire, P., Jones, R., Harvey, I., Williams, M., McGuffin, P. & Murray, R. (1995). Morbid risk of schizophrenia for relatives of patients with cannabis associated psychosis. *Schizophrenia Research* **15**, 277–281.
- McKay, D. R. & Tennant, C. C. (2000). Is the grass greener? The link between cannabis and psychosis. *Medical Journal of Australia* **172**, 284–286.
- Martinez-Arevalo, M. J., Calcedo-Ordóñez, A. & Varo-Prieto, J. R. (1994). Cannabis consumption as a prognostic factor in schizophrenia. *British Journal of Psychiatry* **164**, 679–681.
- Mason, P., Harrison, G., Glazebrook, C., Medley, I. & Croudace, T. (1996). The course of schizophrenia over 13 years. A report from the International Study on Schizophrenia (ISOs) coordinated by the World Health Organization. *British Journal of Psychiatry* **169**, 580–586.
- Mueser, K. T., Drake, R. E. & Wallach, M. A. (1998). Dual diagnosis: a review of etiological theories. *Addictive Behaviors* **23**, 717–734.
- Rolfe, M., Tang, M., Sabally, S., Todd, J., Sam, E. & Hatib N'Jie, A. (1993). Psychosis and cannabis abuse in the Gambia: a case-control study. *British Journal of Psychiatry* **163**, 798–801.
- Salysers, M. & Mueser, K. (2001). Social functioning, psychopathology, and medication side effects in relation to substance use and abuse in schizophrenia. *Schizophrenia Research* **48**, 109–123.
- Solomons, K., Neppe, V. M. & Kuyl, J. M. (1990). Toxic cannabis psychosis is a valid entity. *South African Medical Journal* **78**, 476–481.
- Thornicroft, G. (1992). Is 'cannabis psychosis' a distinct category? *European Psychiatry* **7**, 277–282.
- Tien, A. Y. & Anthony, J. C. (1990). Epidemiological analysis of alcohol and drug use as risk factors for psychotic experiences. *Journal of Nervous and Mental Disease* **178**, 473–480.
- Van Os, J., Bak, M., Hanssen, M., Bijl, R. V., de Graaf, R. & Verdoux, H. (2002). Cannabis use and psychosis: a longitudinal population-based study. *American Journal of Epidemiology* **156**, 319–327.
- Verdoux, H., Gindre, C., Sorbara, F., Tournier, M. & Swendsen, J. (2003). Cannabis use and the expression of psychosis vulnerability in daily life: an experience sampling test. *Psychological Medicine* **33**, 23–32.
- Wylie, A. S., Scott, R. T. A. & Burnett, S. J. (1995). Psychosis due to 'skunk'. *British Medical Journal* **311**, 125.