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Letters to the Editor

COMMENTS ON RITTER *ET AL.*'S REPORT OF A COMPARATIVE TRIAL OF LAAM AND METHADONE MAINTENANCE

Sir—Ritter *et al.*'s [1] claims their results show 'LAAM maintenance has equivalent efficacy to methadone' and 'both treatments were equally effective in retaining clients in maintenance treatment' are misleading. Their retention results actually favour methadone and their study was too small to identify confidently a clinically significant difference between the two maintenance drugs.

The triallists randomly assigned 101 primary care maintenance patients who had been receiving methadone for at least 8 weeks to either continue with methadone or to receive l-alpha acetylmethadol (LAAM). Treatment and assessment were unblinded with doses determined by the subjects' general practitioner. After 12 months, 35 of the 52 methadone subjects and 28 of the 49 LAAM subjects were still receiving their assigned treatment.

Unfortunately, Ritter *et al.* did not use these data in their analysis. Rather, they excluded three methadone and five buprenorphine subjects who either left or withdrew before receiving their first dose. This violates the principle of analysis by intention to treat under which all randomized patients should be accounted for and analysed in their assigned groups [2]. The violation biases retention in favour of buprenorphine.

The triallists also classified as retained in treatment an additional nine LAAM patients who had switched back to methadone. As methadone subjects did not have a similar opportunity to change maintenance drugs, this also biased the published retention results in favour of buprenorphine. This is why Ritter *et al.*'s results suggest that methadone subjects tended to be more likely to leave in the first year of treatment RR 1.12 (95% CI, RR 0.95–1.47, $P = 0.14$) and that buprenorphine reduced the absolute risk of leaving by 12.7% (95% CI, ARD –4.0%–29.3%).

When retention in assigned treatment data from all randomized subjects are considered, methadone subjects were 85% as likely to leave treatment as LAAM subjects (95% CI, RR 0.62–1.15, $P = 0.29$). Using the absolute reduction in the risk of subjects' leaving maintenance prematurely (10.2%; 95% CI, ARD –8.7%–29.0%), it is necessary to treat 10 patients for a year with methadone to prevent one premature loss that would have occurred with LAAM.

Table 1 The number of subjects required to detect differences in the five outcomes; $\beta = 0.80$, $\alpha = 0.05$.

Outcome	*Study result*	*Control result*	*SD*	*n*
Retention at 12 months	0.72	0.60		520
No use of heroin in last month	0.60	0.50		814
Cost of heroin, Aus$/day	20	40	75	444
Days used heroin in last 28	3.0	6.0	8.0	434
OTI Q scores[4]	0.45	0.25	0.75	444
Actual study size				101

β: The probability of a type II error, i.e. of finding no difference when there is one. α: The probability of a type I error, i.e. of finding a difference when there is none. SD: assumed standard deviation of continuous variables. *n* = the total number of subjects required assuming two equal groups.

While these effects are clinically important, they are not statistically significant. The width of the confidence intervals suggests this was because trial lacked statistical power. This was confirmed by a series of power calculations. If one treatment actually increased by 20% the proportion of subjects retained for a year, a study of 100 subjects would have only an 18% chance of identifying a statistically significant difference in retention (experimental 0.72, control 0.60, $\alpha = 0.05$).

The trial also lacked the power to identify statistically significant differences in the four self-reported outcomes: the proportion of subjects using heroin in the previous month; cost of heroin per day; days used heroin in the last 28; and changes in the OTI Q score, (Table 1). At least 450 subjects are needed to be confident that a study would detect clinically significant differences between methadone and buprenorphine. Indeed, even this estimate is optimistic as the assumed differences in outcome are greater than would be expected [3].

Ritter *et al.* were wrong to claim their failure to identify a statistically significant difference in outcome provides evidence that methadone and LAAM are equivalent. Rather, it was almost certainly caused by their study's lack of statistical power. To the contrary, when properly analysed, their data suggest retention was better in methadone maintenance. This is consistent with the results of comparisons of methadone and LAAM conducted in maintenance clinics [3].

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REFERENCES

1. Ritter, A. J., Lintzeris, N., Clark, N., Kutin, J. J., Bammer, G. & Panjari, M. (2003) A randomized trial comparing levo-alpha acetylmethadol with methadone maintenance for patients in primary care settings in Australia. *Addiction*, **98**, 1605–1613.
2. Jüni, P., Altman, D. G. & Egger, M. (2002) Assessing the quality of randomised controlled trials. In: Egger, M., Smith, G. D. & Altman, D. G., eds. *Systematic Reviews in Health Care: Meta-analysis in Context*, 2nd edn, p. 91. London: BMJ Books.
3. Clark, N., Lintzeris, N., Gijsbers, A., Whelan, G., Dunlop, A., Ritter, A. & Ling, W. (2003) LAAM maintenance vs methadone maintenance for heroin dependence (Cochrane Review). In: *The Cochrane Library*, Issue 3. Oxford: Update Software.
4. Darke, D., Ward, J., Hall, W., Heather, N. & Wodak, A. (1991) The Opiate Treatment Index (OTI) Researchers' Manual Technical Report II. Sydney: National Drug and Alcohol Research Centre.

LAAM VS. METHADONE: A RESPONSE TO CAPLEHORN

Sir—We thank Caplehorn for his commentary on our research report. His primary point is that the lack of difference between LAAM and methadone in our paper is the result of lack of statistical power and bias, rather than a 'true' negative finding. We note that the lack of statistical power does not prevent Caplehorn from concluding that methadone is more effective than LAAM!

Regarding bias from the intention-to-treat (ITT) analysis, we note first that this analysis has limitations and that there is little shared understanding of the principles and application [1,2]. ITT is a statistical method where the outcomes for each patient are included irrespective of what treatment they actually receive. That is, it is the 'intention' to treat that is the focus, not what treatment was actually received (in the end). Thus, we have analysed our data according to ITT and included participants, irrespective of whether they were on methadone or LAAM. We understand that this is the correct ITT analytical procedure. In drug trials, ITT is varied to include all those randomized and who receive at least one dose. This is to overcome some of the bias that critics attribute to the ITT method.

Whilst a proportion of experimental (LAAM) participants were treated with methadone by the end of the study, ITT analysis still assigns the outcomes to the randomized group; it would not be ethically appropriate to withhold treatment with methadone from the experimental group; and we should not necessarily assume, as has Caplehorn, that these clients would have dropped out of LAAM treatment had methadone not been available to them. Caplehorn has calculated his RR on the assumption that the LAAM to methadone transfers are indeed treatment drop-outs, and this is somewhat erroneous.

Despite the limitations of our sample size, which we acknowledge freely, we did find significant differences between LAAM and methadone on abstinence rates, including in the more conservative imputed data analysis. We chose, however, a cautious interpretation precisely because of the sample size issue, and have concluded equivalent efficacy. We did not extend our conclusions beyond the strength of the data.

Caplehorn states that 'at least 450 subjects are needed to . . . detect clinically significant differences between methadone and buprenorphine [sic]'. We concur that there are not clinically meaningful significant differences between LAAM and methadone and the efficacy can be regarded as equivalent. Thus it is very curious that Caplehorn goes on to suggest that our conclusions were wrong—as we appear to agree with each other.

Caplehorn's table is a useful reference and points to the importance of power analysis and appreciation of the degree to which statistical significance can be interpreted within studies of varying sample sizes. Nonetheless, we agree that there is no significant difference, nor a clinically meaningful difference between these two important treatments for heroin dependence.

An aside: the Caplehorn letter makes reference to buprenorphine. The study had no participants in buprenorphine, nor was buprenorphine offered as a treatment. We presume Caplehorn means LAAM.

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REFERENCES

1. Hollis, S. & Campbell, F. (1999) What is meant by intention

to treat analysis? Survey of published randomized controlled trials. *BMJ*, **319**, 670–674.
2. Newell, D. J. (1992) Intention to treat analysis: implications for quantitative and qualitative research. *International Journal of Epidemiology*, **21**, 837–841.

THE PSYCHOTOGENIC EFFECTS OF CANNABIS USE: CHALLENGES IN REDUCING RESIDUAL UNCERTAINTIES AND COMMUNICATING THE RISKS

Sir—The research reviewed by Smit, Bolier & Cuijpers (2004) has substantially reduced our uncertainty about the relationship between cannabis use and psychosis. A convergence of evidence from five large longitudinal studies in three different societies (Israel, New Zealand, Sweden) shows that: cannabis use precedes psychosis, that the risk of psychosis is higher for those who begin use at an earlier age, are regular cannabis users and have a history of psychotic symptoms. Smit *et al.* argue that the fact that all of these relationships persist after controlling for potential confounding factors makes it more likely than not that cannabis use plays a causal role in the onset of psychosis. This is a view that Rosalie Pacula and I support (Hall and Pacula, 2003).

Does cannabis use primarily precipitate psychosis in those who are at increased risk for a variety of other reasons? Or can cannabis use cause psychotic disorders in some people who would not have developed a disorder in the absence of cannabis use? Recent modelling indicates that it is not easy to choose between these hypotheses using epidemiological data. None the less, the former hypothesis seems more plausible than the latter because there has been no change in the incidence of schizophrenia in Australia during 40 years when life-time cannabis use increased from zero to 60% of young adults (Degenhardt *et al.* 2003).

Some sceptics will no doubt argue that the risk ratio is only 2 after adjustment for a limited range of confounders, and is consistent with residual uncontrolled confounding. We do not need to be certain about a causal relationship before we advise people about how to reduce their risk. Given other precedents in public health [e.g. sleeping prone and sudden infant death syndrome (SIDS)] and the seriousness of psychotic illness in young people, it would, as Smit *et al.* argue, be irresponsible not to tell young people about the possible risk. The challenge is communicating about the risk while acknowledging honestly the uncertainties that remain.

The potential leverage that a causal relationship has in the debate about the legal status of cannabis will complicate our task. We can expect a strong causal interpretation to be embraced by those who defend cannabis prohibition, while proponents of cannabis liberalization will dismiss this research as the latest incarnation of 'reefer madness'. This type of debate will amplify scepticism among young people about health messages about the risks of cannabis use. The following are offered in the spirit of tentative suggestions that need to be modified in the light of research on young adults' views on the issue, and the type of information that should be presented, by whom and how.

Young people with psychosis or a first-degree relative with psychosis are at highest risk of experiencing psychotic symptoms after using cannabis. They should be advised to avoid using cannabis and other psychotogenic drugs, including alcohol and stimulants. As Smit *et al.* note, this advice has a limited utility because 81% of people who develop schizophrenia do *not* have an affected first-degree relative (Gottesman 1991). Given the heterogeneous prodromal symptoms of psychosis we may, as Smit *et al.* suggest, need to expand our definition of 'at risk' to include young people who have experienced symptoms of anxiety and depression.

There are a number of things we can say about risk among the majority of young people who do not belong to this 'at risk' group. First, one in seven people who use cannabis report unpleasant, psychotic-like symptoms (Thomas 1996). This substantial minority of users are probably at greatest risk of psychosis and should be encouraged to cease use. Young people who do not experience such effects need to be persuaded that some of their peers may, and hence to avoid putting peers under pressure to use cannabis.

Secondly, another group who are probably at higher risk are young people who are daily or near daily cannabis users. Daily cannabis use is associated with a variety of other adverse adolescent outcomes (such as cannabis dependence, early school leaving, the use of other illicit drugs, and depression) and so it is worth discouraging for a number of reasons (Hall & Pacula 2003). Persuading young people that daily cannabis use is not a 'safe' pattern of use may also reduce any role it plays in precipitating psychosis.

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REFERENCES

Degenhardt, L., Hall, W. & Lynksey, M. (2003) Testing hypotheses about relationships between cannabis use and psychosis in Australia. *Drug and Alcohol Dependence*, **71**, 37–48.

Gottesman, I. I. (1991) *Schizophrenia Genesis*. New York: W.H. Freeman and Co.

Hall, W. & Pacula, R. L. (2003)*Cannabis Use and Dependence: Policy Health and the Public Policy*. Cambridge: Cambridge University Press.

Smit, F., Bolier, L. & Cuijpers, P. (2004) Cannabis use and the risk of later schizophrenia: a review. *Addiction*, **99**, 426–431.

Thomas, H. (1996) A community survey of adverse effects of cannabis use. *Drug and Alcohol Dependence*, **42**, 201–207.

CANNABIS AND PSYCHOSIS: TWO KINDS OF LIMITATIONS WHICH ATTACH TO EPIDEMIOLOGICAL RESEARCH

Sir—The report by Smit *et al*. (2004) is timely, given the growing longitudinal evidence on the linkages between cannabis use and psychosis/psychotic symptoms. These authors point out that there is clear evidence to suggest some form of causal link in which the heavy use of cannabis increases susceptibility to psychosis, with these increases being more likely in those with a predisposition to psychosis. While the review is scholarly and thoughtful in its conclusions, it a serves to highlight two limitations of epidemiological research, as follows.

Elimination of confounding

Establishing a causal link requires the demonstration that in the absence of all other factors, exposure to cannabis leads to increases in rates of psychosis. Such conclusions are best achieved by randomized experiments, but for many outcomes in epidemiology such experiments are not possible. This means that evidence about causation has to be based on correlational designs in which associations between cannabis and psychosis are controlled for observed sources of confounding. Subject to the assumption that the observed confounders adequately represent all confounders it becomes possible to draw causal inferences. The difficulty is that this assumption can always be challenged by suggesting the presence of non-observed covariates. Smit *et al.* acknowledge this point in their comment 'The confounding hypothesis still leaves room for further debate' (p. 10).

This raises the issue of what steps might be taken to control omitted confounders in future research. Although it is widely believed that epidemiological studies can only control observed sources of confounding, this is not strictly correct. The first approach to addressing this problem is to employ the discordant twin pairs design (Kendler & Prescott 1998; Lynskey *et al*. 2002; Lynskey *et al*. 2003). In the simplest form of this design monozygotic (MZ) twin pairs who are discordant for given risk factors (for instance, cannabis use) may be compared on the outcome measure (psychosis). Because the MZ twin pairs share common genes and common environment, these comparisons control for non-observed genes and common environmental factors. An example of this methodology to the cannabis debate is the study by Lynskey *et al*. (2003), who used the discordant twin design to test the gateway hypothesis. What this study showed was that in twin pairs discordant for cannabis use, the twin using cannabis was more likely to use other illicit drugs.

An approach that may be applied to longitudinal data gathered on singletons is to apply the fixed effects model (Hersch & Stratton 1997; Duncan *et al.* 1998; Fergusson, Horwood & Swain-Campbell 2002). This model uses the changing properties of longitudinal data to take into account the effects of factors which exert fixed effects on the outcome risks. An example that used this approach was the recent study by Fergusson *et al*. (2002), which used the fixed effects model to examine the effects of cannabis use on a wide range of outcomes in adolescence. That study showed that even when non-observed fixed confounding factors were taken into account, the increasing use of cannabis was associated with a wide range of adverse psycho-social outcomes. These examples show clearly that further and more searching tests of the confounding hypothesis may be possible by using more sophisticated research designs and analysis.

Association and process

The second limitation of the epidemiological method is that the conclusions drawn are interpretations of the patterns of association observed within population-level data. The limitation of this method is that it usually tells us very little about the underlying causal processes that are inferred from the observed associations. This limitation is clearly evident in the review by Smit *et al*.; while these authors produce clear evidence of a causal link, there is no account of the underlying neurophysiological processes which lead the heavy consumption of cannabis to be transformed into an increased risk of psychosis. It is now clear that cannabis use has complex effects on brain chemistry that is mediated via the cannabinoid receptors (see for example, Ameri 1999; Leweke *et al.* 1999; Ujike *et al*. 2002). What is needed to supplement the review by Smit *et al*. is a parallel review of the neurophysiological evidence examining the possible pathways

by which the heavy use of cannabis may lead to psychotic symptoms.

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REFERENCES

Ameri, A. (1999) The effects of cannabinoids on the brain. *Progress in Neurobiology*, **58**, 315–348.

Duncan, G. J., Brooks-Gunn, J., Yeung, W. J. & Smith, J. R. (1998) How much does childhood poverty affect the life chances of children? *American Sociological Review*, **63**, 406–423.

Fergusson, D. M., Horwood, L. J. & Swain-Campbell, N. R. (2002) Cannabis use and psychosocial adjustment in adolescence and young adulthood. *Addiction*, **97**, 1123–1135.

Hersch, J. & Stratton, L. S. (1997) Housework, fixed effects, and wages of married workers. *Journal of Human Resources*, **32**, 285–307.

Kendler, K. S. & Prescott, C. A. (1998) Cannabis use, abuse and dependence in a population-based sample of female twins. *American Journal of Psychiatry*, **155**, 1016–1022.

Leweke, F. M., Giuffrida, A., Wurster, U., Emrich, H. M. & Piomelli, D. (1999) Elevated endogenous cannabinoids in schizophrenia. *Neuroreport*, **10**, 1665–1669.

Lynskey, M. T., Heath, A. C., Bucholz, K. K., Slutske, W. S., Madden, P. A. F., Nelson, E. C., Statham, D. J. & Martin, N. G. (2003) Escalation of drug use in early-onset cannabis users vs co-twin controls. *Journal of the American Medical Association*, **289**, 427–433.

Lynskey, M. T., Heath, A. C., Nelson, E. C., Bucholz, K. K., Madden, P. A. F., Slutske, W. S., Statham, D. J. & Martin, N. G. (2002) Genetic and environmental contributions to cannabis dependence in a national young adult twin sample. *Psychological Medicine*, **32**, 195–207.

Smit, F., Bolier, L. & Cuijpers, P. (2004) Cannabis use and the risk of later schizophrenia: a review. *Addiction*, **99**, 426–431.

Ujike, H., Takaki, M., Nakata, K., Tanaka, Y., Takeda, T., Kodama, M., Fujiwara, Y., Sakai, A. & Kuroda, S. (2002) CNR1, central cannabinoid receptor gene, associated with susceptibility to hebephrenic schizophrenia. *Molecular Psychiatry*, **7**, 515–518.

CANNABIS AND PSYCHOSIS: HOW IMPORTANT IS THE LINK?

Sir—Does cannabis use cause a psychotic illness? About 150 years ago this question was already being asked, particularly recognizing the risk of 'madness' among young people, while at the same time the practice of using cannabis as a 'medicine for insanity' was being carried out in asylums (Mills 2003). It is interesting that over a century later the same question still remains unanswered, despite the fact that cannabis has continued to be the most widely used illegal substance around the world. The illegal status of cannabis has hindered research on humans for many years, even though biological studies on animals have been carried out. Fortunately, clinical observations of the worsening effect of cannabis on psychosis and the significantly high percentage of cannabis use in new onset psychoses cases has revived interest in this subject. Over the last few years there has been some carefully carried out and well-designed epidemiological research published, shedding light on this significant question, particularly at a time when the decriminalization of cannabis is being reviewed in some countries.

In this issue the article by Smit *et al.* (2004) reviews five such population-based, longitudinal studies on the relationship between cannabis use and psychosis, by formulating five hypotheses to examine the link. Even though there are, as yet, no biological studies showing a causal link, the evidence merging from these epidemiological studies points towards a significant link between cannabis use and a psychotic clinical state, especially in those who are vulnerable to develop psychosis. In one of the studies the risk difference is reported to be 54.7% (van Os *et al.* 2002). The same study shows that there is a 2.2% risk difference even for those who are not apparently vulnerable.

The self-medication hypothesis is ruled out by the authors due to the findings of the five reviewed studies that cannabis use came before the onset of psychosis, rather than the other way around. Even though this explanation does not lead to a causal relationship, it is important to examine why patients still continue using cannabis on a regular basis. Studying the reasons for ongoing use may add to our knowledge about how cannabis is processed in the human body and may also help towards finding better methods to treat patients with dual diagnosis. The findings of the five studies do not show a significant link between other drug use and the emergence of psychosis, but cannabis appears to be different and 'unique' in increasing the risk of psychosis. As the authors point out, both the Swedish and the Dutch studies also show a dose-related effect of cannabis, the more frequent use leading to a higher risk of the development of a psychotic illness (van Os *et al.* 2002; Zammit *et al.* 2002). This finding increases the possibility of cannabis having a causal link with the development of psychosis.

There is ample evidence in the psychiatric literature that cannabis use worsens the outcome of psychosis in those who are already ill and leads to more frequent hospitalization. Many in-patient units are full of patients with psychosis who continue to use cannabis

and appropriate treatment models need to be developed to reduce the risk of future use, by the use of randomized treatment trials. There are only a few such studies (Barrowclough *et al.* 2001; Castle *et al.* 2003, personal communication) which appear to have promising outcomes, but more studies of this kind are needed.

Even though the available well-designed longitudinal, epidemiological studies point towards a strong link between frequent cannabis use and the development of psychosis, especially among vulnerable individuals, what is needed is more biological evidence to confirm such a link. There are only a few PET scan studies carried out on human volunteers (Volkow *et al.* 1991; Volkow *et al.* 1996; O'Leary *et al.* 2002) and none published on 'vulnerable' or psychotic individuals.

It is important to be aware that cannabis is a complex plant with over 60 compounds, some of which have opposite effects. For instance, -9-tetrahydrocannabinol (THC), the main psychoactive ingredient of the plant, is known to increase the release of dopamine (Fritzsche 2002) which may explain the emergence or the worsening of psychotic symptoms. On the other hand another major compound, cannabidiol (CBD), is devoid of psychological effects associated with THC, but appears to have anti-anxiety and possibly antipsychotic effects in humans (Zuardi *et al.* 1995; Zuardi & Guimaraes 1997). This may explain why some patients are very keen to point out how smoking cannabis makes them feel 'calmer and better'. On the other hand, it has to be remembered that the street cannabis available in recent times is far more potent than previously, due to its high THC content and low levels of CBD.

The available research findings regarding the links between cannabis use and the emergence of psychoses and other mental health problems, especially among young people, are quite worrying. This is especially so as there appears to be a view among the young that cannabis is 'harmless' and there is a notable increase of teenage use, especially in the developed countries.

The message that regular cannabis use significantly increases the risk of developing a severe mental illness, especially for the young, needs to be discussed more publicly, albeit with sensitivity and balance. It is important to recognize at the same time that some compounds of the cannabis plant can be used successfully as a treatment for certain medical conditions. At present, public awareness of the possible harmful effects on mental health remains limited and better education is essential. The target audience for this has to be young people, perhaps as young as 11-year-olds, before they start secondary education. It is possible that the relaxation of the legal status of cannabis may lead to more openness and encouragement for further research, but it will not solve the problem by itself. We ultimately need to regulate the dose of THC and control under-age use, as we do with cigarettes. In any event, the public need to be given more information about the risks involved, in order to make their own informed choices. This is a task that we clinicians and researchers have to tackle, in conjunction with education authorities, government organizations and the media.

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REFERENCES

Barrowclough, C., Haddock, G. & Tarrier, N. (2001) Randomized controlled trial of motivational interviewing, cognitive behavior therapy, and family intervention for patients with comorbid schizophrenia and substance use disorders. *American Journal of Psychiatry*, **158**, 1706–1713.

Castle, D. J., James, W., Preston, N. J., Koh, G., Spence, C., Wightman, P. & Kisely, S. R. (2004) A group intervention which assists patients with dual diagnosis to reduce their drug and alcohol use: a randomsed controlled trial. *Psychological Medicine*, in press.

Fritzsche, M. (2002) Impaired information processing triggers altered states of consciousness. *Medical Hypotheses*, **58**, 352–358.

Mills, J. H. (2003) *Cannabis Britannica*. Oxford: Oxford University Press.

O'Leary, D. S., Block, R. I., Koeppel, J. A., Flaum, M., Schultz, S. K., Andreassen, N. C., Ponto, L. B., Watkins, G. L., Hurtig, R. R. & Hichwa, R. D. (2002) Effects of smoking marijuana on brain perfusion and cognition. *Neuropsychopharmacology*, **26**, 802–816.

Smit, F., Bolier, L. & Cuijpers, P. (2004) Cannabis use and the risk of later schizophrenia: a review. *Addiction*, **99**, 426–431.

Van Os, J., Bak, 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**, 19–27.

Volkow, N. D., Gillespie, H., Mullani, N., Tancredi, L., Grant, G., Ivanovic, M. & Hollister, L. (1991) Cerebellar metabolic activation by delta-9-tetrahydro-cannabinol in human brain: a study with positron emission tomography and 18F-2-Fluoro-2-deoxyglucose. *Psychiatry Research: Neuroimaging*, **40**, 69–78.

Volkow, N. D., Gillespie, H., Mullani, N., Tancredi, L., Grant, G., Valentine, A. & Hollister, L. (1996) Brain glucose metabolism in chronic marijuana users at baseline and during marijuana intoxication. *Psychiatry Research: Neuroimaging*, **67**, 29–38.

Zammit, S., Allebeck, P., Andreasson, S., Lundberg, I. & Lewis, G. (2002) Self-reported cannabis use as a risk factor for schizophrenia in Swedish conscripts of 1969: historical cohort study. *BMJ*, **325**, 1199–1201.

Zuardi, A. W. & Guimaraes, F. S. (1997) Cannabidiol as an anxiolytic and antipsychotic. In: Mathre, M. L., ed. *Cannabis in Medical Practice.* Jefferson, NC: Mcfarland and Company.

Zuardi, A. W., Morais, S. L., Guimaraes, F. S. & Mechoulam, R. (1995) Anti-psychotic effect of cannabidiol. *Journal of Clinical Psychiatry*, **56**, 485–486.

POSTSCRIPT FROM SMIT *ET AL.*

More converging evidence

The review by Smit *et al.* (Smit, Bolier & Cuijpers 2004) has been unwittingly replicated by another group of researchers (Arsenault *et al.* 2004). Arsenault and colleagues based their review on virtually the same studies and came up with exactly the same conclusion: cannabis use must be seen as one of the component risk factors in the pathogenesis of schizophrenia.

In about the same period a second study was published by a Dutch team of researchers (Veen *et al.* 2004). This study shows that the onset of schizophrenia occurs at a significantly earlier age in male cannabis users as compared to men who have no history of cannabis use.

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REFERENCES

Arsenault, L., Cannon, M., Witton, J. & Murray, R. M. (2004) Causal association between cannabis and psychosis: examination of the evidence. *British Journal of Psychiatry*, **184**, 110–117.

Smit, F., Bolier, L. & Cuijpers, P. (2004) Cannabis use and the risk of later schizophrenia: a review. *Addiction*, **99**, 425–430.

Veen, N. D., Selten, J. P., Van der Tweel, I., Feller, W. G., Hoek, H. W. & Kahn, R. S. (2004) Cannabis use and age at onset of schizophrenia. *American Journal of Psychiatry*, **161**, 501–506.