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 trialists 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 trialists 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 is 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.

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, α = 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].

<table>
<thead>
<tr>
<th>Outcome</th>
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<th>Control result</th>
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<td>OTI Q scores⁴</td>
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<td>Actual study size</td>
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Table 1 The number of subjects required to detect differences in the five outcomes. β = 0.80, α = 0.05.

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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 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 . . . 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.

REFERENCES

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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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 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; Ferguson, 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 Ferguson 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; Uijke 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 psy-
chotic symptoms.

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logical Medicine, 32, 195–207.

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 & Guimarães 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


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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