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EDITED BY KHALIDA ISMAIL

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Cannabis and psychosis

Arseneault et al (2004) very accurately reviewed recent epidemiological data and concluded that cannabis use should now be considered as a component cause leading to psychosis. Yet at least two unanswered questions remain. How can cannabis lead to psychosis? Are some subjects specifically vulnerable to the psychotogenic effect of cannabis?

Several studies, including the Dunedin study, have suggested that adolescents are more vulnerable to cannabis (Arseneault et al, 2004). Interestingly, the effects of cannabis on cognitive function also seem more pronounced in adolescents (Ehrenreich et al, 1999; Pope et al, 2003). This difference might also reflect pre-existing differences in cognitive ability between groups.

Cannabis interferes with endocannabinoid systems, known to be involved in neurodevelopment. In rats, chronic cannabionoid treatment during puberty induces behavioural and cognitive changes that are not found when the treatment is done in adulthood (Schneider & Koch, 2003).

Together, these observations are compatible with the idea that cannabis consumption could alter the last steps of brain maturation, leading to cognitive dysfunction and, in turn, enhancing the risk of psychosis. On the other hand, we recently suggested that genetic variants of the cannabinoid receptor type 1 could be associated with a specific sensitivity to cannabis (Krebs et al, 2002). Further studies are now needed to identify subjects ‘highly sensitive’ to the psychotogenic effect of cannabis, by coupling genetic analysis and cognitive testing to prospective follow-up.

The February 2004 issue contained a good review of evidence linking cannabis use to risk for developing schizophrenia (Arseneault et al, 2004). Three plausible causal explanations for this association are given. First, that cannabis and/or related drug use is a causal factor for schizophrenia. Second, that the altered mental state induced by cannabis may be mistaken for schizophrenia. Third, that cannabis use may be increased in individuals with the premorbid features of schizophrenia. Arsenault et al believe that the evidence favours the first alternative, and we agree. However, we call attention to a fourth possibility. Consider two propositions: (a) features of schizophrenia such as negative symptoms and cognitive impairments precede the onset of psychosis and are considered early morbidity rather than premorbid; and (b) schizophrenia is associated with high rates of substance misuse. The cause of substance misuse in schizophrenia is not known. We suggest a fourth hypothesis to explain the cannabis/schizophrenia association. Substance misuse may be a morbidity manifestation of some forms of schizophrenia. Vulnerability to substance use may be considered similar to vulnerability to psychosis.

The data review by Arsenault et al suggests that the cannabis/schizophrenia association is not based on shared genetic vulnerability. This is of interest to us in that a rodent model of schizophrenia has been developed by one of us (J.I.K.) based on the application of repeated stresses to pregnant rats during the rat equivalent to the second trimester of human pregnancy. The offspring of the stressed dams, once achieving adulthood, manifest the following schizophrenia-like behaviours: diminished cognitive ability on a hippocampal-dependent memory task; impaired gating of event-related potentials and sensory information; augmented behavioural responses to psychostimulants; social apathy and incompetence (Koenig et al, 2001; further details available from the authors on request).

In addition, adult rats exposed to stressful gestation consume alcohol in excess compared with control animals. We therefore raise the possibility that aspects of the non-genetic environment may contribute simultaneously to increased risk for cannabis use and increased risk for schizophrenia diathesis.

Declaration of interest

A research contract from Novartis Pharma, AG supported development of the rat model.


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I read with great interest the article by Arsenault et al (2004). It demonstrates without any doubt that cannabis use in adolescence acts as a causal risk factor for schizophrenia in adulthood. It is, therefore, a pity that the authors had to add the caveat that, since not all adults with schizophrenia used cannabis in adolescence and since the majority of cannabis users do not develop schizophrenia in adulthood, cannabis can be neither a sufficient nor a
necessary cause for psychosis. This formulation is erroneous and was used, in exactly the same words, many years ago when prospective studies in the UK established the aetiological role of tobacco in lung cancer. In an elementary textbook on statistics, Schwartz (1999) explains that this error arises from the faulty use of the term ‘cause’, which applies to the domain of certainty, whereas in the domain of uncertainty (i.e. of illness) the definition of a causal factor is that it provokes an increase in risk, as perfectly demonstrated by the authors. One wonders why they make this elementary error. It is unlikely to be due to psychological resistance, as was the case with tobacco smokers at that time. Perhaps they believe that schizophrenia (or psychosis) is a known disease entity, as defined according to international systems of classification (DSM–IV, ICD–10) which, unfortunately, continue to exclude substance use from their diagnostic criteria.


Child sexual abuse and substance use disorders: role of psychiatric comorbidity

We read with interest the paper by Spataro et al (2004) considering associations between child sexual abuse and subsequent psychopathology using a prospective cohort design. This study clearly indicates a positive association between child sexual abuse and a range of mental disorders, although not substance use disorders. We think that the authors make an important point in their discussion that this latter absence of an association might be at least partly due to their methodology for assessing psychiatric outcome. They implemented a diagnostic hierarchy in such a way that when substance use problems were accompanied by other psychiatric disorders, these comorbid conditions were counted and not the substance use.

It is important for the reader to know that substantial comorbidity between substance use disorders and other psychiatric disorders is consistently reported (e.g. Kessler et al, 1997a). Thus, one could suggest that this prospective study does not demonstrate an association between child sexual abuse and more pure forms of substance use disorders. This would be in line with other findings suggesting a lack of association between childhood trauma (including child sexual abuse) and pure substance use disorders, but a strong relationship between childhood trauma and psychiatric comorbidity in substance use disorders (Kessler et al, 1997b; de Graaf et al, 2002).


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Insulin-like growth factors, insulin resistance and schizophrenia

Abel (Abel, 2004) speculates that imprinting of the gene for insulin-like growth factor-II (IGF-II) as well as other genes may be one pathway through which environmental exposures influence the risk of schizophrenia. We too have hypothesised that factors influencing the growth-hormone–IGF axis may contribute to the well-recognised associations of pre-adult exposures with schizophrenia (Gunnell & Holly, 2004).

We feel that evidence for a direct role of IGF-I is more compelling than that for IGF-II (whose biological functions are poorly understood). Possible pathways for an association with IGF-I lie not only in its role in neurodevelopment but also through its role in neuroprotection following brain damage (e.g. following birth asphyxia, head injury or meningitis) (Gluckman et al, 1998). Insulin-like growth factors exert powerful anti-apoptotic actions and low levels may reduce the survival probability of damaged cells. The influence of IGF-I may extend beyond foetal life as low IGF-I is associated with low birth weight, reduced childhood growth and low body mass index, which are, in turn, associated with the development of psychosis (Wahlbeck et al, 2001; Gunnell et al, 2003). It is therefore possible that low IGF-I levels not only impair neurodevelopment but also render individuals more susceptible to neurodevelopmental insults such as traumatic brain injury and hypoxic brain damage (Gunnell & Holly, 2004).

Several lines of direct and indirect evidence support a possible role of IGF-I in the aetiology of schizophrenia (Gunnell & Holly, 2004). Intriguing indirect evidence for the role of IGF-I, as Abel points out, comes from the observation that low levels protect against a range of different cancers (Renehan et al, 2004) and individuals with psychosis, and their families, appear to be at reduced risk of some malignancies. This may well reflect shared genetic influences on IGF levels influencing susceptibility to both schizophrenia and cancer. Evidence for aetiological associations of IGF-II with cancer risk are less consistent than those for IGF-I. A further indirect line of evidence comes from current concern that insulin resistance may both be more common in people with schizophrenia and be precipitated by antipsychotic medication. Prospective studies indicate that low IGF-I levels are associated with the development of insulin resistance (Sandhu et al, 2002). We speculate that the co-occurrence of insulin resistance and psychosis may in part arise through the shared susceptibility of both these disorders associated with low IGF-I levels.

Evaluation of the possible role of the IGF-system in schizophrenia might not only further our understanding of the aetiology of this disorder but also give insights into its prevention and the reduction of comorbidities such as insulin resistance.


Pharmaceutical influence and psychiatrists: an introspection

The Monday afternoon journal club brings us all together from the several community centres in the trust. Today, unexpectedly, the drug rep is not on time and the meeting has begun without lunch. Most of us are restless. It is difficult to listen when you are hungry. I catch myself looking out of the window, but I am also looking at the entrance to the room from the corner of my eye. Where is this drug rep anyway?

Gilbody et al. (2004) have elaborated very topical concerns about the growing influence of direct-to-consumer advertising of psychotropic medications. In this movement, greater empowerment of consumer choice is used as a catch-phrase and, more importantly, the clinicians who oppose it stand accused of ‘guarding professional territory’ (Bonaccorso & Sturchio, 2002). But to begin tracing this debate to its ethical roots, we ought to pause and first consider the merits of clinician-targeted advertising. The editorial rightly states that $2.5 billion was spent in the year 2000 on direct-to-consumer advertising in the USA. However, this was a small fraction of the massive $15.7 billion spent on drug promotion as a whole (Rosenthal et al., 2002; Wolfe, 2002). Budgets for the same have increased exponentially over the past few years (Wolfe, 2002). With the introduction of the newer, more expensive atypical antipsychotics and selective serotonin reuptake inhibitors, this is particularly so in psychiatry. Since advertising in professional journals seems to be fairly static (as demonstrated by brief inspection of the number of drug advertisements in the Journal in any given month over the past decade), it can only be assumed that the bulk of this finance caters toward sponsoring conferences, hotel stays, lunches and other ‘promotional’ activities aimed at the clinician writing the prescriptions.

Such practice seems to be woven into the very fabric of the medical profession in general, and psychiatry in particular. Yet what evidence is there to suggest that this culture of hyperbolic symbiosis is beneficial to our patients?

Several studies have been done recently that investigate the possible changes in prescription patterns as a result of aggressive consumer-directed advertising. Surprisingly, on the other hand, there is very scant research indeed to elucidate the association of our prescription patterns and the influence of any concurrent clinician-directed advertising. Of the little evidence available, most suggests a worse scenario (Wang et al., 1999). Is there a professional bias that explains this paucity of interest?

Before riding our moral high horse and being outraged at the blurring of boundaries as the pharmaceutical industry makes independent forays into the public domain, should we not consider what boundaries we set big business when it entered our own fold? I imagine it would be difficult for a clinician who writes with a drug company pen, on a drug company pad, which he takes out of his drug company bag, to tell his patient not to invest much faith in drug company advertisements. On how many occasions do clinicians turn down offers by pharmaceutical companies to fund their attendance at conferences, flights abroad, hotel stays, social banquets, gifts? The list is long, and there is no such thing as a free lunch.

Meanwhile, in my own little way, I wait for the drug rep. The doctor presenting the paper rambles on. ‘An intention to treat analysis would have been more appropriate to validate this particular therapy,’ I think to myself. But at the same time I wonder, ‘I hope it’s the pretty lady from the risperidone company. She brings those lovely sandwiches from Marks & Spencer’.

Declaration of interest
I regularly attend the twice-weekly journal clubs and case conferences at my centre, during which lunch is sponsored by pharmaceutical companies.


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Defining delusion
The clear definition of primary delusions helpfully provided by Owen et al. (2004) includes both that one comes to believe new things (change in meaning) and arrives at such beliefs in a new way (transformation of experience). This requirement for a transformation of experience seems to me to require an abnormal mental mechanism that is permitted in a rationalist account of delusions. The distinction between primary and secondary delusions is one that eludes many authors (e.g. Hales et al., 1999: pp. 432–434) in addition to myself and Professors van Os and Delespaul. We would differ I suppose in that while they view all delusions as secondary, I think those that do not share the mechanism of primary delusions are not really delusions at all.

Wernicke’s work on aphasia suggested that mental functions were localised, but this is quite a separate issue from whether their mechanism is modular. This is evident in Wernicke’s description of mental pathology as a ‘loosening up of the firm network of association’ (Jaspers, 1963: p. 536). Such an empiricist account of mental pathology is surely incompatible with modularity as proposed by the rationalist philosopher Fodor.


Two hundred years ago

Clinical note on a case of obstinate constipation due to collection of plum-stones in the rectum. By J. Ogilvie Veitch, MB, CMEdin, Second Assistant Medical Officer, the Asylum, Worcester

A FEMALE patient, M. W—, in this asylum, suffering from dementia, and who had previously been cleanly in her habits, was noticed by the nurse to soil her clothes daily, and that, although this occurred, she never had a proper movement of the bowels. She was sleepless and restless at night, but complained of no pain, and took her food in a satisfactory manner. This state of affairs had been progressing for about ten days, when it was brought under the notice of her medical attendant. Various purgatives were administered by the mouth, and these proving ineffectual, and on purgative enemata being tried and also proving abortive, a rectal examination was made, when it was discovered that the lower bowel was filled with plum-stones, which were caked with the faeces into a hard mass. These were digitally removed, and numbered about fifty. After this treatment the patient’s bowels acted normally. The special feature of this case seems to be the facility with which these stones, considering their size and sharp edges, passed through the whole length of the intestine, without giving rise to any serious symptoms.

REFERENCE


Researched by Henry Rollin, Emeritus Consultant Psychiatrist, Horton Hospital, Epsom, Surrey.