Interpreting the association between cannabis use and increased risk for schizophrenia

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Recent longitudinal studies from Sweden, the Netherlands, New Zealand, and Israel report that cannabis use during childhood and adolescence doubles the risk of later appearance of psychosis or schizophrenia. These data have been interpreted as indicating that cannabis has a causal effect along the pathway to psychosis. In this paper, we will offer an alternative explanation of these data. Recent investigations of patients with schizophrenia found increased density of cannabinoid receptors in the dorsolateral prefrontal cortex and the anterior cingulate cortex. Others reported higher levels of endogenous cannabinoids in the blood and cerebrospinal fluid of patients; these findings were independent of possible cannabis use. Several genetic studies have reported an association between genes encoding the cannabinoid receptor and schizophrenia. Thus, an alternative explanation of the association between cannabis use and schizophrenia might be that pathology of the cannabinoid system in schizophrenia patients is associated with both increased rates of cannabis use and increased risk for schizophrenia, without cannabis being a causal factor for schizophrenia.

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Patients with schizophrenia use cannabis at higher rates than those of the general population.[1-3] This has been reported in chronic patients, and other studies have shown that at the time of the first psychotic episode, up to 40% of patients already use cannabis.[4,5] Although some authors understood these findings as being due to self-medication of symptoms of schizophrenia, one prospective study from 1987 and four more studies published in 2002 and 2003 found that persons using cannabis were at increased risk of later suffering from psychosis and/or schizophrenia. These findings were interpreted by some as indicating that cannabis use lies upon a causal pathway of later psychosis or schizophrenia. In this paper, we will review these findings, and present an alternative explanation for the association between cannabis use and later schizophrenia.

Review of the data

The first longitudinal study of the relationship between cannabis use and later schizophrenia utilized data on cannabis use by 50 000 18-year-old recruits into the Swedish army, and ascertained hospitalization for schizophrenia using a hospitalization registry. After a 15-year follow-up, they found that frequent cannabis use (more than 50 times in a lifetime) was associated with a sixfold increased risk for later hospitalization for schizophrenia. After controlling for possible confounders, the odds ratio (OR) was 2.3.[6] This same cohort was later reanalyzed using the same design,[7] 27 years after cannabis use had been ascertained. They found that use of cannabis at least once by age 18 was associated with increased risk for later schizophrenia, and, when adjusted for nonpsychotic diagnosis at conscription, low IQ, poor social integration, cigarette smoking, and behavioral disturbances in child-

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hood, the OR was 1.5. Frequent cannabis use (more than 50 times in a lifetime) was associated with a threefold increased risk for schizophrenia.

The Netherlands Mental Health Survey and Incidence Study (NEMESIS)[8] assessed a random sample of 4104 persons aged 18 to 64 and followed them for 3 years. Compared with persons not reporting cannabis use at baseline, persons using cannabis at baseline were 2.8 times more likely to manifest psychotic symptoms at follow-up, after controlling for age, gender, ethnic group, education, unemployment, single marital status, urbanicity, and discrimination. A dose–response relationship was present, with the highest risk (adjusted OR=6.8) for the highest level of cannabis use.

The Dunedin Multidisciplinary Health and Development Study[9] examined 759 persons from a general population birth cohort of individuals born in Dunedin, New Zealand. They assessed cannabis use at ages 15 and 18, and presence of schizophreniform disorder was ascertained at age 26. Their results indicated that use of cannabis at age 15 was associated with higher incidence of schizophreniform disorder (OR=3.1) after controlling for social class and presence of psychotic symptoms at age 11. Finally, in a similar longitudinal, historical-prospective design, 50 413 male adolescents who had been suspected of having behavioral or personality disturbances were asked about cannabis use in the Israeli draft board.[10] Self-reported drug use was associated with a twofold increase in later hospitalization for schizophrenia, after adjustment for intellectual and social functioning, and the presence of a nonpsychotic psychiatric diagnosis at the draft board assessment.

Inferring causality from epidemiological data is often problematic, and the classic criteria suggested by Hill[11] are often used when deliberating over these issues. The Hill criteria include strength, consistency, specificity, biological gradient, temporality, coherence, and plausibility. Regarding the strength of the association, an OR of 2, especially for a relatively rare illness like schizophrenia, does not represent a particularly strong association, but on the other hand, many other, well-established risk factors for illness have similar ORs, such as cigarette smoking and later lung cancer,[12] and hypercholesterolemia and later atherosclerotic cardiovascular disease.[13] The data across these different studies are remarkably consistent, using different patient populations and different research methodologies, with very similar results. Several of the studies on the topic examined the specificity of the relationship between cannabis use and schizophrenia: Zammit et al,[7] Van Os et al,[8] and Arseneault et al[9] controlled for use of other drugs in their analyses, thus addressing the issue of specificity of exposure. Van Os et al[8] found that cannabis use was not associated with other psychotic disorders, whereas Arseneault et al[9] and Weiser et al[10] did not find an association between cannabis use and later depression, indicating specificity of outcome.

The presence of a biological gradient is supported by the presence of a dose–response relationship, with increasing amounts of cannabis used associated with increasing risk for psychosis[8] or schizophrenia.[6,7] As these are all longitudinal studies, which assessed cannabis use at baseline and ascertained later appearance of psychotic illness, the temporality criterion is clearly met. Coherence refers to how the proposed association relates to the generally known facts regarding the illness. This seems problematic, as the use of cannabis has increased tremendously over the past four decades: according to the National Survey on Drug Use and Health (NSDUH, previously known as the National Household Survey on Drug Use), "… the percentage of young adults aged 18 to 25 who had ever used marijuana was 5.1% in 1965, but increased steadily to 54.4% in 1982. Although the rate for young adults declined somewhat from 1982 to 1993, it did not drop below 43% and actually increased to 53.8% by 2002."[14] This represents an increase of approximately 10-fold in the use of cannabis in adolescents; if cannabis does, in fact, cause psychotic illness, then one would expect that the prevalence of psychotic illness would increase in parallel to the greatly increased use of the "causative" substance in the Western world. This is clearly not the case, as there are reports both of increases and decreases in the prevalence of schizophrenia[15-18] in the Western world, with no clear evidence of a significantly increased prevalence that would be expected if the use of a causative substance increased 10-fold.

In addressing this issue, some authors have suggested that cannabis use in early adolescence is associated with particularly strong association with later psychotic illness, and that this is a fairly new phenomenon, in that cannabis use among adolescents under the age of 16 years in the USA has appeared only since the early 1990s.[12] This indicates that the hypothesized effect of cannabis use on the prevalence of schizophrenia will only be observed in the years to come. However, data from the NSDUH[14] indicate that there has been a significant increase in cannabis use in this age group as well: the number of 12 to 17 year

olds using cannabis for the first time rose from 9.2 per 1000 in 1965, to 58.2 per 1000 in 1980, and to 83.2 per 1000 in 1996. Thus, there has been a very significant increase in cannabis use in young adolescents as well, which would be expected to lead to an increase of schizophrenia in the population, if cannabis were in fact causative. Regarding biological plausibility, there are some reports on changes in the endogenous cannabinoid system in schizophrenia, which might be related to the effects of cannabis on the brains of patients; this will be discussed in greater detail below.

To summarize, based on commonly accepted criteria for causality, there seems to be a reasonable case to be made for cannabis causing schizophrenia; this is clearly delineated in a recent review.[19]

Alternative explanation

We would like to present an alternative explanation of these findings, based on the work of others and ourselves on premorbid adjustment and schizophrenia. Several prospective longitudinal studies suggest that adolescents who manifest abnormal behavior or personality traits may be at high risk of later manifesting schizophrenia as adults. Persons with obsessive-compulsive disorder (OCD), social phobia, and panic attacks examined in the Epidemiologic Catchment Area (ECA) study[20] were at increased risk for future schizophrenia. The Minnesota Multiphasic Personality Inventory (MMPI) traits of depression, anxiety, internalized anger, social alienation, and withdrawal are associated with increased risk for future schizophrenia.[21] A follow-up study of conscripts screened by the Swedish army found that 18 year olds with personality disorders or neurosis were at increased risk for future schizophrenia, and a study on a British birth cohort reported that neuroticism at age 16 was associated with increased risk for later schizophrenia.[22] A separate set of studies indicates that these nonpsychotic psychiatric disorders are associated with increased rates of cannabis use.[23] The National Comorbidity Survey[24] found that 90% of respondents with cannabis dependence had a lifetime mental disorder, compared with 55% without cannabis dependence. Antisocial personality disorder (OR=11.2) and conduct disorder (OR=6) had the strongest associations with cannabis dependence, followed by anxiety (OR=2.6) and mood disorders (OR=2.0). In Australian adolescents aged 13 to 17,[25] cannabis use was associated with depression (OR=3.1) and conduct problems (OR=3.6).

These data raise the possibility that future schizophrenia patients have increased rates of premorbid behavioral disturbances and psychiatric diagnoses, and these, in turn, are associated with increased rates of cannabis use. One might say that future patients are using cannabis as self-medication of premorbid behavioral disturbances and psychiatric diagnoses.

These epidemiological data are supported by studies indicating that similar neuropathologies might be involved in both cannabis use and schizophrenia, and other reports indicating that patients with schizophrenia have impairments in the endogenous cannabinoid system. Research on the neurobiology of drug abuse and schizophrenia[26] indicates that the mesolimbic dopamine system is involved in both cannabis abuse[27] and schizophrenia.[28] Furthermore, dysregulation in cortical, temporal, limbic, and mesoaccumbens circuits is implicated both in schizophrenia[29] and in substance abuse disorders,[30] and behavioral disturbances modulated by the hippocampus and mediated by the nucleus accumbens are associated with schizophrenia[31] and with cannabis abuse.[32] Thus, it is plausible that developmental neuropathology in hippocampal and prefrontal cortical pathways contributes to vulnerability to both schizophrenia and cannabis use, via dysfunctional interactions with the nucleus accumbens. More recent reports indicate that specific receptors exist in the brain that recognize cannabinoids, and a series of endogenous cannabinoids have been discovered that act as ligands for these receptors. The density of these receptors has been found to be increased in the anterior cingulate cortex[33] and dorsolateral prefrontal cortex[34] in schizophrenia patients compared with controls. These findings were independent of cannabis use. Two studies on the genetics of the central CB_1 cannabinoid receptor have reported an association between polymorphisms of the *CNR1* gene and schizophrenia.[35,36] Levels of the endogenous cannabinoid anandamide have been found to be elevated in the blood[37] and cerebrospinal fluid[38,39] of patients with schizophrenia, independent of cannabis use. All of these findings point to possible structural and functional impairments in the endogenous cannabinoid system in schizophrenia patients. On this basis, we suggest that these impairments in the endogenous cannabinoid system might be related to the slightly increased propensity of future schizophrenia patients to smoke cannabis, and are also associated with increased risk for schizophrenia.

Conclusion

The data presented above indicate that: (i) future schizophrenia patients have premorbid behavioral abnormalities that might increase their propensity to use cannabis; (ii) cannabis use and schizophrenia might be the manifestations of a common brain pathology; and (iii) schizophrenia patients have dysfunctions of the endogenous cannabinoid system independent of cannabis use. The nature of the association between cannabis use and schizophrenia awaits further elucidation from research into the biology of schizophrenia, but, at this point in time, based on the available evidence, it seems premature to claim that cannabis use causes schizophrenia. ❑

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La interpretación de la asociación entre el uso de cannabis y el aumento del riesgo de esquizofrenia

Estudios longitudinales recientes realizados en Suecia, Holanda, Nueva Zelandia e Israel señalan que el empleo de cannabis durante la niñez y la adolescencia duplica el riesgo de aparición posterior de psicosis o de esquizofrenia. Estos resultados se han interpretado como indicadores de que el cannabis tendría un efecto causal en la vía que lleva a la psicosis. En este artículo se ofrecerá una explicación alternativa de estos resultados. Investigaciones recientes en pacientes con esquizofrenia encontraron un aumento en la densidad de los receptores de cannabinoides en la corteza prefrontal dorsolateral y la corteza cingulada anterior. Otros trabajos han informado acerca de altos niveles de cannabinoides endógenos en sangre y líquido céfalo-raquídeo de pacientes y estos resultados fueron independientes del posible uso de cannabis. Varios estudios genéticos han dado cuenta de una asociación entre genes que codifican el receptor de cannabinoides y la esquizofrenia. De tal forma que una explicación alternativa para la asociación entre el empleo de cannabinoides y la esquizofrenia podría ser que la patología del sistema cannabinoide en pacientes esquizofrénicos se relacione tanto con un aumento en el porcentaje de uso de cannabis como con un incremento en el riesgo de tener esquizofrenia, sin que el cannabis sea un factor causal para la esquizofrenia.

Interprétation de l'association entre consommation de cannabis et augmentation du risque de schizophrénie

De récentes études longitudinales issues de Suède, des Pays-Bas, de Nouvelle-Zélande et d'Israël rapportent que l'utilisation de cannabis pendant l'enfance ou l'adolescence double le risque d'apparition ultérieure de psychose ou de schizophrénie. Ces résultats ont été interprétés de façon à suggérer que le cannabis a un effet causal pouvant mener à une psychose. Dans cet article, nous allons proposer une autre interprétation de ces données. Des travaux récents sur des patients atteints de schizophrénie ont mis à jour une augmentation de la densité des récepteurs cannabinoïdes dans le cortex préfrontal dorsolatéral et dans le cortex cingulaire antérieur. D'autres recherches ont indiqué des concentrations plus élevées de cannabinoïdes endogènes dans le sang et le liquide cérébrospinal des patients ; ces constatations étaient indépendantes d'un usage éventuel de cannabis. Plusieurs études génétiques ont rapporté une association entre les gènes codant le récepteur cannabinoïde et la schizophrénie. Ainsi, une autre explication de l'association entre l'usage du cannabis et la schizophrénie pourrait être que la pathologie du système cannabinoïde chez les patients atteints de schizophrénie est associée à la fois à l'augmentation des taux d'utilisation du cannabis et à l'augmentation du risque de schizophrénie, sans que le cannabis soit le facteur causal de la schizophrénie.

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