Cannabis use and psychosis: a review of clinical and epidemiological evidence*

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Objective: This paper evaluates evidence for two hypotheses about the relationship between cannabis use and psychosis: (i) that heavy cannabis use causes a 'cannabis psychosis', i.e. a psychotic disorder that would not have occurred in the absence of cannabis use and which can be recognised by its pattern of symptoms and their relationship to cannabis use; and (ii) that cannabis use may precipitate schizophrenia, or exacerbate its symptoms.
Method: Literature relevant to drug use and schizophrenia is reviewed.
Results: There is limited clinical evidence for the first hypothesis. If 'cannabis psychoses' exist, they seem to be rare, because they require very high doses of tetrahydrocannabinol, the prolonged use of highly potent forms of cannabis, or a pre-existing (but as yet unspecified) vulnerability, or both. There is more support for the second hypothesis in that a large prospective study has shown a linear relationship between the frequency with which cannabis had been used by age 18 and the risk over the subsequent 15 years of receiving a diagnosis of schizophrenia.
Conclusions: It is still unclear whether this means that cannabis use precipitates schizophrenia, whether cannabis use is a form of 'self-medication', or whether the association is due to the use of other drugs, such as amphetamines, which heavy cannabis users are more likely to use. There is better clinical and epidemiological evidence that cannabis use can exacerbate the symptoms of schizophrenia.
Key words: cannabis, psychosis, schizophrenia.

Australian and New Zealand Journal of Psychiatry 2000; 34:26–34

We need to distinguish two hypotheses about the relationship between cannabis use and psychosis [1]. The strongest hypothesis is that heavy cannabis use causes a 'cannabis psychosis'. This hypothesis assumes that the psychosis would not occur in the absence of cannabis use and its causal role can be inferred from the symptoms and their relationship to cannabis use, for example, the onset of psychotic symptoms is preceded by heavy cannabis use and these symptoms remit after abstinence.

A weaker hypothesis is that cannabis use may precipitate an episode of schizophrenia. This hypothesis assumes that cannabis use is one factor among many others (including genetic predisposition and other unknown causes) that brings about schizophrenia. It does not assume that the role of cannabis can be inferred from the symptoms of the disorder, or that it will remit when cannabis use ceases. If cannabis use can precipitate schizophrenia it is also likely that it can exacerbate the symptoms of the disorder. However, cannabis use may exacerbate symptoms of schizophrenia (even if it is not a precipitant of the disorder) by reducing compliance with treatment or

* This paper was presented at the Cannabis and Psychosis Conference held in Melbourne, Australia, on 15–16 February 1999. An earlier more detailed version of this paper was published as: Hall W. Cannabis and psychosis. *Drug and Alcohol Review* 1998; 17:433–444.

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Received 25 June 1999; accepted 13 August 1999.

by interfering with the effects of the neuroleptic drugs used to treat its symptoms.

Making causal inferences

In order to infer that cannabis use is a cause of psychosis in any of these ways we need evidence that there is an association between cannabis use and psychosis, that chance is an unlikely explanation of the association, that cannabis use preceded the psychosis, and that plausible alternative explanations of the association can be excluded [2].

Evidence that cannabis use and psychosis are associated and that chance is an unlikely explanation of the association is readily available. There are a smaller number of prospective studies which show that cannabis use precedes psychoses. The most difficult task is excluding the hypothesis that the relationship between cannabis use and psychosis is due to other factors (e.g. other drug use, or a genetic predisposition to develop schizophrenia and use cannabis).

As ethical reasons limit experimental humans studies and there are no suitable animal models, epidemiological methods must be used to rule out common causal hypotheses. These estimate the relationship between cannabis use and the risk of developing a psychosis after adjusting for variables that may affect the risk (e.g. personal characteristics prior to using cannabis, family history of psychotic illness and other drug use). If the relationship persists after statistical adjustment, then we can be confident that it is not due to the variables for which statistical adjustment has been made.

'A cannabis psychosis'

There are a substantial number of case reports of cannabis psychoses [3–6]. These describe individuals who develop psychotic symptoms or disorders after using cannabis.

Chopra and Smith [4], for example, described 200 patients who were admitted to a psychiatric hospital in Calcutta between 1963 and 1968 with psychotic symptoms following the use of cannabis. The most common symptoms were 'sudden onset of confusion, generally associated with delusions, hallucinations (usually visual) and emotional lability…amnesia, disorientation, depersonalisation and paranoid symptoms'. Most psychoses were preceded by the ingestion of a large dose of cannabis and there was amnesia for the period between ingestion and hospitalisation. They argued that it was unlikely that excessive cannabis use was a sign of pre-existing psychopathology because one-third of their cases had no prior psychiatric history, the symptoms were remarkably uniform regardless of prior psychiatric history and those who used the most potent cannabis preparations experienced psychotic reactions after the shortest period of use.

The findings of Chopra and Smith have received some support from other smaller case series which suggest that large doses of potent cannabis products can be followed by a 'toxic' psychotic disorder with 'organic' features of amnesia and confusion. These disorders have been reported from the Caribbean [7], New Zealand [8], Scotland [6], South Africa [5], Sweden [3], the UK [9] and the USA [10].

These disorders have been attributed to cannabis use for combinations of reasons: the onset of the symptoms followed closely upon ingestion of large quantities of cannabis; the affected individuals often exhibited 'organic' symptoms such as confusion, disorientation and amnesia; some had no reported personal or family history of psychoses prior to using cannabis; their symptoms rapidly remitted after a period of enforced abstinence from cannabis use, usually within several days to several weeks; recovery was usually complete with the person having no residual psychotic symptoms of the type often seen in persons with schizophrenia; and if the disorder recurred it was after the individual started using cannabis again [11].

Some commentators [12,13] have criticised the poor quality of information on cannabis use and its relationship to the onset of psychosis, and of information on the person's premorbid adjustment and their family history of psychosis. They also emphasise the wide variety of clinical pictures of 'cannabis psychoses' reported by different observers. These weaknesses impair the evidential value of these case series.

Controlled studies

A small number of controlled studies have been conducted over the past 20 years [14–18]. Some case–control studies have either compared persons with 'cannabis psychoses' with persons who have schizophrenia, or compared psychoses occurring in persons who do and do not have biochemical evidence of cannabis use prior to presenting for treatment. Their results have differed, in part because of the small sample sizes in studies that have failed to replicate positive findings and because of variations in research methods.

Psychotic symptoms and cannabis use in community samples

Several studies have examined the relationship between cannabis use and psychotic symptoms in the general population. Tien and Anthony [19] used data from the Epidemiologic Catchment Area (ECA) study to compare the drug use of individuals who reported one or more 'psychotic experiences' during a 12-month period. These experiences consisted of four types of hallucinations and seven types of delusional belief. They compared 477 cases who reported one or more psychotic symptoms in the 1-year follow up with 1818 controls who did not. Cases and controls were matched for age and social and demographic characteristics. Daily cannabis use was found to double the risk of reporting psychotic symptoms (after statistical adjustment for alcohol use and psychiatric diagnoses at baseline).

Thomas [20] reported the prevalence of psychotic symptoms among cannabis users in a random sample of people drawn from the electoral role of a large city in the North Island of New Zealand. One in seven (14%) cannabis users reported 'strange, unpleasant experiences such as hearing voices or becoming convinced that someone is trying to harm you or that you are being persecuted' after using cannabis.

The National Survey of Mental Health and Wellbeing (NSMHWB) conducted in Australia in 1997 included a screening questionnaire for the presence of psychotic symptoms [21]. Among those under 50 years of age who screened positive for a psychotic disorder on a five-item scale, 12.6% (n = 13) met ICD-10 criteria for cannabis dependence in the past 12 months. (The scale was based on a cut-off point of three derived from ROC analyses; further information on the derivation of the cut-off point may be obtained from authors.) This constituted 6.5% of those under 50 years of age who were diagnosed with cannabis dependence. After adjusting for age, affective and anxiety disorders, smoking status and alcohol dependence, a diagnosis of cannabis dependence increased by 2.39 times the odds of reporting more than three psychotic symptoms (95% CI: 1.21–4.72).

Overall evaluation

The hypothesis that there is a 'cannabis psychosis' is still contentious. In its favour are the equivocal case series evidence and the small number of positive controlled studies. Critics of the hypothesis emphasise the fallibility of clinical judgments about aetiology, the poorly specified criteria used in diagnosing these psychoses, the dearth of controlled studies and the striking variations in the clinical features of 'cannabis psychoses' [22].

It is plausible that high doses of cannabis may produce psychotic symptoms but the evidence for a specific clinical syndrome that is identifiable as a 'cannabis psychoses' is much less compelling because the clinical symptoms reported by different observers have been so mixed. In many of these reports these symptoms rapidly remit, with full recovery, after abstinence from cannabis.

If cannabis-induced psychoses exist, they are either rare or they only rarely receive medical intervention in developed societies. The total number of cases of putative 'cannabis psychoses' in the 12 case series reviewed by Hall [11] was 397 and 200 of these came from a single series collected over 6 years from a large geographic area in which heavy cannabis use was endemic [4].

Cannabis use and schizophrenia

Clinical studies

In case–control studies (e.g. [23,24]), schizophrenic patients are more likely to have used psychotomimetic drugs such as amphetamines, cocaine and hallucinogens than other psychiatric patients or normal controls [25]. The prevalence of substance use in schizophrenic patients has varied between studies but it is generally higher than comparable figures in the general population [25]. These variations are probably due to differences in the sampling of patients, with younger newly incident cases reporting higher rates than older persons with chronic disorders. Studies have also differed in the criteria for diagnosing schizophrenia and in the way that substance use has been assessed [26].

Alcohol use abuse and dependence are probably more common in the schizophrenic population than in the general population [27] but findings on cannabis use have differed [11]. Generally, cannabis is the most commonly used drug after alcohol and tobacco, and it is often used with alcohol [26,28,29].

Correlates of cannabis use in schizophrenia

The controlled clinical studies disagree about the correlates of substance abuse in schizophrenia. Most have found that young men are over-represented

among cannabis users with schizophrenia [11], as they are in the general community [30]. In some studies, substance users have been reported to have an earlier onset of psychotic symptoms, a better premorbid adjustment, more episodes of illness and more hallucinations [29,31,32] but other well-controlled studies have failed to replicate some or all of these findings [33,34,35].

Population studies

Surveys of psychiatric disorders in the community have reported higher rates of substance abuse disorders among persons with schizophrenia. The ECA study found an association between schizophrenia and alcohol and drug abuse and dependence [36]. Nearly half of the patients identified as schizophrenic in the ECA study had a diagnosis of substance abuse or dependence (34% had an alcohol disorder and 28% had another drug disorder) [37]. These rates were higher than the rates in general population, which are 14% for alcohol disorders [38] and 6% for drug abuse [36]. The ECA findings have been replicated [39].

More recently, Cuffel *et al.* [33] have reported on patterns of substance use among 231 cases of schizophrenia identified in the ECA study. The most commonly used substances were alcohol (37%) and cannabis (23%), followed by stimulants and hallucinogens (13%), narcotics (10%) and sedatives (8%). The most common combination of drugs was alcohol and cannabis use (31%).

In the Australian NSMHWB, among those under 50 years of age who reported that they had received a diagnosis of schizophrenia, 17.8% met ICD-10 criteria for a cannabis use disorder in the past 12 months and 21.7% met criteria for an alcohol use disorder. After adjusting for the presence of affective and anxiety disorders, and for unemployment status, those who met criteria for a diagnosis of ICD-10 cannabis dependence were 2.9 times more likely to report that they had been diagnosed with schizophrenia than those without cannabis dependence (95% CI: 1.1–7.3).

Explanations of the association

One explanation is that cannabis use precipitates schizophrenic disorders in vulnerable persons. Proponents of this hypothesis cite the earlier age of onset of psychotic symptoms among cannabis users (with their drug use typically preceding the onset of symptoms), and the fact that they have better premorbid adjustment, fewer negative symptoms and a better treatment response [40].

Another possibility is that the association between cannabis use and an early onset and good prognosis are spurious. Arndt *et al.* [32] argued that persons with schizophrenia with a better premorbid personality are more likely to be exposed to illicit drug use among peers than persons with schizophrenia who are socially withdrawn. There is also evidence [41] that persons with acute onset psychoses usually have a better premorbid adjustment and a better prognosis. They also have greater opportunities to use cannabis and other illicit drugs than persons who have an insidious onset and are socially withdrawn.

A third possibility is that cannabis use is a consequence (rather than a cause) of schizophrenia. For example, cannabis and other drugs may be used to medicate the unpleasant symptoms of schizophrenia, such as depression, anxiety, lethargy and anhedonia, or the unpleasant side effects of the neuroleptic drugs that are often used to treat the disorder [31].

Precipitation of schizophrenia

The most convincing evidence that cannabis use may precipitate schizophrenia comes from a 15-year prospective study of cannabis use and schizophrenia in 50 465 Swedish conscripts [42]. This study investigated the relationship between self-reported cannabis use at age 18 and the risk of receiving a diagnosis of schizophrenia in the subsequent 15 years, as indicated by inclusion in the Swedish psychiatric case register.

Andreasson *et al.* [42] found that the relative risk of receiving a diagnosis of schizophrenia was 2.4 times higher among those who had tried cannabis by age 18 compared to those who had not. There was also a dose–response relationship between a diagnosis of schizophrenia and the number of times that cannabis had been used by age 18. Compared with those who had not used cannabis, the risk of developing schizophrenia was 1.3 times higher for those who had used cannabis on one to 10 occasions, three times higher for those who had used cannabis on between one and 50 occasions, and six times higher for those who had used cannabis more than 50 times.

These risks were substantially reduced after statistical adjustment for variables that were related to the risk of developing schizophrenia, namely, having a psychiatric diagnosis at conscription, and having parents who had divorced (as a proxy for parental

psychiatric disorder). Nevertheless, the relationship remained statistically significant after adjustment. Compared with those who had never used cannabis, the adjusted relative risk of a diagnosis of schizophrenia was 1.5 times greater for those who had smoked cannabis for one to 10 times, and 2.3 times greater for those who had used more than 10 times. Andreasson *et al.* [42] and Allebeck [40] have argued that this evidence shows that cannabis use precipitates schizophrenia in vulnerable individuals.

Other authors have offered a number of alternative explanations of the Swedish finding. First, there was a large temporal gap between self-reported cannabis use at age 18 and the development of schizophrenia over the next 15 years or so [43]. Because the diagnosis of schizophrenia was based on a case register, there were no data on how many individuals used cannabis up until the time that their schizophrenia was diagnosed. Andreasson *et al.* [42] argued that cannabis use persisted as a risk factor for schizophrenia because cannabis use at age 18 was also strongly related to the risk of attracting a diagnosis of drug abuse.

A second possibility is that schizophrenia was misdiagnosed. On this hypothesis, the excess rate of 'schizophrenia' among the heavy cannabis users was due to cannabis-induced psychoses which were mistakenly diagnosed as schizophrenia [43]. Andreasson *et al.* [44] examined 21 cases of schizophrenia among conscripts in the case register (eight of whom had used cannabis and 13 of whom had not). They found that 80% of these cases met the DSM-III requirement that the symptoms had been present for at least 6 months, thereby excluding the diagnoses of transient drug-induced psychotic symptoms.

A third hypothesis is that the relationship between cannabis use and schizophrenia is due to the use of other drugs. Longitudinal studies of illicit drug use have indicated that persons who had used cannabis a large number of times by late adolescence were at increased risk of subsequently using other illicit drugs, such as amphetamine [45]. Amphetamines that can produce an acute paranoid psychosis [46] were the major illicit drugs of abuse in Sweden during the study period [47]. On this hypothesis, amphetamine-induced psychoses may explain the spurious association between cannabis use and schizophrenia. The evidence that psychotic symptoms persisted beyond 6 months [44] would also seem to exclude this hypothesis, although it has been argued that chronic amphetamine use can produce a persistent psychosis [48].

A fourth hypothesis is that cannabis use at age 18 was a symptom of emerging schizophrenia. Andreasson *et al.* [44] rejected this hypothesis, noting that the cannabis users who developed schizophrenia had better premorbid personalities, a more abrupt onset and more positive symptoms than the non-users who developed schizophrenia. Moreover, although 58% of the heavy cannabis users had a psychiatric diagnosis at the time of conscription, there was still a dose–response relationship between cannabis use and schizophrenia among those who had no history. The persuasiveness of this evidence depends upon how confident we can be that a failure to identify a psychiatric disorder at conscription meant that no disorder was present.

A fifth hypothesis depends upon the validity of the self-reported cannabis use at conscription. Andreasson *et al.* [42] acknowledged that cannabis use was probably under-reported because this information was not collected anonymously. They argued, however, that this would produce an underestimate of the relationship between cannabis use and the risk of schizophrenia. This will be true if the schizophrenic and non-schizophrenic conscripts were equally likely to under-report. If, for example, pre-schizophrenic subjects were more candid about their drug use, then the apparent relationship between cannabis use and schizophrenia could be due to response bias [43]. This seems unlikely in view of the strong dose–response relationship between the frequency of cannabis use by age 18, and the large unadjusted relative risk of schizophrenia among heavy users.

Exacerbation of schizophrenia

Clinical reports suggest that schizophrenic patients who continue to use cannabis experience more psychotic symptoms [49], respond poorly to neuroleptic drugs [50] and have a worse clinical course than those patients who do not [51]. These reports have been supported by controlled studies.

Negrete *et al.* [52] conducted a restrospective study of the relationship between self-reported cannabis use and symptoms using clinical records in 137 patients with schizophrenia who had a disorder of at least 6 months duration. They compared the prevalence of hallucinations, delusions and hospitalisations among the active cannabis users with that among patients who had previously used cannabis, and those who had never used cannabis. There were higher rates of continuous hallucinations and delusions, and more hospitalisations among active

cannabis users. These relationships persisted after statistical adjustment for age and sex differences between the user groups.

Cleghorn *et al*. [53] compared the symptom profiles of schizophrenic patients with histories of substance abuse, among whom cannabis was the most heavily used drug. Drug abusers had a higher prevalence of hallucinations, delusions and positive symptoms than those who did not abuse drugs.

Jablensky *et al*. [54] reported a 2-year follow up of 1202 patients with first-episode schizophrenia enrolled in 10 countries as part of a World Health Organization (WHO) Collaborative study. They found that the use of 'street drugs', including cannabis and cocaine, during the follow-up period predicted more psychotic symptoms and periods of hospitalisation. Martinez-Arevalo *et al*. [55] also reported that continued use of cannabis during a 1-year follow up of 62 DSM-diagnosed patients with schizophrenia predicted a higher rate of relapse and poorer compliance with anti-psychotic drug treatment.

Linszen *et al*. [56] recently reported a prospective study of outcome in 93 psychotic patients whose symptoms were assessed monthly over 1 year. Twenty-four of their patients were cannabis abusers (11 were less than daily users and 13 were daily cannabis users). Despite the small sample sizes, they found that the cannabis users as a whole relapsed to psychotic symptoms sooner, and had more frequent relapses in the year of follow up, than the patients who had not used cannabis. There was also a dose–response relationship, with the daily users relapsing earlier and more often than the less than daily users who, in turn, relapsed sooner, and more often, than the patients who did not use cannabis. These relationships persisted after multivariate adjustment for premorbid adjustment, and alcohol and other drug use during the follow-up period.

The major cause of uncertainty about this relationship is assessing the contribution of confounding factors. It may be, for example, that the difference in psychotic symptoms between schizophrenia patients who do and do not use cannabis is due to differences in premorbid personality, family history and other characteristics. This is unlikely in the WHO schizophrenia study [54] and the Linszen *et al.* [56] study, both of which used multivariate statistical methods to adjust for many of these confounders.

The other difficulty is separating the contributions that cannabis and alcohol make to the exacerbation of schizophrenic symptoms. The concurrent use of alcohol is common, and the heavier their cannabis use, the more likely they are to use psychostimulants and hallucinogens [26]. Only the study of Linszen *et al.* [56] statistically adjusted for the effects of concurrent alcohol and drug use and found that the relationship persisted. Our confidence that the effect is attributable to cannabis would be increased by replications of the findings of Linszen *et al*. [56].

Intervention studies

If we could reduce cannabis use among patients with schizophrenia who use cannabis, then we could discover whether their disorders improved and their risk of relapse was substantially reduced. The major difficulty is that this presupposes that we can successfully treat substance abuse in persons with schizophrenia. Dependence on alcohol and other drugs is difficult to treat [57] and many persons with schizophrenia have characteristics that predict a poor treatment outcome, namely they lack social support, they may be cognitively impaired, they are unemployed and they do not comply with treatment [26,58].

There are very few controlled outcome studies of substance abuse treatment in patients with schizophrenia [59]. Few of these have produced large enough benefits of treatment, or treated a large enough number of patients, to provide an adequate chance of detecting any positive impacts of abstinence on the course of disorders. The few that have been large enough (for example, [60]) have not reported results separately by diagnosis.

Self-medication

The self-medication hypothesis is superficially plausible but the evidence in its favour is not very compelling. The reasons that most persons with schizophrenia give for using alcohol, cannabis and other illicit drugs are similar to those given by persons who do not have schizophrenia, namely, to relieve boredom, to provide stimulation, to feel good and to socialise with peers [26,61,62]. The drugs that are most often used by patients with schizophrenia are also those that are most readily available, namely tobacco, alcohol, and cannabis.

In favour of the self-medication hypothesis, is the evidence that some schizophrenic patients report using cannabis because its euphoric effects relieve negative symptoms and depression [23,31,63]. Dixon *et al.* [31], for example, surveyed 83 patients with schizophrenia who reported that cannabis reduced

anxiety and depression, and increased a sense of calm but at the cost of increased suspiciousness.

More recently, Hamera *et al.* [64] examined correlations over 84 consecutive days between self-reported psychotic symptoms, licit and illicit drug use and medication compliance in 17 persons with schizophrenia. They only found relationships between nicotine and prodromal psychotic symptoms and between caffeine use and symptoms of anxiety and depression but no relationships were found between psychotic symptoms and alcohol or cannabis use. This study does have limitations. The difficulty of the self-monitoring task probably selected patients who were more compliant and less disordered than a representative sample of schizophrenics. There were also relatively low rates of heavy drug use. The time period of 84 days may have been too short to examine the relationship between drug use and major exacerbations of the illness and the task of self-monitoring may have had reactive effects on drug use.

An overall evaluation

The epidemiological evidence most strongly supports the hypothesis that cannabis use exacerbates the symptoms of schizophrenia. This is supported by the findings of a number of retrospective and prospective studies that have controlled for confounding variables. It is also biologically plausible. Psychotic disorders involve disturbances in the dopamine neurotransmitter systems as evidenced by the fact that drugs that increase dopamine release produce psychotic symptoms when given in large doses and neuroleptic drugs that reduce psychotic symptoms also reduce dopamine levels [65]. Cannabinoids, such as tetrahydrocannabinol (THC), increase dopamine release [66].

It is also probable that cannabis use precipitates schizophrenia in persons who are vulnerable because of a personal or family history of schizophrenia. This hypothesis is consistent with the stress–diathesis model of schizophrenia [67,41] in which the likelihood of developing schizophrenia is the product of stress acting upon a genetic 'diathesis' to develop schizophrenia. Although plausible, there is very little direct evidence that genetic vulnerability increases the risk that cannabis users will develop psychosis. McGuire *et al.* [18] reported that persons with a history of heavy cannabis use who developed a psychosis were 10 times more likely to have a family history of schizophrenia than persons with a psychosis who had not used cannabis.

It is also difficult to identify a genetic diathesis in the majority of cases of schizophrenia. Having a first-degree relative (parent or sibling) who has schizophrenia increases the risks of developing the disorder between nine and 18 times [67]. But, according to Gottesman [67], 81% of persons with schizophrenia will not have a first-degree relative with the disorder, and 63% will not have an affected first- or second-degree relative.

The most contentious issue is whether cannabis use can cause schizophrenia that would not have occurred in its absence. Although one cannot rule out this hypothesis, if true it is unlikely to account for more than a minority of cases. Most of the 274 conscripts in the study of Andreassen *et al.* [42] who developed schizophrenia had not used cannabis. Only 21 of those who did develop schizophrenia were heavy cannabis users, and at most 7% of cases of schizophrenia could be attributed to cannabis use. Moreover, the treated incidence of schizophrenia, and particularly early onset, acute cases, declined (or remained stable) during the 1970s and 1980s [68] despite very substantial increases in cannabis use among young adults in Australia and North America [30]. Although there are complications in interpreting such trends [69], a large reduction in treated incidence of schizophrenia has been observed in a number of countries which have a high prevalence of cannabis use and in which the reduction is unlikely to be a diagnostic artefact [70].

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