CANNABINOIDS AND PSYCHOSIS

Deepak Cyril D'Souza

Department of Psychiatry, Yale University School of Medicine
VA Connecticut Healthcare System
West-Haven, Connecticut 06516, USA

I. Introduction
II. Ancedotal Reports
  A. Autobiographical Accounts
  B. Surveys of Cannabis Users
  C. Psychosis in Cannabis Users from Community Samples
  D. Naturalistic Case Series
III. Epidemiological Studies
IV. Pharmacological Studies
V. Cannabis and Psychosis: Causality
VI. Cannabinoid Receptor Dysfunction and Psychotic Disorders
VII. Summary and Conclusions
  References

Recent epidemiological studies and advances in understanding of brain cannabinoid function have renewed interest in the long-recognized association between cannabinoids and psychosis. This chapter presents evidence supporting and refuting the association between cannabinoids and psychosis. Cannabinoids can induce acute transient psychotic symptoms or an acute psychosis in some individuals. What makes some individuals vulnerable to cannabinoid-related psychosis is unclear. Also clear is that cannabinoids can also exacerbate psychosis in individuals with an established psychotic disorder, and these exacerbations may last beyond the period of intoxication. Less clear is whether cannabis *causes* a persistent *de novo* psychosis. The available evidence meets many but not all the criteria for causality, including dose–response, temporality, direction, specificity, and biological plausibility. On the other hand, the large majority of individuals exposed to cannabinoids do not experience psychosis or develop schizophrenia and the rates of schizophrenia have not increased commensurate with the increase in rates of cannabis use. Similar to smoking and lung cancer, it is more likely that cannabis exposure is a component cause that interacts with other factors, for example, genetic risk, to "cause" schizophrenia. Nevertheless, in the absence of known causes of schizophrenia, the role of component causes such as cannabis

INTERNATIONAL REVIEW OF
NEUROBIOLOGY, VOL. 78
DOI: 10.1016/S0074-7742(06)78010-2

exposure (exogenous hypothesis) is important and warrants further study. There is also tantalizing evidence from postmortem, neurochemical, and genetic studies suggesting CB1 receptor dysfunction (endogenous hypothesis) in schizophrenia that warrants further investigation. Further work is necessary to identify those factors that place individuals at higher risk for cannabinoid-related psychosis, to identify the biological mechanisms underlying the risks and to further study whether CB1 receptor dysfunction contributes to the pathophysiology of psychotic disorders.

I. Introduction

> . . . acute psychotic reactions, generally lasting but a few hours, but occasionally as long as a week; the reaction seemed dose related and its main features included paranoid ideation, illusions, hallucinations, delusions, depersonalization, confusion, restlessness and excitement. There can be delirium, disorientation and marked clouding of consciousness . . .
>
> In 'Du Haschisch et d l'alientation mentale' J. J. Moreau de Tours (1845) (Moreau, 1973).

An association between cannabis and psychosis has long been recognized. However, recent advances in the understanding of cannabinoid receptor function have renewed in the association between cannabis and psychosis. In addition to epidemiological studies, there are case reports of psychosis following cannabis use, reports of psychosis in surveys of cannabis users from community samples, and pharmacological studies with various cannabinoid compounds. These data are relevant to an exogenous hypothesis according to which the consumption of cannabinoid compounds is associated with psychotic disorders. We also suggest an endogenous hypothesis according to which brain cannabinoid receptor (CB1) dysfunction may contribute to the pathophysiology of psychosis and/or schizophrenia, and further, that the putative CB1 receptor dysfunction maybe unrelated to the consumption of cannabinoid compounds. These two hypotheses are by no means mutually exclusive, and may in fact interact.

The data supporting an association between cannabis consumption and the manifestation of psychotic symptoms in humans is now reviewed. However, a review of the literature will not be complete without a discussion about the constituents of cannabis. The principal active ingredient of cannabis is delta-9-tetrahydrocannabinol (Δ-9-THC). However, in addition to Δ-9-THC, herbal cannabis contains nearly 70 cannabinoid compounds, including cannabidiol (CBD), Δ-8-tetrahydrocannabinol, cannabinol, cannabigerol, and also terpenoids and flavonoids (Elsohly and Slade, 2005). These constituent compounds may modulate the effects of Δ-9-THC and may also have "entourage" effects (Mechoulam and Ben-Shabat, 1999; Russo and McPartland, 2003). The principal active metabolite of Δ-9-THC, 11-hydroxy-THC is more potent than Δ-9-THC. The time course of 11-hydroxy-THC blood levels correlates well with the psychological effects of

inhaled and oral Δ-9-HC reviewed in Agurell *et al.* (1986). CBD may offset some Δ-9-THC effects by its anxiolytic effects (Guimaraes *et al.*, 1994; Zuardi *et al.*, 1982), antipsychotic-like effects (Zuardi *et al.*, 1991, 1995, 2006), and may block the conversion of Δ-9-THC to the more psychoactive 11-hydroxy-THC (Bornheim *et al.*, 1995). Therefore, the net effect of herbal cannabis is a composite of its constituents. The CBD content of cannabis varies greatly and some samples of cannabis have been reported to be devoid of CBD (Pitts *et al.*, 1990, 1992). Thus, a relatively lower CBD content of cannabis has been implicated in the occurrence of psychotic and anxiety reactions with cannabis use (Solomons and Neppe, 1989; Solomons *et al.*, 1990). An example is South African cannabis, also known as dagga, which has very low levels of CBD compared to other varieties of cannabis obtained elsewhere. Naturalistic studies suggest an association between dagga consumption and high rates of psychotic symptom (Solomons and Neppe, 1989; Solomons *et al.*, 1990).

There are some data from studies with synthetic cannabinoids including dronabinol, nabilone, and levonantradol that are informative about the psychotic adverse effects of cannabinoids (Fig. 1). Dronabinol is synthetic Δ-9-THC. The 9-*trans*-ketocannabinoid Nabilone (Cesamet®) is a synthetic analogue of Δ-9-THC that was developed as an antiemetic and is available in Europe and Canada. Levonantradol, also a synthetic cannabinoid, was developed as an analgesic agent but abandoned because of a high incidence of intolerable behavioral side effects.

Evidence for an association between cannabis and psychosis comes from several sources, including case series of psychosis following cannabis use, autobiographical accounts, and surveys of cannabis users in the general population, epidemiological studies, and pharmacological studies with various cannabinoid compounds.

II. Ancedotal Reports

A. Autobiographical Accounts

There are several exquisitely detailed autobiographical accounts of the effects of cannabinoids. In perhaps one of the first detailed accounts of cannabis effects, Moreau de Tours (1845) described acute, transient, dose-related psychotic reactions lasting hours to days following hashish use (Moreau, 1973). The reaction was characterized by paranoid ideation, illusions, hallucinations, delusions, depersonalization, confusion, restlessness, and excitement. Among other effects of cannabis, Marshall described grandiosity ("my powers became superhuman, my knowledge of the universe was infinite, and so on") (Marshall, 1897). At higher doses he described disturbing hallucinations ("demons"). While informative, these individual accounts have limited generalizability.

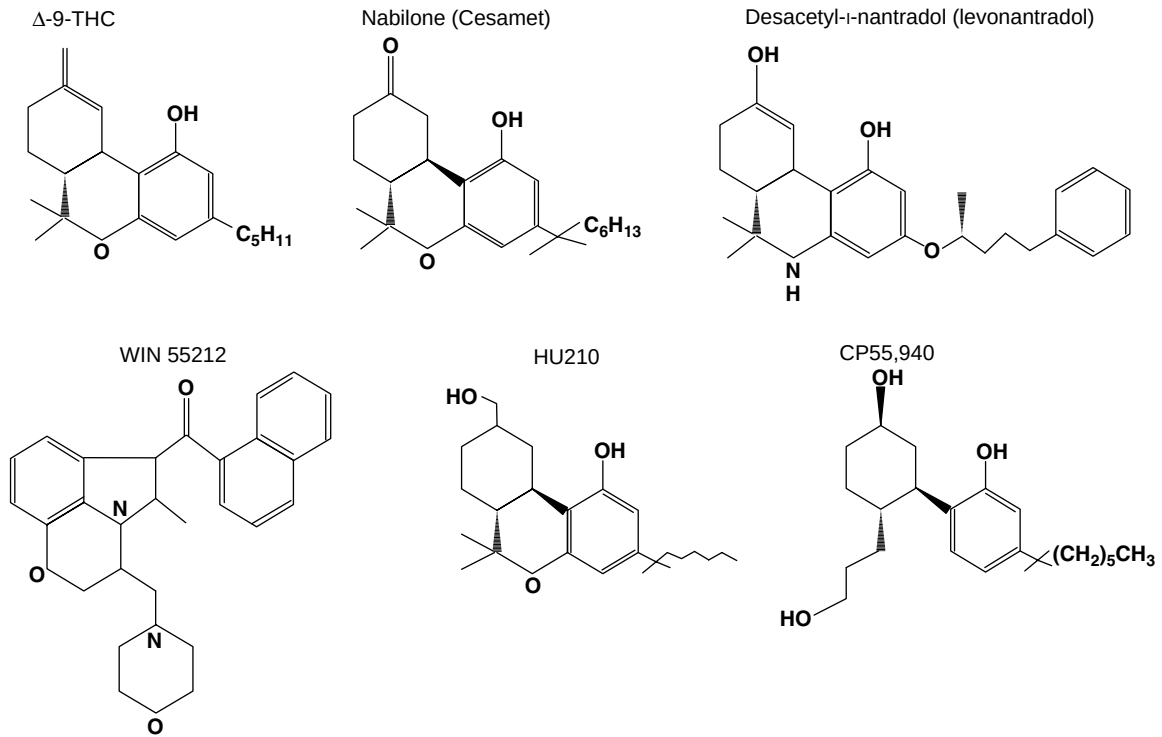

FIG. 1. Natural and synthetic cannabinoid receptor agonists.

B. Surveys of Cannabis Users

Some of the limitations of individual accounts can be addressed in surveys of large groups of cannabis users from community samples. Thomas surveyed 1000 New Zealanders aged 18–35 years about the effects of cannabis (Thomas, 1996). Thirty-eight percent of respondents admitted to cannabis use. The most common adverse effects included anxiety and panic attacks (22%) followed by psychotic symptoms such as auditory hallucinations and persecutory ideas (15%). A significant relationship between panic attacks and psychosis was found. However, the survey, failed to find a dose–response relationship between the levels of cannabis use and the occurrence of these symptoms. As discussed later, there are challenges to accurately estimate dose–response relationships from naturalistic data. In a study of young Australian cannabis users ($n = 268$), about 21% reported negative effects that included paranoia (Reilly *et al.*, 1998). Green *et al.* (2003) reviewed pooled data ($n > 2500$) from surveys of cannabis users that used closed questions and found that 51.4% of the sample reported paranoia whereas 19.8% reported hallucinations while under the influence of cannabis. Thus, psychotic symptoms are not uncommonly experienced under the influence of cannabis. However, survey data too have their limitations, including sampling bias, reliance on self-report, lack of structured scales to assess psychosis, lack of reliable dose–response data, and so on.

At this point, it would be important to make the distinction between a psychotic disorder and psychotic symptoms, since these terms are somewhat poorly defined in the literature. Psychotic disorder refers to a condition characterized by *persistent* psychotic symptoms accompanied by functional deficits. Further, most discussions associating cannabis and psychosis have referred mainly to positive symptoms (hallucinations, perceptual alterations, delusions, paranoia, ideas of reference, disorganized speech, and disorganized behavior). However, any discussion of schizophrenia would be incomplete without reference to negative symptoms (emotional withdrawal, blunted affect, amotivation, alogia, and social withdrawal) and cognitive deficits (deficits in memory, attention, and executive function). Furthermore, the inclusion of schizophrenia-spectrum conditions such as schizotypy makes for some interesting findings. Several groups have found higher scores on measures of schizotypy, positive psychotic symptoms, and perceptual alterations in cannabis users (Dumas *et al.*, 2002; Nunn *et al.*, 2001; Skosnik *et al.*, 2001). Verdoux *et al.* (2003c) studied the association between cannabis use and psychotic dimensions in a nonclinical sample (571 college students) 18–51 years of age and found an association between cannabis use and positive and negative dimensions of psychosis and a correlation between the frequency of use and intensity of symptoms. This relationship appeared to be specific for cannabis use as alcohol use was not associated with dimensions of psychosis. Further the association with cannabis use was specific to positive and negative symptoms of psychosis but not depression.

Another limitation of cross-sectional surveys is that they are not very informative on the direction of causality. Thus, cannabis use may be a consequence rather than a cause of psychosis or cannabis use and psychosis may be independently associated with some common risk factor(s). Prospective studies have addressed some of these limitations. Verdoux *et al.* (2003a) investigated the impact of cannabis use on the onset of psychotic experiences using an experience sampling method, a self-reported structured diary technique that has been validated as a method of collecting information on psychotic experiences in daily life. Subjects were instructed to respond to randomly programmed cues from a wristwatch to describe their present substance use and psychotic experiences five times a day over 7 consecutive days. There was a clear temporal relationship between cannabis use and the acute occurrence of psychotic-like abnormal perceptions.

C. Psychosis in Cannabis Users from Community Samples

Using data from the US Epidemiological Catchment Area (ECA) study, Tien and Anthony (1990) found that daily cannabis use doubled the risk of reporting psychotic symptoms after adjusting for baseline alcohol use and psychiatric diagnosis. Similarly, in the Australian National Survey of Mental Health and Well-Being, 17.2% of individuals diagnosed with cannabis dependence screened positive for a psychotic disorder (Degenhardt *et al.*, 2001).

D. Naturalistic Case Series

In a review, Hall and Degenhardt (2004) found 397 cases of "cannabis psychosis" reported in the literature. In perhaps the earliest case series, Chopra and Smith (1974) described 200 patients admitted to a psychiatric hospital in India for psychosis following cannabis use (Chopra, 1973; Chopra and Smith, 1974). The psychosis was typically preceded by ingestion of large doses of cannabis and was characterized by hallucinations, paranoia, delusions, depersonalization, emotional lability, amnesia, confusion, and disorientation. One-third of the patients reportedly had no previous psychiatric history, suggesting that the heavy cannabis abuse in these subjects was not a sign of preexisting psychopathology. Further, the use of more potent forms of cannabis, for example, hashish, was associated with a quicker onset of psychosis suggesting a dose–response. Similar case series have been reported from other geographical areas, including Denmark (Arendt *et al.*, 2005), Sweden (Bernhardson and Gunne, 1972), the Carribean (Harding and Knight, 1973), the United Kingdom (Carney *et al.*, 1984; Mathers *et al.*, 1991), the United States (Talbott and Teague, 1969b; Tennant and Groesbeck, 1972a), Scotland (Wylie *et al.*, 1995), and South Africa (Rottanburg *et al.*, 1982).

Most of the these studies suggest that psychotic episodes resolved completely when cannabis use stopped but recurred with the resumption of cannabis use reviewed in Hall and Solowij (1998) and typically resolved fairly quickly in comparison with endogenous psychoses (Basu *et al.*, 1999; Carney *et al.*, 1984; Chaudry *et al.*, 1991; Cohen, 1994; Kolansky and Moore, 1971a; Rottanburg *et al.*, 1982; Talbott and Teague, 1969a; Thacore, 1973; Thacore and Shukla, 1976; Wylie *et al.*, 1995). Further, some studies suggested that patients with preexisting mental problems had a less favorable outcome (Bernhardson and Gunne, 1972; Bromberg, 1939; Chopra and Smith, 1974; Palsson *et al.*, 1982; Tennant and Groesbeck, 1972b).

In most of the studies discussed thus far, cases/patients were followed no greater than 3 months after remission of psychosis and hence, long-term outcome of these cases could not be conclusively determined. Arendt *et al.* (2005) reported the long-term outcome of a cohort of patients treated for cannabis-induced psychotic disorder extracted from the Danish Psychiatric Central Register. All patients treated for ICD-10 cannabis-induced psychotic disorder between 1994 and 1999 who had never been previously treated for psychosis ($n = 535$) *were* examined for the development of schizophrenia-spectrum disorder in the ensuing years (Table I). Schizophrenia-spectrum disorders were diagnosed in 44.5% of the sample. When the diagnosis was broadened to include new psychotic episodes of *any* type, the diagnosed sample increased to 77.2%. Further, only 15.9% of individuals were not in psychiatric care at the time of long-term follow-up. About half of the patients received the diagnosis of schizophrenia-spectrum disorder more than a year after seeking treatment for a cannabis-induced psychosis. The patients had an earlier age of onset of schizophrenia compared to a control group without a history of cannabis-induced psychosis. This study is the first to show that such psychotic symptoms induced by cannabis may be the first manifestations of a long-term psychotic disorder such as a schizophrenia-spectrum disorder.

These case series have some shortcomings. First, it is possible that the individuals who developed psychosis after using cannabis were not "healthy" and carried some risk for developing a psychotic disorder. Here, it is important to point out that other than family history there are no other known risks factors that are either specific and/or sensitive predictors of the future development of a psychotic disorder. Further, even though having a first-degree relative diagnosed with schizophrenia increases the risk of developing schizophrenia by 9–18 times, more than 80% of individuals diagnosed with schizophrenia do not have an affected first-degree relative and over 60% do not have an affected first- *or* second-degree relative (Gottesman and Shields, 1982). As discussed later, genetic factors may influence the risk of psychosis associated with cannabis exposure (Caspi *et al.*, 2005). Second, since individuals who use cannabis often co-use other drugs, it is unclear whether the use of other drugs contributed to the development

TABLE I
RISK OF MENTAL ILLNESS FOLLOWING HOSPITALIZATION FOR CANNABIS-INDUCED PSYCHOSIS PATIENTS TREATED FOR MENTAL OR BEHAVIORAL DISORDERS AFTER INDEX POINT ($N = 535$)

Diagnosis[a]	Within 3 years *n* (%)	After 3 years *n* (%)	Total follow-up *n* (%)
Schizophrenia-spectrum disorder[b]	197 (36.8)	41 (7.7)	238 (44.5)
Persistent delusional disorder (F22)	18 (3.4)	4 (0.7)	22 (4.1)
Other or non-organic psychotic disorder (F28/F29)	5 (0.9)	3 (0.6)	8 (1.5)
Bipolar affective disorder	12 (2.2)	6 (1.1)	18 (3.4)
Acute and transient psychotic disorder	28 (5.2)	7 (1.3)	35 (6.5)
Cannabis-induced psychosis	78 (14.6)	1 (0.2)	79 (14.8)
Other drug-induced psychosis	11 (2.1)	2 (0.4)	13 (2.4)
Depression, anxiety or personality disorder	29 (5.4)	8 (1.5)	37 (6.9)
No treatment			85 (15.9)
Total			535 (100)

[a]Patients are entered only once, in a hierarchical manner as described in the method section.
[b]Schizophrenia (ICD–10 code F20), schizotypal disorder (F21) or schizoaffective disorder (F25).

of psychosis. Third, only a minority of case series studies employed standardized measures of psychosis. Fourth, the amount of cannabis use preceding the psychotic episode was not quantified limiting any speculation about dose–response relationships. In contrast, the temporal relationship between cannabis use and psychosis, the fact that psychosis resolved with abstinence from the drug and recurred with renewed use, lends support to the notion that the relationship between cannabis exposure and the development of psychosis is not merely coincidental.

On the basis of some similarities between the phenomenology of psychosis associated with cannabis use and the psychosis of schizophrenia, some (Chaudry *et al.*, 1991; Ghodse, 1986; Mathers *et al.*, 1991; Rolfe *et al.*, 1993; Rottanburg *et al.*, 1982; Thacore, 1973; Thacore and Shukla, 1976) but not others (Hall and Degenhardt, 2004; Imade and Ebie, 1991; McGuire *et al.*, 1994, 1995; Thomas, 1993; Thornicroft, 1990) have argued for the inclusion of "cannabis psychosis" as a distinct nosological entity. Arguments challenging the validity of "cannabis psychosis" as a distinct diagnostic entity should not be confused with the debate on the association between cannabis and psychosis.

As mentioned earlier, it is difficult to derive dose–response relationships from naturalistic data for a number of reasons. The reliability of self-reported, long-term, retrospective estimates of cannabis use is unclear. Individuals who use cannabis will often share a "joint" with one or more individuals, thus estimating

the dose consumed by the individual may be difficult. Cannabis is consumed in many different ways, for example, "joints," "bongs," and so on, which are not equivalent. The estimates of the number of lifetime exposures cannot accurately reflect the actual dose of Δ-9-THC that is consumed. Finally, the Δ-9-THC content of cannabis varies greatly. The Potency Monitoring program, a collaboration between the University of Mississippi and the National Institute on Drug Abuse (NIDA), provides analytical data about the potency of confiscated marijuana seized in the United States. In the most recent report covering the last 10 years on ∼30,000 cannabis samples, 207 hashish samples, and 86 hash oil samples there appears to be an upward trend in the average THC content of confiscated cannabis (Mehmedic *et al.*, 2005). The Δ-9-THC content of cannabis doubled from 3.48% in 1994 to 7.08% in 2004. While there was no consistent increase in Δ-9-THC content in hashish samples from 1994 to 1999, the average potency of hashish samples increased from 4.16% Δ-9-THC in 2000 to 11.2% in 2004. No potency trends were observed for hash oil samples. Finally, there was no change in the average levels of the other cannabinoids (CBD, CBC, CBG, and CBN) in the cannabis samples over the reported time frame. Similarly, the average Δ-9-THC content of Dutch cannabis, Dutch hashish, and imported hashish has significantly increased between 1999 and 2005 (Niesink *et al.*, 2005). For example, in 2005, the average Δ-9-THC content of Dutch home-grown cannabis (Nederwiet) was 17.73%, and was nearly three times higher than that of imported cannabis (6.7% Δ-9-THC). Dutch hashish (Nederhasj) contained 26% Δ-9-THC in 2005, compared with 16.9% THC in imported hashish. In summary, deriving accurate dose–response from naturalistic data may have significant limitations.

III. Epidemiological Studies

Epidemiological studies have provided *the* major contribution to the evidence supporting an association between cannabis and psychosis (Table II). The study that first brought significant attention to the topic was a large historical, longitudinal cohort study of all Swedes conscripted between 1969 and 1970 (Andreasson *et al.*, 1987). Since Sweden mandates military service, 97% of males aged 18–20 years were included. The relationship between self-reported cannabis use at the time of conscription and psychiatric hospitalization for schizophrenia in the ensuing 15 years was examined. A dose–response relationship was observed between cannabis use at conscription (age 18 years) and schizophrenia diagnosis in the following 15 years. Individuals who reported having used cannabis more than 50 times were 6 times more likely than nonusers to have been diagnosed with schizophrenia 15 years later. Adjusting for other relevant risk factors including

TABLE II
EPIDEMIOLOGICAL STUDIES

References	*N*	Design	Instrument	Age range at f/u (years)	Outcome		Adjusted Risk
Arendt *et al.* 2005	535	Longitudinal follow up of cannabis-induced psychosis (Denmark)	Registry	Not specified (estimated as 32 years)	New psychotic episode of any type diagnosed in 77.2%. Schizophrenia-spectrum disorders diagnosed in 44.5% Earlier onset of schizophrenia		–
Ferdinand *et al.* 2005	1580	Prospective cohort (The Netherlands)	CIDI CBCL	18–30	Psychotic symptoms	Lifetime CB use	2.8
Henquet *et al.* 2005	2437	Prospective cohort (Germany)	M-CIDI	18.3–21.8	Any psychotic symptom	Lifetime CB use	1.7
Stefanis *et al.* 2004	3500	Cross-sectional cohort of adolescents (Greece)	CAPE PDI	18	Positive and negative symptoms	Lifetime CB use until age 19 years	4.3
Fergusson, 2003	1011	Birth cohort (Christchurch)	SCL90	21	Psychotic symptoms	DSM-IV CB dependence at 21 years	1.8
Arseneault *et al.* 2002	759	Longitudinal, prospective, birth cohort (Dunedin)	DSM-IV	26	Schizophrenia and schizophreniform disorders	Lifetime CB use until age 15 and 18 years	3.12
Weiser *et al.* 2002	50,413	Longitudinal conscript cohort (Israel)	registry	4–15	Hospitalization for schizophrenia	Lifetime drug use at 16–17 years	2
van Os *et al.* 2002	4095	Longitudinal population-based 3 year follow-up (The Netherlands)	CIDI, SCID	18–64	Any psychotic symptoms	Lifetime CB use at 16–17 years	2.76
Zammit *et al.* 2002	50,053	Longitudinal conscript cohort (Sweden)	Registry	45–47	Hospitalization for schizophrenia	>50 exposures to CB at age 18 years	3.1
Andreasson *et al.* 1987	45,570	Longitudinal conscript cohort (Sweden)	Registry	33–35	Hospitalization for schizophrenia	>50 exposures to CB at age 18 years	2.3

psychiatric diagnosis other than psychosis at conscription reduced but did not eliminate the higher risk (odds ratio = 2.3) of schizophrenia conferred by cannabis use.

A reanalysis and extension of the same Swedish conscript cohort reconfirmed that heavy cannabis users by the age of 18 years were 6.7 times more likely than nonusers to be hospitalized for schizophrenia in the following 27 years (Zammit *et al.*, 2002). This study addressed the confounding effects of concomitant use of other drugs of abuse, premorbid personality traits, and cannabis use as a form of self-medication of schizophrenia. The adjusted odds ratio for cannabis use and schizophrenia remained significant (1.2), despite adjusting for a number of confounds, including low IQ, urbanicity, cigarette smoking, poor social integration, function, and stimulant use. Further, after controlling for the possibility that cannabis use is a consequence of prodromal manifestations of psychosis by excluding subjects who developed schizophrenia within 5 years of conscription, the finding of an increased risk of schizophrenia conferred by cannabis use persisted. The authors concluded that cannabis use was associated in a causal way with an increased risk of developing schizophrenia and that 13% of cases of schizophrenia would be averted if cannabis use were prevented.

The historical studies have been complemented by a number of recent prospective cohort studies. In a general population birth cohort study of 1037 people born in Dunedin, New Zealand, and followed through until age 26 years, cannabis use conferred a higher risk for the subsequent development of schizophrenia (Arseneault *et al.*, 2002). One of the strengths of this study was that it collected data on self-reported psychotic symptoms at age 11 years, that is, to address whether psychosis preceded cannabis use. Self-reported cannabis at both ages 15 and 18 years use was also collected. Further, the entire sample was assessed at age 26 years using a standardized psychiatric interview that allowed the determination of both schizophrenia symptoms and disorder. Compared to nonusers, individuals using cannabis at ages 15 and 18 years had higher rates of psychotic symptoms and schizophreniform disorder at age 26 years, even after controlling for psychotic symptoms pre-dating the onset of cannabis use. Cannabis users at age 15 years had a higher rate (OR = 3.1) of developing schizophreniform disorder at age 26 years, even after controlling for psychotic symptoms pre-dating the onset of cannabis use (Fig. 2).

In The Netherlands Mental Health Survey and Incidence Study (NEMESIS), 4045 psychosis-free individuals and 59 individuals with a psychotic disorder were assessed at baseline, 1 and 3 years (van Os *et al.*, 2002) using a measure of psychosis. Individuals using cannabis at baseline were nearly three times more likely to manifest psychotic symptoms at follow-up even after adjustment for a range of factors. Further, a dose–response relationship was established with the highest risk (odds ratio = 6.8) for the highest level of cannabis use. The relationship between cannabis use and psychotic symptoms was stronger for cases with

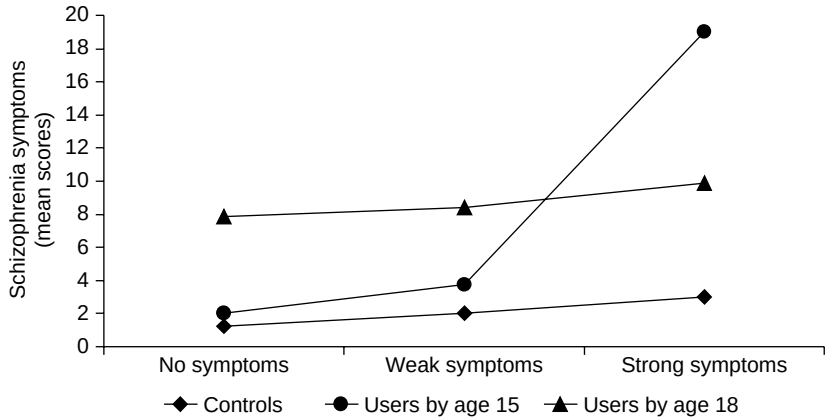

FIG. 2. Interaction between cannabis use at age 18 and psychotic symptoms at age 11 in predicting schizophrenia symptoms.

more severe psychotic symptoms. Individuals who reported psychotic symptoms at baseline were also more likely to develop schizophrenia if they used cannabis than were individuals who did not. The attributable risk of cannabis to psychosis was estimated at 13% for psychotic symptoms and 50% for cases with psychotic disorders that required psychiatric treatment.

Henquet *et al.* (2005) studied the relation between cannabis use and psychotic symptoms in individuals at risk for psychosis who first used cannabis during adolescence.

They tracked 2437 subjects (14–24 years) with and without risk for psychosis from the general population for 4 years and found a dose-dependent increased risk of psychosis in subjects exposed to cannabis (Henquet *et al.*, 2005). Interestingly, predisposition to psychosis was not found to be a predictor of future cannabis use at 4-year follow up. Adding to these studies, Stefanis *et. al.* (2004) reported that both positive and negative symptoms can be induced by cannabis consumption and are independent of each other. Finally, a number of cohort studies have reported a dose–response relationship in the increased risk of psychosis with cannabis exposure (Ferdinand *et al.*, 2005; Fergusson *et al.*, 2003; Henquet *et al.*, 2005; Stefanis *et al.*, 2004; van Os *et al.*, 2002; Weiser *et al.*, 2002).

Collectively, these epidemiological studies suggest that cannabis use may confer a nearly twofold higher risk for developing schizophrenia. This increased risk is comparable to the better known associations, such as the risk conferred by cigarette smoking in the development of lung cancer and the risk of heart disease from hypercholesterolemia.

Temporal relationship between cannabis use and the onset of schizophrenia: The onset of cannabis use may precede, follow, or co-occur with the onset of schizophrenia. However, schizophrenia begins insidiously, and evolves through several identifiable stages with the emergence of psychotic symptoms as the final step in the evolution of the disorder. As a result, while it maybe easy to pinpoint the emergence of positive psychotic symptoms in retrospective studies, pinpointing the onset of the less obvious prodromal symptoms is extremely challenging. Thus, while there is evidence suggesting a temporal association between cannabis use and the onset of positive psychotic symptoms, the temporal relationship between cannabis use and the less obvious symptoms has not been studied. Further, if as the neurodevelopmental hypothesis posits, that the pathophysiological processes underlying the illness precede the clinical manifestations by years or even decades and that these processes may even begin *in utero*, then, the argument about a temporal relationship is no longer relevant.

Nevertheless, there are a few studies that have systematically investigated the temporal order of cannabis use and the onset of schizophrenia. Allebeck and colleagues reported that in 69% of a schizophrenic patient sample from a Swedish case registry ($n = 112$), cannabis abuse preceded the onset of psychotic symptoms by at least 1 year (Allebeck *et al.*, 1993b). Further, in only 11% did the onset of psychotic symptoms precede the onset of cannabis abuse. Similarly, Linszen *et al.* (1994) found that cannabis abuse preceded the onset of psychotic symptoms by at least 1 year in 23 of 24 cannabis-abusing recent onset schizophrenic patients. Hambrecht and Hafner (1996, 2000) in their study of first-episode schizophrenic patients found that 14.2% of the sample had a lifetime history of drug abuse with cannabis being the most frequently abused drug (88%). Furthermore, drug abuse preceded the first sign of schizophrenia by more than a year but typically by more than 5 years in 27.5% of patients. In 37.9% of individuals, drug abuse followed the first sign of schizophrenia, and in 34.6% of individuals the first sign of schizophrenia and drug abuse started within the same month.

Effects of cannabis in individuals at high risk for developing schizophrenia: Another way to assess the risk of psychosis conferred by cannabis exposure is by studying the effects of cannabis in individuals at high risk for developing schizophrenia. In the Edinburgh High Risk study, individuals with a high genetic risk of schizophrenia, as evidenced by two or more affected relatives, cannabis use increased the risk for psychosis (Miller *et al.*, 2001). Furthermore, frequent cannabis use conferred a sixfold higher risk of schizophrenia in individuals with a family history of schizophrenia. In contrast, cannabis use or dependence in the previous year was not associated with a heightened risk of developing psychosis over the following 12-month period in a group of individuals at ultrahigh risk for developing schizophrenia (Phillips *et al.*, 2002). While the authors concluded that cannabis use did not appear to contribute to the onset of psychosis, they acknowledged

several limitations to the study design, including a low level of cannabis use in the sample and the lack of monitoring of cannabis use.

Cannabis is associated with an earlier onset of psychotic symptoms in schizophrenia: Some studies suggest that cannabis and other substance use is associated with an earlier age of and more abrupt onset of psychotic symptoms in schizophrenic patients (Addington and Addington, 1998; Allebeck *et al.*, 1993a; Andreasson *et al.*, 1987, 1989; Cleghorn *et al.*, 1991; Green *et al.*, 2004; Hambrecht and Hafner, 1996; Linszen *et al.*, 1994; McGuire *et al.*, 1994; Van Mastrigt *et al.*, 2004; Veen *et al.*, 2004).

Parallels in the association between amphetamines and psychosis and cannabis and psychosis: At this juncture, it would be illustrative to review an older but relevant story about the association between cannabis and psychosis. As early as 1938, Young and Scoville first reported an association between amphetamine use and psychosis. Nearly 20 years later, in a seminal report of 42 cases, Connell (1958) reported that high-dose amphetamine use by amphetamine addicts was associated with a florid psychosis. Despite some supporting data (dose–response, temporal association, and phenomenological similarities), there was considerable skepticism about the suggested association between amphetamines and psychosis as reviewed in (D'Souza *et al.*, 1999). First, it was not possible to determine whether amphetamine precipitated latent psychosis or *de novo* psychosis. Second, at the time "thought disorder," which was not a prominent feature described in early reports of amphetamine psychosis, was believed to be fundamental to and diagnostic of schizophrenia in American Psychiatry. Third, the prevailing diagnostic criteria of schizophrenia were poorly defined. Fourth, the role of sleep deprivation induced by amphetamines, in the development of amphetamine psychosis could not be excluded. Finally, it was unclear whether other drugs (sedative hypnotics, marijuana, and hallucinogens) taken along with amphetamines may have contributed to the development of psychosis in amphetamine abusers reviewed in (D'Souza *et al.*, 1999).

Prospective, controlled pharmacological studies with amphetamine provided critical support for the early DA hypothesis by addressing the limitations of naturalistic studies. In a series of studies, amphetamine loading was shown to induce psychosis in nonschizophrenic volunteers that spontaneously resolved (Angrist and Gershon, 1970; Angrist *et al.*, 1971; Bell, 1965, 1973; Griffith *et al.*, 1972). Drawing a parallel, pharmacological studies with cannabinoids address some of the limitations of naturalistic data similar to pharmacological studies with amphetamines. In particular, pharmacological studies offer the advantages of providing more accurate dose–response data, a sample carefully screened for preexisting illness, a more precise estimation of temporality and control of various confounds. While there are several reports of pharmacological studies with cannabinoids in humans, most of the studies were not specifically designed to study psychosis.

IV. Pharmacological Studies

In order to better interpret the pharmacological studies, it would be essential to understand some of the pharmacokinetic issues relevant to cannabis and Δ-9-THC. The pharmacokinetics and effects of Δ-9-THC vary as a function of route of administration. Herbal cannabis and cannabinoid compounds are typically consumed during recreational use by the inhaled or oral route. However, cannabinoids have also been administered for therapeutic or experimental purposes by the intravenous, rectal, sublingual, transdermal, topical (eye drops), and aerosolized route. Δ-9-THC administered by inhalation results in peak plasma concentrations within minutes, with psychotropic effects starting within seconds to a few minutes, reaching a peak after 15–30 min, and then tapering off within 2–3 h (Fig. 3). In attempting to quantify the dose of Δ-9-THC extracted from a typical cannabis joint several factors need to be considered including, but not limited to, the weight of a cannabis joint, the potency of Δ-9-THC in the herbal cannabis preparation, and the presence of other cannabinoids in herbal cannabis that might contribute to the effects of cannabis and/or alter the effects of Δ-9-THC (Karniol and Carlini, 1973; Karniol *et al.*, 1974, 1975; Turner *et al.*, 1980). Further, the amount of THC delivered is influenced by several factors, including the rate of inhalation, depth of puffs, duration of puffs, volume inhaled, extent of breath-holding after inhalation,

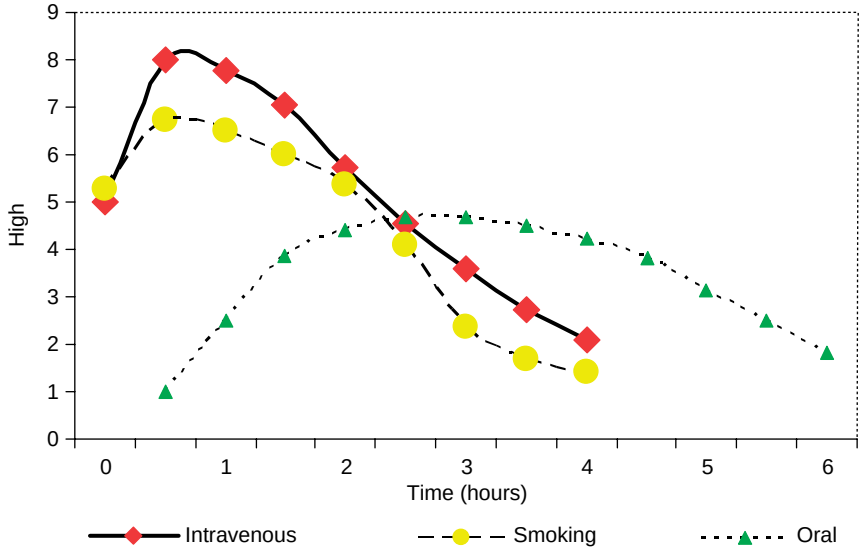

FIG. 3. Time course of subjective effects according to route of administration.

amount lost by smoke escaping into the air or respiratory dead space, vital capacity, length of cigarette smoked, adeptness of smoking, and subject's overall experience in titrating the dose. In fact, only 10–25% of the Δ-9-THC content of a cannabis joint enters the circulation when smoked (Adams and Martin, 1996). Thus, quantifying the typical dose of Δ-9-THC that a typical cannabis joint delivers is not without challenges. Intravenous dosing follows the pharmacokinetics of the inhaled route, though blood levels tend to be higher. Following oral ingestion, psychotropic effects set in with a delay of 30–90 min, reach their maximum after 2–3 h, and last for about 4–12 h (Hollister *et al.*, 1981; Ohlsson *et al.*, 1980, 1981). Nabilone is administered by oral route while levonantradol is administered by intramuscular route.

Psychosis associated with the consumption of medicinal cannabinoids: Cannabinoids including cannabis, natural and synthetic Δ-9-THC, nabilone, and levonantradol have been used in the treatment of chemotherapy-induced nausea, spasticity in multiple sclerosis, pain syndromes, glaucoma, stimulation of appetite, Tourette's syndrome, parkinsonism, dyskinesia, and traumatic brain injury. Adverse events causally linked to Marinol that occurred at >1% in the clinical trials included hallucinations, abnormal thinking, paranoid reaction, amnesia, and so on, all of which are symptoms of psychosis (Marinol Product monograph). Further, the incidence of "disturbing" psychiatric reactions increased with dose escalation. Similarly, studies with oral and intramuscular levonantradol have reported "loss of control," hallucinations, other perceptual alterations, thought disturbance, feelings of unreality, fear and paranoia, apprehension, difficulty concentrating, dissociation, depersonalization, dysphoria, anxiety, and panic (Citron *et al.*, 1985; Cronin *et al.*, 1981; Diasio *et al.*, 1981; Heim *et al.*, 1981, 1984; Jain *et al.*, 1981; Kenny and Wilkinson, 1982; Laszlo *et al.*, 1981; Sheidler *et al.*, 1984; Stuart-Harris *et al.*, 1983). Psychotropic adverse effects increased both with increasing dose and with repeated dosing (Citron *et al.*, 1985; Stambaugh *et al.*, 1984). Further, some subjects refused further testing because of the disturbing psychotropic effects. Nabilone (CESAMET^{TM}) was developed by Eli Lilly and marketed in Europe as an analgesic agent. A "toxic psychosis" has been reported as one of its side effects.

In a systematic review of randomized controlled trials comparing the antiemetic effects of cannabinoids with placebo or other antiemetics, 6% of patients receiving cannabinoids presented with hallucinations and 5% with "paranoia," while no patient treated with control drugs presented with such side effects (Tramer *et al.*, 2001). The same group conducted a systematic review of randomized controlled trials comparing the analgesic effects cannabinoids with placebo or other analgesics (codeine and benzopyranoperidine), but they did not specifically mention psychotic symptoms (Campbell *et al.*, 2001).

Experimental studies: There are a small number of pharmacological studies that were specifically designed to examine the behavioral and/or cognitive effects of

cannabinoids. As far back as the 1940s, pharmacological investigations were conducted under the direction of the "LaGuardia Committee on Marihuana" (Mayor's, 1944). With cannabis doses of about 30–50 mg (oral) and 8–30 mg (smoked), 12.5% of subjects experienced psychotic reactions. However, these subjects were prisoners and their mental status cannot be presumed to be healthy. Ames (1958) studied the effects of unassayed oral doses of cannabis extract (about 50–70 g Δ-9-THC) in 12 medical house staff who were presumably healthy. Subjects reported immediate recall deficits, thought fragmentation, dissociation between thoughts and action, disturbed temporal and spatial perception, visual illusions and hallucinations, derealization and depersonalization, mood alterations, and anxiety. Some subjects reported delusions of the presence of hidden recorders, fear of being hypnotized, fear of ECT, and fear of developing schizophrenia. One subject refused to answer questions for fear of being certified as insane. Isbell and colleagues (1967) studied the effects of varying doses of Δ-9-THC (120–480 μg/kg orally and 50–250 μg/kg smoked) in 40 former opiate addicts. At Δ-9-THC 120 μg/kg orally and 50 μg/kg smoking, in addition to recognizing the effects as being similar to marijuana, the subjects reported alterations in visual, auditory, and time perception. However, at Δ-9-THC doses of 300–480 μg/kg orally and 200–250 μg/kg by smoking there were marked auditory and visual distortions, depersonalization, derealization, and hallucinations. Of note, "occasional" individuals experienced psychosis even at low doses of Δ-9-THC. In a related study, Isbell and Jasinski (1969) compared the effects of Δ-9-THC (75–225 μg/kg, smoked) and LSD (0.5–1.5) in 10 "normal" controls. Both drugs produced perceptual distortions, mood changes, and at higher doses hallucinations. Of note, two subjects dropped out from the study after experiencing psychotic "reactions" from Δ-9-THC. However, Hollister showed that Δ-9-THC was not associated with as prominent psychotomimetic effects as LSD (reviewed in Hollister, 1986).

Melges *et al.* (1970) in a double-blind, placebo-controlled study with high and low dose Δ-9-THC reported that cannabis users were noted to have core symptoms of psychosis, including thought disorder and paranoia. The authors specifically described "tracking difficulties" that subjects reported, including racing thoughts, thought blocking, losing their train of thought, and so on. Jones and Stone (1970) did not observe robust psychotomimetic effects in studies of "normal" controls with Δ-9-THC (20 mg smoked or 40 mg orally). However, a few subjects reported ideas of reference and delusions that the researcher was using secret (unexplained) tests and hidden recording devices. At doses higher than 20 mg smoked or 40 mg orally, psychotomimetic effects including delusions, loosening of associations, and marked illusions began to emerge. In a ^{18}F-2-fluoro-2-deoxyglucose positron emission tomography (FDG-PET) study of intravenous Δ-9-THC (2 mg) on regional brain metabolism, two of eight healthy subjects who occasionally used cannabis, experienced paranoid-anxious reactions (Volkow *et al.*, 1991).

The pharmacological studies discussed thus far had several limitations, including the absence of placebo/control, lack of a double-blind, inclusion of psychiatrically ill individuals, and lack of standardized measures of psychosis. Recently, there have been a few laboratory studies examining the psychotogenic effects of cannabinoids that address some of these limitations.

Leweke *et al.* (1999b) reported the effects of synthetic Δ-9-THC (120 μg/kg) by oral route in 17 healthy individuals under controlled laboratory conditions. The study included subjects with past experience but no recent consumption of cannabinoids. The overall lifetime consumption of cannabinoids was limited to 10 times to exclude the long-term effects of cannabis use. Subjects with a history of recurrent abuse of illicit drugs other than cannabinoids or other psychiatric disorders were excluded. The primary outcome measure was binocular depth perception which has described as a model of illusionary perception. While the study was not placebo controlled, subjects were told that they might receive a placebo or active drug, but in fact they always received active drug. Subjective reactions ranged from mild euphoria to more pronounced reactions, including feelings of loss of self-control and body distortion suggestive of psychotic-like symptoms. One subject experienced a transient psychotic episode described as "a paranoid psychotic state with persecutory delusions, delusions of thought insertion, attentional irritability, fear, and—to some extent—verbal aggressive behavior." These symptoms resolved spontaneously within minutes to hours. Leweke *et al.* (2000) repeated the study with nabilone, a synthetic analogue of Δ-9-THC, and observed effects on binocular depth inversion similar that of Δ-9-THC (Leweke *et al.*, 2000).

D'Souza *et al.* (2004) characterized the behavioral and cognitive effects of Δ-9-THC in a double-blind, placebo-controlled study of healthy controls ($n = 22$). Only subjects with past cannabis experience but without lifetime cannabis abuse or dependence were included. Healthy subjects also underwent a Structured Clinical Interview for DSM-IV (healthy) and an unstructured psychiatric evaluation. Subjects were excluded if they had any significant psychiatric disorder and/or a family history of any DSM Axis I disorder. Subjects received in random order 5 or 2.5 mg of Δ-9-THC, or vehicle by intravenous route over 2 min. Positive and negative symptoms of psychosis were measured using the Positive and Negative Syndrome Scale (PANSS). Perceptual alterations that did not quite meet the threshold of psychosis were measured using the Clinician Administered Dissociative Symptoms Scale (CADSS). Cognitive symptoms were measured using tests of immediate recall (learning) and delayed recall, verbal fluency, working memory, and vigilance and distractibility. Δ-9-THC produced transient positive symptoms (Fig. 4), perceptual alterations, negative symptoms, euphoria, anxiety, and deficits in working memory and verbal recall, and the executive control of attention without altering general orientation.

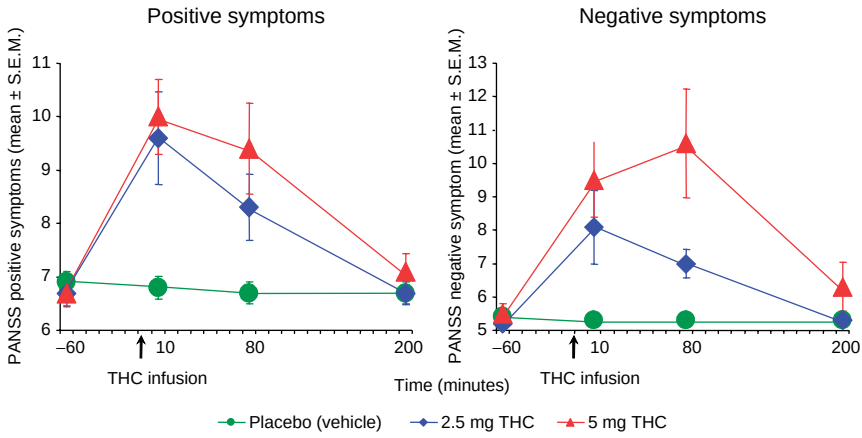

FIG. 4. Δ-9-THC induces positive and negative symptoms in healthy individuals; Positive and Negative Syndrome Scale.

Positive symptoms and perceptual alterations: The positive symptoms induced by Δ-9-THC included suspiciousness, paranoid and grandiose delusions, conceptual disorganization, and illusions. For example, healthy controls reported suspiciousness such as "I thought you all were *trying to trick me* by changing the rules of the tests to make me fail. I thought you were turning the clock back to confuse me," or "I thought that this was real …. I was convinced this wasn't an experiment," or "I thought you all were giving me THC thru the BP (blood pressure) machine and the sheets." Healthy controls also reported conceptual disorganization such as "I couldn't keep track of my thoughts … they'd suddenly disappear," or "It seemed as if all the questions were coming to me at once … everything was happening in staccato," or "my thoughts were fragmented… the past present and future all seemed to happening at once." Healthy subjects also reported unusual thoughts such as "I thought you could read my mind, that's why I didn't answer …. I felt as if my mind was nude," or "I felt I could see into the future …. I thought I was God." These effects reported by carefully screened healthy subjects appear to be remarkably similar to the kinds of psychotic symptoms reported by patients with schizophrenia.

An identical study was conducted in parallel in medicated schizophrenic patients. Δ-9-THC *transiently* exacerbated a range of positive and negative symptoms, perceptual alterations, cognitive deficits, and medication side effects associated with schizophrenia without producing any obvious "beneficial" effects. The increases in psychosis were brief, modest, and occurred even though subjects were clinically stable, medication-responsive, and were receiving therapeutic

doses of antipsychotics. The positive symptoms induced in these patients were similar to their typical symptoms. Using a threshold score of clinically significant positive symptoms (PANSS positive symptom subscale score ≥3 points) defined *a priori*, schizophrenia patients appeared to be more sensitive to the Δ-9-THC effects. Eighty percent of the schizophrenia group but only 35% of controls had a suprathreshold response to 2.5 mg Δ-9-THC and 75% of schizophrenic patients but only 50% of controls had a suprathreshold response to 5 mg Δ-9-THC (Fig. 5). Similarly, (Lindeman and Malamud 1934) administered unassayed doses of hashish to a group of schizophrenic patients, "neurotics," and normals. Normal individuals developed paranoid delusions, impulsivity, and marked perceptual changes and schizophrenic patients experienced an exacerbation of symptoms (Lindemann and Malamud, 1934).

Perceptual alterations: Δ-9-THC also produced depersonalization, derealization, distorted sensory perceptions, altered body perception, feelings of unreality, and extreme slowing of time in both healthy individuals and patients with schizophrenia (Fig. 6). Subjects were reported as being "spaced out," looking "separated or detached," and as if they said or did "something bizarre," or if they needed redirection.

Negative symptoms: Δ-9-THC produced negative symptoms in healthy individuals which included blunted affect, reduced rapport, lack of spontaneity,

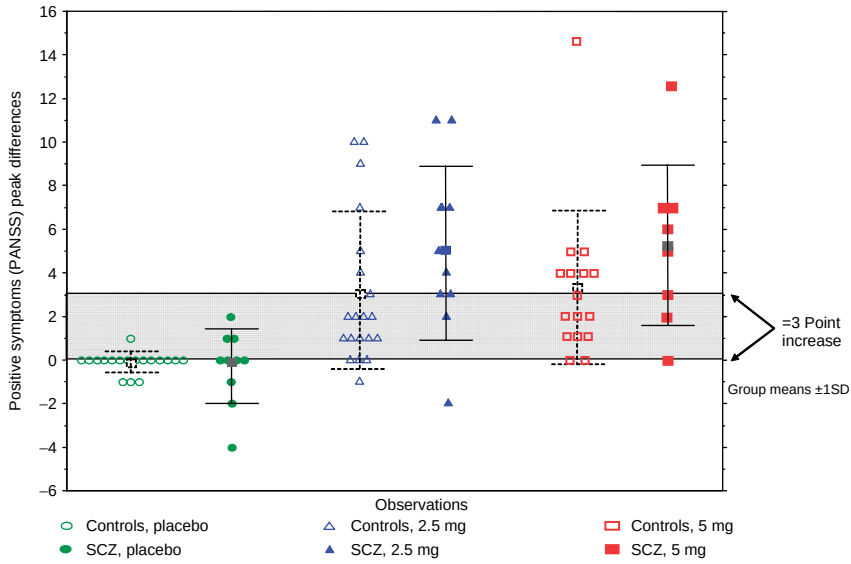

FIG. 5. Enhanced sensitivity to the psychotomimetic effects of d-9-THC in schizophrenia.

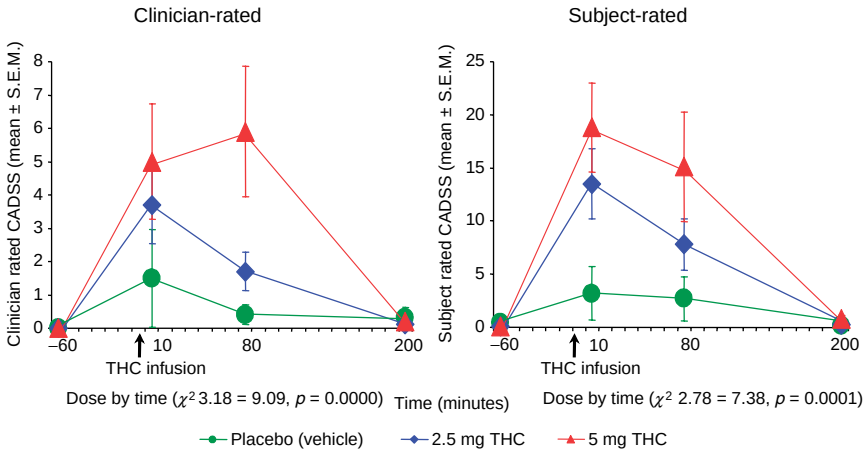

FIG. 6. Δ-9-THC induces transient perceptual alterations in healthy individuals; Clinician Administered Dissociative Symptoms Scale.

psychomotor retardation, and emotional withdrawal (Fig. 4). How much sedation and/or being inwardly preoccupied contributed to the increased ratings of negative symptoms was unclear. These schizophrenia-like negative symptoms may have been confounded by the known cataleptic and sedating effects of Δ-9-THC. Besides, acute pharmacological studies may have limitations in their capacity to "model" negative symptoms. Finally, Δ-9-THC transiently increased negative symptoms in schizophrenic patients.

Of note, a persistent "amotivational syndrome" has been described in chronic heavy cannabis users by some (Halikas *et al.*, 1982; Hall and Solowij, 1998; Kolansky and Moore, 1971b; Millman and Sbriglio, 1986; Tennant and Groesbeck, 1972b) but not others (Carter *et al.*, 1980; Hollister, 1988; Rubin and Comitas, 1975). This so-called "amotivational syndrome" is characterized by apathy, amotivation, social withdrawal, narrowing of interests, lethargy, impaired memory, impaired concentration, disturbed judgment, and impaired occupational achievement. The syndrome has a striking phenomenological similarity with the negative dimension of psychosis and appears to be dose related. However, other drug use, poverty, low socio-economic status, or preexisting psychiatric disorders existing data may confound the interpretation of the existing literature.

Cognitive deficits: The most consistent acute cognitive effects of cannabinoids in humans include deficits in learning, short-term memory, working memory, and attention (Hart *et al.*, 2001; Heishman *et al.*, 1990; Hooker and Jones, 1987; Leweke *et al.*, 1998; Marks and MacAvoy, 1989; Miller *et al.*, 1977). These are also the cognitive deficits observed in schizophrenia (Heinrichs and Zakzanis, 1998). Of note, the most robust effects of cannabinoids are on verbal memory

reviewed in Ranganathan and D'Souza (2006), the latter is also the most robust cognitive deficit observed in schizophrenia (Heinrichs and Zakzanis, 1998).

In healthy subjects (hatched lines), Δ-9-THC significantly impaired immediate free recall in a dose-dependent manner across all three trials of immediate recall (Fig. 7). Δ-9-THC also impaired delayed (+30 min) free recall and delayed cued recall in a significant, dose-dependent manner. The effect on delayed recognition recall trended toward significance. Finally, Δ-9-THC increased the number of false positives and intrusions with a trend toward significance. Relative to controls, schizophrenia patients were specifically more vulnerable to the dose-related learning impairments produced by Δ-9-THC (D'Souza *et al.*, 2005). Under the influence of 5 mg Δ-9-THC schizophrenia patients (solid lines) showed no learning whatsoever (Fig. 7). Δ-9-THC also increased the number of intrusions and false positives generated during recall. Further, 5 mg Δ-9-THC reduced learning and recall in healthy controls to the level of schizophrenia patients on the placebo condition.

While the acute transient effects of cannabinoids on memory are quite clear, whether cannabinoids produce impairments in memory that persist beyond the period of intoxication, remains inconclusive. Heavy and prolonged cannabis exposure may be associated with deficits in memory, sustained attention, and executive functioning (Bolla *et al.*, 2002; Pope and Yurgelun-Todd, 1996; Pope *et al.*, 1995; Solowij, 1995; Solowij *et al.*, 1995, 2002). Eleven of 22 (50%) studies

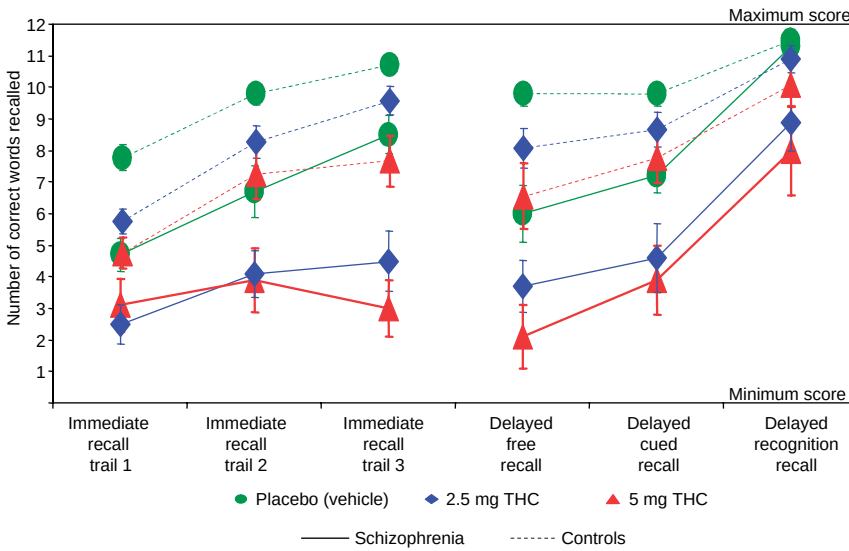

FIG. 7. Δ-9-THC induces memory impairments; Hopkins Verbal Learning Test.

involving clinical samples (cannabis abusers) and 5 of 7 (75%) population-based samples support an association between cannabis use (excluding intoxication) and cognitive deficits. With a few exceptions, the literature has limitations including (1) the lack of any measures of cognitive functioning prior to onset of cannabis use, (2) small samples (range 9–63; median = 26), (3) selection bias, (4) confound of other drug and/or alcohol use, and (5) sensitivity of the cognitive measures, and so on.

In a meta-analysis of 15 studies, Gonzalez *et al.* (2002) concluded that a majority of studies found evidence for persistent but subtle cognitive deficits associated with nonacute (remote) cannabis use. However, whether these cognitive deficits are reversible and persist despite cessation of cannabis use remains an open question. In the first published report examining whether the residual cognitive effects of cannabis persist beyond a period of abstinence longer than 12–72 h, Pope *et al.* (2001) found that deficits in cognitive test performance in cannabis abusers that were present at 7 days normalized by day 28 (Pope *et al.*, 2001). In contrast, Bolla *et al.* (2002) found that cognitive test performance in cannabis abusers with a history of very heavy use of cannabis showed persistent decrements in learning and recall, executive function, psychomotor speed, complex reaction time, and manual dexterity even after 28 days of abstinence. The magnitude of the difference in mean performance between the heavy and light users was between 1.0 and 3.3 S.D. units (Bolla *et al.*, 2002). Similarly, the magnitude of the association between cannabis use and decreasing Wisconsin Card Test Performance (executive functioning) was large (4.1–4.2 S.D. units).

The question of enduring deficits associated with cannabis abuse are only beginning to be investigated with more sensitive measures such as brain imaging and electrophysiology. Cannabis abusers have altered regional cerebral blood flow (rCBF) at rest in several brain regions even after 26 h of monitored abstinence (Block *et al.*, 2000). Similarly, Block *et al.*, have shown decreases in memory-related blood flow in prefrontal cortex in frequent cannabis users in the unintoxicated state relative to nonusers, increases in memory-relevant regions of cerebellum, and altered lateralization in hippocampus. The speed of information processing, measured by the latency of parietal P300, was delayed significantly with increasing frequency of use (Solowij *et al.*, 1995). In summary, there is some overlap between the cognitive effects of cannabinoids and the cognitive deficits observed in schizophrenia.

Δ-9-THC produces a plethora of effects including euphoria, a calm and relaxed feeling state, psychotomimetic symptoms, tachycardia, etc. in the absence of any change in orientation. While some but not other studies reviewed suggest that cannabis can induce a broad range of transient effects in healthy individuals that share some similarities with some, though not all, of the symptoms of schizophrenia, the data from these acute studies do not, however, address the

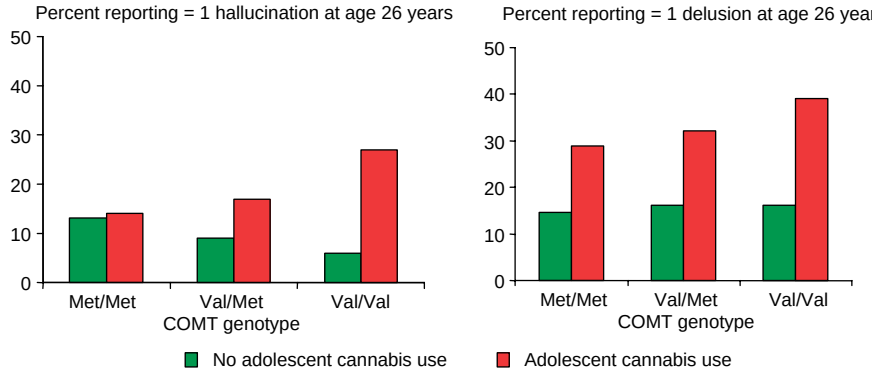

FIG. 8. COMT gene polymorphism moderates influence of adolescent cannabis use on developing psychosis in adulthood.

question of whether cannabis can cause a chronic psychotic disorder such as schizophrenia, that persists through life.

What puts some individuals at higher risk for experiencing psychotic symptoms following exposure to cannabinoids? Individuals with a vulnerability to psychosis as estimated by a psychosis proneness scale were more likely to report psychotic symptoms with cannabis use (Verdoux *et al.*, 2003b). In a preliminary report, no structural mutations in CB1R were found in individuals who developed acute psychotic symptoms after cannabis intake (Hoehe *et al.*, 2000). Caspi *et al.* (2005) reported that a polymorphism of the catechol-*O*-methyl transferase (COMT) gene modulates the risk of schizophrenia conferred by cannabis (Fig. 8). After adolescent exposure to cannabis, individuals homozygous for the COMT valine158 allele were most likely to exhibit psychotic symptoms and to develop schizophreniform disorder later. The effects of cannabinoids on dopamine function may be involved in this gene by cannabis interaction.

V. Cannabis and Psychosis: Causality

Some of the criteria that have been used to establish disease causality include temporality, strength of the association, direction, dose–response or biological gradient, consistency, specificity, coherence, strength of the relationship, experimental evidence, and biologic plausibility (Aiello and Larson, 2002; Hill, 1965).

Most studies provide evidence of direction by showing that the association between cannabis use and psychosis persists even after controlling for many potential confounding variables such as gender, age, ethnicity, low IQ, level of

education, urbanicity, disturbed behavior, cigarette smoking, poor social integration, unemployment, single marital status, and previous psychotic symptoms. While there is a strong association between cigarette smoking and schizophrenia, there is little evidence to support the notion that cigarette smoking "causes" schizophrenia. In contrast, the high rates of cigarette smoking in schizophrenia may reflect an attempt by schizophrenia patients to self-medicate deficits in information processing. Several studies reviewed here provide evidence of a dose–response relationship between cannabis exposure and the risk of psychosis. With regard to temporality, some, though not all, studies suggest that cannabis use precedes or coincides with the onset of psychosis in about two-third of patients with schizophrenia who use cannabis. Related to this, cannabis use may be associated with an earlier age of onset of schizophrenia. Further, there is also evidence that the earlier the onset of cannabis use, the stronger the effect on schizophrenia outcomes. There is also some evidence for both the relative specificity of exposure (i.e., cannabis) and specificity of the outcome (i.e., psychosis). Experimental evidence from laboratory studies suggests that cannabinoids can induce a wide range of transient schizophrenia-like symptoms in healthy individuals and relative to controls, schizophrenia patients are more vulnerable to the psychotomimetic effects of Δ-9-THC. Whether exposure to cannabis can result in a chronic psychotic state that persists beyond the period of intoxication is unclear.

However, not all patients with psychosis have been exposed to cannabis and not all cannabis users develop psychosis. Furthermore, there is a disparity in the incidence and prevalence of cannabis abuse (7–12%) and that of schizophrenia (1–2%), and despite different rates of cannabis consumption across the globe, there is relative uniformity in the incidence of schizophrenia. Further, the increase in cannabis use and the use of more potent forms of cannabis in certain geographical areas has not been accompanied or followed by a commensurate increase in the rates of schizophrenia (Degenhardt *et al.*, 2003). Similarly, if cannabis use is associated with an earlier age of onset, then the increase rates of cannabis use should result in a trend toward a lower age of onset of schizophrenia. This does not seem to be the case.

Taken collectively, it appears that cannabis is neither a necessary nor a sufficient cause of schizophrenia. Similarly, cigarette smoking is neither a necessary nor a sufficient cause of lung cancer. More likely, cannabis exposure is a component or contributing cause which interacts with other known, for example, genetic and heretofore unknown factors, leading to schizophrenia. In terms of strength, cannabis confers about a two- to threefold increase in the relative risk for schizophrenia. Arsenault *et al.* (2004) have suggested that the number of cases of schizophrenia in a population that could be eliminated by removal of cannabis use, the population attributable fraction (PAF), is about 8% (Arsenault *et al.*, 2004). In the absence of known causes of schizophrenia, the role of component causes such as cannabinoid exposure remains important and warrants further study.

As reviewed by Piomelli, advances in the understanding of brain cannabinoid receptor function now offer several biologically plausible mechanisms by which cannabis exposure might induce psychosis. While it is out of the scope of this chapter, the interactions between cannabinoid receptor function and dopamine, glutamate and GABA receptor function provide potential mechanisms by which cannabis contribute to the pathophysiology of psychosis reviewed in D'Souza *et al.* (2004, 2005).

VI. Cannabinoid Receptor Dysfunction and Psychotic Disorders

Emerging findings from postmortem (Dean *et al.*, 2001; Zavitsanou *et al.*, 2004), neurochemical (Giuffrida *et al.*, 2004; Leweke *et al.*, 1999a), and genetic (Ujike *et al.*, 2002) studies suggest that cannabinoid receptor system dysfunction that may contribute to the pathophysiology of schizophrenia.

Leweke *et al.* (1999a) and colleagues were the first to suggest altered cannabinoid receptor function in schizophrenia. Levels of anandamide, 2-AG, palmitoylethanolamide (PEA), and a noncannabinoid acylethanolamide, oleylethanolamide (OEA) as a positive control, were measured in cerebrospinal fluid (CSF) sampled from 10 schizophrenia patients and 11 healthy controls (Fig. 9). Mean anandamide and PEA levels were approximately twofold higher in the schizophrenia patients. These differences could not be attributable to drug use, and neither age, gender nor medication correlated with CSF endocannabinoid levels. However, since some subjects were neuroleptic naïve and others were not, it was not possible to fully exclude an effect of antipsychotic drugs.

These data were replicated in a larger sample and the confound of medication status was also addressed (Giuffrida *et al.*, 2004). CSF anandamide levels were eightfold higher in antipsychotic-naive first-episode paranoid schizophrenics than in healthy and psychiatric controls (Fig. 10). The elevations in CSF anandamide seen in antipsychotic naive schizophrenic patients were absent in schizophrenics treated with "typical" antipsychotics but not in those treated with "atypical" antipsychotics ($n = 34$). Finally, CSF anandamide levels negatively correlated with psychotic symptoms in unmedicated patients. Since anandamide release may serve as an inhibitory feedback signal countering dopamine activation, the increase in CSF anandamide levels in unmedicated acutely psychotic patients was interpreted as a compensatory increase in endocannabinoids secondary to psychosis-related hyperdopaminergia. While CSF studies of endocannabinoids have served to draw attention to possible endocannabinoid dysfunction in schizophrenia, they are not without limitations. Endocannabinoids are very challenging to assay. Anandamide has a very short half-life and therefore differences in collection and processing of samples might explain the group differences. Finally, CSF

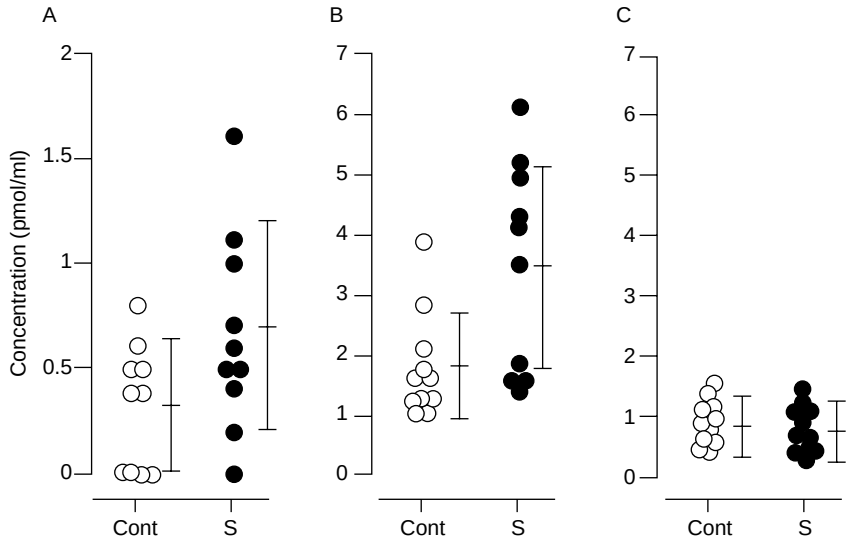

FIG. 9. Cerebrospinal fluid endocannabinoid levels in schizophrenia. Concentrations of anadamide (A), palmitylethanolamide (B), and OEA oleylethanolamide (C) in CSF of schizophrenic (S) and nonschizophrenic (Cont) subjects. Bars indicate mean ± S.D. for each group [(A) and (B), $p < 0.05$; Student's *t*-test]; Leweke *et al.* (1999).

endocannabinoid levels may reflect global rather than regional changes. Studies directly examining CB1 receptor may address some of these limitations.

There are two postmortem studies of CB1 receptor changes in schizophrenia in the literature. Compared with control subjects, schizophrenia patients showed a 19% increase ($p < 0.05$) in CB1 receptor density only in the dorsolateral prefrontal cortex (DLPFC) (Dean *et al.*, 2001). These differences could not be attributable to postmortem interval, brain pH, age, or gender. Further, there were no significant correlations between CB-1R binding and duration of illness or antipsychotic drug dose in those with schizophrenia. Of note, chronic antipsychotic drug treatment study in rats does not result in changes in CB1-receptor binding in the cerebral cortex, caudate-putamen (CP), or hippocampus (Sundram *et al.*, 2004). There were no significant differences between the groups in the CP or hippocampal formation. In subjects who had recently consumed cannabis, there was a significant ($p < 0.05$) 23% increase in CB1 receptor density in the CP compared to nonusers independent of schizophrenia. Zavitsanou *et al.* (2004) compared CB1 receptor in the anterior cingulated cortex (ACC) taken postmortem from patients with schizophrenia ($n = 10$) and matched control subjects ($n = 9$) using [^{3}H]SR141716A. Compared to the control group schizophrenia patients had a significant 64% increase in CB1 receptor density in the ACC. The effects of

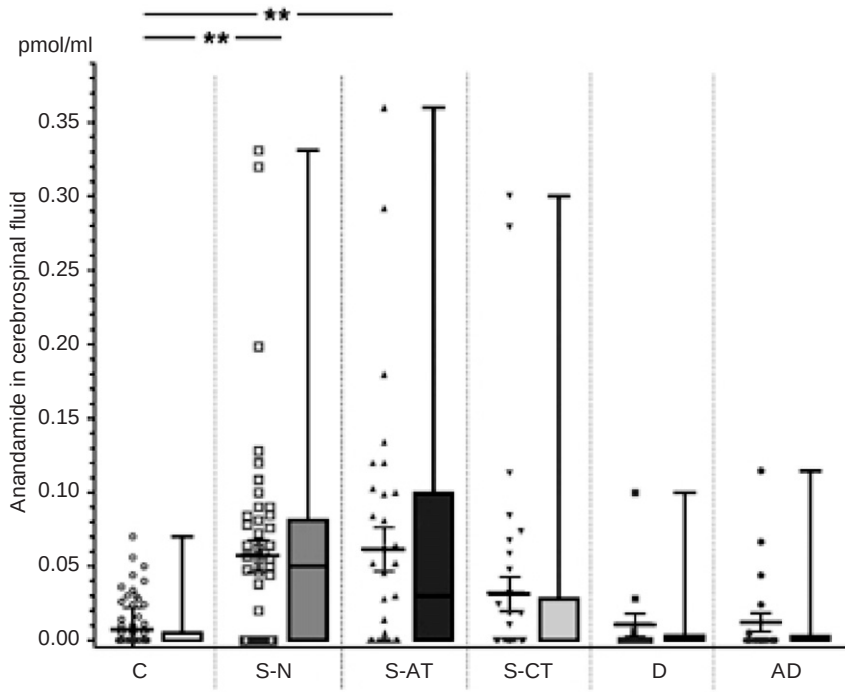

FIG. 10. Elevated anandamide in the CSF of antipsychotic-free first-episode schizophrenic patients. CSF anandamide levels in healthy volunteers (C); antipsychotic-free schizophrenics with paranoid schizophrenia (S-N); acute schizophrenics (paranoid type) on "atypical" (S-AT) or "typical" (S-CT) antipsychotic drugs; and patients with dementia (D) or affective disorders (AD) without psychotic symptoms. Single values with mean ± SEM as well as corresponding ox-plots illustrating median, range, and quartiles for each group. Statistically significant differences between groups are shown (*$p < 0.01$; **$p < 0.001$; Kruskal-Wallis test followed by Mann–Whitney test; a Bonferroni correction (5 tests) of the α-level was applied: $\alpha = 0.05/5 = 0.01$).

antipsychotic treatment or premorbid cannabis use explaining the group differences could not be ruled out. Together the postmortem studies provide some preliminary evidence suggestive of endocannabinoids dysfunction in schizophrenia. The development of good radioligands that permit *in vivo* imaging of the CB1 receptor in schizophrenia patients would help confirm the limited postmortem findings.

Finally, several groups have looked for associations between schizophrenia and genes relevant to cannabinoid receptor function. The CB1 receptor gene is mapped to chromosome 6q14–15, and linkage studies have produced evidence for a schizophrenia-susceptibility locus in this region. Two polymorphisms for the

CB1 receptor gene have been identified, a triplet repeat (AAT)n in the 3′-flanking region (Dawson *et al.*, 1995) and a biallelic silent mutation of 1359 G-to-A at the 453 codon in the coding exon (Gadzicki *et al.*, 1999). Dawson failed to show a significant association between the (AAT)n triplet repeat polymorphism of the CB1 receptor gene and schizophrenia in 135 schizophrenic subjects compared to 101 control subjects (Dawson, 1995). Similarly, Tsai replicated these findings in a study comparing 127 subjects with schizophrenia and 146 control subjects in a Han Chinese population (Tsai *et al.*, 2000). They concluded the (AAT)n triplet repeat in the promoter region of the CB1 receptor gene is not directly involved in the pathogenesis of schizophrenia in Chinese populations. In contrast, Ujike *et al.* (2002) reported that the (AAT)n triplet repeat polymorphism of the CB1 receptor gene was significantly associated with patients with schizophrenia, especially the hebephrenic subtype. The functional effect of this triplet repeat on the CB1 receptor gene transcription rate remains unclear. Leroy studied the 1359 A/G polymorphism in a French Caucasian sample of 102 subjects with schizophrenia and 63 healthy controls (Leroy *et al.*, 2001). Overall there were no significant differences between the two groups either in allele frequency or genotype distribution. However, when the patient group was divided into a substance using ($n = 42$) and nonusing, they found a significant decrease in homozygosity for the G allele in nonusers compared to users ($p < 0.04$). Fatty acid amide hydrolase (FAAH) is the primary catabolic enzyme of endocannabinoids. Morita *et al.* (2005) found no significant association of a nonsynonymous polymorphism (Pro129Thr) of the FAAH gene with schizophrenia.

VII. Summary and Conclusions

Cannabinoids can induce acute transient psychotic symptoms or an acute psychosis in some individuals. What makes some individuals vulnerable to cannabinoid-related psychosis is unclear. Cannabinoids can also exacerbate psychosis in individuals with an established psychotic disorder, and these exacerbations may last beyond the period of intoxication. Less clear is whether cannabis *causes* a persistent *de novo* psychosis. The available evidence meets many but not all the criteria for causality, including dose–response, temporality, direction, specificity, and biological plausibility. On the other hand, the large majority of individuals exposed to cannabinoids do not experience psychosis or develop schizophrenia. It is more likely that cannabis exposure is a component cause that interacts with other factors, for example, genetic risk, to "cause" schizophrenia. Nevertheless, in the absence of known causes of schizophrenia, the role of component causes such as cannabis exposure (exogenous hypothesis), is important and warrants further study. There is also tantalizing evidence from postmortem,

neurochemical, and genetic studies, suggesting CB1 receptor dysfunction (endogenous hypothesis) in schizophrenia that warrants further investigation. Further work is necessary to identify those factors that place individuals at higher risk cannabinoid-related psychosis, to identify the biological mechanisms underlying the risks and to further study whether CB1 receptor dysfunction contributes to the pathophysiology of psychotic disorders. Finally, from a treatment perspective, given the negative impact of cannabis use on the course and expression of schizophrenia, and the potential for precipitating psychosis in individuals at risk for schizophrenia, efforts need to be directed toward developing effective treatments for cannabis use disorders.

Acknowledgments

The author wishes to acknowledge support from the (1) Department of Veterans Affairs (Schizophrenia Biological Research Center), (2) National Institute of Mental Health (R01MH61019–02 to DCD), (3) National Institute of Drug Abuse (RO1DA12382–01), (4) Stanley Medical Research Institute, and (5) Donaghue Foundation.

References

Adams, I. B., and Martin, B. R. (1996). Cannabis: Pharmacology and toxicology in animals and humans. *Addiction* **91,** 1585–1614.

Addington, J., and Addington, D. (1998). Effect of substance misuse in early psychosis. *Br. J. Psychiatry Suppl.* **172,** 134–136.

Agurell, S., Halldin, M., Lindgren, J. E., Ohlsson, A., Widman, M., Gillespie, H., and Hollister, L. (1986). Pharmacokinetics and metabolism of delta 1-tetrahydrocannabinol and other cannabinoids with emphasis on man. *Pharmacol. Rev.* **38,** 21–43.

Aiello, A. E., and Larson, E. L. (2002). Causal inference: The case of hygiene and health. *Am. J. Infect. Control* **30,** 503–511.

Allebeck, P., Adamsson, C., Engstrom, A., and Rydberg, U. (1993a). Cannabis and schizophrenia: A longitudinal study of cases treated in Stockholm County. *Acta Psychiatr. Scand.* **88,** 21–24.

Allebeck, P., Adamsson, C., Engstrom, A., and Rydberg, U. (1993b). Cannabis and schizophrenia: A longitudinal study of cases treated in Stockholm County. [erratum appears in *Acta. Psychiatr. Scand.* (1993) **88**(4), 304]. *Acta Psychiatr. Scand.* **88,** 21–24.

Ames, F. (1958). A clinical and metabolic study of acute intoxication with cannabis sativa and its role in model psychoses. *J. Ment. Sci.* **104,** 972–999.

Andreasson, S., Allebeck, P., Engstrom, A., and Rydberg, U. (1987). Cannabis and schizophrenia. A longitudinal study of Swedish conscripts. *Lancet* **2,** 1483–1486.

Andreasson, S., Allebeck, P., and Rydberg, U. (1989). Schizophrenia in users and nonusers of cannabis. A longitudinal study in Stockholm County. *Acta Psychiatr. Scand.* **79,** 505–510.

Angrist, B. M., and Gershon, S. (1970). The phenomenology of experimentally induced amphetamine psychosis: Preliminary observations. *Biol. Psychiatry* **2,** 95–107.

Angrist, B. M., Shopsin, B., and Gershon, S. (1971). Comparative psychotomimetic effects of stereoisomers of amphetamine. *Nature* **234,** 152–153.

Arendt, M., Rosenberg, R., Foldager, L., Perto, G., and Munk-Jorgensen, P. (2005). Cannabis-induced psychosis and subsequent schizophrenia-spectrum disorders: Follow-up study of 535 incident cases. *Br. J. Psychiatry* **187,** 510–515.

Arseneault, L., Cannon, M., Poulton, R., Murray, R., Caspi, A., and Moffitt, T. E. (2002). Cannabis use in adolescence and risk for adult psychosis: Longitudinal prospective study. *BMJ* **325,** 1212–1213.

Arsenault, L., Cannon, M., Witton, J., and Murray, R. (2004). "Cannabis as a Potential Causal Factor in Schizophrenia." Cambridge University Press, New York.

Basu, D., Malhotra, A., Bhagat, A., and Varma, V. K. (1999). Cannabis psychosis and acute schizophrenia: A case-control study from India. *Eur. Addict. Res.* **5,** 71–73.

Bell, D. S. (1965). Comparison of amphetamine psychosis and schizophrenia. *Br. J. Psychiatry* **111,** 701–707.

Bell, D. S. (1973). The experimental reproduction of amphetamine psychosis. *Arch. Gen. Psychiatry* **29,** 35–40.

Bernhardson, G., and Gunne, L. M. (1972). Forty-six cases of psychosis in cannabis abusers. *Int. J. Addict.* **7,** 9–16.

Block, R. I., O'Leary, D. S., Hichwa, R. D., Augustinack, J. C., Ponto, L. L., Ghoneim, M. M., Arndt, S., Ehrhardt, J. C., Hurtig, R. R., Watkins, G. L., Hall, J. A., Nathan, P. E., *et al.* (2000). Cerebellar hypoactivity in frequent marijuana users. *Neuroreport* **11,** 749–753.

Bolla, K. I., Brown, K., Eldreth, D., Tate, K., and Cadet, J. L. (2002). Dose-related neurocognitive effects of marijuana use. *Neurology* **59,** 1337–1343.

Bornheim, L. M., Kim, K. Y., Li, J., Perotti, B. Y., and Benet, L. Z. (1995). Effect of cannabidiol pretreatment on the kinetics of tetrahydrocannabinol metabolites in mouse brain. *Drug Metab. Dispos.* **23,** 825–831.

Bromberg, W. (1939). Marihuana: A psychiatric study. *JAMA* **113,** 4–12.

Campbell, F. A., Tramer, M. R., Carroll, D., Reynolds, D. J., Moore, R. A., and McQuay, H. J. (2001). Are cannabinoids an effective and safe treatment option in the management of pain? A qualitative systematic review. *BMJ* **323,** 13–16.

Carney, M. W., Bacelle, L., and Robinson, B. (1984). Psychosis after cannabis abuse. *Br. Med. J. Clin. Res. Ed.* **288,** 1047.

Carter, W. E., Coggins, W., and Doughty, P. L. (1980). Cannabis in Costa Rica: A study of chronic marijuana use.

Caspi, A., Moffitt, T. E., Cannon, M., McClay, J., Murray, R., Harrington, H., Taylor, A., Arseneault, L., Williams, B., Braithwaite, A., Poulton, R., and Craig, I. W. (2005). Moderation of the effect of adolescent-onset cannabis use on adult psychosis by a functional polymorphism in the catechol-O-methyltransferase gene: Longitudinal evidence of a gene X environment interaction. *Biol. Psychiatry* **57,** 1117–1127.

Chaudry, H. R., Moss, H. B., Bashir, A., and Suliman, T. (1991). Cannabis psychosis following bhang ingestion. *Br. J. Addict.* **86,** 1075–1081.

Chopra, G. S. (1973). Studies on psycho-clinical aspects of long-term marihuana use in 124 cases. *Int. J. Addict.* **8,** 1015–1026.

Chopra, G. S., and Smith, J. W. (1974). Psychotic reactions following cannabis use in East Indians. *Arch. Gen. Psychiatry* **30,** 24–27.

Citron, M. L., Herman, T. S., Vreeland, F., Krasnow, S. H., Fossieck, B. E., Jr., Harwood, S., Franklin, R., and Cohen, M. H. (1985). Antiemetic efficacy of levonantradol compared to delta-9-tetrahydrocannabinol for chemotherapy-induced nausea and vomiting. *Cancer Treat. Rep.* **69,** 109–112.

Cleghorn, J. M., Kaplan, R. D., Szechtman, B., Szechtman, H., Brown, G. M., and Franco, S. (1991). Substance abuse and schizophrenia: Effect on symptoms but not on neurocognitive function. *J. Clin. Psychiatry* **52,** 26–30.

Cohen, S. I. (1994). Cannabis consumption and schizophrenia. *Br. J. Psychiatry* **165,** 410–411.

Connel, P. H. (1958). Amphetamine Psychoses. Oxford University Press. London.

Cronin, C. M., Sallan, S. E., Gelber, R., Lucas, V. S., and Laszlo, J. (1981). Antiemetic effect of intramuscular levonantradol in patients receiving anticancer chemotherapy. *J. Clin. Pharmacol.* **21,** 43S–50S.

D'Souza, D. C., Berman, R. M., Krystal, J. H., and Charney, D. S. (1999). Symptom provocation studies in psychiatric disorders: Scientific value, risks, and future. *Biol. Psychiatry* **46,** 1060–1080.

D'Souza, D. C., Perry, E., MacDougall, L., Ammerman, Y., Cooper, T., Wu, Y. T., Braley, G., Gueorguieva, R., and Krystal, J. H. (2004). The psychotomimetic effects of intravenous delta-9-tetrahydrocannabinol in healthy individuals: Implications for psychosis. *Neuropsychopharmacology* **29,** 1558–1572.

D'Souza, D. C., Abi-Saab, W. M., Madonick, S., Forselius-Bielen, K., Doersch, A., Braley, G., Gueorguieva, R., Cooper, T. B., and Krystal, J. H. (2005). Delta-9-tetrahydrocannabinol effects in schizophrenia: Implications for cognition, psychosis, and addiction. *Biol. Psychiatry* **57,** 594–608.

Dawson, E., Powell, J. F., Sham, P., Shaikh, S., Taylor, C., Clements, A., Asherson, P., Sargeant, M., Collier, D., and Nanko, S. (1995). Systematic search for major genes in schizophrenia: Methodological issues and results from chromosome 12. *Am. J. Med. Genet.* **60,** 424–433.

Dean, B., Sundram, S., Bradbury, R., Scarr, E., and Copolov, D. (2001). Studies on [3H]CP-55940 binding in the human central nervous system: Regional specific changes in density of cannabinoid-1 receptors associated with schizophrenia and cannabis use. *Neuroscience* **103,** 9–15.

Degenhardt, L., Hall, W., and Lynskey, M. (2001). Alcohol, cannabis and tobacco use among Australians: A comparison of their associations with other drug use and use disorders, affective and anxiety disorders, and psychosis. *Addiction* **96,** 1603–1614.

Degenhardt, L., Hall, W., and Lynskey, M. (2003). Testing hypotheses about the relationship between cannabis use and psychosis. *Drug Alcohol. Depend.* **71,** 37–48.

Diasio, R. B., Ettinger, D. S., and Satterwhite, B. E. (1981). Oral levonantradol in the treatment of chemotherapy-induced emesis: Preliminary observations. *J. Clin. Pharmacol.* **21,** 81S–85S.

Dumas, P., Saoud, M., Bouafia, S., Gutknecht, C., Ecochard, R., Dalery, J., Rochet, T., and d'Amato, T. (2002). Cannabis use correlates with schizotypal personality traits in healthy students. *Psychiatry Res.* **109,** 27–35.

Elsohly, M. A., and Slade, D. (2005). Chemical constituents of marijuana: The complex mixture of natural cannabinoids. *Life Sci.* **78,** 539–548.

Ferdinand, R. F., Sondeijker, F., van der Ende, J., Selten, J. P., Huizink, A., and Verhulst, F. C. (2005). Cannabis use predicts future psychotic symptoms, and vice versa. *Addiction* **100,** 612–618.

Fergusson, D. M., Horwood, L. J., and Swain-Campbell, N. R. (2003). Cannabis dependence and psychotic symptoms in young people. *Psychol. Med.* **33,** 15–21.

Gadzicki, D., Muller-Vahl, K., and Stuhrmann, M. (1999). A frequent polymorphism in the coding exon of the human cannabinoid receptor (CNR1) gene. *Mol. Cell. Probes* **13,** 321–323.

Ghodse, A. H. (1986). Cannabis psychosis. *Br. J. Addict.* **81,** 473–478.

Giuffrida, A., Leweke, F. M., Gerth, C. W., Schreiber, D., Koethe, D., Faulhaber, J., Klosterkotter, J., and Piomelli, D. (2004). Cerebrospinal anandamide levels are elevated in acute schizophrenia and are inversely correlated with psychotic symptoms. *Neuropsychopharmacology* **29,** 2108–2114.

Gonzalez, R., Carey, C., and Grant, I. (2002). Nonacute (residual) neuropsychological effects of cannabis use: A qualitative analysis and systematic review. *J. Clin. Pharmacol.* **42,** 48S–57S.

Gottesman, I. I., and Shields, J. (1982). "Schizophrenia: The Epigenetic Puzzle." Cambridge University Press, Cambridge.

Green, A. I., Tohen, M. F., Hamer, R. M., Strakowski, S. M., Lieberman, J. A., Glick, I., Clark, W. S., and Group, H. R. (2004). First episode schizophrenia-related psychosis and substance use disorders: Acute response to olanzapine and haloperidol. [see comment]. *Schizophr. Res.* **66,** 125–135.

Green, B., Kavanagh, D., and Young, R. (2003). Being stoned: A review of self-reported cannabis effects. *Drug Alcohol Rev.* **22,** 453–460.

Griffith, J. D., Cavanaugh, J., Held, J., and Oates, J. A. (1972). Dextroamphetamine: Evaluation of psychomimetic properties in man. *Arch. Gen. Psychiatry* **26,** 97–100.

Guimaraes, F. S., de Aguiar, J. C., Mechoulam, R., and Breuer, A. (1994). Anxiolytic effect of cannabidiol derivatives in the elevated plus-maze. *Gen. Pharmacol.* **25,** 161–164.

Halikas, J. A., Weller, R. A., Morse, C., and Shapiro, T. (1982). Incidence and characteristics of a motivational syndrome, including associated findings, among chronic marijuana users. *In* "Marijuana and Youth: Clinical Observations on Motivation and Learning" (N. I. O. D. Abuse, Ed.), pp. 11–23. National Institute on Drug Abuse, Rockville, Maryland.

Hall, W., and Degenhardt, L. (2004). "Is There a Specific 'Cannabis Psychosis'?" Cambridge University Press, Cambridge.

Hall, W., and Solowij, N. (1998). Adverse effects of cannabis. *Lancet* **352,** 1611–1616.

Hambrecht, M., and Hafner, H. (1996). Substance abuse and the onset of schizophrenia. *Biol. Psychiatry* **40,** 1155–1163.

Hambrecht, M., and Hafner, H. (2000). Cannabis, vulnerability, and the onset of schizophrenia: An epidemiological perspective. *Aust. N.Z. J. Psychiatry* **34,** 468–475.

Harding, T., and Knight, F. (1973). Marihuana-modified mania. *Arch. Gen. Psychiatry* **29,** 635–637.

Hart, C. L., van Gorp, W., Haney, M., Foltin, R. W., and Fischman, M. W. (2001). Effects of acute smoked marijuana on complex cognitive performance. *Neuropsychopharmacology* **25,** 757–765.

Heim, M. E., Romer, W., and Queisser, W. (1981). Clinical experience with levonantradol hydrochloride in the prevention of cancer chemotherapy-induced nausea and vomiting. *J. Clin. Pharmacol.* **21,** 86S–89S.

Heim, M. E., Queisser, W., and Altenburg, H. P. (1984). Randomized crossover study of the antiemetic activity of levonantradol and metoclopramide in cancer patients receiving chemotherapy. *Cancer Chemother. Pharmacol.* **13,** 123–125.

Heinrichs, R. W., and Zakzanis, K. K. (1998). Neurocognitive deficit in schizophrenia: A quantitative review of the evidence. *Neuropsychology* **12,** 426–445.

Heishman, S. J., Huestis, M. A., Henningfield, J. E., and Cone, E. J. (1990). Acute and residual effects of marijuana: Profiles of plasma THC levels, physiological, subjective, and performance measures. *Pharmacol. Biochem. Behav.* **37,** 561–565.

Henquet, C., Krabbendam, L., Spauwen, J., Kaplan, C., Lieb, R., Wittchen, H. U., and van Os, J. (2005). Prospective cohort study of cannabis use, predisposition for psychosis, and psychotic symptoms in young people. *BMJ* **330,** 11.

Hill, A. B. (1965). The environment and disease: Association or causation? *Proc. R. Soc. Med.* **58,** 295–300.

Hoehe, M. R., Rinn, T., Flachmeier, C., Heere, P., Kunert, H. J., Timmermann, B., Kopke, K., and Ehrenreich, H. (2000). Comparative sequencing of the human CB1 cannabinoid receptor gene coding exon: No structural mutations in individuals exhibiting extreme responses to cannabis. *Psychiatr. Genet.* **10,** 173–177.

Hollister, L. E. (1986). Health aspects of cannabis. *Pharmacol. Rev.* **38,** 1–20.

Hollister, L. E. (1988). Cannabis 1988. *Acta Psychiatr. Scand. Suppl.* **345,** 108–118.

Hollister, L. E., Gillespie, H. K., Ohlsson, A., Lindgren, J. E., Wahlen, A., and Agurell, S. (1981). Do plasma concentrations of delta 9-tetrahydrocannabinol reflect the degree of intoxication? *J. Clin. Pharmacol.* **21,** 171S–177S.

Hooker, W. D., and Jones, R. T. (1987). Increased susceptibility to memory intrusions and the Stroop interference effect during acute marijuana intoxication. *Psychopharmacology* **91,** 20–24.

Imade, A. G., and Ebie, J. C. (1991). A retrospective study of symptom patterns of cannabis-induced psychosis. *Acta Psychiatr. Scand.* **83,** 134–136.

Isbell, H., and Jasinski, D. R. (1969). A comparison of LSD-25 with (−)-delta-9-trans-tetrahydrocannabinol (THC) and attempted cross tolerance between LSD and THC. *Psychopharmacologia* **14**(20), 115–123.

Isbell, H., Gorodetzsky, C. W., Jasinski, D., Claussen, U., Von Spulak, F., and Korte, F. (1967). Effects of (−)delta-9-trans-tetrahydrocannabinol in man. *Psychopharmacologia* **11,** 184–188.

Jain, A. K., Ryan, J. R., McMahon, F. G., and Smith, G. (1981). Evaluation of intramuscular levonantradol and placebo in acute postoperative pain. *J. Clin. Pharmacol.* **21,** 320S–326S.

Jones, R. T., and Stone, G. C. (1970). Psychological studies of marijuana and alcohol in man. *Psychopharmacologia* **18,** 108–117.

Karniol, I. G., and Carlini, E. A. (1973). Pharmacological interaction between cannabidiol and delta 9-tetrahydrocannabinol. *Psychopharmacologia* **33,** 53–70.

Karniol, I. G., Shirakawa, I., Kasinski, N., Pfeferman, A., and Carlini, E. A. (1974). Cannabidiol interferes with the effects of delta 9-tetrahydrocannabinol in man. *Eur. J. Pharmacol.* **28,** 172–177.

Karniol, I. G., Shirakawa, I., Takahashi, R. N., Knobel, E., and Musty, R. E. (1975). Effects of delta9-tetrahydrocannabinol and cannabinol in man. *Pharmacology* **13,** 502–512.

Kenny, J. B., and Wilkinson, P. M. (1982). Levonantradol effectiveness in cancer patients resistant to conventional anti-emetics. *Clin. Oncol.* **8,** 335–339.

Kolansky, H., and Moore, W. T. (1971a). Effects of marihuana on adolescents and young adults. *JAMA* **216,** 486–492.

Kolansky, H., and Moore, W. T. (1971b). Effects of marihuana on adolescents and young adults. *J. Psychiatr. Nurs. Ment. Health Serv.* **9,** 9–16.

Laszlo, J., Lucas, V. S., Jr., Hanson, D. C., Cronin, C. M., and Sallan, S. E. (1981). Levonantradol for chemotherapy-induced emesis: Phase I-II oral administration. *J. Clin. Pharmacol.* **21,** 51S–56S.

Leroy, S., Griffon, N., Bourdel, M. C., Olie, J. P., Poirier, M. F., and Krebs, M. O. (2001). Schizophrenia and the cannabinoid receptor type 1 (CB1): Association study using a single-base polymorphism in coding exon 1. *Am. J. Med. Genet.* **105,** 749–752.

Leweke, M., Kampmann, C., Radwan, M., Dietrich, D. E., Johannes, S., Emrich, H. M., and Munte, T. F. (1998). The effects of tetrahydrocannabinol on the recognition of emotionally charged words: An analysis using event-related brain potentials. *Neuropsychobiology* **37,** 104–111.

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

Leweke, F. M., Schneider, U., Thies, M., Munte, T. F., and Emrich, H. M. (1999b). Effects of synthetic delta9-tetrahydrocannabinol on binocular depth inversion of natural and artificial objects in man. *Psychopharmacology (Berl.)* **142,** 230–235.

Leweke, F. M., Schneider, U., Radwan, M., Schmidt, E., and Emrich, H. M. (2000). Different effects of nabilone and cannabidiol on binocular depth inversion in Man. *Pharmacol. Biochem. Behav.* **66,** 175–181.

Lindemann, E., and Malamud, W. (1934). Experimental analysis of the psychopathological effects of intoxicating drugs. *Am. J. Psychiatry* **90,** 853–881.

Linszen, D. H., Dingemans, P. M., and Lenior, M. E. (1994). Cannabis abuse and the course of recent-onset schizophrenic disorders. *Arch. Gen. Psychiatry* **51,** 273–279.

Marks, D. F., and MacAvoy, M. G. (1989). Divided attention performance in cannabis users and non-users following alcohol and cannabis separately and in combination. *Psychopharmacology* **99,** 397–401.

Marshall, C. R. (1897). The active principle of Indian hemp: A preliminary communication. *Lancet* 235–238.

Mathers, D. C., Ghodse, A. H., Caan, A. W., and Scott, S. A. (1991). Cannabis use in a large sample of acute psychiatric admissions. *Br. J. Addict.* **86,** 779–784.

Mayor's, C. (1944). "The Marijuana Problem in the City of New York." Jacques Catell Press, Lancaster, PA.

McGuire, P. K., Jones, P., Harvey, I., Bebbington, P., Toone, B., Lewis, S., and Murray, R. M. (1994). Cannabis and acute psychosis. *Schizophr. Res.* **13,** 161–167.

McGuire, P. K., Jones, P., Harvey, I., Williams, M., McGuffin, P., and Murray, R. M. (1995). Morbid risk of schizophrenia for relatives of patients with cannabis-associated psychosis. *Schizophr. Res.* **15,** 277–281.

Mechoulam, R., and Ben-Shabat, S. (1999). From gan-zi-gun-nu to anandamide and 2-arachidonoylglycerol: The ongoing story of cannabis. *Nat. Prod. Rep.* **16,** 131–143.

Mehmedic, Z., Martin, J., Foster, S., and ElSohly, M. A. (2005). Δ9-THC and other cannabinoids content of confiscated marijuana: Potency trends, 1994–2004. *In* "International Association for Cannabis as Medicine (IACM) 3rd Conference on Cannabinoids in Medicine." Leiden, The Netherlands.

Melges, F. T., Tinklenberg, J. R., Hollister, L. E., and Gillespie, H. K. (1970). Marihuana and temporal disintegration. *Science* **168,** 1118–1120.

Miller, L. L., McFarland, D., Cornett, T. L., and Brightwell, D. (1977). Marijuana and memory impairment: Effect on free recall and recognition memory. *Pharmacol. Biochem. Behav.* **7,** 99–103.

Miller, P., Lawrie, S. M., Hodges, A., Clafferty, R., Cosway, R., and Johnstone, E. C. (2001). Genetic liability, illicit drug use, life stress and psychotic symptoms: Preliminary findings from the Edinburgh study of people at high risk for schizophrenia. *Soc. Psychiatry Psychiatr. Epidemiol.* **36,** 338–342.

Millman, R. B., and Sbriglio, R. (1986). Patterns of use and psychopathology in chronic marijuana users. *Psychiatr. Clin. North Am.* **9,** 533–545.

Moreau, J. (1973). "Hashish and Mental Illness." Raven Press, New York.

Morita, Y., Ujike, H., Tanaka, Y., Uchida, N., Nomura, A., Ohtani, K., Kishimoto, M., Morio, A., Imamura, T., Sakai, A., Inada, T., Harano, M., *et al.* (2005). A nonsynonymous polymorphism in the human fatty acid amide hydrolase gene did not associate with either methamphetamine dependence or schizophrenia. *Neurosci. Lett.* **376,** 182–187.

Niesink, J. M., Rigter, S. M., Pijlman, F. T. A., and Bossong, M. G. (2005). Increase in total delta-9-THC in Nederweit as sold in Dutch Coffee Shops. *In* "International Association for Cannabis as Medicine (IACM) 3rd Conference on Cannabinoids in Medicine." Leiden, The Netherlands.

Nunn, J. A., Rizza, F., and Peters, E. R. (2001). The incidence of schizotypy among cannabis and alcohol users. *J. Nerv. Ment. Dis.* **189,** 741–748.

Ohlsson, A., Lindgren, J. E., Wahlen, A., Agurell, S., Hollister, L. E., and Gillespie, H. K. (1980). Plasma delta-9 tetrahydrocannabinol concentrations and clinical effects after oral and intravenous administration and smoking. *Clin. Pharmacol. Ther.* **28,** 409–416.

Ohlsson, A., Lindgren, J. E., Wahlen, A., Agurell, S., Hollister, L. E., and Gillespie, H. K. (1981). Plasma levels of delta 9-tetrahydrocannabinol after intravenous, oral, and smoke administration. *NIDA Res. Monogr.* **34,** 250–256.

Palsson, A., Thulin, S. O., and Tunving, K. (1982). Cannabis psychoses in south Sweden. *Acta Psychiatr. Scand.* **66,** 311–321.

Phillips, L. J., Curry, C., Yung, A. R., Yuen, H. P., Adlard, S., and McGorry, P. D. (2002). Cannabis use is not associated with the development of psychosis in an 'ultra' high-risk group. *Aust. N. Z. J. Psychiatry* **36,** 800–806.

Pitts, J. E., O'Neil, P. J., and Leggo, K. P. (1990). Variation in the THC content of illicitly imported Cannabis products: 1984–1989. *J. Pharm. Pharmacol.* **42,** 817–820.

Pitts, J. E., Neal, J. D., and Gough, T. A. (1992). Some features of Cannabis plants grown in the United Kingdom from seeds of known origin. *J. Pharm. Pharmacol.* **44,** 947–951.

Pope, H. G., Jr., Gruber, A. J., and Yurgelun-Todd, D. (1995). The residual neuropsychological effects of cannabis: The current status of research. *Drug Alcohol Depend.* **38,** 25–34.

Pope, H. G., Jr., and Yurgelun-Todd, D. (1996). The residual cognitive effects of heavy marijuana use in college students. *JAMA* **275,** 521–527.

Pope, H. G., Jr., Gruber, A. J., Hudson, J. I., Huestis, M. A., and Yurgelun-Todd, D. (2001). Neuropsychological performance in long-term cannabis users. *Arch. Gen. Psychiatry* **58,** 909–915.

Ranganathan, M., and D'Souza, D. (2006). The Acute effects of cannabinoids on memory in humans: A review. *Psychopharmacology.* **188**(4), 425–444. EPub.

Reilly, D., Didcott, P., Swift, W., and Hall, W. (1998). Long-term cannabis use: Characteristics of users in an Australian rural area. *Addiction* **93,** 837–846.

Rolfe, M., Tang, C. M., Sabally, S., Todd, J. E., Sam, E. B., and Hatib N'Jie, A. B. (1993). Psychosis and cannabis abuse in The Gambia. A case-control study [see comment]. *Br. J. Psychiatry* **163,** 798–801.

Rottanburg, D., Robins, A. H., Ben-Arie, O., Teggin, A., and Elk, R. (1982). Cannabis-associated psychosis with hypomanic features. *Lancet* **2,** 1364–1366.

Rubin, V., and Comitas, L. (1975). "Ganja in Jamaica: A Medical Anthropological Study of Chronic Marihuana Use." Mouton Publishers, The Hague.

Russo, E. B., and McPartland, J. M. (2003). Cannabis is more than simply delta(9)-tetrahydrocannabinol. *Psychopharmacology (Berl.)* **165,** 431–432; author reply 433–434.

Sheidler, V. R., Ettinger, D. S., Diasio, R. B., Enterline, J. P., and Brown, M. D. (1984). Double-blind multiple-dose crossover study of the antiemetic effect of intramuscular levonantradol compared to prochlorperazine. *J. Clin. Pharmacol.* **24,** 155–159.

Skosnik, P. D., Spatz-Glenn, L., and Park, S. (2001). Cannabis use is associated with schizotypy and attentional disinhibition. *Schizophr. Res.* **48,** 83–92.

Solomons, K., and Neppe, V. M. (1989). Cannabis: Its clinical effects. *S. Afr. Med. J.* **76,** 102–104.

Solomons, K., Neppe, V. M., and Kuyl, J. M. (1990). Toxic cannabis psychosis is a valid entity. *S. Afr. Med. J.* **78,** 476–481.

Solowij, N. (1995). Do cognitive impairments recover following cessation of cannabis use? *Life Sci.* **56,** 2119–2126.

Solowij, N., Michie, P. T., and Fox, A. M. (1995). Differential impairments of selective attention due to frequency and duration of cannabis use. *Biol. Psychiatry* **37,** 731–739.

Solowij, N., Stephens, R. S., Roffman, R. A., Babor, T., Kadden, R., Miller, M., Christiansen, K., McRee, B., Vendetti, J., and Marijuana Treatment Project Research, G. (2002). Cognitive functioning of long-term heavy cannabis users seeking treatment.[comment][erratum appears in *JAMA* (2002) April 3 **287**(13), 1651]. *JAMA* **287,** 1123–1131.

Stambaugh, J. E., Jr., McAdams, J., and Vreeland, F. (1984). Dose ranging evaluation of the antiemetic efficacy and toxicity of intramuscular levonantradol in cancer subjects with chemotherapy-induced emesis. *J. Clin. Pharmacol.* **24,** 480–485.

Stefanis, N. C., Delespaul, P., Henquet, C., Bakoula, C., Stefanis, C. N., and Van Os, J. (2004). Early adolescent cannabis exposure and positive and negative dimensions of psychosis. *Addiction* **99,** 1333–1341.

Stuart-Harris, R. C., Mooney, C. A., and Smith, I. E. (1983). Levonantradol: A synthetic cannabinoid in the treatment of severe chemotherapy-induced nausea and vomiting resistant to conventional anti-emetic therapy. *Clin. Oncol.* **9,** 143–146.

Sundram, S., Dean, B., and Copolov, D. (2004). "The Endogenous Cannabinoid System in Schizophrenia." Cambridge University Press, New York.

Talbott, J. A., and Teague, J. W. (1969a). Marihuana psychosis. Acute toxic psychosis associated with the use of Cannabis derivatives. *JAMA* **210,** 299–302.

Talbott, J. A., and Teague, J. W. (1969b). Marihuana psychosis: Acute toxic psychosis associated with the use of cannabis derivatives. *JAMA* **210,** 299–302.

Tennant, F. S., and Groesbeck, C. J. (1972a). Psychiatric effects of hashish. *Arch. Gen. Psychiatry* **27,** 133–136.

Tennant, F. S., Jr., and Groesbeck, C. J. (1972b). Psychiatric effects of hashish. *Arch. Gen. Psychiatry* **27,** 133–136.

Thacore, V. R. (1973). Bhang psychosis. *Br. J. Psychiatry* **123,** 225–229.

Thacore, V. R., and Shukla, S. R. (1976). Cannabis psychosis and paranoid schizophrenia. *Arch. Gen. Psychiatry* **33,** 383–386.

Thomas, H. (1993). Cannabis and the PSE. *Br. J. Psychiatry* **162,** 271–272.

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

Thornicroft, G. (1990). Cannabis and psychosis. Is there epidemiological evidence for an association? *Br. J. Psychiatry* **157,** 25–33.

Tien, A. Y., and Anthony, J. C. (1990). Epidemiological analysis of alcohol and drug use as risk factors for psychotic experiences. *J. Nerv. Ment. Dis.* **178,** 473–480.

Tramer, M. R., Carroll, D., Campbell, F. A., Reynolds, D. J., Moore, R. A., and McQuay, H. J. (2001). Cannabinoids for control of chemotherapy induced nausea and vomiting: Quantitative systematic review. *BMJ* **323,** 16–21.

Tsai, S. J., Wang, Y. C., and Hong, C. J. (2000). Association study of a cannabinoid receptor gene (CNR1) polymorphism and schizophrenia. *Psychiatr. Genet.* **10,** 149–151.

Turner, C. E., Elsohly, M. A., and Boeren, E. G. (1980). Constituents of Cannabis sativa L. XVII. A review of the natural constituents. *J. Nat. Prod.* **43,** 169–234.

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

Van Mastrigt, S., Addington, J., and Addington, D. (2004). Substance misuse at presentation to an early psychosis program. *Soc. Psychiatry Psychiatr. Epidemiol.* **39,** 69–72.

van Os, J., Bak, M., Hanssen, M., Bijl, R. V., de Graaf, R., and Verdoux, H. (2002). Cannabis use and psychosis: A longitudinal population-based study. *Am. J. Epidemiol.* **156,** 319–327.

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

Verdoux, H., Gindre, C., Sorbara, F., Tournier, M., and Swendsen, J. D. (2003a). Effects of cannabis and psychosis vulnerability in daily life: An experience sampling test study. *Psychol. Med.* **33,** 23–32.

Verdoux, H., Gindre, C., Sorbara, F., Tournier, M., and Swendsen, J. D. (2003b). Effects of cannabis and psychosis vulnerability in daily life: An experience sampling test study. [comment]. *Psychol. Med.* **33,** 23–32.

Verdoux, H., Sorbara, F., Gindre, C., Swendsen, J. D., and van Os, J. (2003c). Cannabis use and dimensions of psychosis in a nonclinical population of female subjects. *Schizophr. Res.* **59,** 77–84.

Volkow, N. D., Fowler, J. S., Wolf, A. P., and Gillespi, H. (1991). Metabolic studies of drugs of abuse. *NIDA Res. Monogr.* **105,** 47–53.

Weiser, M., Knobler, H. Y., Noy, S., and Kaplan, Z. (2002). Clinical characteristics of adolescents later hospitalized for schizophrenia. *Am. J. Med. Genet.* **114,** 949–955.

Wylie, A. S., Scott, R. T., and Burnett, S. J. (1995). Psychosis due to "skunk." *BMJ* **311,** 125.

Young, D., and Scoville, W. B. (1938). Paranoid Psychosis in narcolepsy and the possible dosages of benzedrine treatment. *Medical clinics of North America* **22,** 673.

Zammit, S., Allebeck, P., Andreasson, S., Lundberg, I., and Lewis, G. (2002). Self reported cannabis use as a risk factor for schizophrenia in Swedish conscripts of 1969: Historical cohort study. [comment]. *BMJ* **325,** 1199.

Zavitsanou, K., Garrick, T., and Huang, X. F. (2004). Selective antagonist [3H]SR141716A binding to cannabinoid CB1 receptors is increased in the anterior cingulate cortex in schizophrenia. *Prog. Neuro-Psychopharmacol. Biol. Psychiatry* **28,** 355–360.

Zuardi, A. W., Shirakawa, I., Finkelfarb, E., and Karniol, I. G. (1982). Action of cannabidiol on the anxiety and other effects produced by delta 9-THC in normal subjects. *Psychopharmacology* **76,** 245–250.

Zuardi, A. W., Rodrigues, J. A., and Cunha, J. M. (1991). Effects of cannabidiol in animal models predictive of antipsychotic activity. *Psychopharmacology* **104,** 260–264.

Zuardi, A. W., Morais, S. L., Guimaraes, F. S., and Mechoulam, R. (1995). Antipsychotic effect of cannabidiol. *J. Clin. Psychiatry* **56,** 485–486.

Zuardi, A. W., Hallak, J. E., Dursun, S. M., Morais, S. L., Faria Sanches, R., Musty, R. E., and Crippa, J. A. (2006). Cannabidiol monotherapy for treatment-resistant schizophrenia. *J. Psychopharmacol.* **20**(5), 683–686. Epub.