Cannabinoids and Psychosis: Pharmacological Evidence
Deepak Cyril D’Souza, MD
“...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’alienation mentale’ JJ Moreau de Tours (1845)(Moreau, 1973).

As described above, the association between cannabis use and psychosis has long been recognized. However, recent advances in understanding how cannabis and other cannabinoids produce their effects has renewed interest in this association. Case series of psychosis following cannabis use, autobiographical accounts, surveys of cannabis users in the general population, epidemiological studies, and pharmacological studies with various cannabinoid compounds collectively suggest an association between cannabis and psychosis.

The chapter by Corcoran reviews the epidemiological data associating cannabis and psychosis. This chapter will focus exclusively on pharmacological studies investigating the association between cannabis and psychosis. First, the term psychosis needs to be defined. Psychosis is a generic psychiatric term for a mental state often described as involving a loss of contact with reality. Psychotic symptoms include hallucinations and other alterations in perceptions, delusions, disorganized thinking and speech, and loss of insight. A psychotic disorder refers to a condition characterized by persistent psychotic symptoms accompanied by functional deficits.

**Cannabis, Δ-9-THC and other cannabinoids**

Herbal cannabis contains nearly 70 cannabinoid compounds (Elsohly, 2005). Since Δ-9-THC is the main active ingredient of cannabis, the more the Δ-9-THC content of herbal cannabis, the
stronger its effects. Hashish or hash, a preparation composed of the compressed trichomes collected from the cannabis plant, has a very high concentration of Δ-9-THC, and is therefore a potent form of cannabis. There is great variability in the Δ-9-THC content of herbal cannabis worldwide. 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 U.S. In the most recent report covering the last ten years on approximately 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, 2005). This may be related to the use of sophisticated growing techniques and the cloning of cannabis plants yielding high levels of Δ-9-THC. 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. Similarly, the average Δ-9-THC content of Dutch cannabis, Dutch hashish and imported hashish has significantly increased between 1999 and 2005 (Niesink, 2005). For example, in 2005, the average Δ-9-THC content of Dutch home-grown cannabis (Nederwiet) was 17.73%, and was nearly 3 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. What impact this has on the adverse effects of cannabis is unclear, but if they are related to its Δ-9-THC content then it would be reasonable to expect that cannabis with high Δ-9-THC content might be associated with greater adverse effects.
Δ-9-THC is broken down (metabolized) into 11-hydroxy-THC, a compound that is more potent than Δ-9-THC. The time course of 11-hydroxy-THC blood levels correlates well with the psychological effects of Δ-9-THC reviewed in (Agurell, 1986).

The other constituent cannabinoids present in herbal cannabis may have an influence on the effects of Δ-9-THC. Cannabidiol (CBD) has been shown to have anxiolytic (anxiety-lowering) and antipsychotic-like effects (Guimaraes, 1994; Zuardi, 2006; 1995; 1991; 1982) and may block the conversion of Δ-9-THC to the more psychoactive 11-hydroxy-THC (Bornheim, 1995). Thus, CBD may offset some of the adverse effects of Δ-9-THC. Interestingly, some studies have reported significant variability in the CBD content of cannabis, with some samples of cannabis being devoid of CBD (Pitts, 1992; 1990).

Another potential source of data on the association between cannabis and psychosis comes from the known effects of synthetic cannabinoids, including dronabinol, nabilone, and levonantradol.

**Psychosis associated with the therapeutic use of cannabinoids.**

Cannabinoids including cannabis, natural and synthetic Δ-9-THC, nabilone and levonantradol have been used in the treatment of nausea and vomiting from anticancer drugs, muscle stiffness (spasticity) in multiple sclerosis, pain syndromes, glaucoma, stimulation of appetite, etc. Δ-9-THC is marketed under the trade name Marinol® in the U.S as an oral drug. It should be noted that Δ-9-THC produces slightly different effects depending on whether it is smoked or consumed orally. Adverse events causally linked to Marinol® that occurred at > 1% in the clinical trials included hallucinations, abnormal thinking, paranoid reaction, amnesia etc, all of which are symptoms of psychosis (Marinol® Product monograph). Further, as the dose was increased, the
incidence of “disturbing” psychiatric reactions also increased. Levonantradol developed by Pfizer for the treatment of nausea and vomiting was withdrawn from the market because of unacceptable psychiatric side effects. Studies with oral and intramuscular levonantradol 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, 1985; Cronin, 1981; Diasio , 1981; Heim,1984; 1981; Jain, 1981; Kenny, 1982; Laszlo, 1981; Sheidler, 1984; Stuart-Harris , 1983). Psychotropic adverse effects increased both with increasing dose and with repeated dosing (Citron,1985; Stambaugh,1984). Further, some subjects refused further testing because of the disturbing psychotropic effects. Nabilone (CESAMET™) 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. Finally, in a systematic review of randomized controlled trials comparing the cannabinoids with placebo or other drugs used to treat nausea and vomiting, 6% of patients receiving cannabinoids presented with hallucinations and 5% with “paranoia”, while no patients treated with control drugs reported such side effects (Tramer, 2001). Thus, psychotic symptoms and psychosis have been reported with the medicinal use of cannabinoids; these effects appear to be dose-related. However, these kinds of naturalistic data have limitations.

Experimental pharmacological studies with cannabinoids address some of the limitations of naturalistic data. 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.
Experimental Pharmacological 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 1940’s, pharmacological investigations were conducted under the direction of the “LaGuardia Committee on Marihuana” (Mayor's, 1944). At doses of cannabis between 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.

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 & Jasinski (1969) compared the effects of Δ-9-THC (75-225 µg/kg, smoked) and LSD (0.5 to 1.5) in 10 “normal” controls. Both drugs produced perceptual distortions, mood changes and, at higher doses, hallucinations. Of note, 2 subjects dropped out from the study after experiencing psychotic “reactions” from Δ-9-THC. However, Hollister and Gillespie showed that Δ-9-THC was not associated with as prominent psychotomimetic effects as LSD (Hollister, 1986).

Ames studied the effects of unassayed oral doses of cannabis extract (about 50-70 g Δ-9-THC) in 12 student doctors who were presumably healthy (Ames, 1958). 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, fears of ECT and fears of developing schizophrenia. One subject refused to answer questions for fear of being “certified as insane”.

In a double-blind, placebo-controlled study with high and low dose Δ-9-THC Melges reported that cannabis users noted psychotic symptoms including thought disorder (“tracking difficulties” that subjects reported including racing thoughts, thought blocking, losing their train of thought, etc.) and paranoia (Melges, 1970). Jones did not report robust psychotomimetic effects in studies of “normal” controls with Δ-9-THC (20 mg smoked or 40 mg orally) (Jones, 1970). 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.

The pharmacological studies discussed thus far had several limitations including the absence of placebo/control, lack of a double-blind, the inclusion of psychiatrically ill individuals and the 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 reported the effects of synthetic Δ-9-THC (120 μg/kg) administered orally to 17 healthy individuals under controlled laboratory conditions (Leweke, 1999). The study included subjects with past experience but no recent consumption of cannabinoids. Subjects with a history of drug abuse, psychiatric disorders or lifetime consumption of cannabis more than 10
times were excluded. Subjects reported a range of effects 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.

More recently, D’Souza (2004) characterized the behavioral and cognitive effects of Δ-9-THC in a double-blind, placebo-controlled study of healthy controls (n=22). This experiment was specifically designed to study whether Δ-9-THC can induce schizophrenia-like psychotic symptoms in healthy individuals. Only subjects with past cannabis experience but without lifetime cannabis abuse or dependence were included. Healthy subjects were very carefully screened to rule out any psychiatric disorder and/or a family history of a major psychiatric disorder. Subjects were administered in random order 5 mg or 2.5 mg of Δ-9-THC, or placebo by intravenous injection.
The symptoms of schizophrenia include positive symptoms, negative symptoms and cognitive deficits and are described below.

**Positive symptoms.** The positive symptoms induced by Δ-9-THC included suspiciousness, paranoid and grandiose delusions, conceptual disorganization, and illusions (fig. 1). 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.

*Perceptual Alterations.* $\Delta$-9-THC also produced depersonalization, derealization, distorted sensory perceptions, altered body perception, feelings of unreality and extreme slowing of time in healthy individuals (fig. 2). 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.* $\Delta$-9-THC produced negative symptoms in healthy individuals which included blunted affect, reduced rapport, lack of spontaneity, psychomotor retardation, and
emotional withdrawal (fig. 1). Of note, a persistent “amotivational syndrome” has been described in chronic heavy cannabis users by some (Halikas, 1982; Hall, 1998; Kolansky, 1971b; Millman, 1986; Tennant, 1972b) but not others (Carter, 1980; Hollister, 1988; Rubin, 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 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, 2001; Heishman, 1990; Hooker, 1987; Leweke, 1998; Marks, 1989; Miller, 1977). These are also the cognitive deficits observed in schizophrenia (Heinrichs, 1998). Of note, the most robust effects of cannabinoids are on verbal memory (Ranganathan, 2006), the latter is also the most robust cognitive deficit observed in schizophrenia (Heinrichs, 1998).

In healthy subjects (hatched lines), Δ-9-THC significantly impaired immediate free recall in a dose-dependent manner across all 3 trials of immediate recall (fig. 3). Δ-9-THC also impaired delayed (+30 minutes) free recall and delayed cued recall in a significant, dose-dependent manner. The effect on delayed recognition recall trended towards significance. Finally, Δ-9-THC increased the number of false positives and intrusions with a trend towards significance.
In summary, in carefully screened healthy controls, Δ-9-THC produced transient schizophrenic-like positive symptoms, perceptual alterations, negative symptoms and cognitive deficits. In addition, Δ-9-THC also produced transient euphoria and anxiety.

**Effects of Δ-9-THC in Individuals Diagnosed with Schizophrenia**
Lindeman (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 symptom. D’Souza conducted an identical study as the one described earlier, in individuals diagnosed with schizophrenia (D’Souza, 2005). Δ-9-THC transiently exacerbated positive and negative symptoms, perceptual alterations, cognitive deficits in these chronic, stable patients who were being treated with antipsychotic medications. 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. However, schizophrenia patients appeared to be more sensitive to some of the Δ-9-THC effects relative to healthy controls (fig. 3, 4).
Henquet (2006) studied the interactions of Δ-9-THC and genes in a double-blind, placebo-controlled cross-over design in healthy controls, patients with a psychotic disorder and relatives of patients with a psychotic disorder. They concluded that the experimental effects of Δ-9-THC i.e., the induction of psychosis and cognitive impairments, was under genetic influences, and further, that the genetic moderation of Δ-9-THC–induced psychosis varied as a function of psychosis liability.

Summary
Pharmacological studies suggest that acute exposure to cannabis, Δ-9-THC, and synthetic cannabinoids can produce transient effects in healthy individuals that resemble the symptoms of psychosis. These effects include positive symptoms, negative symptoms and cognitive impairments, along with other effects that are not typically associated with psychosis. These effects appear to be dose-related. Not all people experience these effects from cannabinoids. In fact, only a minority of healthy people experience psychosis when exposed to cannabinoids; why some individuals and not others experience such effects is unclear but is being actively investigated. Preliminary evidence suggests that genetic factors, other environmental factors, and psychosis-proneness interact with exposure to cannabinoids. What is clear is that individuals with an established psychotic disorder such as schizophrenia, or individuals at risk for a psychotic disorder are at much greater risk. Finally, given that many of the adverse effects of cannabinoids including psychosis are dose-related, if the Δ-9-THC content of herbal cannabis continues to rise, one might expect to see a rise in rates of adverse effects including psychosis.
Finally, the pharmacological data reviewed above converges with other lines of evidence including case reports of cannabis psychosis, surveys of cannabis users and epidemiological studies in supporting an association between cannabis/cannabinoids and psychosis.
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