Cannabinoids and psychosis

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Abstract
Recent advances in knowledge about cannabinoid receptor function have renewed interest in the association between cannabis and psychosis. Case series, autobiographical accounts, and surveys of cannabis users in the general population suggest an association between cannabis and psychosis. Cross-sectional studies document an association between cannabis use and psychotic symptoms, and longitudinal studies suggest that early exposure to cannabis confers a close to two-fold increase in the risk of developing schizophrenia. Pharmacological studies show that cannabinoids can induce a full range of transient positive, negative, and cognitive symptoms in healthy individuals that are similar to those seen in schizophrenia. There is considerable evidence that in individuals with an established psychotic disorder such as schizophrenia, exposure to cannabis can exacerbate symptoms, trigger relapse, and worsen the course of the illness. Only a very small proportion of the general population exposed to cannabis develop a psychotic illness. It is likely that cannabis exposure is a ‘component cause’ that interacts with other factors to ‘cause’ schizophrenia or other psychotic disorder, but is neither necessary nor sufficient to do so alone. Further work is necessary to identify the factors that underlie individual vulnerability to cannabinoid-related psychosis and to elucidate the biological mechanisms underlying this risk.

Introduction

Its first effect is sudden, violent, uncontrollable laughter; then come dangerous hallucinations – space expands – time slows down, almost stands still...fixed ideas come next, conjuring up monstrous extravagances – followed by emotional disturbances, the total inability to direct thoughts, the loss of all power to resist physical emotions...leading finally to acts of shocking violence...ending often in incurable insanity.

Reefer Madness, 1936.

The observed relationship between cannabis consumption and psychosis has long been recognized (Moreau, 1973; Warnock, 1903). The rise in cannabis use worldwide, recent advances in our understanding of the brain cannabinoid system, and a series of epidemiological studies have renewed interest in the association between cannabis use and psychosis (Murray, Morrison, Henquet, & Di Forti, 2007). The purpose of this paper is to review the evidence supporting and refuting the association between cannabis exposure and psychotic disorders that include schizophrenia.

Cannabis contains nearly 70 cannabinoids (Elsohly & Slade, 2005) including its most active constituent, Δ9-tetrahydrocannabinol (Δ9-THC). Several reports suggest that the average Δ9-THC content of cannabis may be increasing (ONDCP, 2008). The psychoactive effects of cannabis vary according to its Δ9-THC content. Cannabidiol (CBD), another constituent in cannabis, has been shown to have anxiolytic and antipsychotic effects (Leweke, Koethe, & Gerth, 2005; Zuardi et al., 2006) leading to the suggestion that CBD may offset some of the adverse effects of Δ9-THC. Just as there is variability in the Δ9-THC content of cannabis, there is variability in the CBD content of cannabis. Thus, if the consequences of cannabis exposure are related to Δ9-THC content and if CBD offsets some of the negative effects of Δ9-THC, then exposure to cannabis with a higher Δ9-THC content and/or low CBD content might be associated with greater negative consequences, and there is some experimental evidence to support this (Morgan & Curran, 2008).

In reviewing the association between cannabis and psychosis, two important points need to be considered – the distinction between psychotic
symptoms and a psychotic disorder such as schizophrenia, and the fact that symptoms of schizophrenia include not just positive psychotic symptoms, but also negative symptoms (amotivation, social withdrawal, and emotional blunting, among others) and cognitive deficits (impairments in memory, attention and executive function).

**Can cannabinoids cause transient positive, negative, or cognitive symptoms in healthy individuals?**

Several lines of evidence suggest that cannabis and other cannabinoids can produce a range of transient psychotic symptoms in an otherwise clear sensorium (D’Souza, 2007). The evidence, in order of increasing strength, comes from case reports, surveys, studies with ‘medicinal’ cannabinoids, and uncontrolled pharmacological studies. The symptoms that can be induced by cannabinoids include depersonalization, derealization, paranoia, ideas of reference, flight of ideas, pressured thought, disorganized thinking, persecutory delusions, grandiose delusions, auditory and visual hallucinations, impairments in attention and memory, anxiety and panic reactions, and psychomotor agitation. These symptoms are transient (minutes to hours), dose-related, and can occur in otherwise healthy individuals without any obvious risk for psychosis. Finally, psychotic symptoms sometimes recur when the individual resumes using cannabis. There have been a few reports of symptoms persisting beyond the period of intoxication for weeks; however, severe or persistent psychotic reactions are rare, and are more likely to occur in individuals with a pre-existing psychiatric condition (Chopra & Smith, 1974).

In large community surveys, between 20% and 50% of individuals report acute transient psychotic symptoms including paranoia, persecutory ideas, and hallucinations while under the influence of cannabis (Green, Kavanagh, & Young, 2003; Reilly, Didcott, Swift, & Hall, 1998). Others have reported very low rates of psychotic symptoms or psychosis in cannabis users (Halikas, Goodwin, & Guze, 1972).

Recently, D’Souza reported the first placebo-controlled, double-blind study characterizing the effects of Δ-9-THC (0 mg, 2.5 mg, and 5 mg), using well-validated behavioural and cognitive measures in healthy controls ($n = 22$) who were screened for the presence of any significant psychiatric disorder or family history of Axis I disorders (D’Souza et al., 2004). Without altering general orientation, Δ-9-THC produced transient positive symptoms (Figure 1), perceptual alterations, negative symptoms, euphoria, anxiety, and deficits in working memory, verbal recall, and the executive control of attention.

**Positive symptoms**

Δ-9-THC induced a range of positive symptoms of schizophrenia including suspiciousness, paranoid and grandiose delusions, conceptual disorganization, fragmented thinking, and perceptual alterations. These effects, reported by carefully screened healthy subjects, appear remarkably similar to the psychotic symptoms reported by patients with schizophrenia.

![Figure 1. Δ2-THC induces transient psychotomimetic effects in healthy individuals.](image-url)
Δ-9-THC also produced depersonalization, derealization, distorted sensory perceptions, altered body perception, feelings of unreality, and extreme slowing of time in healthy individuals (Figure 1). Subjects were reported as have spoken or done ‘something bizarre’ and to have appeared ‘spaced out’ and ‘separated or detached’. Subjects were also rated as requiring more redirection.

**Negative symptoms**

Δ-9-THC produced effects similar to the negative symptoms of schizophrenia, including blunted affect, reduced rapport, lack of spontaneity, psychomotor retardation, and emotional withdrawal. An ‘amotivational syndrome’ resembling the negative symptoms of schizophrenia and characterized by apathy, amotivation, social withdrawal, narrowing of interests, lethargy, impaired memory, impaired concentration, disturbed judgement, and impaired occupational achievement has been described in chronic heavy cannabis users (Millman & Sbriglio, 1986; Tennant & Groesbeck, 1972). However, others have refuted the existence of the syndrome and have offered alternative explanations (Hollister, 1988).

**Cognitive deficits**

Healthy subjects had significantly impaired immediate and delayed (30-minute) recall of a word list that was learned under the influence of Δ-9-THC; these effects were dose-dependent (Figure 3). Δ-9-THC also increased the number of false positives and intrusions during verbal recall. More recently, Henquet showed that smoked Δ-9-THC impairs verbal learning and recall, sustained attention, selective attention, and psychomotor speed in healthy subjects, schizophrenia patients, and relatives of patients with schizophrenia (Henquet et al., 2006). Henquet’s and D’Souza’s observations are consistent with other reports showing acute dose-related effects of cannabinoids in humans on learning, short-term memory, working memory, executive function, abstract ability, decision making, and attention (Heishman, Huestis, Henningfield, & Cone, 1990; Hooker & Jones, 1987; Ranganathan & D’Souza, 2006). Of note, the most robust cognitive deficit induced by Δ-9-THC, verbal memory, is also the most robust cognitive deficit observed in schizophrenia (Heinrichs & Zakzanis, 1998).

To summarize, cannabinoids administered via different routes can produce a range of positive symptoms, negative symptoms, and cognitive deficits in healthy individuals that resemble the symptoms of schizophrenia. These effects are dose-related, do not disrupt orientation, and last for minutes to hours. A small number of vulnerable individuals experience robust psychotomimetic effects, but what produces that vulnerability is unclear.

**Do cannabinoids exacerbate symptoms in patients with schizophrenia?**

Several lines of evidence suggest that cannabis use exacerbates the symptoms of schizophrenia, and continued use predicts the presence of more psychotic symptoms and may worsen the prognosis of people who already have schizophrenia (D’Souza, 2007; Knudsen & Vilmar, 1984; Negrete, Knapp, Douglas, & Smith, 1986). There are very few pharmacological studies on the effects of cannabinoids in individuals with schizophrenia. Unassayed doses of hashish induced exacerbation of symptoms in schizophrenic patients (Lindemann & Malamud, 1934).

A recent double-blind, randomized controlled pharmacological study examining this topic characterized the effects of Δ-9-THC (0 mg, 2.5 mg, and 5 mg) in schizophrenic patients using the methods identical to the similar study in healthy subjects (D’Souza et al., 2005). All patients were taking stable doses of antipsychotic medications and were clinically stable. 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. Schizophrenics were more sensitive to the effects of Δ-9-THC (Figure 2) increases in positive symptoms experienced were brief, modest, similar to the patients’ typical symptoms, and occurred even though subjects were clinically stable and receiving therapeutic doses of antipsychotics.

Similarly, relative to controls, schizophrenia patients were more vulnerable to Δ-9-THC-related learning impairments. At 5 mg, schizophrenics (solid lines) were unable to learn at all (Figure 3). It is possible that the group differences in Δ-9-THC effects would have been even greater in schizophrenic patients who were not taking antipsychotic medications or were clinically unstable.

**Possible mechanisms by which cannabinoids cause psychotic symptoms**

Δ-9-THC is a partial agonist at cannabinoid receptors (CB1Rs) where it has modest affinity ($K_i = 35–80\text{nmol}$) and low intrinsic activity (Compton, Johnson, Melvin, & Martin, 1992). CB1Rs are G-protein-mediated receptors that are distributed with high density in the cerebral cortex, particularly frontal regions, basal ganglia, hippocampus, anterior cingulate cortex, and cerebellum, brain regions that have been implicated in the putative neural circuitry of...
psychosis (see Breivogel & Sim-Selly, pp.113–121 in this journal issue). The primary effect of cannabinoids is the modulation of neurotransmitter release via activation of presynaptic CB1Rs (see Breivogel & Sim-Selly, pp.113–121 in this journal issue). There are several possible neurotransmitter systems through which cannabinoids could induce positive, negative, and cognitive symptoms of schizophrenia.

**Dopamine**

According to the dopamine (DA) hypothesis, some of the symptoms of psychosis may be attributed to disturbed and hyperactive dopaminergic activity. CB1 and DA-D2 receptors are co-expressed in several brain regions (Hermann, Marsicano, & Lutz, 2002). Cannabinoids induce firing of dopaminergic mesolimbic neurons (Gardner, 2005), and induce DA release in the striatum in animals (Fadda et al., 2006; Tanda, Pontieri, & Di Chiara, 1997). Recently, Bossong et al. (2008) have provided the first in vivo evidence of Δ9-THC-induced striatal DA release in humans (2008). CB1-R mediated increase in mesolimbic dopaminergic activity may explain the positive psychotic symptoms induced by Δ9-THC.
However, DA-D₂ receptor antagonism fails to block either Δ-9-THC-induced c-fos expression in both the striatum and nucleus accumbens of rats (Miyamoto et al., 1996), or Δ-9-THC-induced psychotomimetic, cognitive, and perceptual altering effects in humans (D’Souza et al., 2008a). Collectively, these data suggest that it is unlikely that D₂ receptor mechanisms play a major role in mediating the positive (psychotomimetic) effects of Δ-9-THC.

The cognitive deficits induced by cannabinoids may be explained by the effects of CB₁R activation in the prefrontal cortex (PFC). Given that either too much or too little dopaminergic activity in the PFC can lead to impairments in PFC-related cognitive functions (Goldman-Rakic, 1996), Δ-9-THC-induced working memory deficits may be a result of stimulation of mesoprefrontal dopaminergic transmission by CB₁R activation (Diana, Melis, & Gessa, 1998; Pistis, Porcu, Melis, Diana, & Gessa, 2001).

**Gamma-aminobutyric acid (GABA)**

In the hippocampus and neocortex, CB₁Rs are present on the terminals of axons in cholecystokinin (CCK)-containing GABA neurons that target the perisomatic regions of pyramidal cells (Eggan & Lewis, 2007). These inhibitory neurons express more CB₁Rs than do excitatory terminals, and consequently are more sensitive to the effect of CB₁R agonists. CB₁R activation reduces GABA release, resulting in disinhibition of pyramidal cell activity. Furthermore, these CCK-containing, CB₁R-expressing GABA neurons are believed to play an important role in orchestrating pyramidal cell synchrony in the gamma (40 Hz) frequency range (Hoffman & Lupica, 2000). Both in vivo and in vitro studies have reported that CB₁R agonists reduce the power of 40-Hz oscillations (Hajos et al., 2000, Hajos, Hoffmann, & Kocsis, 2008; Robbe et al., 2006). Disruption in neural synchrony could interfere with memory consolidation, associative functions, and normal gating mechanisms, eventually leading to psychotic symptoms. Since schizophrenic patients already display GABAergic deficits (Lewis & Hashimoto, 2007), further reduction of GABA release by cannabinoids in the presence of a pre-existing GABA deficit may explain why schizophrenics show heightened sensitivity to the effects of cannabinoids.

**Glutamate**

Deficits in glutamate receptor function have been implicated in the neurobiology of schizophrenia (Stone, Morrison, & Pilowsky, 2007). CB₁Rs are expressed in glutamatergic cortical principal neurons (Domenici et al., 2006; Takahashi & Castillo, 2006). Cannabinoids reduce glutamatergic synaptic transmission in several brain regions involved in the regulation of gating functions (Auclair, Otani, Soubrie, & Crepel, 2000; Azad et al., 2003; Fujiwara & Egashira, 2004; Misner & Sullivan, 1999; Robbe, Alonso, Duchamp, Bockaert, & Manzoni, 2001). In addition, studies in CB₁R-knockout mice suggest that cannabinoids may also reduce glutamate release via some non-CB₁R-related mechanism (Hajos, Lendert, & Freund, 2001).

**Can cannabinoids cause a persistent psychotic disorder?**

Interest in the association between cannabis and schizophrenia was sparked by a large longitudinal cohort study of over fifty thousand Swedish males aged 18 to 20 years who were conscripted into military service between 1969 and 1970 (Andreasson, Allebeck, Engstrom, & Rydberg, 1987). Individuals who reported having used cannabis more than 50 times were six times more likely than non-users to have been diagnosed with schizophrenia in the ensuing 15 years. Adjustment for other relevant risk factors reduced but did not eliminate the higher risk (OR = 2.3) of schizophrenia associated with cannabis use. A more recent reanalysis and extension of the same study reconfirmed that heavy cannabis users at the age of 18 years were 6.7 times more likely than non-users to be hospitalized for schizophrenia over the following 27 years (Zammit, Allebeck, Andreasson, Lundberg, & Lewis, 2002). The adjusted odds ratio remained significant (1.2), albeit lower than in the original study, despite adjusting for a number of confounds, e.g. low IQ, urbanicity, poor social integration and stimulant use. Further, the increased risk of schizophrenia conferred by cannabis use persisted even when subjects who developed schizophrenia within five years of conscription were excluded from the analysis, in order to control for the possibility that cannabis use had been merely a manifestation of the schizophrenia prodrome.

Several recent prospective cohort studies complement the historical studies. In a prospective general population birth cohort study (n = 759), subjects using cannabis at ages 15 and 18 years had higher rates (OR = 3.1) of developing psychotic symptoms or schizophreniaiform disorder at age 26 years compared to non-users, even after controlling for psychotic symptoms that pre-dated the onset of cannabis use (Arseneault et al., 2002).

A systematic review of longitudinal studies of cannabis use and subsequent psychotic outcomes reported a 40% increased risk of psychotic outcome...
in individuals who had ever used cannabis (pooled adjusted OR = 1.41, 95% CI 1.20 ± 1.65) (Moore et al., 2007). The risk rose in a dose-dependent fashion with greater cannabis exposure (OR = 2.09, 1.54 ± 2.84). Meta-analyses suggest that cannabis might account for between 8% and 14% of schizophrenia cases (Henquet, Murray, Linszen, & van Os, 2005b; Moore et al., 2007), although the quintupling of rates of cannabis use over the last four decades (Aust, Sharp, & Goulden, 2002; Zammit et al., 2002) has not been matched by a commensurate 40% to 70% increase in prevalence of schizophrenia; indeed, rates may actually be decreasing (Der, Gupta, & Murray, 1990).

**Can cannabinoids cause persistent cognitive deficits?**

Even though cognitive symptoms are a core feature of schizophrenia and psychotic disorders, few studies that examine the risk of schizophrenia from cannabis exposure have specifically studied cognitive symptoms. Acute exposure to cannabinoids clearly produces cognitive impairments that are transient. Heavy and prolonged cannabis exposure may be associated with deficits in memory, sustained attention, and executive functioning (Solowij et al., 2002). But whether these impairments persist and for how long is less clear. Some studies suggest full recovery after 28 days (Pope, Gruber, Hudson, Huestis, & Yurgelun-Todd, 2001) or three months of abstinence (Fried, Watkinson, & Gray, 2005), but others show some recovery only after an average of two years’ abstinence (Hall & Solowij, 1998; Solowij, 1995). Others have found persistent cognitive impairments and other indices of alterations in brain function even after four weeks of abstinence (Bolla, Brown, Eldreth, Tate, & Cadet, 2002, Bolla, Eldreth, Matochik, & Cadet, 2005; Eldreth, Matochik, Cadet, & Bolla, 2004; Pillay et al., 2008; Schweinsburg et al., 2008; Sneider et al., 2008), although these findings may have been a pre-existing baseline. Early adolescent cannabis use may be associated with greater vulnerability to persistent cognitive deficits (Ehrenreich et al., 1999; Pope et al., 2003). Finally, prenatal exposure to cannabinoids has been reported to produce long-term cognitive, motor and social deficits that last into adulthood (Fried, Watkinson, & Gray 2003; Goldschmidt, Richardson, Cornelius, & Day, 2004).

**Why are some individuals more vulnerable to psychotic outcomes with exposure to cannabinoids?**

Even though millions of people use cannabis, only a minority experience psychotic symptoms and even fewer develop a psychotic disorder. Clearly, other factors must interact with exposure to cannabis to increase the likelihood of a psychotic outcome, and Henquet has argued forcefully that cannabis exposure clearly has different effects on different people in different environments, and therefore a concept of ‘relative risk of psychosis’ cannot be uniformly applied (Henquet & Van Os, 2008).

**Psychosis proneness**

Psychosis proneness may be defined psychometrically or by the presence of some other obvious risk, such as family history of psychosis. Cannabis exposure has been shown to be associated with higher rates of psychotic outcomes in individuals with higher scores on measures of psychosis proneness (Barkus & Lewis, 2008; Henquet et al., 2005a; Stirling et al., 2008; Verdoux, Gindre, Sorbara, Tournier, & Swendsen, 2003) and individuals with a high risk for developing psychosis (either because of family history or prodromal symptoms) (Corcoran et al., 2008; Kristensen & Cadenhead, 2007).

It may be that psychosis-prone individuals are attracted to using cannabis (an association model), that cannabis use increases psychosis proneness (a causal model), or that there is another factor that causes both psychosis proneness and cannabis use (an indicator-variable model) (Henquet, Di Forti, Morrison, Kuepper, & Murray, 2008; Schiffman, Nakamura, Earleywine, & LaBrie, 2005). Cannabis users as a group tend to exhibit higher schizotypy scores (Dumas et al., 2002; Schiffman et al., 2005; Skosnik, Spatz-Glenn, & Park, 2001). However, psychosis-prone individuals are not more likely to use cannabis (Henquet et al., 2005a). A recent study showed that individuals with schizophrenia showed higher rates of cannabis use than either their siblings or controls, while their siblings had similar rates of cannabis use to controls, suggesting that (1) cannabis use predicted schizophrenia and (2) that risk for developing schizophrenia does not confer a higher risk for cannabis use (Veling, Mackenbach, van Os, & Hoek, 2008). Conversely, subjects with a schizophrenic father had a risk ratio of 4.5 compared with individuals with no family history for developing a cannabis psychosis, clearly indicating a familial component (Arendt, Mortensen, Rosenberg, Pedersen, & Waltoft, 2008).

**Genetic vulnerability**

A number of recent studies suggest a possible interplay between genetic factors and cannabis exposure in the development of psychosis (Henquet et al., 2008). Catechol-O-methyltransferase (COMT) is the enzyme that degrades dopamine, epinephrine,
and norepinephrine. In a longitudinal birth cohort study (n=1000), adolescents homozygous for the COMT Val108Met allele were more likely than those without the allele to exhibit psychotic symptoms or develop schizophrenia if they used cannabis (Caspi et al., 2005). Similarly, in a randomized, double-blind, placebo-controlled study, carriers of the Val/Met allele were more sensitive to Δ-9-THC-induced psychotomimetic and amnestic effects than Met carriers, but only if they were already psychosis-prone (Henquet et al., 2006).

Neuregulin 1 (NRG1), a candidate gene for schizophrenia, is relevant to several schizophrenia-related neurodevelopmental processes (Munafo, Attwood, & Flint, 2008). Heterozygous deletion of NRG1 results in increased sensitivity of mice to the neurobehavioural effects of Δ-9-THC on an array of different behaviours including those that model symptoms of schizophrenia, especially under stressful conditions (Boucher et al., 2007).

Neurodevelopmental mechanisms

One view of schizophrenia is that it is a neurodevelopmental disorder. The endocannabinoid system is involved in several processes important in neurodevelopment, including neurogenesis, neural specification, neural maturation, neuronal migration, axonal elongation, and glia formation (Galve-Roperh, Aguado, Palazuelos, & Guzman, 2007). Thus, non-physiologic stimulation of the cannabinoid system by acute and repeated exposure to cannabis may further compound an already abnormally developing brain in adolescents and young adults at risk for psychotic disorder. While admittedly speculative, this may provide a mechanism underlying the observation that cannabis precipitates schizophrenia or alters the course of the disorder.

In preclinical studies, Δ-9-THC has been shown to alter the expression of brain-derived neurotrophic factor (BDNF), a neurotrophin that is involved in the regulation of the genesis, differentiation, survival, and repair of neurons (Butovsky et al., 2005; Derkinderen et al., 2003). Rats exposed to cannabinoids in their prenatal period (through maternal exposure) show significantly lower BDNF levels in the hippocampus and frontal cortex in adulthood (Maj et al., 2007). More recently, socially relevant doses of Δ-9-THC were shown to increase serum BDNF levels in humans (D’Souza, Pittman, Perry, & Simen, 2008b). Thus, cannabis may precipitate schizophrenia or alter the course of the disorder by disrupting neurodevelopment via effects on neurotrophins.

Do cannabinoids cause psychotic illness?

Several possible associations between cannabis and psychosis have been proposed (Arendt, Rosenberg, Foldager, Perto, & Munk-Jorgensen 2005).

• First, there may be no relationship at all between cannabis exposure and psychosis.

• Second, cannabis use may uncover a previously latent psychosis: psychosis-prone individuals may be more vulnerable to psychotic outcomes following exposure to cannabis.

• Third, cannabis use may precipitate relapse of a pre-existing psychosis – this has been shown quite clearly.

• Fourth, cannabis use may result from an already existing psychotic disorder; however, those at risk for psychosis do not have higher rates of cannabis use.

• Fifth, cannabis intake may cause psychosis where none would have otherwise existed.

This last ‘causal’ alternative is the most controversial. The commonly applied criteria to establish disease causality include temporality, strength and direction of the association, biological gradient (dose), consistency, specificity, coherence, experimental evidence and biological plausibility (D’Souza, 2007). Below we review the arguments for each criterion.

Temporality

Experimental evidence from laboratory studies clearly demonstrates a robust temporal relationship between exposure to cannabinoids and psychotic symptoms. While less robust, several studies suggest that cannabis use precedes or coincides with the onset of psychotic disorder and cannabis use may be associated with an earlier and more abrupt onset of psychotic disorder (Iversen, 2003). However, pinpointing the onset of a disorder with an insidious onset such as schizophrenia is challenging.

Dose

Several studies reviewed here provide evidence of a dose-response relationship between cannabis exposure and the risk of both psychotic symptoms and disorder.

Strength

The association between cannabis use and psychosis persists even after controlling for many potential confounding variables (Moore et al., 2007).

Specificity

While there is a strong association between cigarette smoking and schizophrenia, there is little evidence
to support the notion that cigarette smoking ‘causes’ schizophrenia. Further, the association with cannabis use is weaker for anxiety and affective disorders (Moore et al., 2007).

**Direction**

The case of reverse causality has been proposed whereby risk for schizophrenia predisposes to cannabis use, rendering the association between cannabis and psychotic illness merely an epiphenomenon of a shared vulnerability for both psychosis and cannabis (Collip, Myin-Germeys, & Van Os, 2008; Macleod, 2007). Since several longitudinal studies excluded people with psychosis at baseline, or adjusted for psychotic symptoms in the analysis, the observed association between cannabis and psychosis is unlikely to reflect reverse causation.

**Biological plausibility**

As reviewed above, the effects of cannabinoids on neurodevelopmental processes and key neurotransmitters known to be implicated in psychosis, as well as the identification of alleles that appear to increase vulnerability to psychosis provide biological plausibility for the association.

Despite such empirical support for a causal hypothesis between cannabis use and psychotic illness, most people who use cannabis do not develop schizophrenia, and most people with schizophrenia have never used cannabis. Further, there is a mismatch between the rates of cannabis abuse and those of schizophrenia. Finally, the increase in cannabis use, the use of more potent forms of cannabis and the earlier age of first use over the last few decades has not been accompanied or followed by a commensurate increase in the rates of schizophrenia or an earlier age of onset of the illness.

Taken collectively, exposure to cannabis is neither a necessary nor a sufficient cause of schizophrenia – similar to cigarette smoking being neither necessary nor sufficient to cause lung cancer. More likely, cannabis exposure is a component or contributing cause which interacts with other known (genetic, environmental) and unknown factors, culminating in schizophrenia. In the absence of known causes of schizophrenia, however, and the implications for public health policy should such a link be established (Hall & Pacula, 2003), the role of component causes such as cannabinoid exposure should remain a focus of further study. The public health implications of the findings are discussed elsewhere (Murray et al., 2007).

**Declaration of interest:** The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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