Cannabis and Recovery in Schizophrenia

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Introduction

In this chapter, we will explore the nuanced topic of cannabis and recovery in schizophrenia. Addressing this demands knowledge of what cannabis is and a broader understanding of how it relates to schizophrenia. Therefore, we will first explore the composition of cannabis before considering its role in causality and relate this to the question of why it is used so prevalently in those suffering from this condition. From this platform, we will then review and compare recovery-based interventions. Ultimately, the conflicted nature of cannabis will be considered with attention paid to its potential role in the treatment of schizophrenia.

Does Cannabis Cause Schizophrenia?

This commonly asked question implies a compositional unity; it suggests that cannabis is a single article. It is therefore first important to understand what we are describing with the term cannabis and appreciate its complexities before attempting to answer this question. Knowledge of the plant, its components, and its apparent contradictions will allow us to consider its influence in the context of recovery in schizophrenia.

Cannabis is at present the most-consumed illicit drug in the world—the prevalence of which in 2010 was 2.6–5.0%, amounting to 120–224 million users. It is produced and consumed in every country in the world and in amounts that far exceed other illicit drugs. The proportion of people with schizophrenia who use cannabis varies, yet surveys commonly find prevalence rates to be about 40%, much higher than the general population. It is a plant that grows wild throughout the world [1]. It has been used to make rope and material and has been used as a psychoactive drug for at least 2700 years. When used as a recreational drug, it is normally consumed either as a compressed resin or made from the flowering tops and leaves, which is then either smoked or ingested.

The myriad properties of cannabis are better understood by appreciating that it is composed of a range of substances. It is known to contain over 400 compounds, including over 60 cannabinoids, most of which are classed as aryl-substituted meroterpenes unique to the plant genus Cannabis [2]. Amongst these exists the best-known cannabinoid, the major active psychoactive constituent Δ^9 tetrahydrocannabinol (Δ^9-THC, or THC). THC produces a euphoric high, a feeling of relaxation, and intensification of sensation but is notorious for its apparent ability to induce psychotic symptoms.

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A. Shrivastava, A. De Sousa (eds.), *Schizophrenia Treatment Outcomes*,
https://doi.org/10.1007/978-3-030-19847-3_6

Alongside this may be found various cannabinoids, which range from producing synergistic, additive, or antagonistic effects with THC. Cannabidiol (CBD) is one such coexisting counterpart. As neither a spare part in the cannabis plant nor a psychoactive co-conspirator with THC, cannabidiol is in fact theorised to play an antipsychotic role. This component will be explored in greater depth later in the chapter.

The cultural change in cannabis cultivation has heralded a shift in the average baseline composition of street-bought cannabis. In the mid- to late twentieth century, less THC content existed in the naturally grown plants. However, with the advent of hydroponic growing systems and a culture that favoured more densely THC-laden product, a change was observed that found customers buying cannabis with an increasingly potent psychoactive profile. It is suggested that over time, the average THC content of a joint transitioned from approximately 10 mg in the 1960s and 1970s to 150 mg in the present day [3–7]. What is the relevance of a cannabis market offering high THC content? An understanding of the role of cannabinoids in relation to psychosis is key to answering this question. Let us consider some essential pharmacokinetics and pharmacodynamics.

Inhalation of cannabinoids produces rapid absorption into the bloodstream and prompts contact with the brain. Oral bioavailability is vastly lower, with approximately 25–30% of the blood concentration seen when taken via inhalation [8]. This is in part due to the first-pass metabolism via the liver. Metabolites formed in this process include 11-hydroxy-THC, which is theorised as being equally if not more potently psychoactive than Δ^9-THC. This is touted as being responsible for the delayed, yet intense, psychoactive sensations experienced following the ingestion of cannabis [9]. When ingesting cannabinoids, the onset of psychoactive effects is delayed but endures longer due to a process of slow release from the gut. As highly lipid-soluble compounds, cannabinoids sequester in adipose tissue following distribution via the bloodstream. This trait leads to a tissue elimination half-life of approximately 7 days. Furthermore, one dose may take up to 30 days to undergo complete elimination form the body's tissues [10].

Following metabolism in the liver, excretion occurs partly via urine, yet predominantly via the gut. Difficulties in accurately representing the degree of intoxication via urine and plasma analysis arise due to the confounding influence of sequestration in fat and the presence of active metabolites.

With regard to exerting their effects, cannabinoids primarily act through cannabinoid receptors, CB1 and CB2. Neuronal CB1 receptors are distributed within the central nervous system, as well as in various peripheral organs and tissues. CB1 neuronal receptors occupy sites in the cerebral cortex, basal ganglia, thalamus, brainstem, cerebellum, and limbic regions such as the hippocampus and amygdala. This distribution is broadly mirrored by uptake patterns of THC [11]. The location of CB receptors may explain the effects of cannabis use on learning, memory, emotion, motivation, and motor ability [12]. In the absence of ingested cannabis, these receptors are activated by endogenous cannabinoids, the major effects of which are largely mediated by their control of neurotransmitter release such as gamma-aminobutyric acid (GABA) and glutamate within the brain. These substances have been explored in terms of their influence with relation to a diaspora of functions including appetite, memory, stress response, and immunity.

It is clear that an endogenous framework exists for cannabinoids. Without digressing into discussions on this vast topic, let us interrogate instead the influence of exogenous cannabis on this system in terms of psychoactivity. This will form a key part of our attempt to consider whether cannabis is a cause of schizophrenia.

When interrogating a cause, it is useful to define what is meant by the term "cause." Cecile Henquet suggests that causality is generally found to be plausible in the context of studies if they (i) report an association between the exposure and the outcome consistently and with a strong effect size, (ii) show dose–response relationships between the exposure and the outcome,

(iii) show that the exposure precedes the outcome, and (iv) show that there is a plausible biological mechanism linking the exposure and the outcome [13].

On mechanism, the psychomimetic properties of cannabis have long been observed, and research into plausible avenues for these effects has been conducted. Moreover, the direct mimicry of schizophrenia-like symptoms has been demonstrated using the intravenous injection of D-9-THC in double-blind, randomised controlled trials (RCT). It is not simply a matter of casual observation. Deepak D'souza used a 3-day, double-blind RCT to assess the behavioural, cognitive, and endocrine effects of variable concentrations of intravenous THC with a view to investigating its induction of psychosis [14]. The trial was conducted over 3 days in 22 healthy individuals before post-study data was collected at 1, 3, and 6 months. The investigating team observed that THC led to the following outcomes: It produced schizophrenia-like positive and negative symptoms, altered perception, increased anxiety, and euphoria, as well as disrupted immediate and delayed word recall whilst sparing recognition recall. It impaired performance on tests of distractibility, verbal fluency, and working memory and yet did not impair orientation. Importantly, however, all of these findings in healthy individuals were transient.

In a useful review collating evidence on the major mechanisms by which cannabis may contribute to psychosis, Don Linszen explores further the possible mechanisms that might explain the apparent psychotogenic effects of cannabis [15]. It has been observed that memory impairments can be induced by cannabis use, yet Linszen suggests that no evidence points to long-term cognitive disruption following cannabis use. Alterations in patterns of cerebral blood flow have been found, with short-term increases and long-term attenuation; however, the longevity and impact of such changes remain questionable. Work has been performed assessing the influence of THC on dopaminergic neurotransmission in brain regions implicated in psychosis. It has been observed in animal models, specifically in mice, for example, that mesolimbic dopamine transmission occurs via a common opioid receptor mechanism located in the ventral mesencephalic tegmentum [16]. The relevance of this in relation to psychosis, and indeed the propagation of long-term psychotic-type disorders, remains unclear. Further studies have looked at how genetic vulnerability might predispose individuals to be easier targets for the development of cognitive deterioration and psychosis following cannabis use. A study using a New Zealand birth cohort sample demonstrated a functional polymorphism in the catechol-O-methyltransferase (COMT) gene-led individuals who were homozygous for the COMT allele to be more likely to exhibit psychotic symptoms and schizophreniform disorder following adolescent exposure to cannabis [17]. Others again focus on the transient emergence of psychotic-like states and memory changes in healthy individuals following THC administration.

We have thus explored in general terms the major theorised mechanisms of cannabis-induced psychosis. Yet it is worth considering at this point the focus of trials assessing mechanism necessarily concentrates on psychosis as a description of symptoms. They generally focus on transient psychosis. In reviewing the role of cannabis in schizophrenia, we are drawn to consider the long-term studies which review causality in wider terms. Unfortunately, randomised controlled trials are scant in this sphere.

Nonetheless, major reviews of the available trials exist. In a short yet compelling summary of the suggested role of cannabis use in schizophrenia, Henquet et al. amasses the major prospective studies published up to 2005 and considers their evidence [13].

A meta-analysis of the odds ratios of these included prospective studies found a pooled estimate for the development of psychosis associated with prior cannabis use at an odds ratio (OR) of 2.1 (95% CI: 1.7–2.5; test for heterogeneity: $Q = 5.0$, $p = 0.54$). This outcome appears to agree with the general assertion that cannabis use can lead to psychosis. Let us consider some counter-arguments to this weighty statistic.

Confounders clearly exist in populations exposed to higher cannabis use, and the potential

influence of these must be acknowledged when determining causality. Known risk factors such as sex, age, social class, ethnicity, family psychiatric history, urban living, and concomitant substance misuse all cloud the water. It is a function of observational studies that confounding factors cannot be eliminated; however, Henquet affirms that the included studies attempt to take account of these factors in adjustments and concludes it is unlikely given the lengths taken that confounding factors alone suffice to explain the outcomes.

Related to the concept of confounding influences is that of reverse causality. It asserts that sufferers of social anxiety and subtle expressions of psychosis-like experiences are more likely to attempt ameliorating these feelings through use of cannabis. This touches on the dissociative and apathy-inducing properties of cannabis. Alterations in striatal dopamine synthesis, for example, have been touted as a mechanism underlying reduced reward sensitivity and a motivation that associates with chronic cannabis use [18]. The activity of THC as a dissociative agent has been explored in terms of its effects as an analgesic via amygdala-mediated actions [19]. The relevance of these properties of cannabis in the setting of psychosis may be profoundly relevant. It has been suggested that individuals suffering psychotic-type disorders might "self-medicate" on the basis of these properties, achieving transient states of apathy and dissociation from their conditions. This could prove a major incentive for sufferers of schizophrenia to continue cannabis use despite the possible long-term consequences of its use on their condition. In terms of its relevance in the reverse causality argument, the assertion states that those more predisposed to use cannabis for these purposes on account of their proclivity to psychotic-type experiences will also be those individuals more likely to go on to develop psychotic-type illnesses. In this argument, their psychosis comes as a result of other factors, and their cannabis use is secondary.

Henquet references longitudinal studies that attempted to account for this phenomenon. A Dutch cohort study excluded at baseline all individuals who reported having ever had psychosis-like experiences and still found an association with psychosis and cannabis use [20]. A New Zealand study assessing for associations between cannabis use at age 15 and schizophrenia at 26 years in a birth cohort study found a significant association, even on adjusting for psychosis liability at 11 years [17]. We have therefore prospective evidence suggestive of an association between cannabis use and the development of psychotic symptoms whilst accounting for confounders.

We know that schizophrenics use cannabis at higher rates than the general population. Therefore, despite the possibility that cannabis may well be a factor in causing psychosis, its transient promotion of apathy and dissociation is a plausible incentive for its continued use. This bidirectionality is not contradictory, nor is it aberrant. We observe the use of drugs and substances for their escapist properties across the world, in spite of the fact that users acknowledge their deleterious long-term impact.

A review for the *British Journal of Psychiatry* by Arseneault et al. concludes that the relationship between cannabis use and schizophrenia is dose-dependent, [17] and that the relationship is linear in temporal terms. In D'Souza's randomised controlled trial utilising IV Δ^9-THC in healthy subjects, transient effects are found, including on positive symptoms, negative symptoms, and perceptual alterations as referenced earlier in this chapter [14]. It appears that these effects are dose-dependent across the 2.5 mg and 5 mg preparations. However, they remain transient, and the work concludes that further work is needed to clarify whether cannabis consumption does indeed contribute to the pathophysiology of psychosis or by extension, schizophrenia, despite the increasingly wide body of literature in this field.

When referring back to Henquet's criteria for cause, we can say that the prospective studies give evidence of an association between exposure and outcome (lacking a large effect size), a dose-dependent relationship, and a temporal relationship. Further studies offer possible mechanisms, with their plausibility open for discussion. Henquet concludes that cannabis use is

a co-dependent cause of schizophrenia, one that is dependent on the presence of other variables. If we are to take the available evidence as representative of this view, and agree with this assertion, it has clear implications for the healthy cannabis user. The possibility of vulnerable individuals developing psychotic-type illnesses such as schizophrenia via the co-dependent cause of cannabis use has profound public health implications.

For the practicing clinical psychiatrist, however, the daily focus is patients suffering psychotic-type illnesses, not healthy individuals. Therefore, whilst we might be ready to accept the influence of cannabis as a co-dependent cause in schizophrenia, a study of the effects of cannabis use on the outcomes of psychotic disorders may be more pertinent. In a comprehensive systematic review of this point, Stanley Zammit and colleagues suggest that evidence specifically indicative of worse outcomes amongst patients with psychotic-type disorders using cannabis is interestingly not watertight [21].

The team claim the achievement of presenting the first systematic review into outcomes in the field of cannabis and schizophrenia. Their literature search amassed 15,303 references before they brought down the number suitable for analysis to 13. The vast number excluded was felt to lack suitable relevance, and then studies were further discounted if they included cross-sectional analyses or cannabis as an endpoint exposure. It should be noted that the authors acknowledge all of those studies excluded on the basis of the latter two points pointed towards worse outcomes with cannabis use. Each included study was longitudinal in design, and in the absence of suitable randomised controlled trials, such studies are often seen as second best for assessing causality.

The outcomes included focused on relapse and rehospitalisation, severity of symptoms, and response to treatment.

The burden of relapse on patients and inpatient units is familiar in clinical psychiatry. A rigorous review of the factors involved in this process is, of course, desirable. In the clinical sphere, it is broadly agreed that cannabis associates with more frequent visits to units. Here, the review attempts to consider the longitudinal studies that have sought to critically assess this point. Concerning relapse, the review highlights two studies which use the Brief Psychiatric Rating Scale (BPRS) score to report increased risk of relapse with cannabis use. One included study conducted in Brisbane cites an apparent dose-dependent relationship between cannabis use recorded over days per week and an increased risk of relapse in psychosis [22]. Continued use of cannabis at follow-up was also highlighted as associating with increased relapse rates with seemingly clear differentiating stats between users (64%) and non-users (17%). With regard to readmission, the review includes three studies which point towards associations. One study found associations between cannabis use and rehospitalisation, [23] whilst another pointed towards a greater number of overall admissions [24]. Overall, four studies included in the review contained focuses on relapse, and three on rehospitalisation. The review notes here that of the four studies included for comment on relapse, two of them failed to define relapse. Nevertheless, the studies seem to portray strong effect sizes and adherence to Henquet's definition of what constitutes an identified cause, particularly with attention to the dose-dependent relationship. This study claims to have controlled for medication adherence, other substance use, and duration of untreated psychosis.

It may seem intuitive that relapse rates and rehospitalisation would correlate with symptom severity. If cannabis is reportedly an independent variable for prompting more frequent relapses and more numerous hospital visits, one might assume that the symptom severity of cannabis-using schizophrenics is greater. The review by Zammit et al. included seven studies that examined psychopathology symptom scores covering measures of psychosis, mood, aggression, and cognitive function. Of these, one reported a slight increase in BPRS score at follow-up with cannabis use after making adjustments for baseline BPRS scores [25]. Less change was noted in the cannabis misuse group compared against non-users with regard to their scoring on the Positive and Negative Syndrome Scale (PANSS) in

another study, [26] yet the review notes that statistical power was reduced due to a lack of combined analyses across the two trial groups. In one further study based at the South London Hospitals, baseline regular cannabis use was associated with increased levels of positive symptoms at follow-up [27]. None of the other seven studies focusing on symptom severity found a change in symptom scores from baseline to follow-up. Here, we find a minority of studies amongst a small pool able to demonstrate any clear change in positive symptoms severity on account of cannabis use. Only one of seven found a reduced PANNS score in relation to negative symptoms at follow-up. In the three studies that considered other measures such as depression and anxiety, no association was found between cannabis misuse and participants scores. In terms of neurocognitive ability, the one study assessing this demonstrated an apparent improvement from baseline in participants' neurocognitive ability [28]. The lack of substantial evidence indicating an association between cannabis use and more intense psychopathology is an interesting feature of this review.

Response to treatment is the final area considered in the scope of the review. Numerous outcomes relevant to treatment response were considered across the included studies: length of inpatient stay, course of illness, presence of deficit schizophrenia, global assessment score (GAS), service contact, productivity or employment, marital status, living alone, and quality of life [17]. Here again, we find a reasonably sparse set of evidence in support of anything like an arresting disruption of treatment response. In the study conducted in South London, it is suggested that a more continuous illness course was seen in individuals who used cannabis more frequently. This generalised assertion is supported by weak data. More interesting evidence from the study performed in Madrid suggested that baseline cannabis use was associated with non-adherence at follow-up; however, a dose-dependent link was found not to be statistically significant when adjusting for confounding [29]. A study in Navarra matched this assertion yet again presented fallible data ($p = 0.06$) [23].

Interestingly, two studies included in the review found associations between cannabis and improved outcomes. The study reviewed from Sydney found weak evidence that baseline cannabis use conferred a clinically important shorter admission duration $p = 0.07$, whilst one performed in Manchester suggested that a state of deficit schizophrenia was less common in baseline cannabis users [26, 29]. In relation to response to treatment therefore, we once again encounter an area vexed by confounders. It is difficult to confidently isolate cannabis use as a clear independent variable in conferring worse outcomes for patients in this specific area.

It is of significance to note the indication that cannabis use appears to associate with more frequent relapse and more recurrent hospital stays yet interesting to note the weak associations in terms of treatment response and psychopathology evidenced here. It is highly unlikely, however, that the lack of resounding evidence on latter two points serves as sufficient grounds to reverse the trend of discouraging cannabis use amongst patients.

If then we have concluded thus far that there is an imperative on clinicians to reduce cannabis use amongst schizophrenics, the question turns to how this is best done. The 2014 Cochrane Review considers this point primarily. This full-scale literature review identified a total of 250 references, with three more found through other sources; 226 studies were identified for initial screening once duplicates had been removed. Fifty studies were then screened via the abstract, resulting in 15 studies retrieved in full text that were assessed for eligibility. Finally, eight studies were considered acceptable for inclusion in the quantitative analysis. [1]

The interventions focused on cannabis use reduction and included psychoeducation versus psychological treatment (cannabis and psychosis therapy), treatment as usual versus psychological treatment, clozapine versus any antipsychotic, olanzapine versus risperidone, and amisulpride versus cannabidiol. These were interrogated using a number of measures for outcomes: rating scales, global state, behaviour, general functioning, adverse effects, and dichotomous data (this

last outcome measured whether the participant had used cannabis in the past 4 weeks, either yes or no). Here, we will review in turn each of the compared interventions, with summaries of the results.

The first section of the review considered "cannabis reduction: adjunct psychological therapy versus treatment as usual." In relation to behaviour, the main aim of the three studies selected was to see if there was a decrease in cannabis consumption and if there was any subsequent improvement in schizophrenia symptoms; however, the comparison suffered due to the trials being small, and little data were directly comparable. None of the studies demonstrate any significant difference between treatment as usual and the psychological intervention being tested for outcomes of cannabis use, mental state, or general functioning. The majority of the data for this outcome was skewed. Skewed data marred any meaningful conclusions for general functioning where none of the outcomes showed a significant difference in general functioning between psychological intervention and treatment as usual. In terms of mental state, only three studies could be included due to skewed data where useful conclusions could not be drawn, and seven may have been eligible had their authors responded to requests for further information.

The review concluded that more research would need to be conducted to see if the extra psychological interventions improve outcomes, for as the data stands at the moment, they provide no evidence of improvement.

The second comparison was entitled "cannabis reduction: psychological therapy (specifically about cannabis and psychosis) versus non-specific psychoeducation." In relation to cannabis use specifically, the aim of the included study was to minimise the usage of cannabis in people with first-episode psychosis. None of the outcomes revealed any significant difference between groups. Had the study been larger, it was felt differences might have emerged. On global state, the Knowledge About Psychosis Questionnaire (KAPQ) was used to inform participants about psychosis but did not reveal any differences in the groups' understanding at the 3- and 9-month assessment points. It was felt to have been possible that the lack of significant differences to emerge may, in part, have been due to using an active control group. Again, in terms of mental state, using the available data on the positive symptoms of psychosis measured with the Brief Psychiatric Rating Scale (BPRS), no differences emerged that demonstrated an overall benefit for cannabis and psychosis (CAP) therapy compared with psychoeducation. Other scales were used, but these reported skewed data. On social functioning, that of the participants' did not improve in either group during the trial whilst interventions were given for 3 months or at the follow-up stage 6 months later.

The scope of the comparisons was not limited to psychological interventions solely. The next comparison looked at "cannabis reduction – antipsychotic A versus antipsychotic B." Here, the review compared antipsychotic medication in those with schizophrenia and who used cannabis, comparing the ability to alter the amount of cannabis consumed and comparing antipsychotic side-effect profile in specifically that group of patients. Three studies looked at differing antipsychotic medication interventions and their effect on cannabis usage. Two studies looked at olanzapine versus risperidone, and the other study looked at clozapine versus the participant's current antipsychotic medication.

The objective of the three trials that measured the impact of antipsychotics on cannabis usage was to deduce whether use and/or cravings subsided differentially when comparing exposure to certain drugs. In none of the outcomes did any study provide evidence for significant differences between groups. Each trial was limited by a small sample size and skewed data; therefore, reliable conclusions regarding the comparative effect of antipsychotics could not reliably be drawn. In Brunette et al. 2011, [30] data suggest therapy with clozapine may reduce cannabis use more than treatment as usual amongst patients with schizophrenia and co-occurring cannabis use disorder; however, data were again skewed and the sample size small. It was concluded nonetheless that there appears to be scope for further exploration of the comparative utility of antipsychotics

in future trials with larger sample sizes. Adverse events of interventions were considered in two trials relating to this comparison.

In Brunette et al. 2011, significant differences in somnolence and hypersalivation were observed that suggest clozapine associates with better outcomes here. In all other adverse effects measured in Brunette et al. 2011, there were no significant differences between groups; however, in several instances (including constipation, weight gain, and dizziness), the differences were almost significant. In Akerele et al. 2007, [31] there was no significant difference in terms of movement disorders between groups using the Simpson–Angus Scale. The study noted that sedation was reported as the most common side effect by both groups; however, no patient was withdrawn due to side effects, suggesting a limited need for future investigations into the comparative side effects of olanzapine and risperidone in this context. No significant differences were found in the time until dropout in the olanzapine and risperidone groups in Akerele et al. 2007, and nor were there any significant differences in the reasons for dropout between participants across the two groups. In neither group were intolerable side effects cited by participants as a reason for dropping out. On the outcome of mental state, in van Nimwegen et al. 2008, there were no significant differences found between groups relating to the Obsessive Compulsive Drug Use Scale (OCDUS), which pertains to craving for cannabis [32]. The study noted that most of the changes associated with the scale took place in the first week of the trial; thus, it was felt a trial extension is unlikely to have uncovered further changes.

Across these three overarching comparisons from the most pertinent, least biased randomised controlled trials, we are shown that evidence for superiority amongst psychological or pharmacological measures for reducing cannabis use amongst schizophrenics is lacking. Treatment as usual appears to be non-inferior to any of the reviewed novel techniques. Clinicians can take reassurance from this point in so far as knowing that normal practice is not inferior to other novel strategies. However, in the absence of larger trials, we are left without clear guidance on what strategies to pursue should cannabis reduction be felt to be of paramount importance amongst schizophrenic patients.

In the fourth comparison of the study, there is a departure from a focus on cannabis reduction towards a seemingly disparate concept: that of cannabinoids as treatment. In this final portion of the chapter, we will consider the role of cannabidiol in terms of its role in cannabis and recovery in schizophrenia.

Cannabidiol is a cannabinoid that has received much attention for a number of touted potential properties, encompassing analgesic, anti-inflammatory, antineoplastic, and chemopreventive effects. It is marketed to relieve spasticity in multiple sclerosis and as a treatment in a form of juvenile epilepsy. However, it is its potential utility as an antipsychotic agent that warrants its inclusion here.

A study marked for inclusion in the Cochrane review by Leweke et al. 2012 [33] compares it against amisulpride for the treatment of schizophrenia. The study proposed that the mechanism of its impact in psychosis may relate to its enhancement of anandamide.

This substance has been found to attenuate psychotic-like behaviours in rodent models where amphetamine and phencyclidine were used [34, 35]. A derivative of arachidonic acid, a fatty acid, its name hails after the Sanskrit word for bliss. It appears to play key link in effecting the actions of cannabinoids as diverse as THC and cannibidiol, and more recent work suggests that a whole network of cannabinoid receptors and anandamide-related substances could exist. Anandamide(s) appear to reside alongside their receptors within neuronal lipid membranes and neuromodulate via intracellular G-proteins controlling cyclic adenosine monophosphate formation and Ca^{2+} and K^{+} ion transport[2].

Cannabidiol is suggested to enhance endogenous anandamide signalling by inhibiting anandamide's degradation via its influence on fatty amide hydrolase, the enzyme responsible for anandamide's breakdown [36]. The idea of CB1 receptor inhibition as a useful antipsychotic mechanistic pathway was largely refuted by large-scale trials exploring this option.

Cannabidiol nonetheless binds loosely to CB1 receptors. A focus on the anandamide pathway as its sole point of action is almost certainly reductive; however, it may be a useful starting point.

More striking than the theories surrounding mechanism in this case is the suggested impact cannabidiol could have as an antipsychotic agent. Exploring mental state in the Cochrane review, BPRS total endpoint scores appeared to favour cannabinoid compared to amisulpride at 7 days; however, the difference in scores was not significant, and this slight advantage for cannabinoid was not apparent at days 14, 21, and 28. Leweke et al. 2012 also measured mental state using the PANSS and found no differences in mental state using this scale. The apparent difference in mental state at 7 days is an interesting finding as there is some slight suggestion that cannabidiol may have some antipsychotic characteristics; however, this result is based on one short-term follow-up and from a very small trial. This overall lack of effect may have been because there was a lack of power to detect a difference in this one very small study.

The drudgery of tolerating the side-effect profile of neuroleptics is a recognised reason for poor compliance. That of cannabidiol appears to be very minimal, and it is generally very well tolerated. In Leweke's study, the side-effect profile for cannabidiol seemed to be superior to that of amisulpride. However, it must be noted that the data were once more heavily skewed.

Excitement around cannabidiol in psychosis treatment has driven patents to be filed and large-scale investment to be injected into the area by GW Pharmaceuticals. They currently market Sativex for MS and in 2015 released a summary announcing positive proof of concept data in schizophrenia:

> Over a series of exploratory endpoints, CBD was consistently superior to placebo, with the most notable differences being in the PANSS positive subscale ($p = 0.018$), the Clinical Global Impression of Severity ($p = 0.04$) and Clinical Global Impression of Improvement ($p = 0.02$). The proportion of responders (improvement in PANSS Total score greater than 20%) on CBD was higher than that of participants on placebo, with an Odds Ratio of 2.65. In the area of cognition, CBD was superior to placebo ($p = 0.07$) with marked differences being seen in subdomains of particular relevance to improving the outlook for people suffering with schizophrenia. With respect to negative symptoms, the Scale for Assessment of Negative Symptoms showed a trend in favour of CBD, which reached statistical significance for patients taking CBD together with one of the leading first line anti-psychotic medications. The majority of other endpoints in the study were in favour of CBD and approached statistical significance in many cases [37].

This was drawn from a trial meeting this description: "The multi-center, double-blind, placebo-controlled trial enrolled a total of 88 patients who were treated over a period of 6 weeks. Participants must have been treated for a minimum of 4 weeks on a first line anti-psychotic medication and still have a PANSS Total score in excess of 60."

The only reference listed with this release by GW Pharmaceuticals was that of Leweke et al. 2012.

GW Pharmaceutical will, it seems, continue to work through the relevant trial phases with a view to obtaining license for cannabidiol as a lone treatment or adjunct for schizophrenia. This may provide an exciting, novel, and largely unanticipated use for cannabinoids in schizophrenia.

Conclusions

The relationship between cannabis and recovery in schizophrenia is nuanced. Its suggested role in causality and relapse instils it as a thorn in the side of any treating clinician. Yet despite its evidenced influence in relapse and rehospitalisation, questions remain over its role in exacerbating psychopathology and interfering with treatment response. Clearly, the causal relationship is complex, and the field would benefit from further rigorous work on this point. Techniques to reduce its consumption amongst patients are limited, and the evidence for more novel strategies is limited. However, perhaps the most exciting prospect with regard to cannabis and recovery is the potential role cannabidiol could play in treatment. Many questions remain over its potential utility here, including how this might influence the

cannabis-use habits of patients. Further exploration of the endocannabinoid system is needed, which may provide interesting answers on mechanism in schizophrenia and guide future treatment approaches.

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