

Editorial

Does cannabidiol protect against the negative effects of THC?[†]

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**Summary**

A recent study by Morgan and colleagues found that cannabidiol attenuates the acute cognitive effects of delta-9-tetrahydrocannabinol (THC). This is of interest as THC has been associated with the detrimental effects of cannabis on mental health in at-risk users,

and the potency of cannabis is increasing across Europe.

Declaration of interest

None.

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The paper by Morgan and colleagues published in this issue¹ adds to the idea that cannabidiol (a cannabis compound) antagonises the effects of delta-9-tetrahydrocannabinol (THC, the main psychoactive compound of cannabis). Cannabidiol itself has no psychoactive properties but instead, as Morgan *et al* showed, may protect against the cognitive effects of THC. In their naturalistic study, participants consumed their own, self-chosen cannabis and were subsequently tested on a number of cognitive task and questionnaires. Individuals whose self-chosen cannabis contained high levels of cannabidiol showed no memory impairment after consumption of their cannabis, in contrast to the individuals whose self-chosen cannabis contained low levels of cannabidiol: here, cannabis significantly worsened memory performance.

Cannabis is the most frequently used drug in the world and although recent data suggest a stabilisation of cannabis use in most countries in Europe, its use remains particularly popular among young adolescents. That this is of great concern follows from epidemiological studies showing that heavy use during adolescence is particularly detrimental with respect to long-term effects on cognition and mental health. The findings by Morgan and colleagues¹ emphasise the importance of taking into account differences in potency of cannabis preparations. Cannabis potency varies widely between and within countries and between different products. Data from the UK, for instance, show that, on average, cannabis resin contains approximately equal levels of THC and cannabidiol, whereas herbal cannabis contains only moderate levels of THC and almost no cannabidiol. By contrast, sinsemilla, or skunk, contains high levels of THC and almost no cannabidiol.² European data show that the use of resin has remained relatively stable over the past years. The use of skunk, however, has significantly increased in the UK and other European countries. It is quite established that the detrimental effects of cannabis on mental health are primarily attributable to THC. In this light, the findings by Morgan and colleagues are relevant as they show that different types of cannabis may moderate the risk for mental health problems to different extents, depending largely on the potency of the cannabis preparation. This is also of relevance

for the cannabis–psychosis causality debate and could help to explain why not everyone exposed to cannabis will develop cognitive impairments or psychiatric symptoms.

Although a clear dose–response association has consistently been shown between cannabis exposure and psychosis risk, none of the published epidemiological studies differentiated between potency and content of the cannabis they studied. The first evidence that different strains of cannabis may indeed have a differential impact on mental health risk was provided by Di Forti and colleagues.³ They investigated different types of self-chosen cannabis and found that individuals with a first episode of psychosis had used higher-potency cannabis (i.e. skunk) for a longer period of time and with greater frequency than healthy controls.³ Thus, use of skunk containing high concentrations of THC but low concentrations of cannabidiol was associated with a higher risk of mental health problems.

Does cannabidiol reverse the acute effects of THC?

In Morgan and colleagues' current study, cannabidiol antagonised the effects of THC on memory.¹ However, no such reversal effects were observed for transient psychotic-like symptoms or anxiety. In a previous study, the authors did show that individuals who smoked cannabis low in cannabidiol reported significantly more psychotic experiences compared with those who smoked cannabis containing high levels of cannabidiol.⁴ Although the authors assessed psychosis proneness as opposed to state-related psychotic experiences in that study, the results suggest that cannabidiol may protect against the psychotogenic properties of THC. Experimental studies are in line with this, showing that cannabidiol has the ability to reduce anxiety and psychotomimetic symptoms as well as psychosis-related cognitive distortions induced by THC.^{5,6} It remains largely unknown, however, how cannabidiol brings about the THC-antagonising effects, since its pharmacological actions are still elusive. Although cannabidiol seems to have only low affinity for the cannabinoid 1 (CB₁) receptor (the main binding site for THC), some interaction between cannabidiol and the CB₁ receptor has been suggested.⁷ Also, cannabidiol may exert its effects by inhibiting reuptake of the endogenous cannabinoid anandamide.⁷ In an effort to understand the biological mechanisms underlying the interaction between THC and cannabidiol, Bhattacharyya and colleagues⁵ demonstrated opposing effects of THC and cannabidiol on brain activity by using functional magnetic resonance imaging. Delta-9-tetrahydrocannabinol attenuated striatal activity and concurrently induced psychotic symptoms, whereas the reverse (i.e. increases in striatal activity)

[†]See pp. 285–290, this issue

was observed under cannabidiol conditions. Clearly, the molecular actions of cannabidiol are in urgent need of further investigation.

Cannabidiol as a potential antipsychotic drug

The fact that cannabidiol is able to reduce the acute anxiety-inducing and psychotomimetic effects of THC has raised the question whether cannabidiol might also be effective in treating patients with established psychotic disorder.⁸ Evidence, although limited, seems promising: Zuardi and colleagues reported improvement in two patients treated with cannabidiol, whose symptoms worsened after discontinuation of cannabidiol. In two other patients, cannabidiol had no therapeutic effects; however, these two patients did not respond to other antipsychotic medication either.⁸ Preliminary data on a clinical trial including 42 patients described similar positive effects for cannabidiol on Positive and Negative Syndrome Scale scores, but with fewer side-effects than regular treatment with amisulpride.⁹

Cannabis and genetic liability

It seems clear from the above that cannabidiol has the ability to reverse some of the acute effects of THC and may even reduce psychotic symptoms in some patients. Differences in cannabidiol content and THC/cannabidiol ratio between different cannabis preparations may furthermore help to explain why only a minority of cannabis users develop a psychotic illness. Underlying genetic liability for psychosis, however, has been found to determine cannabis sensitivity as well. In a recent study, it was found that individuals at (genetic) risk for psychosis may be more sensitive not only to the psychosis-inducing effects of cannabis in daily life, but also to the positive, mood-enhancing effects of cannabis.¹⁰ Moreover, the rewarding effects of cannabis on mood seem to be acute, whereas psychotic experiences emerge subacute. These findings fit with the idea that different components may have different or even opposing effects, with THC being responsible for the psychosis-inducing effects and cannabidiol for the anxiolytic effects. Although numerous studies have shown that cannabis has a negative impact on mental health, especially in individuals with established psychotic disorder, the intriguing question remains as to why patients continue to use these high-potency types of cannabis. Di Forti's data seem to indicate that individuals at increased genetic risk for psychosis (i.e. patients with first-episode psychosis) prefer smoking the higher-potency cannabis. Morgan and colleagues, however, found no evidence that healthy controls with elevated schizotypy scores show preference towards the high-THC/low-cannabidiol variants, as the 'high-cannabidiol' and 'low-cannabidiol' groups did not differ with regard to schizotypy.¹

Thus, as different types of cannabis clearly affect mental health differentially, more research is needed to understand how genetic

liability may increase sensitivity to and preference for specific types of cannabis. Furthermore, the study by Morgan and colleagues stresses the importance of taking into account differences in cannabis potency when studying acute and long-term effects of cannabis use. Also, when treating patients with psychosis and comorbid cannabis dependence, the type of self-chosen cannabis needs to be considered in order to better understand how not only the rewarding and anxiolytic, but also the psychosis-inducing properties of the drug determine patterns and continuation of use.

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