



Risks of increasingly potent *Cannabis*: The joint effects of potency and frequency

As THC levels rise, the risk of psychosis, cognitive deficits, and structural brain changes increases

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Disclosure

The author reports no financial relationship with any company whose products are mentioned in this article or with manufacturers of competing products.

In the United States, the average potency of *Cannabis* has increased significantly over the past few decades in response to consumer demand and policies in some states that have legalized marijuana for medicinal and recreational purposes.¹ Whereas the delta-9-tetrahydrocannabinol (THC) content of “street” marijuana was <1% in the 1970s and 4% in the 1990s, by 2012, analyses of *Cannabis* samples seized by law enforcement agencies documented a rise in average THC potency to >12%.¹⁻³

Although this increase in potency has been overstated in the media because studies did not control for the effects of changes in sampling methods on freshness, it is estimated that *Cannabis* potency increased 7-fold from 1970 to 2010.³ Also, *Cannabis* preparations such as hashish and hash oil extracts containing THC well above average—from 35% to 90% THC—are now more widely available. In states where marijuana has been legalized, high-potency *Cannabis* (HPC) in the form of “edibles” (eg, marijuana added to baked goods, candy, or drinks) and hash oil extracts (Table 1, page 16)⁴⁻¹³ can be readily obtained from dispensaries or even at local farmers’ markets.

The potency of *Cannabis*, typically defined as the percentage of THC, its chief psychoactive component, varies depending on the genetic strain of the plant, cultivation techniques, and methods of processing and storage. For example, relative to “average marijuana,” hemp (*Cannabis* bred for industrial purposes) has very little THC, while sinsemilla (flowering buds from unpollinated female plants), hashish (*Cannabis* resin), and extracted hash oil contain increasing amounts of THC (Table 2, page 18).^{1,2}

As THC levels in *Cannabis* have risen over time, cannabidiol (CBD) levels have dropped to <0.2%.² Although THC appears to be largely



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The rise in the THC:CBD ratio raises the possibility that Cannabis use today might carry a greater risk of psychiatric sequelae



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Table 1

Ultra-high potency Cannabis facts: Edibles and hashish oil extracts

Marijuana 'edibles'

- Marijuana "edibles" are food products (eg, baked goods, candy, drinks) that contain Cannabis
- Edibles can contain significantly more THC compared with average smoked marijuana, although advertised potencies have been found to be inaccurate⁵
- Slow gastrointestinal absorption can result in a longer time to achieve a "high," with accumulation of more Cannabis than was intended,⁶ difficulty predicting dosing effects,⁷ and potentially serious adverse events including death⁸
- Edibles often are attractively packaged to resemble popular brand-name products, with particular appeal to minors⁹

Hash oil extracts

- Ultra-high potency hash oil extracts are also known as "wax," "dabs," "crumble," "budder," or "shatter"¹⁰
- Hashish oil extracts may contain as much as 80% to 90% THC¹¹
- Compared with conventional marijuana, hashish oil extracts may be associated with a greater risk of tolerance and withdrawal,¹¹ psychosis,^{4,12} and burns associated with preparation¹³

THC: delta-9-tetrahydrocannabinol

responsible for the psychiatric morbidity associated with Cannabis, CBD may have neuroprotective and antipsychotic properties.^{14,15} The sharp spike in the THC:CBD ratio in recent years therefore raises the possibility that Cannabis use today might carry a much greater risk of psychiatric sequelae than it did in previous generations.

This article reviews the evidence for an increased risk of psychiatric morbidity with increasing Cannabis potency.

Cannabis use disorder

Recent data indicate that the prevalence of Cannabis use disorders (eg, abuse and dependence) in the United States is approximately 3% among the general population and >30% among Cannabis users.¹⁶ The availability of increasingly potent forms of Cannabis has been cited as a possible explanation for this rise, despite no change in the prevalence of overall marijuana use between 1991 to 1992 and 2001 to 2002.¹⁷ However, while the prevalence of marijuana use disorders has continued to rise—nearly doubling from 2001 to 2002 to 2012 to 2013—this latest increase occurred with a significant increase in overall marijuana use, such that the actual rate of Cannabis use disorders among users seems to have plateaued, despite the continued rise in marijuana potency.¹⁶

This discrepancy could be explained if Cannabis users cut back past a specific threshold of increasing potency. However, 2 studies have called into question how effective such titration efforts might be in practice. In one study, Cannabis users who preferred more potent Cannabis inhaled lower volumes of smoke, but did not fully compensate for the increased potency, such that use of HPC still resulted in greater THC exposure.¹⁸ Another study found that HPC users rolled less marijuana into their joints but not enough to mitigate the impact of greater potency.¹⁹ Therefore, it appears that HPC users typically expose themselves to greater amounts of THC, which could place them at higher risk of addiction.

Although a causal association between increasing Cannabis potency and the rate of substance use disorders among users remains unclear based on epidemiologic studies from the United States, a recent study from the United Kingdom examined the impact of Cannabis potency on dependence.²⁰ This cross-sectional survey found that, although HPC was preferred by users and was rated as offering the "best high," its use was associated with increasing severity of dependence, especially among young people. The limited available evidence supports a greater risk of Cannabis use disorders with increasing potency.

Psychosis

Based on longitudinal studies published over the past 30 years, it is clear that using *Cannabis* at a young age (age <15 to 18) increases the risk of developing a psychotic disorder.²¹ This association appears to be dose-dependent, with studies consistently demonstrating that psychosis risk increases with greater frequency of *Cannabis* use.²² The accumulated evidence to date is strong enough to view the psychotic potential of *Cannabis* as a significant public health concern.²¹

If risk of psychosis is proportional to the amount of *Cannabis* used as measured by frequency, it follows that this risk might be affected similarly by *Cannabis* potency. In another paper, I discussed the potential for greater risk of psychosis in the context of medical marijuana and synthetic cannabinoids.²³ My colleagues and I also have published case reports describing emerging psychosis among regular *Cannabis* users after escalating to higher potency medical marijuana²⁴ and a hyperconcentrated form of hash oil known as *Cannabis* “wax” or “dabs” that contains as much as 90% THC.⁴ Preliminary anecdotal evidence supports the plausibility of HPC being more psychotoxic than less potent forms.

Several studies from a research group in the United Kingdom, where sinsemilla has increasingly dominated the drug market, likewise have reported that the use of HPC is associated with a greater risk of psychosis. The first of these studies, published in 2009, found that adults hospitalized for first-episode psychosis were more likely to have used HPC than healthy controls.²⁵ Among *Cannabis* users, HPC use was associated with a 7-fold increased risk of psychosis, with daily HPC use associated with a 12-fold increased risk.

Based on a larger dataset, a second study reported that high-potency, but not low-potency, *Cannabis* increased the risk of first-episode psychosis with increasing frequency of use.²⁶ Daily users of HPC had a 5-fold higher risk of psychosis compared with those that had never used *Cannabis*. A third study reported that HPC use and daily *Cannabis* use were independently associated with an earlier onset of

first-episode psychosis, with daily HPC users developing first-episode psychosis an average of 6 years earlier than non-*Cannabis* users.²⁷ Finally, a prospective study following patients with first-episode psychosis over 2 years found that the greatest risk of relapse—defined by hospital admission caused by exacerbation of psychotic symptoms—was found among self-reported daily users of HPC, while the lowest risk was among those who stopped using *Cannabis* after their initial psychotic episode.²⁸

The findings from these 4 studies suggest that the increased risk of psychosis with *Cannabis* is proportional to overall exposure, determined by both frequency of use and *Cannabis* potency.

Cognition

There is little doubt that using *Cannabis* can impair cognition acutely, “after all, this is the basic reason for its recreational use,” as one author wrote.²⁹ As with psychosis, the available evidence indicates that the degree of cognitive impairment is related to the frequency and duration of *Cannabis* use as well as age of onset of use.^{30,31}

Few studies have assessed cognitive functioning in relation to *Cannabis* potency with most only examining the effects of relatively low-potency *Cannabis* with inconsistent results. For example, 2 studies compared cognitive performance in individuals smoking *Cannabis* with 1.8% and 3.9% THC. One study found that using higher potency *Cannabis* resulted in prolonged time needed to complete certain cognitive tasks,³² whereas the other found greater impairment in performance on a decision-making task at both potencies compared with non-users but no differences between the 2 dosages.³³ Detecting significant differences may be difficult within the narrow range of low *Cannabis* potency studied where any findings have limited applicability in the context of today’s *Cannabis* with much higher THC content.

To date, only 1 study has assessed cognition at higher *Cannabis* potencies, comparing *Cannabis* with 4% THC to 13% THC.³⁴ Cognitive impairments increased with

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The increased risk of psychosis with *Cannabis* is proportional to overall exposure, determined by both frequency and potency



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Research provides preliminary support of Cannabis use associated with white matter changes that are correlated with cognitive impairment

Table 2

Average THC content of different types of Cannabis

	THC, 1995	THC, 2014
Hemp (“ditchweed”) ¹	0.4%	0.4%
Marijuana (“weed” or “grass”) ²	4%	6%
Sensimilla (“skunk”) ²	10%	13%
Cannabis resin (“hashish”) ²	<5%	>35%
Hash oil ²	<15%	>50%

THC: delta-9-tetrahydrocannabinol

higher potency, especially in tasks that measured motor control and executive functioning. Therefore it appears that higher potency Cannabis use is associated with greater acute cognitive impairment.

The longer-term effects on cognition are less clear, with conflicting evidence about whether Cannabis use can result in residual cognitive impairment despite abstinence.^{30,35} A recent review concluded that “the magnitude of neuropsychological impairment and the extent to which it persists after abstinence may depend on the frequency and the duration of Cannabis use, length of abstinence, and age at onset of use.”³¹ The effects of HPC on long-term cognitive deficits have not been studied.

Structural brain changes

A number of studies have determined an association between Cannabis use and brain changes involving structures governing memory and emotional processing, including reduced volume of the hippocampus,³⁶ temporal cortex, insula, and orbitofrontal cortex.³⁷ Although many of these changes appear to be dose-related, some morphologic changes have been reported among young recreational users without Cannabis dependence.³⁸ This has resulted in an understandable concern about the effects of Cannabis on the brains of young people with limited exposure; however, it is not yet clear to what extent detected brain changes are pathological and reflect functional deficits.

Recent research using newer neuroimaging modalities provides preliminary support of Cannabis use associated with

white matter changes that, in turn, are correlated with cognitive impairment.³⁹ One study comparing low-potency Cannabis and HPC users with and without first-episode psychosis found a significant effect of Cannabis potency on disturbances in white matter microstructural organization in the corpus callosum.⁴⁰ These findings provide sufficient cause for concern that structural brain changes associated with cognitive impairment are more likely to occur with HPC use.

Recommendations for clinicians

Similar to any drug, the effects of THC and its psychiatric sequelae can be expected to increase with dosage. To date, much of the information about psychiatric risks has been based on studies of low- and moderate-potency Cannabis rather than the much higher potency Cannabis products, such as hyper-concentrated “wax dabs,” that are available today. Data from social media suggest that these products may be associated with novel patterns of use, such as with the intention of “passing out.”⁴¹ It is likely that clinicians will encounter greater psychiatric morbidity associated with HPC use.

Although clinicians may be accustomed to asking about the frequency and duration of Cannabis use, it is now prudent also to ask patients about Cannabis potency to better assess the potential risks of use. The potency of different marijuana products is openly advertised within some “medical marijuana” dispensaries, although the accuracy of information in products such as “edibles” has been called into question.⁵

Physicians are increasingly asked to provide recommendations on “medical marijuana” use. A recent paper outlined characteristics of appropriate candidates for “medical marijuana” including:

- having a debilitating condition that might benefit from *Cannabis*
- multiple failed trials of conventional pharmacotherapies including FDA-approved cannabinoids
- lack of substance use disorders, psychosis, or unstable mood or anxiety disorders
- residence in a state where “medical marijuana” is legal.⁴²

As part of the informed consent process, physicians providing recommendations for “medical marijuana” now must consider the effects of HPC when weighing potential risks against any benefits of *Cannabis* use. Those monitoring patients using *Cannabis* should be aware of the potential for greater psychiatric morbidity with HPC and should educate patients about that risk. Failure to adequately warn patients about such morbidity or to screen for risk factors such as psychosis could leave physicians vulnerable to malpractice litigation.

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Related Resources

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- Marijuana: letter from the director. National Institute on Drug Abuse. www.drugabuse.gov/publications/research-reports/marijuana.
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- Public policy statement on marijuana, cannabinoids, and legalization. American Society of Addiction Medicine. www.asam.org/docs/default-source/public-policy-statements/marijuana-cannabinoids-and-legalization-9-21-2015.pdf?sfvrsn=0.
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continued

Clinical Point

In addition to asking about frequency and duration of use, ask patients about *Cannabis* potency to better assess the potential risks of use

Bottom Line

Cannabis potency has risen significantly over the past several decades, with available evidence pointing to an increased risk of *Cannabis* use disorder, psychosis, acute cognitive impairment, and structural brain changes with use of high-potency *Cannabis*. Clinicians should consider asking patients who use marijuana about potency to better assess risk of psychiatric adverse effects.



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Consider the effects of HPC when weighing potential risks and benefits of Cannabis use when recommending 'medical' marijuana

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