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HOT TOPICS

Rewired realities: novel insights into the neurobiology of cannabis use disorder and psychosis

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CANNABIS USE DISORDER AND PSYCHOSIS: A DEVELOPING PROBLEM

Mounting epidemiological evidence indicates that the development of cannabis use disorder (CUD) may potentiate psychosis risk. Recent large-scale studies have shown a four-fold increase over the last two decades in the proportion of schizophrenia that can be attributable to CUD in Denmark (cited in [1, 2]) and a near tripling of CUD-associated psychosis cases in Ontario [2]. The largest-to-date genetic study also indicated that CUD was most associated with schizophrenia compared to other psychiatric

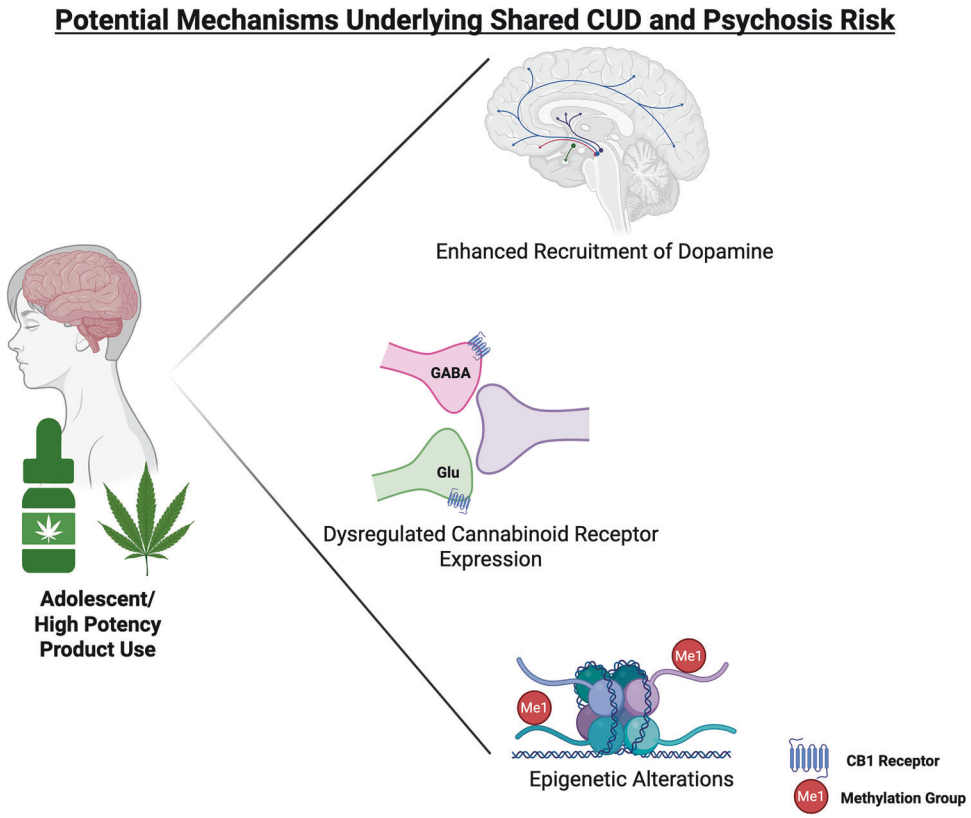

Fig. 1 Large-scale epidemiological studies are reporting that co-occurring cases of cannabis use disorder (CUD) and psychosis are becoming more prevalent and often emerge during adolescence. Use of cannabis during adolescence or use of potent products is associated with increased risk for both psychosis and CUD. Recent clinical and preclinical data show that cannabinoid use/exposure during adolescence or use of potent products is associated with epigenetic and molecular perturbations, which may influence dopaminergic signaling as well glutamatergic and GABAergic signaling in regions important for salience and reward, influencing both CUD and psychosis risk. Created in BioRender (2025). https://BioRender.com/by4ub9e.

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disorders [3]. Psychosis most often develops during late teens and early adulthood, while cannabis use is often initiated at a younger age [4]. In Ontario, the prevalence of CUD among adolescents has risen substantially, and CUD-associated psychosis cases are most evident from ages 19–24 [2]. Alongside rising rates of CUD, cannabis potency has increased dramatically, which has raised concerns for impacts on these psychiatric outcomes [5]. A multi-site study indicated that daily users of potent products are 5x more likely to develop a psychotic disorder [4], and use of these products increases the likelihood of developing CUD/problematic use [5]. Neurobiological substrates that develop during adolescence and are vulnerable to cannabis likely contribute to the emergence of CUD, psychosis, or both.

PARALLEL MECHANISMS UNDERLYING CUD AND/OR PSYCHOSIS

Recent clinical data now show that individuals with first-episode psychosis with a comorbid CUD have increased neuromelanin (a proxy for dopamine) in psychosis-associated midbrain dopaminergic nuclei, which scaled with CUD severity [6]. Results from a novel preclinical model suggest that disrupted dopaminergic signaling may be the result of adolescent THC consumption, as male rats that consumed THC during development had potentiated reward learning and reduced expression of cannabinoid receptors on glutamatergic terminals in the VTA, which may lead to increased dopamine cell firing [4]. Potency has also recently been shown to affect other phenotypes relevant to CUD and psychosis. Exposure to high-dose THC during adolescence impaired decision-making, recapitulating a phenotype observed in chronic cannabis users, which was paired with altered cannabinoid receptor expression in GABAergic and glutamatergic neurons in the amygdala and prelimbic cortex [4]. Recent clinical epigenetic data show that potent cannabis use was also associated with distinct DNA methylation affecting immune and mitochondrial pathways in individuals with psychosis [1]. These results indicate potency and/or adolescent exposure can impact processes mediating excitatory/inhibitory balance, immune function, and metabolism which can have broad impacts on reward, cognition, and salience, which are often impacted in CUD and psychosis (Fig. 1).

ONGOING CHALLENGES AND OPPORTUNITIES

It is challenging for research to inform policy, as it often takes several years to determine outcomes of changes in product availability and use. Rapid implementation of translational assessments of the impact of adolescent cannabis use and changes in the use landscape (potency, patterns of use) as well as genetic/epigenetic factors is necessary to determine mechanisms that promote CUD and psychosis risk. These efforts will provide opportunities to prevent or treat these conditions. Converging evidence from animal and human research calls for public health campaigns that translate a clear and engaging message to mitigate the rising rates of CUD and psychosis during adolescence.

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AUTHOR CONTRIBUTIONS

JMF and MDF conceived, wrote, revised, and approved the paper.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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