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## Cannabis Use Linked With Risk for Psychosis in Later Life

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August 1, 2007 — A systematic review of longitudinal studies suggests there is sufficient new evidence that the use of cannabis (marijuana) increases the risk for later psychotic illness by roughly 40%. The study showed a trend towards an increased risk for depression in people who had used cannabis, but the evidence was not as strong.

The article by Theresa H.M. Moore, MSc, from the University of Bristol in the United Kingdom, and colleagues is published in the July 28 issue of *The Lancet*.

Study author Stanley Zammit, PhD, from Cardiff University in Wales, told Medscape that individuals who used cannabis on a weekly or daily basis had about a 2- to 3-fold increase in risk for psychotic outcomes, independent of transient intoxication or other confounding factors. He added, "We looked at the quality of the studies quite rigorously and feel the evidence is strong enough to warrant advising everyone, particularly young people, that the use of cannabis does potentially have some health risks, especially if they are using it on a regular basis."

Cannabis is the most commonly used illegal substance in most countries, the authors write, adding that in the United Kingdom and New Zealand, about 1 in 5 young people report using cannabis weekly or having used it more than 100 times. Previous studies have suggested that cannabis use can produce transient, usually mild, psychotic and affective experiences, but whether it increases the incidence of mental health outcomes such as schizophrenia or depression is unclear.

The group searched for population-based longitudinal studies that looked at the relationship between cannabis use and subsequent psychotic and affective outcomes. They found 11 studies from 7 cohorts that looked at psychotic outcomes and 24 studies from 15 cohorts that looked at affective outcomes.

### Increased Risk, Dose-Response Effect

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The researchers found a consistent increased risk for psychotic outcomes in the people who had ever used cannabis (adjusted odds ratio [OR], 1.41; 95% confidence interval [CI], 1.20 - 1.65), with a greater risk in individuals who had used it most frequently (OR, 2.09; 95% CI, 1.54 - 2.84).

Most studies excluded people with psychosis at baseline, so this association between cannabis use and psychosis is unlikely to result from reverse causation, the group writes. The studies also adjusted for about 60 confounding factors. "People who use cannabis might be different from other people in a number of factors and some of those might increase their risk of mental health disease, but even once we had adjusted for these factors, there was still an association," Dr. Zammit said.

The evidence that cannabis use leads to depression, suicidal thoughts, and anxiety outcomes was less consistent. "Overall, the quality of the studies wasn't as robust as the studies for psychosis," said Dr. Zammit, adding that for example, many of the studies did not try to adjust for confounding factors.

Although an individual's lifetime risk of developing a serious psychotic illness is only about 2% or 3%, he added, cannabis can be expected to have a large impact at a population level because exposure to this drug is so common.

"The overall message is that people who use cannabis on a regular basis need to be aware of this risk, so they can make an informed judgement about whether they want to continue using it, or perhaps try to cut down their use," or seek treatment of dependency, he concluded.

The study was funded by the Department of Health, United Kingdom. Dr. Zammit is funded by the National Assembly for Wales. Ms. Moore has disclosed no relevant financial relationships. Dr. Zammit has disclosed receiving honoraria for lectures and talks or consultancy fees (for work unrelated to cannabis) from pharmaceutical companies. The financial disclosures of the other authors are listed in the original article.

#### **Editorial: "Need to Warn the Public... Establish Treatment"**

In an accompanying editorial, Merete Nordentoft, MD, and Carsten Hjorthøj, from Copenhagen University Hospital in Denmark, write that the study is the most comprehensive meta-analysis to date of this possible causal relationship and the adjustment for confounding factors and transient effects "is done more thoroughly than in previous reviews." They report, "We therefore agree with the authors' conclusion that there is sufficient evidence to warn young people that cannabis use will increase the risk of psychosis later in life."

The general public has considered cannabis to be relatively harmless in comparison with alcohol and opioids, they note, cautioning that, "however, the potential long-term hazardous effects of cannabis with regard to psychosis seem to have been overlooked, and there is a need to warn the public of these dangers, as well as to establish treatment to help young frequent cannabis users."

Dr. Nordentoft and Mr. Hjorthøj have disclosed no relevant financial relationships.

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#### **Clinical Context**

According to the authors of the current study, cannabis is the most commonly used illegal substance in the United Kingdom and United States, with 20% of young people reporting use at least once weekly or heavy use on 100 or more occasions. Although it is known that cannabis can cause transient intoxication with mild psychotic and affective symptoms, the long-term and chronic effects of cannabis have not been well reported, and randomized clinical trials are not available because of ethical considerations of conducting such trials.

This is a systematic review and meta-analysis of cohort studies to examine the long-term risk for

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psychotic disorders and affective disorders associated with cannabis exposure.

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## Study Highlights

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- Included were population-based longitudinal studies or case-control studies nested within longitudinal designs.
- Excluded were cohorts with mental illness, substance-related problems, and cannabis for medicinal use and prison cohorts.
- Diagnostic categories for psychotic outcomes included schizophrenia, nonaffective and affective psychoses, psychotic symptoms, delusions, thought disorders, or hallucinations.
- For affective outcomes, diagnostic categories included depression, anxiety, suicidal ideation or attempts, neurosis, and mania.
- Databases searched included MEDLINE, EMBASE, CINAHL, OVID, PsychINFO, WebSPIRS, ISI Web of Knowledge, ISI Proceedings, ZETOC, BIOSIS, and LILACS.
- Study quality was assessed, and pooled analysis was conducted on similar and homogenous studies.
- Quality assessment included consideration of reverse causality, bias and confounding factors, transient intoxication effects, response rate, and sampling strategy.
- There were 11 studies of psychosis, of which 7 were included for analysis and examined psychotic disorders.
- 24 reports included affective outcomes.
- Most studies excluded participants with psychosis at baseline.
- Half of the studies did not account for alcohol or other substance abuse.
- The study adjusted for confounding factors, including other substance use, personality disorders, family relationships, criminality, socioeconomic factors, intellect, and mental problems.
- Pooled analysis showed an increased risk of 40% of any psychotic outcome in individuals who had ever used cannabis (pooled OR, 1.41; 95% CI, 1.20 - 1.65).
- The findings were consistent with a dose-response effect, with greater risk in those with higher frequency of use (OR, 2.09; 95% CI, 1.54 - 2.84).
- The most frequent users showed a 50% to 200% increase in risk for psychosis.
- Results of studies restricted to clinically relevant psychotic disorders were similar.
- Evidence on risks for depression, suicidal thoughts, and anxiety outcomes were less consistent vs studies on psychotic disorders.
- 6 studies examined depression, and increased risk was found for men but not women in 1 study and results were not replicated in another study.
- 7 studies examined suicidal ideation or suicide attempts, and 4 reported an increased risk, whereas 1 showed no association.
- 7 studies examined anxiety outcomes, and 2 reported a positive association that persisted after adjustment for confounders.
- Effect sizes for affective outcomes were small and for depression ranged from 1.3 to 1.6 for the highest categories of exposure (weekly or monthly cannabis use).
- In the United Kingdom, about 800 cases of schizophrenia per year could be prevented through cessation of cannabis consumption.
- The authors concluded that use of cannabis was associated with increased risk of developing a psychotic illness in later life.

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## Pearls for Practice

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- Use of cannabis is associated with increased risk for psychosis in later life, with an OR of 1.41 and a dose-response relationship.
- Risk for affective outcomes may be increased with cannabis use, but evidence is not consistent.

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