

## **Safety for Use: Documented Safety of Long Term Cannabis Use**

Studies have shown the long-term use of cannabis to be safe. In contrast to many other medicinal drugs, the long-term use of cannabis does not harm stomach, liver, kidneys and heart.

The Missoula Chronic Clinical Cannabis Use Study examined the effects of long-term and legal medical marijuana use. Russo et al. (2002) demonstrated that regular use of cannabis for more than ten years does not cause major harm to patients:

"The Missoula Chronic Clinical Cannabis Use Study was proposed to investigate the therapeutic benefits and adverse effects of prolonged use of "medical marijuana" in a cohort of seriously ill patients. Use of cannabis was approved through the Compassionate Investigational New Drug Program (IND) of the Food and Drug Administration (FDA). Cannabis is obtained from the National Institute on Drug Abuse (NIDA), and is utilized under the supervision of a study physician. The aim of this study is to examine the overall health status of 4 of the 7 surviving patients in the program. This project provides the first opportunity to scrutinize the long-term effects of cannabis on patients who have used a known dosage of a standardized, heat-sterilized quality-controlled supply of low-grade marijuana for 11 to 27 years. (...)

Results demonstrate clinical effectiveness in these patients in treating glaucoma, chronic musculoskeletal pain, spasm and nausea, and spasticity of multiple sclerosis. All 4 patients are stable with respect to their chronic conditions, and are taking many fewer standard pharmaceuticals than previously. (...)

Mild changes in pulmonary function were observed in 2 patients, while no functionally significant attributable sequelae were noted in any other physiological system examined in the study, which included: MRI scans of the brain, pulmonary function tests, chest X-ray, neuropsychological tests, hormone and immunological assays, electroencephalography, P300 testing, history, and neurological clinical examination. (...)

These **results would support the provision of clinical cannabis to a greater number of patients in need.** We believe that cannabis can be a safe and effective medicine with various suggested improvements in the existing Compassionate IND program" (Russo et al. 2002).

The Missoula Chronic Clinical Cannabis Use Study resulted in several important conclusions and recommendations:

1. "Cannabis smoking, even of a crude, low-grade product, provides effective symptomatic relief of pain, muscle spasms, and intraocular pressure elevations in selected patients failing other modes of treatment."
2. "These clinical cannabis patients are able to reduce or eliminate other prescription medicines and their accompanying side effects."
3. "Clinical cannabis provides an improved quality of life in these patients."
4. "The side effect profile of NIDA cannabis in chronic usage suggests some mild pulmonary risk."
5. "No malignant deterioration has been observed."
6. "No consistent or attributable neuropsychological or neurological deterioration has been observed."
7. "No endocrine, hematological or immunological sequelae have been observed."
8. "Improvements in a clinical cannabis program would include a ready and consistent supply of sterilized, potent, organically grown unfertilized female flowering top material, thoroughly cleaned of extraneous inert fibrous matter."
9. "It is the authors' opinion that the Compassionate IND should be reopened and extended to other patients in need of clinical cannabis."
10. "Failing that, local, state and federal laws might be amended to provide regulated and monitored clinical cannabis to suitable candidates" (Russo et al. 2002).

Research on prenatal marijuana exposure found that cognitive functions of children at school age may be impaired. However, these effects seem to be mild and were considerable less compared to alcohol and

tobacco. A report from a longitudinal study of the effects of prenatal alcohol and marijuana exposure investigated whether these drugs affect neuropsychological development at 10 years of age (Richardson et al. 2002). 593 children completed a neuropsychological battery. Prenatal alcohol use was found to have a significant negative impact on learning and memory skills. Prenatal marijuana exposure also had a minor effect on learning and memory. Another study assessed cognitive performance in new-borns of 354 mothers at age 6.5, 12, and 13 months (Jacobson et al. 2002). Alcohol use during pregnancy was associated with poorer cognitive performance. The use of cocaine and tobacco was associated with a smaller size at birth. No effects were detected in relation to cannabis use. Low density of cannabinoid receptors in the fetal brain may explain the low prenatal toxicity of cannabis (Biegon and Kerman 2001). Researchers found that low numbers of cannabinoid receptors could be observed as early as the 14th week of gestation. Receptor density increased slowly but did not reach adult levels by the end of the 24th week. The distribution pattern in the fetal brains was markedly different from the adult pattern. Authors conclude:

"The relatively low and regionally selective appearance of cannabinoid receptors in the fetal human brain may explain the relatively mild and selective nature of postnatal neurobehavioral deficits observed in infants exposed to cannabinoids in utero" (Biegon and Kerman 2001).

The long-term consequences on cognitive function are also a major topic of discussion with regard to adult cannabis use. The first longitudinal study examining the development of cognitive functioning conducted in the U.S. did not find any influence of cannabis use (Lyketsos et al. 1999). This was confirmed by a later Canadian study (Fried et al. 2002)

According to the large-scale study by Lyketsos et al. (1999), the age-related decline of cognitive functioning "...does not appear to be associated with cannabis use." Constantine Lyketsos and colleagues of Johns Hopkins Hospital in Baltimore conducted a follow-up study of 1,318 people, divided into heavy users, light users, and nonusers of cannabis. All participants had completed a special test, the Mini Mental State Examination (MMSE), in 1981, 1982, and 1993-1996. The individual score differences between 1982 and 1993-1996 were calculated for each study participant. Within these 12 years, the mean score decline for all groups was 1.2 points. The Mini Mental State Examination (MMSE) is a brief and widely used standardized method for assessing cognitive mental status. It assesses orientation, attention, immediate and short-term recall, language, and the ability to follow simple verbal and written commands. The maximum achievable score is 30. Researchers found a decline in all age groups. There was "no significant differences in cognitive decline between heavy users, light users, and nonusers of cannabis." There were also no differences attributable to sex in these subgroups.

Former studies have been hampered by the fact that they are based on retrospective studies with single measurements. In a commentary by Martha Clare Morris and colleagues of the Rush Institute for Healthy Aging in Chicago, the difficulties encountered with the use of single measurements of cognition and the importance of measuring changes are stressed (Morris et al. 1999).

In the second longitudinal study ever conducted, Canadian researchers did not find any long-term effect of heavy cannabis use on overall intelligence (Fried et al. 2002). They compared the intelligence quotient (IQ) of 15 current heavy users of cannabis, 9 current light users, 9 former regular users and 37 non-users in a group of 70 young people. Participants had been followed since birth and now were 17-20 years of age. Current marijuana use was significantly correlated in a dose-related fashion with a decline in IQ when compared to the IQ measured at age 9-12. In current heavy users, the IQ showed a decrease of 4.1 points, compared to gains in IQ points for light current users (5.8), former users (3.5) and non-users (2.6). The authors concluded that current cannabis use "had a negative effect on global IQ score only in subjects who smoked 5 or more joints per week" and that "marijuana does not have a long-term negative impact on global intelligence."

U.S. research at Harvard Medical School showed that cognitive impairment after regular heavy use is reversible (Pope et al. 2001). Three groups of individuals aged 30 to 55 years were compared with regard to their cognitive abilities: (1) 63 current heavy users who had smoked cannabis at least 5000 times in their lives and who were smoking daily at study entry; (2) 45 former heavy users who had also smoked at least 5000 times but fewer than 12 times in the last 3 months; and (3) 72 control subjects who had smoked no

more than 50 times in their lives. Results showed that some cognitive deficits appear detectable at least 7 days after discontinuation of heavy cannabis use. By day 28, however, there were virtually no significant differences among the groups on any of the test results. Authors concluded

"Some cognitive deficits appear detectable at least 7 days after heavy cannabis use but appear reversible and related to recent cannabis exposure rather than irreversible and related to cumulative lifetime use" (Pope et al. 2001).

However, the discussion on whether regular cannabis use causes a decline in cognitive function continues, as can be seen from a discussion in the Journal of the American Medical Association in March and May 2002 (Solowij et al. 2002, Nyquist 2002, Watson 2002, Gunderson et al. 2002, Pope 2002).

**Governmental and expert committees in several industrialized countries have also concluded that the side effects of cannabis are relatively benign, supporting its safety even for prolonged use.** The **Institute of Medicine Report** of 1999 states:

"Marijuana is not a completely benign substance. It is a powerful drug with a variety of effects. However, except for the harms associated with smoking, the adverse effects of marijuana use are within the range of effects tolerated for other medications. (...)

The Canadian Senate's Special Committee on Illegal Drugs has studied the effects of cannabis use for 14 months. The committee states in a preliminary report issued in May 2002 that scientific evidence suggests that marijuana "may have some negative effects on the health of individuals," but that these effects would be "relatively benign" and that marijuana is no gateway drug to the use of hard drugs. Only approximately 10 percent of the users would become chronic users and 5 to 10 percent would become addicted. The preliminary report is available at the web site of the parliament at <http://www.parl.gc.ca/illegal-drugs.asp>.

A select committee of Britain's House of Lords recommended that cannabis should be rescheduled from a schedule 1 to a schedule 2 drug under the Misuse of Drugs Regulations Act of 1985, since it was not a dangerous drug and in order to facilitate medical research with cannabis (House of Lords 1998). The committee accused the **Medicines Control Agency of not dealing with cannabis-based medicines in the same impartial manner as with other medicines** (House of Lords 2001). In the second report released on 22 March 2001, the select committee on science and technology also called for an end to the prosecution of therapeutic cannabis users who possess or grow cannabis for their own use.

After eight months of deliberation, a health select committee of the parliament of New Zealand tabled its report on research into the mental health effects of cannabis on December 17, 1998, finding that the drug has probably been unduly criticised (New Zealand Herald from 18 December 1998). "Based on the evidence we have heard in the course of this inquiry," the committee concluded, "the negative mental health impact of cannabis appears to have been overstated, particularly in relation to occasional adult users of the drug." "Evidence received in the course of this inquiry has raised serious doubts about commonly held beliefs about cannabis," wrote the committee. "Evidence received during the inquiry supports the view that there can be subtle cognitive impairment in cannabis users," the report says. In this respect, the committee drew to a large extent on the work of Prof. Wayne Hall of the Australian National Drug and Alcohol Research Centre, who was commissioned to report on scientific research in this area. He found that long-term use of cannabis may cause subtle impairment in the higher cognitive functions of memory, attention and the organisation and integration of complex information. The committee said the evidence also suggested that cannabis did not cause behavioral difficulties, but rather that cannabis was frequently used by youths who misbehaved; neither was it a cause of suicide.

On 22 November 2001, the French National Health and Medical Research Institute (Inserm, Institut National de la Santé et de la Recherche Médicale) presented a 58-page literature review with the title "Cannabis - which effects on behaviour and health?" (Inserm 2001). The report was ordered by a governmental working group on the fight against drugs and drug addiction. Main topics of the report are factors that influence use, acute and chronic effects, and groups of special interest (pregnant women, individuals with mental disorders). It did not deal with the medical use of cannabis. The report stated that about 10 percent of those

who ever used cannabis have a risk to become dependent, compared to 30 percent with tobacco, and that cannabis effects on the nervous system are functional and reversible, and do not cause long-term damage.

In response to these findings on the long-term safety of cannabis use, many countries are now relaxing their cannabis laws or are discussing legal access to medical cannabis, among them several European countries, Australia, New Zealand, and Canada.

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[http://www.drugscience.org/sfu/sfu\\_longterm.html](http://www.drugscience.org/sfu/sfu_longterm.html)