WHO/MSA/PSA/97.4
English Only
Distr.: General

PROGRAMME ON SUBSTANCE ABUSE

Cannabis: a health perspective and research agenda

DIVISION OF MENTAL HEALTH AND
PREVENTION OF SUBSTANCE ABUSE
WORLD HEALTH ORGANIZATION

Abstract

The use of cannabis, a psychoactive substance under international control, is widespread throughout the world. Reliable information on the actual and potential health consequences of cannabis use is thus an important input into health policy analysis and for the development of national and international drug control strategies.

The last WHO report on this topic was issued jointly with the Addiction Research Foundation of Ontario in 1981 (*ARF/WHO Scientific Meeting on Adverse Health and Behavioural Consequences of Cannabis Use*). In the intervening years, there have been many requests for an updated WHO report on the health consequences of cannabis use.

In response to these requests, WHO convened a group of scientific experts on cannabis in Geneva in November 1993. The present report is the end-product of a review and update process which started at that meeting. This report provides a review and summary of current knowledge about cannabis use and health effects, and is likely to be relevant for policy makers, public health officials, educators, and others concerned with health promotion.

Epidemiological studies from Australia, Canada, Europe, and the USA have indicated an increase in the prevalence of cannabis use by young people over the last decade. In other regions, mostly in developing countries, data available is more scarce, making it difficult to draw any conclusions about the general levels of cannabis use in these countries.

There have been significant advances in research over the last 15 years. These include: basic research on the mechanism of action of cannabinoids (of which Δ-9-tetrahydrocannabinol or THC is the most potent), the molecular structure needed for such action, the discovery of a specific receptor molecule to which the cannabinoid molecule attaches in brain cells and other tissue sites, the discovery of a natural chemical substance in the brain that normally acts on those receptor sites, and the mapping of the receptor sites in various parts of the brain and elsewhere in the body. Cannabis acutely impairs cognitive development and psychomotor performance, which increases the risk of motor vehicle accidents among those who drive intoxicated by cannabis. There has also been substantial progress in understanding the chronic effects of cannabis on the respiratory system and on various types of cells in the body's immune system. Chronically, there are selective impairments of cognitive functioning, and a dependence syndrome may develop. Chronic cannabis use may also exacerbate schizophrenia in affected individuals. On the other hand, several studies have demonstrated therapeutic effects of THC for nausea and vomiting in advanced stages of cancer and AIDS and studies on other therapeutic uses are underway.

There is a clear need for both epidemiological and applied research on cannabis and its derivatives. There are important gaps in knowledge about the health consequences of cannabis use which need to be addressed by well-controlled studies, including data on the patterns and consequences of cannabis use in developing countries, the chronic adverse effects of cannabis use and on the relative effectiveness of cannabinoids for medical use.

Contents

Acknowledgements

Many individuals have assisted the Programme on Substance Abuse (PSA) in the preparation of this document. The contribution of the members of the WHO Expert Working Group on the Health Effects of Cannabis Use (see Annex 1) and the authors of the background documents for the Working Group meeting in May 1995 (see Annex 2) is gratefully acknowledged.

Based on the deliberation of the Working Group meeting, an editorial group consisting of Drs Harold Kalant, William Corrigall and Reginald Smart prepared a summary report which has served as the basis for this document. Their contribution was substantial and much appreciated. Subsequent drafts were reviewed by over 100 external reviewers, including selected scientists of the WHO Expert Advisory Panel on Drug Dependence and Alcohol Problems, and all WHO Collaborating Centres in the field of substance abuse. We wish to specifically acknowledge their input, as well as the contribution of Dr Wayne Hall and of the various experts at the US National Institute on Drug Abuse (NIDA) who have commented on various drafts of this report. Several helpful comments and suggestions were also made by the United Nations International Drug Control Programme (UNDCP).

1. Why this report now ?

1.1 Need for the report

The goal of the World Health Organization (WHO) is to promote the highest possible level of health for all peoples of the world. Psychoactive substances are a major cause of disease and injury in all regions of the world and a significant impediment to progress of 'health for all' strategies.

The use of cannabis, a psychoactive substance under international control, is widespread throughout the world. Reliable information of the actual and potential health consequences of cannabis use, including the costs and benefits of different interventions, is thus an important input into health policy analysis and for the development of national and international drug control strategies.

The last WHO report on this topic was issued jointly with the Addiction Research Foundation of Ontario in 1981 (*ARF/WHO Scientific Meeting on Adverse Health and Behavioural Consequences of Cannabis Use*). In the intervening years, there have been many requests for an updated WHO report on the health consequences of cannabis use.

In response to these requests, WHO convened a group of scientific experts on cannabis in Geneva in November 1993. The participants at this meeting (listed in Annex 1) agreed that an updated report on the health consequences of cannabis use should be prepared, and adopted a two-stage plan to produce such a report. First, scientists were commissioned to produce extensive literature reviews in the form of background papers on various topics, and these were reviewed by other experts. The authors and titles of the background documents are listed in Annex 2. Second, based on these reviews, a summary report was drafted by the original group of experts during a second meeting held in Geneva from 22-24 May 1995.

The draft summary report was then circulated to selected scientists of the WHO Expert Advisory Panel for Drug Dependence and Alcohol Problems, WHO Collaborating Centres, as well as other scientists and various technical units within WHO. Subsequently, the report was revised on the basis of these comments and in collaboration with the authors of the relevant sections of the summary report. The present report is thus a collaborative review based on inputs from scientists and public health specialists in all regions of the world.

1.2 Purpose and content of the report

This report provides a review and summary of current knowledge about cannabis use and health effects, and is likely to be relevant for policy makers, public health officials, educators, and others concerned with health promotion. The report is intended less for the use of research scientists and clinical experts, who usually have access to detailed information and studies through specialty journals and monographs, and computerized bibliographic services. In preparing this report, an effort has been made to summarize knowledge without using excessively technical language where possible, or with only essential bibliographic documentation, and with an emphasis on the major changes in knowledge in the past fifteen years and their potential implications.

There have indeed been significant advances in some areas in the last fifteen years. These include: basic research on the mechanism of action of cannabinoids, the molecular structure needed for such action, the discovery of a specific receptor molecule to which the cannabinoid molecule attaches in brain cells and other tissue sites, the discovery of a natural chemical substance in the brain that normally acts on those receptor sites, and the mapping of the receptor sites in various parts of the brain and elsewhere in the body. There has also been substantial progress in understanding the effects of cannabis on the respiratory system and on various types of cells in the body's immune system. Issues such as the link between cannabis use and schizophrenia, and the nature of cannabis dependence, have been substantially clarified. In contrast, in a number of other areas there has been no fundamental change in understanding. All of these matters are developed in greater depth in the body of this report.

1.3 Other sources of recent information

The background papers that served as the basis of this summary report contain much more detailed information and more complete lists of bibliographic references on the individual topics which they cover (see Annex 2 for a complete list).

In addition, a number of major reviews of the cannabis literature have appeared during the past few years (e.g. Arif & Westermeyer, 1988; Hall et al., 1994; Kandel, 1993; Mechoulam et al., 1994; Musty et al., 1991; Adams & Martin, 1996), and these have been taken into account when preparing this report. More detail on various issues discussed in this report can be found in these reviews.

2. Cannabis and health: some issues about inference

The approach to assessing the health effects of cannabis use followed in this report is the same as has been adopted by WHO/PSA to assess the health effects of the use of alcohol, tobacco and other psychoactive substances, namely that a reasonable standard of scientific proof is required to arrive at conclusions about the probable adverse health effects of cannabis. Some of these issues involved in assessing whether scientific evidence does indeed constitute causality are outlined below.

2.1 Making causal inferences

Causal inferences require, among other things, evidence of an association between cannabis use and an adverse health outcome; evidence that cannabis use preceded the health outcome; evidence that chance is an unlikely explanation of the association; and the exclusion of plausible alternative explanations of the association.

Reasonable evidence of an association between cannabis use and a health outcome is provided by the observation of such a relationship in case-control, cross-sectional, cohort, or experimental studies.

If cannabis use is the cause of an adverse health effect then there should be good evidence that cannabis use precedes the health effect. The strongest such evidence is provided by an observational cohort study or an experiment. In the case of cannabis, such studies are difficult to conduct due to the fact that cannabis is an internationally controlled psychoactive substance.

Chance can be ruled out if proper statistical evaluation indicates that the likelihood that the result may have occurred by chance is very small.

The alternative explanation that is much harder to exclude is that any relationship between cannabis use and a health outcome is due to an unmeasured variable which causes both cannabis use and the adverse health effect, i.e. a 'confounding' factor or factors. Experimental evidence provides the 'gold standard' for ruling out such explanations. This would require the random assignment of persons to use or not use cannabis, so as to ensure that users and non-users were equivalent in all relevant respects prior to their cannabis exposure. However, such random assignment is unethical, except in studies of innocuous health effects, because of the unacceptable risks imposed on volunteer subjects, quite apart from legal considerations in the case of cannabis.

Experiments using laboratory animals permit random assignment of subjects to cannabis or placebo exposure. There may be, however, considerable problems in extrapolating results across species. These may be minimized by proper attention to the importance of different routes of administration (e.g. oral, intravenous), different forms of cannabis (e.g. pure cannabinoids versus smoked cannabis plant material), and the question of equivalence of doses in different species (e.g. rat versus human).

When an appropriate animal model does not exist, or when human experiments are unethical, observational studies are necessary and provided they are properly conducted, non-causal factors can be controlled. If the relationship persists after such statistical adjustment, then the probability is increased that the health outcome is due to the effect of the exposure, in this case cannabis use.

Causal inferences can be drawn from research findings by judging the extent to which the evidence meets widely accepted criteria. These include: strength of association, consistency of association, specificity, dose-response, biological plausibility, and coherence with other knowledge. These criteria are not sufficient to show that an association is causal but the more that are met, the more likely it is that the association **is** causal.

2.2 Acute and chronic health effects

Any attempt to summarize the health effects of cannabis, or of any other psychoactive substance, runs the risk of oversimplification. The health effects experienced by a user will depend not only on the fact that cannabis was used, but also on a host of other factors. Acute drug effects, for example, will be influenced by the dose, the mode of administration, the user's prior experience with the drug, concurrent drug use, and the user's expectation, mood state and attitudes towards substance use, as well as environmental, biological and genetic factors.

The acute health effects of any psychoactive substance are conceptually easier to appraise than its chronic health effects: the temporal order of substance use and effect is clear; drug use and its effects typically occur closely together in time; and if the effects are not life-threatening or otherwise dangerous, they can be reliably reproduced by administering the psychoactive substance experimentally under controlled conditions. However, in such studies, the possibility of controlling for blood levels of THC (▵-9- tetrahydrocannabinol, the main active principle of cannabis) would allow stronger causal inferences between effects and THC levels as there is a great variability in bioavailability (amount of a substance which is available after absorption by any route) according to the route of administration. It is more difficult to attribute relatively rare acute adverse experiences (e.g. flashbacks, psychotic symptoms) to substance use. It is difficult to decide whether these are: rare events that are coincidental with substance intake; the effects of other psychoactive substances which are often taken together with cannabis; rare consequences of substance use that only occur at very high doses; manifestations of unusual forms of personal vulnerability; or the results of interactions between different substances.

Causal inferences about the long-term effects of chronic cannabis use become more difficult the longer the interval between use and the occurrence of the ill effects; the longer the interval, the more numerous the alternative explanations that need to be excluded. With continued chronic use this interval does not exist although it is still difficult to make causal inferences due to concurrent factors. The most rigorous evidence of chronic health effects is provided by laboratory studies of experimental animals in which well controlled doses are administered over a substantial period of the animals lives. However, a great many assumptions have to be made in extrapolating from health effects observed in laboratory animals to the probable health effects of equivalent doses and patterns of use in humans. In addition, there may be problems in extrapolating from studies with pure THC to human experience with crude cannabis preparations. The plant material contains many other compounds, both cannabinoid and non-cannabinoid in nature, and the possibility must always be considered that differences between experimental and clinical observations may be due in part to the effects of these other substances. Ideally, as bioavailability following the smoking route varies considerably between and within subjects, the measurement of blood levels of tetrahydrocannabinols should be included in any study design.

Epidemiological studies of the relationship between cannabis use and disease in humans are clearly relevant for public health policy, but they are less rigorous in assessing the degree of exposure to cannabis and in excluding alternative explanations of observed associations. There is consequently uncertainty about the interpretation of both 'positive' and 'negative' human epidemiological evidence. In the case of positive findings, cannabis use is often correlated with the use of other psychoactive substances (e.g. alcohol and tobacco) which are known to affect health adversely. This makes it difficult to confidently attribute (or exclude) some of these adverse health effects to cannabis use. When epidemiological studies fail to find adverse health effects of chronic cannabis use, it is

nonetheless uncertain whether the substance has indeed few, if any, chronic effects in humans, or whether we have not used sufficiently sensitive methods or procedures (e.g. cohort size) to reliably detect such effects. Studies on cannabis-related impairments conducted in cultures with traditional, social use of cannabis, might be helpful in distinguishing between the effects of cannabis use *per se* and those of a lifestyle often associated with illicit substance use.

3. Epidemiology of cannabis use

3.1 Methodological aspects of assessing cannabis use

The earlier literature on patterns of cannabis use is largely based on studies in developed countries, reflecting the emergence of widespread cannabis use among adolescents and young adults in these countries, and the health, legal and social concerns that this has led to. However, an increasing number of studies (for example, Smart et al., 1980; Carlini et al., 1990; Adelekan, 1989; Kramer, 1990) have been carried out in developing countries (in this case, Bahamas, Brazil, Nigeria and Venezuela, respectively), which provide some insight into cannabis use in developing countries as well.

Because cannabis is an illegal psychoactive substance, (cannabis and cannabis resin and extracts and tinctures of cannabis are included in Schedule I of the Single Convention on Narcotic Drugs, 1961, as amended by the 1972 Protocol), data on the levels and patterns of its use are much less widely available than on the use of alcohol and tobacco. Moreover, the illegality of cannabis gives rise to a number of potential biases that operate to underestimate the prevalence of its use. First, illicit substance users are likely to be under-sampled in household surveys, and those who are contacted may be reluctant to participate in a survey. Second, even if users agree to participate they may be less inclined to give truthful responses. Despite these biases there is sufficient evidence for the validity of self-reported substance-use in carefully designed studies to permit inferences about trends in illicit substance use.

No attempt has been made to estimate global figures on the prevalence of cannabis use, given the different methods of data collection, analysis, definitions and periods when surveys have been carried out. However, the United Nations Drug Control Programme has estimated the number of cannabis 'abusers' (annual prevalence) in the 1990s at 141 million people, i.e. 2.45 per cent of the world's population, based on figures given by Member States (UNDCP, 1997).

3.2 North America

3.2.1 United States of America

The United States have regularly undertaken surveys of illicit substance use over the last 15 to 20 years; these