Cannabis - better 'con' than 'pro'
Part 1: The Push for Legalization and the Gateway Hypothesis

The arguments for the present worldwide wave to allow the use of cannabis and reaching Thailand avoid indicating biomedical, clinical, and public health issues.

A primary argument for cannabis is that once you allow alcohol consumption, you should not be against the drug (1). It is not clear whether such an argument inspired the decision to allow cannabis for medical use in Thailand. What transpired is that at the beginning of 2019, marijuana (Cannabis indica) was allowed for medical purposes, and in August 2021, Kratom was decriminalized, covering consumption, production, disposal, and possession. At the beginning of 2022, only cannabis extract from marijuana and hemp with Δ9-tetrahydrocannabinol (THC) of more than 0.2% by weight will be classified as a category 5 narcotic. Not saying it directly, but the legislation allowed to own seeds, cannabis plants, and inflorescences (the parts of the complete plant) as long as harvested in Thailand (2). Meanwhile, another legislation is underway to restrict the recreational use of cannabis and stress the purpose of the drug for medical use.

<u>The endocannabinoid system (eCBS)</u>

Cannabis consists not only of Δ9-tetrahydrocannabinol (THC) but also more than 120 phytocannabinoids and cannabidiol (CBD). The chemical formulas of both THC and CBD are almost similar but have different pharmacological effects. Both function on the endocannabinoid system (eCBS), but with different effects on the central nervous system, in that THC is psychoactive while CBD relieves anxiety, tension, and irritation (3).

<u>Cannabis legislation – a political issue</u>

Thailand's legislation followed a worldwide movement to legalize and regulate cannabis. The trend was best expressed by the editor of the British Medical Journal, who stated that 'in any public debate, there may come a point when evidence for a shift in direction clearly outweighs that against' (the former direction) (4). The present wave of countries legalizing cannabis is not the first one. The first one was started around 1990 by California in the USA and the Netherlands, which not only reduced the criminal consequences but also allowed small shops and coffee houses to sell the drug (5).

The US states Colorado and Washington triggered the more present push by allowing commercial cannabis production and the sale of cannabis for non-medical use, euphemistically called recreational use, in 2012 (5). Since then, many other countries allowed the medical use of the drug, with some exceptions for recreational purposes. In the USA, so far, 45 out of 51 states (as of January 2023) have legalized medical marijuana, and out of them, 22 states allow recreational use (3). Attempts are underway to get rid of the restriction against the drug on the federal level. Initiated by the White House last year, the U.S. Department for Human Health and Services (HHS) asked the U.S. Drug Enforcement Administration (DEA) to soften the restriction on cannabis because research on the use of the drug would be more easily facilitated (6, 7).

Arguing for cannabis use

The ten most used arguments supporting cannabis in the USA and otherwise are articulated by the 'Marijuana Policy Project, an NGO initiative stating that 'a country that values liberty should not be punishing using cannabis' is the first point leading the list of arguments (8). Seven of the ten points made follow the line of argumentation that legalizing cannabis will reduce crime, which is supposed to be generally good in many ways. Even the environment is not forgotten, since for growing the plant, monitoring a regulated cannabis business can be applied, no banned pesticides will be used, no hazardous waste will be left, and it will not be grown in national parks. Hints that the drug is safer than smoking and alcohol are not missed to be mentioned several times (8). This line of arguments avoids indicating biomedical, clinical, and public health issues. The line of reasoning has worked well for some politicians and those in favor of that controversial drug.

Spread of the obsession

Up to the year 2020, with 209 million users around the world, cannabis turned out to be the most-used drug. Those very much in favor of it are adolescents. The highest annual prevalence of youngsters is found in North America, some Western European countries, South Africa, Australia, and New Zealand (3). Young adults, such as college students, use cannabis to conform socially, want to experiment with it and look for enjoyment (9). Additional motivations are having stress and wanting to relax, relieve depression, and post-traumatic disorder (9-13).

Most of those in the vulnerable group seem to discontinue the habit once they have an intimate friend, followed subsequently by marriage and being parents. Quite a few realize that the habit doesn't promote their careers (14, 15). Yet, becoming addicted to the drug as an adult is not uncommon. It was found that Canadian young adults 44% used cannabis within the last year, and 10% admitted they used it daily (16). It is estimated that of all who tried the drug, nine percent become addicted, and it is not uncommon that addiction started in adolescence (17).

Cannabis as an addiction

Hence, cannabis disorder is not unusual and can go along with intoxication with delirium, other psychotic disorders, and withdrawal symptoms (18). Smoking cannabis together with tobacco might not only be harmful because the substances in the cigarettes affect the lungs, the respiratory tract, and the cardiovascular system. The effect of cannabis as such while smoking still needs further evaluation (19, 20). Fortunately, it is hardly possible to kill themselves with ordinary cannabis products; however, in the illegal efforts to increase the psychoactive effect of THC, serious harm could result.

An early attempt to increase the potential of THC by removing male plant parts might go back to 12,000 years ago, as palaeobotanical studies revealed (18). Nowadays, more sophisticated methods to increase the cannabis effect are used. Severe lung injury in the US was caused by vaping (an electronic cigarette) enriched with THC (21, 22). A group with 'zombie-like' behavior puzzled observers in New York in 2016, calling for the authorities. It turned out that an 'herbal

product' sold as 'AK-$& 24 Karat Gold' contained a potent synthetic cannabinoid AMB-FUBINACA, which was 85 times more potent than the ordinary known THC (23, 24). For those in favor of cannabis use in general, the FUBINACA episode can be judged as an extraordinary event that falls under the competence of the police and the legal system and should be controlled accordingly. Such a lenient approach is commonly counteracted by quoting the 'gateway hypothesis.'

The gateway hypothesis

The hypothesis goes back to a publication in the Science magazine in 1973, based on a random sample of high school students in New York followed up for five- to six months. It was stated that to bridge the gap between not using marihuana and starting to use it, legal drugs are necessary. Four stages in the use of legal drugs for this development were postulated, starting from beer or wine or both, to cigarettes or hard liquor, and finally ending up with marihuana. The drug then is a 'crucial' step to illicit substances. Twenty-seven percent of cannabis users turned to LSD, amphetamine, or heroin. Only one percent of those on marijuana alone and four percent of legal drug users turned into the use of illicit drugs (25). Further investigation found a connection between illegitimate drugs and marijuana in a 'retrospective' approach, in that most cannabis users didn't use drugs, but those who did use illicit drugs had cannabis before (26). A more direct approach to examining the association between cannabis use and other illegal drugs was conducted using part of the data of the Christchurch Health and Development Study (27).

The Christchurch study

The results of a carefully conducted and evaluated 25-year longitudinal study of a birth cohort of 1265 urban children born in Christchurch supported the credibility of the thesis to a great extent. The cohort was followed up annually to age 16 and again to 18, 21, and 25. Information was collected from parents, teachers, self-reports, medical data, aptitude tests, and personality questionnaires. Statistics were applied, among others, by using regression models and controlling for confounding.

It was observed that 'the frequency of cannabis was associated significantly with the use of other illicit drug abuse and dependence and the use of a diversity of other drugs.' The strong association in adolescents declined with increasing age. But the association of frequency of cannabis use and other illicit drug use remained' (28).

Objecting the study

The results of the Christchurch investigation were questioned. The use of sophisticated statistics seems to generally give rise to someone claiming that the method applied was wrong. Reevaluating the data with the 'correct' approach resulted in precisely the same outcome as the previous (29). However, the fact that the 'environment' of adolescent cannabis users provides a good opportunity to get other illicit drugs cannot be easily dismissed. As long as cannabis is not legalized, it will be purchased on the same black market (30, 31). A causal link between cannabis and hard drug use will be needed to accept the getaway hypothesis. This would need to test genetic influences and neurophysical deficits together with environmental factors (2). Relevant

experiments, such as randomized control trials with humans, are out of the question. Instead, several studies performed with rats support the gateway hypothesis.

Animal experiments

A causal link between cannabis and hard drugs was established by manipulating proenkephalin, an opioid neuropeptide gene, by knockdown and overexpression of the gene in adolescent THC-exposed rats. Those rats with the overexpressed gene enhanced heroin self-administration, while those adult animals with the knockdown gene 'attenuated' heroin administration (32).

Sex differences were found by injecting THC intraperitoneal into adolescent rats. As adults, the animals longed for a heroin substrate through self-administration (33). THC vapour inhalation in adolescent rats affected females more than males. In addition, repeated THC inhalation in the adulthood of female rats reduced the THC effect on thermoregulation. THC affects the body by increasing the temperature in the brain and muscles and decreasing it in the skin. The getaway thesis was tested with oxycodone, a drug used to relieve pain in cancer patients, and the opioid fentanyl. Neither male nor female rats didn't long for oxycodone, but female rats increased fentanyl self-administration (34).

A review of a number of rat experiments combined a wide scope of sophisticated assays testing the role of Δ9-THC on the behavior, brain, and genes to verify the gateway thesis was published by a Spanish group (35). The final result, in summary, is that THC in adolescents modifies some psychological indicators and the brain. THC also influences gene expression in the nucleus accumbens (a part of the brain that has a role in feeding, sexual behavior, longing for reward, reaction to stress, and drug self-administration (36)). However, to a final causal proof of the gateway hypothesis could not be pointed.

Conclusion so far

How valid results are obtained from experiments with laboratory rats is debatable. Those in favor of getting marijuana free of legal restriction probably are not prepared to accept arguments based on animal trials. On the other hand, given the tremendous problem with opioid use disorder (OUD) in the US and elsewhere, it is argued that 'genetic predisposition, trauma, unstable psychiatric symptoms, thrill-seeking, impulsivity, and environmental exposure' that made an individual use cannabis increase her or his likelihood to shift to the use of opioids (37).

The most vulnerable groups for softening the restriction on cannabis are children and adolescents. For the developing brain, cannabis bears the risk of psychiatric problems up to schizophrenia. Pregnant women on cannabis might harm their children in utero by having mental health problems in childhood and later life. New developments in neuroscience and omics technologies more and more challenge the perception of cannabis being generally a safe drug (38). Part two of this entry will elaborate on these aspects and look into what so far happened in Thailand after 'losing the brake' on cannabis use in 2019.

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For comments and questions, please contact <awuso11@gmail.com.