The acute side effects caused by cannabis use are mainly related to psyche and cognition, and to circulation. Euphoria, anxiety, changes in sensory perception, impairment of memory and psychomotor performance are common effects after a dose is taken that exceeds an individually variable threshold. Cannabis consumption may increase heart rate and change blood pressure, which may have serious consequences in people with heart disease. Effects of chronic use may be induction of psychosis and development of dependency to the drug. Effects on cognitive abilities seem to be reversible after abstinence, except possibly in very heavy users. Consequences of cannabis smoking may be similar to those of tobacco smoking and should be avoided. Use by young people has more detrimental effects than use by adults. There appear to be promising therapeutic uses of cannabis for a range of indications. Use of moderate doses in a therapeutic context is usually not associated with severe side effects. Current prohibition on cannabis use may also have harmful side effects for the individual and the society, while having little influence on prevalence of use. Harm is greatest for seriously ill people who may benefit from a treatment with cannabis. This makes it difficult to justify criminal penalties against patients.

1. Introduction. – Because the prevalence of cannabis use has in recent years been on the rise in Europe and North America, and because the potency of cannabis preparations has increased in the past decades, there is growing concern about potentially harmful effects of this drug, and an ongoing debate on the policy implications of these developments and of our scientific knowledge on the health effects of cannabis [1]. During the past decade, the literature on adverse effects of cannabis and cannabinoids in humans had focused on effects that are thought to be mediated by the CB1 receptor, including effects on cognitive function, psychiatric effects, and dependence and decline of psychomotor performance that may result in traffic accidents [2]. In addition, there is a discussion on the pulmonary and cancer-causing effects of smoking cannabis. These are not attributed to any inherent cannabis compounds but to combustion products generated when dried plant material is smoked rather than taken orally or through other advisable modes of administration [3]. Scientists generally agree on the acute and short-lasting effects of cannabis, while questions and controversy remain on possible chronic and long-term effects.

The primary CB1 receptor agonist and psychoactive compound in botanical cannabis (Cannabis sativa L.) is dronabinol ((−)-trans-Δ9-tetrahydrocannabinol, Δ9-THC).
THC, THC). Consumption of isolated THC, whose concentrations in the flowering
tops and upper leaves of the female plant range from 2 to 30%, produces similar
psychological effects as whole plant drug cannabis in healthy volunteers [4][5] and
patients [6–8]. This review will focus on the toxicity of cannabis and dronabinol
(THC), leaving adverse effects of other cannabinoids that do not activate the CB1
receptor aside. This restriction is justified by the fact that, both with recreational and
medicinal use of cannabis products, the main problems concerning adverse effects are
associated with CB1 receptor activation. Acute psychological side effects, the causation
of psychosis and depression, as well as the fear of dependency are among the main
reasons for reservation and scepticism towards the therapeutic application of cannabis
products by some authors who assign cannabis an unfavourable risk/benefit ratio
[9][10]. Also, most of the studies conducted on the toxicity of cannabis have focussed
on THC and on some synthetic CB1 receptor agonists (nabilone, WIN55,212-2, etc.),
while much less evidence is available for other cannabinoids of interest.

One cannot easily draw a clear line between desired medicinal and undesirable side
effects of cannabis and THC, and this line may vary with the indication. Desirable
effects in one case may be unwanted in another. This is not only the case for
psychological effects, such as euphoria and sedation, but also for somatic effects such as
increase in appetite or muscle relaxation, which are regarded as therapeutic in most
cases but may be unwanted in others. For example, some patients find sedation or
somnolence desirable under certain circumstances, e.g., during chemotherapy [10]. In
severe illness such as AIDS and cancer, not only the physical effects (analgesia,
appetite enhancement, and anti-emetic effects) but also psychological effects (mood
enhancement and anxiolytic action) may be of great value [11].

2. Acute Adverse Effects. – The acute toxicity of THC is low. Acute lethal human
toxicity for cannabis has not been substantiated. The median lethal dose ($LD_{50}$) of oral
THC in rats was 800–1900 mg/kg depending on sex and strain [12]. There were no
cases of death due to toxicity following the maximum THC dose in dogs (up to
3000 mg/kg THC) and monkeys (up to 9000 mg/kg THC) [12].

Above a person’s individual threshold, consumption of cannabis and isolated THC
may cause adverse effects on the central nervous system and peripheral organ systems,
of which possible unwanted effects on psyche and circulation are the most relevant for
the health of the user. The large intra-individual variation of this threshold is illustrated
by the different daily doses tolerated by patients in clinical studies. In a study by Wade
et al., with 160 multiple sclerosis patients who received an oral cannabis extract, the
maximum daily doses varied between 2.5 and 120 mg of THC [13]. Hagenbach et al.
studied the effects of THC in 25 patients with spinal cord injury; maximum daily oral
doses varied between 15 and 60 mg. With inhalation, the threshold for psychological
effects is lower (a single dose of ca. 2–3 mg of THC) compared to oral intake (a single
dose of usually ca. 5–20 mg of THC) [14].

Since tolerance develops to THC in the central nervous system and regarding
several other effects, regular cannabis users may tolerate considerably higher doses. In
a study by Bowman and Phil on cognitive performance of cannabis users in Jamaica,
participants reported a mean daily intake of ca. 24.5 g of cannabis, corresponding to ca.
1000 mg of THC [15].
2.1. Psyche, Cognition, and Psychomotor Performance. Consumer self-reports of acute clinical effects of cannabis in low-to-medium doses (2–10 mg of inhaled THC) mostly point to qualitative changes in sensory perception with a heightened external and internal sensitivity, especially with regard to visual stimuli, and to distortions of the subjective perception of time. Further effects comprise feelings of well-being, of mild euphoria (the ‘high’), of relaxation, anxiolysis, and sedation [16]. However, the individual response to cannabinoids varies between subjects [17].

Inhaled doses of medium strength (10–20 mg of THC) may lead to an intensification of emotional responses and reactivity, and to more prominent changes in perception and transient hallucinatory experiences [18]. But these effects are usually avoidable if users inhale cannabis, whereby the fast bioavailability gives the consumer good individual control of these responses. In a therapeutic context, users should slowly increase the oral dose to avoid overdosing.

Serious unwanted effects generally occur at high single inhaled doses of more than 20 mg of THC, but due to the high inter-individual variability, some persons may also experience such effects at lower doses. The most frequent unwanted psychic response is an acute panic reaction that occurs most often in inexperienced users or at high doses of cannabis [19]. The most prominent sign of a panic reaction is the user’s concern of losing control. It usually remits spontaneously. In a small number of cases, longer lasting or recurrent experiences of depersonalization have been observed. However, as for the more frequent panic reaction and because of their generally mild severity, experiences of depersonalization in acute cannabis intoxication rarely require further pharmacological intervention [17].

Psychotic symptoms following acute cannabis consumption have been described. Their severity, duration, and frequency heavily depended on cultural and personality-related factors, as well as on the frequency and intensity of previous cannabis consumption [20]. Nevertheless, even a single intake of THC has been shown to cause so-called short substance-induced psychotic disorders that mimic complex schizophreniform psychotic disorders. These psychotic states generally remit completely, either shortly after subsidence of the acute THC effect, or after a few days [21][22]. Hall and Degenhardt performed a review on the frequency of acute toxic cannabis psychosis and concluded that true cannabis psychosis, if it exists, must be very rare [23]. On the other hand, Johns concluded in his review that an appreciable proportion of cannabis users report short-lived adverse effects, including psychotic states following heavy consumption [24].

A toxic delirium due to cannabis has been observed hitherto only after ultra-high dosages. It becomes manifest by disturbances of memory function, orientation, and consciousness [25]. Such a delirium has to be regarded as a non-specific reaction that can be triggered by a variety of substances, and whose origins cannot yet be conclusively explained. However, deliriant reactions to cannabis are self-limited, and thus do not call for any special intervention.

Among acute cognitive impairments caused by cannabis are difficulties with concentration, disturbances of short-term memory, and stimulation of associations that might impede goal-directed mental activities. For example, an increased error rate in simple visual or auditory tasks has been demonstrated that suggest an inversely dose-related decrease in attention [26][27]. Other reported effects of THC include...
disturbances of fine motor control and co-ordination, a reduction in psychomotor activity, and prolonged, but also unaffected reaction times [26][28]. In addition, the clinically reported aberrations in visual perception [21][29] and the subjective overestimation of the duration of a given time period [30] have been replicated under experimental conditions. In summary, easy learning and remote memory are probably unaffected by cannabis, simple reaction time, disinhibition, and vigilance were affected in some studies and not in others, whereas complex reaction time, perception, reading aloud, arithmetic performance, recall and intrusions in recognition memory were affected in all studies [31]. Acute cannabis smoking produced minimal effects on complex cognitive task performance in experienced cannabis users who used an average of 24 cannabis cigarettes per week, a clear indication of tolerance [32]. As with conventional hypnotics, cannabis decreases REM sleep time in a dose-dependent fashion [33].

2.2. Physical Effects. THC produces reversible and dose-dependent tachycardia with increased cardiac labor and oxygen demand, and increased diastolic blood pressure (in horizontal position) associated with a decreased parasympathetic tone [34]. Due to tolerance to these effects, chronic use can lead to bradycardia [35]. At higher dosages, orthostatic hypotension may occur due to a dilation of blood vessels, which may result in dizziness and syncope. Myocardial infarction may be triggered by THC due to these effects on circulation [36][37]. Dilation of blood vessels also causes conjunctival reddening.

THC has a cholinergic effect on the salivary glands leading to hyposalivation and dry mouth. This effect is mediated by both CB1 and CB2 receptors [38]. Concerning ophthalmic effects, the use of cannabis may disturb accommodation and the pupils’ reaction to light is slowed. Tear flow is decreased [17]. Hyposalivation and decreased tear flow may potentially increase the risk of infections of the upper respiratory tract and the eye (keratitis, conjunctivitis).

Rare adverse effects are headache or nausea and vomiting. The relaxation of muscles may be accompanied by a reduction in strength and impaired coordination, leading to possible falls. Cannabis rarely causes allergies. In most cases, they are not caused by the plant material itself but by contamination with other substances [39].

Reports on the effects of cannabinoids on platelet aggregation are conflicting. While Formukong et al. reported an inhibition by cannabigerol, cannabidiol, THC, and cannabinol in in vitro studies, Deusch et al. observed procoagulatory effects of THC in human platelets in vitro [40][41]. The clinical significance of these observations is unclear. In clinical studies, laboratory investigations did not reveal any trends of clinical significance in haematological parameters, including parameters relevant for coagulation [42].

In one study, the THC derivative nabilone deteriorated choreatic movements in Huntington’s disease [43]. Thus, cannabinoid receptor agonists may be contraindicated in Huntington’s disease.

Gastric activity is slowed by THC [44]. Results of THC effects on the transit of food in the bowel are somewhat conflicting. While one group found no significant effect in humans [44], THC produced an inhibition in rats of small intestinal transit and, to lesser extent, of large bowel transit [45]. This difference may be explained by lower doses used in the study with humans.
2.3. Adverse Effects of Cannabis and THC in Clinical Studies. The most frequent adverse effects of cannabis and THC in clinical studies comprise effects on psyche and cognition (euphoria, dizziness, anxiety, sedation, depression etc.) and dry mouth. In addition, nausea may be observed in a considerable number of patients, but it is unclear why it is observed in some studies (see Table 1) but nearly absent in others (Tables 2 and 3). Other acute effects, including spasms and pain, differed much as a function of disease and showed no relevant difference between verum and placebo. This supports the assumption that these effects are often not caused by the treatment but the underlying disease (Tables 1–3).

Table 1. Side Effects of the Cannabis Extract Sativex® According to the Product Information of the Approval in Canada [42]*. Data were taken from clinical studies with 166 patients treated with Sativex and 162 patients treated with placebo. The table lists all side effects that were observed in 2% of the cases or more.

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Cannabis (n = 166)</th>
<th>Placebo (n = 162)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dizziness</td>
<td>41.6%</td>
<td>13.0%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>11.4%</td>
<td>5.6%</td>
</tr>
<tr>
<td>Nausea</td>
<td>10.2%</td>
<td>7.4%</td>
</tr>
<tr>
<td>Somnolence</td>
<td>8.4%</td>
<td>3.1%</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>7.8%</td>
<td>1.9%</td>
</tr>
<tr>
<td>Application site pain</td>
<td>7.8%</td>
<td>6.8%</td>
</tr>
<tr>
<td>Feeling drunk</td>
<td>7.2%</td>
<td>0.6%</td>
</tr>
<tr>
<td>Oral pain</td>
<td>6.6%</td>
<td>6.8%</td>
</tr>
<tr>
<td>Disturbance in attention</td>
<td>6.6%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>6.0%</td>
<td>3.1%</td>
</tr>
<tr>
<td>Euphoric mood</td>
<td>5.4%</td>
<td>0.6%</td>
</tr>
<tr>
<td>Disorientation</td>
<td>4.8%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Dysgeusia (abnormal taste)</td>
<td>4.2%</td>
<td>2.5%</td>
</tr>
<tr>
<td>Weakness</td>
<td>3.6%</td>
<td>1.2%</td>
</tr>
<tr>
<td>Appetite increased</td>
<td>3.6%</td>
<td>1.9%</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>3.6%</td>
<td>1.9%</td>
</tr>
<tr>
<td>Mouth ulceration</td>
<td>3.0%</td>
<td>0.6%</td>
</tr>
<tr>
<td>Fall</td>
<td>3.0%</td>
<td>1.2%</td>
</tr>
<tr>
<td>Lethargy</td>
<td>3.0%</td>
<td>0.6%</td>
</tr>
<tr>
<td>Thirst</td>
<td>3.0%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Dissociation</td>
<td>3.0%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>2.4%</td>
<td>0.6%</td>
</tr>
<tr>
<td>Sensation of heaviness</td>
<td>2.4%</td>
<td>0.6%</td>
</tr>
<tr>
<td>Cough</td>
<td>2.4%</td>
<td>1.9%</td>
</tr>
</tbody>
</table>

*) In addition to the adverse events reported in these controlled acute studies, the following adverse events were observed in patients (> 2%) on long-term treatment with Sativex®: headache (8.7%), impaired balance (5%), depressed mood (4%), memory impairment (3.1%), and oral mucosal disorder (3.1%).

Tables 2 and 3 show adverse drug events for THC (Marinol®) observed in controlled clinical studies. Adverse events from oral cannabis preparations are presented in Table 1 (Sativex®) and Table 2 (Cannador®). Sativex is applied as an oro-mucosal spray and Cannador as well as Marinol in capsules. Events from smoked
Comparisons between cannabis and THC are presented in Tables 2 and 3. Table 2 also compares the frequency of side effects caused by cannabis, THC, and a placebo observed in a short study of 15 weeks and a follow-up study of 52 weeks in duration.

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Short-term study (15 weeks)</th>
<th>Long-term study (52 weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>THC</td>
<td>Cannabis</td>
</tr>
<tr>
<td>Dizzy or light-headedness</td>
<td>59%</td>
<td>50%</td>
</tr>
<tr>
<td>Sleep</td>
<td>35%</td>
<td>40%</td>
</tr>
<tr>
<td>Spasms or stiffness</td>
<td>34%</td>
<td>33%</td>
</tr>
<tr>
<td>Gastrointestinal tract</td>
<td>30%</td>
<td>37%</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>28%</td>
<td>30%</td>
</tr>
<tr>
<td>Pain</td>
<td>26%</td>
<td>24%</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>26%</td>
<td>20%</td>
</tr>
<tr>
<td>Weakness or reduced mobility</td>
<td>25%</td>
<td>23%</td>
</tr>
<tr>
<td>Bladder</td>
<td>24%</td>
<td>26%</td>
</tr>
<tr>
<td>Infection</td>
<td>15%</td>
<td>16%</td>
</tr>
<tr>
<td>Tremor or lack of coordination</td>
<td>12%</td>
<td>10%</td>
</tr>
<tr>
<td>Depression or anxiety</td>
<td>10%</td>
<td>9%</td>
</tr>
<tr>
<td>Numbness or paraesthesia</td>
<td>9%</td>
<td>7%</td>
</tr>
<tr>
<td>Vision</td>
<td>6%</td>
<td>8%</td>
</tr>
<tr>
<td>MS-relapse or exacerbation(*)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Falls(*)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Memory or concentration(*)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Other skin problems(*)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Pressure sores(*)</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

Table 2. Adverse Events Observed in a 15-Week study [6] and in a 12-Month Follow-up Study [7] in MS Patients Who Received Either THC (Marinol®) the Cannabis Extract Cannador®, or Placebo. In the short-term study, 611 patients and in the long-term study 502 patients were evaluated. In the short-term study, doses were slowly increased up to the occurrence of side effects or until the maximum dose (10–25 mg THC depending on body weight daily) was reached.

There was little difference in side-effect profiles between an oral cannabis extract (Cannador) and THC (Marinol) (Table 2), and smoked cannabis vs. THC (Table 3). Compared to a short-term study in patients with multiple sclerosis a long-term therapy with cannabis and THC over a course of 12 months resulted in a dramatic reduction of adverse effects (Table 2). This may be due to the development of tolerance for some symptoms and to the establishment of an individual tolerable dose for every patient. Many clinical acute studies with cannabis or THC start with low doses and slowly increase the dose until side effects appear, or a maximum daily dose is reached. Thus, one expects to observe side effects frequently in acute studies. However, they are usually mild or moderate in intensity [6]. In the long-term study by Zajicek et al. with 502 patients, the incidence of side effects was no longer higher in the verum groups (THC and cannabis) compared to the placebo group except for the events ‘dizzy or lightheadedness’ and ‘falls’ (Table 2) [7]. In studies with THC taken by patients with HIV, similar observations of a reduction in frequency of side effects were made. While ca. 25% of patients reported a minor CNS-related adverse drug event during the first
two weeks, only ca. 4% reported such an event during each of the following six weeks [46].

2.4. Cannabis and Accidents. THC impairs perception, psychomotor performance, and cognitive and affective functions, which may all contribute to a driver’s increased risk of causing a traffic accident. A fatal accident is the most serious acute adverse consequence of cannabis use, which may not only harm the user but also other subjects involved. After alcohol, cannabis and benzodiazepines are the drugs most frequently found in impaired drivers and in drivers involved in accidents [47][48]. The detection of THC or THC metabolites in a driver’s body usually results from illegal use and rarely from medicinal use. In clinical studies with low doses of THC or nabilone, psychomotor and cognitive performance were not reduced, suggesting that driving skills may not be impaired by these doses [49][50]. The effects of cannabis are dose-related, ranging from no relevant to strong effects. The review by Tunbridge et al. for the EU’s CERTIFIED project categorized the overall traffic safety risk caused by a particular type of drug as ‘high risk’ for alcohol and benzodiazepines, ‘high-to-moderate risk’ for cocaine, ‘moderate risk’ for cannabis and amphetamines, and ‘low-to-moderate risk’ for opiates and antihistamines [48]. It is estimated that acute cannabis use doubles the risk of causing an accident [47], while regular users who are not acutely intoxicated seem to have no increased risk [51][52]. The combined use of cannabis and alcohol or other drugs may increase accident risk considerably [48][53][54]. However, chronic cannabis use (in the absence of acute administration) did not per se potentiate the effects of alcohol [55]. In fact, regular cannabis users showed lower scores for dizziness and a superior tracking accuracy compared to infrequent users after alcohol.

Simulator and experimental on-road studies have demonstrated that cannabis may impair some driving skills at smoked THC doses of as low as 6.25 mg [56]. However, results varied considerably between the skills tested and among studies, and some of the tested skills were not impaired at doses as high as 18 mg. Some of the impairment caused by cannabis is mitigated, since subjects appear to perceive that they are indeed impaired. Where they can compensate, they do, for example, by not overtaking, by

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Smoked cannabis (n = 98)</th>
<th>Oral THC (n = 257)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dry mouth</td>
<td>56.5%</td>
<td>44.8%</td>
</tr>
<tr>
<td>Sedation</td>
<td>52.1%</td>
<td>64.0%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>33.1%</td>
<td>26.8%</td>
</tr>
<tr>
<td>Ataxia</td>
<td>27.1%</td>
<td>12.8%</td>
</tr>
<tr>
<td>Elated mood</td>
<td>26.6%</td>
<td>24.4%</td>
</tr>
<tr>
<td>Confusion</td>
<td>26.6%</td>
<td>31.6%</td>
</tr>
<tr>
<td>Anxiety</td>
<td>20.2%</td>
<td>18.8%</td>
</tr>
<tr>
<td>Depressed</td>
<td>18.1%</td>
<td>13.2%</td>
</tr>
<tr>
<td>Perceptual</td>
<td>15.9%</td>
<td>22.8%</td>
</tr>
<tr>
<td>Fantasizing</td>
<td>10.7%</td>
<td>11.6%</td>
</tr>
<tr>
<td>Orthostatic</td>
<td>7.5%</td>
<td>12.8%</td>
</tr>
<tr>
<td>Panic/Fear</td>
<td>7.5%</td>
<td>7.6%</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>6.4%</td>
<td>10.0%</td>
</tr>
</tbody>
</table>

Table 3. Side Effects Observed in a State Clinical Trial on Oral THC and Smoked Cannabis Conducted in California in the 1970s (cited according to [8])
slowing down, and by focusing their attention when they know a response will be required. Such compensation is not always possible, however, where drivers are faced with unexpected events.

Epidemiological evaluations of accident data using culpability analysis yielded somewhat conflicting results (Table 4). Drivers with low THC blood concentrations may not have a higher accident risk than drug-free controls, but THC blood concentrations above 5 ng/ml may be associated with an increased accident risk. Responsibility or culpability studies analyze the responsibility assigned to drivers involved in accidents as a function of drug levels found in samples taken after an accident. In this kind of studies, the drivers responsible for an accident serve as cases and drivers not responsible as controls.

Table 4. Results of Culpability Studies on Drivers with THC or THC-COOH (a metabolite) in Whole Blood or Urine

<table>
<thead>
<tr>
<th>Authors</th>
<th>Drivers (n)</th>
<th>Specimen</th>
<th>Percentage of drivers with cannabinoids only</th>
<th>Odds ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Terhune (1982) [57]</td>
<td>497</td>
<td>blood</td>
<td>3.4%</td>
<td>2.1</td>
</tr>
<tr>
<td>Williams et al. (1985)</td>
<td>440</td>
<td>blood</td>
<td>4.3%</td>
<td>0.2</td>
</tr>
<tr>
<td>Terhune et al. (1992)</td>
<td>1882</td>
<td>blood</td>
<td>1.0%</td>
<td>0.7</td>
</tr>
<tr>
<td>Drummer (1994) [60]</td>
<td>1045</td>
<td>blood</td>
<td>4.1%</td>
<td>0.7</td>
</tr>
<tr>
<td>Longo et al. 2000 [61]</td>
<td>2500</td>
<td>blood</td>
<td>7.1%</td>
<td>0.9 (all)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.36 (&lt; 1 ng/ml)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.52 (1 – 2 ng/ml)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.8 (&gt; 2 ng/ml)</td>
</tr>
<tr>
<td>Lowenstein, Koziol-McLain (2001) [51]</td>
<td>414</td>
<td>urine</td>
<td>8.2%</td>
<td>1.1</td>
</tr>
<tr>
<td>Drummer et al. (2004) [53][62]</td>
<td>3398</td>
<td>blood</td>
<td>1.7%</td>
<td>2.7 (all)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.7 (&lt; 5 ng/ml)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>6.6 (&gt; 5 ng/ml)</td>
</tr>
<tr>
<td>Laumon et al. (2005) [54]</td>
<td>9772</td>
<td>blood</td>
<td>not given</td>
<td>1.78 (all)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.57 (&lt; 1 ng/ml)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.54 (1 – 2 ng/ml)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2.13 (3 – 4 ng/ml)</td>
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The two major responsibility studies conducted so far underline the importance of alcohol as the major causal factor in traffic accidents [53][54]. The responsibility study by Drummer et al., conducted in Australia and using information on 3398 fatally injured drivers, showed an odds ratio (OR) of 6.0 for alcohol above a blood alcohol concentration (BAC) of 0.05% with an OR of 3.7 for the BAC range of 0.1–0.15% and of 25 for a BAC of more than 0.2% [53]. THC was associated with an increased overall risk of 2.7. A THC blood concentration of less than 5 ng/ml was associated with an OR of 0.7 [62], while a blood concentration above 5 ng/ml was associated with an OR of 6.6. The French study by Laumon et al., with 9772 drivers involved in an accident, in which at least one subject was fatally injured, found an OR of 8.5 for all alcohol-positive drivers and an OR of 1.8 for all THC-positive drivers after adjustment for substances,
age, time of accident, and vehicle type [54]. A BAC of below 0.05% was associated with an OR of 2.7 and a BAC of above 0.2% with an OR of 39.6. A THC blood concentration of below 1 ng/ml was associated with an OR of 1.6 and a THC blood concentration above 5 ng/ml with an OR of 2.1, which is a considerably lower dose–effect relationship than in the study by Drummer [60].

These findings on the impact of cannabis on driving skills and accident risk suggest that the use of cannabis or THC at low doses that do not cause psychotropic effects is also not associated with an increased accident risk. Regular users of cannabis have no increased risk, if they are not acutely impaired by the drug, but acute use may increase the risk by more than twofold, depending on the dose and the time passed between cannabis use and driving. Low THC concentrations in the blood were not associated with increased culpability rates, while higher concentrations were. Cannabis use in combination with alcohol may considerably increase accident risk.

The results from studies on the correlation between cannabis use and injuries from a range of accidents and requiring hospitalization are somewhat conflicting. Vinson found no increased risk for cannabis users in 2,161 injured subjects requiring emergency-room treatment and 1,856 controls [63]. Among the cases, 27% were injured in a fall, 19% were struck by an object, 18% were in a motor vehicle crash, and the rest were injured by a variety of mechanisms. Self-reported cannabis use in the previous seven days was associated in this study with a decreased risk of injury, while the use of other illicit drugs and recent use of alcohol was associated with an increased risk. In contrast, a study by Gerberich et al. found a small risk increase of hospitalized injury in cannabis users. In their retrospective study with 64,657 subjects who completed a questionnaire about health behaviors including cannabis use, that use was independently associated in the follow-up with an increased risk for injury hospitalizations of 1.28 for men and for women of 1.37 [64].

3. Chronic Adverse Effects. – The long-term use of cannabis was not associated with an increased mortality in animals [65] and humans [66]. Chan et al. administered 50 mg/kg of THC to rats for a period of two years. At the end of the observation, overall survival was higher in the treated animals (70%) than in the untreated controls (45%) [65]. The higher survival rate in the THC group was ascribed to the lower incidence of cancer. No relationship between cannabis use and mortality has been discovered in a longitudinal epidemiological study with 65171 citizens of the USA [66], although this may be due to methodic limitations.

A multitude of chronic effects of cannabis use on the immune and endocrine systems, respiratory tract (when inhaled), psyche, cognition, and psychomotor performance have been described. Adverse effects of medical cannabis use are within the range of effects tolerated for other medications [11][67]. Long-term medical use of cannabis for more than 15 years is reportedly well-tolerated without significant physical or cognitive impairment [68]. Side effects observed in acute clinical studies diminish considerably with longer medicinal use [7].

3.1. Risks of Smoking. The risks of cannabis smoking are often regarded as inherent risks of cannabis use resulting in an unfavorable risk/benefit ratio in a therapeutic context [9]. However, as with the use of other drugs, the risks caused by an inherently unsafe method of administration must be distinguished from the risks of the drug itself.
For example, the risks of needle sharing or of overdose in a recreational context cannot be used as an argument against the use of opioids in pain therapy.

One of the greatest concerns about chronic effects of recreational cannabis use pertains to the inhalation of combustion products that may damage the mucous membranes, if the drug is smoked as a cannabis cigarette (‘joint’) or in a pipe. In contrast, during the 19th century, oral cannabis use was common for medical and recreational use. The cannabis plant contains ca. 500 chemical compounds, most of which are also found in other organisms such as hydrocarbons (50 compounds detected), terpenes (120), amino acids (18), flavonoids (21), fatty acids (22), and sugars and related compounds (34), among others [69]. These compounds themselves generally have a very low toxic potential. Pyrolysis creates at least 200 thermal degradation products in smoke not found in cannabis, including mutagenic polycyclic hydrocarbons such as benz[a]anthracene, benzo[a]pyrene, naphthalene, and several cresols and phenols [70]. The composition of these combustion products is at least qualitatively similar to that of tobacco smoke or that of the smoke generated from other dried plant material, despite some minor differences [71]. Thus, one would expect similar damage to the mucosa by cannabis smoke as that of the smoke generated from tobacco. Indeed, signs of airway inflammation (vascular hyperplasia, submucosal oedema, inflammatory cell infiltrates, and goblet cell hyperplasia) were found in bronchial biopsies of cannabis smokers similar to the changes in tobacco smokers [72]. Regular cannabis smoking in young adults was associated with wheezing, shortness of breath during exercise, and the production of sputum, as it is known for tobacco smokers [73]. Another group found that heavy cannabis smokers had a significantly higher prevalence of chronic cough (18 vs. 0%, resp.), chronic sputum production (20 vs. 0%), wheeze (25 vs. 3.5%), and episodes of acute bronchitis (13 vs. 2%) than nonsmokers, while the prevalence of symptoms of chronic and acute bronchitis were not significantly different between cannabis and tobacco smokers [74].

Biopsies from cannabis smokers have also yielded a higher rate of precancerous pathological changes compared to non-smokers [75][76], which is suggestive of an increased cancer risk of the respiratory tract and other cancers. So far, the epidemiological data is inconclusive. A review of two cohort studies and 14 case-control studies by the International Agency for Research on Cancer (IARC) did not find a clear association between cannabis use and cancer [77]. Authors noted that sufficient studies are not available to adequately evaluate the impact of cannabis smoking on cancer risk, and available studies often have limitations including too few heavy cannabis users in the study samples. The largest epidemiological study conducted so far with 1212 incident cancer cases and 1040 cancer-free controls did not find a positive association between cannabis smoking and the investigated cancer types (mouth, larynx, lung, pharynx) [78]. There was no dose–effect relationship, and even heavy use was not associated with an increased risk.

Until better data are available, it is reasonable to avoid smoking, but to use other less risky modes of administration, i.e., inhalation with a vaporizer, which allows inhalation of cannabinoids and terpenes without burning the plant material, oral or oro-mucosal ingestion, or other routes under investigation (rectal, transdermal, topical) [3].
3.2. Psychosis and Schizophrenia. There is some biological plausibility from the role of the endocannabinoid system in dopaminergic actions that exogenous ligands of the CB₁ receptor may play a causal role in the development of psychosis. On the other hand, heightened levels of endocannabinoids in cerebrospinal fluid in patients with schizophrenia may reflect compensatory adaptation to the disease state [79]. Anandamide levels in cerebrospinal fluid were eightfold higher in first-episode paranoid schizophrenics than in healthy controls, and this level was negatively correlated with psychotic symptoms.

Evidence from several longitudinal studies published in the past five years suggests that the use of cannabis predicts an increased risk of a schizophrenia diagnosis or of reporting symptoms of psychosis [80–86]. A three-year longitudinal study with 4044 psychosis-free persons and 59 subjects with a baseline diagnosis of psychotic disorder was conducted in the Netherlands [85]. Baseline cannabis use predicted the presence at follow-up of any level of psychotic symptoms (adjusted OR 2.76). There was a dose–response relationship between frequency of cannabis use and risk of psychotic symptoms. Researchers concluded that their observations confirm previous findings that cannabis use increases the risk of both the incidence of psychosis in psychosis-free persons and of a poor prognosis for persons with an established vulnerability to psychotic disorder. In the so-called Christchurch Health and Development Study with 1011 New Zealanders, the association between cannabis dependence and the presence of psychotic symptoms at ages 18 and 21 years was examined [82]. Participants were followed from birth into early adulthood allowing for the control for previous psychotic symptoms and for clarifying the temporal sequence of drug use and symptoms. Individuals who met the diagnostic criteria for cannabis-dependence disorder at age 21 had a 2.3 times higher risk of psychotic disorders than non-users. After adjustment for previous psychotic symptoms and a range of other confounding factors, this association was still significant (rate ratio 1.8). A four-year follow-up of a cohort of 2437 young people aged 14 to 24 years with and without predisposition for psychosis in Munich confirmed a much stronger effect of cannabis use on the development of psychosis in predisposed individuals [83]. After adjustment for age, sex, socioeconomic status, urbanicity, childhood trauma, predisposition for psychosis at baseline, and use of other drugs, tobacco, and alcohol, cannabis use at baseline increased the cumulative incidence of psychotic symptoms at follow up by 1.67. The risk difference between users and non-users of cannabis in the ‘predisposition’ group was significantly greater than the risk difference in the ‘no predisposition’ group. There was a dose–response relation with increasing frequency of cannabis use. The results of the other longitudinal studies are in accordance with these three studies.

In their review Arseneault et al. concluded that cannabis use confers an overall twofold increase in the relative risk for later schizophrenia, and that it appears to be neither a sufficient nor a necessary cause for psychosis but a component cause, part of a complex constellation of factors leading to psychosis [87]. They assume that cases of psychotic disorder could be prevented by discouraging cannabis use among vulnerable youths and would reduce the incidence of schizophrenia by ca. 8% if the association is causal. Degenhardt and Hall concluded that it is most likely that cannabis use precipitates schizophrenia in individuals who are vulnerable because of a personal or family history of schizophrenia [88]. This hypothesis is consistent with the stress-
diathesis model of schizophrenia and evidence that a genetic vulnerability to psychosis increases the risk that cannabis users will develop psychosis. Instead of being a causal factor for schizophrenia, Weiser and Noy suggested that the pathology of the cannabinoid system in schizophrenia patients may be associated with both increased rates of cannabis use and increased risk for schizophrenia [89]. De Irala et al. pointed out that, from a public health perspective, actions are required since a causal relationship between cannabis use and psychosis is likely [90].

Adolescents are thought to be more susceptible to possible toxic effects of cannabis to the brain. Kumra et al. presented data at the 2005 Meeting of the Radiological Society of North America according to which cannabis use may damage certain brain regions applying diffusion tensor imaging (DTI) [91]. They concluded that, in addition to interfering with normal brain development, heavy cannabis use in adolescents may also lead to an earlier onset of schizophrenia in individuals who are genetically predisposed to the disorder. In contrast to this result, Delisi et al. did not find any differences in brains of individuals who were frequent cannabis users in adolescence and control subjects using magnetic resonance imaging (MRI) [92]. They concluded that frequent cannabis use is unlikely to be neurotoxic to the normal developing brain, refuting the hypothesis that cannabis alone can cause a psychiatric disturbance such as schizophrenia by directly producing brain pathology.

It is generally agreed that cannabis use increases the incidence of psychosis in high-risk groups and worsens the course of psychosis. However, not all recent studies confirm this concept. Cannabis use was not associated with development of psychosis in a very high-risk group of 100 young people identified by the presence of sub-threshold psychotic symptoms, or a combination of a first-degree relative with a psychotic disorder and recent functional decline [93]. In the twelve-months follow-up period, 32% developed an acute psychotic episode, which was not associated with the level of cannabis use prior to enrolment in the study. A Canadian study of 147 patients with schizophrenia-spectrum disorders, who were followed prospectively for twelve months did not find an influence of substance abuse (cannabis or alcohol) on symptoms of schizophrenia, but substance abuse was associated with higher levels of depression and anxiety in this patient group [94].

3.3. Depression and Other Psychiatric Co-Morbidity. It is well-established that persons with mental disorders such as schizophrenia, anxiety, and depression have a higher rate of tobacco use, cannabis use, and alcohol dependence, and some scientists have proposed causal relationships between these disorders, and alcohol dependency and cannabis use [95]. Cannabis and THC may cause anxiety and depression but also ameliorate these conditions. Cannabis is often used to alleviate psychological problems [96], especially by patients who suffer from chronic somatic diseases [11][97]. An antidepressive effect was also observed in clinical studies [98][99]. A rationale for these observations has been offered by experimental studies, which found that endocannabinoids may have an anti-depressive [100] and anxiolytic effect [101], and CB1 agonists reduced blood corticosterone levels in stressed mice while a CB1 receptor antagonist increased corticosterone levels [102].

Particularly, the use of cannabis by young people may have negative effects on their mental and social development. In his review of 48 long-term studies on cannabis use, and psychological and social problems, Macleod et al. did not find a strong support for...
an important causal relation between cannabis use by young people and psychosocial harm, but could not exclude the possibility that such an association exists [103]. Others see a strong support for a causal relationship [90]. 736 subjects from New York were interviewed at the ages of ca. 14, 16, 22, and 27 years, and psychiatric disorders were assessed. Early alcohol use and early marijuana use were associated with major depressive and drug-use disorders at age 27 [104]. In the so-called Dunedin study, a long-term prospective study in New Zealand, a linkage between cannabis use and mental health problems was observed [105]. Mental health problems at age 15 were a predictor of cannabis use at age 18, whereas cannabis use at age 18 predicted a higher risk of mental illnesses at age 21. Both cannabis use and mental problems were linked to low socioeconomic status, childhood behavioral problems, and separation from the parents during adolescence. In the other New Zealand birth-cohort study, the Christchurch study, with 1265 children there was a strong correlation between at least weekly cannabis use and several indicators of poor psycho-social outcome, including crime, depression, and suicide attempts [106]. Amotivational symptoms observed in heavy cannabis users during treatment were attributed to depression [107].

Cannabis use seems to have less effect on the mental health of adults than on adolescents [108–109]. After adjusting for differences in baseline risk factors of cannabis use and depression, past-year cannabis use did not significantly predict later development of depression in 8759 adults (age range 29–37 years) [108]. In a sample of 6792 young adults, a small but significant increase in the risk of developing a major depression was found among current cannabis users [109]. Green and Ritter found a weak association between adult cannabis use and depression in 1941 participants of a representative sample of U.S. males from the 1944–1954 birth cohort, but the association disappeared after adjustment for educational attainment, employment status, marital status, and other drug use, notably alcohol and tobacco use [110]. Depression was associated with earlier age of first cannabis use rather than with the current level of use. In an Australian twin study, Lynskey et al. found a substantial contribution of genetic vulnerabilities to the association between cannabis use and depression [111].

3.4. Cognitive Function. Neuropsychological studies have indicated that chronic heavy users may, depending on intensity and duration of use, show impairments of memory, attention, and ability to organize and integrate complex information. A partial explanation for cognitive impairment may be the influence of cannabis use on blood flow in the brain. Cerebrovascular resistance and systolic velocity were significantly increased in cannabis users compared to control subjects, and these increases persisted in very heavy users (131 joints per week on average) after a month of monitored abstinence [112]. The clinical significance to humans, of observations that the regular use of CB1 receptor agonists may promote neurogenesis in the hippocampus of adult rats [113], and that mice lacking CB1 receptors showed an accelerated decrease of cognitive functions [114], is unclear.

In a meta-analysis of studies on cannabis use and cognitive function Grant et al. found only a small effect of the drug on long-lasting deficits, which would offer an acceptable margin of safety if the drug is used medicinally [115]. They analyzed 15 studies that met essential inclusion criteria with 704 cannabis users and 484 nonusers. Neuropsychological results were grouped into eight ability domains, and effect sizes
were calculated by domain for each study individually, and combined for the full set of studies. With the exception of both the learning and forgetting domains, effect size confidence intervals for the remaining six domains included zero, suggesting a lack of effect.

Among these studies is the one by Pope et al. who compared three groups of individuals aged 30 to 55 years with regard to their cognitive abilities following cessation of cannabis use: 63 current heavy users of cannabis, 45 former heavy users, and 72 nonusers [116]. Some cognitive deficits were detectable at least seven 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, suggesting that cannabis effects on cognition in heavy users appear to be reversible and related to recent cannabis exposure. However, another investigation suggests that very heavy use of cannabis may be associated with irreversible decline in cognitive performance [117].

Participants were divided according to the number of joints smoked per week into light users (mean: 11 joints), medium users (mean: 42 joints), and heavy users (mean: 94 joints). Very heavy users performed significantly worse on 5 of the 35 tests compared to light users even after 28 days of controlled abstinence. Memory, executive functioning, psychomotor speed, and manual dexterity were affected. In a more recent study, no differences in the performance of moderate regular cannabis users, who were abstinent from the drug for one week, and non-users in tasks on working memory and selective attention were observed [118].

The effect of the drug on cognitive performance may be more pronounced in adolescence [82][119]. Early-onset users who started using cannabis before age 17 differed significantly from both late-onset users (onset at age 17 or later) and from nonusing controls on several measures of cognitive function, most notably verbal IQ [119]. Few differences were found between late-onset users and controls on the test battery. After adjustment for verbal IQ, virtually all differences between early-onset users and controls on test measures ceased to be significant. The authors suggested three alternative explanations for poorer cognitive performance in early-onset cannabis users: 1) innate differences between groups in cognitive ability, antedating first cannabis use; 2) an actual neurotoxic effect of cannabis on the developing brain; or 3) poorer learning of conventional cognitive skills by young cannabis users who have eschewed academics and diverged from the mainstream culture. In the Christchurch birth cohort, there was a significant correlation between level of cannabis use during adolescence and young adulthood, and failure to complete school or university programs, even after controlling for confounding factors [82]. According to these authors, it is likely that this reflects the effects of the social context within which cannabis is used rather than any direct effect of cannabis on cognitive ability or motivation.

3.5. Tolerance and Dependency. Humans can develop tolerance to cannabis-induced cardiovascular and autonomic changes, decreased intraocular pressure, sleep and sleep EEG, mood, and certain behavioral changes [35]. In a number of studies, Jones and Benowitz administered daily doses of 210 mg of oral dronabinol to ca. 120 volunteers for 11–21 days [120]. Participants developed tolerance to cognitive and psychomotor impairment, and to the psychological high by the end of the studies [121]. After a few
days, an increased heart rate was replaced by a normal or a slowed heart rate. Tolerance develops also to cannabinoid-induced orthostatic hypotension [122].

Clinical long-term studies with THC and cannabis in patients suffering from multiple sclerosis [7][123], spasticity and pain [124], and AIDS [125] did not find tolerance to the medicinal effects of moderate doses (usually 5–30 mg of THC daily) within 6–12 months.

As with tolerance, withdrawal symptoms are dose-dependent [126]. In experimental studies, comparatively high doses were administered to volunteers (80–120 mg and 210 mg daily, resp.) [35][120][127]. In the study by Haney et al., abstinence from THC increased ratings of ‘anxious’, ‘depressed’, and ‘irritable’, decreased the reported quantity and quality of sleep, and decreased food intake [127]. In the studies by Jones and Benowitz, most of the participants (55–89%) experienced irritability, restlessness, insomnia, anorexia, nausea, sweating, salivation, increased body temperature, altered sleep and altered waking EEG, tremor, and weight loss after discontinuation of THC administration [35][120]. These withdrawal symptoms that were described as ‘mild and transient’ started within 5–6 h after intake of the last dose and disappeared within 4 days. Sleep disturbances were observed for several weeks after discontinuing therapy. Withdrawal symptoms were alleviated by the administration of a cannabis cigarette or oral THC [120]. In another study, withdrawal symptoms, e.g., aggression, anxiety, decreased appetite, irritability, restlessness, and sleep problems, typically set in between days 1–3, peaked at days 2–6 and lasted 4–14 days [128]. Planned, sudden interruption of long-term therapeutic cannabis administration for two weeks in 25 patients did not cause a consistent withdrawal syndrome, although 11 (46%) patients reported at least one withdrawal symptom (tiredness, interrupted sleep, hot and cold flushes, mood alteration, reduced appetite, emotional liability, intoxication or vivid dreams) [123].

The U.S. National Comorbidity Study indicated that 9% of lifetime cannabis users met DSM-R-III criteria for dependence at some time in their life, compared to 32% of tobacco users, 23% of opiate users, and 15% of alcohol users [129]. In a representative sample of German adolescents (N=1228), who were followed for 20 months, the cumulative life-time incidence for DSM-IV cannabis abuse was 3.5% [130]. Similar data were obtained from an Australian sample of 10,641 adults of whom 1.5% were dependent according to DSM-IV, and 0.7% were diagnosed with cannabis abuse [131]. The natural course of cannabis use, abuse, and dependence is rather variable [132]. Cumulative incidence and patterns of cannabis use and disorders were examined in a prospective longitudinal design (mean follow-up period 42 months) in a representative sample (N=2446) aged 14–24 years at the outset of the study. Cannabis use was widespread in this sample, but the probability of developing cannabis abuse or dependence was relatively low (8%), and about half of all cannabis users spontaneously gave up their use in their twenties [132]. In cannabis users, the percentage of dependency may be much higher than in the general population. It was reported to be up to 50% in long-term heavy users [133].

Genetic and environmental risk factors are thought to contribute to dependency [134]. Young age at first use of cannabis is associated with an increased risk of later development of dependency [135]. In a group of boys, early-onset of use was associated with earlier onset of substance use disorder symptoms and more rapid acceleration of problems with drugs than late-onset use [135]. In another study, adolescents were
dependent at a lower frequency and quantity of cannabis use compared to adults and twice as many adolescents as adults who used cannabis near-daily or daily within the last year were identified as being dependent (35 vs. 18%) [136]. There is a correlation between cannabis dependence, and the dependence on tobacco, alcohol, and other drugs [137].

3.6. Hormonal System and Fertility. Cannabis and Δ⁹-THC act on the hypothalamic-pituitary adrenal axis, and, in animal studies, a multitude of endocrine processes are influenced by the drug, thus affecting sexual and other hormones (ACTH, TSH, HGH, melatonin) as well as glucose metabolism [138]. Changes in human hormone levels due to acute cannabis or THC ingestion are minor and usually remain in the normal range [17]. Tolerance develops to these effects, however, and even regular cannabis users demonstrate normal hormone levels. Reductions in male fertility by cannabis are reversible and only seen in animals at THC blood concentrations higher than those found in chronic cannabis users. After several weeks of daily smoking 8–10 cannabis cigarettes, a slight decrease in sperm count was observed in humans, without impairment of their function [139]. In animal studies, high doses of cannabinoids inhibited the acrosome reaction [140].

There is no conclusive evidence on any cannabis-associated influences on the menstrual cycle length, the number of cycles without ovulation or on the plasma concentrations of estrogens, progesterone, testosterone, prolactin, LH, or FSH in female cannabis users [141–143]. A transient cannabis-induced suppression of prolactin and LH levels was observed if the drug was inhaled during the luteal phase of the menstrual cycle [144].

There are few epidemiological data on influences of cannabis on fertility, and these provide no definitive answers. In an Indian study, 150 married male cannabis users that initiated cannabis use shortly before marriage were compared to an equal number of opium users and non-users of drugs. 1% of non-users, 2% of cannabis users, and 10% of opium users were childless [145]. Noteworthy sterility rate in bhang users (cannabis leaves) with an average daily consumption of ca. 150 mg of THC was lower (0.4%) than in nonusers, whereas the users of ganja and charas (flowers and resin) with a daily consumption of ca. 300 mg of THC was clearly higher (5.7%).

Mueller et al. investigated effects on female sterility. There was a low increase of sterility risk in association with marijuana use (rate ratio, 1.7; 95% CI, 1.0–3.0) [146]. The risk was only increased in occasional users and not in more heavy users. Joesoef et al. investigated the period of time from child wish until conception in 2817 women [147]. Regular users of cannabis became pregnant most quickly (mean 3.7 months). Tobacco smokers needed an average of 5.1 months, and drug-free women 4.3 months.

Grotenhermen reviewed the effects of cannabis and THC on other hormones [148]. A single oral administration did not elevate plasma cortisol in man [149]. However, smoking two cannabis cigarettes caused a transient significant increase in plasma cortisol level [150]. Chronic heavy cannabis users did not show any significant differences in their cortisol levels [151]. Cannabis use does not result in measurable changes in blood glucose level, but may influence glucose tolerance [152]. However, relatively high doses are needed. 6 mg of intravenously applied THC influenced glucose tolerance in some volunteers, while others remained unaffected [153].
3.7. Pregnancy and Foetal Development. The endocannabinoid system plays a crucial role in pregnancy. Successful pregnancy implantation and progression seem to require low levels of anandamide [154]. At term, anandamide levels dramatically increase during labor and are affected by the duration of labor, which may explain a sometimes observed shorter gestation in cannabis users. For example, Fried et al. found a reduction of approximately one week in the gestational age of infants born to mothers who used cannabis six or more times per week [155]. Both, higher than normal anandamide concentrations and cannabis use disturbed normal development of embryos, their oviductal transport and deferred on-time implantation [156].

THC rapidly crosses the placenta, and the course of THC levels in foetal blood coincides well with that in the maternal blood, though foetal plasma concentrations are lower than maternal level in rats [157]. It is unlikely that cannabis causes embryonic or foetal malformations. There are inconsistent epidemiological data on its effect on birth weight. There is evidence of subtle disturbances of cerebral development resulting in cognitive impairment in offspring of cannabis users from two longitudinal studies conducted in Canada and the USA [158][159]. This impairment might not be observed before preschool or school age. Thus, Jacobson et al. found poorer cognitive performance in new-borns at 12 months associated with prenatal exposure to alcohol but no association with cannabis exposure [160]. In 13- to 16-year-old adolescents, the strongest relationship between prenatal maternal cigarette smoking and cognitive variables was seen with overall intelligence and aspects of auditory functioning, whereas prenatal exposure to cannabis was negatively associated with tasks that required visual memory, analysis, and integration [158].

3.8. Other Organ Systems. The long-term use of cannabis may have a negative health impact on other organ systems, including immune system and circulation.

It has been demonstrated that THC may cause a shift in the development of Th1 and Th2 cells. THC Treatment of cell cultures [161] and the use of cannabis [162] was associated with a decrease of pro-inflammatory Th1 cytokines, such as IFN gamma and IL 2 (interleukin 2), and an increase in anti-inflammatory Th2 cytokines, such as IL 4 and IL 10. In clinical studies, no such changes were observed [163], which may be due to lower doses. These effects on the immune system may be beneficial in inflammatory diseases such as Crohn’s disease and multiple sclerosis, but may have a negative impact in immunocompromised subjects such as AIDS and cancer patients. Studies investigating the effects of cannabis or THC on the course of AIDS have yielded conflicting results. In a prospective study by Kaslow et al., the use of cannabis in HIV-infected persons was not associated with the onset of AIDS [164]. Di Franco et al. also did not observe any such influence of cannabis in HIV-infected men in a six-year epidemiological study [165]. In a three-week clinical study with smoked cannabis and THC in HIV-positive adults taking protease inhibitor-containing highly active antiretroviral therapy (HAART), no relevant effects on immune parameters were detectable [166]. On the other hand, Tindall et al. and Whitfield et al. found evidence for such an association [167][168].

The use of cannabis may acutely increase the risk of suffering from a heart attack due to its effect on blood pressure and heart frequency (see above). However, chronic use was not associated with cardiovascular risk factors such as blood triglycercide levels and blood pressure in the longitudinal CARDIA study, which began in 1986 [169].
Cannabis use was also not associated with a higher body mass index (BMI) compared to controls [170]. In an animal model of atherosclerosis, low doses of THC inhibited disease progression [171]. This was associated with a decreased interferon-gamma secretion by lymphoid cells and reduced macrophage chemotaxis. There are several case reports of an association between arteriopathies such as Buerger’s disease and cannabis use, but it is unclear whether this relation is causal, since the study subjects usually also smoked tobacco [172].

Daily cannabis use was a risk factor for progression of fibrosis in chronic hepatitis C in one epidemiological study, while occasional use was not [173]. The development of liver fibrosis may be regulated by cannabinoid receptors, and, in cirrhotic patients, CB1 receptors are markedly increased in nonparenchymal cells within and at the edge of fibrous septa, while there is only a faint expression of CB1 receptors in normal liver. On the other hand, cannabis use improved retention and virological outcomes in patients treated for hepatitis C with interferon and ribavirin [174].

3.9. Cannabis Prohibition. In contrast to other social activities that may be harmful to the individual and/or society, notably alcohol use, the use of cannabis remains illegal in most countries. Advocates of cannabis prohibition believe that it reduces trafficking and use, thereby improving productivity and health. Critics believe that prohibition curbs trafficking and use only modestly, while causing several negative side effects, such that the ‘toxicity’ of prohibition in fact enhances the toxicity from consumption of the drug itself. Brief reviews of several potential benefits and cost of cannabis prohibition follow.

3.9.1. Medical Use. In most western countries, cannabis remains prohibited even for medicinal purposes. Where individual cannabinoids (dronabinol, nabilone) or cannabis preparations that may be prescribed legally in some countries are not available or too expensive, therapeutic use of cannabis may cause considerable repercussions for the patient who requires it and has to obtain it illegally. They include criminal prosecution or fear thereof, exposure to possible contamination in low-quality drugs, and use of an unknown concentration of THC with possible variability in dosing. Since cannabis may be an effective painkiller, and people suffering from chronic pain are at a high risk of committing suicide [175], prohibition of medical cannabis use may increase mortality among this group of patients. The argument that other effective painkillers are available is no consolation for those, whose pain is not effectively treated by these. A person in his 50s, bound to a wheelchair and with little social interaction, will find it hard to obtain an illegal drug. Ironically, prohibition of medical cannabis tends to affect much more those adult patients with chronic pain and other severe diseases that respond positively to cannabis treatment than adolescents, who are the main focus of protection from drug use by prohibition.

The medical benefits of cannabis for some indications and the problems caused by continued prohibition of its medical use, recently prompted several medical journals to endorse reconsideration and reclassification of medical cannabis. In 2005, the editors of MedGenMed and the Journal of the American Medical Association pleaded for a reclassification of cannabis in the USA, so that its medical use would be allowed under federal law [176][177].

3.9.2. Individual and Societal Cost of Prohibition. The Editors of the Journal of the Canadian Medical Association not only advocated the legal medical use of cannabis but
also the general decriminalization of cannabis for personal use. They argued that the social and legal consequences of being arrested for cannabis possession and obtaining a criminal record far outweigh the minimal health effects of moderate cannabis use [178]. Since most of today’s regular cannabis users are young adults [179], over-reactive laws on cannabis may be regarded as a modern version of the generational conflict [180].

Aside from having a criminal record, losing one’s driver’s license may be another serious consequence of cannabis use. In the large French epidemiological study on drugs and traffic safety cited above, the risk of causing an accident increased 1.8-fold if THC was present in blood. Yet, it increased even more for drivers with a blood alcohol concentration of less than 0.05% and for drivers older than 70 years of age. In both cases, the risk increased by a factor of 2.7 [54]. To date, these findings only brought about heavier sanctions in France for drivers testing positive for THC, while no sanctions for drivers with a blood alcohol concentration of less than 0.05% or older drivers have been proposed. This suggests that sanctions against cannabis and driving are not necessarily based on a rational assessment of potential risks to traffic safety.

Cannabis prohibition may cause several other undesirable social and health effects. They include the need for cannabis users to interact with a criminal milieu and an erosion of the credibility of governments that created laws considered by many to be unjust and unenforceable. Cannabis prohibition also may have disrupted small-scale outdoor production, drove commercial growers indoors, and likely contributed to the observed increase in the potency of illegal cannabis, as its producers tried to maximize profits and minimize their risks [1].

These and other consequences of cannabis prohibition, such as the need to build and maintain a growing criminal system, including courts and prisons, also generate considerable costs to society. Based on a report on the economics of cannabis prohibition, the late Nobel Prize-winning economist Milton Friedman and more than 500 of his colleagues released an open letter to President Bush calling for an open and honest debate about marijuana prohibition. They added, ‘We believe such a debate will favor a regime in which marijuana is legal but taxed and regulated like other goods’. The report estimated that replacing cannabis prohibition with a system of taxation and regulation, similar to that used for alcoholic beverages, would generate combined savings and tax revenues of between 10 and 14 billion US Dollars per year in the USA alone [181].

Currently, the profits from drug trafficking only benefit the traffickers and are often used to finance criminal activities, including terrorist acts. On the forty-sixth session of the Commission on Narcotic Drugs of the United Nations in April 2003, 142 representatives approved a joint statement which expressed deep concern for the threats posed by continuing links between illicit drug trafficking and terrorism and other criminal activities, such as trafficking in human beings. [182].

3.9.3. Decriminalization and Prevalence of Cannabis Use. There is no agreement among scientists on how decriminalization or legalization of cannabis would affect key parameters, such as the prevalence of cannabis use by adults and adolescents, price trends, and the extent of unregulated home production. Effects will vary between countries and their socio-cultural settings. Decriminalization and legalization would certainly increase availability of cannabis, and there is great concern that this will also
increase use [183]. Other authors fear that legalization of cannabis could trigger noisy advertising campaigns for its use, some of which might be directed towards adolescents [183].

The developments following decriminalization of cannabis in some states or countries, and the comparison between countries with different drug laws offer some indication on how decriminalization may affect prevalence of use in other jurisdictions. When comparing cannabis prevalence statistics from the USA, Australia, the Netherlands, and other European nations, MacCoun and Reuter found that depenalization of small-scale possession of cannabis in some U.S. and Australian states, and in some European countries did not increase cannabis prevalence [184]. However, the authors concluded from the Dutch experience that commercial promotion and public sale of cannabis might significantly increase cannabis prevalence. Currently, the prevalence of cannabis use in the 15–34-year-age bracket in the Netherlands, which decriminalized cannabis more than 20 years ago, is higher than in Norway, Sweden, Ireland, Bulgaria, Portugal, Poland, and Greece, but lower than in Austria, Italy, Germany, the United Kingdom, France, and Spain [185]. Most studies on the effects of decriminalization of cannabis, including a report by the U.S. Institute of Medicine, conclude that depenalization and increased availability will have no significant impact on use (e.g., [11][186][187]). Recent experience in the UK confirmed this experience. There, cannabis was moved in 2004 from a Class-B to a Class-C drug, making its possession a misdemeanor, which did not increase cannabis use.

Instead, several studies found that social background, emotional, and other psychosocial factors were more reliable predictors of cannabis use and generally problematic drug use than the availability of the drug or its legal status. These factors included childhood behavioral problems [105], ‘qualitative aspects of family life, particularly attachment to mothers’ [188], peer-oriented lifestyle and ‘patterns of antisocial behavior and truancy’ [189], and separation from parents during adolescence [105][188].

4. Conclusions. – As Hollister already found in 1986, cannabis is now firmly established as another social drug in Western countries [17]. The recently observed increase in cannabis use, particularly among younger people, poses potential harm to individuals and society at large, and must clearly be attended to by society. The extent of the risks associated with cannabis use depend on several factors. According to the above review, young age among users, regular and heavy use, and the smoking of cannabis cigarettes are factors most likely to increase the negative effects of cannabis use. The greatest concerns should be associated with minimizing cannabis use by young adolescents. Potentially negative long-term effects of cannabis use, including dependence, induction of psychosis, effects on cognition and academic achievement are more severe in young people than in adults. Factors that tend to protect users from undesirable effects of cannabis are adult age, low-to-moderate use, and consumption of single cannabinoids and whole plant preparations in a therapeutic context.

This review of the toxicology of cannabis and the effects of currently used control strategies suggests that cannabis is a drug of moderate toxicity, particularly when used by adults. Because it may create undesirable effects on personal development and health, cannabis use by adolescents should be discouraged effectively. The medical use of cannabis appears to offer some persons benefits for a wide range of indications.
Cannabis prohibition appears to have only moderate success in reducing cannabis consumption. At the same time, it may have side effects resulting in harm to the individual and society, particularly with people who suffer from severe illnesses and may benefit from the therapeutic properties of the drug. Thus, unless it can be shown that decriminalizing personal use and regulating medical cannabis will increase the harmful effects of the drug itself, it is difficult to see what society gains from continued prohibition [183]. If their shared objective is to minimize the negative effects of cannabis use to society as a whole and the youth in particular, both critics and proponents of cannabis prohibition must be open to assessing and balancing the risks associated with the use of the drug, particularly for adolescents, and the costs incurred by any approach to damage control.

REFERENCES


[62] O. Drummer, Victorian Institute of Forensic Medicine, Department of Forensic Medicine, Monash University, Victoria, Australia, personal communication, April 2004.


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