Marijuana use: sequelae and implications for health promotion

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As of 2003, 40% of Americans aged 12 years and older had smoked marijuana at least once. Approximately 30% of Canadian youths from Grades 7-12 have tried cannabis at least once. Marijuana is the most widely-used illicit substance in Canada, with 10.6% of the Canadian population reporting use in 2009. This is similar to the US annual figure of 9%. Global reports indicate that the average age of first marijuana use is decreasing, even as the average delta-9-tetrahydrocannabinol (THC) content of cannabis is on the rise. This may lead to an increase in both addictive potential and adverse effects of marijuana use.

A survey of the adult US population comparing figures from 1992 and 2002 suggested that the prevalence of marijuana use remained stable over the decade, but the prevalence of marijuana dependence increased significantly. This increase in marijuana use disorders has occurred in the absence of increased frequency or quantity of marijuana use, suggesting that the enhanced potency of THC may have lead to the rise in rates. Treatment admissions for cannabis abuse have risen steadily over the past ten years, including a 2-fold increase in the US and 3-fold increases in Australia and Europe.

Although public perception remains that cannabis is “softer” and less dangerous than other illicit substances, cannabis use is becoming a major public health concern; some research even suggests it may serve as a gateway drug to “harder” substances. Furthermore, multiple studies have shown an increased risk in marijuana users of other long-term health consequences. In this paper, we review current research and understanding of marijuana’s impact on health outcomes. We also provide an overview of at-risk populations for use and abuse of marijuana, summarize marijuana’s potential positive effects, and discuss implications for health promotion and various levels of prevention.

PULMONARY EFFECTS

Numerous studies have shown that the combustion of tobacco and marijuana produces similar harmful compounds. The risks of marijuana may be increased by three factors. Marijuana smoke has three times more tar and 1.5 times more carcinogenic substances than tobacco smoke. Marijuana smoke is typically inhaled more deeply and held in the lungs longer: there is more time for deposition of particulate matter. Furthermore, marijuana cigarettes do not contain the same filter apparatus as conventional tobacco cigarettes. On the other hand, even heavy marijuana use involves far less smoke inhalation than the equivalent amount of tobacco in a pack-a-day smoker. One analysis of 19 previous studies defined marijuana use as smoking 10 or more marijuana cigarettes per week for 5 or more years. One pack of tobacco cigarettes contains 20-25 cigarettes, and the cigarettes generally contain more combustible material than their marijuana counterparts.

The extant literature on marijuana and lung cancer presents conflicting information. On the one hand, marijuana smoke contains benzopyrene, a carcinogenic hydrocarbon also found in tobacco smoke, which has been implicated in mutations related to lung cancer. Experimental studies have also demonstrated THC-induced malignant cell proliferation and suggested that THC inhibits antitumour immunity, thus promoting tumor growth. In contrast, other vitro models suggest that cannabinoids may actually exhibit anticarcinogenic effects. In an attempt to reconcile these divergent streams of thought, Mehrara, Moore, Crothers et al. undertook a systematic review to determine the associations between marijuana smoking and lung cancer incidence, risk factors, or premalignant changes. The authors found that marijuana smoking has increased tar delivery to lungs compared with cigarettes, and marijuana smoke contains similar carcinogens as tobacco smoke, often in increased quantities.

One systematic review found that inhaling marijuana smoke can cause clinical dyspnea and pharyngitis, as well as exacerbating pre-existing pulmonary illnesses such as asthma and cystic fibrosis; these effects persisted after adjusting for concurrent tobacco use. Despite these apparently harmful effects, the review found no association between marijuana smoke inhalation and effects on FEV1 (forced 1-second expiratory volume) or FVC (forced vital capacity), Dlco (diffusing capacity of the lung of carbon monoxide) or airway hyperreactivity. The authors explained these findings by suggesting that cannabinoids promote the Th2 anti-inflammatory immune response while nicotine suppresses it. One study noted that the use of a vapourizer when consuming marijuana was associated with decreased respiratory symptoms. A vapourizer is a device that heats the marijuana to the vaporization point of the cannabinoids without the use of flame, thereby obviating the consequences of smoke inhalation. Although there are many confounders in these analyses, not the least of which is the fact that many marijuana users cut the dried marijuana with commercially-available tobacco, it can be concluded that smoking marijuana exacerbates pre-existing respiratory complaints by directly irritating the respiratory epithelium. However, contrary to tobacco smoke, marijuana smoke does not seem to cause obstructive pulmonary diseases.

LUNG CANCER

The risks of marijuana use can be mitigated by smoking marijuana through a vapourizer rather than a conventional tobacco cigarette. A vapourizer is a device that heats the marijuana to the vaporization point of the cannabinoids without the use of flame, thereby obviating the consequences of smoke inhalation. A vapourizer is a device that heats the marijuana to the vaporization point of the cannabinoids without the use of flame, thereby obviating the consequences of smoke inhalation. Although there are many confounders in these analyses, not the least of which is the fact that many marijuana users cut the dried marijuana with commercially-available tobacco, it can be concluded that smoking marijuana exacerbates pre-existing respiratory complaints by directly irritating the respiratory epithelium. However, contrary to tobacco smoke, marijuana smoke does not seem to cause obstructive pulmonary diseases.
concentrations. Marijuana smoking was associated with the presence of more metaplastic cells, impaired alveolar macrophage function, and increased oxidative stress when compared with non-smokers. Six studies included in the systematic review reported histopathologic and molecular findings from bronchial biopsy; in all studies, marijuana smoking was associated with abnormal and/or precancerous alterations when compared with either non-smokers or tobacco smokers. One study in particular reported an additive effect between marijuana and tobacco use. All these findings suggest a biological plausibility for the association between marijuana use and lung carcinogenesis. However, a cohort study of 65,000 subjects showed no increase in lung cancer incidence in marijuana smokers after controlling for tobacco use. The authors suggested that there may be methodological concerns underpinning the lack of empirical support for increased lung cancer incidence in marijuana users, including the need for more detailed assessment of marijuana exposure and longer follow-up periods. They also cautioned that physicians should still advise their patients of the potential adverse health effects of marijuana use, including premalignant lung changes. 1

While methodological factors may well account for the lack of evidence for an association between lung cancer and marijuana use, Melamede13 has summarized another line of thought: although marijuana and tobacco smoke contain similar carcinogens, cannabinoids and nicotine present with very different cellular effects. Firstly, although low-doses of THC may indeed promote tumour growth, the response appears to be biphasic; alternate doses of cannabinoids have been capable of destroying cancer cells (including lung, breast, prostate, skin, and glioma) in vitro and in animal models. Secondly, both nicotine and cannabinoid receptors are linked to signaling pathways that can turn on anti-apoptosis (i.e. preventing cell death). Nicotine receptors are found in respiratory epithelial cells, while cannabinoid receptors are not. As such, when nicotine receptors are stimulated in respiratory cells, there is an anti-apoptotic signal; the prevention of cell death under exposure to such mutagenic conditions (i.e. smoking) is likely to amplify carcinogenic potential. Thirdly, while nicotine promotes neovascularization and thus tumour growth, cannabinoids inhibits angiogenesis and results in tumour regression. Finally, the introduction of particulate matter and cannabinoids into the respiratory system results in the creation of a pro-inflammatory state. In this circumstance, cannabinoids reduce the associated free radical production by driving a relatively anti-inflammatory Th2 immune cytokine profile. Melamede suggests that all these critical factors can explain the lack of association between cannabis use and lung cancer. 13

Even in light of this controversy surrounding cannabinoids and their association with lung carcinogenesis, Guzmán has gone so far as to suggest that cannabinoids could be used to develop novel anticancer therapies. 14 In addition to evidence suggesting inhibition of tumour growth, marijuana may also be beneficial to chemotherapy patients – it has the potential to mitigate nausea, vomiting, and pain while also stimulating appetite.

NEUROPSYCHOLOGICAL EFFECTS

Aside from its respiratory and pulmonary effects, marijuana use has been associated with neuropsychological consequences. Chronic marijuana use has historically been associated with impaired cognition, including reduced attention, memory, higher cognitive function (e.g. executive function) and psychomotor deficits. One study showed that after 25 days of abstinence, moderate (8-35 marijuana cigarettes/week) and heavy (53-84 marijuana cigarettes/week) users had decreased activity in the right lateral orbitofrontal cortex and the right dorsolateral prefrontal cortex, and increased activity in the left cerebellum, compared to the control group, during a decision-making game. 15 Another imaging study, using transcranial Doppler sonography, showed increased cerebrovascular resistance in chronic light to heavy users. 16 However, these studies were small, with 11 and 54 subjects, respectively. One meta-analysis of studies totalling 623 chronic marijuana users found that although these individuals may show decreased ability to learn and remember new information in the long term, other cognitive processes were unaffected. Thus, while there may be neurophysiological and neurovascular effects of chronic marijuana use, some of these effects may be silent.

Marijuana use has been shown to have negative psychological consequences, specifically an increased risk of psychosis. It is possible that cannabinoids’ effects on dopamine release contribute to the onset of psychosis. 17 A systematic review of 35 population-based longitudinal studies concluded that individuals who had ever used marijuana had an increased risk of developing psychosis later in life. 18 Furthermore, a dose-dependent relationship was observed where heavier users had a further increased risk of psychosis (adjusted OR 1.41, 95% CI 1.20-1.65 vs. 2.09, 1.54-2.84, respectively). Of course, a possible interpretation of these results is that an underlying, undiagnosed psychotic disorder leads to cannabis use, which facilitates the discovery of the pre-existing psychological illness.

Similarly, the oft-cited ‘amotivational syndrome,’ in which the sufferer is chronically unproductive, aimless and unmotivated, is associated with chronic marijuana use. One study found that individuals who have used marijuana a minimum of 5000 times were significantly less likely to graduate from college and less likely to earn more than $30 000 (US) per year. 19 However, like psychosis, this may be explained by the presence of many confounders including pre-existing depression. Gruber et al. have recently published data indicating significant alterations in frontal white matter tracts in chronic marijuana smokers. The authors suggest that these changes are associated with increased impulsivity, which may contribute to the initiation of chronic marijuana use or the inability to discontinue use. 20

HEALTH PROMOTION

Risk factors for marijuana use and abuse: Risk factors for marijuana use include male gender and age 18-25, while risk factors for dependence, defined as a maladaptive pattern of use despite negative effects, increased use, unsuccessful attempts at cessation and physiologic withdrawal, include male gender, age 12-17 and absence of post-secondary education. Stinson et al. have underscored that cannabis abuse and dependence are generally phenomena of adolescence and young adulthood, and onset of dependence after age 30 is rare. Stinson et al.’s results confirmed that, unlike with alcohol (where risk of dependence persists for decades after first use), there is a shorter developmental period of risk for cannabis dependence. As such, there is a window of opportunity in early adolescence for the implementation of prevention and intervention programs, in order to have maximum impact. A prospective longitudinal study of a community sample (n = 3021) aged 14–24 years in Munich, Germany, found that 56% of all repeated cannabis users (five times or more) still reported cannabis use at 4-year follow-up. At 10-year follow-up, this proportion had decreased only slightly to 46.3%. Among youth who are repeated cannabis users, patterns of use remain stable, and rates of cessation are low, until age 34. Such patterns suggest that preventive measures should delay first use and reduce the number of uses, as these factors appear crucial in the transition to persistent and dependent use of cannabis. 22

Although males may have higher rates of marijuana use, Schepis et al. have suggested, based on results from a cross-sectional survey of Connecticut adolescents, that females may have a more rapid transition from initial marijuana use to regular or dependent use. The
Health promotion for marijuana cessation is particularly important given the high co-morbidity between marijuana and tobacco use, and the potentially damaging interaction of these two substances on respiratory outcomes. Leatherdale, Hammond, Kaiserman et al. described results from a 2004 tobacco use survey of 20,000 young adult Canadians (aged 15-24). The rates of marijuana use were highest among current tobacco smokers, and lowest among youth who had never smoked. Those who use marijuana are less likely to quit smoking (odds ratio 1.94); those who use marijuana daily are even less likely to quit than those who have used at some point in the past 30 days. Thus, while marijuana use itself may or may not be associated with an increased risk of lung cancer, marijuana use may secondarily increase the risk of lung cancer through its association with persistent tobacco use. Conversely, through use of prospective survey methodology, Schaub et al. found that nicotine use increases the risk for both the initiation and the progression of cannabis use. The authors also reported that tobacco use remained high even after reduction or cessation of cannabis use. Thus, there appears to be a bidirectional risk between tobacco and marijuana use, with use of either substance increasing the likelihood of using the other. Clinicians should ask about marijuana history and take marijuana use into account when recommending tobacco smoking cessation measures for their patients, and vice versa.

Mental health disorders and use of cannabis: A study of 8841 Australian adults aged 18–85 years found that participants with affective disorders and anxiety disorders were at increased risk of harmful drug use and drug dependence. This correlation was particularly strong for young males, a group already identified earlier as high-risk for marijuana dependence. Another study reporting on cannabis use disorders and mood and anxiety disorder co-morbidity showed that bipolar disorders, panic disorder with agoraphobia, and generalized anxiety disorder had the strongest associations with cannabis abuse and dependence. While the directionality of this association remains unclear, one theory is that the experience of untreated affective disorders and anxiety disorders may lead to self-medication with psychoactive substances such as marijuana. As such, it is important for health practitioners to identify and treat underlying mental health conditions in a timely and effective manner. Indeed, there is evidence that such practices can reduce marijuana use, as demonstrated by two randomized controlled trials included in a systematic review. For example, in a fluoxetine treatment group, cannabis use decreased in patients with depression. In patients with psychotic disorders, both olanzapine and risperidone treatment groups also reduced cannabis use. From a health system-level perspective, overcoming the treatment fragmentation between mental health and drug and alcohol services would mean that the issue of comorbidity among clients (particularly young people) can be more adequately addressed.

Treatment of marijuana use disorders: Despite public perceptions of marijuana as a relatively innocuous drug, exposure to psychoactive cannabinoids can induce strong drug-seeking behaviours; these are mediated by increased dopamine release in the brain’s reward pathway. Abrupt withdrawal of cannabinoids after long-term exposure can produce dysphoric effects, which may contribute to relapse. Although cannabis shares neurobiological features associated with dependence on other drugs, only approximately one-tenth of individuals who abuse cannabis had ever received treatment. Psychosocial interventions, although effective in the short-term, often lead to long-term relapse, and the available behavioural treatments are only modestly effective. As such, there is a need to develop pharmacological intervention, and currently none have been validated through clinical trials.

As described above, cognitive impairments may not be fully reversible even 1 month after cessation of marijuana use. It remains unclear if these findings reflect long-term effects of marijuana, or simply an impairment of baseline cognitive functioning in marijuana users. Nonetheless, cognitive impairments in marijuana users may result in poor treatment response, particularly in light of the lack of motivation and increased impulsivity that is associated with chronic marijuana use. Studies have suggested that cholinesterase inhibitors may have a role in improving cannabis-induced cognitive impairments, but these drugs have not yet been evaluated in humans for the treatment of marijuana dependence. Cognitive rehabilitation has improved function and treatment outcomes in individuals addicted to other drugs. Sofuoglu et al. have thus suggested that improving cognitive function may serve as an important treatment strategy for marijuana use disorders.

Harmon reduction through use of vapoourizers: Given the widespread use of marijuana, the increasing abuse and dependence on this substance, and the paucity of effective treatment strategies, it is important to consider harm reduction approaches to mitigate marijuana’s potential adverse consequences. This pragmatic approach is particularly compelling given marijuana’s increasing use for medicinal purposes. According to results from a 1998 Canadian survey, medical use of marijuana was less common than its recreational use (2% versus 7%), but this picture may change in light of the shifting legal landscape surrounding medicinal marijuana. Cannabinoids activate the same neurotransmitter pathways as endocannabinoids, producing effects ranging from analgesia to appetite stimulation to nausea reduction. They also cause a reduction in intraocular pressure, hence the usefulness of marijuana in treating the symptoms of glaucoma. The main challenge for the medical use of cannabinoids is the development of safe and effective methods of use that lead to therapeutic benefit, without respiratory consequences or other adverse effects.

Earleywine and Barnwell have described the use of vapoourizers among marijuana smokers: vapoourizers release active cannabinoids but not smoke or carcinogens associated with combustion. The use of a vapoourizer is associated with decreased respiratory symptoms, and this effect increases with the amount of cannabis used. Furthermore, vapoourizers can deliver cannabis with no carcinogenic potential. This has important implications for safe use of medical marijuana as well as harm reduction among recreational smokers. In one study, twenty frequent cannabis users who reported respiratory complaints were evaluated before and after the use of a vapoourizer for one month. Among participants who did not develop a respiratory illness during the trial, there was a significant improvement in respiratory symptoms and FVC, and a non-significant improvement in FEV1. These improvements could be even more meaningful in cannabis users who also smoke tobacco. The authors concluded, given these meaningful recovery of respiratory function, that a randomized clinical trial of the cannabis
vapourizer should be performed. The vapourizer has potential for the administration of medical cannabis and as a harm reduction technique, particularly for those uninterested in marijuana cessation or who have been chronic, heavy users.

CONCLUSION

Although the prevalence of marijuana use has not changed significantly in recent years, the higher cannabinoid content of current plants may be contributing to the observed increase in rates of dependence in adolescents. Both phenomena – increased dose of psychoactive drug, and increased rates of serious dependence – have catalyzed more research into the long-term neuropsychiatric effects of marijuana use. Long-term marijuana use is associated with an increased risk of psychosis and ‘amotivational syndrome’. However, the direction of causation remains unclear, not least because the risk of marijuana dependence during adolescence is clearly increased by co-morbid psychiatric disorders and has been characterized as a form of ‘self-medication’. Marijuana is also associated with specific long-term cognitive abnormalities; the possibility of reverse causation seems remote for these findings, but further research is needed. Marijuana has immediate adverse effects on respiratory mucosa similar to tobacco; however, evidence for chronic respiratory disease related to marijuana is weak. For lung cancer, similarly, heavy marijuana use produces metabolic changes but there is no compelling evidence for an association with clinical disease. The contradictory evidence for both conditions may reflect differences in the chemistry and cellular effects of marijuana as contrasted with tobacco, as well as the high frequency of joint exposure. In that latter regard, the more significant risk for respiratory illness, including malignancy, may arise from the strong association of tobacco and marijuana use, and the reduced likelihood of smoking cessation in the presence of joint dependence.

From the standpoint of health promotion, we can draw a number of key conclusions. Primary prevention of marijuana dependence will require health education targeting pre-adolescence. The prevalence of comorbid psychiatric disorders in dependent adolescents highlights the need for an integrative approach to treatment and secondary prevention. Awareness of the conjoint use of tobacco and marijuana is important for clinicians seeking to promote smoking cessation. Lastly, vapourizers have the advantage of mitigating respiratory risk and may serve as an effective harm reduction strategy for those who are chronically dependent or using cannabinoids for clinical indications.

REFERENCES