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Cannabis toxicity and adverse biological activity

Ronald Bartzatt

University of Nebraska, College of Arts & Sciences, Durham Science Center, Chemistry Department, 6001 Dodge Street, Omaha, Nebraska - 68182, (U.S.A.)

E-mail : rbartzatt@mail.unomaha.edu

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ABSTRACT

Consideration of cannabis as a medicinal entity is an ongoing discussion that requires additional clinical and laboratory research. Marijuana smoking deposits 4x times more tar in the lungs as compared to tobacco smoke and amount of some pro-carcinogens are up to 2x times greater in marijuana tar. Determination of Dependence/Physical Harm relationship by investigators shows a proximity of cannabis to khat, LSD, ecstasy, alkyl nitrites, and methylphenidate. Non-users that are exposed to cannabis inhalant may suffer loss of coordination, dizziness, confusion, difficulty walking, blurred vision, and vomiting. Illicit drug use has been shown to be strongly associated with homicide events. Psychotropic effects from THC inhalant reaches a maximum after 15 to 30 minutes. Psychotropic effects from oral ingestion of THC reaches maximum level after 2 to 3 hours. Marijuana smoke contains higher levels of specific toxins than tobacco smoke. Ongoing research outcome challenges the concept that marijuana smoke is less harmful than tobacco smoke. Marijuana smoke causes lung damage quickly and could out pace tobacco smoke by as much as 20 years. Studies has shown cannabis usage worsens the course of schizophrenia spectrum disorders and that adolescents possess a greater risk from cannabis than older individuals. Cannabis abuse could be an independent risk factor for the further development of psychotic disorders. Further research and study is warranted concerning clinical application of cannabis.

KEYWORDS

Cannabis;
Marijuana;
Toxic;
Hallucinogen;
Hemp.

INTRODUCTION

It would be erroneous medical judgment to presume the safety of cannabis usage as a consequence of findings suggesting some lesser danger than that known for substances such as cocaine and heroine. Even in the casual context of discourse it is accepted that cannabis utilization affects brain activities, memory effectiveness, and general health[1]. Dangerous side effects have been reported with casual usage of cannabis. Various works have been presented indicating that cannabis application in treatment of medical disorders actually exacerbates the condition that is in treatment[1]. Potential adverse medical reaction to use of cannabis can contribute to the medical dangers of the disease to which it is applied[1]. Major after effects of cannabis consumption as an inhalant include respiratory related manifolded and aggravated infectious disorders[1]. Cannabis expresses

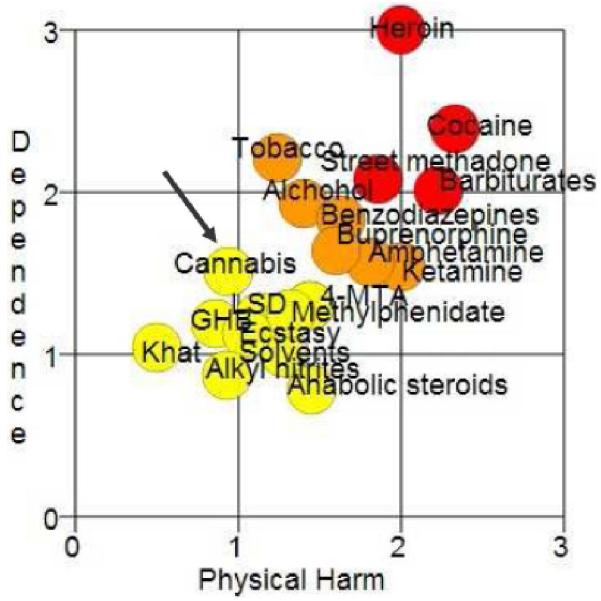

Figure 1 : Rational scale 2-way plot of dependence (dependent variable) compared to physical harm (independent variable) indicating relative harm of cannabis (see inset arrow) and other abused substances[2]. A cluster of substances are in close proximity to cannabis and include khat, LSD, GHB, anabolic steroids, alkyl nitrites, ecstasy, 4-MTA, and methylphenidate

the target physiological reactions quickly if applied as an inhalant, which in addition to the target effects, it impairs function of the smaller air passages, inflames lung tissue, effects chronic bronchitis, etc.[1]. Consequences of inhalant use of cannabis will be the major focus of discussion presented in this work. Cannabis use as an inhalant has been promoted extensively as a medically defined application for the treatment of serious conditions of HIV infection, cancer treatment, and medical ramifications of organ transplantation. Studies have indicated that cannabis utilization can actually accelerate the progression of HIV condition to whole AIDS, in addition to the increased possibility of Kaposi's sarcoma and of infections that endanger during an already disabled immune system[1]. Previous studies have shown a fourfold increase of plant tar deposited in the lungs occurs from marijuana smoke[1], when compared to tobacco smoke. In addition, the tar phase of marijuana delivers increased concentrations of polycyclic aromatic hydro- carbons (inclusive of benzo-[α]-pyrene) compared to tobacco smoke[1]. Investigators have made attempts to compare adverse effects of cannabis from harm induced by other drugs such as alkyl nitrites, khat, cocaine, heroin, ketamine, etc.[2], however differences in delivery methods, concentration variations, uncertainties in poly drug usage, uncertainties in individual scoring, and other difficulties complicates and undermines the practicality of such scoring. One such scoring is shown as a 2-way plot is presented in figure 1, in which cannabis is placed adjacent to LSD, ecstasy, khat, GHB (gamma hydroxybutyric acid), and methylphenidate (see inset arrow). From such comparisons the dubious argument is advanced that cannabis is less hazardous than the profoundly dangerous cocaine, tobacco, and heroin. Marijuana utilized as an inhalant can incur damage on cells found in bronchial passages decreasing efficacy of the immune cells to resist bacteria and fungi[1]. This adverse effect is presumably more significant in patients who are immune compromised such as in HIV disease, patients receiving cytotoxic chemotherapy of cancer treatment, and organ transplant patients (all these the very category of patients promoted as targets for cannabis regimen). Although many studies have been completed concerning the pharmaceutical aspects of cannabis utilization, there remains much work to pursue in rumination of the continued assertion of applying marijuana for the treatment of various diseases.

GENERAL CONSIDERATIONS

Although hemp has been used in some industrial applications those working with the material in this capacity have been shown to develop dermatitis and the potential for skin dermatitis[3]. Incorporation of marijuana into simple food preparations has been documented to induce vomiting, dizziness, confusion, blurred vision, dry mouth, dysphagia, dysarthria, and difficulty in walking and concentration[3]. An odds ratio (O.R.) analysis describes the strength of association (or non-independence) between two data values. A descriptive statistic, a value of O.R. greater than one implies an event is more likely in the initial group. Whereas an O.R. value equal to one implies equal likelihood of event in both groups and less than one implies event occurrence less likely in initial group. Outcome of previous studies showing that drugs play a role in premature death that extends beyond overdose and disease, including illicit drug association with homicide[4], present a compelling contention while determining extent of medically intended marijuana. Cannabis present in homicide cases has been determined to present an O.R. value of 2.39, which is

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even greater than that for opioids (O.R. = 1.53) and psycho-stimulants (O.R. = 1.59)[4]. This result clearly supports the contention that marijuana is associated in homicide events. Non-drug using persons are determined to be at greater risk as homicide victims when residing in homes with illicit drug abusers[5]. In general, the use of alcohol and illicit drugs is associated with an increased risk of violent death[5]. Therefore the potential for violent events leading to death for non-drug users present in homes of illicit drug users poses a particular when considering comprehensive program for self-administration of cannabis.

Pharmacology considerations

Delta(9)-Tetrahydrocannibinol (THC) does bring on a myriad of pharmacological effects in animals as well as humans[6]. Among these are activation of cytochrome P4501A1gene which thereby potentially enhances the transformation of polycyclic aromatic hydrocarbons to active carcinogens[1]. In habitual marijuana smokers an overexpression of cell proteins associated with malignant transformations has been identified in bronchial epithelium cell[1].

Cannabinoids exert many effects in vitro which are initiated by activation of G-protein-coupled cannabinoid receptors in both the brain and the peripheral tissues, with some evidence for non-receptor dependent mechanisms[7]. The pharmacokinetics aspects of THC will vary as a function of the route of administra-tion, with pulmonary assimilation (inhaled THC) presenting the maximum plasma concentration within minutes, while psychotropic effects initiating in mere seconds to few minutes (reaching maximum in 15 to 30 minutes)[7]. Oral administration of THC initiate psychotropic with 30 to 90 minutes and maximize within 2 to 3 hours[7]. Acute adverse effects of anxiety, panic attacks, increased heart rate, and alteration of blood pressure occur with overdosage[7]. Extended usage may initiate a condition of dependency[7]. Cannabinoid receptors are distributed in peripheral tissues including the immune system, reproductive system, gastrointestinal tract, sympathetic ganglia, arteries, lung, heart, endocrine glands, as well as the central nervous system[8]. This finding strengthens the necessity of careful evaluation of all activity of cannabis when considering medicinally oriented application. Evidence also exists for various non-receptor dependent mechanisms of biological activity[8].

Comparison to tobacco smoke

Various studies have shown that the biological effects of cannabis abuse are significant and potentially dangerous. The use of cannabis as an inhalant for medical purposes presents problematic toxicity issues as well as pharmaceutical activity that is not well understood. Although some information have been made public that suggests cannabis is less harmful than profoundly toxic illicit drugs of cocaine and heroine[2], it is improper and unsafe to determine that marijuana smoke is therefore benign. Studies have shown that marijuana smoke contains significantly higher levels of toxic agents such as hydrogen cyanide and ammonia[9]. Among the host of toxic substances identified in marijuana smoke are 50 that are known to cause cancer, ammonia level is 20x times greater in marijuana smoke than tobacco smoke, with some aromatic amines occurring at a level 3x to 5x times greater in marijuana smoke[9]. The impact of marijuana smoke on pulmonary tissue is substantial. The tissue damage occurring to the lungs by marijuana smoke is damage that is 20 years ahead that caused by tobacco smoke[10]. Current studies are discerning the possible deleterious effects on pulmonary DNA that is caused by toxic substances in marijuana smoke[11]. Marijuana smoke has been associated with numerous adverse pulmonary effects in human tissue, that include edema, bronchitis, and hypersecretion of mucus[12]. Various studies have demonstrated that condensates of marijuana smoke are genotoxic[12]. Human lung explants have been used to show that marijuana smoke may alter the DNA content and chromosome number[12]. In addition, previous studies have shown that in human consumption (inhalant) of marijuana smoke impairs large airway function and lung efficiency 2.5x to 5x times greater than tobacco smoke[12]. Marijuana smoke contains harmful substances and qualitatively the same chemicals as tobacco smoke[12,13]. Marijuana smoke contains selected polycyclic aromatic hydrocarbons (PAH) and in secondary smoke it is at levels greater than tobacco smoke[13]. Mari-juana smoke has been associated with long term pulmonary injury and pulmonary inflammation[13]. Some organic compounds found in marijuana smoke include: toluene, benzene, pyridine, quinoline, isoprene, acrylonitrile, styrene, and 1,3-butadiene[13].

Cannabis and psychiatric effects

Studies in mice have shown that the feeding of marijuana would produce in dominant males an increase of flight activity, social activity, and sexual activity labeled as investigative in nature[14]. Upon removal of cannabis the same dominant males demonstrated elevated aggressive behavior[14]. Other animal research demonstrated identifiable behavioral pharmacology of cannabinoids that interact with cannabinoid neurotransmission modifiers that exhibit rewarding-reinforcing properties in the experimental animals[15]. Studies of human interaction have been completed. Individuals that have experienced childhood trauma and coupled with cannabis use are associated with significantly greater risk of psychotic symptoms than for each risk factor alone[16]. However different work determined that cannabis alone may be sufficient risk factor itself for the development of psychotic disorder[17]. Epidemiology studies have been executed to investigate the possible link between cannabis use and appearance or exacerbation of psychotic symptoms. What was determined is that individuals at risk of or already expressing psychotic symptoms had an increase risk with cannabis usage. Essentially, results indicated that cannabis usage may precipitate schizophrenia (or exacerbate its symptoms) and cannabis usage exacerbates the symptoms of psychosis already apparent[18]. Previous studies corroborated the finding that cannabis usage worsens the course of schizophrenia spectrum disorders and adolescents possess greater risk from cannabis use than older individuals[19]. Male gender and age has been shown to be significantly related to a personal history of cannabis abuse or dependence. In addition, schizophrenic patients who were also users of cannabis were likely to be younger and male, as compared to those who were non-users[20]. Attempts at suicide while during schizophrenia was found to be closely correlated to cannabis usage[20]. Canna-bis abuse may be a risk factor for the occurance of as spectrum of psychiatric disorders ranging from schizophrenia to mood/anxiety disorders and a dose response relationship has been identified between cannabis exposure with risk of psychosis[21]. A plausible linkage of cannabis usage precipitating a schizophrenia condition within individuals already at risk due to personal or family history of schizophrenia has been elucidated[22]. Early exposure to cannabis, during adolescence, may be an environmental stressor that has interaction with a previous genetic predisposition to induce a psychotic disorder[17]. In addition, cannabis usage could be an independent risk factor for the further development of psychotic disorders[17]. Evaluations for cognition function activity have been evaluated for group adolescents that were regular cannabis abusers and showed that significantly poorer perfomance on four measures reflecting attention, learning, and spatial working memory[23]. In addition, cannabis use was found to be an independent predictor on working memory and strategy measures[23]. Aspects of adolescent cognitive function are independently related to the frequency of cannabis usage[23]. Use of cannabis by psychiatric patients possibly produces some anxiolytic effect and antidepressive influence however it is accompanied by exacerbated psychotic and manic symptoms[24]. While cannabis use can produce or worsen psychotic symptoms in risk patients an early exposure, expecially in combination with genetic factors, does increase the risk of subsequent and primary psychotic disorder[25]. Adolescents also using cocaine and upon onset cannabis usage have a greater risk of cocaine induced paranoia[25]. While cannabis has a deleterious effects, halting exposure following after an initial psychotic episode clearly contributes to improved outcome[26]. Young adults practicing moderate drug use were studied and outcome findings corroborated earlier studies that showed decrements in memory and attention preformance, with ecstasy and cannabis combined usage significantly related to poorer episodic memory function[27].

Additional cannabis toxic effects

As further studies of cannabis abuse continue, one of many outcomes is the realization that cessation of cannabis usage results in withdrawal symptoms and difficulty in abstention[28]. Further studies are pursued in the role of the CB1 receptor in regulating the behavioral effects of THC, which is the primary psychoactive portion of cannabis, that actually cross a range of species[28]. In addition, further investigation of CB1 receptor and its possible role in marijuana dependence is a necessary topic particularly when considering medicinal application of cannabis[28]. Meanwhile cannabinoids have become the most frequently abused illicit class of drugs in the United States[29]. Despite discussion of medical marijuana, the abuse liability of THC is comparable to other abused drugs under specific condi-

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tions[29]. In laboratory studies it has been observed that THC causes an inhibition of incorporation of 5-3H-uridine into ribosomal RNA (17S and 25S RNA) and in synchronized cells the precusor RNA (35S RNA)[30]. THC suppresses the incorporation of 5-3H-uridine, 2-14C-thymidine, and L-3-14C-phenylalanine into RNA and progressive dose-dependent activity of THC on division delays in division synchronized cell cultures was also correlated with concomitant reduction of division maxima and percent of cells completing division I[30]. In vitro studies of THC revealed that at a concentration of 10^{-5} molar concentration in human cell culture appears to inhibit DNA, RNA, and protein synthesis by 50%, 40%, and 30%, respectively, these being significant levels of deleterious cellular effects[31]. While THC inhibited semiconservative DNA synthesis it did not appear to have any effect on DNA repair synthesis in human cells[31]. The constitutive cannabinoids of marijuana and marijuana have been shown to markedly affect cells of mammals[32]. In both in vitro and in vivo investigation it has been shown that cannabinoids induce chromosome aberrations[32]. Aberrations of this sort includes hypoploidy, deletions, translocations, and errors in chromosomal segregation, all of which are due to clastogenic activity or to cannabinoid induced disruption of mitotic events (or both)[32]. Corroborative work accomplished also indicated THC activity that inhibits protein synthesis and nucleic acid synthesis[33]. The affect on animals by THC is significant even in neurobiological data. Cannabis induces psychological dependence that is common to all addictive drugs as well as a physical dependence[34] (which hitherto was considered to be descript of "hard addictive drugs"). THC invigorates an incentive to abuse other addictive drugs and in particular heroin[34]. A close relationship between cannabis and schizophrenia has been elucidated by some studies[34]. Ongoing clinical evaluation and research outcomes have changed the previous view of cannabis as being more benign. Cannabis usage is being found to have a multitude of physical and mental effects on human beings. Further research and study is warranted concerning cannabis clinical application that should elucidate concepts of cannabis dependence[35].

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