Review of Medicinal Use of *Cannabis* Derivatives and the Societal Impact of Legalization

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Abstract

Background: In recent past, there has been a rush to legalize marijuana along with a lot of support for its medicinal uses. This review intends to discuss the medicinal uses of marijuana and its adverse effects based on the current available evidence. Furthermore, it discusses the impact of legalization of marijuana. **Methodology:** This was a narrative review for which a thorough literature search was conducted on the Medline and PubMed databases. A detailed search of the Internet to find relevant information on webpages was also performed. **Results:** High-quality evidence for the majority of medical indications of marijuana remains investigational. Most of the available literature compares it against placebos. Postlegalization usage of marijuana has increased. **Conclusion:** It would be prudent to wait for studies which prove beyond doubt the advantages of marijuana over the existing drugs and also outweigh its side effects and addiction potential. Moreover, further legalization of marijuana should only be considered after evaluating its effects at places where it is already legally available.

Keywords: Addictions, *Cannabis*, marijuana

Introduction and Historical Usage

Cannabis is a generic term which usually denotes the various psychoactive substances in *Cannabis sativa* as per the WHO.[1] *Cannabis* can be divided into three main strains – sativa (gives a euphoric effect), indica (gives a sedating effect), and hybrid (features of both indica and sativa).[2]

Marijuana (*C. sativa*) is a drug of plant origin that contains more than sixty compounds known as cannabinoids.[3-5] Marijuana is a more commonly used term; in this article, we have used *Cannabis* and marijuana interchangeably depending on the article being discussed. The two main components of marijuana are 6-tetrahydrocannabinol (6-THC) and cannabidiol (CBD). THC acts as a psychoactive component, whereas CBD acts as a nonpsychoactive component. THC content is 0.4% higher in sativa than indica.[6] Cannabinoid composition differs in different marijuana preparations, thus impacting their effectiveness.[7]

The estimated population which consumes marijuana in any of its form each year is said to be around 160 million. This forms about 4% of the world population in the age group of 15–64 years.[8]

The *Cannabis* plant is indigenous to Central and South Asia. It has been cultivated in Japan and China since pre-Neolithic and Neolithic ages. It spread to the new world in the post-Columbian times. Historically, it has been used for manufacturing clothes, shoes, ropes, and an early form of paper. In Sanskrit and other modern Indo-Aryan languages, *Cannabis* is referred to as "Bhang." It intends to show how the use of Marijuana was propagated from one civilization to another. In India and Nepal, it has been used in an entheogen, a chemical substance that is used in a religious, shamanic, or spiritual context. The earliest known reports regarding the sacred status of *Cannabis* in India and Nepal come from the *Atharva Veda* which is estimated to have been written sometime around 2000–1400 BCE.[9] *Cannabis* has historically been consumed in many different ways – smoking in the form of small pipes, bongs (portable

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versions of hookahs with a water chamber), and paper-wrapped joints or tobacco-leaf-wrapped blunts, and other items such as *Cannabis* tea, as a beverage, bhang.

Marijuana has a long history of use for medicinal purposes. Literature is currently divided on the therapeutic uses of marijuana. The use of marijuana for medicinal purposes is promising; however, the research in this field is still primitive.[10-12]

It may be used for the purpose of treating or alleviating the symptoms of several diseases. Its use is presently recommended by the local drug-controlling authority across various countries in certain conditions or diseases. Its use in various other conditions is currently investigational. This review intends to discuss the medicinal uses of marijuana and its adverse effects based on the current available evidence. Furthermore, it discusses the impact of legalization of marijuana on health as well as other aspects of life.

Methodology

A thorough search of the Medline (from 1950 to 2018) and PubMed (from 1946 to 2018) databases was done. A detailed search of the Internet to find relevant information on webpages was also done. The search terms used were "Marijuana," "Medicinal Marijuana," "*Cannabis*," and "Complications of Marijuana." These were searched as text word and as subject headings individually as well as in combination. The reference lists of relevant articles were also searched for appropriate studies. No language restrictions were used in either the search or study selection. Articles or webpages which failed to describe the factors of interest for the study were excluded. Among these, only 96 articles and online webpages were considered in this review. The information has been presented in the form of a narrative review.

Medicinal uses of marijuana

A study looking at the demographic pattern of medical usage of *Cannabis* in 2736 patients noted that the mean age of such patients was 74.5 ± 7.5 years, with a slight female predominance (53.5%).[13] Marijuana can be administered via various routes of administration, with the most common being smoking followed by others such as vaporization, oral administration, oro-mucosal spray, and topical use.[14] An epidemiological study held in Israel found that the most common route of administration of *Cannabis* was oil (37.3%), followed by smoking (24.4%) and vaporization (6.4%).[13] According to them, the most common indications of marijuana were pain (1822, 66.6%) and cancer (1482, 60.8%), with significant overlap between the two groups.[13]

The following are the medicinal uses of *Cannabis*:

Nausea and vomiting

Several studies have looked at the use of *Cannabis* to treat symptoms such as nausea and vomiting. It is hypothesized that inactivation of CB_1 receptors leads to vomiting. The antiemetic action of *Cannabis* is mediated via the activation of CB_1 receptors. In a meta-analysis looking at 28 studies where marijuana was used for nausea and vomiting,[15] marijuana showed benefits in their control in majority of the studies when compared with placebo as well as other alternatives. The comparator agents commonly used were prochlorperazine, chlorpromazine, and domperidone. The number of patients who showed complete resolution of symptoms with cannabinoid group was greater than the number of patients in the placebo group with an odds ratio of 3.82 (95% confidence interval [CI], 1.55–9.42). All these studies suggested that there was a benefit of cannabinoids compared with both active comparators and placebo, although the benefit was not statistically significant.[15-17] However, when a review compared *Cannabis* against various other antiemetics, it was noted that *Cannabis* was associated with greater central nervous system side effects such as drowsiness, postural dizziness and hypotension, lightheadedness, and euphoria [Table 1].[18]

Appetite stimulation

Marijuana has also been used for appetite stimulation in patients suffering from anorexia nervosa, HIV, and cancer. Appetite stimulation is extremely important in these patients. Patients suffering from cancer and undergoing treatment have high nutritional requirements; however, delivering adequate nutrition may not always be possible due to the disease itself, any previous surgical intervention, or any ongoing treatment. The action of marijuana is exerted through the agonist action of CB1 receptors; it causes increased food craving and enjoyment, along with the promotion of deposition of energy as fat into adipose tissues.[19,20]

A meta-analysis looked at the use of *Cannabis* for appetite stimulation as compared to a placebo or comparator agent such as Megastrol acetate among patients suffering from HIV/AIDS. Most of the studies included had a placebo as the comparative agent. The results showed evidence for increased appetite using marijuana as compared to placebo,[15] however, Megastrol acetate showed a significant advantage over patients using *Cannabis* both for appetite (75% vs. 49% [$P = 0.0001$]) and baseline weight gain (11% vs. 3% [$P = 0.02$]) [Table 1].[21]

Marijuana may be beneficial for appetite stimulation; however, further studies comparing it to known comparator agents are needed to conclusively determine its usefulness.

Chronic pain

Pain can be generally associated with several conditions, such as neuropathy, cancer pain, diabetic peripheral neuropathy, fibromyalgia, HIV-associated sensory neuropathy, refractory pain due to multiple sclerosis (MS), rheumatoid arthritis, musculoskeletal problems, and chemotherapy-induced pain. Most of these are chronic conditions and often, these patients are generally resistant to other pain medications. Marijuana has often been used for pain relief in such situations.

In a meta-analysis comparing *Cannabis* with a placebo for various painful conditions such as neuropathic pain,

Table 1: Overview of studies on medical usage of marijuana

Use of marijuana	Study	Type of study	Sample size	Comparator agent	Study parameters	Results	Level of evidence	Demerits
Nausea and Vomiting	1) Risto Johansson (1982)	RCT	27	Prochlorperazine	Number of Vomiting ejections between Cannabis and Prochlorperazine groups	Lesser in Cannabis group as compared to Prochlorperazine, (P <0.001)	Ib	1)Small sample size 2)Greater incidence of side effects with Cannabis
	2) Chan HS, 1987	RCT	30	Prochlorperazine	Rate of Improvement in Vomiting between Cannabis and Prochlorperazine groups	Cannabis vs Prochlorperazine- 70% vs 30% (P=.003, chi 2 test)	Ib	1)Small sample size 2)Greater incidence of side effects with Cannabis
	3) Pomeroy M, 1986	RCT	38	Domperidone	Number of Vomiting episodes between Cannabis and Domperidone groups	Cannabis vs Domperidone, 4.76 vs 12.95 (P< 0.02)	Ib	1)Small sample size 2)Greater incidence of side effects with Cannabis
	4) Niederle N, 1986	RCT	20	Alizapride	Number of episodes of vomiting between Cannabis and Alizapride groups	Cannabis vs Alizapride, 1.1 vs 2.9 (P<0.01)	Ib	1)Small sample size 2)Greater incidence of side effects with Cannabis
	5) Niiranen A, 1985	RCT	24	Prochlorperazine	Number of episodes of vomiting between Cannabis and Prochlorperazine groups	Cannabis vs Prochlorperazine, 6.5 vs 11(P<0.05)	Ib	1)Small Sample size 2)Cannabis use unpredictable 3)Greater incidence of side effects with Cannabis
	6) Salllan 1975	RCT	22	Placebo	Response between the Cannabis and Placebo groups	Greater response in patients on Cannabis compared to Placebo Ib (p<0.001) Greater incidence of side effects with Cannabis	Ib	1) Small sample size 2) Placebo controlled 3) No comparison between placebo and no placebo
	7) Stephen E. Jones, 1982	RCT	54	Placebo	Mean episodes of Vomiting between Cannabis and Placebo groups. Severity of Nausea between both groups	Lesser number of Vomiting episodes and in patients receiving Cannabis over Placebo (P<0.001) Reduced Nausea in Cannabis group over placebo (P<0.001)	Ib	1)Greater Incidence of side effects 2)Relatively small sample size
	8) Jerry K. Wada (1982)	RCT	112	Placebo	Incidence of Nausea and Vomiting between the Cannabis and Placebo groups	Nausea and Vomiting Reduced in Cannabis group as compared with placebo (P<0.001)	Ib	1) Greater incidence and severe nature of side effects due to Cannabis
	9) Duran M *et al*. 2010	RCT	16	Placebo	Complete response in Vomiting between Cannabis and Placebo groups	Complete Response between Cannabis and Placebo groups - 71.4% of patients vs 22% of patients (95% CI 1%, 75%)	Ib	1) Small sample size. 2) Placebo controlled
	10)Chang *et al*.	RCT	15	Placebo	Number of Vomiting and Retching episodes, Degree of Nausea, Duration of nausea and volume of emesis	Cannabis significantly more effective than placebo all parameters (P<0.001)		1) Small sample size. 2) Placebo controlled

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Table 1: Contd...

Use of marijuana	Study	Type of study	Sample size	Comparator agent	Study parameters	Results	Level of evidence	Demerits
Appetite Stimulation	1)Beal JE 1995	RCT	139	Placebo	Improvement in appetite above basement between Cannabis and placebo groups	Increased appetite in Cannabis group as compared with Placebo (38% vs 8% for placebo, *P*=0.015)	Ib	1)Placebo Controlled
	2) Struwe M, 1993	RCT	12	Placebo	Increase in percentage of body fat and trend towards weight gain between Cannabis and placebo groups	Increased percent body fat in Cannabis group (one percent, *P*=0.04) Trends towards weight gain in cannabis group (0.5 kg, *P*=0.13)	Ib	1)Small sample size 2)Placebo Controlled
Chronic Pain	1)Jeremy R. Johnsn, 2010	RCT	177	Placebo	In patients suffering from Cancer, Numerical Rating Scale (NRS) score were compared between the Cannabis and Placebo groups	Statistically significantly results in favor of Cannabis compared with placebo (improvement of −1.37 vs. −0.69, *P*<0.014)	Ib	1)Placebo Controlled
	2) Ronald J Ellis, 2009	RCT	28	Placebo	Pain relief in patients suffering from Neuropathic pain between the Cannabis and Placebo groups	Pain relief greater with cannabis than placebo (median difference in DDS pain intensity change, 3.3 points, effect size=0.60; *P*=0.016)	Ib	1)Small Sample size 2)Placebo Controlled
	3)Skrabek RQ, 2008	RCT	40	Placebo	Visual analogue scale(VAS) in patients suffering from fibromyalgia	Significant decrease in the VAS (-2.04, *P* < .02), in Cannabis group as compared to Placebo	Ib	1)Comparatively small Sample size 2)Placebo Controlled
	4) B Frank, 2008	RCT	96	Dihydrocodiene	Pain compared using Visual Analogue Scale (VAS) between Cannabis group and Dihydrocodeine group	Mean score on VAS scale was 6.0 mm longer for Cannabis than for Dihydrocodeine (95% confidence interval 1.4 to 10.5)	Ib	1)Greater side effects associated with Cannabis
Multiple Sclerosis	1) Zajicek, 2012	RCT	279	Placebo	Spasticity compared using change in Ashworth score from baseline to 12 months between Cannabis group, Cannabis extract group and placebo	Change in Ashworth score from baseline to 12 months in Cannabis=1·82 (*n*=154, 95% confidence interval (CI) 0.53 to 3.12), cannabis extract=0.10 (*n*=172, 95% CI −0.99 to 1.19), placebo=0.23 (*n*=176, 95% CI −1.41 to 0.94); (*P*=0.04)	Ib	1)Placebo Controlled
	2) Corey-Bloom, 2012	RCT	37	Placebo	Muscle spasticity between Cannabis and Placebo groups compared using modified Ashworth scale	Reduction in patient scores on the modified Ashworth scale by an average of 2.74 points with Cannabis more than placebo (*P* < 0.0001)	Ib	1)Small Sample size 2)Placebo controlled

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Table 1: Contd...

Use of marijuana	Study	Type of study	Sample size	Comparator agent	Study parameters	Results	Level of evidence	Demerits
	3) C. Collins 2006	RCT	189	Placebo	Muscle spasticity compared between Cannabis and Placebo group	primary efficacy analysis on the intention to treat (ITT) population (n=184) showed the Cannabis to be significantly superior to Placebo (*P*=0.048)	Ib	1)Placebo Controlled 2)Greater incidence of adverse effects with Cannabis
Epilepsy	1) Devinsky *et al*. 2017	RCT	120	Placebo	Median frequency of convulsive seizures in Children and young adults with the Dravet syndrome between Cannabis group or Placebo group	median frequency of convulsive seizures per month decreased from 12.4 to 5.9 with Cannabis, as compared with a decrease from 14.9 to 14.1 with placebo (adjusted median difference between the Cannabis group and the placebo group in change in seizure frequency, −22.8 percentage points; 95% confidence interval [CI], −41.1 to −5.4; P=0.01)	Ib	1)Placebo Controlled 2)Greater incidence of Adverse effects with Cannabis
	2) Thiele *et al*., 2018	RCT	171	Placebo	Percentage change from baseline in monthly frequency of drop seizures during the treatment period in patients suffering from Lennox-Gastaut syndrome.	median percentage reduction in monthly drop seizure frequency from baseline was 43·9% (IQR −69·6 to −1·9) in the cannibidiol group and 21·8% (IQR −45·7 to 1·7) in the placebo group The median percentage reduction in monthly drop seizure frequency from baseline was 43·9% (IQR −69·6 to −1·9) in the cannabis group and 21·8% (IQR −45·7 to 1·7) in the placebo group. The estimated median difference between the treatment groups was −17·21 (95% CI −30·32 to −4·09; *P*=0.0135)	Ib	Placebo controlled Statistically not significant results
Crohn's Disease	1)Naftali T, 2013	RCT	20	Placebo	Complete remission in symptoms were compared between Cannabis and placebo group	Complete remission (CDAI score, <150) was achieved by 5 of 11 subjects in the cannabis group (45%) and 1 of 10 in the placebo group (10%; *P*=.43)	Ib	1)Small sample size 2)Placebo controlled

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Table 1: Contd...

Use of marijuana	Study	Type of study	Sample size	Comparator agent	Study parameters	Results	Level of evidence	Demerits
Glaucoma	1)Tomida *et al.* 2006	RCT	6	Placebo	Cannabis group and placebo groups were compared for Intraocular pressure	Intraocular pressure in Cannabis group significantly lower than after placebo (23.5 mm Hg vs. 27.3 mm Hg, *P*=0.026)	Ib	1)Small sample size 2)Placebo controlled
Tourrette Syndrome	1) Muller Vahl, 2003	RCT	20	Placebo	Memory span was compared between Cannabis and placebo group using the German version of auditory verbal learning test (VLMT)	Cannabis group was superior to the Placebo group (*P*<0.039)	Ib	1)Small sample size 2)Placebo controlled
	2) Muller Vahl, 2003	RCT	24	Placebo	Cannabis and placebo groups were compared using various scales such as Tourette Syndrome Clinical Global Impressions scale (TS-CGI), Shapiro Tourette-Syndrome Severity Scale (STSSS), Yale Global Tic Severity Scale (YGTSS), Self-rated Tourette Syndrome Symptom List (TSSL), Videotape-based rating scale.	On various scales such as Significant difference (*P* <.05) or a trend toward a significant difference (*P* <.10) between Cannabis and placebo groups at visits 2, 3, and/or 4	Ib	1)Small sample size 2)Placebo controlled
	3) Muller Vahl, 2002	RCT	12	Placebo	Tics ad obsessive compulsive behavior (OCB) between Cannabis and placebo group.	Significant improvement of tics (*P*=0.015) and obsessive-compulsive behavior (OCB) (*P*=0.041 in Cannabis vs Placebo	Ib	1)Small sample size 2)Placebo controlled

cancer-induced pain, diabetic peripheral neuropathy, and fibromyalgia, it was noted that the average number of patients who reported a reduction in pain of at least 30% was greater with an odds ratio of 1.41 (95% CI, 0.99–2.00). It is to be noted that 27 out of 28 studies had compared marijuana against a placebo agent.[15] In another study where *Cannabis* was compared with amitriptyline to manage insomnia due to chronic pain, it was seen that *Cannabis* was superior to amitriptyline (Insomnia Severity Index difference = 3.2; 95% CI, 1.2–5.3).[22] A randomized controlled trial (RCT) performed across three centers in the United Kingdom (96 patients) had two groups; one received marijuana followed by dihydrocodeine and *vice versa* was administered in the other group. The Visual Analog Scale was used to evaluate the pain relief in patients suffering from neuropathic pain. The authors found that dihydrocodeine was more effective when compared with *Cannabis* with a mean score of 6.0 mm longer for nabilone than for dihydrocodeine (95% CI, 1.4–10.5) in the available case analysis.[23] Few other reviews evaluated studies in which *Cannabis* has been compared to a placebo for the treatment of chronic pain and have shown promising results [Table 1].[18,24] The evidence for use of marijuana as an analgesic, when compared with alternative drugs such as opioids, antiseizure medications, and nonsteroidal anti-inflammatory drugs, is still evolving.

Multiple sclerosis

MS is a potentially disabling disease of the brain and spinal cord (central nervous system). In MS, the immune system attacks the myelin sheath, leading to degeneration of nerves. An estimated 2.3 million people suffer from MS around the world.[25] A meta-analysis[15] included 11 studies comparing marijuana to a placebo. It showed that use of *Cannabis* can offer some benefit in reducing spasm in patients suffering from MS, however the results of these studies were not statistically significant (weighted mean difference, −0.12 [95% CI, −0.24–0.01]). A RCT with 37 patients showed that *Cannabis* resulted in a reduction in patient scores on the modified Ashworth scale by an average of 2.74 points more than placebo ($P < 0.0001$).[26] Another randomized, double-blinded, placebo-controlled, crossover study with fifty patients concluded that a standardized *C. sativa* plant extract might lower spasm frequency and increase mobility with tolerable side effects in patients of MS with persistent spasticity [Table 1].[27] The current data for the use of marijuana for MS is limited by small sample size and placebo-controlled trials.

Epilepsy

Cannabis has been tried in patients suffering from rare epileptic disorders, such as Dravet syndrome and Lennox–Gastaut syndrome, which are often resistant to standard anti-epileptic medications. The exact incidence of these rare disorders has not been conclusively studied yet; however, few studies have shown an incidence of around 1:40,000 children. A systematic review on drug-resistant epilepsy found that *Cannabis* was more effective than placebo in reducing seizure frequency by over 50% (relative risk [RR] 1.74, 95% CI, 1.24–2.43, RCTs, 291 patients, low grade of recommendation), complete freedom from seizures (RR 6.17, 95% CI, 1.50–25.32, three RCTs, 306 patients, grade of recommendation), and improving quality of life (RR 1.73, 95% CI, 1.33–2.26).[28] A few other studies have also shown the efficacy of marijuana-related products in drug-resistant epilepsy (more so in rare forms and in pediatric population) though the definitive evidence to recommend its generalized use for this indication is lacking and requires further evaluation [Table 1].

Crohn's disease

Marijuana is known to have anti-inflammatory properties. Keeping this in mind, it has been used to treat inflammatory bowel conditions such as Crohn's disease. A RCT on twenty patients suffering from Crohn's disease, demonstrated that a complete remission (Crohn's Disease Activity Index [CDAI] score, <150) was achieved by 5 of the 11 patients in the *Cannabis* group (45%) and 1 of 10 in the placebo group (10%; $P = 0.43$) (Naftali *et al*.). A clinical response (decrease in CDAI score of >100) was observed in 10 of the 11 patients in the *Cannabis* group (90%; from 330 to 105-152-109) and 4 of 10 in the placebo group (40%; from 373 to 94-306-143; $P = 028$)[29] Further long-term studies against standard treatment regimen are required to evaluate the utility of marijuana in such cases [Table 1].

Anti-cancer

There is some evidence in literature that *Cannabis* has antitumor properties and prolongs life. Studies have shown its exact mechanism, which may involve suppression of proliferative cell signaling pathways, inhibition of angiogenesis and cell migration, stimulation of apoptosis, and/or induction of autophagy.[30,31] Few investigational studies have been conducted on various tumors such as gliomas, lymphomas, prostate cancer, breast cancer, lung cancer, skin cancer, and pancreatic cancer.[32] A Phase 1 study was done on nine patients suffering from glioblastoma multiforme to assess the antitumoral effects of *Cannabis*. It showed that *Cannabis* may be administered safely without significant adverse effects. The study further showed that *Cannabis* inhibited tumor cell proliferation *in vitro* and decreased tumor cell Ki67 immunostaining when administered to two patients.[33] *Cannabis* has been shown to be effective when used in combination with other anticancer drugs. This has particularly been seen in pancreatic cancers and gliomas.[34] Thus, the evidence for the anticancer effect of *Cannabis* does exist, but it is exploratory and evolving. Addiction potential, risk of developing other malignancies, and various other side effects have precluded the use of *Cannabis* for antitumor effects. Majority of the existing studies have been conducted *ex vivo,* and further studies are required to confirm or refute such effects.

Glaucoma

Cannabis has neuroprotective properties and effectively reduces the intraocular pressure (IOP). A randomized, double-masked, placebo-controlled, four-way, crossover study on six patients showed that a single 5-mg sublingual dose of Delta-9-THC reduced the IOP temporarily for a duration of 4 h and was well tolerated by most patients; hence, this may form a future pathway for the management of glaucoma.[35] This was a single study which evaluated the use of marijuana for this purpose and moreover, the sample size was small, hence there is a requirement of gathering further evidence [Table 1].

Sleep disorder

There is some evidence that *Cannabis* may be beneficial in patients suffering from sleep disorders due to chronic pain or any other obstructive disorders. A meta-analysis evaluated two studies where marijuana was used for the management of sleep disorders. One study compared *Cannabis* versus placebo and showed a greater benefit on sleep apnea/hypopnea index (mean difference from baseline, −19.64; $P = 0.02$). Another study compared *Cannabis* to a comparator drug (amitriptyline) and showed improvements in insomnia (mean difference from baseline, −3.25 [95% CI, −5.26–−1.24]) and with greater sleep restfulness (mean difference from baseline, 0.48 [95% CI, 0.01–0.95]). Their long-term efficacy and efficacy at higher doses needs to be compared.[15]

Tourette syndrome

Tourette syndrome is a chronic, childhood-onset, neuropsychiatric disorder characterized by waxing and

waning motor and vocal tics that persist for more than 1 year. The estimated incidence of this syndrome is around 5 in 10,000. Patients suffering from Tourette syndrome have shown improvement in tic severity when these patients were administered *Cannabis*. Two RCTs, with small sample sizes, have evaluated *Cannabis* versus placebo and found that there was statistically significant improvement with *Cannabis* [Table 1].[15] It needs to be reiterated that such patients actually requiring *Cannabis* are too few in numbers, and that this is a very specific indication of the drug.

Adverse effects of marijuana

Marijuana is associated with various adverse effects like any other narcotic substance. Till date, no death due to marijuana poisoning has been reported. The severity of the adverse effects of marijuana is dependent on the duration and frequency of its use. The various adverse effects of marijuana are enlisted below.

Effect on development of brain

The effect of marijuana on the development of brain has been seen particularly in addicted adolescents, with weekly usage impact on their learning abilities and memory can last even up to 28 days post last usage.[36] When compared with people who do not use marijuana, adults who smoke marijuana regularly show impaired neural connectivity. This has been assessed using diffusion-weighted imaging, a magnetic resonance imaging modality capable of elucidating axonal directionality and microstructure *in vivo* performed in 59 *Cannabis* users with a history of long-standing, heavy use and 33 nonusers.[37] The areas of brain which are affected are the precuneus node, which is involved in functions which need high degree of integration, and the hippocampus, which is involved in learning and memory functions.[38]

Addiction

The International Classification of Diseases and the Diagnostic and Statistical Manual of Mental Disorders designate *Cannabis* as an addictive substance, with recognized *Cannabis*-related dependence disorders.[39] Around 9% of the users, more significantly teenagers who try *Cannabis,* ultimately become addicts.[38] *Cannabis* withdrawal syndrome is a known condition with symptoms such as irritability, sleeping difficulties, and dysphoria.[38] A study showed that the relapse rates for marijuana addicts were as high as 71% at 6 months.[40] There has been an increased incidence of motor vehicle accidents in patients who may be either short-term or long-term users of marijuana. In a study which retrospectively analyzed the Fatality Analysis Reporting System for 1999–2010, marijuana was the second most common cause after alcohol for the increased number of road traffic accidents in young adult victims.[41] Patients who are under the influence of marijuana have been shown to have longer response times and slower driving speeds in a dose–response fashion. The combined effect of alcohol with marijuana increases impairment, and the risk of road traffic accidents is more than using either substance alone.[42,43] For less-than-weekly users of marijuana, 10 mg or more of THC[44] or a blood THC level of 2–5 ng/ml causes significant impairment[42] and should wait for 6–8 h for the impairment to resolve.[45]

Mental illness

Marijuana users are at an increased risk to develop chronic psychotic disorders (including schizophrenia). A study prospectively evaluated 2437 young adults with or without a predisposition to psychosis. The authors noted that *Cannabis* use moderately increases the risk of psychosis in young adults, with the incidence being much higher in younger people with a predisposition for psychosis (difference of risk test for interaction 18.2%, 1.6–34.8, $P = 0.032$).[46] These patients also suffered from anxiety and depression disorders and have an increased suicidal tendencies.[38]

Risk of cancer

Marijuana smoking leads to exposure to a number of harmful by-products. Some of the carcinogens present in tobacco are present in Marijuana smoke as well. These include polycyclic hydrocarbons and benopyrenes.[47] Animal studies have shown the carcinogenic effect of Marijuana both *in vitro* and *in vivo*.[48] A few studies also show that at a lower dose, *Cannabis* may stimulate the growth of cancer cells.[49] Various studies have hypothesized an increased risk of cancers of the upper aerodigestive tract and the lungs in Marijuana smokers.[50] Few others have shown a positive association between Marijuana smoking and cancers of the lung, showing a twofold increase in its incidence (hazard ratio 2.12, 95% CI, 1.08–4.14). In contrast, few studies found no positive association between cancer and Marijuana use on adjusting for confounders such as cigarette smoking.[51] Another review opined that its association with lung cancer may not be appreciated so clearly because of smaller quantities being smoked compared to tobacco.[52] Studies have also noted an increased risk of developing other cancers such as nonseminoma testicular germ cell cancer, prostate cancer, and cervical cancer.[53,54]

As can be understood from these studies, some association between Marijuana use and subsequent cancer development does exist; although to clarify it further, research on this aspect is required.

Pulmonary disease

The exposure of the upper aerodigestive tract to a number of harmful by-products of Marijuana smoking often leads to various complications. These by-products affect the functioning of the immune system and also alter the expression of inflammatory cytokines. *Cannabis* smoking is associated with smaller butt length of the joint, deeper and prolonged inhalation, and higher combustion temperature as compared to tobacco smoking. This increases the concentration of harmful chemicals in the airway, thereby increasing their absorption.[55] A review of literature noted that Marijuana smoking affected the bronchial dynamics and the lung volumes. Thus, its use is associated with an increased risk of bronchitis, pneumonia, respiratory distress, and emphysema.[56] In individuals <40 years, daily or near-daily marijuana use may be associated with bullous lung

disease complicating to pneumothorax.[57] Changing over from marijuana smoking to vaporizing may have fewer respiratory symptoms and improved pulmonary function.[58]

Cannabis hyperemesis syndrome

Few case reports have described a condition which is known as *Cannabis* hyperemesis syndrome and is specifically seen in Marijuana addicts. A study showed that there was a higher incidence of this syndrome in young adults with a history of long-term use of Marijuana.[59] These patients with chronic *Cannabis* use show a triad of symptoms such as cyclic vomiting, abdominal pain, and compulsive hot water bathing.[60] Though the pathophysiology of the condition is not well understood, it has been proposed that central effects of long-term *Cannabis* use on the hypothalamic–pituitary–adrenal axis might play a major role in the development of cannabinoid hyperemesis syndrome.[59] However, as only a few cases have been reported, a detailed description of this condition is, therefore, elusive.

Vascular conditions

Patients smoking Marijuana are at an increased risk of suffering from transient ischemic attacks, stroke, myocardial infarctions, and *Cannabis* arteritis. A recent 5-year observational study presented at the 11th Stroke Congress showed that among 2.3 million hospitalizations for patients who had used marijuana recreationally, 32,231 (1.4%) had a stroke. Of these, 19,452 patients presented with acute ischemic stroke.[61] There have been several studies which have demonstrated that Marijuana use is associated with higher chances of having angina and myocardial infarction. It has also been found to be associated with peripheral vascular diseases and cerebrovascular accidents.[62]

Nondriving injuries

People under the influence of marijuana are more susceptible to workplace injuries.[63] Severe burns from explosions resulting from home extraction of butane hash oil and electronic smoking devices leading to trauma and burns have also been reported.[64] Adolescent girls who use marijuana may be more likely to commit physical violence against their dating partners.[65]

Effect on pregnancy and breastfeeding

Biological evidence shows that THC passes through the placenta to the fetus, so the unborn child is exposed to THC if the mother uses marijuana. THC also passes through the breastmilk from the lactating mother to the breastfeeding child if the mother is consuming marijuana during her pregnancy or lactation period;[66] this has been associated with an increased risk of stillbirth,[67] heart defects such as ventricular septal defect,[68] decreased growth, and impaired cognitive function and attention.[69] Decreased academic ability or increased depressive symptoms may also occur in children born to mothers who were consuming marijuana during the pregnancy or lactating period as a delayed effect.[70]

International guidelines for medical use of Marijuana

Various organizations across different countries in the world (such as the United States of America [USA] Food and Drug Administration [FDA] and various state medical boards in the USA, Health Canada in Canada, Federal Institute for Drugs and Medical Devices in Germany, the Office of Medical *Cannabis* in the Netherlands, and Therapeutic goods administration in Australia) regulate the use of narcotics. The framework for the development of the *Cannabis* program is based on the United Nations Single Convention on Narcotic Drugs of 1961.[71,72] Although *Cannabis* was considered to be a softer drug, its widespread and frequent use made it a gateway to other substance abuse. Thus, it was decided to curb its use.

Across the world, Marijuana use has been legalized in various countries such as the USA, Argentina, Canada, and Uruguay. Such use may be for recreational or medicinal purposes. Its use for recreational purposes is approved in various places, based on public demand, political motives, and the belief that among the various narcotics, Marijuana is the safest. In the USA, use of marijuana for medicinal purposes is legal in a number of states, whereas its use for recreational purpose has been legalized in various states such as Alaska, California, Colorado, New York, and Washington.[73] The FDA has recently approved, for the first time, a drug with a marijuana derivative, CBD, as an active ingredient to treat severe form of epilepsy such as Lennox–Gastaut syndrome.[74] Canada has also legalized the use of marijuana for recreational as well as medicinal purposes.[75] Europe recognizes the use of marijuana for recreational purposes as a criminal offence; however, its use for medical purposes (MS, HIV/AIDS, cancer, long-term neurogenic pain, and Tourette's syndrome) is permitted across many countries.[76] In contrast to the Western world, the use of marijuana for medicinal or recreational purposes is not permitted in Asia.

Even in the states/countries where marijuana has been legalized, it can only be purchased through registered retailers. There are restrictions on the amount of marijuana an individual can purchase and cultivate. Most of the developing countries do not have the resources and the infrastructure to allow and monitor such recreational use.

In India, *Cannabis* is the second most common substance to be abused, with close to 3 crore people using it. Dependence was seen in one out of every seven persons using it.[77] About 2.2 crore individuals used *Cannabis* products such as bhang, ganja, and charas and about 1.3 crore people used illegal *Cannabis* products such as ganja and charas. The high-prevalence states in India were recorded as the following – Uttar Pradesh, Punjab, Sikkim, Chhattisgarh, and Delhi.[77] Overall, about one in 11 *Cannabis* users suffered from *Cannabis* dependence, which could be counted as being in the category of problem *Cannabis* users. One in 16 users of bhang were dependent on *Cannabis,* whereas one in seven cases of ganja/charas users were *Cannabis* dependent, showing a significant difference in both the groups.[77]

The guidelines in various countries currently acknowledge a paucity of evidence for the medicinal usage of marijuana. These guidelines simply define the medicinal indications of marijuana

and also, there are no recommendations stating a safe dose for its use.[78] The onus of prescription lies solely on the clinical judgment of the physician, thus highlighting the need for proper guidelines to prescribe marijuana for medicinal purposes.

Consequences of legalization

As noted above, in recent times, various countries have legalized the use of marijuana. As a result of this, various newer products with marijuana are available in the market and on online portals without proper prescription procedures. These products include marijuana-containing chewing gum and candies.[79,80] Bearing in mind the addiction potential of the marijuana, we should probably go slow in allowing such products in the open market.

After legalization of the drug in Uruguay in 2013, there were several issues in matching demand to supply because of the small number of pharmacies (16 out of 1200) which enrolled in the scheme to sell these drugs; this further dropped to 12 pharmacies by 2018 due to the banking difficulties.[81] The legalized system produces almost 10 tonnes less/year in relation to the demand.[82] Strict laws have been made to prevent "marijuana tourism;" this prevented the access of marijuana to non-Uruguay citizens. Moreover, the quantity of drug for Uruguay citizens has been capped at 40 mg/month.[83] The other constant problem faced by the consumers was the quality of marijuana provided in the legal system which gave them less "kick" than the ones procured illegally.[82] These reasons have further led to an increase in the illegal trade of drugs. It has also been noted that there has been no decrease in crime rates because the drugs have been made legally available for purchase. Crime rates have been 8.1/1 lakh persons in 2017, which is the 2nd highest in 30 years. In the first quarter of 2018, drug-related violence was responsible for 59% of homicides, which was twice that of 2012.[82]

Marijuana sales post legalization have been a major source of income for the various governments, for example, Washington has marijuana sales crossing 1 billion dollars post legalization. Other states such as Michigan and Arizona have also recorded sales of 400–500 million dollars post legalization.[84] Although this source of income would have been welcomed by those on the financial side, this has raised concerns about the increased and more widespread usage and subsequent effects of marijuana. States such as New Mexico have 25 registered medical marijuana users per 1000 residents.[85] Several studies have noted that there is an increasing prevalence of marijuana use in the USA, with approximately 7.6% of the population believed to be marijuana users. The actual number of marijuana users had dipped down in the previous decade, but after legalization, their numbers have increased.[86-89] It has also been observed that in states with legalization of marijuana, there is a decreasing perception of health risks associated with marijuana use among the general public. According to a study conducted in Colorado, it was found that marijuana use post legalization among adults in Colorado is higher than the national American average, with one in four adults of the age group 18–25 years reporting to have used it ever and one in eight using it daily or near daily.[90] Following legalization of marijuana in Colorado, it was found that about 6% of pregnant women chose to use marijuana while pregnant. Majority of them were below 24 years of age and with less than 12th grade education.[91] Organized crime cases almost tripled in 5 years, increasing to 119 in 2017 from 31 in 2012 post legalization of the drug in Colorado.[92]

According to a study done in Colorado post legalization, marijuana-related adolescent emergency hospital visits increased significantly from 1.8 per 1000 visits in 2009 to 4.9 in 2015. Another study done by the Institute for Highway Safety found that Colorado, Washington, and Oregon experienced a 5.2% higher police-reported crash rate overall than would have been expected had they not legalized recreational marijuana.[93] It was also observed that rates of hospitalization with marijuana exposures increased steadily from 2000 through 2015 and the number of adults who use marijuana increased between 2014 and 2017, with men getting high more often than women and young adults aged 18–25 being the most frequent users.[92] Due to the various known harmful effects and lack of definitive evidence for use, even the American College of Pediatricians supports the restricted use of marijuana limited to evidence as supported by the scientific studies.[94]

In 2015, among high school seniors in Colorado who had used marijuana at least once in the past, an estimated 84.4% of them first used it by the age of 16 years or before, 41.3% first used it by age 14 or before, and 14.3% first used it by age 12 or before; this change in marijuana use pattern can be attributed to the free availability of product.[95] Due to the easy availability of product post legalization, at least 14,000 children in Colorado are at risk of accidental ingestion of marijuana and at least 16,000 are at risk of being exposed to marijuana smoke in the home.[96]

Conclusion

Although marijuana use has been legalized recently in several regions, high-quality evidence for the majority of its medical indications remains investigational. Most of the available literature compares it against placebos, and it would be prudent to wait for studies which prove beyond doubt the advantages of Marijuana over the existing drugs and also outweigh its side effects and addiction potential. Moreover, further legalization of Marijuana should only be considered after evaluating its effects at places where it is already legally available.

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Conflicts of interest

There are no conflicts of interest.

References

1. Available form: https://www.who.int/substance_abuse/facts/cannabis/en/. [Last accessed on 2019 Oct].
2. Available form: https://www.shopbotanistohio.com/sativa-vs-indica. [Last accessed on 2019 Oct].
3. Versteeg PA, Slot DE, van der Velden U, van der Weijden GA. Effect

of cannabis usage on the oral environment: A review. Int J Dent Hyg 2008;6:315-20.
4. Berthiller J, Lee YC, Boffetta P, Wei Q, Sturgis EM, Greenland S, *et al*. Marijuana smoking and the risk of head and neck cancer: Pooled analysis in the INHANCE consortium. Cancer Epidemiol Biomarkers Prev 2009;18:1544-51.
5. Liang C, McClean MD, Marsit C, Christensen B, Peters E, Nelson HH, *et al*. A population-based case-control study of marijuana use and head and neck squamous cell carcinoma. Cancer Prev Res (Phila) 2009;2:759-68.
6. Available form: https://www.leafly.com/news/cannabis-101/indica-vs-sativa-which-produces-more-cbd-thc. [Last accessed on 2019 Oct].
7. Huestis MA. Human cannabinoid pharmacokinetics. Chem Biodivers 2007;4:1770-804.
8. United Nations Office of Drug and Crime. Cannabis Market–Abuse. In: United Nations, editors. World Drug Report. Geneva: United Nations Publication; 2007. p. 114-21.
9. Courtwright D. Forces of Habit: Drugs and the Making of the Modern World. Harvard University Press; 2001. p. 39. Available from: https://www.hup.harvard.edu/catalog.php?isbn=9780674010031. [Last accessed on 2019 Dec 10].
10. Bridgeman MB, Abazia DT. Medicinal Cannabis: History, Pharmacology, and Implications for the Acute Care Setting. P T. 2017;42:180-8.
11. Quinnipiac University. Allow Marijuana for vets with PTSD, U. S. Voters say 10-1, Quinnipiac University National Poll Finds; Slim Majority Say Legalize Marijuana in General. Available from: http://www.qu.edu/news-and-events/quinnipiac-university-poll/national/release-detail?ReleaseID = 2354. [Last accessed on 2016 Aug 05].
12. Adler JN, Colbert JA. Clinical decisions. Medicinal use of Marijuana-polling results. N Engl J Med 2013;368:e30.
13. Abuhasira R, Schleider LB, Mechoulam R, Novack V. Epidemiological characteristics, safety and efficacy of medical cannabis in the elderly. Eur J Intern Med 2018;49:44-50.
14. Mouhamed Y, Vishnyakov A, Qorri B, Sambi M, Frank SS, Nowierski C, *et al*. Therapeutic potential of medicinal marijuana: An educational primer for health care professionals. Drug Healthc Patient Saf 2018;10:45-66.
15. Whiting PF, Wolff RF, Deshpande S, Di Nisio M, Duffy S, Hernandez AV, *et al*. Cannabinoids for medical use: A systematic review and meta-analysis. JAMA 2015;313:2456-73.
16. Musty RE, Rossi R. Effects of smoked cannabis and oral ?9-Tetrahydrocannabinol on nausea and emesis after cancer chemotherapy: A review of state clinical trials. J Cannabis Therapeutics 2001;1:29-56.
17. Darmani NA. Mechanisms of broad-spectrum antiemetic efficacy of cannabinoids against chemotherapy-induced acute and delayed vomiting. Pharmaceuticals (Basel) 2010;3:2930-55.
18. Kramer JL. Medical Marijuana for Cancer. CA Cancer J Clin 2015;65:109-22.
19. Kirkham T. Endocannabinoids and the neurochemistry of gluttony. J Neuroendocrinol 2008;20:1099-100.
20. Kalant H, Porath-Waller AJ. Clearing the Smoke on Cannabis: Medical use of Cannabis and Cannabinoids: An update. Canadian Centre on Substance Abuse; 2016. p. 1-11.
21. Jatoi A, Windschitl HE, Loprinzi CL, Sloan JA, Dakhil SR, Mailliard JA, *et al*. Dronabinol versus megestrol acetate versus combination therapy for cancer-associated anorexia: A North Central Cancer Treatment Group study. J Clin Oncol 2002;20:567-73.
22. Ware MA, Fitzcharles MA, Joseph L, Shir Y. The effects of nabilone on sleep in fibromyalgia: Results of a randomized controlled trial. Anesth Analg 2010;110:604-10.
23. Frank B, Serpell MG, Hughes J, Matthews JN, Kapur D. Comparison of analgesic effects and patient tolerability of nabilone and dihydrocodeine for chronic neuropathic pain: Randomised, crossover, double blind study. BMJ 2008;336:199-201.
24. Grotenhermena F, Muller-Vahl K. Medicinal uses of marijuana and cannabinoids. CRC Crit Rev Plant Sci 2016;35:378-405.
25. Browne P, Chandraratna D, Angood C, Tremlett H, Baker C, Taylor BV, *et al*. Atlas of Multiple Sclerosis 2013: A growing global problem with widespread inequity. Neurology 2014;83:1022-4.
26. Corey-Bloom J, Wolfson T, Gamst A, Jin S, Marcotte TD, Bentley H, *et al*. Smoked cannabis for spasticity in multiple sclerosis: A randomized, placebo-controlled trial. CMAJ 2012;184:1143-50.
27. Vaney C, Heinzel-Gutenbrunner M, Jobin P, Tschopp F, Gattlen B, Hagen U, *et al*. Efficacy, safety and tolerability of an orally administered cannabis extract in the treatment of spasticity in patients with multiple sclerosis: A randomized, double-blind, placebo-controlled, crossover study. Mult Scler 2004;10:417-24.
28. Stockings E, Zagic D, Campbell G, Weier M, Hall WD, Nielsen S, *et al*. Evidence for cannabis and cannabinoids for epilepsy: A systematic review of controlled and observational evidence. J Neurol Neurosurg Psychiatry 2018;89:741-53.
29. Naftali T, Bar-Lev Schleider L, Dotan I, Lansky EP, Sklerovsky Benjaminov F, Konikoff FM. Cannabis induces a clinical response in patients with Crohn's disease: A prospective placebo-controlled study. Clin Gastroenterol Hepatol 2013;11:1276-800.
30. Pisanti S, Malfitano AM, Grimaldi C, Santoro A, Gazzerro P, Laezza C, *et al*. Use of cannabinoid receptor agonists in cancer therapy as palliative and curative agents. Best Pract Res Clin Endocrinol Metab 2009;23:117-31.
31. Salazar M, Carracedo A, Salanueva IJ, Hernández-Tiedra S, Lorente M, Egia A, *et al*. Cannabinoid action induces autophagy-mediated cell death through stimulation of ER stress in human glioma cells. J Clin Invest 2009;119:1359-72.
32. Sarfaraz S, Adhami VM, Syed DN, Afaq F, Mukhtar H. Cannabinoids for cancer treatment: Progress and promise. Cancer Res 2008;68:339-42.
33. Guzmán M, Duarte MJ, Blázquez C, Ravina J, Rosa MC, Galve-Roperh I, *et al*. A pilot clinical study of Delta9-tetrahydrocannabinol in patients with recurrent glioblastoma multiforme. Br J Cancer 2006;95:197-203.
34. Velasco G, Sánchez C, Guzmán M. Anticancer mechanisms of cannabinoids. Curr Oncol 2016;23:S23-32.
35. Tomida I, Azuara-Blanco A, House H, Flint M, Pertwee RG, Robson PJ. Effect of sublingual application of cannabinoids on intraocular pressure: A pilot study. J Glaucoma 2006;15:349-53.
36. Pope HG Jr, Gruber AJ, Hudson JI, Cohane G, Huestis MA, Yurgelun-Todd D. Early-onset cannabis use and cognitive deficits: What is the nature of the association? Drug Alcohol Depend 2003;69:303-10.
37. Zalesky A, Solowij N, Yücel M, Lubman DI, Takagi M, Harding IH, *et al*. Effect of long-term cannabis use on axonal fibre connectivity. Brain 2012;135:2245-55.
38. Volkow ND, Baler RD, Compton WM, Weiss SR. Adverse health effects of marijuana use. N Engl J Med 2014;370:2219-27.
39. Hasin DS, O'Brien CP, Auriacombe M, Borges G, Bucholz K, Budney A, *et al*. DSM-5 criteria for substance use disorders: Recommendations and rationale. Am J Psychiatry 2013;170:834-51.
40. Moore BA, Budney AJ. Relapse in outpatient treatment for marijuana dependence. J Subst Abuse Treat 2003;25:85-9.
41. Brady JE, Li G. Trends in alcohol and other drugs detected in fatally injured drivers in the United States, 1999-2010. Am J Epidemiol 2014;179:692-9.
42. Drummer OH, Gerostamoulos J, Batziris H, Chu M, Caplehorn J, Robertson MD, *et al*. The involvement of drugs in drivers of motor vehicles killed in Australian road traffic crashes. Accid Anal Prev 2004;36:239-48.
43. Hartman RL, Huestis MA. Cannabis effects on driving skills. Clin Chem 2013;59:478-92.
44. Berghaus G, Sticht G, Grellner W. Meta-analysis of Empirical Studies Concerning The Effects of Medicines And Illegal Drugs Including Pharmacokinetics on Safe Driving. Centre for Traffic Sciences at the University of Wurzburg; 2011.
45. Ramaekers JG, Moeller MR, van Ruitenbeek P, Theunissen EL, Schneider E, Kauert G. Cognition and motor control as a function of Delta9-THC concentration in serum and oral fluid: Limits of impairment. Drug Alcohol Depend 2006;85:114-22.
46. Henquet C, Krabbendam L, Spauwen J, Kaplan C, Lieb R, Wittchen HU, *et al*. Prospective cohort study of cannabis use, predisposition for psychosis, and psychotic symptoms in young people. BMJ 2005;330:11.
47. Zhang LR, Morgenstern H, Greenland S, Chang SC, Lazarus P, Teare MD, *et al*. Cannabis smoking and lung cancer risk: Pooled analysis in the International Lung Cancer Consortium. Int J Cancer 2015;136:894-903.
48. Zhu LX, Sharma S, Stolina M, Gardner B, Roth MD, Tashkin DP,

et al. Delta-9-tetrahydrocannabinol inhibits antitumor immunity by a CB2 receptor-mediated, cytokine-dependent pathway. J Immunol 2000;165:373-80.
49. Preet A, Ganju RK, Groopman JE. Delta9-Tetrahydrocannabinol inhibits epithelial growth factor-induced lung cancer cell migration *in vitro* as well as its growth and metastasis *in vivo*. Oncogene 2008;27:339-46.
50. Callaghan RC, Allebeck P, Sidorchuk A. Marijuana use and risk of lung cancer: A 40-year cohort study. Cancer Causes Control 2013;24:1811-20.
51. Hashibe M, Morgenstern H, Cui Y, Tashkin DP, Zhang ZF, Cozen W, *et al*. Marijuana use and the risk of lung and upper aerodigestive tract cancers: Results of a population-based case-control study. Cancer Epidemiol Biomarkers Prev 2006;15:1829-34.
52. Huang YH, Zhang ZF, Tashkin DP, Feng B, Straif K, Hashibe M. An epidemiologic review of marijuana and cancer: An update. Cancer Epidemiol Biomarkers Prev 2015;24:15-31.
53. Gurney J, Shaw C, Stanley J, Signal V, Sarfati D. Cannabis exposure and risk of testicular cancer: A systematic review and meta-analysis. BMC Cancer 2015;15:897.
54. Park S, Myung SK. Cannabis smoking and risk of cancer: A meta-analysis of observational studies. J Global Oncol 2018;4 Suppl 2:196s-196s.
55. Wu TC, Tashkin DP, Djahed B, Rose JE. Pulmonary hazards of smoking marijuana as compared with tobacco. N Engl J Med 1988;318:347-51.
56. Gates P, Jaffe A, Copeland J. Cannabis smoking and respiratory health: Consideration of the literature. Respirology 2014;19:655-62.
57. Beshay M, Kaiser H, Niedhart D, Reymond MA, Schmid RA. Emphysema and secondary pneumothorax in young adults smoking cannabis. Eur J Cardiothorac Surg 2007;32:834-8.
58. Earleywine M, Barnwell SS. Decreased respiratory symptoms in cannabis users who vaporize. Harm Reduct J 2007;4:11.
59. Simonetto DA, Oxentenko AS, Herman ML, Szostek JH. Cannabinoid hyperemesis: A case series of 98 patients. Mayo Clin Proc 2012;87:114-9.
60. Iacopetti CL, Packer CD. Cannabinoid hyperemesis syndrome: A case report and review of pathophysiology. Clin Med Res 2014;12:65-7.
61. Press Release, 12th World Stroke Congress 19/12/2018. Available from: https://eso-wso-conference.org/. [Last accessed on 2020 Mar 22].
62. Thomas G, Kloner RA, Rezkalla S. Adverse cardiovascular, cerebrovascular, and peripheral vascular effects of marijuana inhalation: What cardiologists need to know. Am J Cardiol 2014;113:187-90.
63. Shipp EM, Tortolero SR, Cooper SP, Baumler EG, Weller NF. Substance use and occupational injuries among high school students in South Texas. Am J Drug Alcohol Abuse 2005;31:253-65.
64. Porter CJ, Armstrong JR. Burns from illegal drug manufacture: Case series and management. J Burn Care Rehabil 2004;25:314-8.
65. Epstein-Ngo QM, Cunningham RM, Whiteside LK, Chermack ST, Booth BM, Zimmerman MA, *et al*. A daily calendar analysis of substance use and dating violence among high risk urban youth. Drug Alcohol Depend 2013;130:194-200.
66. Joya X, Pujadas M, Falcón M, Civit E, Garcia-Algar O, Vall O, *et al*. Gas chromatography-mass spectrometry assay for the simultaneous quantification of drugs of abuse in human placenta at 12th week of gestation. Forensic Sci Int 2010;196:38-42.
67. Varner MW, Silver RM, Rowland Hogue CJ, Willinger M, Parker CB, Thorsten VR, *et al*. Association between stillbirth and illicit drug use and smoking during pregnancy. Obstet Gynecol 2014;123:113-25.
68. Williams LJ, Correa A, Rasmussen S. Maternal lifestyle factors and risk for ventricular septal defects. Birth Defects Res A Clin Mol Teratol 2004;70:59-64.
69. Fried PA, Watkinson B, Gray R. Differential effects on cognitive functioning in 13- to 16-year-olds prenatally exposed to cigarettes and marihuana. Neurotoxicol Teratol 2003;25:427-36.
70. Zammit S, Thomas K, Thompson A, Horwood J, Menezes P, Gunnell D, *et al*. Maternal tobacco, cannabis and alcohol use during pregnancy and risk of adolescent psychotic symptoms in offspring. Br J Psychiatry 2009;195:294-300.
71. Medicinal Cannabis in Europe: The GMP Standards Guide; 2018.
72. Guidance for the Use of Medicinal Cannabis in Australia: Overview. Version 1; 2017.
73. Medical Board of California's Guidelines for the Recommendation of Cannabis for Medical Purposes; 2018.
74. Available form: https://www.fda.gov/newsevents/newsroom/pressannouncements/ucm611046.htm. [Last accessed on 2019 Oct].
75. Cannabis Act, Canada; 2018. Available from: https://laws-lois.justice.gc.ca/eng/acts/c-24.5/. [Last accessed on 2019 Oct].
76. Cannabis Legislation in Europe: An Overview. Corrected Edition. European Monitoring Centre for Drugs and Drug Addiction, Cannabis legislation in Europe: An overview, Publications Office of the European Union, Luxembourg. 2018. Available from: https://idpc.net/publications/2017/03/cannabis-legislation-in-europe-an-overview. [Last accessed on 2019 Oct].
77. Available from: http://socialjustice.nic.in/writereaddata/UploadFile/Magnitude_Substance_Use_India_REPORT.Pdf. [Last accessed on 2019 Oct].
78. Madras BK. Update of Cannabis and its Medical Use. 37th ECDD Agenda Item 6.2, Cannabis. McLean Hospital; 2015.
79. Available from: https://rockymountainbob.com/what-we-do. [Last accessed on 2019 Oct].
80. Available from: https://www.healthline.com/health/weed-infused-gum-and-5-other-surprising-marijuana-products-for-chronic-pain#1. [Last accessed on 2019 Oct].
81. Hudak J, Ramsey G, Walsh J. Uruguay's Cannabis Law: Pioneering a New Paradigm. WOLA Centre for Effective Public Management at Brookings. 2018. p. 1-24.
82. Availablefrom:https://apnews.com/77d5e17147174241ae1d73529d42febc. [Last accessed on 2019 Oct].
83. Ramsey G. Uruguay: Marijuana, Organized Crime and the Politics of Drugs. InSight Crime; 2013. p. 1-16.
84. Available from: https://www.forbes.com/sites/andrewdepietro/2018/05/04/how-much-money-states-make-cannabis-sales/#2e19e7f8f181. [Last accessed on 2019 Oct].
85. Available from: https://www.statista.com/topics/3064/medical-marijuana-in-the-us/. [Last accessed on 2019 Oct].
86. Substance Abuse and Mental Health Services Administration. Results from the 2012 National Survey on Drug Use and Health: Summary of National Findings, NSDUH Series H-46, HHS Publication No. (SMA) 13-4795; 2013.
87. Johnston LD, O'Malley PM, Miech RA, Bachman JG, Schulenberg JE. Overview, Key Findings on Adolescent Drug Use. Ann Arbor: The University of Michigan Institute for Social Research; 2014.
88. Lloyd D. Patrick JM. O'Malley Richard A. Miech Jerald G. Bachman John E. Schulenberg. Monitoring the Future-National Survey Results on Drug Use; 1975-2013.
89. Lipari RN, Hedden SL, Hughes A. Substance Abuse and Mental Health Services Administration C, Quality. fBHSa. The NSDUH Report: Substance Use and Mental Health Estimates from the 2013 National Survey on Drug Use and Health: Overview of Findings. Rockville, MD; 2014.
90. Centers for Disease Control and Prevention. Behavioral Risk Factor Surveillance System: Annual Survey Data. Centers for Disease Control and Prevention. Available from: http://www.cdc.gov/brfss/annual_data/annual_data.htm. [Last accessed on 2016 Oct 07].
91. Centers for Disease Control and Prevention. PRAMS. Centers for Disease Control and Prevention; 2016. Available from: https://www.cdc.gov/prams/, https://www.cdc.gov/prams/. [Last accessed on 2019 Oct].
92. Available from: https://www.denverpost.com/2018/10/26/colorado-marijuana-impact-report/. [Last accessed on 2019 Oct].
93. Available from: https://www.iihs.org/frontend/iihs/documents/masterfiledocs.ashx?id = 2173). [Last accessed on 2019 Oct].
94. Available from: https://www.acpeds.org/the-college-speaks/position-statements/effect-of-marijuana-legalization-on-risky-behavior/marijuana-use-detrimental-to-youth. [Last accessed on 2019 Oct].
95. Centers for Disease Control and Prevention. Youth Risk Behavioral Surveillance System. Adolescent and School Health. Centers for Disease Control and Prevention. Available from: http://www.cdc.gov/healthyyouth/data/yrbs/. [Last accessed on 2019 Oct].
96. Colorado Department of Public Health and Environment. Maternal and Child Health Data, Colorado Child Health Survey Data; 2016. Available from: http://www.chd.dphe.state.co.us/topics.aspx?q=Maternal_Child_Health_Data. [Last accessed on 2017 Jan 01].