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Views & Comments

Cannabis, Cannabidiol, Cannabinoids, and Multigenerational Policy

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1. Introduction

While classical laboratory and animal data have long established cannabinoid genotoxicity, it is only recently, with the application of modern analytical techniques, that the scale of epidemiological disease that may be attributable to cannabinoid exposure has been revealed. The importance and urgency of this work is heightened by the increased cannabis use that is accompanying the relaxation of legislation around cannabis use in many places, the widespread global movement toward cannabis legalization, and the general increase in the cannabinoid potency of available strains. Building on an original pathfinding epidemiological study of congenital anomalies in Hawaii, the United States [1] and confirmed by similar findings from Colorado in the United States, Canada, and Australia [2–4], contemporary studies in the United States and Europe have found that 46/62 and 90/95 congenital anomalies [5,6], respectively, are causally related to various metrics of cannabinoid exposure. Similar studies of cancer in the United States and Europe have found that 25/28 and 33/40 cancers, respectively, could be related to indices of cannabinoid exposure [7]. Importantly, there was an almost complete overlap of findings wherever data allowed comparison. Recent investigations have utilized mixed effects, panel, robust, and spatiotemporal regression modeling; inverse probability weighting; and expected values (E-values) as primary tools of causal inference [5–7]. The E-value measures the extent to which an association can be ascribed to confounding by other extraneous covariates [8]. It has a 95% confidence interval (CI). Values greater than 9 are considered high [9].

More recently, clinical-epidemiologic studies of acute and chronic disease [10] and epigenetic clock studies based on DNA methylation age with the latest version of epigenetic clocks [11] have confirmed accelerated aging following cannabis exposure by some 30% at 30 years of age [11]. Cannabis use in this study was quantitated as an average of only 3.39 days per month use of cannabis during the previous four years, with a lifetime mean cannabis use of a mere 2.68 days per month [11]. Moreover, biophysical studies in human patients indicate that this effect increases with age and is proportional to the square of the chronological age [12]. Indeed, studies have reported global DNA hypermethylation following cannabinoid exposure [13]. This change in gene promoter methylation is stereotypical of aging and clearly accounts for the progressive loss of function. These findings are concisely summarized in more detail below and are notable for their number and marked diversity across many body systems and processes.

2. Evidentiary context

The following contexts have all been causally associated with cannabinoids.

2.1. Cancer

These cancers have been causally associated with cannabinoids in studies based in the United States and Europe:

- **United States (25/28 cancers):** All cancer, acute lymphoid leukemia, acute myeloid leukemia, bladder, brain, breast, chronic myeloid leukemia, chronic lymphoid leukemia, colorectal, Kaposi, kidney, liver, lung, melanoma, myeloma, Hodgkins and non-Hodgkins lymphoma, esophagus, oropharynx, ovary, pancreas, prostate, stomach, testis, and thyroid [7];
- **Europe (33/40 cancers):** Acute lymphoid leukemia, acute myeloid leukemia, bladder, breast, chronic myeloid leukemia, chronic lymphoid leukemia, colorectal, hepatocellular, Kaposi, kidney, liver, lung, myeloma, melanoma, Hodgkins and non-Hodgkins lymphoma, esophagus, oropharynx, ovarian dysgerminoma germ cell tumor, pancreas, prostate, stomach, testis, non-seminoma of testis, and thyroid. In addition to those identified in the United States: Anus, penis, corpus uteri, gall bladder, larynx, mesothelioma, testis seminoma, and vulva.

2.2. Congenital anomalies

These systems and congenital anomalies have been causally associated with cannabinoids:

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- **Systems found to be particularly affected in both the United States and Europe:** Central nervous system, cardiovascular, chromosomal, orofacial, limb, gastrointestinal, uro-nephrological, body wall, and general;
- **Congenital anomalies found to be particularly affected in the United States:** 46 of 62 anomalies [6];
- **Congenital anomalies and systems found to be particularly affected in Europe:** 90 of 95 anomalies and systems [5];
- **Forty shared anomalies:** anotia/microtia, interrupted aortic arch, aortic valve stenosis, atrial septal defect, atrioventricular septal defect, bilateral renal agenesis, bladder extrophy, choanal atresia, chromosomal anomalies, cleft lip and cleft palate, cleft palate alone, club foot, coarctation of the aorta, congenital cataract, diaphragmatic hernia, double-outlet right ventricle, Down syndrome (trisomy 21), Edward syndrome (trisomy 18), encephalocele, deletion 22q11.2, congenital hip dislocation, Hirschsprung's disease (congenital megacolon), holoprosencephaly, hypoplastic left heart, hypospadias, large intestinal/rectal/anorectal atresia/stenosis, limb reduction anomalies, microphthalmos/anophthalmos, esophageal atresia/stenosis (+ tracheoesophageal fistula), omphalocele, Patau syndrome (trisomy 13), congenital posterior urethral valve, pulmonary valve atresia, single ventricle, small intestinal stenosis or atresia, spina bifida (without anencephalus), tetralogy of Fallot, total anomalous pulmonary venous return, Turner syndrome (female X0), and ventricular septal defect [5,6].

2.3. Aging

Fourteen lines of evidence for accelerated aging are linked to cannabis: cardiovascular age acceleration, cirrhosis and hepatoinflammation, chromosomal damage, a 30% advance in epigenetic clock age by late-generation DNA methylation clocks [11], changes to oocytes and sperm, endocrine disruption, genotoxicity and cancerogenesis, genotoxicity as congenital malformations, a 50% reduction in histones, mitochondrial inhibition, neuroinflammatory mental illnesses, elevated senescence and mortality, syndromic pattern of acute and chronic illnesses, and telomerase inhibition. These are not only age-defining illnesses but also age-generating illnesses [14].

3. Discussion

Among other notable findings, the well-documented cannabinoid exponential dose–response effects seen in the laboratory have been shown to be similarly seen epidemiologically in the congenital anomaly and cancers datasets [5–7]. This finding becomes important in the modern context, where an increasing prevalence of use, intensity of daily use, and cannabinoid potency are being identified concurrently in many places—trends that together abruptly catapult the community into the high-exposure genotoxic zones [15,16]. Moreover, studies on both cancer and congenital anomalies show that cannabinoids are much more genotoxic than tobacco and alcohol combined [5–7]—a finding that applies to numerous cannabinoids [6,7,17–24].

Many mechanisms of cannabinoid genotoxicity have been identified, including chromosomal breaks and translocations [21,25], oxidation of the bases of DNA [21], abnormal sperm and oocyte morphology [26,27], and mitochondrial inhibition [28], with secondary downstream inhibition of the epigenetic machinery at both the substrate and energy-supply levels [29]. A recent flow of penetrating and insightful papers document the centrality of the epigenomic perturbations of cannabinoids. Cannabinoids have a heavy epigenetic footprint that mediates aging, cancer, and congenital anomalies. These papers culminate with a paper by Schrott et al. [30] on the epimutations of both cannabis dependence and cannabis withdrawal. The remarkable findings of the 359 pages of evidence in the supplementary data for that paper are summarized here in Table 1 [30]. There were 25 hits on the fundamental epigenetic machinery of the cell, including the DNA methyltransferases and the ten–eleven translocation 1–3 (TET1–3) oxygenases that initiate CpG demethylation. Moreover, there were 382 hits on the histone methyltransferases, demethylases, acetyltransferases, and deacetylases, which control the accessibility of the genome to the transcription machinery. There were 47 hits on the stem cell factors identified by Takahashi and Yamanaka [31], Yu et al. [32], and Ocampo et al. [33], 127 hits on the centrosomal machinery that binds the anaphase chromosomes to the mitotic spindle, and 225 hits on the motor proteins that control the spindle poles and chromosomal separation after spindle check-point release. Finally, there were 242 hits on the key embryonic morphogens Sonic hedgehog, Notch, vascular endothelial growth factor (VEGF), bone morphogenetic proteins (BMPs), and a member of the Eph receptor tyrosine kinase family (EphB2).

Importantly, there were many system-specific hits indicating effects on the brain, cardiovascular system, limbs, and other body systems. For example, detailed predictions are implied by the failure of parasympathetic ganglion cell migration from the neural crest characterizing Hirschsprung's disease and defects of atrial and ventricular septal morphogenesis. The European data shows a strong signal for congenital vertebral, anal, cardiac, tracheal, esophageal, renal, and limb (VACTERL) multisystem syndrome consistent with the inhibition of the major Sonic hedgehog morphogen pathway and its pleiotropic multisystem impacts [5]. Interestingly, this severe syndrome has become common with the rise of cannabis. In this study, the P value of the association between the VACTERL rate and the rate of daily cannabis use was 6.16×10^{-6}, the E-value was 1.70×10^{20}, and the lower bound of its CI was 8.94×10^{11} [5].

The exuberant outgrowth of the human neocortex has been variously ascribed to Slit–Robo signaling and to retinoic acid gradients and the high number of synapses in the neocortex to cerebellins. Cannabinoids inhibit these key morphogen signaling systems both directly [13,34] and epigenomically [30]. There is little wonder, therefore, that cannabis exposure has been linked to a spectrum of congenital neurological disease severities from neurodevelopmental delays and neurobehavioral disturbances

Table 1
Key findings for cannabis effects on epigenomics.

Structure/function	Epigenetic hits
Key cell function	
Fundamental epigenomic machinery	25
Histone post-translational machinery	382
Stem cell factors	47
Tubulin	110
Centrosomes and kinetochores	127
Motor proteins: dynein-dynactin and kinesins	225
Embryonic morphogenesis	
Morphogens: Sonic hedgehog, Notch, VEGF, EphB2, BMP	242
System	
Brain	166
Limbs	131
Uro-nephrological	73
General	60
Gastrointestinal	37
Cardiovascular	29
Face	22
Body wall	15
Chromosomes	4
Cancer	810

Reproduced from Ref. [30] with permission.
VEGF: vascular endothelial growth factor; EphB2: a member of the Eph receptor tyrosine kinase family; BMP: bone morphogenetic protein.

[35,36] to microcephaly [1], severe microcephaly [5], anencephaly [1,5,6], and a plethora of severe mental illnesses [37], and has been noted to be driving the exponential US autism epidemic [38–40]. In addition, the Schrott epigenome-wide association study (EWAS) database yielded 810 hits on various kinds of cancers, which collectively predicted 20 of the different kinds of cancers seen epidemiologically [30].

Taken together, these data make a strong case that cannabinoid genotoxicity is causally and exponentially related to multiple adverse outcomes, including mental illness, developmental neurological syndromes including autism spectrum disorders, many cancers and congenital anomalies, and clinically significant acceleration of aging. These adverse outcomes exceed those from tobacco and alcohol, which strongly indicates that cannabinoids should be regulated similarly to all other potent genotoxic agents.

At present, cannabidiol is widely touted yet not well understood. A recent editorial in the *South China Morning Post* erroneously stated that cannabidiol had no known side effects [41]. In fact, cannabidiol has been shown to be genotoxic even in low doses and has been linked with DNA fragmentation, single- and double-strand breaks, micronucleus formation, and the oxidation of DNA bases [21]. As long ago as 1999, cannabidiol was shown to be as genotoxic as toxic cancer drugs [26]. Moreover, cannabidiol has been shown to interact both directly and indirectly with the Sonic hedgehog pathway. Cannabidiol interacts directly with the smoothened receptor, which is one of the seven transmembrane receptors at the head of the Sonic hedgehog signaling pathway [42]. Cannabinoids also interact epigenomically with many members of the Sonic hedgehog signaling pathway, including the patched receptor (PTCH1), its negative regulators (patched domain containing 4 (PTCHD4) and suppressor of fused homolog (SUFU) negative regulator of hedgehog signaling), multiple endothelial growth factor-like domains 8 (MEGF8), transmembrane protein 107 (TMEM107), BMP4, and chromodomain helicase DNA binding protein 7 (CHD7). Furthermore, there were 185 hits on the key transcription factor at the nuclear end of the Sonic hedgehog pathway GLI family zinc finger 3 (Gli3) [30]. Sonic hedgehog is a major tissue morphogen involved in the morphogenesis of most body tissues, which necessarily implicates cannabinoids in the disordered structuring of many human tissues in embryology.

In the United States, data estimates of cannabidiol exposure were found to be significantly bivariately associated with nine congenital anomalies (out of a total of 62 anomalies), while tobacco and monthly alcohol exposure were related to 11 and five anomalies, respectively [7]. The sum of the exponents of the lower CI of the E-value of the congenital anomalies linked with cannabidiol was 39, while that for tobacco and monthly alcohol was eight and zero, respectively, making cannabidiol a far more potent teratogen than presently legal drugs [7].

It is no secret that many people in China historically had opium forced upon them by expatriate colonial powers. Cannabis has a well-established gateway effect as a pathway to other addictive drugs, which raises the very serious potential specter of the future repeating the horrors of the past, as has occurred in modern cities such as San Francisco. In that city, homelessness and mental illness are widespread and quickly increasing, and many mentally ill vagrants wander the streets as victims of a vicious downward spiral that frequently commenced with cannabis use [43–46]. For these reasons, restricting the exposure of populations to genotoxic cannabinoids is a primary responsibility of public health authorities—not only for their own populations but for at least four generations to come. This responsibility is heightened at the present time, when the alleged benefits of cannabinoids are largely hypothetical, mythical, and/or theoretical, and their extremely serious risks are increasingly clearly defined and transgenerationally evident. Clear indications of major genotoxic and age-related morphological changes to sperm and oocytes not only imply aging of the gametes but also provide presumptive evidence of preconceptional aging of the fertilized zygote, the far-reaching transgenerational implications of which are yet to be fully explored.

Authors' contribution

Conceptualization was done by Albert Stuart Reece, Gary Kenneth Hulse, and Wei Wang; methodology and investigation by Albert Stuart Reece; and funding acquisition, project administration, and supervision by Gary Kenneth Hulse and Wei Wang. Albert Stuart Reece wrote the original draft, which was reviewed and edited by Gary Kenneth Hulse and Wei Wang.

Compliance with ethics guidelines

Albert Stuart Reece, Gary Kenneth Hulse, and Wei Wang declare that they have no conflict of interest or financial conflicts to disclose.

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