Cannabinoid Genotoxicity

Introduction

The genotoxic effects of cannabis have been known since the 1960's when cannabis administered to pregnant rats and rabbits was shown to produce a wide range of congenital anomalies in the exposed offspring [1,2]. In the 1970's cannabis was found to be linked with cancer-inducing neoplastic changes in the airways of humans [3-6]. Cellular studies from the 1970's showed increased age-related nuclear changes in cannabis exposed cells grown in culture [3] which is indicative of accelerated aging. Genotoxicity would be expected to be expressed in increased aging, birth defects, and cancer outcomes [7-9]. This pattern of disease has now been reproduced in a large number of basic sciences and epidemiological studies which are further introduced below. It is also important to note that these features can occur together in different – and frankly, frightening - combinations.

Multigenerational

Given that the debate surrounding cannabis legalization is usually framed in terms of personal civil liberties it is important to note that genotoxic outcomes can persist for multiple generations and up to three to four generations for epigenetic effects [10].

Passive Cannabis Smoke

Passive smoking of cannabis fumes is real and significant [11-19] and is associated with cannabis dependence, withdrawal [20] and even extreme allergy and anaphylaxis [21]. Thus cannabis use exposes not only users but children, babies and babies *in utero* to cannabinoid genotoxic effects.

All Cannabinoids

With many different cannabinoids now becoming available there is much confusion about which cannabinoids are implicated in cannabinoid genotoxicity. It becomes important to appreciate that the genotoxic moiety has been shown to be the olivetol nucleus on the C-ring which is a dihydroxylated phenolic compound with a pentanyl aliphatic tail [22]. Phenols are well known carcinogens [23]. This means that all cannabinoids are implicated in these actions (cannabidiol, Δ8-, 9-, 10-, 11- THC, cannabichromene, cannabigerol etc.) [22,24]. These experimental results have been verified in real world epidemiological space-time and causal inference studies [9,25-27].

Congenital Anomalies

Congenital anomalies (CA's or birth defects) have been linked with cannabis since a 1969 study showed a series of severe birth defects linked with *in utero* cannabis exposure including miscarriage, foetal resorption, spina bifida, hydrocephalus, exencephaly, amelia (limblessness) and meningomyelocoele in laboratory animals [1,2]. Detailed space-time and causal inferential epidemiological studies have been performed in Hawaii, Colorado, Australia, Canada, USA and Europe which confirm such findings with effects seen particularly in the cardiovascular, brain and neurological, limbs (limblessness), body wall, genitourinary, gastrointestinal, chromosomal and other body systems [8,9,25,28-46]. USA epidemiological studies identified 44 (of 63) CA's linked with cannabis exposure 90% of which were confirmed in the European comparative epidemiological study [33,46]. The commonest form of birth defects is cardiovascular (CVS). 12 CVS CA's were linked with cannabis including atrial septal defect, ventricular septal defect and patent ductus arteriosus [38,47]. All five chromosomal anomalies studied in USA [8,9] and six in Europe [37] were linked to cannabis use. VACTERL (Vertebral, Anus, Cardiac, Tracheal, Eosphagus, Renal and Limb) syndrome is an interesting multi-organ system disorder which has been rapidly becoming more common in recent years which has now been linked to disruption of the major foetal morphogen sonic hedgehog by cannabis with downstream effects across numerous organ systems [45,48-50]. In affected children early foetal death is common [49,50]. Many mechanisms have been invoked to account for these diverse patterns of birth defects including widespread genetic and epigenetic machinery damage, oxyradical damage, disruption of centromeres, kinetochores, the mitotic spindle and the machinery of mitosis, inhibition of mitochondrial functions, perturbation of mitochondrial cannabinoid signaling, chromothripsis [34], reduced histone synthesis, and inhibition of all of the morphogen gradients which control foetal development especially the growth of brain, heart and limbs *in utero* [7,51-60].

Cancers

Although the subject of the association of cannabis with cancer has produced studies with both positive and negative results, results of classical studies with positive findings have now been confirmed by a series of recent space-time and causal inferential epidemiological studies in human populations in both USA and Europe with closely parallel and confirmatory findings [27,61-67]. 28 cancers were studied in USA and 41 in Europe. Bivariate regression of the cancer rates of USA and Europe against metrics of cannabis exposure revealed almost complete overlap between the positive findings in the two datasets with 100% of 23 USA cannabis-related cancers and 25/27 (95.6%) European cannabis-related cancers being confirmed where data permitted comparison [65]. P-values ranged to 2.20×10^{-307}. In the USA cancers linked with THC were: thyroid, liver, pancreas, AML, ALL, breast, oropharynx, CML, CLL, Kaposi, testis and kidney. Cancers linked with cannabidiol were: prostate, bladder, ovary, all cancers, colorectum, Hodgkins, brain, Non-Hodgkins lymphoma, esophagus, breast and stomach [27,61,62,64,66,67]. This makes 23 cancers in all. Importantly cancer of the pancreas and liver are growing rapidly in recent years in direct parallel to cannabis use [68-70]. Pancreatic cancer has been shown to be rising in similar demographics to cannabis use, which are both disproportionately more common in young African-American women [71,72]. Pediatric cancers linked with cannabis (mostly in American studies) include rhabdomyosarcoma, brain cancer, acute myeloid and lymphoid leukaemias, and total pediatric cancer [63,73-83]. Since many of the classical studies were done when cannabis was much weaker it has been argued by NIDA Director Dr Nora Volkow that the epidemiology of cannabis related malignancy needs to be reappraised now in the high potency cannabis era.

Aging

Some of the earliest studies of cellular genetic damage by cannabis smoke identified single and double stranded DNA and chromosomal breaks, nuclear blebbing, budding and rupture, the formation of micronuclei, and tripolar, quadripolar and pentapolar mitotic spindles which lead inexorably and inevitably to grossly disorganized cell divisions [84,85]. All of these changes are age-related deleterious cellular nuclear changes. Systemic exposure to cannabinoids implies accelerated aging of the whole organism. This has been directly verified biophysically in human populations by studying arterial stiffness as a measure of cardiovascular age which is a major hallmark of biological age [86]. It has also been verified by noting a pattern of accelerated age related disease including frailty, falls, myocardial infarction, stroke, accidents, injuries and inpatient and outpatient admissions in cannabis exposed patients [87]. It has been further verified by demonstrating elevated epigenetic age in cannabis users, by 29% at 30 years of age [88].

Combinations

Perhaps the most worrying aspects of cannabinoid genotoxicity is what happens when the three domains of genotoxic disease – congenital anomalies, cancer and aging – co-occur. Rather than being the exception, this is of course the rule, since the same underlying cellular events drive genotoxic outcomes across all three domains. As noted above several pediatric cancers can occur after in utero exposure which comprise therefore a form of inherited malignant teratogenesis (or teratogenic malignancy) as children inherit both the anomaly and the cancer. Cancer usually occurs in older people so it makes sense that cannabis exposed tissues, which are biologically older have a higher cancer rate. Pediatric cancer is an expression of intergenerational genotoxicity [89,90] so it makes sense that it increases with genotoxic cannabinoid exposure. If all the cells in the organism are aged by genotoxic processes it follows also that the gametes, the egg and sperm, also must be aged. This is actually consistent with published morphological studies of the male and female gametes [85,91]. It follows therefore that the zygote (fertilized ovum) must also be aged from the moment of conception which is consistent with higher foetal loss and miscarriage rates in cannabis using females. It follows also that in fact the conceptus must be prematurely aged even from before conception since the gametes from which it forms are known to be aged.

Clearly such considerations carry far reaching public health and transgenerational implications. Formal health econometric studies to quantitate the explicit and implicit costs to Government across each health domain including transgenerationally, are presently being undertaken.

CANNABIS POLICY OUTLINE

- **Medical Profession.** Many professional organizations have made strong statements warning against widespread cannabis use. e.g. AMA, RACGP, AAP, ACOG, British Lung Foundation.

- **Common Pattern.** The almost ubiquitous pattern in which medical cannabis is used today is to treat decades long cannabis addiction, with the other indications serving as mere "tickets" to engage whilst simultaneously avoiding legal censure.

- **Higher Concentrations.** At 25-35% cannabis now is about ten times stronger than earlier and forms (Waxes, "Shatter", Dabs) up to 100% THC are coming. In USA organized crime is often associated with legal cannabis operations.

- **Parallel Drug Approval Pathway.** It is obvious that whilst all other drugs are held to a strict approvals and regulatory pathway cannabis products are held to no serious control whatsoever with the industry in an effectively unregulated exponential growth phase.

- **Limited Benefits.** Despite the international rhetoric of many governments and the cannabis industry there is either nil or very poor evidence for the efficacy of the vast majority of cannabinoid products in the management of most indications presenting to GPs (Ref RACGP Review).

- **Known Harms.** Alternately, there is increasing direct and indirect evidence from cellular, mechanistic, case data and epidemiological studies of "likely" harm from cannabis, both within and across generations (epigenetics). This is supported by large epidemiological studies, confirming increased cancers and neonatal congenital abnormalities in areas of increased cannabinoid use, not dissimilar from those used to identify links between tobacco or alcohol and morbidities. Numerous aging pathologies are accelerated 30% at 30 years.

- **Further Harms.**
  - **i)** **Gateway role** – Into harder drugs and criminal lifestyle is now well established by studies in numerous countries. Whilst few cannabis users progress to harder drugs, virtually all users of harder drugs have used cannabis, with much higher rates of drug and criminal progression amongst ever users of cannabis.
  - **ii)** **Adult Brain** – Most major psychiatric syndromes have been linked with cannabis viz: sedation, amotivational state, anxiety, PTSD, serious mental disorders, depression, psychosis, bipolar disorder, schizophrenia, suicidal thoughts and completed suicides. Also linked with homicide and violence and over 70 mass shootings in USA thought to be linked with aggression (seen in both cannabis withdrawal and intoxication), impaired judgement and psychosis
  - **iii)** **Child Brain** – ADHD-like and autism-like features; extreme aggression; impaired cortical processing; learning difficulties; smaller brain; microcephaly; anencephaly (which causes death within hours)
  - **iv)** **Chest disease** – COPD, chronic bronchitis, emphysema, lung cysts, elevated residual volume, premalignant changes in upper and lower airways
  - **v)** **Immunomodulation** – Both immunosuppression and immunostimulation are described mediated via T-cells, B-cells, NK Cells, T-reg cells, antibodies and cytokines
  - **vi)** **Endocrinopathy** – Central and peripheral hypogonadism, Prolactin elevated

vii) **Cardiovascular** - accelerated coronary artery and atherosclerotic disease; strongly arrythmogenic (many tachyarrhythmias both atrial and ventricular; asystole kills within seconds); strokes.

viii) **Driving, machine operating, workplace safety, critical skills.** Evidence here is overwhelmingly negative and very concerning. Highly associated with motor vehicle fatalities (which kill). Alcohol-cannabis vehicular impairments are common.

ix) **Overdose.** Especially with new highly concentrated forms and in combination with alcohol and other drugs. In Colorado overdoses from cocaine, amphetamines opioids and fentanyl have risen massively since legalization. Includes psychotic reactions. In Colorado, Texas and elsewhere **fatal child overdose** has become a major problem.

- **Genetic Toxicity.** These include gestationally and neonatal congenital abnormalities, cancers both childhood and adult, and the occurrence of premature age-related morbidities, and powerful direct effects on the aging process etc.

- **Known Mechanisms.** These findings are underpinned by clear cellular mechanistic studies on how cannabinoids (both THC and CBD based) can cause the above by interfering with normal cellular and body functions creating antecedents of disease. This of course is not surprising given the increasing understanding of the role of endogenous cannabinoids in normal development, body functioning, and cellular reproduction and maintenance, chromosomes, gene maintenance and control (epigenome) and that use of large doses or prolonged exogenous cannabinoids can significantly disrupt these functions.

- **"Do No Harm."** Given the aforementioned, it is clear that caution needs to be applied to the medical use of cannabinoids, that although in the most positive interpretation may have a nominal impact managing morbidities, may in turn cause greater harm transgenerationally.

- **Multigenerational Impacts** Genetic and epigenetic effects are believed to persist for at least three to four generations. Cannabinoids have been shown to be driving several childhood (and thus cross-generational) cancers including total childhood cancer. Cannabis, THC and cannabidiol have been shown to be linked with the cancers of the: breast, prostate, ovary and testis showing carcinogenesis to the reproductive organs. Also many birth defects including the absence of arms and legs and congenital brain, face, and heart defects. Also aging of the sperm and ovum themselves in rodents and humans.

- **Rigorous Trials – Evidence Base.** It is therefore not only reasonable but essential that each cannabinoid product marketed should be assessed by the established international standards for pharmaceutical development, and to which all other pharmaceutical products, prior to being released and used in populations must conform. There is need for a robust evidence base. At present cannabis is not performing impressively in hundreds of clinical trials. In the case of cannabinoids this must include rigorous and long term tests of genetic, epigenetic and epitranscriptomic toxicity including: genotoxicity, carcinogenicity, mutagenicity, teratogenicity and gametotoxicity in both sexes.

- **Not Incarceration.** We do not believe that period of incarceration for possession of small amounts of cannabis is appropriate. Nor has the law ever worked in this way either in this country nor in other western nations.

- **Education Needed.** Clearly widespread community education on this subject is needed. The leaders of our profession are superbly placed to spearhead the delivery of needed messages. However the educational effort needs to be a much broader whole of Government approach.

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