Known Cannabis Teratogenicity Needs to be Carefully Considered

It is no accident that in almost the same week both Australia and UK have decided that cannabis is to be recommended for a host of medical disorders mostly in advance of gold standard clinical trials. This is a direct product of the organized transnational global drug liberalization movement orchestrated from New York [1].

I wish to most respectfully disagree with the points made by BMJ editor Dr. Godlee. Diarrhoea and colic occur in cannabis withdrawal; Crohn's disease has a prominent immune aspect, and cannabinoids are likely acting partly as immune modulators. Statements from patients are uninterpretable without understanding the treatments tried, their withdrawal symptomatology and their personal preferences.

Most importantly, as Dr Godlee states, cannabis is a mixture of 104 cannabinoids. The tide cannot be both out and in at the same time. Medicines in western nations are universally pure substances. This comprises a fundamental difficulty.

Medical research has confirmed that the body's endocannabinoid system is a finely regulated and highly complex system which is involved in the detailed regulation of essentially all body systems including the brain and cardiovascular systems and stem cell niches.

Studies have shown that the rate of use of cannabis by expecting mothers closely parallels that in the wider community. In fact given the long half-life of cannabis in tissues even were a maternal habitual smoker to stop when she discovered her pregnancy, her infant would continue to be exposed to her on-board cannabinoid load for several months afterwards during critical periods of organogenesis. And other studies show that the father's cannabis use is even more damaging that the mothers' [2].

Whilst much research has focussed on the effects of endocannabinoids in the adult brain relatively little research has looked at the impact of these same effects in the developing brain of the foetus and neonate. Whilst the brain stem is almost devoid of type 1 cannabinoid receptors (CB1R's) they are in high concentration in many parts of the midbrain, limbic system, subcortical regions and cerebral and cerebellar cortices [3]. Foetal CB1R's have been shown to play key roles in virtually all aspects of brain development including neural stem cell function, determining the ratio of glial v neuronal differentiation, brain inflammation, axonal growth cone guidance, stem cell niche function and signalling, blood flow signalling, white matter and CNS tract formation, glial cell differentiation, myelination, dendrite formation, neural migration into the developing cortex, synapse formation and integration of newly formed neurons into the neural network. They are also found in high density on endoplasmic reticulum and mitochondria from which latter they indirectly control major issues including cognition, DNA maintenance and repair systems both by supplying energy and by metabolite shuttle and RNA signalling [4 5].

Hence it is not surprising that gestational cannabis has been linked with a clear continuum of defects including in protracted longitudinal studies from Pittsburgh, Ottawa and Netherlands impaired cortical and executive functioning; reduced spatial judgement; the need to recruit more brain to perform similar computational tasks [6]; microcephaly [7]; lifelong smaller heads and smaller brains [6]; anencephaly (in two CDC studies [8]), and increased foetal death. This

progression clearly reflects a spectrum of congenital neurological impairment which is quite consistent with the known distribution of CB1R's mainly across the foetal and adult forebrain and midbrain and its derivatives [3].

It is also consistent with a recent explosion of autism in Colorado, California, New Jersey and many other sites in USA and internationally in recent years [9]. Moreover cannabis induced synpatopathy closely mimics that seen in autism [10 11], as do similar white matter disconnection endophenotypes [3 12].

A similar scenario plays out in the cardiovasculature. The American Heart Association and American Academy of Pediatrics issued a joint statement as long ago as 2007 noting that foetal cannabis exposure was linked with increased rates of ventricular septal defect and Ebsteins anomaly (complex tricuspid valvopathy) [13]. This is consistent with recent Colorado experience where ventricular septal defect has risen from 43.9 to 59.4 / 10,000 live births, or 35.3% 2000-2013. Both of these structures are derivatives of the endocardial cushions which are rich in CB1R's. Concerningly Colorado has also seen a 262% rise in atrial septal defects over the same period. Exposure to other drugs does not explain this change as they were falling across this period. It has also been reported that the father's use of cannabis is the strongest environmental factor implicated in cardiovascular defects, here involving transposition of the great arteries [2], which is a derivative of the conoventricular ridges immediately distal and continuous with embryonic endocardial cushions, and also rich in CB1R's.

Similar findings play out in gastroschisis. There is an impressive concordance amongst the larger studies of the relationship of gastroschisis and congenital cannabis exposure where senior Canadian authors concluded that cannabis caused a three-fold rise in gastroschisis [14], consistent with a high density of CB1R's on the umbilical vessels [15].

And cannabis has also been implicated as an indirect chromosomal clastogen and indirect genotoxin through its effect to disrupt the mitotic spindle by microtubule inhibition [16], and likely DNA maintenance and repair [17] by its effect on nuclear actin filaments [18].

Moreover cannabidiol has been shown to alter the epigenome, to be genotoxic, and to bind to CB1R's at high doses, so the simplistic case that "Cannabidiol is good" – fails.

These considerations imply that if clinical trials continue to show efficacy for additional indications for cannabinoids, their genotoxic and teratogenic potential, from both mother and father, will need to be carefully balanced with their clinical utility. They also imply that these issues will need to be more widely canvassed and discussed in order to introduce more balance into the heavily biased present global media coverage of the highly misleading misnomer "medical cannabis".

Only once before has a known teratogen been marketed globally: the thalidomide disaster is the proximate reason for modern pharmaceutical laws. With its widespread uptake, rising concentrations, asymptotic genotoxic dose-response curves and actions through the paternal line cannabis could be much worse.

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