

side effects, contraindications, and risks vs. benefits of its use for approved medical conditions.

Medical cannabis is seen as a legitimate medical therapy by many Missouri physicians and is here to stay. Labeling physicians who advocate medical cannabis as “unethical” is a disservice to reputable Missouri physicians and to current MSMA members who see a benefit of medical cannabis use in their patients. The MSMA should be an inclusive organization and embrace scientific cannabis education for its members and readers of *Missouri Medicine*.

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Cannabis and Pregnancy Don't Mix

In the September/October 2020 *Missouri Medicine*, Polcaro and Vettrano raise the important issue of the transgenerational effects of prenatal cannabinoid exposure (PCE) on subsequent generations.¹ The implications of multigenerational toxicity of cannabinoids is very far-reaching with major policy implications.

The picture presented by Polcaro and Vettrano relating to the mental health implications of PCE is correct if too conservative. As they observe the subject is deeply confounded with multiple other factors impacting post-natal neurological development. For these reasons the significant concordance between reports from five longitudinal studies of childhood development relating to impaired indices of concentration, startle, excitability, poor visuospatial processing and executive functioning including ADHD-like and autism-like features are of particular concern.²⁻⁶ Under a legalization paradigm the state effectively condones unlimited all day every day exposure to extremely high concentrations of THC, other cannabinoids and cannabis tars. What is especially concerning about this is that many of the neurotoxic and neurodevelopmental toxicities of cannabis exhibit threshold dose effects above which severe damage becomes commonplace.⁷ In the context of an increasingly solid consensus relating to the harmful impacts of adult and adolescent cannabis exposure⁸ the implications of PCE-neurotoxicity have not been carefully considered. It has been shown that

nationwide autism rates are undergoing an exponential rise and indeed New Jersey has been shown to have 4.5% of 8-year-old boys who carry an autism spectrum disorder diagnosis.^{9,10} Our space-time and causal inference studies demonstrate that indeed cannabinoid exposure to THC and cannabigerol amongst other fractions of cannabis, is a principal driver of this nationwide epidemic (manuscript submitted).^{9,10}

A very concerning consensus is now emerging relating to cannabis-induced teratogenesis, embryotoxicity and fetotoxicity. A 2007 Hawaiian study found that 21 birth defects including many cardiovascular defects, Downs syndrome, orofacial clefts, gastroschisis and arm and hand defects were elevated in offspring of women exposed only to cannabis gestationally with odds ratios up to 40-fold and upper confidence intervals to 123-fold.¹¹ A report on Canada found that total congenital defects were three times more common in the northern territories where cannabis is smoked about three times as much.^{12,13} In October 2018 Colorado Health reported an excess of 20,152 total birth defects beyond their baseline expected 67,620 defects 2000-2013 across the period of cannabis legalization when the use of other drugs was falling, representing an elevation of 29.8% above background rates.¹⁴ In a high cannabis use area of Australia 13 defects were found to be elevated compared to Queensland, which for methodological reasons is a conservative estimate.¹⁵ Concerningly elevated rates of Downs syndrome in Colorado, Hawaii, Australia and Canada clearly indicate that heritable cannabis genotoxicity can occur at the hundred megabase chromosomal scale.^{11,12,14,15} A close association of atrial septal defect (secundum type) with rising patterns of cannabis use across space and time in the US was recently reported, suggesting that the list of known teratological associations of prenatal cannabis exposure is as yet incomplete.¹⁶ This epidemiological literature is closely concordant with studies in experimental animals.¹⁷⁻¹⁹ Again an abrupt rise in genotoxicity with increasing cannabinoid exposure has been demonstrated for many cannabinoids and is of particular concern.²⁰⁻²³

Links between cannabis and several paediatric cancers including acute lymphoid leukaemia (ALL), acute myeloid leukaemia, rhabdomyosarcoma and neuroblastoma suggest further implications of cannabinoid genotoxicity.²⁴⁻²⁸ Since these tumours together encompass the common tumours of childhood, it is at least possible that cannabis is

responsible for the 43% elevation in total childhood cancer across US 1975-2017.²⁹ Indeed Downs syndrome is well known to be associated with a 2,000-fold elevated risk of childhood ALL from 2/100,000 to around 5/100.^{30,31}

This diverse assemblage of highly congruent evidence of severe cannabis-related neurotoxicity and genotoxicity from varied locations can only be described as extremely concerning indeed. In view of its well described epigenetic and chromoanagenetic effects³²⁻³⁴ and its clearly transgenerational-multigenerational impacts one can only conclude that if the evidence base is not admitted to the cannabis debate and access to fetotoxic and embryotoxic cannabinoids is not immediately restricted the community will inevitably pay a heinous price in terms of avoidable paediatric neurotoxicity, congenital birth defects, heritable cancerogenesis and multigenerational epigenotoxicity.

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