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What a downer: The dark side of cannabis

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It has been known for decades that cigarette smoking is associated with an increased risk of stroke. In 1988, the Framingham Heart Study cohort showed that even after age and hypertension were taken into account, smoking was significantly related to stroke [1]. This risk increased with greater number of cigarettes smoked, and conversely, after two years of cessation, decreased significantly, and by five years reached the level of nonsmokers.

What about marijuana? Is there an increased stroke risk for cannabis, one of the most commonly used illicit drugs in the United States? Although it is listed as Schedule I by the Drug Enforcement Administration (DEA), many laypersons consider it to have few adverse effects [2]. Recently, voters in 23 states supported legalization of medical marijuana in conditions where it is "possibly" or "probably effective" for compassionate use and, in four states, for "adult recreational use" [3]. Despite this trend, or perhaps because of it, attention has shifted to closer scrutiny of the safety of cannabis, which may not be as benign as people perceive, but rather associated with both serious cardiovascular and cerebrovascular events which have not been fully recognized or appreciated [4].

In this Journal of the Neurological Sciences, Rumalla and colleagues [5] report the results of a retrospective cohort analysis of the Nationwide Inpatient Sample (NIS) comparing the incidence of acute ischemic stroke between marijuana and non-marijuana users, and identifying characteristics of marijuana users hospitalized with stroke. The NIS is a valid, reliable, epidemiological inpatient data source collected by the Healthcare Cost and Utilization Project of the Agency for Healthcare Research and Quality, providing a yearly sample of hospital discharges with unique subject identifiers that conceal patient identity.

The authors found that, after adjusting for potential confounders, marijuana use was independently associated with a 17% increased likelihood of ischemic stroke hospitalization. This likelihood rose to 31% for those who smoked marijuana and tobacco, and then jumped to 42% when combined with cocaine. Interestingly, alcohol and hallucinogen use did not impact stroke hospitalization risk.

A retrospective population-based study in Texas [6] and a prospective case-control study in New Zealand reported that marijuana use, in conjunction with tobacco use, is associated with ischemic stroke and transient ischemic attack [7]. A comprehensive review of marijuana's benefits and harms concluded that cannabis smokers may be at increased risk for atrial fibrillation and heart attack, cognitive impairment (which could contribute to morbidity and mortality from motor vehicle, industrial, domestic and other accidents), pneumonia, COPD, head-and-neck cancer, and lung cancer [3].

As an alternative, or even an adjunct, to regular marijuana, synthetic marijuana – colloquially known as "Spice" or "K2" – has gained increasing popularity among young adults due to its euphoric effects and the ease with which it is purchased, in shiny packets labelled "potpourri" and "herbal incense" at convenience stores, gas stations, head shops, and via the internet. Since 2009, the DEA, law enforcement, hospitals, and poison control centers have noted gradually increasing use of Spice in the United States, especially among current marijuana smokers, recreational drug users, and curious experimenters who are drug-naïve and seeking "a legal high." Reported abreactions from Spice include seizures, myocardial infarction, supraventricular tachycardia, suicide, and psychosis [3,8]. In 2011, five synthetic cannabinoids identified in Spice were categorized as Schedule I substances, including JWH-018, which is a full agonist to the cannabinoid receptors CB1 and CB2. In 2013, we reported debilitating, acute ischemic strokes in two otherwise healthy young siblings following use of Spice, one of whom tested positive to JWH-018 on extended drug screen [9]. After an exhaustive workup, including hypercoagulability and genetic testing, was unremarkable, we speculated their strokes' etiology was either arrhythmogenic cardioembolic or transient, severe cerebral vasospasm [9].

In 2015, we reported cases of hemorrhagic stroke (intraparenchymal and subarachnoid) following use of Spice, again in otherwise healthy young people [10]. At our request, federal DEA laboratory analysis of the Spice (brought in to the hospital by the father of one of our stroke patients) isolated the compound XLR-11, which has been associated elsewhere with renal failure [10].

Routine urine toxicology screening identifies marijuana reliably, but cannot detect synthetic cannabinoids such as JWH-018 or XLR-11. If

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Spice use is suspected, liquid chromatography-tandem mass spectroscopy from the serum may detect a limited number of its known toxic compounds, but the test is not routinely available, and results may be delayed by weeks. Spice manufacturers are mostly anonymous, as Spice is often purchased via internet vendors (wholesale and retail). By following the criminal playbook of the "designer drug" dealers of the late twentieth century and continuously modifying these chemicals and creating new ones, they evade legal restrictions, and make it difficult to identify, charge and prosecute them. The DEA is hard-pressed to keep up by updating the list of banned cannabinoids.

Using ICD-9 codes for acute ischemic stroke, and cross-linking those with use of marijuana, tobacco, cocaine, alcohol and other substances, Rumalla and colleagues calculated likelihoods of hospitalization. This cannot be done for Spice – even if ICD-10 codes were available – as practitioners may not be able to test for Spice and for its continuously metamorphosing constituents. Hence, the full risk of stroke with Spice use is likely underestimated. This suggests a possible confounder of the NIS article: could the marijuana users also have smoked Spice, which contributed to the 17% increased stroke risk? This was not evaluated in the NIS marijuana smokers (because Spice was unlikely to be tested, coded, or known). However, this does not change the overall message.

As the evidence mounts for association of deadly medical illnesses such as stroke and cancer with use of synthetic and non-synthetic marijuana – practitioners may opt to counsel against its use, until any number of quality clinical research trials currently being conducted on cannabis shows its benefits to outweigh its risks.

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