

Since publication of their article, the authors report no further potential conflict of interest.

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## Adverse Health Effects of Marijuana Use

**TO THE EDITOR:** In their article, Volkow et al. (June 5 issue)<sup>1</sup> state that marijuana may have adverse health effects, particularly on the vulnerable brains of young people. Potential mechanisms underlying the effect of marijuana on the cerebrovascular system are indeed complex, although a temporal relationship between the use of marijuana (natural or synthetic) and stroke in young people has recently been described.<sup>2,3</sup> Simultaneously, the presence of multifocal intracranial arterial vasoconstriction was observed, which was reversible in some cases after cessation of cannabis exposure.<sup>3</sup> Thus, stroke, which is still underdiagnosed, may potentially play a role in neuronal damage related to marijuana use, even in young people without cardiovascular risk factors. Furthermore, tetrahydrocannabinol (THC), a major component of cannabis, has been shown experimentally to impair the function of the mitochondrial respiratory chain and to increase the production of reactive oxygen species in the brain.<sup>4</sup> Both of these processes are key events during stroke,<sup>5</sup> suggesting that THC may also increase a patient's vulnerability to stroke. In the ongoing shift toward marijuana legalization, physicians should probably inform marijuana users, whether they are using it for recreational purposes or therapeutic indications, about the risk of stroke with potential severe disability.

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**TO THE EDITOR:** Volkow et al. focus primarily on the neurocognitive and societal effects of marijuana use. We wish to note the known and potentially unknown infectious risks of marijuana, which were not discussed.

Recreational use of marijuana has been associated with a multistate outbreak of salmonellosis, illustrating the potential for widespread exposure through either inadvertent contamination during growing and storage or purposeful adulteration.<sup>1</sup> More worrisome are the risks of marijuana use for medical purposes, particularly by the population of immunocompromised patients. Prior reports have documented the frequent contamination of marijuana with fungal organisms and the potential for severe complications, including death.<sup>2-4</sup> These risks are not well studied and thus are poorly defined.

To date, 23 states allow the medical use of marijuana; however, dispensaries are currently not subject to regulation or quality control. We believe that the infectious risks need to be better defined, which would allow for appropriate regulatory oversight. The current approach places patients (unknowingly) at undue risk for acquisition of severe, and often lethal, infections.

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**TO THE EDITOR:** One safety aspect that is not discussed by Volkow et al. is the potential for interactions between marijuana and medications. *Cannabis sativa* Linnaeus products contain more than 700 distinct chemical entities. The relative abundance of these chemical entities in marijuana products and in human plasma can vary considerably depending on numerous factors, including the geographic location of cultivation, the method of preparation or administration, and the cultivar administered.

In vitro studies have shown that constituents of cannabis are potent and broad-spectrum inhibitors of key drug-metabolizing enzymes and transporters, including CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4, and P-glycoprotein.<sup>1-4</sup> Other data from in vitro studies suggest the potential for enzyme induction, especially of CYP1A2.

Case reports support the risk of pharmacokinetic interactions; however, clinical studies have been equivocal. Notably, these studies have not replicated the long-term high potency and high dose achieved by some marijuana users (e.g., hashish users). Health care providers need to maintain a high level of suspicion for drug interactions in their patients who use marijuana products.

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**THE AUTHORS REPLY:** We thank Wolff et al., Thompson and Tuscano, and Collins for their correspondence regarding potential adverse consequences of marijuana use that were not explicitly highlighted in our recent review. Given the shifting landscape of marijuana use, it is critically important that we be on the lookout for the emergence of predictable or unexpected health effects. This is particularly important when it comes to the potential of marijuana to negatively affect persons with various medical conditions, to interact with specific medications, or to influence the course of heretofore unstudied conditions. It will also be important to support the targeted research needed to understand the effects, both positive and negative, that may result from patients experimenting with marijuana in an attempt to relieve their specific symptoms. These studies should also focus on the possibility that such patients may forego evidence-based treatments while chasing after the purported therapeutic benefits of marijuana. Finally, we encourage particular attention to research targeting the effects of marijuana and other substances on adolescents, whose actively developing brains make them a particularly vulnerable population.<sup>1,2</sup>

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