So-called 'synthetic marijuana' linked to serious health problems

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Synthetic marijuana compounds are marketed as safe, legal alternatives to marijuana that cannot be detected by standard drug testing, but these substances differ chemically from marijuana; are linked to dangerous side effects, including seizures, psychosis, dependence, and death; and are not safe substitutes, say University of Arkansas for Medical Sciences (UAMS) scientists in a Review published February 2 in *Trends in Pharmacological Sciences*.

Researchers discovered several decades ago that the primary psychoactive compound in marijuana, Δ9-THC, activates two receptors, CB1, found in high abundance in the brain and central nervous system, and CB2, found primarily in the immune system. To study these receptors, researchers identified other naturally occurring chemicals and

developed synthetic cannabinoid (SCB) compounds that also bind to them; collectively, these compounds are known as cannabinoids. Although they activate the CB1 and CB2 receptors, SCBs and other cannabinoids are otherwise chemically distinct from marijuana and often from each other.

SCBs are now marketed and sold as synthetic marijuana under names such as "K2" and "Spice." "It started in the early 2000s in Europe, and in the U.S., in 2007 or so, we started seeing all kinds of people coming into emergency rooms saying they smoked marijuana, but then they had these really bizarre symptoms that did not correspond with the effects you see with marijuana," says Paul L. Prather, a cellular and molecular pharmacologist at UAMS.

SCBs are often sold as safe alternatives to marijuana that, because of their chemical structures, will not be discovered through standard drug screenings. This feature makes them popular among groups who want to elude detection, such as adolescents and military personnel. SCBs are also more potent than Δ9-THC; "these are highly efficacious drugs; they tend to activate the CB1 receptor to a greater degree than we can ever get to with THC from marijuana," says William E. Fantegrossi, a behavioral pharmacologist at UAMS. As a result, some users turn to them to achieve a more intense high.

A range of both acute and long-term adverse effects of SCB use are reported in clinical case studies, including seizures and convulsions, kidney injury, cardiotoxicity, strokes, anxiety, and psychosis in susceptible individuals, as well as tolerance, withdrawal, and dependence. Twenty deaths have also been linked to SCB use.

Prather and his co-authors note that in addition to the efficacy of SCBs in activating the CB1 receptors, they pose other health risks. Since they are chemically distinct from Δ9-THC, there is a chance that they may be

activating other cellular receptors in addition to CB1 and that these receptors could be responsible for some of the adverse health effects seen in SCB users.

Another risk is that users purchasing these drugs over the internet or elsewhere simply do not know what they are getting in each purchase. "Not only does the amount of the active pharmacological agent change with different batches of drugs, made by different labs, but the active compound itself can change,"says Fantegrossi. "And there are usually a minimum of three, if not five, different synthetic cannabinoids in a single product," adds Prather.

The authors caution against dismissing the therapeutic potential of cannabinoids entirely, noting that just as with opioids, improper use or abuse can lead to adverse effects or death, but proper use can provide significant benefits. But Prather cautions that "the public sees anything with the marijuana label as potentially safe, but these synthetic compounds are not marijuana, ... you never know what they are, and they are not safe."

More information: Trends in Pharmacological Sciences, Ford, et al., "Synthetic Pot: Not Your Grandfather's Marijuana" www.cell.com/trends/pharmacolo … 0165-6147(16)30185-7 , DOI: 10.1016/j.tips.2016.12.003

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