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Potential Treatment for Overdose with Synthetic Cannabinoids

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Emergency departments are increasingly reporting overdoses with synthetic cannabinoids (SCs), such as K2 and Spice, presenting not only as agitation, paranoia, anxiety, and confusion, but also medical complications, such as palpitations, hypertension, nausea, vomiting, and seizures [1]. Multiple deaths have also been reported with SC overdoses [2]. One of the reasons for such high level of toxicity with SCs is their potent agonist activity at cannabinoid type-1 (CB1) receptor without any action on the cannabinoid type-2 (CB2) receptor, which further adds to the adverse effect profile of SCs, as CB2 receptors have been shown to neutralize some of the CB1 receptor activation. However, in contrast to SCs, delta-9-tetrahydrocannabinol (THC; primary psychoactive substance in botanical marijuana) is a partial agonist at CB1 and CB2 receptors. We believe that it is the difference between partial and full agonism at CB1 receptors that makes the SCs so much more toxic than botanical marijuana or THC. In addition, SCs have longer half-lives along with active metabolites, whereas THC is primarily metabolized into the inactive metabolite 11-nor-9-carboxy-9-tetrahydrocannabinol (THC-COOH). Additionally, the effects of THC in botanical marijuana may also be modified by the presence of other cannabinoids and terpenes within the plant [3]. Cannabidiol (CBD) is another important psychoactive agent in marijuana (usually present at much lower concentrations than THC), which is neither an agonist nor a partial agonist but modifies CB1 receptor activity via allosteric modulation [1]. It is shown to be nonaddictive and safe as reflected by LD50, which is more than 100 times greater than the oral dose [3]. More importantly, CBD has also been shown to have preliminary evidence in the management of atonic seizures [4], social anxiety [5], and psychosis in patients with Parkinson's disease [6]. In addition, CBD is the only marijuana agent that has been approved by the FDA to manage treatment-refractory seizures in children. Although it is theoretically plausible that partial agonism with THC may neutralize some of the neurotoxic effects of SCs, CBD represents a safer and more acceptable approach to neutralize toxic effects of SCs due to its nonaddictive potential and selective allosteric modulation of CB1 receptors. In this context, CBD may provide a specific antidote to the neurotoxicity with SCs [7]. More importantly, approval of CBD formulation (i.e., Epidiolex™) can ensure qualitative and quantitative monitoring by the FDA. Therefore, we propose to explore CBD treatment to manage overdose and toxicity with SCs, which is increasingly recognized as a life-threatening emergency, especially in the emergency settings across the United States.

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Author Contributions

Corresponding author, Mujeeb U. Shad conceived the idea of presenting this, and all authors equally contributed to the drafting of the manuscript. MS and VA reviewed the final version of the manuscript. All authors read and approved the final manuscript.

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