Pharmacology, Toxicology, and Adverse Effects of Synthetic Cannabinoid Drugs

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ABSTRACT: Synthetic cannabinoid drugs have become an established part of the recreational drug landscape in the United States and internationally. These drugs are manufactured in clandestine laboratories internationally and distributed in the United States in smoking mixtures, use of which produces effects very similar to use of marijuana. The adverse-effect profile of the drugs has not been studied in humans and infrequently in animal models, so much of the information about their toxicity comes from emergency department and treatment reports and forensic case studies. This review considers the discovery and characterization of the endocannabinoid system, approaches to receptor-binding studies of various synthetic cannabinoids from the first wave of naphthoylindoles (e.g., JWH-018) to the emerging adamantoylindole drugs (e.g., AKB-48), and their analogs, to evaluate the potential activity of drugs in this class. Currently employed approaches to assessing functional activity of the drugs using in vitro and in vivo models is also described, and comparisons made to the effects of THC. The physiological effects of activation of the endocannabinoid system in humans are reviewed, and the physiological effects of cannabinoid use are described. Case reports of adverse events including emergency department admissions, mental health admissions, and clinical and forensic case reports are presented in detail and discussed to summarize the current state of knowledge of adverse effects, both clinical and forensic in humans, including effects on driving ability, and tissue injury and death. The greatest weight is accorded to those reports that include toxicological confirmation of use. Finally, we discuss the current status of attempts to schedule and control the distribution of synthetic cannabinoids and the relevance of receptor binding and functional activity in this context. There is growing toxicological and pharmacological evidence of impairment, psychosis, tissue injury, and isolated deaths attributable to this emerging class of drugs.

KEY WORDS: Designer drugs, drug toxicity, synthetic cannabinoids, synthetic drug scheduling.

INTRODUCTION

After alcohol, marijuana ranks as the most pervasive recreational drug in the United States [49], although its legal status and patterns of use are rapidly changing. Currently 18 states and the District of Columbia have laws permitting and regulating the possession of marijuana for medical purposes [64]. Six additional states have legislation pending to legalize the medical use of marijuana. Two states, Washington [108] and Colorado [110], have additionally legalized recreational use of marijuana through ballot initiatives. Marijuana is still controlled under federal law, and possession, distribution, and use of marijuana continue to be offenses in federal jurisdictions. The illegal status of marijuana has motivated drug distributors and entrepreneurs to devise various classes of synthetic compounds with cannabinoid-like effects that could be manufactured, distributed, displayed, and marketed to the recreational marijuana-using population and prospective new users as a legal alternative to marijuana but with the desired effects, including mood elevation, euphoria, relaxation, creative thinking, and increased sensory awareness.

Cannabinoid receptor agonists produce neutral, possibly therapeutic effects such as appetite stimulation and nausea suppression, but also negative effects. Delta-9-tetrahydrocannabinol (THC) is the most studied drug in this class, and adverse and paradoxical effects reported by some THC users include difficulties with short-term memory, agitation, feeling tense, anxiety, dizziness or lightheadedness, confusion, and loss of coordination [55]. These effects can have significant consequences in the performance of some motor tasks and activities requiring high levels of attention, coordination, and mental acuity, most notably driving. While some of the similarities in effects between plant-derived cannabinoids and synthetic cannabinoids are assumed based on their receptor binding, no systematic dosing study has been possible in humans as a result of the unknown side-effect profile of the drugs.

Harm-reduction efforts are receiving a lot of attention in public health and policy forums with respect to management of drug abuse, especially where the adverse effects are of low severity and marijuana represents relatively little risk of toxicity beyond its intoxicating effects [92]. To adequately educate and inform users about the risks of the adverse consequences of synthetic cannabinoid drugs, it is essential

Each new class contains many chemically related members which are referred to in places in this manuscript as “analogs”. We use the term in its chemical sense, meaning having some chemical structural similarity, without implying any assessment as to whether they meet the various technical legal definitions for drug analogs used in statutory construction.