

Pharmacology, Toxicology, and Adverse Effects of Synthetic Cannabinoid Drugs

S. M. R. Gurney¹, K. S. Scott², S. L. Kacinko³, B. C. Presley^{3,4}, B. K. Logan^{3,5,*}

¹Drexel University
Department of Biology
Philadelphia, Pennsylvania
United States of America

³NMS Labs
Willow Grove, Pennsylvania
United States of America

²Arcadia University
Forensic Science
Glenside, Pennsylvania
United States of America

⁴Temple University
Department of Chemistry
Philadelphia, Pennsylvania
United States of America

⁵Center for Forensic Science Research and Education
Fredric Rieders Family Renaissance Foundation
Willow Grove, Pennsylvania
United States of America

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* Corresponding author: Dr. Barry K. Logan, NMS Labs, Willow Grove, PA 19090; +1 215 366 1513 (voice); barry.logan@nmslabs.com.

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REFERENCE: Gurney SMR, Scott KS, Kacinko SL, Presley BC, Logan BK: Pharmacology, toxicology, and adverse effects of synthetic cannabinoid drugs; *Forensic Sci Rev* 26:53; 2014.

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.

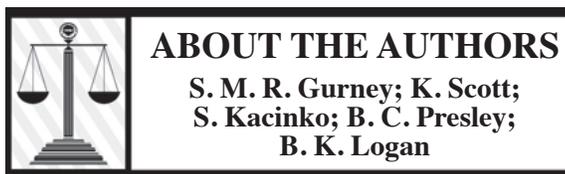
INTRODUCTION

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^a 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

^aEach new class contains many chemically related members which are referred to in places in this manuscript as “analog”. 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.



Susan M. R. Gurney earned a bachelor's degree (2000) in cell biology and pathology from the University of St. Andrews (St. Andrews, UK), an M.Sc. in forensic science (2007) from Anglia Ruskin University (Cambridge, UK), an M.Sc. in molecular biology (2011) from the University of Cambridge (Cambridge, UK), and a Ph.D. in genetics (2012) from the University of Münster (Münster, Germany). Dr. Gurney is an assistant teaching professor at the Department of Biology, Drexel University (Philadelphia, PA). Courses taught at Drexel University include forensic toxicology, forensic biology, and advanced immunology.

Dr. Gurney's doctoral research involved examining human and equid mitochondrial DNA for forensic and evolutionary applications, and she continues to pursue new research developments on these topics. In 2011–12, Dr. Gurney carried out an internship in forensic toxicology in the Department of Forensic Medicine and Science at Glasgow University (Glasgow, UK), performing analyses on biological samples provided as forensic casework and specializing in LC/MS/MS.

Since 2012, Dr. Gurney has worked as a co-director for Roots for Real (Fluxus Technology: Cambridge, UK), a DNA ancestry service that performs autosomal, mitochondrial, and Y-chromosomal profiling.

Karen Scott has a bachelor of science (honors) degree (1994) in forensic and analytical chemistry from the University of Strathclyde (Glasgow, UK) and a Ph.D. (1998) in forensic toxicology from the University of Glasgow (Glasgow, UK). Dr. Scott has been director of the Forensic Science Program and an associate professor at Arcadia University (Glenside, PA) since October 2012.

On completion of her degrees, Dr. Scott carried out postdoctoral research in Tokyo, Japan, investigating incorporation rates and detection of drugs in hair. Prior to joining Arcadia University, Dr. Scott held the position of senior lecturer and consultant forensic toxicologist at Forensic Medicine and Science, University of Glasgow. She has over 18 years of experience in the fields of forensic and clinical toxicology.

Dr. Scott has published in the areas of postmortem toxicology and hair and alternative matrix testing and is a reviewer for three of the main forensic toxicology journals. She is a chartered scientist, a chartered chemist, and an authorized analyst for the purposes of Section 16 of the Road Traffic Offenders Act (UK).

Sherri Kacinko earned her bachelor of science degree in chemistry at the University of Pittsburgh (Johnstown, PA,) and took graduate classes in forensic science at George Washington University (Washington, DC). She received her doctor of philosophy in toxicology at the University of Maryland (Baltimore, MD). Dr. Kacinko is now a toxicologist at NMS Labs (Willow Grove, PA) and an adjunct faculty in the chemistry department at Arcadia University.

Upon finishing her bachelor education, Dr. Kacinko performed pharmaceutical quality control at Lancaster Laboratories (Lancaster, PA), then worked for 3 years as a crime laboratory analyst in the chemistry section of the Florida Department of Law Enforcement Orlando Regional Operations Center (Orlando, FL).

Dr. Kacinko is board certified by the American Board of Forensic Toxicologists (ABFT). In recognition of her work and contributions, Dr. Kacinko has received the American Academy of Forensic Sciences (AAFS) Irving Sunshine Award.

Brandon C. Presley earned his bachelor's degree in chemistry in 2010 from Temple University (Philadelphia, PA). He is currently a Ph.D. candidate studying analytical chemistry at Temple. Mr. Presley is also employed as a forensic chemist at NMS Labs (Willow Grove, PA) performing analyses of drug evidence to identify substances contained therein.

During his tenure as an undergraduate, Mr. Presley conducted several research projects in analytical, organic, and inorganic chemistry. These research projects included the analysis of prostaglandins and thromboxanes as inflammatory biomarkers for rheumatoid arthritis; synthesis of heterocyclic indole derivatives for use as inhibitors in disease modeling; and synthesis and characterization of transition metal complexes using benzenedithiol for use in scintillators. In 2009, he joined Intertek Testing Services in Essington, PA, and began working as a chemist performing analyses of various petrochemical products. He has worked in the clinical and forensic toxicology laboratory at NMS Labs, performing analyses of biological specimens for pharmaceuticals and illicit substances. He

has also participated in a drug diversion study to determine the ease of tamperability and abuse of pharmaceutical preparations by drug users.

Mr. Presley has given a number of research presentations on his findings at various locations including Drexel University, the Eastern Analytical Symposium, American Chemical Society national meetings, and the Pennsylvania Senate and House of Representatives.



Barry K. Logan earned his bachelor's degree (1982) in chemistry and Ph.D. degree (1986) in forensic toxicology from the University of Glasgow (Glasgow, UK). Dr. Logan is director of forensic and toxicological services for NMS Labs (Willow Grove, PA), a leading US provider of esoteric toxicological testing services, specializing in new drug detection and forensic analysis for criminal justice and death-investigation agencies.

Dr. Logan has over 80 publications in toxicology and analytical chemistry, including treatises on the effects of methamphetamine, cocaine, marijuana, alcohol, hallucinogens, and depressant drugs on drivers; postmortem redistribution of drugs; and synthetic drug analysis. Since 2010, Dr. Logan has served as executive director at the Center for Forensic Science Research and Education at the Fredric Rieders Family Renaissance Foundation in suburban Philadelphia. The center supports educational programs in the forensic sciences for high school and graduate students, and continuing professional education for forensic science professionals. He is also executive director of the Robert F. Borkenstein Courses at Indiana University (Bloomington, IN).

Dr. Logan is board certified by the American Board of Forensic Toxicologists (ABFT). In recognition of his work and contributions, Dr. Logan has received the American Academy of Forensic Sciences (AAFS) Rolla N. Harger Award, the National Safety Council's Robert F. Borkenstein Award, and the 2013 Widmark Award from the International Council on Alcohol Drugs and Traffic Safety (ICADTS). He is currently president of AAFS.