# ACUTE TOXICITY OF SYNTHETIC CANNABINOIDS

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**Objectives**: This presentation discusses the acute synthetic cannabinoid receptor agonists (SCRAs) toxicity and contrasts those effects with acute marijuana (MJ) toxicity.

**Methods:** The authors performed a literature search and will present preliminary data from a comparison of the effects of SCRAs and MJ in over 3600 patients (1400 SCRA vs 2200 MJ).

**Results:** The pharmacokinetics of SCRAs are poorly evaluated in either animals or man. While SCRAs are typically smoked, they are also orally absorbed. Intravenous administration is studied in animals and allegedly reported in humans. The bioavailabilities of different routes of administration are not documented. Some trials report metabolites, but the metabolism of the majority of SCRAs remains unknown. As may have been expected, there is a lack of high quality human evidence characterizing the clinical effects of SCRAs with most data being obtained from case reports and small case series. These data are significantly limited by: 1) a lack of confirmation of exposure in many cases, and 2) the ever changing profile of compounds found in SCRA packets. While original cases reported JWH, AM and HU series, XLR series became more prevalent in some areas and the most recent reports include the indazole-3-carboxamide derivatives known as APINACA, FUBINACA, and CHMINICA. The clinical effects of SCRAs are attributed to higher affinity at the CB1 receptor resulting in greater perceptual and cognitive effects. Unlike MJ, vomiting and seizures are common and case reports suggest and association with sympathomimetic-like agitation or deep sedation, rhabdomyolysis, acute kidney injury, stroke, and myocardial infarction. Death from arrhythmia or complications (diabetic ketoacidosis) is infrequently reported. There is a suggestion that ingestion produces greater toxicity but because of limited information it is impossible to determine whether this is related to dose, bioavailability, or first-pass hepatic activation. Preliminary data from our case-controlled cohort suggests that when compared to MJ, SCRA users are more likely to have chest pain, nausea, seizures, dyspnea and diaphoresis. Therapy currently consists of supportive care with targeted treatment of clinical effects. Because CB1 antagonists and inverse agonists exist, agents such as SR141716 (Rimonabant) and AM251 are undergoing preclinical studies. Data suggest that these drugs can reverse many of the effects of SCRAs in animals.

**Conclusions:** The toxic profile of SCRAs is significantly different from marijuana but a thorough understanding is hindered by the constantly changing chemical composition of SCRAs. For now treatment is largely supportive, but there is a potential new antidotes.