EDUCATIONAL COMMENTARY – CANNABINOIDS

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Learning Objectives

On completion of this exercise, the participant should be able to

- identify the classes of natural and synthetic cannabinoids;
- describe the physiologic effects of natural and synthetic cannabinoids;
- describe the legal status of natural and synthetic cannabinoids; and
- explain currently available laboratory testing for natural and synthetic cannabinoids and the challenges associated with it.

Introduction

Dating back as early as 2700 BCE, cannabis, or marijuana, has been recognized for its psychoactive and healing properties. Early Chinese physicians noted its analgesic, anesthetic, and antiemetic properties. Modern-day chemists are still enthralled by its chemical composition, biological activity, and the possibility that its healing powers might be synthesized to produce a drug with predictable pharmacologic therapeutic effects. As with many other psychoactive substances, the properties of cannabis have attracted a lot of attention outside of the health care setting as well, leading to the development of synthetic compounds capable of producing similar psychoactive effects and very lucrative illicit drug trafficking. Synthetic cannabinoids include illicit abused substances as well as medications like dronabinol and nabilone, but for the purposes of this commentary, synthetic cannabinoids will refer only to those illicit drugs developed to mimic the effects of psychoactive cannabinoids.

Chemical Origin

Cannabinoids

Cannabinoids are a group of C21 terpenophenols which interact with the body's cannabinoid receptors and are found only in plants of the genus Cannabis. There are a wide variety of Cannabis species, but Cannabis sativa is the species most commonly used as recreational marijuana. Cannabis sativa contains nearly 500 compounds, including nitrogen-containing compounds, terpenoids, hydrocarbons, carbohydrates, flavonoids, fatty acids, noncannabinoid phenols, simple alcohols, aldehydes, ketones, and acids. It also contains 66 cannabinoids with and without psychoactive effects. Cannabinoids are divided into ten subclasses, each of which contains several different types. A few of the more common subclasses are the cannabidiol class (CBD), the cannabigerol class (CBG), and the
delta(Δ)9-tetrahydrocannabinol class (THC).\(^1\) Cannabis potency is measured by THC concentration, as THC is the primary and most potent of the psychoactive cannabinoids.

**Synthetic Cannabinoids**

Synthetic cannabinoids entered the US market in late 2008 with street names such as: K2, Spice, Fake Weed, and Black Mamba.\(^2\) The synthetic cannabinoids are typically sprayed on dried plant material and marketed online and in gas stations, tobacco shops, and convenience stores as herbal blends, incense, and potpourri for the buyer to smoke or ingest. They may also be maintained in liquid form for sale as incense or e-cigarette fluids. Traditionally, synthetic cannabinoids have been divided into three main categories: classical cannabinoids (dibenzopyran derivatives such as THC and its isomers), cyclohexylphenols, and aminoalkylindoles.

Synthesized in the 1980s at Hebrew University, HU-210 is one of the most recognized of the synthetic classical cannabinoids. Although HU-210 was found on the market in 2009 in relatively large amounts, classical cannabinoids are not currently popular in the illicit drug market because they are difficult to synthesize. Cyclohexylphenols like CP-47479 were developed as analgesics in the late 1970s by Pfizer and were some of the first synthetic cannabinoids found in herbal incense. The aminoalkylindoles are the most common category of synthetic cannabinoids found on the illicit drug market today. They were developed in the late 1990s and include compounds like JWH-018, JWH-073, and JWH-200.\(^3\) As of 2016, more than 170 synthetic cannabinoids have been identified on the illicit drug market, and new compounds are constantly appearing. To accommodate the ever-changing compositions of synthetic cannabinoids, several scientists have proposed more comprehensive and inclusive classifications with continual updates to better represent these new classes of compounds.\(^4\)

**Effects**

**Cannabinoids**

Tetrahydrocannabinol acts on two G-protein–coupled cannabinoid receptors, CB\(_1\) and CB\(_2\). Although CB\(_1\) receptors are distributed throughout the body, their highest concentrations are in the central nervous system, making them responsible for the psychoactive effects of THC. Activation of the CB\(_1\) receptors by THC results in the inhibition of voltage-gated calcium channels and cyclic adenosine monophosphate (AMP), and the activation of potassium channels.\(^5\) CB\(_2\) receptors are found in the brain to a much lesser extent than CB\(_1\) receptors. CB\(_2\) receptors are predominantly found on immune cell surfaces throughout the body and are thought to mediate anti-inflammatory and immunosuppressive effects, as opposed to behavioral effects. Activation of CB\(_2\) receptors inhibits cyclic AMP, but unlike CB\(_1\) receptors, CB\(_2\) receptors are not involved with ion channel inhibition or activation.
Cannabinoid receptor CB₁ activation induces appetite stimulation, muscle relaxation, pain suppression, nausea and vomiting abatement, intraocular pressure reduction, and a sense of euphoria and well-being. Frequent (daily or almost daily) use is associated with an increased risk for psychoses and cognitive and psychomotor impairment due to excessive CB₁ activation. Signs of cannabis intoxication include but are not limited to tachycardia, increased blood pressure, ataxia, slurred speech, and increased respirations.

**Synthetic Cannabinoids**

Synthetic cannabinoids are often referred to as a legal marijuana alternative. These compounds, structural modifications of cannabis, were developed to mimic the effects of cannabinoids by interacting with the cannabinoid receptors. Although synthetic cannabinoids do result in psychoactive effects similar to those of their natural counterparts, several important factors must be considered. First, THC is a weak, partial CB₁ receptor agonist, whereas synthetic cannabinoids are full receptor agonists. Also, natural cannabis contains compounds that counteract the effects of THC by acting on noncannabinoid receptors; synthetic cannabinoids do not. These differences result in similar psychoactive effects as natural cannabinoids, but with a 4 to 5 times greater binding affinity to CB₁ receptors and no action on noncannabinoid receptors. As a result, synthetic cannabinoids may be up to 100 times more potent than THC and have more intense and longer-lasting effects. Symptoms of acute toxicity are potentially more serious than those of natural cannabis toxicity.

**Prevalence**

**Cannabinoids**

Cannabis is the most common illicit drug in the United States and worldwide. Based on data collected between 2002 and 2014, the Centers for Disease Control and Prevention reported that in 2014, 2.5 million people in the United States aged 12 and older had used marijuana for the first time, for an average of almost 7000 new users each day. Between 2002 and 2014, the prevalence of marijuana use increased among persons older than 18 years, but not among those aged between 12 and 17 years. In 2016, 35.6% of high school seniors reported having used marijuana in the past year.

**Synthetic Cannabinoids**

Promoted as safe and natural, and with the appeal of a stronger high, ease of availability, relatively low cost, and difficulty in detection on traditional drug screens, synthetic cannabis has quickly taken its place after natural cannabis as the second most frequently used illicit drug in the United States. In 2010, 11,406 emergency department visits were associated with synthetic cannabinoid use; in 75% of these visits, the patients were adolescent males. Of high school seniors surveyed in 2016, 3.5% had used synthetic cannabinoids in the past year, most of those also young males. Since 2013, the number of calls to poison centers regarding synthetic cannabinoid exposure has steadily increased.
EDUCATIONAL COMMENTARY – CANNABINOIDs (cont.)

reported 2668 exposure calls in 2013, 3682 in 2014, and 7794 in 2015. As of April 30, 2017, preliminary numbers indicate poison centers have received 656 exposure calls in 2017.10

Legal Status

Cannabinoids

Although marijuana use is legal in some form in many states, it is still considered an illegal substance under federal law. The first governmental regulation of marijuana was enacted as the Marihuana [sic] Tax Act of 1937. Although it did not specifically prohibit marijuana use, the Marihuana Tax Act did control the possession and sale of marijuana by regulating and taxing it. Under President Richard Nixon, in 1970 Congress passed the Controlled Substances Act, which classified drugs based on their potential for abuse and medical usefulness. Due in part to the efforts of President Nixon, cannabis was added to Schedule 1, substances having a high potential for abuse and no currently accepted medical use. It did not take long for citizens to push for the decriminalization of marijuana at the state and local levels.11 At present, marijuana is legal in some form in 29 states and the District of Columbia.12

Synthetic Cannabinoids

There were no state or federal laws regulating synthetic cannabinoids before 2010. Noting increased potency and abuse, in 2012 President Obama signed the Synthetic Drug Abuse Prevention Act. The bill named 26 types of synthetic drugs as Schedule 1 drugs under the Controlled Substances Act, 15 of which were synthetic cannabinoids. Consequently, as of 2015, all 50 states have enacted legislation to control one or more synthetic cannabinoids.13 Legislatures are faced with an uphill battle when it comes to synthetic cannabinoid legislation. New synthetic cannabinoids with slightly modified chemical structure are constantly being developed to circumvent existing laws.

Laboratory Testing

Cannabinoids

Laboratory testing for the presence of cannabinoids may be indicated for a number of reasons: evaluating drug-overdose patients, screening employees for drug use, and monitoring adherence to substance-abuse treatment. Urine is the most frequently used specimen for drugs of abuse screening, as it is easy to obtain and contains high concentrations of drugs and/or their metabolites. Although urine specimens are most often used, cannabinoid testing can also be performed on blood, oral fluid, meconium, sweat, and hair.

Qualitative immunoassays are the most widely used methodology for urine drug screening. They offer a quick, easy-to-perform, and relatively inexpensive testing method with a relatively high degree of
specificity and sensitivity. Most immunoassays do not detect the primary psychoactive constituent in marijuana, THC; rather, they detect the primary inactive urinary metabolite, 11-nor-9-carboxy-Δ9-tetrahydrocannabinol (THC-COOH). Confirmation of positive immunoassay drug screens is most commonly accomplished by gas chromatography–mass spectrometry (GC-MS), which is highly sensitive and specific for drugs and their metabolites. Tetrahydrocannabinol’s lipophilic nature results in its wide distribution throughout fatty tissues of the body and its slow release from these storage tissues, making THC-COOH detectable in the urine of infrequent users for up to 2 to 5 days. Heavy, long term users can test positive up to months after their last use.

Synthetic Cannabinoids

The advent of synthetic cannabinoids and their increased use as recreational drugs has complicated drugs of abuse screening. Synthetic cannabinoids are not detected by traditional screening tests, as their chemical composition and metabolites do not cross-react with assays for THC-COOH. Most reference/toxicology laboratories are using liquid chromatography/tandem mass spectrometry (LC-MS/MS) and GC-MS, but these methods present a number of challenges such as a lack of reference standards, quality control materials, and cutoff values.

Making matters more difficult, those developing synthetic cannabinoids constantly alter the chemical structures and compounds to elude regulations and avoid legal ramifications. In an effort to develop testing and stay ahead of those making the new drugs, toxicologists and chemists in laboratories around the country spend a significant amount of time identifying the latest synthetic cannabinoids and their metabolites. Gas chromatography–mass spectrometry and LC-MS/MS can be used to identify synthetic cannabinoids, but this testing is not routinely performed in clinical laboratories because it requires expertise and takes hours to complete. Research is also being conducted to detect different classes of synthetic cannabinoids via matrix-assisted laser desorption ionization-time of flight mass spectrometry (MALDI-TOF-MS), direct analysis in real time mass spectrometry (DART-MS), nano-liquid chromatography (nano-LC), and nuclear magnetic resonance (NMR)², but these methods are not feasible for most laboratories.

Summary

Although marijuana still tops the charts as the most commonly used illicit drug worldwide, synthetic cannabinoids hold a certain appeal for drug abusers. Manufacturers of synthetic cannabinoids have successfully made compounds that are much more potent than natural cannabis, are not detectable in routine drug screening, and evade legislatures’ attempts at criminalization. Chemists and lawmakers constantly struggle to stay ahead of the manufacturers’ structural modifications of synthetic cannabinoids.
to develop laboratory testing, and laws to prohibit its use. As long as there is a market for synthetic cannabinoids, manufacturers will continue to profit from that market.

References


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