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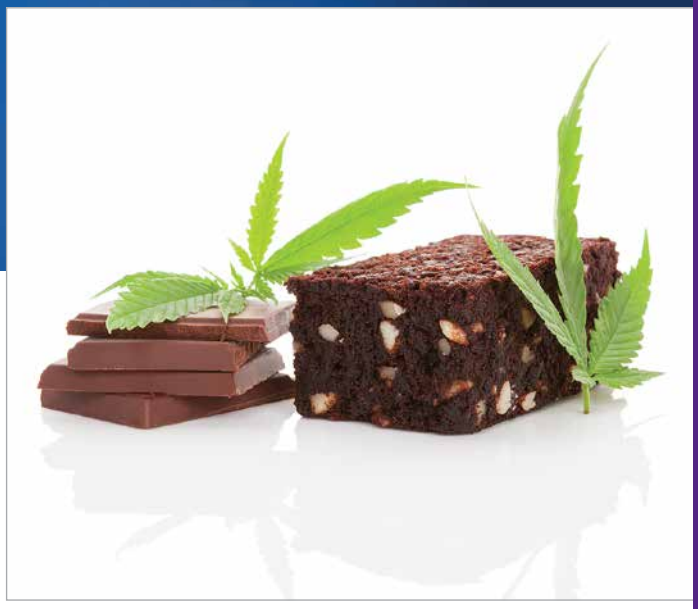

Tasty THC: Promises and Challenges of Cannabis Edibles

Daniel G. Barrus, Kristen L. Capogrossi, Sheryl C. Cates, Camille K. Gourdet, Nicholas C. Peiper, Scott P. Novak, Timothy W. Lefever, and Jenny L. Wiley

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RTI International
3040 East Cornwallis Road
PO Box 12194
Research Triangle Park, NC
27709-2194 USA

Tel: +1.919.541.6000
E-mail: rtipress@rti.org
Website: www.rti.org

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About the Authors

Daniel G. Barrus, BS, is a laboratory technician in the Pharmacology group of RTI International's Center for Drug Discovery. Mr. Barrus conducts nonclinical behavioral pharmacology and toxicology research.

Kristen L. Capogrossi, PhD, is a research economist in RTI's Food, Nutrition, and Obesity Policy Research Program. Dr. Capogrossi conducts economic analysis of nutrition policy, food safety regulation, food production and marketing, and related areas using econometrics, simulation modeling, statistical analysis, and other methods.

Sheryl C. Cates, BA, a senior research policy analyst in RTI's Food, Nutrition, and Obesity Policy Research Program, has more than 25 years of experience conducting consumer behavior research related to nutrition and food safety. She conducts studies to assess consumer use and understanding of labeling features and response to alternative label formats. Her research also assesses the impact of educational interventions on outcomes related to healthy eating and foodborne illness prevention.

Camille K. Gourdet, JD, MA, is a public health research policy analyst in the Center for Health Policy Science and Tobacco Research at RTI International. She has worked with the US Food and Drug Administration's Center for Tobacco Products evaluating state and local tobacco control policies, and has served as project manager on two internally funded nationwide surveys to gather the opinions of adults around the country about marijuana use and legalization and the types of e-cigarette products adolescents use most often.

Nicholas C. Peiper, PhD, is a research epidemiologist in RTI International's Behavioral and Urban Health Program. His research concentrates on the etiology, correlates, and consequences of psychiatric disorders, with a particular focus on early intervention for adolescents and young adults. Dr. Peiper works with Dr. Scott Novak on National Institutes of Health (NIH)- and SAMHSA-funded grants related to prescription drugs, injection drug use, marijuana, and psychiatric comorbidity.

Scott P. Novak, PhD, is a senior research public health analyst in RTI's Behavioral Health Research Division. His current work focuses on characterizing the epidemiological trends and identifying the at-risk populations for prescription drug abuse and co-occurring illicit drug use.

Timothy W. Lefever, MA, manages RTI International's Neurobehavioral Laboratory. Mr. Lefever has been conducting preclinical behavioral research for over 13 years and has been testing the effects of cannabinoids in these models extensively during the past 5 years.

Jenny L. Wiley, PhD, is a leading expert in behavioral pharmacology. Dr. Wiley designs and supervises a program of in vivo research at RTI International, including the synthesis and development of candidate medications and investigation of neural mechanisms underlying substance abuse. She also conducts independent NIH grant-supported research in the area of cannabinoid pharmacology.

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Abstract

Food products containing cannabis extract (edibles) have emerged as a popular and lucrative facet of the legalized market for both recreational and medicinal cannabis. The many formulations of cannabis extracts used in edibles present a unique regulatory challenge for policy makers. Though edibles are often considered a safe, discreet, and effective means of attaining the therapeutic and/or intoxicating effects of cannabis without exposure to the potentially harmful risks of cannabis smoking, little research has evaluated how ingestion differs from other methods of cannabis administration in terms of therapeutic efficacy, subjective effects, and safety. The most prominent difference between ingestion and inhalation of cannabis extracts is the delayed onset of drug effect with ingestion. Consumers often do not understand this aspect of edible use and may consume a greater than intended amount of drug before the drug has taken effect, often resulting in profoundly adverse effects. Written for the educated layperson and for policy makers, this paper explores the current state of research regarding edibles, highlighting the promises and challenges that edibles present to both users and policy makers, and describes the approaches that four states in which recreational cannabis use is legal have taken regarding regulating edibles.

Introduction

To provide a better understanding of the implications of increased use of edible cannabis products, we describe promises and challenges associated with use of cannabis-infused edibles and critically examine extant research on factors related to their use. We have blended science and regulatory factors in order to provide an overview of edibles for the educated layperson and for policy makers. Although some of the issues discussed are relevant for other methods of cannabis use (e.g., smoked, vaped), we emphasize issues primarily related to cannabis-infused edibles. Further, our discussion primarily focuses on consequences of intentional use of edibles in adults.

Medicinal Cannabis Use

Marijuana (or cannabis) is the most commonly used illicit drug in the United States, with 9.5 percent of adults and 23.7 percent of youth reporting use within the past year 2015 (Hasin et al., 2015; Johnston, O'Malley, Miech, Bachman, & Schulenberg, 2016). Further, the population of users is increasing, a finding that is associated with decreased perception of harm from cannabis use (Johnston et al., 2016; Miech et al., 2015; Okaneku, Vearrier, McKeever, LaSala, & Greenberg, 2015) and legalization of medicinal and/or recreational use by a number of states (Cerda, Wall, Keyes, Galea, & Hasin, 2012). As additional initiatives to decrease or eliminate criminal penalties for possession of small amounts of cannabis are already pending in several states, this trend is likely to continue, at least in the short term.

In 1996, California became the first state to legalize medicinal use of cannabis. By April 2016, 24 states and the District of Columbia had passed laws that allow medicinal use, and four states (Alaska, Colorado, Oregon, and Washington) had legalized recreational use, with several other states likely to vote on legalization later in 2016. The District of Columbia has decriminalized the possession of cannabis in amounts of 2 ounces or less but has not established a regulatory framework that allows for recreational cannabis sales (D.C. Code § 48-904.01, 2016). Although specific laws governing cultivation and regulating dispensaries vary across states (Fairman, 2016), most states distinguish between medicinal and recreational use of cannabis.

Medicinal use of cannabis involves obtaining a prescription for cannabis from a licensed medical professional for treatment of a medical issue (e.g., pain, muscle spasm, weight loss due to serious illness, childhood epilepsy). Unlike medications approved through a formal data-driven process by the US Food and Drug Administration (FDA), medicinal cannabis dosage is not specified. Possession of a medicinal cannabis card allows purchase, with details dependent upon state law (e.g., approved conditions and amount allowed to possess).

In contrast, recreational use is defined as use that is not for a specified medical purpose, but rather with the goal of getting "high" (i.e., altering the user's state of mind). However, the two groups of users show considerable overlap: self-medication is common among recreational users (O'Connell & Bou-Matar, 2007; Osborn et al., 2015), and adults who use medicinal cannabis may report prior recreational use (Bostwick, 2012; O'Connell & Bou-Matar, 2007).

Perhaps the largest area of difference between the two types of use is in the disparate regulatory requirements, including taxation. While medicinal and retail cannabis products are similar, regulations may vary between the two marketplaces. For example, only state residents who have a medicinal cannabis card can legally buy medicinal cannabis in Colorado without minimum age restrictions, but any adult aged 21 and older can purchase retail cannabis products in person from cannabis stores, regardless of state of residence (Monte, Zane, & Heard, 2015; 1 Colo. Code Regs. § 212-1, 2016). While popular perception of cannabis use calls up images of smoking a joint or pipe, cannabis has been formulated to allow for other modes of administration, including oral and topical use. In particular, the use of edible cannabis products has been highlighted as an issue of concern, principally in states where cannabis has been legalized (MacCoun & Mello, 2015; Monte et al., 2015).

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Overview of Edibles

Edibles are food products infused with cannabis extract. Edibles come in many forms—including baked goods, candies, gummies, chocolates, lozenges, and beverages—and may be homemade or prepared commercially for dispensaries.

At a basic level, extraction of cannabinoids (such as Δ^9-tetrahydrocannabinol, or Δ^9-THC, and cannabidiol, or CBD) from the cannabis plant involves heating the flowers from the female plant in an oil-based liquid. Although Δ^9-THC is considered to be the major psychoactive ingredient of the cannabis plant responsible for the "high" that users experience (Gaoni & Mechoulam, 1964), the plant contains this chemical primarily in its nonpsychoactive acid form, Δ^9-tetrahydrocannabinolic acid (THCA). Heating is required to convert THCA into Δ^9-THC. Once Δ^9-THC is formed, it diffuses out of the plant and dissolves into the oily liquid, along with other cannabinoids that are present in the plant (such as CBD). The extraneous plant material is then discarded. Recipes for using the resulting cannabinoid-infused oil abound on the internet and in various specialty publications. Cannabinoid-infused oil may also be purchased directly from many dispensaries and retail shops.

Edibles have become popular among users in states where cannabis is legal for recreational or medicinal purposes (or both). For example, in Colorado in 2014, 1.96 million units of edible medicinal cannabis-infused products and 2.85 million units of edible retail cannabis-infused products were sold, which accounted for about 45 percent of the total cannabis sales in the state (Brohl, Kammerzell, & Koski, 2015). Because direct purchase of cannabinoid-infused oil or cannabis used to make homemade edibles is not tracked as an edibles purchase, the actual use of edibles is likely underestimated when examining purchase data. Furthermore, these data show sales but do not reflect the proportion of cannabis users who consume edibles. In addition, the extent to which the retail edibles were used by the purchaser or transferred to someone in another state for medicinal or recreational use is unknown.

Survey data can be used to determine an estimate of actual consumption of edibles, which account for a substantial percentage of current cannabis use in both medicinal and recreational user groups. In general, use of edible cannabis appears more prevalent in states that have legalized medicinal cannabis use, particularly those states that have had legalized medicinal use in place for a longer time, as well as in legalized-medicinal-use states with more dispensaries per capita (Borodovsky et al., 2016). In a nationally representative study of adults in the US, 29.8 percent of respondents who had ever used cannabis reported consuming it in edible or beverage form (Schauer, King, Bunnell, Promoff, & McAfee, 2016). Additional research finds that edibles are especially popular with medicinal cannabis users (Pacula, Jacobson, & Maksabedian, 2015) as well as with the Baby Boomer generation (Murphy et al., 2015). Surveys conducted in several US states (California, Washington, and Colorado) and Canada found that 11 percent to 26 percent of medicinal cannabis users had consumed an edible cannabis product during their lifetimes (Grella, Rodriguez, & Kim, 2014; Walsh et al., 2013).

Anecdotal reports attribute increased interest in edibles to several perceptions shared by users: (1) edibles are a discreet and more convenient way to consume cannabis; (2) edibles offer a "high" that is calmer and more relaxing than smoking cannabis; and (3) edibles avoid the harmful toxins and health risks that come with smoking cannabis. However, scientific evaluation of the accuracy of these perceptions is incomplete.

Promises of Edibles

A fundamental reason for cannabis use via any route of administration is to "feel better," a subjective assessment that may range from feeling "high" (e.g., recreational use) to alleviating an unpleasant subjective state (e.g., anxiety) or ameliorating a physical symptom or condition that produces pain or disability (e.g., spasticity, glaucoma). The vast majority of research on the therapeutic efficacy of cannabinoids has been conducted using oral preparations formulated by pharmaceutical companies for the treatment of these conditions.

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Preparations include dronabinol (Marinol) and nabilone (Cesamet), synthetic analogs of Δ^9-THC, and nabiximols (Sativex), a cannabis-derived oromucosal spray containing Δ^9-THC and CBD (a nonpsychoactive constituent of the cannabis plant) in a 1:1 ratio.

This research has focused primarily on a handful of the multitude of medical conditions and symptoms for which the benefits of cannabis have been proclaimed anecdotally, including muscle spasm and chronic pain (Borgelt, Franson, Nussbaum, & Wang, 2013; Harrison, Heritier, Childs, Bostwick, & Dziadzko, 2015), nausea and vomiting (Smith, Azariah, Lavender, Stoner, & Bettiol, 2015), epilepsy (Friedman & Devinsky, 2015), appetite stimulation (Gorter, 1999), cancer (Pacher, 2013), and several psychiatric disorders (e.g., post-traumatic stress disorder, anxiety, depression; Betthauser, Pilz, & Vollmer, 2015; Zlebnik & Cheer, 2016). To date, the quality of evidence supportive of cannabinoid treatment for spasticity and chronic pain has been moderate, whereas only low-quality evidence was available to support its use for nausea and vomiting and for weight gain in patients with HIV/AIDS or cancer (for a review, see Whiting et al., 2015).

However, all of these conclusions come with a strong caveat: well-controlled clinical studies on the therapeutic effectiveness of cannabis and its constituents are sparse or (dependent upon condition) nonexistent, primarily due to the US Drug Enforcement Agency's classification of cannabis as a Schedule I drug (i.e., defined as having "no medical use"; US DEA, n.d.). However, the increased state-level legalization of cannabis for medicinal or recreational purposes may serve as an impetus for funding additional high-quality studies on the effects of cannabis on health and in treatment of disease.

Despite initial support for the efficacy of oral cannabinoid medication, many medicinal cannabis patients prefer to smoke cannabis (Grella et al., 2014; O'Connell & Bou-Matar, 2007). Nonusers report a greater incidence of negative subjective responses following use of oral Δ^9-THC, especially at higher doses (Calhoun, Galloway, & Smith, 1998; Haney, 2007). Further, in clinical trials of nabiximols, 80 percent of participants who reported adverse effects experienced these effects within the first 28 days of treatment, although incidence of adverse effects was reduced when dose was increased gradually (reviewed in Robson, 2011).

Regular cannabis users also find the effects of oral Δ^9-THC to be qualitatively different from those of smoked cannabis (Calhoun et al., 1998). For example, among HIV/AIDS patients who had tried both cannabis and dronabinol, 93 percent preferred smoking cannabis to taking dronabinol (Ware, Rueda, Singer, & Kilby, 2003). More recently, Cooper and colleagues (2013) found that, while a high dose (20 milligrams [mg]) of dronabinol resulted in a "high" that was liked and resulted in willingness to take the drug again, ratings following a moderate dose (10 mg) of dronabinol did not differ significantly from placebo. Both low and high doses (1.98 and 3.56 percent Δ^9-THC) of smoked cannabis resulted in significantly higher ratings for these effects.

By contrast, several double-blind studies report comparable subjective effects for dronabinol and smoked cannabis when dose and time after administration are taken into account (Haney et al., 2007; Haney, Rabkin, Gunderson, & Foltin, 2005; Issa et al., 2014). One complication with these comparisons is that dronabinol contains only a synthetic version of Δ^9-THC, whereas cannabis contains Δ^9-THC plus a multitude of cannabinoids and other chemicals, including terpenes and cannaflavins (Russo, 2011).

Few laboratory studies have been undertaken using actual cannabis-infused edibles. In one such study, conducted by Cone and colleagues (Cone, Johnson, Paul, Mell, & Mitchell, 1988), subjects with a history of cannabis use received cannabis-infused brownies and completed a series of behavioral and physiological measures of drug effect. Participants experienced drug effects that were rated as favorable, with peak responses occurring an average of 3 hours after ingestion and effects dissipating within 24 hours. Physiological measures of drug effect (i.e., pulse, blood pressure, and pupil dilation), however, were not statistically different from placebo. Although more recent research on the subjective effects of oral administration of cannabis is lacking, one study found that nabiximols, which contains a

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1:1 ratio of Δ^9-THC and CBD, produced slightly lower pleasurable subjective cannabinoid effects than dronabinol did (Schoedel et al., 2011). In sum, ingestion and smoking of Δ^9-THC seem to produce similar subjective effects, and CBD may attenuate these effects, at least in experienced cannabis users.

Certainly, the continued use of edibles despite initial nonpreference by many users suggests other advantages of this route of administration. One of these advantages may be the longer duration of action for edibles (Huestis, 2007). Early research comparing the effects of different Δ^9-THC delivery methods showed that ingestion of a chocolate cookie containing Δ^9-THC produced a longer-lasting and less intoxicating effect than smoking and intravenous administration (Hollister et al., 1981). A recent laboratory study of daily recreational cannabis smokers similarly demonstrated that oral Δ^9-THC resulted in a longer duration of analgesic effect than the relatively transient effect produced by smoked cannabis (Cooper et al., 2013).

For medicinal cannabis users with chronic conditions, an extended duration of action might be helpful in the workplace because smoking cannabis in public is often still prohibited, even in states where medicinal cannabis use is legal (e.g., Ariz. Rev. Stat. § 36-2814, 2016; Cal. Health & Safety Code § 11362.785, 2016; Del. Code Ann. tit. 16 § 4907A, 2016; Haw. Rev. Stat. Ann. § 329-122, 2016). In addition, despite an overall increase in acceptance of cannabis, qualitative studies indicate that patients still report perception of stigma associated with its use (Bottorff et al., 2013; Gates, Copeland, Swift, & Martin, 2012; Satterlund, Lee, & Moore, 2015). Adolescent female recreational users also expressed concern about the lingering odor of cannabis following smoking (Friese, Slater, Annechino, & Battle, 2016). Edibles avoid issues of odors and stigma because they can be consumed discreetly. For example, medicinal users may choose to consume edibles during the work week and smoke or vape when not at work. Consumers may also favor edibles because they are easier to transport, particularly into states where their use is not legal.

One of the most significant factors in the decision to use cannabis-infused edibles is the perception that edibles avoid the harmful toxins and health risks that may be associated with smoking (Murphy et al., 2015). Because the health risks associated with smoking tobacco are substantial (reviewed in Center for Disease Control and Prevention, 2010), the risks of smoked cannabis are often assumed to be similarly severe. However, the accuracy of this assumption is unclear.

Qualitatively, cannabis smoke and tobacco smoke seem similar in toxicity, given that both contain a variety of toxins and known carcinogens (Moir et al., 2008). Further, exposure to cannabis smoke is associated with lung inflammation and bronchitis in humans (reviewed in Reece, 2009; Tashkin, 2005) and with increased oxidative stress and cytotoxicity in animal models of pulmonary function (Maertens, White, Williams, & Yauk, 2013). Although lung inflammation may predispose users to pulmonary infection, the degree to which these changes in lung function may lead to chronic pulmonary disease (e.g., chronic obstructive pulmonary disorder) is unclear (Tashkin, 2005). Epidemiological research has linked habitual cannabis smoking to several forms of cancer (Callaghan, Allebeck, & Sidorchuk, 2013; Hashibe et al., 2005). However, determination of the degree to which cannabis use contributes to development of cancer is complicated by factors such as small sample size and the presence of confounds such as co-occurring tobacco smoking (Volkow, Baler, Compton, & Weiss, 2014). At any rate, eating cannabis-infused edibles does not seem to affect pulmonary function or to increase cancer risk, which provides a solid rationale for choosing this route of administration as opposed to smoking cannabis, particularly for medical conditions such as cancer.

Yet use of cannabis-infused edibles is not without its own set of challenges. In addition to health issues that are likely confined to smoking cannabis, research has suggested that regular cannabis use may have detrimental effects on brain development, psychiatric health, and heart health (Volkow et al., 2014). In the next section, we describe some of the challenges associated with use of edibles.

Challenges of Edibles

Despite the potential promises of edibles for treatment of a variety of ailments, there are also dangers inherent in edible use that present challenges for users and policy makers. Although ample experimental evidence demonstrates that cannabis is not particularly lethal (reviewed in Grotenhermen, 2003, 2007) and, to date, no deaths have been directly attributed to the acute physical toxicity of cannabis, episodes of severe cannabis-induced behavioral impairment are common, experienced by 65 percent of medicinal cannabis users (Novak, Peiper, & Wenger, 2015). These overdoses are highly aversive experiences that can result in cognitive and motor impairment, extreme sedation, agitation, anxiety, cardiac stress, and vomiting (Galli, Sawaya, & Friedenberg, 2011; Grotenhermen, 2007; Hall & Solowij, 1998). Most troubling, high quantities of Δ^9-THC are reported to produce such transient psychotic symptoms as hallucinations, delusions, and anxiety in some individuals (reviewed in Wilkinson, Radhakrishnan, & D'Souza, 2014).

Generally, in healthy adult users, psychotic symptoms brought on by an overdose of cannabis last only for the duration of intoxication, but in some cases, these symptoms can persist for as long as several days. Literature regarding such cases of "cannabis-induced psychosis" is limited, but the condition is believed to be the result of overconsumption of Δ^9-THC, and many of the reported cases occur following ingestion of an edible (Bui, Simpson, & Nordstrom, 2015; Favrat et al., 2005; Hudak, Severn, & Nordstrom, 2015).

Factors directly related to the oral route of administration of edibles may contribute to this finding of a strong association between edible use and overconsumption. Route of administration is a fundamental variable in determining a drug's pharmacokinetics, which is defined as the time course and process through which a chemical (such as Δ^9-THC) enters the body, travels to various tissues and organs, and is metabolized before elimination. Edibles introduce cannabinoids through the gastrointestinal tract. From the gut, Δ^9-THC is absorbed into the bloodstream and travels via the portal vein to the liver, where it undergoes first-pass metabolism. Here, liver enzymes (primarily the cytochrome P450 system) hydroxylate Δ^9-THC to form 11-hydroxytetrahydrocannabinol (11-OH-THC), a potent psychoactive metabolite that readily crosses the blood-brain barrier (Mura, Kintz, Dumestre, Raul, & Hauet, 2005). 11-OH-THC is more potent than Δ^9-THC (Hollister, 1974; Hollister et al., 1981) and appears in blood in higher quantities when Δ^9-THC is ingested than when it is inhaled (Huestis, Henningfield, & Cone, 1992); hence, it may be responsible for the stronger and longer-lasting drug effect of edibles vis-à-vis comparable doses of smoked cannabis (Favrat et al., 2005).

When inhaled through smoking or vaping, Δ^9-THC reaches the brain, takes initial effect within minutes, and shows peak effect in about 20 to 30 minutes, with psychoactive effects tapering off within 2 to 3 hours (Grotenhermen, 2003; Huestis, Sampson, Holicky, Henningfield, & Cone, 1992). Although it takes longer for the initial psychoactive effect of edibles (30 to 90 minutes) to be felt, the resulting "high" is longer-lasting, with a peak at 2 to 4 hours after ingestion (Grotenhermen, 2003). Factors such as weight, metabolism, gender, and eating habits also contribute to how soon and for how long someone will feel intoxicated following oral ingestion (Grotenhermen, 2003; Huestis, 2007).

The amount of Δ^9-THC in edibles can vary across a single product and across batches formulated at different times, making it difficult for users to estimate how much Δ^9-THC they consume. Indeed, compared with smoking or intravenous infusion, with oral administration of cannabis the Δ^9-THC concentration in the plasma is lower and the correlation between the plasma concentration of Δ^9-THC and degree of intoxication varies considerably across individuals (Hollister et al., 1981). Lower Δ^9-THC in the plasma may be the result of low bioavailability (i.e., the amount of Δ^9-THC that reaches circulation after oral administration is only 6-10 percent of the amount contained in the product; Schwilke et al., 2009). The lack of consistency and the delayed intoxication may cause both new and experienced users of cannabis to consume higher than intended amounts of the drug. Edible products

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are responsible for the majority of health care visits due to cannabis intoxication, which is likely due to the failure of users to appreciate the delayed effects (Monte et al., 2015).

The fact that users of edibles often unintentionally ingest greater than intended amounts of Δ^9-THC demonstrates the difficulty of dose titration with edibles, an issue that is not typically of concern with smoked cannabis due to its rapid distribution into the brain. The Δ^9-THC dose in homemade products depends upon the concentration of THCA in the plant from which it is extracted or the Δ^9-THC concentration in purchased oil. However, when Δ^9-THC is obtained from an extraction process, extraction of cannabinoids is usually not complete, which complicates estimates of dosage in the resulting cannabis-infused oil. Consequently, Δ^9-THC concentrations may not be available for products made using homemade oils or may not be accurate if a purchased oil is mislabeled.

Similarly, dosage estimation for retail products may also be inexact (e.g., see Vandrey et al., 2015). While state laws often require that total milligrams of Δ^9-THC and number of servings be included on packages available for retail sale, a single chocolate bar could contain 100 milligrams (10 servings) of Δ^9-THC. In addition, products available for medicinal cannabis patients may not have limits on maximum Δ^9-THC content per serving (Brohl et al., 2015). Hence, regardless of reason for use, only a small amount of the product may be needed to reach the maximum recommended dose of 10 mg/serving. Anecdotal reports from medicinal cannabis patients confirm that even daily users may consume a higher dose than expected (Hudak et al., 2015). Patients reported that, having eaten the suggested serving size initially, they consumed the entire edible product after not feeling any effects. They also reported that it was practical to consume the entire edible product in one sitting, just as they would a normal baked good (Hudak et al., 2015), suggesting a lack of consumer understanding, even among daily cannabis users.

The challenge of dose titration is further compounded by the high degree of variability observed in individual responses to ingested Δ^9-THC. Clinical studies of dronabinol, an orally administered pharmaceutical stereoisomer of Δ^9-THC, have shown that, for some individuals, 2.5 mg is sufficient to produce recognizable effects, while for others, higher doses are necessary—in some cases daily doses exceeding 50 mg (reviewed in Grotenhermen, 2001). Because of this variability, computation of an exact pharmacologic equivalency between a given mass of Δ^9-THC contained in smoked cannabis and a mass of Δ^9-THC contained in an edible is extremely difficult.

An independent report commissioned by the Colorado Department of Revenue used data from Colorado's cannabis market and clinical research findings to develop one such metric for calculating dose equivalency across methods of cannabis delivery (Orens, 2015). Application of this metric to laboratory analysis of edibles and smokable cannabis available in Colorado suggests that 1 mg of Δ^9-THC contained in an edible produces a behavioral effect similar to 5.71 mg of Δ^9-THC contained in smokable cannabis. Current regulations in Colorado and Washington define a single serving of an edible as a unit containing no more than 10 mg of Δ^9-THC. In order to minimize risk of accidental overdose, it is recommended that users of edibles gradually up-titrate their dose until they find an effective dose. It is important to note that evidence suggests that tolerance to the intoxicating effects of oral Δ^9-THC develops after sustained exposure to high doses (reviewed in Grotenhermen, 2003).

Another concern surrounding the use of edibles is that some products available for retail sale are packaged to resemble commercially available products in forms that may be appealing to children (e.g., gummy candies, lollipops, cookies). Thus, children, as well as adults and household pets (Meola, Tearney, Haas, Hackett, & Mazzaferro, 2012), may unintentionally consume edibles if they are not properly safeguarded. A review of data from the National Poison Data System from 2005 to 2011 found that decriminalization of cannabis was associated with increased reports of unintentional exposures in young children (up to 9 years of age; Wang et al., 2014). Cannabis-related calls to poison control centers in decriminalized states increased by 30.3 percent per year, and states undergoing

transition to decriminalization had an average increase of 11.5 percent per year. In contrast, the rate of cannabis-related calls to poison control centers in nonlegal states showed an average increase of only 1.5 percent per year from 2005 to 2011 (Wang et al., 2014). A more recent review of National Poison Data System data showed similar increases in edibles-related calls to poison control centers from 2013 to 2015 (Cao, Srisuma, Bronstein, & Hoyte, 2016), which suggests that accidental exposures may become more common as more states legalize recreational or medical cannabis use.

However, despite the increases in calls to poison control centers, emergency room visits resulting from pediatric exposure to cannabis remain relatively low, even in decriminalized states. For instance, between 2005 and 2009 (before recreational legalization), the Children's Hospital Colorado emergency department saw no cases of accidental ingestion. In 2013, the same emergency department treated eight children (mostly under the age of 3) who ingested edible cannabis. The number increased to 14 children in 2014 (Baskfield, 2015). Another emergency department in Colorado showed an increase in visits from 0 percent to 2.4 percent among children younger than 12 years for symptomatic unintentional cannabis exposure following legislation in October 2009 that expanded decriminalization of medicinal cannabis (Wang et al., 2014). Not unexpectedly, ingestion was the most common route of exposure resulting in most of these emergency room visits (Wang et al., 2014).

In addition to emergency room visits by children, the number of cannabis-related emergency room visits by adult non-Colorado residents compared with those by in-state residents has also increased since recreational cannabis use was legalized in Colorado. Out-of-town patient visits to a hospital in Aurora, Colorado, for health issues following consumption of edibles almost doubled from 85 per 10,000 visits in 2013 to 168 per 10,000 visits in 2014; statistically significant differences were not observed for Colorado residents during the same time period (Kim et al., 2016). The study authors attributed the increase in emergency room visits from out-of-town visitors relative to in-state residents to higher potency of industrially cultivated cannabis and visitors' unfamiliarity with edible cannabis products.

Reports of inadvertent ingestion of cannabis edibles by adults are widespread. For example, a group of preschool teachers in California experienced nausea, dizziness, headache, and other symptoms after consuming brownies containing cannabis. One of the teachers had purchased the brownies from a sidewalk vendor and placed them in the breakroom (Fogleman et al., 2009). In focus groups with teenagers, females who did not use cannabis expressed more concern than female cannabis users and males (users and nonusers) about edibles and compared them to drinks that could be spiked with drugs (Friese et al., 2016).

Tragically, at least one death has occurred following ingestion of an edible cannabis product. In March 2014, a 19-year-old man died as a result of injuries sustained when he jumped from a fourth floor balcony after consuming a cannabis-infused cookie in the state of Colorado (Hancock-Allen, Barker, VanDyke, & Holmes, 2015). The sales clerk instructed the man to eat one serving of the cookie (equal to one-sixth of the cookie and containing approximately 10 mg of Δ^9-THC). However, having not felt intoxicated within 60 minutes, the man ate the whole cookie within 2 hours of ingesting the initial serving. The autopsy identified cannabis intoxication as a chief contributing factor in the man's death. Since this incident, Colorado initiated new packaging and labeling rules requiring that recreational cannabis products contain no more than 100 mg of Δ9-THC and have clear demarcation of each standardized 10-mg serving (1 Colo. Code Regs. § 212-2, 2016). Similar requirements are in place for Washington State (Wash. Admin. Code §§ 314-55-095, 314-55-105, 2016). Additionally, consumer advocacy groups and states have launched campaigns to educate consumers about the potential dangers of consumption (Subritzky, Pettigrew, & Lenton, 2016).

Another challenge related to edibles is the perception that they represent food products containing cannabis, when in reality the cannabis extracts used to produce edibles can be very different from the actual plant material used for smoking. Myriad techniques are used to extract cannabinoids from

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the cannabis plant in a form that can be integrated into the countless forms that edibles can take, resulting in considerable variation in the amount and homogeneity of cannabinoids that make it into the final products.

The cannabis plant contains hundreds of chemical constituents, including around 100 cannabinoids (Radwan et al., 2015), and some scientists have suggested that dozens, if not hundreds, of these compounds function in concert (the "entourage effect") to produce a greater therapeutic effect than any single compound in isolation (reviewed in Russo, 2011). Many of these compounds are eliminated during the processes used to make oils and butters from cannabis, such that edibles may contain high amounts of Δ^9-THC and only a fraction of the cannabis plant's other constituents.

Although little research has examined how the hundreds of compounds found in cannabis interact when combusted and inhaled, studies of Δ^9-THC in isolation suggest that it is responsible not only for the "high" experienced by cannabis users (Hart et al., 2002), but also for the negative psychiatric effects that may be induced by cannabis exposure—that is, its psychosis-like and anxiogenic effects (D'Souza et al., 2004). Other cannabinoids, most notably cannabidiol (CBD), are believed to modulate these effects (Russo, 2011; Schubart et al.), although not all research has supported this idea (Haney et al., 2016). Nevertheless, when edibles contain high concentrations of Δ^9-THC and low concentrations of CBD and other cannabinoids, their users may be at higher risk of experiencing adverse effects.

For consumers, and especially medicinal cannabis users, knowing the precise amounts and relative concentrations of Δ^9-THC and CBD in edibles is vital, as this information largely determines the drug effects that users will experience. Yet, despite evidence of the value of including CBD in edibles, especially those intended for medicinal use, few edible manufacturers report the CBD content of their products. Further, even among products reported to contain CBD, many contain only trace amounts or none at all (Vandrey et al., 2015). In fact, although the FDA has yet to acknowledge the therapeutic applications of the cannabis plant, it has issued warning letters to several manufacturers of products purported to contain CBD. These actions by the FDA highlight the lack of consistency in formulation and labeling of cannabis products.

Unfortunately, inaccuracies in labeling and inconsistencies in formulation are not limited to CBD but also extend to the Δ^9-THC content of edibles. In early 2014, an investigative report from the Denver Post found that the actual Δ^9-THC content of retail edibles often differed significantly from the amounts claimed on product labels (Baca, 2014). Following these findings, the state of Colorado in mid-2014 instituted a requirement that Δ^9-THC concentration for recreational edibles be assessed and reported on the label (Brohl et al., 2015; 2014 Colo. Reg. Text 12885, amending 1 Colo. Code Regs. § 212-2). However, Colorado mandated threshold testing only, which does not measure label accuracy but merely ensures that recreational edibles do not contain more than 100 mg of Δ^9-THC (1 Colo. Code Regs. § 212-2, 2016). This regulation was not originally applied to cannabis sold for medicinal purposes, but effective July 1, 2016, medicinal edible products are only allowed to contain up to 100 mg of Δ^9-THC as well (1 Colo. Code Regs. § 212-1, 2016). Consequently, total Δ^9-THC content in medicinal cannabis edibles may vary substantially from labeled amounts. For example, one study of medicinal edibles sold in California and Washington found that the total Δ^9-THC content of 83 percent of edibles tested differed from labeled amounts by over 10 percent, with more than one-half of these products containing significantly less Δ^9-THC than claimed and nearly one-quarter containing significantly more (Vandrey et al., 2015).

The persistent pattern of inaccuracies in the labeling of Δ^9-THC and CBD content in edibles reflects the broader issue of a lack of standardization in formulation and quality control throughout the edibles industry. Because cannabis is illegal at the federal level, the recreational and medicinal cannabis industries are not subject to federal quality control regulations, but rather are regulated on a state-by-state basis. Consequently, the edibles sold at medicinal and recreational dispensaries do not face

the stringent quality control measures that are used to ensure the quality and consistency of medications or other legalized drugs (e.g., alcohol and tobacco) and, currently, the rules governing the manufacturing and labeling of edibles vary dramatically from state to state.

Even if accurate drug content labeling for edibles can be achieved, this information is only useful if it is used and understood by consumers. A nationally representative survey of US adults conducted by the US FDA found that 50 percent of adults reported that they often read the label on food products when buying a product for the first time and 29 percent sometimes read the label (Lin et al., 2016). Among respondents who reported that they never read labels, 59 percent strongly agreed or agreed that they do not use the information on food labels because it is too hard to understand.

A systematic review of consumer understanding and use of nutrition labeling found that although reported use of nutrition labels is high, more objective measures suggest that actual use of nutrition labels to make purchase decisions may be much lower (Cowburn & Stockley, 2005). This review found that consumers understand some of the more simple terms on nutrition labels but are confused by more complex information. For example, a study to assess consumers' understanding of percent Daily Value (%DV)[1] on food labels found that the majority of respondents could not define %DV and did not know how to use this information to select a diet low in fat (Levy, Patterson, Kristal, & Li, 2000). Rothman et al. (2006) reported that the degree of comprehension of food labels was highly correlated with literacy and numeracy skills; however, even respondents with higher literacy had difficulties interpreting labels.

Similar concerns have been identified when assessing consumer understanding of label information on prescription medications. Davis et al. (2006) found that patients with lower literacy levels and those taking a greater number of medications were less able to understand the meaning of the labels. Further, among patients who understood the labels, only a minority could correctly demonstrate how to take the medication. These findings suggest that consumers of edible cannabis products may not fully understand information provided on Δ^9-THC content and dosing.

Regulation of Edibles in States That Have Legalized Recreational Use

Because cannabis is illegal at the federal level, the recreational and medicinal cannabis industries are regulated on a state-by-state basis. As of 2016, four states (Alaska, Colorado, Oregon, and Washington) have legalized recreational sales and use. Colorado's retail cannabis outlets are regulated by the Marijuana Enforcement Division in the state's Department of Revenue, whereas the Liquor and Cannabis Board and Liquor Control Commission regulate Washington and Oregon cannabis outlets, respectively. In Alaska, the Marijuana Control Board regulates cannabis.

In 2012, Colorado and Washington became the first states to legalize retail sale, purchase, and possession of cannabis by anyone 21 and older. After voters approved legalization, the states spent more than a year setting up regulatory frameworks to develop regulatory systems. Each state put into place a tax structure and set up a licensing system to regulate the cultivation and distribution of cannabis products before allowing retail stores to begin selling to consumers in 2014. Oregon and Alaska are still in the process of establishing regulatory systems for legalized cannabis. In Oregon, the sale of edibles at retail outlets began on June 2, 2016 (Or. Admin. R. 333-008-1500, 2016). In Alaska, the first business licenses have been issued, and retail sales, including marijuana edibles, are expected to begin before the end of 2016, once the state has completed the process of licensing testing facilities (Thiessen, 2015).

Although recreational cannabis policies continue to evolve, all four states with legalized retail sales require labeling of edible cannabis products. Dependent upon the state, edibles must be labeled with specific warnings about potential harmful aspects of cannabis and/or labels that provide nutritional information. For example, warning labels or accompanying

[1] The % Daily Values (%DVs) are based on the Daily Value recommendations for key nutrients for a 2,000 calorie daily diet. The purpose of %DV is to help consumers determine whether a serving of food is high or low in a nutrient.

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material in the states of Colorado, Washington, and Alaska must state that cannabis has intoxicating effects (1 Colo. Code Regs. § 212-2, 2016; Wash. Admin. Code § 314-55-105, 2016; Alaska Admin. Code tit. 3, § 306.345, 2016). In Colorado and Oregon, edibles' labels must contain the state-designated universal symbol for cannabis (1 Colo. Code Regs. § 212-2; Or. Admin. R. 333-007-0070, 2016) and must state that their intoxicating effects may not be felt for up to 2 hours after consumption (1 Colo. Code Regs. § 212-2; Or. Admin. R. 333-007-0070). Washington and Oregon also require or will require that additional informational material be distributed to buyers of edibles with each sale or displayed on posters in the dispensary (Wash. Admin. Code § 314-55-105; Or. Admin. R. 333-008-1500, 2016). Washington State's accompanying material must include warning statements regarding health risks, keeping out of reach of children, impaired judgment, delayed activation, disclosures of pesticides, and extraction methods (Wash. Admin. Code § 314-55-105).

Nutritional information labels for edible cannabis products also vary across states. For example, Colorado (1 Colo. Code Regs. § 212-2, 2016) and Oregon (Or. Admin. R. 333-007-0070, 2016) require that edibles be labeled with a nutrition facts label similar to those on food products, listing information such as number of calories and amount of fat, whereas Washington only requires a list of ingredients (Wash. Admin. Code § 314-55-105). All four states require that information about quality control testing be made available to the consumer (1 Colo. Code Regs. § 212-2, 2016; Wash. Admin. Code §§ 314-55-103, 314-55-105; Or. Admin. R. 333-007-0090, 2016; Alaska Admin. Code tit. 3, § 306.475, 2016). Furthermore, the labels, accompanying material, or information available upon request at retail stores in Colorado, Washington, and Alaska mandate disclosure of all pesticides that were used during production (1 Colo. Code Regs. § 212-2; Wash. Admin. Code § 314-55-105; Alaska Admin. Code tit. 3, § 306.475), require the expiration or "best by" date to be included on the label (1 Colo. Code Regs. § 212-2, 2016; Wash. Admin. Code § 314-55-105; Alaska Admin. Code tit. 3, § 306.310, 2016), and require the edible product label to disclose to the consumer the solvents and chemicals that were used in the process of making the product (1 Colo. Code Regs. § 212-2; Wash. Admin. Code § 314-55-105; Alaska Admin. Code tit. 3, § 306.475).

Each of the four states with legalized retail sales also has specific requirements about how edible cannabis products are manufactured. All four states prohibit packaging edibles in a manner that appeals to children (1 Colo. Code Regs. § 212-2, 2016; Wash. Admin. Code § 314-55-155, 2016; Or. Admin. R. 845-025-7020, 2016; Alaska Admin. Code tit. 3, § 306.510, 2016), require that edible products be packaged in child-resistant packaging, require uniform distribution of Δ^9-THC throughout the product, and require inventory tracking from cultivation to retail sale (1 Colo. Code Regs. § 212-2; Wash. Admin. Code § 314-55-083; Or. Admin. R. 845-025-7540, 2016; Alaska Admin. Code tit. 3, § 306.330, 2016). Washington, Oregon, and Alaska each prohibit the manufacturing of edibles that are likely to appeal to children, such as candy (Wash. Admin. Code § 314-55-077, 2016; Or. Admin. R. 845-025-3220, 2016; Alaska Admin. Code tit. 3, § 306.510, 2016). Specifically, Washington and Oregon do not allow manufacturers to process cannabis items that are modeled after non-cannabis products consumed by children, such as cotton candy or lollipops, or that are shaped like animals, vehicles, persons, or characters (Wash. Admin. Code § 314-55-077; Or. Admin. R. 845-025-3220).

The state of Oregon does not allow extracts to be applied to "commercially available candy" or snack foods (Or. Admin. R. 845-025-3220). Alaska prohibits manufacturers from packaging any product in bright colors or with cartoon characters or other pictures that would appeal to children (Alaska Admin. Code tit. 3, § 306.510, 2016). Furthermore, pesticides are allowed under certain circumstances in all four states as long as records are kept of all pesticides used during certain stages of cultivation and manufacturing and the pesticides do not exceed the allowable amount (1 Colo. Code Regs. § 212-2, 2016; Wash. Admin. Code § 314-55-087, 2016; Or. Admin. R. 333-007-0400, 2016; Alaska Admin. Code tit. 3, § 306.475, 2016).

Conclusions and Recommendations

Edibles have emerged as a popular method of cannabinoid administration in the legalized cannabis market and have proven to be quite lucrative for states, dispensaries, and manufacturers. However, many questions remain unanswered regarding the basic effects of edibles and how consumers understand and use these products. Further research into cannabinoids, and edibles in particular, is needed so that policy makers can be well informed when establishing regulations regarding the manufacture, labeling, and sale of edibles. The need for additional regulation of edibles is evident given the frequency of cannabis overdoses and accidental pediatric exposures. Such risks can be reduced through standardization of product formulations, adequate quality control measures, and appropriate product labeling. In summary, on the production side, much remains to be done to ensure that edibles provide a consistent dosage. On the labeling side, more should be done to ensure that consumers are better educated on how edibles affect the body and that they are aware of how to use edibles safely to avoid concerns such as unintentional "highs" or "highs" lasting longer than anticipated.

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Legal Citations

Alaska

Acts prohibited at marijuana product manufacturing facility, Alaska Admin. Code tit. 3, § 306.510 (2016)

Acts prohibited at retail marijuana store, Alaska Admin. Code tit. 3, § 306.310 (2016)

Labeling of marijuana, Alaska Admin. Code tit. 3, § 306.475 (2016)

Marijuana inventory tracking system, Alaska Admin. Code tit. 3, § 306.330 (2016)

Packaging and labeling, Alaska Admin. Code tit. 3, § 306.345 (2016)

Arizona

Acts not required; Acts not prohibited, Ariz. Rev. Stat. § 36-2814 (2016)

California

Places of employment; Penal institutions; Incarcerated persons; Health insurance providers, Cal. Health & Safety Code § 11362.785 (2016)

Colorado

Adopted emergency rule, 2014 Colo. Reg. Text 12885, amending 1 Colo. Code Regs. § 212-2

Medical marijuana rules, 1 Colo. Code Regs. § 212-1 (2016)

Retail marijuana rules, 1 Colo. Code Regs. § 212-2 (2016)

Delaware

Acts not required, acts not prohibited, Del. Code Ann. tit. 16 § 4907A (2016)

Hawaii

Medical use of marijuana; conditions of use, Haw. Rev. Stat. Ann. § 329-122 (2016)

Oregon

Cannabinoid edible labeling requirements, Or. Admin. R. 333-007-0070 (2016)

CTS user requirements, Or. Admin. R. 845-025-7540 (2016)

General label requirements; Prohibitions; Exceptions, Or. Admin. R. 333-007-0090 (2016)

General processor requirements, Or. Admin. R. 845-025-3220 (2016)

Limited marijuana retail sales, Or. Admin. R. 333-008-1500 (2016)

Packaging for sale to consumer, Or. Admin. R. 845-025-7020 (2016)

Standards for testing pesticides, Or. Admin. R. 333-007-0400 (2016)

Washington

Advertising, Wash. Admin. Code § 314-55-155 (2016)

Good laboratory practice checklist, Wash. Admin. Code §§ 314-55-103

Marijuana servings and transaction limitations, Wash. Admin. Code § 314-55-095 (2016)

Packaging and labeling requirements, Wash. Admin. Code § 314-55-105 (2016)

What are the recordkeeping requirements for marijuana licensees? Wash. Admin. Code § 314-55-087 (2016)

What are the security requirements for a marijuana licensee? Wash. Admin. Code § 314-55-083 (2016)

What is a marijuana processor license and what are the requirements and fees related to a marijuana processor license? Wash. Admin. Code § 314-55-077 (2016)

Washington, DC

Prohibited acts A; Penalties, D.C. Code § 48-904.01 (2016)

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