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Changing landscape of cannabis: novel products, formulations, and methods of administration

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Abstract

Laws regulating cannabis have changed radically in the U.S. and abroad. Historically, users smoked dried cannabis flowers that contained Δ9-tetrahydrocannabinol (THC), the primary psychoactive component of cannabis, as the principal product constituent. Coincident with cannabis legalization and increased interest in medicinal use of the plant, there is now an expansive retail cannabis marketplace with novel cannabis products, formulations, and methods of administration. In this review, we describe emergent cannabis product chemotypes (e.g. THC-dominant, CBD-dominant, balanced or 'hybrid' with high concentrations of THC and CBD), product formulations (e.g. edibles, concentrates), and methods of administration (e.g. smoked, vaporized, orally ingested). Psychologists can play a pivotal role in studying the health impact of cannabis legalization and conducting research to inform product regulation.

There has been a monumental shift in the legal cannabis landscape. As of this writing, cannabis is legal for medicinal purposes in 33 U.S. states and the District of Columbia and is legal for non-medicinal (*aka* 'recreational') purposes in 10 of those states. Many other countries also permit medicinal (e.g. Australia, Israel, most of the European Union) and/or non-medicinal (e.g. Canada, Uruguay) cannabis use. As cannabis has been legalized in more places, stigma and perceived harms associated with its use have decreased [1,2]. Moreover, an unprecedented number of individuals support legalization of cannabis [3]. The combination of legislative reform and the establishment of a retail cannabis marketplace has propelled the development of novel cannabis products to compete for market share in what is arguably the fastest growing industry in the world today. This review describes the diverse array of cannabis products now available to consumers, highlights recent research related to these products, and identifies important knowledge gaps.

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Conflict of interest statement

Dr Vandrey has served as a consultant or received honoraria from Zynerba Pharmaceuticals, Insys Therapeutics, Brain Solutions Inc., Battelle Memorial Institute, and Canopy Health Innovations Inc. Dr. Bonn-Miller is a paid employee of Canopy Growth Corporation and former employee of Zynerba Pharmaceuticals. He is also a former consultant for Tilray. Dr Spindle has no conflicts of interest to declare.

Novel cannabis product chemotypes

The nomenclature for describing different types of cannabis can cause confusion. Classification of cannabis can include the cannabis species (i.e. 'Indica' versus 'Sativa'), and/or various 'strain' names like 'Jack Herer', 'Granddaddy Purple', and 'OG Kush' that ostensibly refer to distinct and carefully preserved genetic lines of cannabis. However, independent of genetics or species, variation in the environmental conditions and methods in which cannabis is grown, cultivated, or processed can substantially impact the chemical composition of the end product [4,5]. Importantly, the chemical composition, or the 'chemotype', of the drug product ultimately determines its pharmacological effects and should thus be the most important factor for product categorization [6,7•].

Although over 100 distinct cannabinoids (chemical constituents believed to be unique to the cannabis plant) have been identified, D-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) are the predominant cannabinoids found in most cannabis products [8]. Indeed, cannabis has been bred to overexpress these two cannabinoids, and most cannabis retail products can be categorized as THC-dominant, CBD-dominant, or a balanced 'hybrid' product that has high concentrations of both THC and CBD. THC is the primary psychoactive constituent of cannabis. A partial agonist at the type 1 and type 2 endogenous cannabinoid receptors, THC can foster dependence among some habitual cannabis users and drives most of the effects associated with acute cannabis intoxication (e.g. euphoria, increased appetite, memory impairment, anxiety/paranoia) [9]. THC is an approved therapeutic for the treatment of nausea and vomiting associated with chemotherapy and as an appetite stimulant for treating cachexia.

THC concentrations in cannabis products have increased over time [8], which has raised concerns about safety and addiction. Several studies have revealed an association between high potency cannabis use and elevated risk/severity of Cannabis Use Disorder (CUD) [10]. Conversely, however, epidemiological data show an overall decrease in rates of CUD among current cannabis users [11]. Many factors likely contribute to these divergent findings. The reduction in rates of CUD among current users likely reflects an increase in cannabis use for medicinal purposes, the emergence of CBD-dominant products that have low abuse liability, and an increase in use among older adults who engage in less hazardous use behaviors than young adults. Further, products with high THC potency may simply be marketed more heavily toward users at higher risk of developing CUD. Additional research is needed to determine whether, and to what extent, high THC potency in cannabis uniquely contributes to CUD risk across various types of users.

CBD, in contrast to THC, does not have a high binding affinity for endogenous cannabinoid receptors and is not associated with intoxicating or THC-like subjective drug effects [9]. CBD interacts with various receptors such as GPR55, TRPV1, and 5-HT1A, and because of its widespread mechanisms of action, CBD is purported to have therapeutic benefits for myriad health conditions including anxiety disorders, autism, and posttraumatic stress disorder [7•,12–14]. Currently, CBD is only approved by the U.S. Food and Drug Administration (FDA) for the treatment of rare seizure disorders [15]. Products containing high concentrations of CBD are often derived from hemp (defined in the U.S. as cannabis

plants with <0.3% THC) [16]. Hemp and hemp-derived products are sold widely, even in locations that do not permit medicinal or non-medicinal cannabis use. In fact, hemp and its derivative products have been removed from the list of controlled substances in many jurisdictions, including federally n the U.S. Presently, it is uncertain how hemp products intended for human consumption will be regulated by the FDA.

In addition to THC and CBD-dominant products, there is a growing market of products for which the primary chemical constituents are other, secondary cannabinoids, such as cannabigerol (CBG), the acid form of THC (THC-A), tetrahydrocannabiverin (THC-V), cannabinol (CBN), as well as terpenes (e.g. myrcene, beta-caryophyllene, limonene). Controlled research to elucidate the pharmacological effects of such less-common cannabis constituents, alone and in combination with THC/CBD, are virtually non-existent. A current controversy in the field is the so-called ‘cannabis entourage effect’, a theory which asserts that multiple chemical constituents of the cannabis plant interact synergistically, and that the therapeutic effects of whole plant products exceeds that which can be obtained from single cannabis constituents (e.g. THC, CBD) alone [7•]. For example, it is commonly alleged that CBD can mitigate acute subjective effects and impairment of cognitive functioning associated with THC exposure. Despite these reports, CBD has not altered acute effects of THC in controlled clinical studies [17••,18], though CBD has modulated anxiogenic and other THC-induced effects in pre-clinical rodent models [19]. Overall, controlled empirical data to support or refute the cannabis entourage effect theory are lacking, particularly for cannabis constituents beyond THC and CBD.

Novel product formulations and methods of administration

Historically, the use of cannabis predominantly consisted of dried cannabis flowers being smoked using instruments such as cigarettes (*aka* joints, blunts), pipes, or water pipes (*aka* bongs) [20]. Smoked cannabis remains the most popular method of administration, even in states that permit legal cannabis use [21••,22,23]. However, raw cannabis is now being processed into a variety of product formulations (foodstuff, tinctures, concentrates, and so on), which may be administered with vaporizers, orally ingested, applied topically, or administered via other routes.

Oral cannabis products (‘Edibles’)

Oral cannabis products, or ‘edibles’, come in a variety of forms. Both THC and CBD-dominant cannabis-infused food/drink products are widely available, and are particularly popular in places where a legal retail cannabis infrastructure exists [22,23,24•]. In addition to food products, cannabis oils and tinctures intended for oral ingestion are also common, especially for CBD-dominant products. Between 30 and 47% of adult and approximately 61% of adolescent cannabis users have consumed edibles [21••,25,26]. Women, older adults, and individuals who use cannabis for medicinal purposes are more likely to prefer cannabis edibles to other administration methods compared with men and younger users [27–29]. Edible users cite less perceived health risk compared with smoking, stronger drug effects, ability to use discretely, and facilitation of sleep as reasons for preferring these products [30,31]. Users report that drug effects from the use of edibles are often unpredictable (i.e.

either too weak or too strong) [30]. The unpredictable nature of drug effects associated with edible use may be due to the fact that labeling for THC and CBD content is often inaccurate for these products [32•,33•].

Vaporized cannabis

Similar to the recent migration from tobacco cigarettes to e-cigarettes for many tobacco users, numerous cannabis users have switched from using smoked instruments to using cannabis vaporizers. These devices heat dried cannabis or cannabis extracts which aerosolizes cannabinoids/terpenes for inhalation. Because vaporizers typically operate at temperatures that do not combust the cannabis product being inhaled, they expose cannabis users to fewer toxicants (e.g. carbon monoxide) compared to smoked methods [34,35]. Recent national surveys ndicate that 44% of adolescents cannabis users and 33% of adults cannabis users report ever having used cannabis vaporizers, with men and residents of states permitting legal cannabis use more likely to use these devices [21••,22,23,27,36]. As with edibles, vaporizer use is common among medicinal cannabis users [28,29,37]. Motivations to use vaporizers include lower perceived health risk, better taste, stronger drug effects, and increased ability to conceal/hide use (e.g. reduced smell) compared to smoked cannabis [36,38]. Users of cannabis vaporizers report fewer respiratory symptoms compared to those who predominantly smoke cannabis, but the comparative long-term health effects between regular users of smoked versus vaporized cannabis remain unclear [39].

Cannabis concentrates

Concentrated extracts of cannabinoids (most often THC or CBD) and terpenes are also now prevalent. Cannabis constituents can be extracted using a solvent such as ethanol or a hydrocarbon gas (e.g. butane or propane), CO_2, a pressurized heat press, or ice water [40–42]. Cannabis extracts are most commonly inhaled or orally administered, but can also be used via other methods [42]. Cannabis concentrates intended for inhalation have names such as ‘dabs’, ‘budder’, ‘wax’, ‘shatter’, that relate to the consistency of the end product, which usually varies by extraction method [21••,42]. Inhalable cannabis concentrates are particularly popular among young adults (e.g. college students), males, and individuals who live in states which permit legal use of cannabis [42,43]. Users of cannabis concentrates cite their increased potency and greater drug ‘high’ relative to other forms of cannabis as a primary reason for use [41,44].

Among THC-dominant cannabis extracts, the THC concentration is typically substantially higher than found in dried cannabis [45•]. Moreover, many cannabis concentrate products have been found to contain pesticides or residual solvent material [45•]. Case reports have documented episodes of acute psychosis, neurotoxicity, and/or cardiotoxicity, following inhalation of cannabis concentrates [46]. It is unclear whether these adverse effects were the result of high THC concentrations, contamination, or a combination of both. These products should be avoided by novice users, and standards for manufacturing and testing these types of products are urgently needed.

Other product formulations/administration methods

There are several other cannabis products/administration methods that warrant mention, but for which detailed discussion is not currently feasible due to a lack of empirical research. Perhaps the most popular of these is the emerging topical cannabis product market. Topical products may be THC or CBD-dominant, and formulations include lotions, balms, creams, salves, gels, and patches [20,24•]. Other novel products include sublingual sprays, tongue strips, lozenges, inhalers, and both rectal and vaginal suppositories [20,24•]. Controlled clinical studies and representative surveys with which to assess the behavioral effects and use characteristics of these products are generally lacking.

Conclusions: need for clinical and regulatory science

Quality scientific research clearly demonstrates that cannabis can be therapeutically beneficial but can also produce dependence or cause significant harm/discomfort for some individuals. Accordingly, it remains a substantial challenge to predict with confidence the health impact of cannabis use for a given person. The increasing diversity with respect to cannabis product types, formulations, and administration methods that have coincided with widespread legalization has complicated matters considerably. Indeed, hundreds of products now fall under the ‘cannabis’ umbrella, but sound science to understand the nuanced differences in product types is scant.

Despite the recent explosion in popularity of oral cannabis products (‘edibles’) and vaporizers, only a few studies have investigated the pharmacokinetic and pharmacodynamic differences between these products and traditional smoked methods. These studies have shown that the time to the onset and duration of drug effects differs significantly between oral and inhaled cannabis and that vaporized cannabis delivers higher concentrations of cannabinoids, and produces stronger drug effects, compared with equivalent doses of smoked cannabis [47•,48•]. Notably, the delayed drug effects after oral consumption of cannabis make it more difficult for users to titrate their THC dose, and increase the likelihood of acute overdose incidents [49,50]. Further, concentrations of THC and its metabolites in bodily fluids vary substantially by route of administration, and are not well correlated with acute cannabis effects or impairment, which creates a legal challenge for identification of individuals who are impaired due to cannabis use while driving or in the workplace [47•,51]. At this time, controlled studies on commercially available topical cannabis products, suppositories, concentrates, and products for which the primary chemical constituent is anything except THC or CBD are mostly absent. Also, of note, few studies have included novice cannabis users or attempted to identify factors (e.g. age, sex, genetics, user puffing behaviors) that may account for inter-individual differences in cannabis pharmacokinetics and pharmacodynamics.

By measuring behavior in both controlled and naturalistic settings, scientists can help elucidate the overall health impact of cannabis legalization and ultimately inform product regulation. Controlled clinical evaluations of cannabis products are urgently needed in order to produce dosing guidelines that are specific to product type, reason for use, and individual user, to determine comparative abuse liability across products, and to refine approaches for the detection of acute cannabis impairment/intoxication. Representative epidemiological

surveys are needed to monitor detailed cannabis product use patterns, determine reasons for and correlates of cannabis use, and evaluate positive/negative effects of cannabis use across different cannabis products and types of users, though a consensus regarding nomenclature used to categorize the litany of available products must be reached. Results from these surveys can be evaluated within the context of larger public health data to inform decisions regarding cannabis product accessibility. This type of policy-oriented research (or 'Regulatory Science'), if combined with proper regulatory oversight to improve product standards, could maximize public health benefits and minimize harms associated with cannabis legalization.

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