Making Cannabis Medical

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Dr. Ruggiero reports that he is an employee of Beyond / Hello, Jushi.
CEI has taken appropriate action for conflict resolution, including external peer review.

Dr. Kane does not report any actual or potential conflicts of interest in relation to this continuing pharmacy education course.

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Since 1970, *Cannabis* has been federally regulated as a Schedule I substance, indicating a high potential of abuse with no widely accepted medical use. As of August 2020, there are 35 states that allow for the regulation of medical *Cannabis* and 11 states that allow for adult/recreational use. Of the 35 states with a medical program, only 7 require the involvement of a pharmacist (20%). These states include Connecticut, Minnesota, New York, Pennsylvania, Ohio, Arkansas, and Louisiana. Pharmacist involvement varies between making clinical recommendations to overseeing dispensing or solely serving in a consultant capacity to educate dispensary personnel. Due to the lack of training for healthcare professionals inside dispensaries, there are noticeable disparities between each medical program. In the majority of states, the overseeing physician formalizes the patient’s diagnosis as a qualifying condition and the patient is left to discuss treatment and dosing with the dispensary staff or ‘budtenders’. Unfortunately, dispensary staff rely on personal experience to formulate their recommendation, as opposed to evidence-based understanding, and may not be aware of the nuisances that accompany complex medical conditions and comorbidities. On top of the knowledge of qualifying conditions there are significant challenges when dispensing and dosing a botanical substance.

There are several commercially available cannabinoids available in the United States. The first approved synthetic version of tetrahydrocannabinol (THC) was dronabinol (Marinol®, Syndros®) and is FDA approved for chemotherapy induced nausea and vomiting and AIDS-associated anorexia. Dronabinol is often excluded from therapeutic guidelines or listed as a last line agent because of its poor tolerability and ineffectiveness. Nabilone (Cesamet®) is another synthetic THC that is 10 times more potent than dronabinol, but poorly tolerated. All preparations of nabilone have been taken off the market and are not available in the United States. Prescription only cannabidiol (CBD), Epidiolex® is FDA-approved for complex pediatric epilepsies including Lennox-Gaustat, Dravet Syndrome, and Tuberous Sclerosis Complex, and has been de-scheduled to improve patient access. Epidiolex® is a botanical extract that is grown and not synthesized in the lab. In 30 countries worldwide, Nabiximols (Sativex®) is commercially available in a near perfect 1:1 ratio of THC to CBD and commonly used for Multiple Sclerosis associated spasticity and neuropathy. While Sativex® is not commercially available in the United States, it has recently announced new Phase 3 clinical programs evaluating nabiximols in spinal cord injury, Multiple Sclerosis spasticity, and post-traumatic stress disorder (PTSD).

With the passing of the 2018 Agricultural Improvement Bill, also known as the Farm Bill, many hemp CBD growers and producers are able to legally sell hemp-based products under the jurisdiction of the USDA; United States Department of Agriculture. The 2018 Farm Bill removed industrial hemp and hemp seeds from the DEA’s controlled substance schedule. This bill very specifically defines industrial hemp as *Cannabis* with less than 0.3% THC by concentration. Industrial hemp is commonly used as a fiber or textile in clothing and can also be used in paper products and building materials. It is important to recognize the USDA does not allow CBD for food, medicine, or cosmetic purposes as this would fall under the Food and Drug Administration (FDA) which has yet to produce regulations to allow for interstate commerce. Individual states may implement mandates that allow for intrastate commerce and protect growers, producers, and users.

Plant-based medications are highly attuned to their growing medium. *Cannabis*, like other plants, absorb their necessary nutrients from their base and can be grown in natural soil or hydroponic (water) solutions. Natural soil is commonly contaminated by heavy metals including lead, mercury, and arsenic. These toxic metals accumulate in the plant and may cause harm if concentrations are not monitored. All state programs require the analysis of heavy metals on their product labels to ensure product safety. Heavy metals can also be found in groundwater so using filtered water is recommended to avoid unnecessary heavy metal accumulation. Hydroponic mediums are typically preferred for creating medical *Cannabis* preparations for their ability to selectively manipulate and control the growth environment. The growth environment, in addition to selective breeding or cloning, supports gene expression to determine overall plant size, growth speed, height, leaf shape, color, and smell. The growing medium can be adjusted to produce desired noticeable effects like color and smell. For example, increasing the pH (more alkaline) produces blue or yellow colored pigments. Selective nutrient addition or deprivation can also affect color, such as creating red or black pigment by reducing phosphorus concentrations. Temperature changes convert green pigment into orange, similar to the natural aging process of chlorophyll during the fall season. These altered pigment colors correspond to various flavonoids like anthocyanins which attract pollinators and filter harmful ultraviolet (UV) radiation. Contrary to their name, flavonoids do not contribute to the flavor or aroma of the plant and instead produce various colors to protect the plant. The touted medicinal effects of flavonoids are not unique to the *Cannabis* plant as they are found as antioxidants throughout nature commonly in “super foods”like blueberries, apples, and broccoli. Most *Cannabis* consumers will choose more exotic colors and pungent smells as they are thought to correspond to more potent activity.

*Cannabis* can be grown outdoors or indoors depending on grower preference. Traditionally, *Cannabis* has been grown outdoors as the sun is a free source of energy with access to the full UV spectrum compared to the high cost of installing and powering artificial indoor lights. There are many drawbacks to outdoor growing as *Cannabis* requires 12-14 hours of direct light for proper growth and the natural seasons and climate limit additional harvests. Outdoor growing also had unpredictable weather and humidity which can affect the quality of the final product. Lower humidity can reduce plant growth and lead to plant death. Cloud cover or shade interferes and blocks cannabinoid production while harsh weather can physically damage the growing plants. Lastly, outdoor growing operations are more susceptible to direct damage by grazing herbivores or pest infestations, the latter of which is difficult to control once infestation has begun. Indoor growing operations, while more expensive, are able to control lighting, moisture/humidity, and can accommodate more growing seasons per year. However, indoor growing is more likely to facilitate microbial growth if the conditions are not properly inspected and infected plants are not identified or adequately quarantined.

Other potential contaminants during the growing process include pesticides and microbes. Insecticides that should be avoided in *Cannabis* medicine preparations include organophosphates like bifenthrin due to potential for cholinesterase poisoning. Other pesticides that should be avoided in *Cannabis* growing include avermectins, carbamates, pyrethroids, and pyrethrins. Myclobutanil is a triazole antifungal that may release cyanide gas when heated and is banned in several countries for use in medical *Cannabis* products. There have been independent reports of unlicensed *Cannabis* products containing myclobutanil, which speaks to the dangers of the unregulated *Cannabis* market. Microbe contamination can occur during growing or processing and include bacteria, mold and mycotoxins, mildew, and yeast. Microbial contamination has the most serious medical implications as *Cannabis* users are more likely to be immunocompromised and more sensitive to the potential infection risk or illness from mycotoxins.

The raw *Cannabis* flower can be used medicinally as a source of tetrahydrocannabinolic acid (THCA) and cannabidiolic acid (CBDA). The raw acid cannabinoids require decarboxylation with temperatures at or above 145°C (293°F) in order to convert into their neutral counterparts; tetrahydrocannabinol (THC) and cannabidiol (CBD). Decarboxylated molecules have a more efficient extraction ratio than their acid counterparts, so decarboxylation typically occurs before extraction to ensure maximum output and potency. The raw flower may be contaminated by pathogens including mold, mildew, bacteria, and yeast, especially if it is not dried correctly.

Quantifying the potency and concentration of cannabinoids in raw flowers is more difficult compared to extracts. It is estimated that most commercially available flowers have a concentration between 15-20% THCA. Extracts are also easier for patients to administer or consume compared to raw flowers since the dose and concentration can be measured. Live resin is one type of extract that seeks to preserve the original molecules of the plant, including the raw acidic forms and terpenes which contribute to the aroma of the plant. Live resins are typically 40-50% THCA and require heating beyond decarboxylation temperatures of 145°C (293°F) to ensure activation into principle, neutral molecules, THC and CBD. Distillate is a high-potency extract produced via distillation with THC concentrations between 80-99% and little-to-no terpene preservation in the final product. The advantage of distillate over live resin is a final product with compounds that can be uniquely selected based on boiling point compared to a whole plant extract that contains hundreds of compounds. Manufacturers of distillate commonly reintroduce terpenes back into the mixture to create a specific flavor or aroma profile.

There are various extraction methods that are used to pull cannabinoids from the raw plant material. Most of these methods require use of a solvent and further filtration like winterization to remove unwanted coextracted molecules including plant waxes and fats. There are various methods to purge these solvents to ensure the final product is safe and free of unwanted contamination.

**CO2: Carbon Dioxide**
 CO2 can be used in supercritical extraction and subcritical extraction. In between the two is what is known as ‘mid-critical’ extractions. Supercritical fluids can be achieved by making a substance at a temperature and pressure above its critical point, in which distinctions between gas states and liquid states can be made. In CO2 supercritical extraction methods, this is the solvent for dissolving the cannabinoids. Whereas in subcritical extraction, the solvent compound of interest (in this case CO2) is put at lower temperatures and pressures, but still in a liquid state to act as the solvent. In the *Cannabis* industry, supercritical CO2 extraction is most common. Through use of pressurized carbon, CO2 extraction pulls cannabinoids from *Cannabis*. As a part of the process, essential waxes, cannabinoids, and terpenes are removed from the plant via additional processing. A part of the reason manufacturers use carbon dioxide is because it is versatile in that it can act as a solvent at specific temperature and pressure range so selectivity is possible. Using CO2 as the solvent proves beneficial as it does not create toxic byproducts like other solvents. The greatest advantage for the use of CO2 is the ability to destroy potential microbial contaminants such as bacteria and mold. Although expensive, CO2 is the current choice for medical product extraction due to its safety profile.
 The process of CO2 extraction begins with taking CO2 in the gas state and funneling it through a chamber. The gas is then put under increased pressures and temperatures as low as -70 degrees Fahrenheit, creating the fluid state. Once reheated and pressurized the liquid becomes a supercritical fluid which is passed through a chamber that contains raw *Cannabis* plant materials. This then dissolves the trichomes' membranes, where cannabinoids are located, and collects many of the active cannabinoids contained in the *Cannabis*. Unfortunately, CO2 as a solvent is not effective at removing cannabinoids from the plant material and requires multiple washes. This process can take up to two hours per batch, increasing price and compromising molecular integrity. The more material you put in, the longer the cycle time will be required. Temperatures and pressures can be manipulated to improve extraction, but CO2 is not as efficient compared to other methods. A benefit to CO2 specifically is that it is a highly ‘turnable solvent’ which means at different pressures and temperatures various compounds can be pulled from plant based substances. When working at higher pressures with well engineered equipment there is little safety concern, but the equipment will be more expensive than other solvent based methods.

**Ethanol**
 Ethanol is known as one of the most efficient methods for extraction especially for high quantities of raw flowers over a wide range of temperatures. The problem with ethanol is that it is an extremely polar solvent, which results in binding to other compounds within the plant. Co-extracted molecules commonly include chlorophyll, creating a green color and an unpalatable grassy flavor.
 Soxhlet extraction technique is typically used in hot alcohol extraction, where the hot alcohol solvent is cycled through *Cannabis* flower, which strips both cannabinoids and terpenes from plant material. A drawback to this process is that it is difficult to run on a large scale. Cooler temperatures achieved in cold alcohol extraction makes it more difficult for co-extracted materials, like plant waxes, to be pulled from the plants. The chilling of ethanol requires other equipment and processes. Room temperature ethanol extraction, however, is more efficient and allows for use on a larger scale, unlike the hot and cold methods. This process involves submerging *Cannabis* flower in a large vat of room temperature ethanol solvent. After the flower is removed, the pulled oil is heated to remove the ethanol solvent and leave behind an oil that is high in purity and contains the most common cannabinoids. One benefit to ethanol extraction is that it does not produce as much pressure as other methods of extraction, therefore there is substantially less vapor pressure (compared to CO2) and flammability (compared to hydrocarbon). Ethanol can be harder to be removed from the resulting oil product due to its higher boiling point, so it is not commonly used for vaporized products.

**Hydrocarbon**
 Hydrocarbon extractions typically use butane or propane as a solvent. These are the best available solvents in terms of efficiency when used for cannabinoid extraction. Hydrocarbons are nonpolar solvents with a low boiling point and bind to the desirable parts of the plants. This method is best for moderate level extraction. These solvents are flammable and have some pressure, which require specific equipment to handle and may be cost-prohibitive. Hydrocarbon extraction allows for consistent profiles for terpenes and cannabinoids in the plant.

One such form is known as Butane Hash Oil (BHO also referred to as Butane Honey Oil). The low boiling point of butane at atmospheric pressure is close to 31 degrees Fahrenheit, which is useful for cold extraction purposes. A cold BHO solvent is washed over *Cannabis* plant materials and extracts the oils. Then the resulting liquid is cold-boiled off to yield oil that has greater amounts of cannabinoids and terpenes, many of which are temperature sensitive. Therefore, the low boiling point preserves many of the compounds sensitive to temperature and leaves them contained in the final oil. There may be some trace amounts of the hydrocarbons, so once the product is extracted it goes through a heating or purging process to remove the solvent. There is still some concern that small trace amounts of hydrocarbons will remain, and manufacturers have the option of requesting their products be tested for residuals using Residual Solvent Analysis.

**Solventless Extraction Methods**

There are several solventless extraction methods that are currently employed. Solventless extraction methods utilize mechanical means to pull cannabinoids out of the *Cannabis* flower. This differs from ‘solvent-free’ products which utilize a solvent to extract, but are distilled to remove any remaining traces of solvent. These processes are safer to do at home since they do not involve equipment or solvents that can be inhaled. Solventless extraction creates a high quality, clean extract with a reduced overall product yield.

**Distillation** (boiling and condensation)

Solvent methods can also incorporate distillation in their processing to increase final concentrations. Distillation is the process of heating a material into a vapor and then recondensing it. Through use of heat, steam, and a vacuum the chemical compounds are separate from any remaining solvent to leave behind a concentrated distillate. Before distillation can begin, the boiling temperatures of the compounds need to be considered.By knowing the various boiling points, we are able to create a product that contains a higher yield of our compounds of interest and selectively chose the final product composition.

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| --- | --- |
| Class or Chemical of Interest | Boiling point range |
| THC | 315 degrees Fahrenheit |
| CBD | 320 - 356 degrees Fahrenheit |
| Terpenes | 320 - 315 degrees Fahrenheit |
| Flavonoids | 273 - 352 degrees Fahrenheit |

**Rosin (thermobaric)**

Rosin or thermobaric extractions use heat, pressure, and parchment paper exerted on *Cannabis* flower or hash to pull out cannabinoids. There are a variety of setups that can vary from small hand held units or industrial grade presses that can be used in professional markets. The result is a pure extract rich in cannabinoids and terpenes. Rosin extraction can create different textures ranging from shatter to sauce, depending on the starting material, genetics, temperature of the press, and storage of the rosin. When pressing *Cannabis* flower to make rosin it is best not to use recently cut *Cannabis* flower, which has a higher moisture content, negatively affecting the stability of the yielded product. Taste will likely be improved when using *Cannabis* flower as the starting material, while hash will increase potency.

Different extraction methods come with their own advantages and disadvantages. CO2 is not as efficient at removing small molecules and results in loss of yield in terms of cannabinoid and terpene content, while this is a drawback it also helps to kills microbes contained in the *Cannabis*. There are additional purification requirements which increase cost to remove and safely dispose of residual plant fats and waxes. Of all the methods, the most efficient at stripping cannabinoids from trichomes in *Cannabis* is hydrocarbon-based extraction methods, followed by ethanol-based extraction methods. Hydrocarbon based extraction, although efficient, are highly flammable solvents and risk the potential for neurotoxic residues in the final product. Whereas the less efficient CO2 extraction results in low levels of any potential for residue, the high cost of equipment to extract and purify may be a limiting factor. Even though this is the most expensive option, some manufacturers have the ability to recycle CO2, which is ultimately better for the environment. In the current state of the world with COVID-19 (coronavirus), ethanol is also facing shortages so companies that have the ability to recycle their ethanol can also save money by not requiring expensive hazardous waste disposal.

 Testing medical *Cannabis* products ensures safety and reliability as a medication. Testing labs will ensure both safety by the verifiable lack of contaminants and potency as a measure that the concentration of cannabinoids on the label matches the analysis in the lab. A lab’s Certificate of Analysis (COA) accompanies the tested batch or lot and is commonly available and visible to consumers or patients. Potency testing consists mainly of cannabinoids, but can also be used to quantify terpene content. Quality testing identifies potential contaminants including pesticides, heavy metals, residual solvents, microbiology, and moisture content, the latter which can increase the likelihood of microbial growth. Water Activity (AW) levels are measured in flower and infused products (edibles) as levels above 0.6 Aw encourage microbial growth. Microbial testing can be completed through plating for broad quantification or using PCR for more narrow identification. Utilizing third-party analyzed products promotes transparency and trust within the medical *Cannabis* industry.

**Gas Chromatography/Mass Spectrometry (GC/MS)**

GC/MS measures chemicals in their gas phase, known as headspace, above the sample the headspace above the sample of chemical and GC/MS is used to measure the potency of decarboxylated cannabinoids and terpenes. GC/MS can also be used to detect the presence of residual solvents, such as butane, isobutane, pentane, and ethanol.

Common detected analytes include; cannabinoids, terpenes, and residual solvents.

**High-Performance Liquid Chromatography (HPLC)**

HPLC measures liquid mobile phase of analytes using high pressure and measures cannabinoid potency as a sum of THC and THCA. The commonly referenced equation to calculate THCtotal= (%THCA) x 0.877 + (%THC).
Common detected analytes include; all phytocannabinoids and their acid forms. HPLC is required for carbamate analysis which cannot be completed by GC/MS.

**Liquid Chromatography/Mass Spectrometry (LC/MS)**

LC/MS is a combination of GC/MS and HPLC that physically separates liquid phases with liquid chromatography or HPLC and then measures mass using mass spectrometry. LC/MS measures pesticides in *Cannabis* which may accumulate during the growing process and can further concentrate during processing. LC/MS is also used to quantify mycotoxins such as aflatoxins from the Aspergillus genus.

Common detected analytes include; pyrethrin, myclobutanil, and fenoxycarb.

**Inductively Coupled Plasma Mass Spectrometry (ICPMS)**

ICPMS measures the presence of heavy metal in samples by using inductively coupled plasma to ionize the sample. ICPMS atomizes the sample, creating atomic and small polyatomic ions, which are then detected by mass spectrometry.

Common detected analytes include; lead, mercury, cadmium, and arsenic.

Testing facilities will commonly retest product samples to ensure products continue to meet safety standards. Third-party testing identifies possible “Best Use By” dates for products that are commercially sold. Some companies are choosing to retest their products once they are in their final dosage form to determine if there is any leaching of plastic or heavy metals from the container. As more states adopt medical *Cannabis* regulations, we must continue to emphasize the importance of safe and quality medicine.

Given the overwhelming product availability and variable interpatient response, it is imperative that dispensaries have a proper plan in place to ensure patients are purchasing the safest products and are properly counseled on correct use and storage. Dispensaries can have varying product lines available and the language to describe the products is not always the same. The International Society of Cannabis Pharmacists (CannabisPharmacist.org) recommends classifying each product as one of three patient-friendly designations; THC dominant, CBD dominant, or Balanced. At present time, THC and CBD are the most commonly dosed cannabinoids so these three classifications are sufficient, but new classifications may be required in the future as additional cannabinoids become available. There is no standard requirement for products that contain both cannabinoids to specifically state THC or CBD first in the ratio, so it is imperative to read product labels and determine the product classification. It is best to avoid botanical classifications such as *Indica* and *Sativa* to describe perceived medical effects, as there is no correlation to demonstrate plant morphology relating to chemical composition. When providing dosing instructions, patients should be instructed on initial dose, frequency, amount to titrate, and frequency of titration to minimize adverse effects. Consultations to provide this information generally gather Personal Health Information (PHI) such as age, medical conditions, concomitant medications, thus staff should treat this information as they would any Personal Health Information (PHI) in any HIPAA-compliant environment. Although HIPAA may not directly apply to dispensaries or consultants providing medical opinions, preserving patient confidentiality should be a priority in any medical setting and should follow standards of practice.

Dispensary staff are required to comply with local regulations to ensure products are dispensed within the allotted days supply. Most states allow up to a 30-day supply, similar to regulations for Schedule II medications in the pharmacy. To calculate a dispensed day supply, take the total amount (weight, volume, pills, puffs) dispensed divided by the maximum dose per day. For example, if a tincture contains 300 mg per 30 mL bottle, and the dose is 0.2 mL (2 mg) to 0.5 mL (5 mg) twice daily, the calculation is 30 mL divided by 1 mL for a calculated days supply of 30 days. Calculating days supplied with tablets or capsules is a similar calculation, while calculating the days supplied for an inhaled product requires an estimated number of puffs per pre-filled cartridge or mL.

Diversion of medical *Cannabis* products can happen in any setting including during growing, processing, testing, dispensing, and at the patients’ home. Patients should be counseled on the importance of not sharing their medications and proper methods of storage. Patients using *Cannabis* in institutional settings like group homes or retirement communities should utilize a lockbox to prevent diversion. Strategies to prevent against diversion in the dispensary setting include having a zero-tolerance policy for any drug diversion or failure to report, closed-circuit cameras facing inventory, limiting access to inventory, conducting regular inventory counts of all *Cannabis* containing products (including products that have been returned), and having an anonymous method to report suspicious behavior. Suspected or confirmed cases of diversion should be handled according to local regulations and may require reporting to the overseeing *Cannabis* agency (like the Department of Health or Office of Marijuana Regulation), local law enforcement, or the DEA. Incorporating barcode scanning is an effective tool to prevent dispensing errors and ensure traceability from plant to person. Traceability and transparency is especially important in the Cannabis industry as there may be cases of product recalls due to safety or potency concerns and dispensaries need to be able to contact the affected patient population.

Proper storage is essential as the potency of the raw flower can be reduced by direct exposure to light or heat and can also be degraded by physical force if crushed. To preserve potency, *Cannabis* should be stored in air-tight containers and out of direct sunlight. It may be helpful to remind patients to store “air-tight, out of light, and out of sight” to encourage proper storage. *Cannabis* should be kept out of the reach of children and pets and those who are unauthorized for its use.

The medical Cannabis industry is rapidly growing and it is imperative that healthcare professionals are engaged to ensure public health and safety. While additional research may change our understanding of the role of cannabinoids in clinical practice, the fundamental principle of ‘Do No Harm’ will always be at the forefront. The preparation of high quality products from botanical sources requires each step of the process to be regulated and validated. Use of any medication requires safety and consistency and always works better under professional supervision.

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