MAYO CLINIC

THE ABC'S ON CBD

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LEARNING OBJECTIVES

- A. Define phytocannabinoids and the difference between CBD and THC
- B. Understand the endocannabinoid system and its interaction with endogenous and exogenous cannabinoids
- C. Identify three therapeutic uses of CBD

LEARNING OBJECTIVES

- A = Action
- B = Bioavailability
- C = Therapeutic Claims

THE ABC'S OF CBD

CBD CRAZE

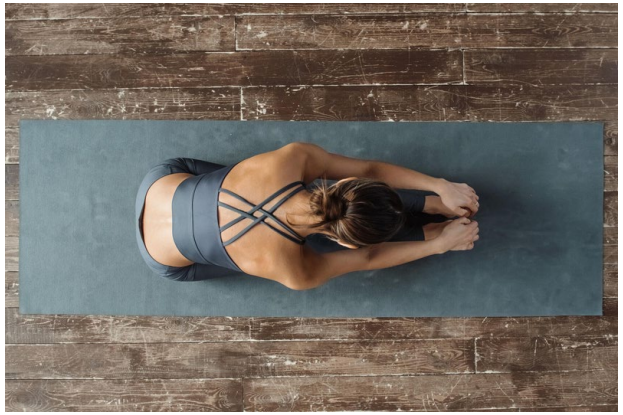
- Many claims to support its use, but due to lack of research, there are many questions remain about CBD
  - Until 2018, Schedule 1 DEA license to conduct studies
  - Safeguards and protections of growth, storage, and handling of cannabis
  - Collaborate with the Food and Drug Administration (FDA) and National Institute on Drug Abuse (NIDA) to obtain research grade cannabis
  - Secure funding
  - Patients prefer whole plant products versus purified or synthetic extracts, which have defined amounts of isolated product
- Despite lack of 'gold standard' research, consumers still use its product for a variety of uses in cooking, health and beauty, skin care, pain relief, etc.
- How did we get here?

THE ABC'S OF CBD

PROHIBITION & BEYOND

- Refer Madness, a propaganda prelude, with a focus on the dangers of marijuana. This film disproportionally targeted minority populations of Hispanic and African ancestry, which intensified during the 1970's and 1980's
- 1937 – Marijuana Taxation Act
- 1942 – Marijuana removed from Pharmacopeia
- 1944 – LaGuardia Report
- 1970 – War on Drugs and Scheduling of Narcotics
  - Defined drugs and their medical utility as well as their addiction potential
- 1972 – Shafer Commission
- 1986 – Anti-drug Abuse Act, mandatory minimum sentences
- 2001 – U.S. government application and patent for cannabinoids as antioxidants and neuroprotectants
- 2018 – U.S. Farm Bill

THE COMMON THEME IS…



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ENDOCANNABINOID SYSTEM (ECS)

PURPOSE

- As summarized by Grinspoon, the **ECS** is involved in the function of learning, sleep, feeding, decision making, reproduction, pain control, stress response, emotional reactions, processing harmful memories, energy regulation, immune system regulation, and temperature control (p. 231, 2023.)
- Promotes homeostasis or maintaining equilibrium between interdependent elements, as maintained by physiological processes via *retrograde transmission …*
  - ability to modulate transmission of neurotransmitters (NT) by providing instant feedback to ‘upstream’ neurons, which can turn *up* or *down* the output of other NT

ENDOCANNABINOIDS

- Lipid based, endogenous ligands that bind to cannabinoid receptors
  - **2AG**, 2-Arachidonoylglycerol – retrograde modulator of neurotransmitter release by influencing CB1 and CB2 receptors
  - **AEA**, Anandamide – retrograde modulator and as a paracrine messenger
- According to Di Marzo, et al. (1998), these messages inhibit "acetylcholine, dopamine, GABA, glutamate, and norepinephrine release, supporting the physiologic effects that are associated with CB1 and CB2 activation" (Clark, 2021, p. 67.)

RECEPTORS

- **CB1,** is the most G protein-coupled receptor in our brains that regulate appetite, memory, fear extinction, motor responses and posture such as the hippocampus, basal ganglia, basolateral amygdala, hypothalamus and cerebellum as found in NASEM (2017, p. 47)
  - Additional sites include, GI tract, adipocytes, liver, and skeletal muscles
  - Not located in the cardiopulmonary center of the brainstem
- **CB2,** predominantly located in the tissues of the immune system, spleen, thymus, tonsils, on white blood cells, osteoclasts, and osteoblasts as found in NASEM (2017, p. 47.)

CLINICAL ENDOCANNABINOID DEFICIENCY (CED)

- Lack of circulating endocannabinoids, changes in receptor densities, or a lack of endocannabinoid tone may be in result of ECS dysfunction and chronic disease states, such as fibromyalgia, irritable bowel syndrome, and migraines (Grinspoon, 2023.)
  - For example, migraine sufferers have less circulating AEA in their cerebral spinal fluid, suggesting the ECS plays a role in inhibiting the pain pathways where migraines originate (Smith, 2014.)

TAXONOMY

- *Cannabis Sativa,* a measure of classification:
  - Hemp - <0.3% THC
  - Marijuana/Cannabis - >0.3% THC
- Origin of “hemp” and “cannabis” varieties all originate from the same plant.
- *Cannabis sativa*, with origins in the Himalayan region of east Asia with medicinal use noted as early as 5,000 B.C..
  - **Indica,** shorter, bushier plant that tends to be more CBD dominants
  - **Sativa**, taller (12 feet) with longer leaves that takes longer to mature and tends to be more THC dominant
    - *Strains no longer relate to effects or perceived benefits of the plant due to hybridization, and the focus should be on chemovars*

Image Source: Getty Images

TERMS

- Phytocannabinoids are plant-based components, that interact with the human endocannabinoid system at the CB1 and CB2 receptor sites and ‘mimic’ endogenous endocannabinoids AEA and 2-AG.
  - **CBD,** cannabidiol, popular cannabinoid known to elicit antiepileptic, anti-inflammatory, antitumorigenic, and immune-modulating, and mood-altering capacity with non-intoxicating properties (Clark, 2021, p. 120.)
  - **THC,** tetrahydrocannabinol, popular cannabinoid known for its intoxicating or euphoric properties and known to help with sleep, pain, and nausea (Clark, 2021, p. 120.)

ADDITIONAL PHYTOCANNABINOIDS

- As listed in Grinspoon (2023) additional phytocannabinoids include:
  - CBG, cannabigerol, potentially useful for nausea, pain, anxiety, inflammation, colitis, and anti-tumor effect
  - CBN, cannabinol, appetite, inflammation, antimicrobial, non-intoxicating sleep-aid
  - CBC, cannabichromene, works with other cannabinoids to assist with pain and inflammation, anti-tumor and antimicrobial agent
  - THCV, tetrahydrocannabivarian, controls appetite, promotes weight loss, and prevents insulin resistance

PHYTOCANNABINOIDS

CBD (CANNABIDIOL)

- Antagonist of CB1/CB2, thereby working indirectly, stimulating the body's endogenous endocannabinoid system by *blocking the enzyme fatty acid amine hydrolase (FAAH) responsible for breaking down anandamide*.
  - As more anandamide is present it equates to *greater CB1 activation* and a more 'vital' (tones up) ECS.
  - Helps block some of the undesirable effects of THC including, intoxication, increased heart rate, increased appetite, and sedation
  - Enhances many of the benefits of THC via the entourage effect

PHYTOCANNABINOIDS

THC (TETRAHYDRACANNABINOL)

- THC is a *partial agonist* at CB1 and CB2; its effects on CB1 are psychoactive and its effects on CB2 are anti-inflammatory and immunological (Boggs et. al., 2017).
- THC is the psychoactive cannabinoid found in the cannabis plant, and it is responsible for cannabis' euphoric effects and with overconsumption is related to many of the plants side effects.

EFFECTS OF CBD AND THC

- Similarities include:
  - anti-inflammatory, anti-seizure, muscle relaxant, pain relief, anti-anxiety, anti-nausea, neuroprotective, and anti-tumor

- Differences include:
  - CBD is non-impairing, THC can be impairing
  - CBD can increase blood pressure and eye pressure, THC reduces
  - CBD can reduce appetite, THC stimulates appetite

CHEMOVARS

STRAINS

- **Chemovar,** refers to the categorization of a plant species due to its chemical composition (i.e. terpenes, cannabinoids, flavonoids, and enzymes)
- **Terpenes**, aromatic compounds, over 100 found in cannabis plants and influence cannabis' effects and are found primarily in trichomes
  - Considered the 'essential oil' of the plant, include Limonene, Alpha-pinene, Linalool, Beta-caryophellene, Beta-myrcene, Humulene, and Terpeniol

Image source: Getty Images

SYSTEMATIC COMBINATIONS OF MAJOR CANNABINOID AND TERPENE CONTENTS IN CANNABIS FLOWER AND PATIENT OUTCOMES: A PROOF-OF-CONCEPT ASSESSMENT OF THE VIGIL INDEX OF CANNABIS CHEMOVARS

VIGIL ET AL., 2023

- Objective: study common examples of unique chemovars and evaluate whether differences exist in their effectiveness at reducing the severity of patients' symptoms, and their associations with experienced side effects

Table 2 Descriptions of frequently consumed *Cannabis* flower chemovar index codes

VICC Index Code	N sessions	Primary terpene	Secondary terpene	THC potency	CBD potency	Commercial names	%Sativa/ Indica/ Hybrid
LM60	231	Limonene (.01–.50%)	Mercene (.01–.50%)	20–25%	0%	Grapefruit Durban, 24K Gold	80/4/16
$M^{+}A50$	212	Mercene (.50—1.0%)	Alpha-pinene (.01–.50%)	15–20%	0%	9 Pound Hammer, Blueberry Cookies	0/28/72
MC61	223	Mercene (.01–.50%)	Beta-caryophyllene (.01–.50%)	20–25%	.01–1.0%	Starfall, Scarlet Queen	0/1/99
MC62	211	Mercene (.01–.50%)	Beta-caryophyllene (.01–.50%)	20–25%	1%-5%	Royal Purple Kush	0/100/0
$T^{+}L60$	222	Terpinolene (.50–1.0%)	Limonene (.01–.50%)	20–25%	0%	Cookies and Cream, Florida Black Haze #14	79/0/21

The VICC (Vigil Index of Cannabis Chemovars) uses a 4-unit coding system to indicate relative primary terpene and cannabinoid concentrations. Concentrations represent approximations with the tenths place rounded up to the next whole digit. Valid percentages of sativa/indica/hybrid label descriptions are shown

Vigil et al., 2023

SYSTEMATIC COMBINATIONS OF MAJOR CANNABINOID AND TERPENE CONTENTS IN CANNABIS FLOWER AND PATIENT OUTCOMES: A PROOF-OF-CONCEPT ASSESSMENT OF THE VIGIL INDEX OF CANNABIS CHEMOVARS

VIGIL ET AL., 2023

- Results: Examination of the five most frequently consumed chemovars showed significant differences in symptom treatment effectiveness for chronic pain and for depression and anxiety.
  - Symptom relief greatest with slightly higher levels of terpenes, mercene and terpinolene and low/no CBD
- Limitations: observational in nature and no control group; limited by the information users have entered into the Releaf App™
  - No individual level information provided

Vigil et al., 2023

PHARMACOKINETICS

- Routes
- Absorption
- Distribution
- Metabolism
- Excretion

Image source: Getty Images

INHALATION

COMBUSTION

- Smoking dry flower and inhaling the components
- May cause a sore throat, irritate lungs and induce coughing

VAPORIZATION

- Heated to a temperature in which the active components of the plant are released a as a vapor that can be inhaled

CONCENTRATES

- Also known as vape liquid, “e-liquid” containing vegetable glycerin and/or polyethylene glycol (PG)
- PG, thinning agent that when heated can be carcinogenic
- May cause a sore throat, irritate lungs and induce coughing

Image source: Getty Images

ORAL/SUBLINGUAL

- Tinctures, easiest and most popular way to consume CBD and diluted in food-grade oil (hemp, olive, or coconut oil)
- Typically contain 1-10% of CBD (10-100mg/dL) allows for precise dosing and absorbed sublingually
- Longest duration 4-10 hours
- Slow onset – (30 min-2 hours) take up to 2 hours; use with caution
  - Absorbed through the GI tract and then directly transported to the liver for metabolism (known as first-pass metabolism), which changes the THC into 11-OH-THC, a form with longer duration of action
  - Absorption depends on many factors: foods consumed, sleep, stress, and other factors that affect the motility of the gastrointestinal tract, which makes it difficult to titrate and may result in over consumption.

Image source: Getty Images

TOPICAL

- Lotions, salves, oils, and patches
- Steady infusion over a long duration, with minimal high peak drug concentrations, which reduces unwanted side effects
- Local skin irritation may occur
- Popular route in novice users or older adults
- Indication for pain, muscle spasms, inflammation, itching, and various skin conditions, including eczema

TITRATION

- RN may provide information, coaching, and education regarding titration, but can not offer specific dosing requirements but may share evidence-based approaches to dosing (Clark, 2021, p. 209.)
- Aim of use is to alleviate symptoms at the lowest possible dose or the ‘sweet spot’ within the therapeutic window
  - Helpful to keep a diary/journal

ABSORPTION

The wide range of bioavailability reported in the literature likely depends on product formulation, inhalation technique, digestive factors, etc.

Inhalation – CBD 13-19%; THC 25-31% → onset 5-10 min

Oral/SL – 6-20%; 20-30% → onset 1-3 hour; 15-45 min

Topical/Transdermal – Varies; 10x more than THC → 20-30 min

DISTRIBUTION

- Enter the bloodstream and travel to areas of the body and most cannabinoids attach to protein molecules (lipoproteins) then are metabolized by the liver
- Once cannabinoids leave the bloodstream, they adhere to cell receptors

METABOLISM OF CBD

- Cannabis substrates undergo biotransformation in the liver via metabolism by the CYP450 pathway, which breaks down the THC into water-soluble metabolites
- Oral intake undergoes first past effect and turns THC into 11-OH-THC (stronger metabolite against CB1 = more intoxicating effect,) then 11-COOH-THC a water-soluble metabolite (Clark, 2021, p. 140.)
- CYP450 Enzymes used in cannabinoid metabolism:
  - THC & CBN: 2C9, 3A4
  - CBD: 2C19, 3A4

INTERACTIONS OF CBD

May occur in the following areas:

- Intestine – cells in the intestine express enzymes that transport and metabolize drugs and increases or decreases bioavailability
- Liver – main organ responsible for metabolism, may increase or decrease drug elimination
- Brain – BBB has drug transporters that determines how much drug penetrates the brain

Image source: Getty Images

INTERACTIONS

- Patients using the following medications or classes of medications should use caution and discuss potential interactions with their medical providers.
  - Warfarin (Coumadin)
  - Statin cholesterol medications (especially at maximum dosages)
  - Erythromycin
  - Azole antifungals
  - Stimulants (potential to increase paranoia and psychiatric side effects in others)
  - Anticholinergic drugs can worsen the adverse psychoactive effects
    - Examples include Benadryl, Dramamine, Spiriva, Atrovent, Wellbutrin, Cogentin, and others.

ELIMINATION

- Depends on previous pharmacokinetics and highly variable
- Chronic cannabis users, THC metabolites are lipophilic and accumulate in fat cells and take longer for the body to eliminate
  - Body fat percentage is a factor in how it is stored, no consistent measurement of body fat percentage as a variable of elimination per Miller et al (2018.)

“CBD… has been shown to produce a plethora of pharmacologic effects, many of them associated with both central and peripheral actions… The plethora of positive pharmacologic effects observed with Cannabidiol makes this compound a highly attractive therapeutic entity in inflammation, diabetes, cancer, and affective or neurodegenerative disorders.”

- DR. RAPHAEL MECHOULAM AND PROFESSOR LIONEL JACOBSON,

AS FOUND IN CLARK, 2021, P. 161

THERAPEUTIC USES OF CBD

PATENT 6,630,507

- Untied States Patent, Cannabinoids as Antioxidants and Neuroprotectants
  - “Antioxidant properties, unrelated to NMDA receptor antagonism… cannabinoids useful in the treatment and prophylaxis of wide variety of oxidation associated diseases, such as ischemic, age-related, inflammatory and autoimmune diseases.”
  - “CBD particularly advantageous to use as it avoids toxicity that is encountered with psychoactive cannabinoids at high doses useful in the method of the present *invention*.”

THERAPEUTIC USES OF CBD

PATENT 6,630,507

- Untied States Patent, Cannabinoids as Antioxidants and Neuroprotectants
  - With particular focus as neuroprotectants and limit neurologic damage following ischemic insults, i.e. stroke and trauma or in neurodegenerative diseases such as Alzheimer's Disease, Parkinson's Disease, and HIV-dementia.

THERAPEUTIC USES OF CBD

NEURODEGENERATIVE EFFECTS

- Alzheimer's Disease
  - Hallmark of the disease process is the accumulation of beta amyloid plaques and tau proteins.
  - 2006 study found that CBD inhibits phosphorylation of tau proteins in A-beta-stimulated PC12 neuronal cells with further pre-clinical research that CBD can reduce the damages of the neuroinflammatory response, as well as memory loss by promoting neurogenesis (Espositio et al, 2006.)

THERAPEUTIC USES OF CBD

NEURODEGENERATIVE EFFECTS

- Parkinson's Disease
  - As found in Clark (2021) 22 patients showed improvement of rigidity, tremors, and slowness of movement, sleep, and pain and PD patients had improved quality of life scores after 1 week of treatment with CBD (Lotan et al, 2014; Chagas et al., 2014.)
    - Lotan et al, found that after 30 minutes of 0.5 of smoked cannabis found significant improvements in sleep, pain, and motor symptoms (tremor, rigidity, and bradykinesia.)
  - Per NASEM, *insufficient evidence* to support cannabinoid as an effective treatment for levodopa dyskinesia or motor-system impairment (2017, p. 110.)

US PATENT # 6,630,507

THERAPEUTIC USES OF CBD

ANTI-EPILEPTIC EFFECTS

- Epidiolex, CBD-based medication approved by the FDA, by G.W. Pharmaceuticals for ages 2 years and older for Lennox-Gastut Syndrome (LGS) or Dravet Syndrome (DS.)
  - Large, open-label, single-center study found that patients with higher plasma levels of CBD had lower frequency of seizure activity
- Retrospective review (2017) as published in Epilepsy & Behavior, reviewing medical refractory epilepsy of mixed etiologies noted that overall, there was an 86% perceived clinical benefit from organic resources (non-standardized preparations, cannabinoid preparations.)

THERAPEUTIC USES OF CBD

ANTI-EPILEPTIC EFFECTS

- Charlotte's Web, CBD dominant chemovar profile, named after a young girl named Charlotte Figi, was having 300 seizures a week or every 30 minutes and with permission from her Pediatrician began using CBD
  - Eventually, she no longer needed her anti-epileptics, was able to walk and talk, and didn’t need a feeding tube.
  - By 2014, after her story was aired on CNN and became world-renowned there were 15,000 families wanting access to the Stanley brother’s extract.
  - More information at www.charloettesweb.com

THERAPEUTIC USES OF CBD

ANTI-INFLAMMATORY PROPERTIES

- The majority of research for pain includes THC and CBD; however, there are still a handful of studies revealing CBD for pain control by increasing circulating endogenous/exogenous cannabinoids by inhibition of FAAH
  - Reduces inflammation at site of injury as there are more CB2 receptors at areas of inflammation
  - CBD can decrease the prescribed dose of opioids for pian management and lessen the symptoms from opioid withdrawal as reviewed by Russo and Hohmann (2013.)

THERAPEUTIC USES OF CBD

ANXIOLYTIC EFFECTS

- CBD
  - In 2010, researchers used brain imaging to study the effects of 400mg of CBD on people diagnosed with social anxiety disorder and found changes in parts of the brain known to process anxiety, as well as subjective tests found the participants to be less anxious, as published in Medical Marijuana (Perlman, et al., 2023.)
  - In 2011, placebo-controlled, double-blinded study, found pre-treatment with CBD- compared to placebo arm noted, “reduced anxiety, cognitive impairment and discomfort in their speech performance, and decreased alert in their anticipatory speech” (Bergamaschi et al., 2011.)
  - No randomized-controlled trials have evaluated CBD treatment regimen in patients with clinical anxiety disorders

THERAPEUTIC USES OF CBD

SLEEP

- A major role of the ECS is sleep regulation
- A 2019, study found improved sleep outcomes, but only for 3 months at a dosage of 25 mg with higher doses included
- In one study, by Carlni and Cunha, a dose of 160 mg improved length and quality of sleep (as noted in Clark, 2021, p. 195.)
- Per NASEM, there is moderate evidences that cannabinoids, nabiximols, are effective treatment for short-term sleep outcomes in individuals with sleep disturbances associated with OSA, fibromyalgia, chronic pain, and multiple sclerosis (2017, p. 123.)

THERAPEUTIC USES OF CBD

SUMMARY

- As published in Drugs and Aging (2022,) real-world evidence study evaluated the use of 10,000 Canadians regarding type, dosage, and perceived effects, found “majority of older adults reported improvements in pain (72%,) sleep (64%,) and mood (56%,) with 35% reduced use of opioids and 20% reduced use of benzodiazepines (Shankar, T. et al., 2022.)
- Recent search of ‘CBD’ on clinicaltrials.gov revealed 987 clinical studies populated with 171 actively recruiting patients with the following focuses: memory tasks, neuroinflammation, focus study, pain in knee osteoarthritis, opioid use disorder, autism spectrum disorder, CV-19, anxiety in breast cancer, epilepsy, Alzheimer’s disease, OCD, chronic pain, appetite effects, sleep, PTSD, and alcoholic use disorder and more…

SIDE EFFECTS OF CBD

- In 2017, WHO conducted an extensive study on CBD and its effects on humans, which concluded, "… CBD is generally well tolerated with a good safety profile in animals and humans, and not associated with any negative public health effects" (WHO, 2017.)
- As summarized by Clark, a few side effects of CBD, depending on dosage, are "dizziness, lightheadedness, increase heart rate, jitteriness, drowsiness, and diarrhea have all been noted, with less common side effects of irritability, decreased appetite, palpitations, and increased" (2023, p. 198.)

CONSUMER SAFETY ISSUES

- Mislabeling
- Pesticides
- Driving
- CV Risk
- Immunosuppression
- Storage
- Addiction
- Intoxication
- Overconsumption

ROLE OF REGISTERED NURSES

- Offer information, coaching, and education about cannabis products
- Per NCSBN (2018) recommended that “nurse[s] shall have an understanding of cannabis pharmacology and the research associated with the medical use of cannabis.”
- As a health coach, using motivational interviewing using a patient centered approach to engage patients in conversations regarding cannabis use through empathy, focus on goals or values or current behavior, avoiding conflict and adjust, and support the patient
  - Open-ended questioning
  - A goal and plan prior to ingestion of cannabis and titration process and follow-up as needed

ROLE OF ADVANCED PRACTICE PROVIDERS

- As reviewed by Clark (2021) APRN should understand the principal areas of cannabis: working knowledge of state and federal legislation, understanding of jurisdiction, understanding of ECS, cannabis pharmacology and research, identify safety considerations, approach the patient without judgement to facilitate MI, shared decision making, documentation and communication, ethical considerations, dosing, and drug-drug interactions (p. 313-362.)

Image source: Getty Images

CBD IS…

Image source: Getty Images

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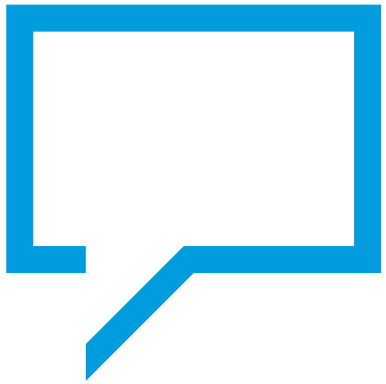
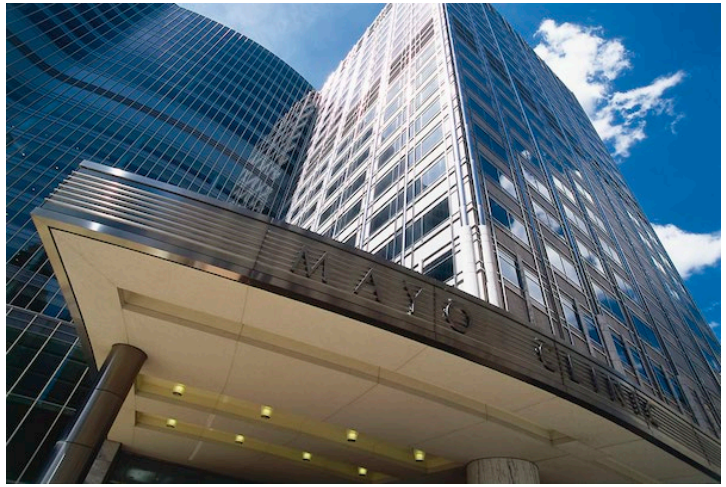
QUESTIONS & ANSWERS



MAYO CLINIC

THANK YOU FOR JOINING US IN THIS COURSE



Rochester, Minnesota

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