VCU Palliative Care ECHO*

August 22, 2019

CBD: What You Need to Know

*ECHO: Extension of Community Healthcare Outcomes

Continuing Medical Education

August 22, 2019| 12:00 PM | teleECHO Conference

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Disclosures

August 22, 2019| 12:00 PM | teleECHO Conference

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The following Planning Committee and Presenting Faculty Members report relevant financial relationships to disclose:

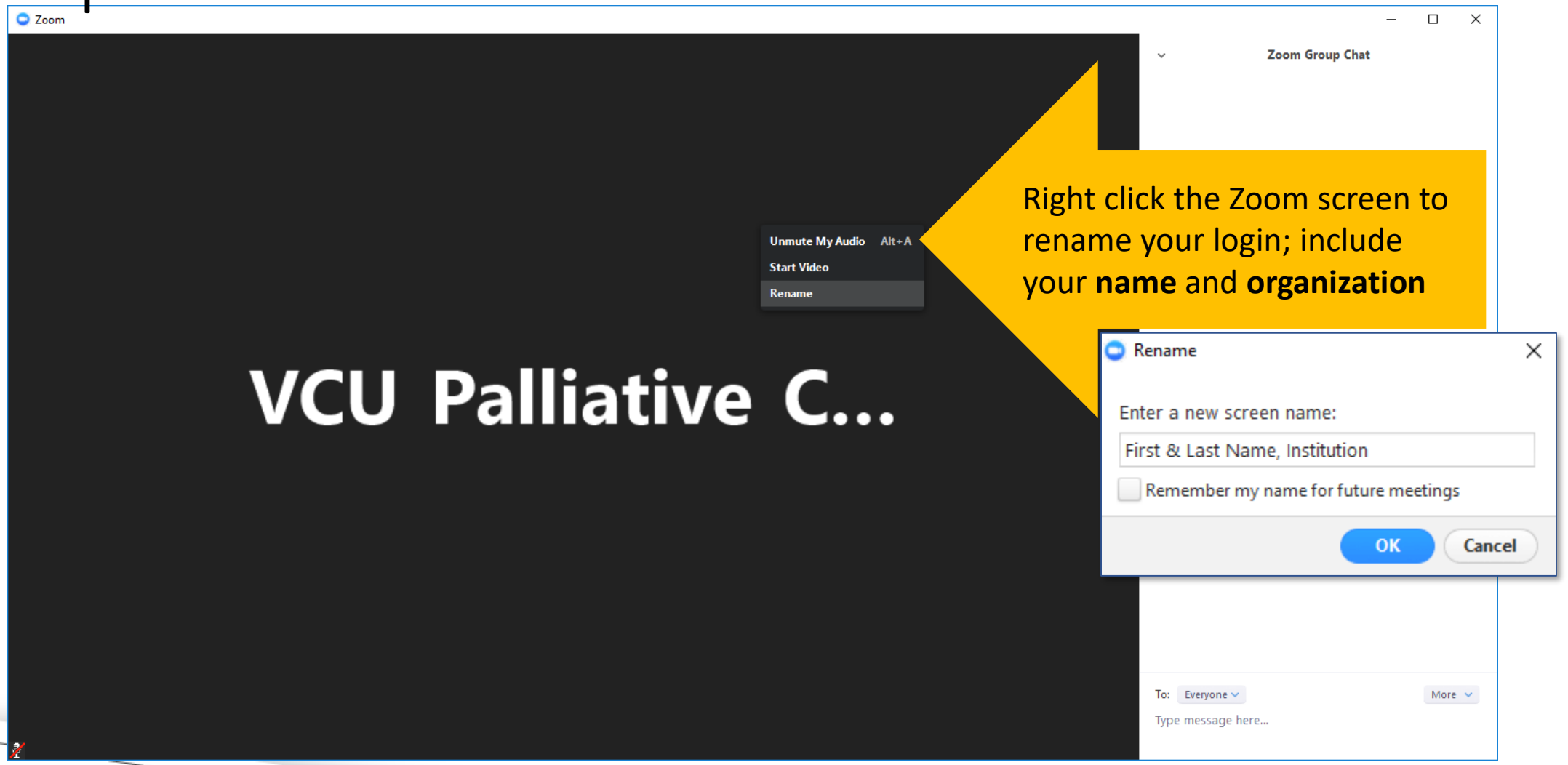
Aron Lichtman, PhD

The following Planning Committee and Presenting Faculty Members report having no relevant financial relationships:

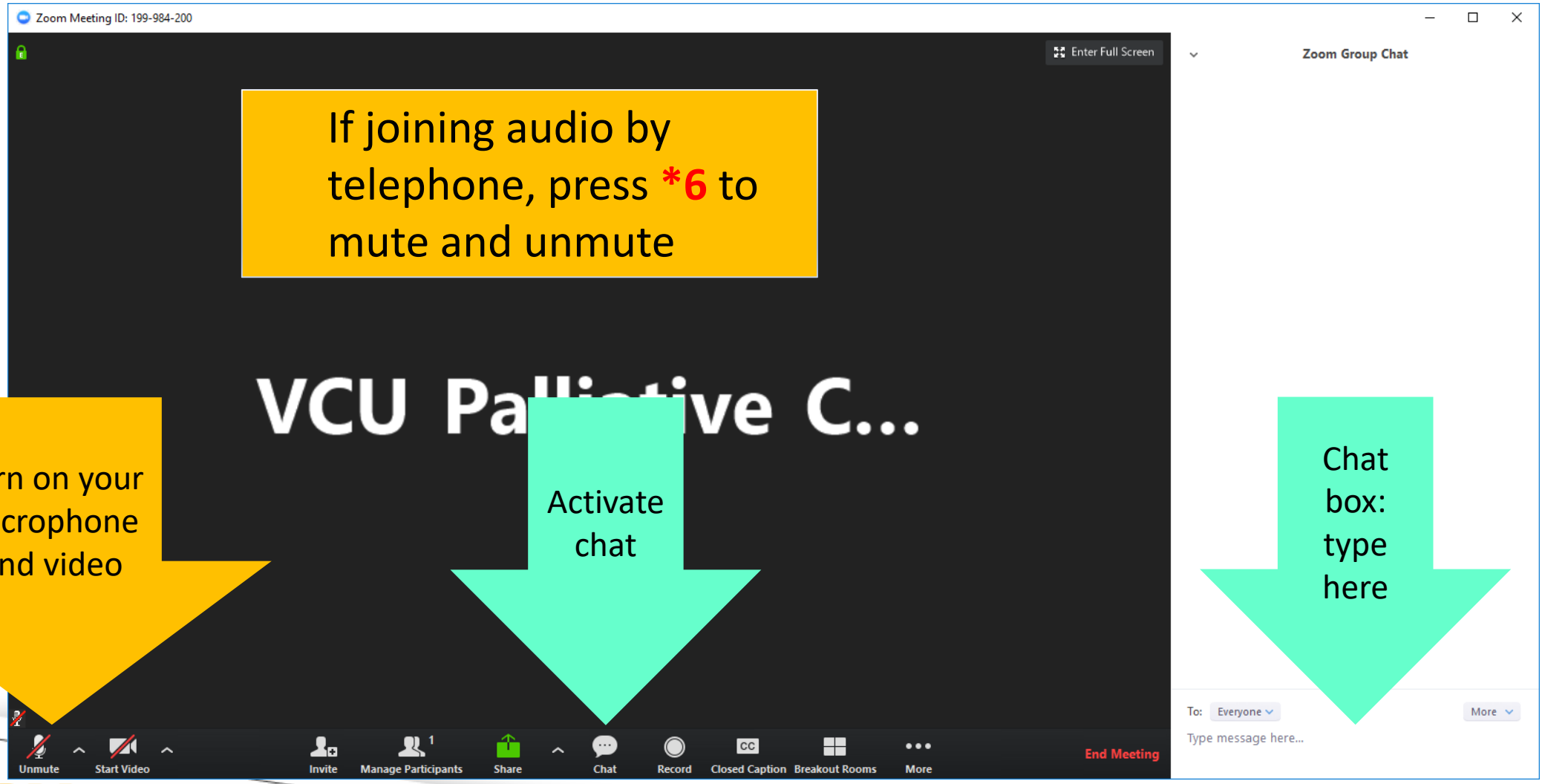
Egidio Del Fabbro, MD; Danielle Noreika, MD

No commercial or in-kind support was provided for this activity

Helpful Reminders



Helpful Reminders



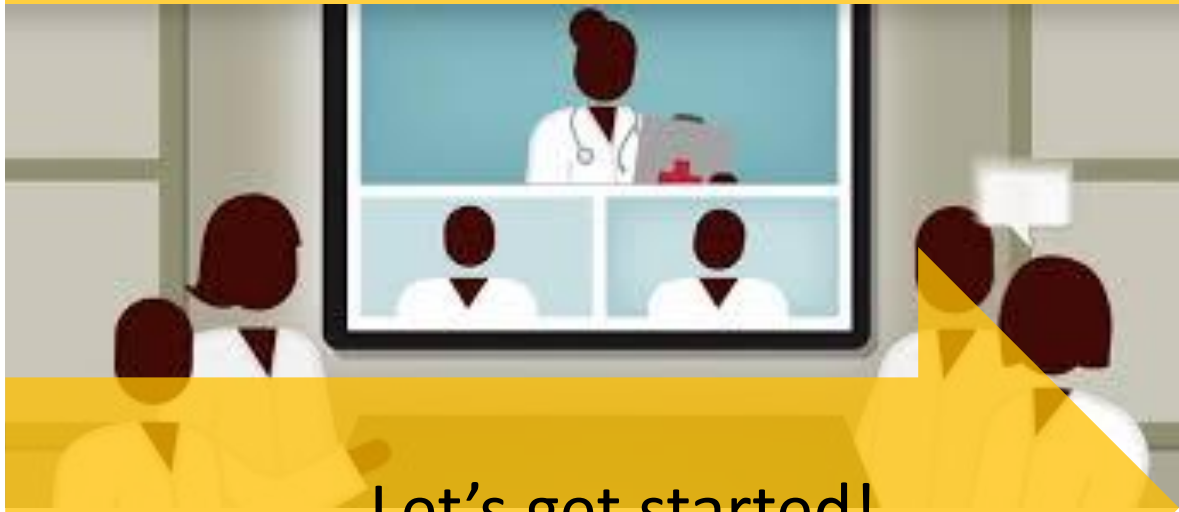
What to Expect

I. Didactic Presentation
   20 minutes + Q&A

II. Case Discussions
   - Case Presentation
     5 min.
   - Clarifying questions from spokes, then hub
     2 min. each
   - Recommendations from spokes, then hub
     2 min. each
   - Summary (hub)
     5 min.

III. Closing and Questions

- Bi-weekly tele-ECHO sessions (1.5 hours)
- Didactic presentations developed by inter-professional experts in palliative care
- Website: www.vcuhealth.org/pcecho
- Email: pcecho@vcuhealth.org



Let's get started!

Hub Introductions

VCU Team	
Clinical Directors	Egidio Del Fabbro, MD VCU Palliative Care Chair and Program Director Danielle Noreika, MD, FACP, FAAHPM Medical Director/Fellowship Director VCU Palliative Care
Clinical Experts	Candace Blades, JD, RN – Advance Care Planning Coordinator Brian Cassel, PhD – Palliative Care Outcomes Researcher Jason Callahan, MDiv – Palliative Care Specialty Certified Felicia Hope Coley, RN Diane Kane, LCSW – Palliative Care Specialty Certified Tamara Orr, PhD, LCP – Clinical Psychologist
Support Staff Program Manager Telemedicine Practice Administrator IT Support	 Teri Dulong-Rae & Bhakti Dave, MPH David Collins, MHA Frank Green

Spoke Participant Introductions

Name and Institution

DISCLAIMER: The federal Controlled Substances Act makes it a crime to lease, rent or maintain a place for the purpose of manufacturing, distributing or using marijuana (21 U.S.C. § 856), to engage in financial transactions to promote illegal activities (21 U.S.C. § 1957), and to conspire to commit such a crime (21 U.S.C. § 846). There is a narrow research exception that permits researchers to grow and study Schedule I drugs, such as marijuana, if the research is registered with and approved by the DEA. VCU Health CE, VCU Health System, or VCU are only associated with marijuana research that meets this exception. This educational material does not constitute legal advice and does not express the views or opinions of VCU Health CE, VCU Health System, or VCU.

CBD: What You Need to Know

Aron H. Lichtman, Ph.D.
Department of Pharmacology and Toxicology

Disclosures

Scientific Advisory Board member

- Abide Therapeutics (ended June 2019)
- Sea Pharmaceuticals

Consulting

- F. Hoffmann-La Roche Ltd
- Corbus Pharmaceutics

Learning Objectives

a. Distinguish between proven and potential therapeutic effects of CBD.
b. Be familiar with concerns and potential untoward effects of CBD

Many originally plant-derived medications work upon endogenous systems

Cannabis
Cannabis sativa

Willow Tree
Salix

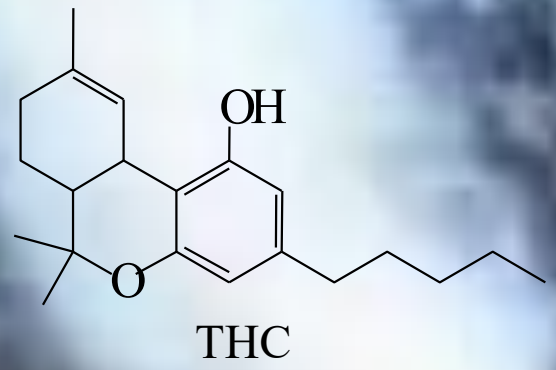
Opium
Lachryma papaveris

Foxglove
Digitalis purpurea

Chemical constituents of cannabis

Chemical classes

Cannabinoids (100+)
Nitrogenous cmpds (27)
Amino acids(18)
Proteins/ enzymes (11)
Sugars (34)
Hydrocarbons (50)
Simple alcohols (7)
Simple aldehydes (12)
Simple ketones (13)
Simple acids (21)
Fatty acids (22)
Simple esters/lactones (13)
Steroids (11)
Terpenes (20)
Non-cannabinoid phenols (25)
Flavoroids (21)
Vitamins (1)
Pigments (2)
Elements (9)
Total known compounds (483)



THC

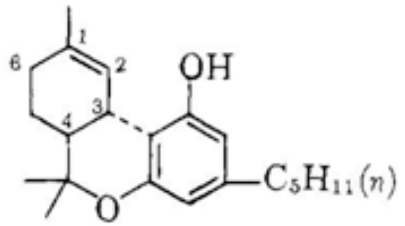
Gaoni and Mechoulam (1964)* Elucidated the Structure of THC

Isolation, Structure, and Partial Synthesis of an Active Constituent of Hashish[1]

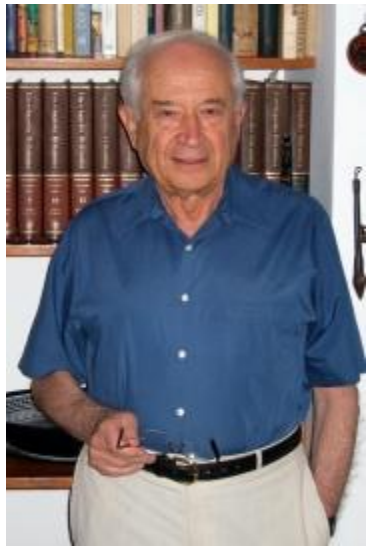
Sir:

Hashish (marihuana), the psychotomimetically active resin of the female flowering tops of *Cannabis sativa* L. is one of the most widely used illicit narcotic drugs. A number of groups have reported the isolation of active constituents.[2] Most of these substances are not fully characterized, and comparisons with or between them are difficult.

We now wish to report the isolation of an active constituent of hashish to which we assign structure I (Δ^1-3,4-*trans*-tetrahydrocannabinol).[3] This is the first active component whose constitution is fully elucidated.[4]

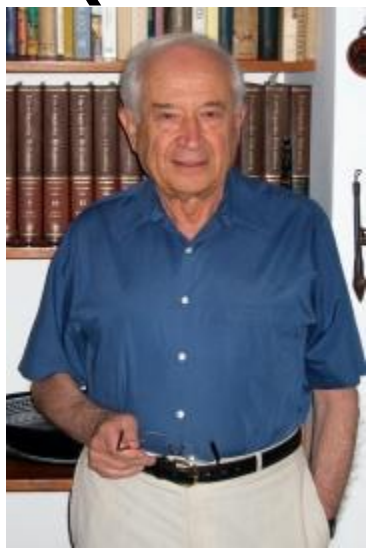


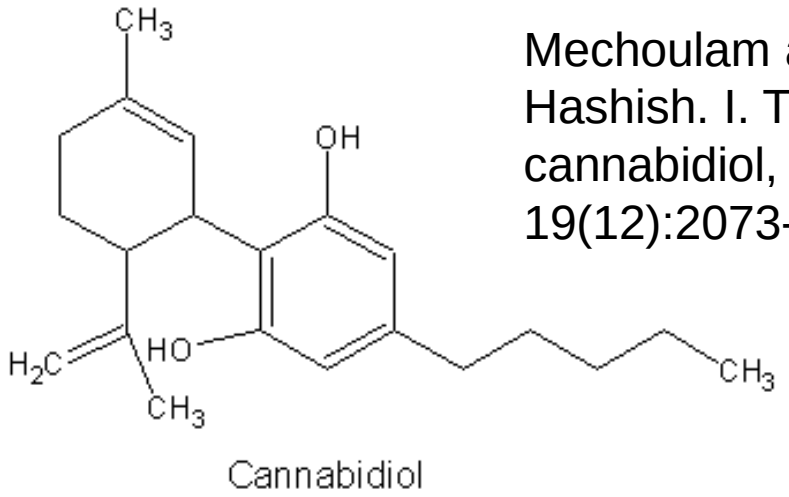
I



*Journal of the American Chemical Society, 86:1646-47

Cannabidiol (CBD)
(Does not elicit cannabis-like effects)





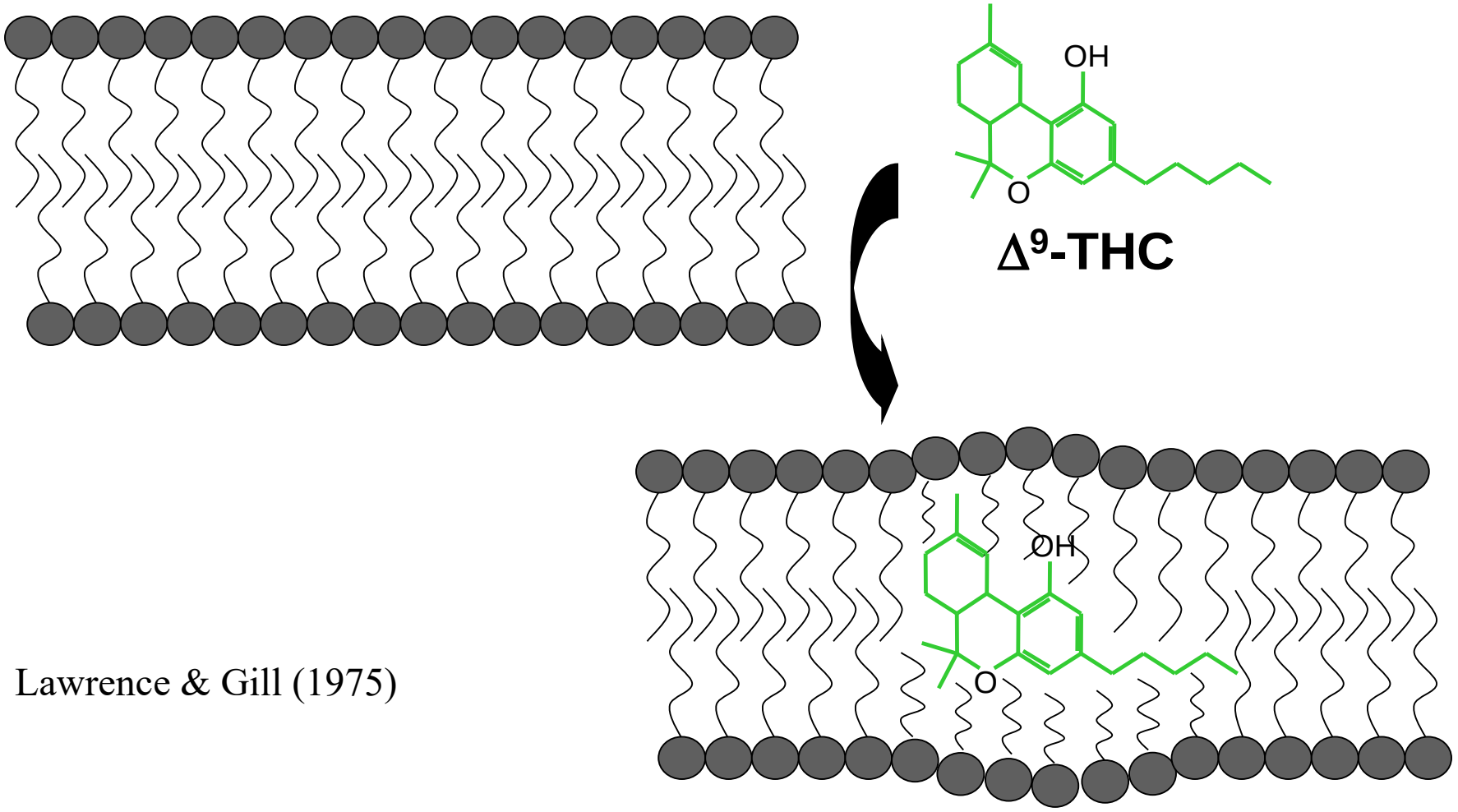
Cannabidiol

Mechoulam and Shvo (1963) Hashish. I. The structure of cannabidiol, Tetrahedron 19(12):2073-8.

Efficacy in Preclinical Models

- Neuropathic pain
- Rheumatoid arthritis
- Anxiety
- Epilepsy
- Cancer
- Anti-emetic/anti-nausea

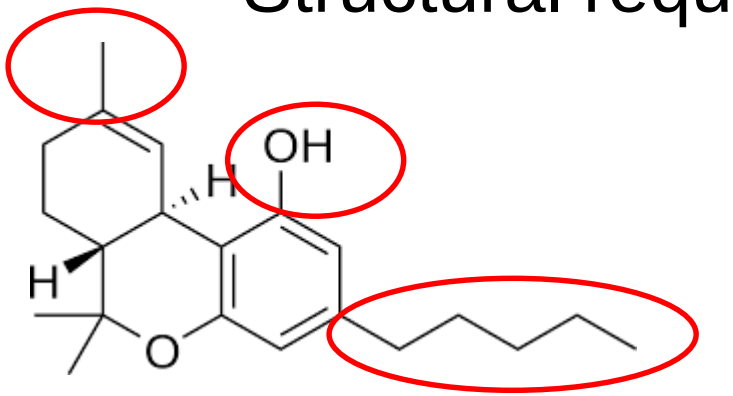
Early Hypothesis: Membrane Perturbation



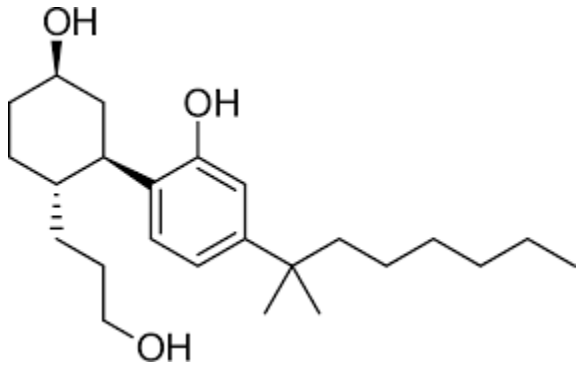
Lawrence & Gill (1975)

Structure Activity Relationship

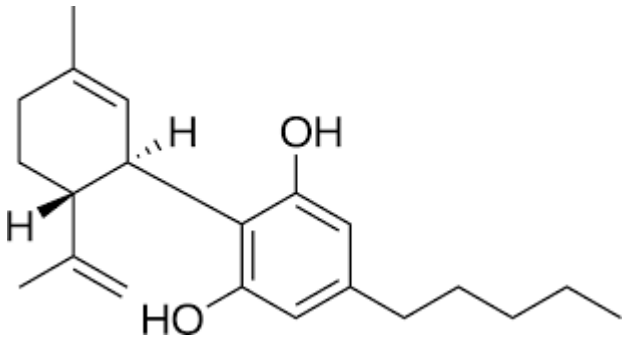
- Unique effects
- Highly potent
- Structural requirements



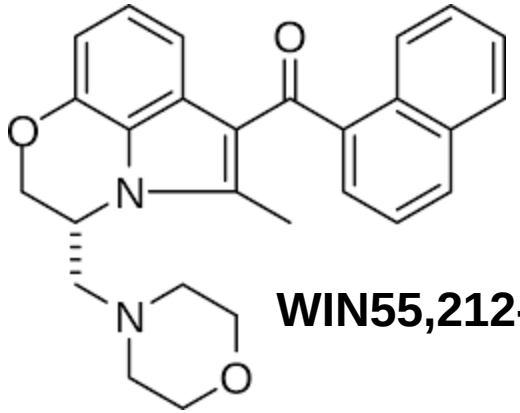
THC



CP55,940



CBD



WIN55,212-2

Specific binding site of THC in Brain Tissue

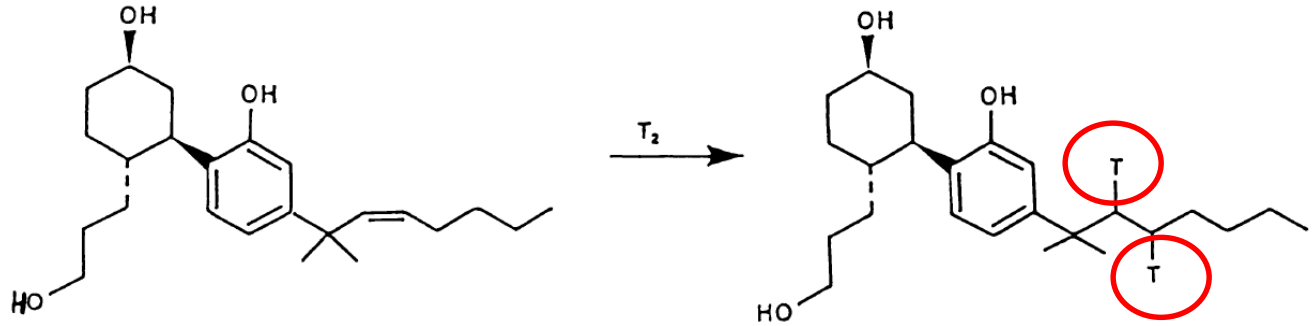
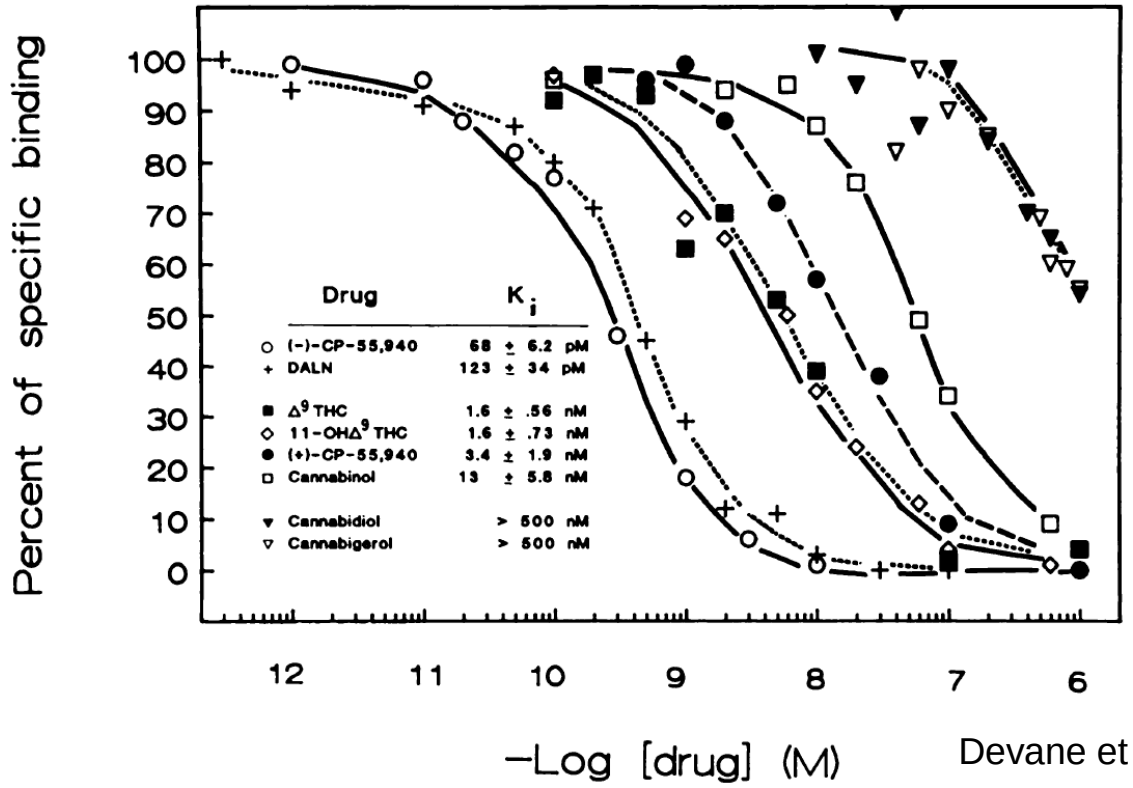


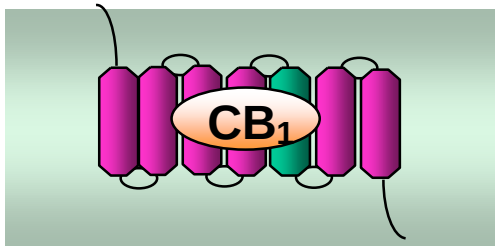
Fig. 1. The synthesis of [^{3}H] CP-55,940 by the tritium reduction of compound 1.

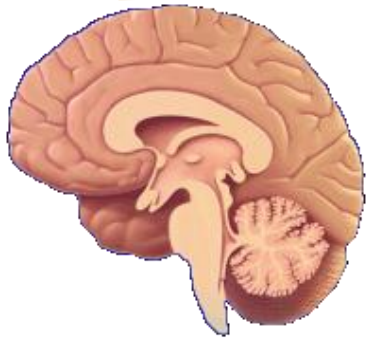
Radiolabeled CP55,940

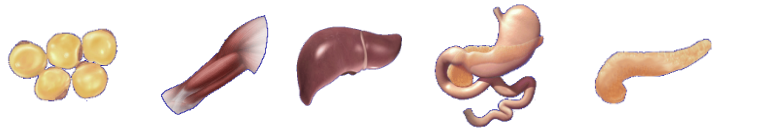


Devane et al (1988) Mol Pharmacol, 34:605-13

CB_1 Receptors







Adipose Tissue | Muscle | Liver | GI Tract | Pancreas

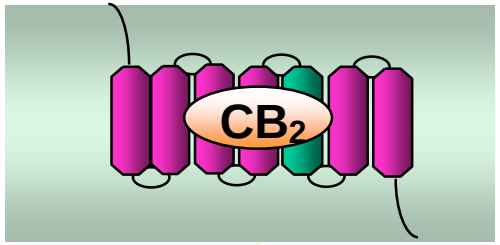
Brain

Responsible for most CNS cannabis effects

Also modulates many physiological functions

Devane et al. (1988) Mol Pharm, 34:605-613
Herkenham et al (1990) PNAS,87:1932-1936
Matsuda et al. (1990) Nature, 346: 561-4

CB_2 Receptors



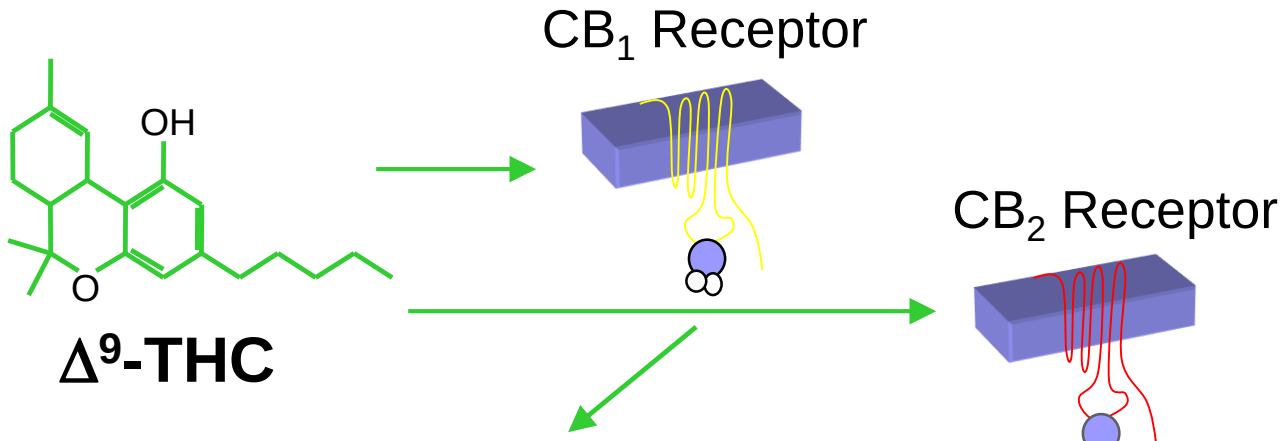
Immune System

T cells **B cells** **Monocytes**
Spleen **Tonsils**

- Expressed primarily in immune cells
- Low expression in CNS, but increased upon microglial activation, neurons
- Agonists reduce nociception, inflammation, neurodegenerative states, and cocaine reward

Munro S et al. *Nature*. 1993;365:61-65.
Van Sickle MD et al. *Science*. 2005;310:329-332.
Whiteside GT et al. *Curr Med Chem*. 2007;14:917-936.

THC Produces Its Effects Through the Activation of Two Types of Cannabinoid Receptors



Δ9-THC

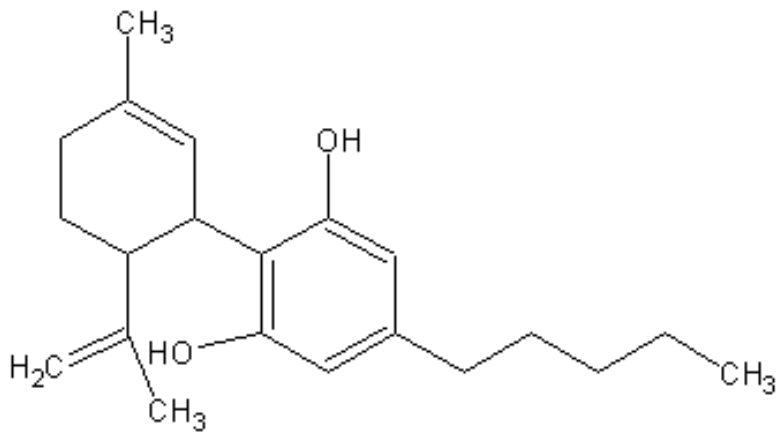
Therapeutic Effects
- Antiemetic/antinausea
- Appetite stimulant
- Increased energy storage
- Analgesia

Side Effects
- Psychomimetic effects
- Abuse liability
- Dependence liability
- Memory impairment

Potential Therapeutic effects
- Analgesia
- Anti-inflammation
  - -periphery
  - -CNS (AD, ALS, etc)
- Anti-cocaine addiction

No apparent adverse side effects at the receptor

What is/are the underlying mechanism(s) of action CBD?



Cannabidiol

CBD does not activate cannabinoid receptors, but interacts with low potency at many sites

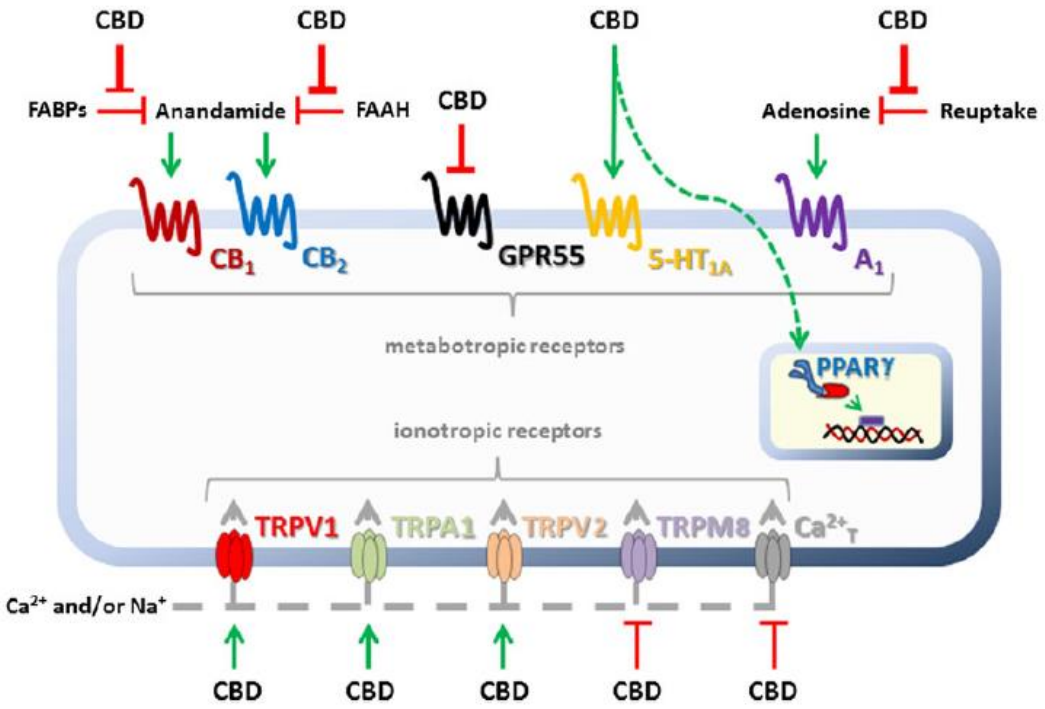


Figure 1

The main molecular targets and potential mechanisms of action of CBD. This drug inhibits both FAAH, the enzyme which metabolizes anandamide, and FABPs, which mediate the transport of anandamide to FAAH; both mechanisms ultimately result in the indirect activation of CB_1 and/or CB_2 receptors. CBD also activates the 5-HT_{1A} receptor, PPARγ and the transient receptor potential channels TRPV1, TRPA1 and TRPV2. Finally, CBD inhibits adenosine reuptake and antagonizes GPR55, TRPM8 and T-type Ca^{2+} channels. 5-HT_{1A} and (indirect) cannabinoid receptor activation are the mechanisms that have been implicated in the anxiolytic effects of CBD to date (see Ibeas Bih *et al.* (2015) and McPartland *et al.* (2015) for further details).

Lee et al (2017) Br J Pharmacol. 174:3242-3256

CBD: Primarily Metabolized by CYP2C19 and CYP3A4

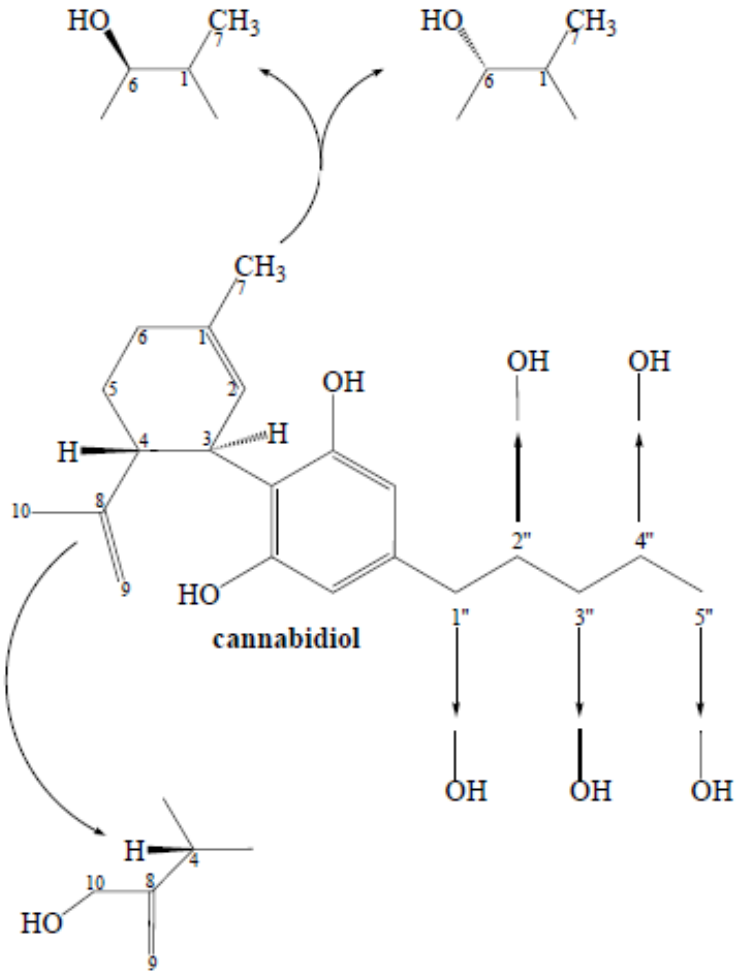


Fig. (7). Hydroxylation of CBD by CYP enzymes [72].

Zendulka et al, Curr Drug Metab. 2016;17(3):206-26.

Four decades ago: Initial CBD clinical trial

Pharmacology *21*: 175–185 (1980)

Chronic Administration of Cannabidiol to Healthy Volunteers and Epileptic Patients[1]

Jomar M. Cunha, E.A. Carlini, Aparecido E. Pereira, Oswaldo L. Ramos, Camilo Pimentel, Rubens Gagliardi, W.L. Sanvito, N. Lander and R. Mechoulam

Dravet Syndrome

- Dravet syndrome (AKA severe myoclonic epilepsy of infancy or SME), a rare genetic form of epileptic encephalopathy primarily due to loss-of-function mutations in the *SCN1A* gene
- *SCN1A* provides instructions for making the alpha subunit of the NaV1.1 sodium channel
- Hundreds of mutations in the *SCN1A* gene exist and are known to cause genetic epilepsy
- These mutations affect the ability of NaV1.1 channels to transport sodium ions into neuron
- Dravet can cause more serious seizures that last longer and may be difficult to control.
- The recurrent seizures (epilepsy) can worsen over time and are often accompanied by a decline in brain function.

https://ghr.nlm.nih.gov/gene/SCN1A

A generation later

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MAY 25, 2017 VOL. 376 NO. 21

Trial of Cannabidiol for Drug-Resistant Seizures in the Dravet Syndrome

Orrin Devinsky, M.D., J. Helen Cross, Ph.D., F.R.C.P.C.H., Linda Laux, M.D., Eric Marsh, M.D., Ian Miller, M.D., Rima Nabbout, M.D., Ingrid E. Scheffer, M.B., B.S., Ph.D., Elizabeth A. Thiele, M.D., Ph.D., and Stephen Wright, M.D., for the Cannabidiol in Dravet Syndrome Study Group*

Primary End Point: CBD Significantly Reduces Seizures

Table 2. Primary Efficacy End Point of Percentage Change in Convulsive-Seizure Frequency in Each Trial Group.*

Variable	Cannabidiol	Placebo	Adjusted Median Difference (95% CI)	P Value†
			percentage points	
No. of convulsive seizures per mo — median (range)				
Baseline	12.4 (3.9 to 1717)	14.9 (3.7 to 718)		
Treatment period	5.9 (0.0 to 2159)	14.1 (0.9 to 709)		
Percentage change in seizure frequency — median (range)	−38.9 (−100 to 337)	−13.3 (−91.5 to 230)	−22.8 (−41.1 to −5.4)	0.01

* CI denotes confidence interval.
† The P value was calculated with the use of a Wilcoxon rank-sum test with the Hodges–Lehmann approach.

Secondary End Points: CBD Significantly Reduces Seizures

Table 3. Summary of Secondary End-Point Results during the Treatment Period (Intention-to-Treat Analysis Set).*

End Point	Cannabidiol vs. Placebo		P Value†
	Difference (95% CI)	Odds Ratio (95% CI)‡	
Change from baseline in CGIC score	−1.0 (−1.0 to 0.0)§		0.02
Reduction in convulsive seizures from baseline¶			
≥25% reduction		2.10 (1.01 to 4.35)	0.05
≥50% reduction: key secondary end point		2.00 (0.93 to 4.30)	0.08
≥75% reduction		2.21 (0.82 to 5.95)	0.11
100% reduction	4.9 (−0.5 to 10.3)‖		0.08
Percentage change from baseline in seizure frequency**			
Total seizures	−19.20 (−39.25 to −1.17)§		0.03
Total nonconvulsive seizures	0.00 (−21.36 to 31.59)§		0.88
Reduction from baseline in duration of seizure subtypes††			
Tonic–clonic seizures		2.48 (0.94 to 6.51)	0.07
Tonic seizures		3.40 (0.52 to 22.23)	0.20
Clonic seizures		1.25 (0.15 to 10.57)	0.84
Atonic seizures		7.44 (0.27 to 204.96)	0.24
Myoclonic seizures		2.89 (0.58 to 14.47)	0.20
Countable partial seizures		6.01 (0.83 to 43.21)	0.08
Other partial seizures		1.00 (<0.01 to >999.99)	1.00
Absence seizures		0.61 (0.14 to 2.62)	0.50
Change from baseline in other variables‡‡			
Sleep-disruption score	−0.4 (−1.5 to 0.7)		0.45
Epworth Sleepiness Scale score	1.5 (−0.2 to 3.2)		0.08
Quality of Life in Childhood Epilepsy score	1.5 (−3.8 to 6.8)		0.58
Vineland-II score	−2.6 (−6.8 to 1.6)		0.21
Inpatient hospitalizations due to epilepsy	0.0 (0.0 to 0.1)		0.54

Adverse Events Associated with CBD

- 93% CBD
  - 84% Mild/moderate
  - 75% related to treatment
  - 16% serious
  - 8 withdrew due to side effects
  - 12 Elevated aminotransferase levels (in patients taking valproic acid)
- 75% Placebo
  - 95% Mild/moderate
  - 36% related to treatment
  - 5% serious
  - 1 withdrew due to side effects
  - 1 Elevated aminotransferase levels

Table 4. Adverse Events Occurring with a Frequency of Greater Than 10% in Either Trial Group, According to System Organ Class and Preferred Term.*

System Organ Class and Preferred Term	Cannabidiol (N=61)	Placebo (N=59)
	no. of patients (%)	
Gastrointestinal		
Diarrhea	19 (31)	6 (10)
Vomiting	9 (15)	3 (5)
General		
Fatigue	12 (20)	2 (3)
Pyrexia	9 (15)	5 (8)
Infections: upper respiratory tract infection	7 (11)	5 (8)
Metabolism: decreased appetite	17 (28)	3 (5)
Nervous system		
Convulsion	7 (11)	3 (5)
Lethargy	8 (13)	3 (5)
Somnolence	22 (36)	6 (10)

Summary/Conclusions

- CBD significant reduction in convulsive-seizure frequency compared with placebo in children and young adults with drug-resistant Dravet syndrome, who were taking other anticonvulsants.
- Significant effect of global impression of change indicates clinical relevance
- CBD side effects: somnolence, loss of appetite, diarrhea

Concerns/Other Considerations

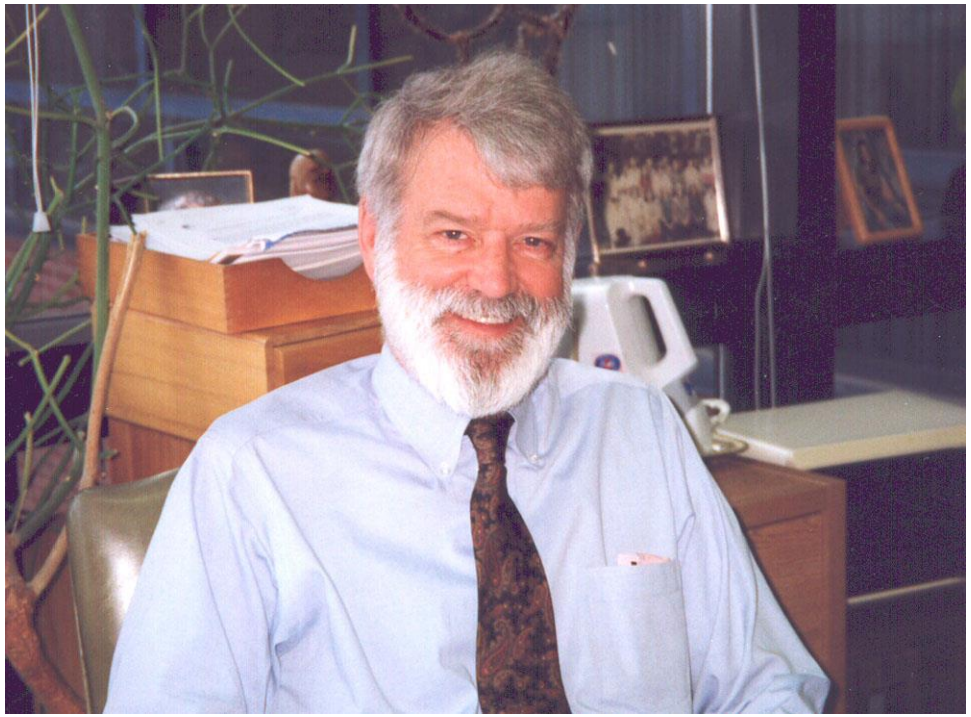
- Drug interactions: CBD metabolized by CYP3A4 and CYP2C19
- Patients obtaining CBD from non-FDA approved sources (e.g., dispensaries, commercially available from Hemp, internet, etc.)
  - Lack of standardized dosing
  - Inaccurate labeling
  - Presence of other chemicals

Potential Therapeutic Indications Cannabinoid-based Drugs

- ✓ Cancer chemotherapy-induced nausea & emesis*
- ✓ Appetite increase in AIDS* and cancer patients
- Metabolic syndrome & weight loss (antagonists)
- Fluid regulation
- Pain and Inflammation
  - Rheumatoid arthritis
  - Spinal/Neuropathic
  - Cancer/chemotherapy
  - Migraine
  - NSAID-induced ulcers
- Pruritus (itching)
- Palliative (quality of life)
- Drug abuse disorders (e.g., cannabis, nicotine, opioids, cocaine, alcohol)
- Psychiatric diseases
  - Anxiety disorders
  - Posttraumatic Stress Disorder
  - Depression
- Brain Injury (e.g., stroke, trauma)
- ✓ Epilepsy*
- Neurodegenerative diseases
  - Spasticity/multiple sclerosis
  - Huntington’s disease
  - Parkinson's disease
  - Alzheimer’s disease
  - Amyotrophic lateral sclerosis
- Cancer

*FDA approved cannabinoid-based medications

Acknowledgements



Professor Billy R. Martin (1943-2008)

NIH National Institute on Drug Abuse
The Science of Drug Abuse & Addiction


Any Questions?

Case Presentation

Dr. Diane Boyer; Region Ten

Case Presentation

DEMOGRAPHIC INFORMATION

- 54 yo male, Caucasian, post-high school
- Carpentry work with father
- With mother and father and two children

- Patient's parents are reliable and supportive

BACKGROUND INFORMATION

- Non small cell cancer of spinal cord with brain mets, opioid use disorder
- Suboxone, Morphine Amitripryline, has completed Gamma knife and radiation interventions
- Is again able to complete ADLs and is working some in carpentry
- Was being seen monthly in OBOT before diagnosis and receiving therapy monthly

Case Presentation

INTERVENTIONS

- No relapse in over a year while dealing with severe chronic pain for last 5 months without diagnosis. MRI during pain management eval revealed cancer

OTHER RELEVANT INFORMATION

- Pain is being well controlled after addition of Morphine to Suboxone

PLAN FOR TREATMENT

Working closely with Palliative Care MD

(my role opioid use disorder treatment; PC role pain management)

Patient's goal: to live as long as he can and be as highly functioning as possible; enjoys working, wants to be around for children (pre-teenagers) as long as possible

Case Presentation

- Patient in Suboxone treatment for opioid use disorder
- Long history of opioid use disorder; past history of methadone treatment and Suboxone treatment
- Currently being treated for Cancer-related pain
- Prescribing MD wanted to continue Suboxone and had added Morphine.

- Looking for additional information on how to best treat opioid use disorder and cancer-related pain.

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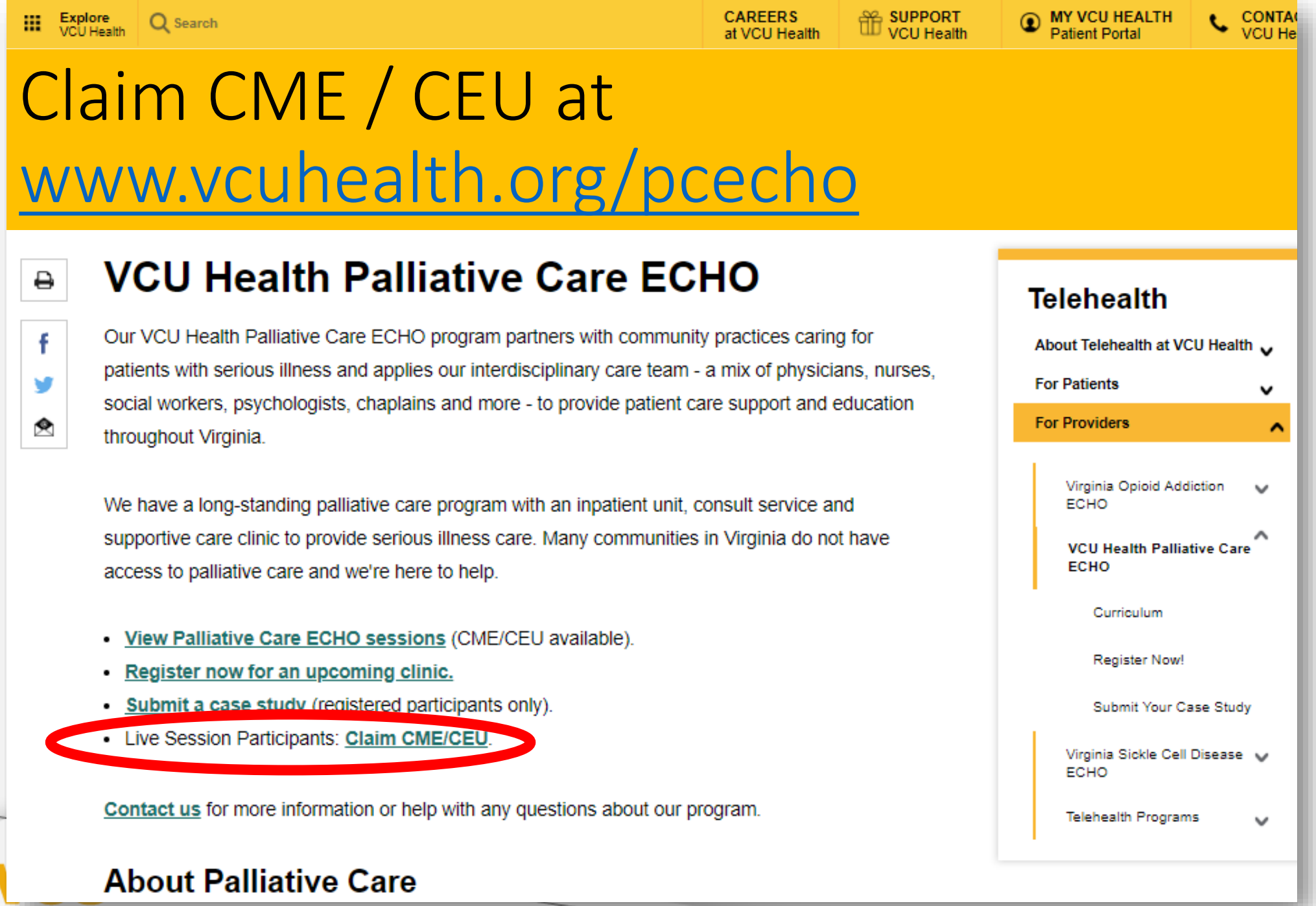

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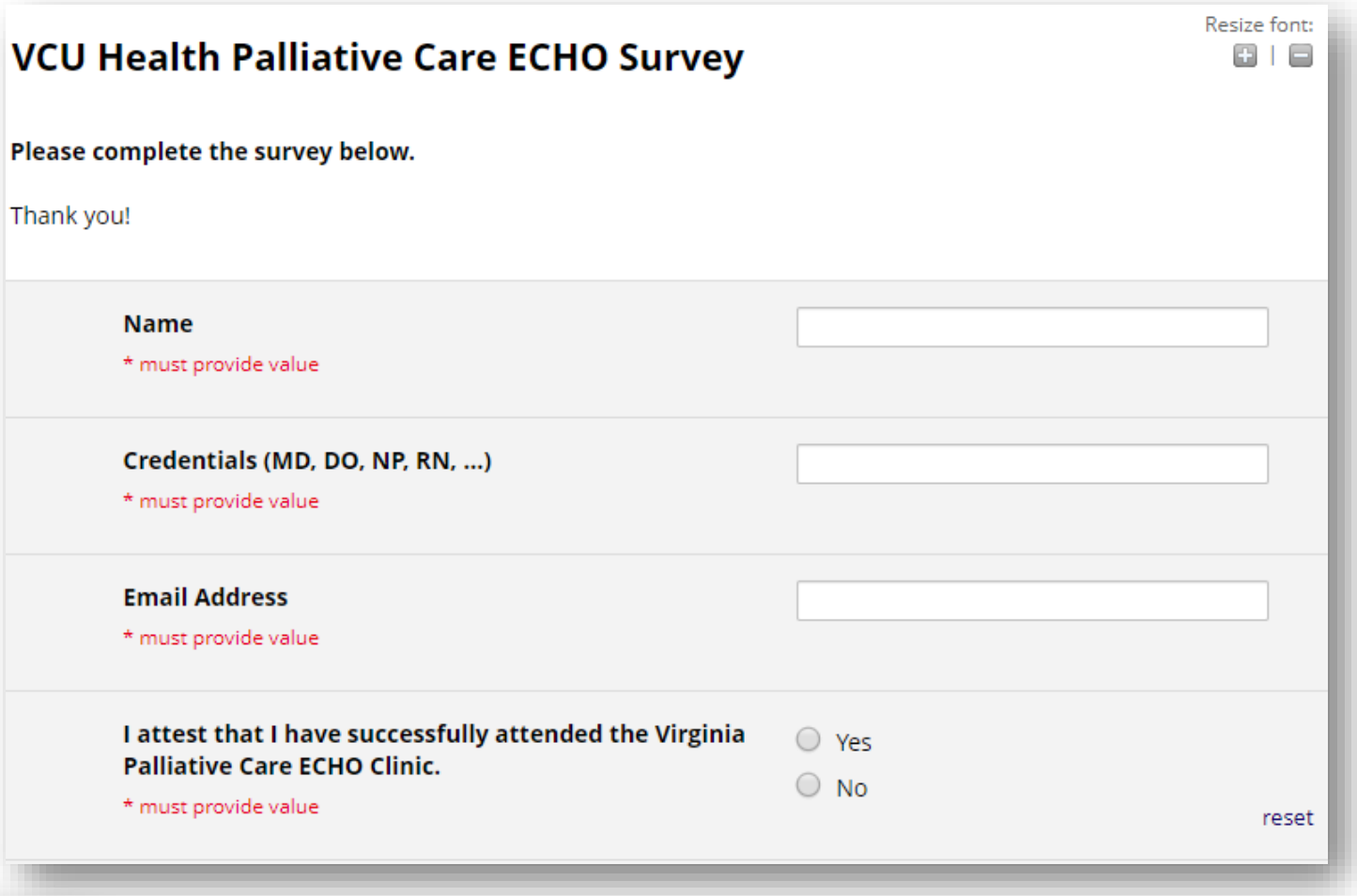

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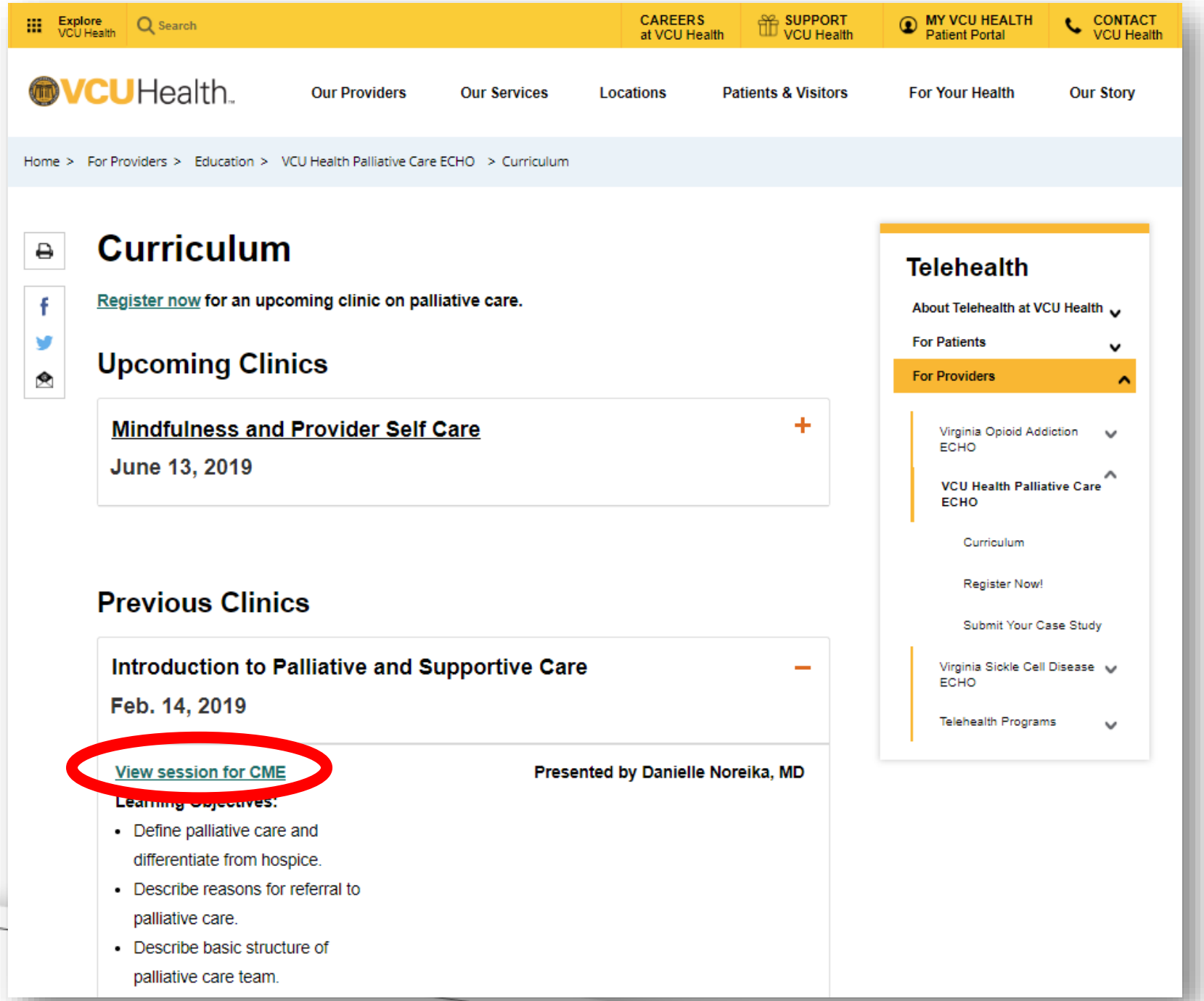

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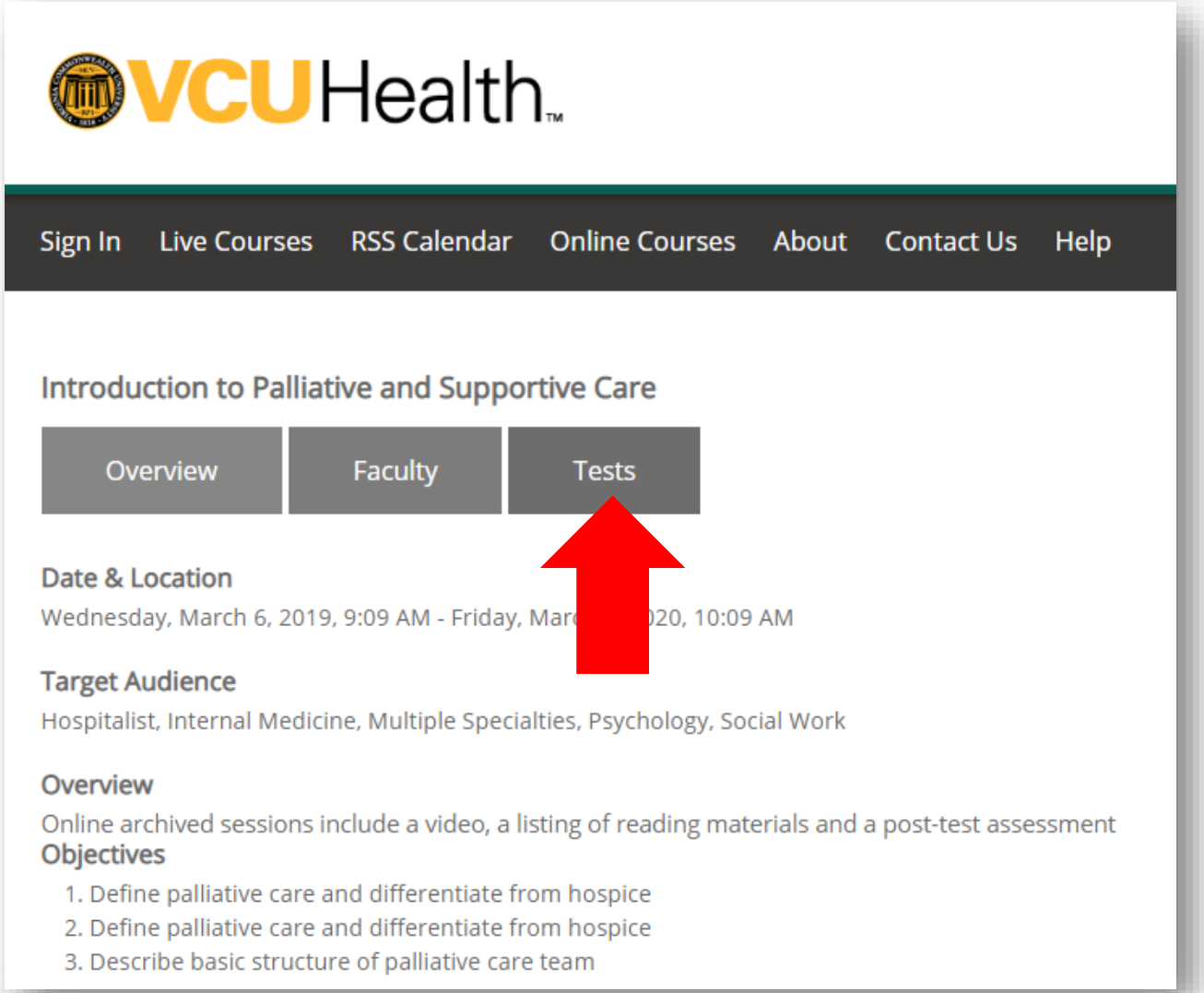

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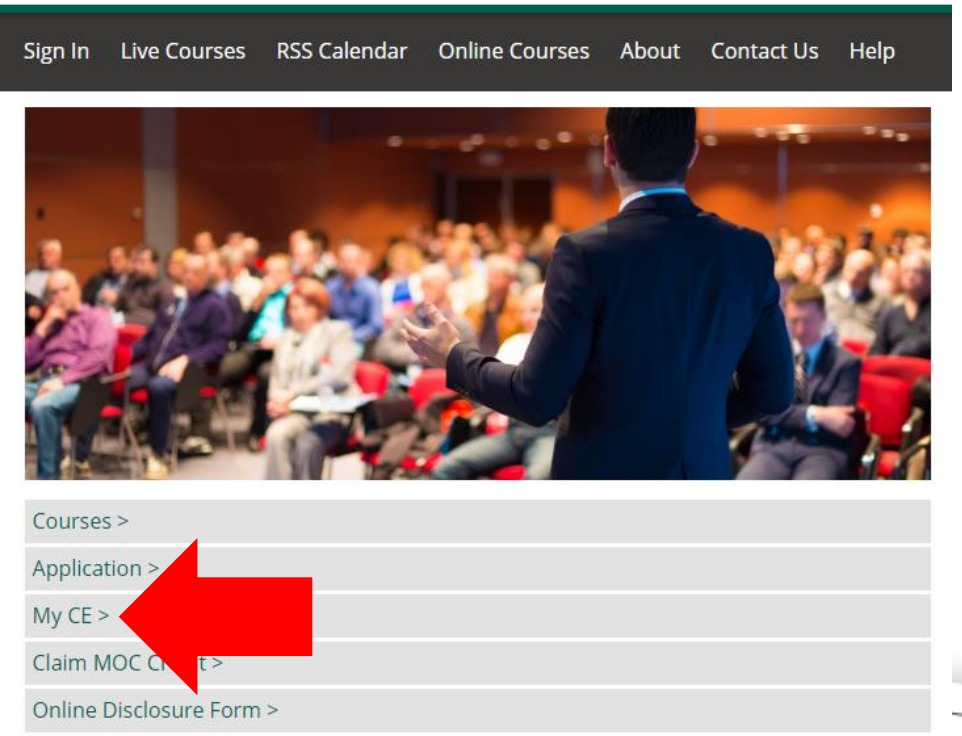

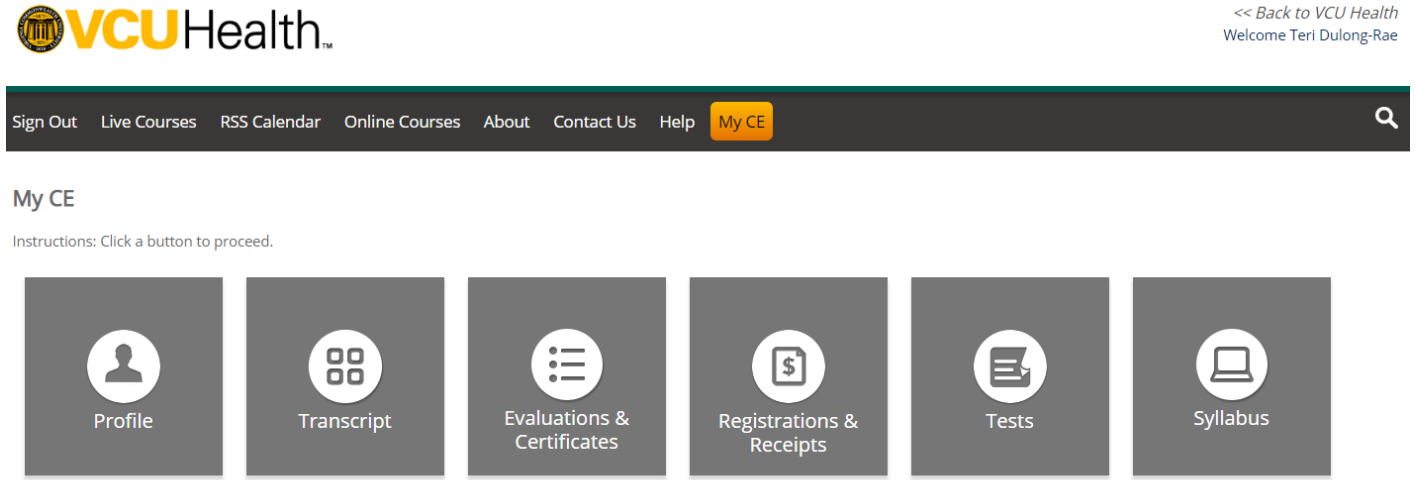

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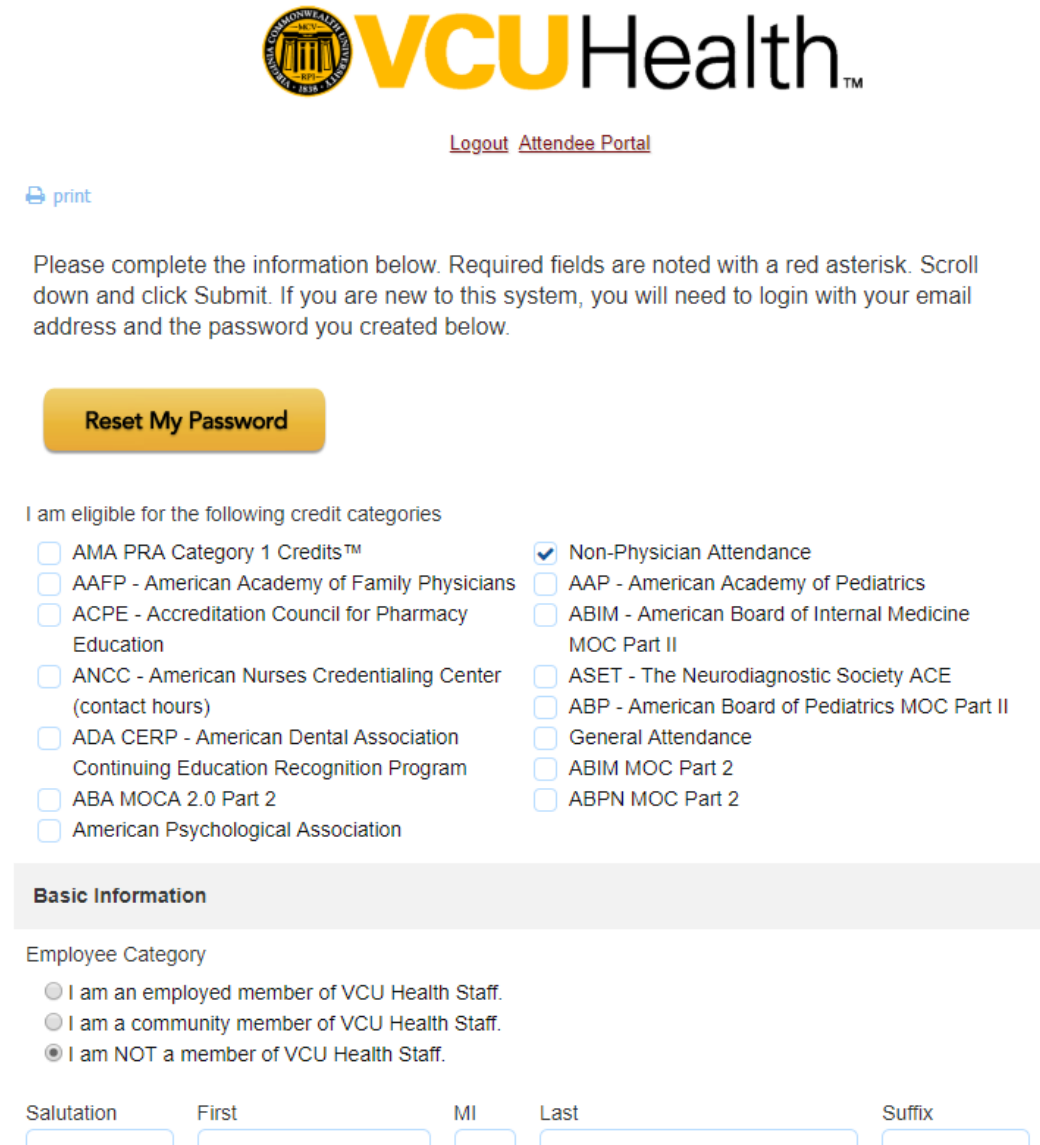

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