VCU Palliative Care ECHO*

August 22, 2019
CBD: What You Need to Know
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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

Right click the Zoom screen to rename your login; include your name and organization.
Helpful Reminders

- Turn on your microphone and video
- If joining audio by telephone, press *6 to mute and unmute
- Activate chat
- Chat box: type here
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     | Teri Dulong-Rae & Bhakti Dave, MPH  
David Collins, MHA  
Frank Green |
| Program Manager   | Teri Dulong-Rae & Bhakti Dave, MPH  
David Collins, MHA  
Frank Green |
| Telemedicine Practice Administrator | Teri Dulong-Rae & Bhakti Dave, MPH  
David Collins, MHA  
Frank Green |
| 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 Pharmaceuticals
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*
- **Foxglove**
  - *Digitalis purpurea*
- **Opium**
  - *Lachryma papaveris*
# Chemical constituents of cannabis

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

![THC molecule](image)
Gaoni and Mechoulam (1964)*
Elucidated the Structure of THC

Isolation, Structure, and Partial Synthesis of an
Active Constituent of Hashish

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. 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 (Δ⁴-3,4-trans-tetrahydrocannabinol). This is the first active component whose constitution is fully elucidated.

*Journal of the American Chemical Society, 86:1646-47
Cannabidiol (CBD)
(Does not elicit cannabis-like effects)


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

CBD

CP55,940

WIN55,212-2
Specific binding site of THC in Brain Tissue

Fig. 1. The synthesis of \([\text{H}] \) CP-55,940 by the tritium reduction of compound 1.

Radiolabeled CP55,940

CB₁ Receptors

Brain
Responsible for most CNS cannabis effects
Also modulates many physiological functions

Devane et al. (1988) Mol Pharm, 34:605-613
CB2 Receptors

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

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

**CB₁ Receptor**

**Potential Therapeutic effects**
- Analgesia
- Anti-inflammation
  - periphery
  - CNS (AD, ALS, etc)
- Anti-cocaine addiction
- No apparent adverse side effects at the receptor

**CB₂ Receptor**

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

**Side Effects**
- Psychomimetic effects
- Abuse liability
- Dependence liability
- Memory impairment
What is/are the underlying mechanism(s) of action CBD?
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 CB₁ and/or CB₂ receptors. CBD also activates the 5-HT₁₆ receptor, PPARγ and the transient receptor potential channels TRPV1, TRPA1 and TRPV2. Finally, CBD inhibits adenosine reuptake and antagonizes GPR55, TRPM8 and T-type Ca²⁺ channels. 5-HT₁₆ and (indirect) cannabinoid receptor activation are the mechanisms that have been implicated in the anxiolytic effects of CBD to date (see Ibeas 8th et al. (2015) and McPartland et al. (2015) for further details).

CBD: Primarily Metabolized by CYP2C19 and CYP3A4

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

Four decades ago: Initial CBD clinical trial

Chronic Administration of Cannabidiol to Healthy Volunteers and Epileptic Patients

Jomar M. Cunha, E.A. Carlini, Aparecido E. Pereira, Oswaldo I. Ramos, Camilo Pimentel, Rubens Gagliardi, W.I. 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

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

* 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).*

<table>
<thead>
<tr>
<th>End Point</th>
<th>Cannabidiol vs. Placebo</th>
<th>P Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change from baseline in CGI score</td>
<td>-1.0 (-1.0 to 0.0)‡</td>
<td>0.02</td>
</tr>
<tr>
<td>Reduction in convulsive seizures from baseline‡</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥25% reduction</td>
<td>2.10 (1.01 to 4.35)</td>
<td>0.05</td>
</tr>
<tr>
<td>≥50% reduction: key secondary end point</td>
<td>2.00 (0.93 to 4.30)</td>
<td>0.08</td>
</tr>
<tr>
<td>≥75% reduction</td>
<td>2.21 (0.82 to 5.95)</td>
<td>0.11</td>
</tr>
<tr>
<td>100% reduction</td>
<td>4.9 (-0.5 to 10.3)</td>
<td>0.08</td>
</tr>
<tr>
<td>Percentage change from baseline in seizure frequency**</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total seizures</td>
<td>-19.20 (-39.25 to -1.17)</td>
<td>0.03</td>
</tr>
<tr>
<td>Total nonconvulsive seizures</td>
<td>0.00 (-21.36 to 31.59)‡</td>
<td>0.88</td>
</tr>
<tr>
<td>Reduction from baseline in duration of seizure subtypes††</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tonic-clonic seizures</td>
<td>2.43 (0.94 to 6.51)</td>
<td>0.07</td>
</tr>
<tr>
<td>Tonic seizures</td>
<td>3.40 (0.52 to 22.23)</td>
<td>0.20</td>
</tr>
<tr>
<td>Clonic seizures</td>
<td>1.25 (0.15 to 10.57)</td>
<td>0.84</td>
</tr>
<tr>
<td>Atonic seizures</td>
<td>7.44 (0.27 to 204.96)</td>
<td>0.24</td>
</tr>
<tr>
<td>Myoclonic seizures</td>
<td>2.83 (0.58 to 14.47)</td>
<td>0.20</td>
</tr>
<tr>
<td>Countable partial seizures</td>
<td>601 (0.83 to 43.21)</td>
<td>0.08</td>
</tr>
<tr>
<td>Other partial seizures</td>
<td>1.00 (&lt;0.01 to &gt;999.99)</td>
<td>1.00</td>
</tr>
<tr>
<td>Absence seizures</td>
<td>0.061 (0.14 to 2.62)</td>
<td>0.50</td>
</tr>
<tr>
<td>Change from baseline in other variables‡‡</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sleep-disruption score</td>
<td>-0.4 (-1.5 to 0.7)</td>
<td>0.45</td>
</tr>
<tr>
<td>Epworth Sleepiness Scale score</td>
<td>1.5 (-0.2 to 3.2)</td>
<td>0.08</td>
</tr>
<tr>
<td>Quality of Life in Childhood Epilepsy score</td>
<td>1.5 (-13.5 to 6.8)</td>
<td>0.58</td>
</tr>
<tr>
<td>Vineland-II score</td>
<td>-2.6 (-8.3 to 1.6)</td>
<td>0.21</td>
</tr>
<tr>
<td>Inpatient hospitalizations due to epilepsy</td>
<td>0.0 (0.0 to 0.1)</td>
<td>0.34</td>
</tr>
</tbody>
</table>
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>
<thead>
<tr>
<th>Table 4. Adverse Events Occurring with a Frequency of Greater Than 10% in Either Trial Group, According to System Organ Class and Preferred Term.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>System Organ Class and Preferred Term</strong></td>
</tr>
<tr>
<td><strong>Gastrointestinal</strong></td>
</tr>
<tr>
<td>Diarrhea</td>
</tr>
<tr>
<td>Vomiting</td>
</tr>
<tr>
<td><strong>General</strong></td>
</tr>
<tr>
<td>Fatigue</td>
</tr>
<tr>
<td>Pyrexia</td>
</tr>
<tr>
<td>Infections: upper respiratory tract infection</td>
</tr>
<tr>
<td><strong>Metabolism: decreased appetite</strong></td>
</tr>
<tr>
<td><strong>Nervous system</strong></td>
</tr>
<tr>
<td>Convulsion</td>
</tr>
<tr>
<td>Lethargy</td>
</tr>
<tr>
<td>Somnolence</td>
</tr>
</tbody>
</table>
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)
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 Amitripyrine, 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.
Journal of Palliative Medicine

FREE ACCESS through August 20, 2019.

Read Now:

Managing Opioid Use Disorder in the Setting of a Terminal Disease: Opportunities and Challenges
Zachary S. Sager, Mary K. Buss, Kevin P. Hill, Jane A. Driver, and Lara M. Skarf
Read Now

Screening for Opioid Misuse in the Nonhospitalized Seriously Ill Patient
Julie L. Mitchell, Leslie J. Blackhall, and Joshua S. Barclay
Read Now

Opioid Screening Practices in the Cancer Pain Patient
Dustin Liebling, Neil Mehta, and Amitabh Gulati
Read Now

Craving Behavior from Opioid Addiction Controlled with Olanzapine in an Advanced Cancer Patient: A Case Report
Se-Il Go, Hae-Na Song, So-Jin Lee, Eduardo Bruera, and Jung Hun Kang
Read Now

[ Open Access ]
Measurement of Chronic Pain and Opioid Use Evaluation in Community-Based Persons with Serious Illnesses
Kathleen Puntillo and Ramana K. Nadu
Read Now

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VCU Health Palliative Care ECHO

Our VCU Health Palliative Care ECHO program partners with community practices caring for patients with serious illness and applies our interdisciplinary care team - a mix of physicians, nurses, social workers, psychologists, chaplains and more - to provide patient care support and education throughout Virginia.

We have a long-standing palliative care program with an inpatient unit, consult service and supportive care clinic to provide serious illness care. Many communities in Virginia do not have access to palliative care and we’re here to help.

- View Palliative Care ECHO sessions (CME/CEU available).
- Register now for an upcoming clinic.
- Submit a case study (registered participants only).
- Live Session Participants: Claim CME/CEU

Contact us for more information or help with any questions about our program.

About Palliative Care
Submit your evaluation to claim your CME

VCU Health Palliative Care ECHO Survey

Please complete the survey below.

Thank you!

Name
* must provide value

Credentials (MD, DO, NP, RN, ...)
* must provide value

Email Address
* must provide value

I attest that I have successfully attended the Virginia Palliative Care ECHO Clinic.
* must provide value

Yes
No
reset
View recorded sessions at www.vcuhealth.org/pcecho

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About Palliative Care
Curriculum

Register now for an upcoming clinic on palliative care.

Upcoming Clinics

Mindfulness and Provider Self Care
June 13, 2019

Previous Clinics

Introduction to Palliative and Supportive Care
Feb. 14, 2019

View session for CME
Presented by Danielle Noreika, MD
View previously recorded ECHOs for CME

Click “Tests” to view video of the session and take a short quiz for continuing education credit.
View your CME/CEU transcript

• Go to vcu.cloud-cme.com and click “My CE”
• Log in with the email you used to register for our ECHO session
View your CME/CEU transcript

If you have never logged in before, you may be prompted to enter more information before you can view your transcript.
THANK YOU!

We hope to see you at our next ECHO