Medical Marijuana High on Drug Interaction
Shahrzad Ghanavi Pharm.D.
PGY1 Resident Pharmacist
Boca Raton Regional Hospital
Baptist Health South Florida

Objectives
1. Understand the pharmacology and pharmacokinetics of cannabis
2. Identify common adverse effects of medical marijuana use
3. Recognize medical marijuana drug interactions

Disclosure Statement
➢ The author of this presentation has no relevant financial or non-financial relationships in the products described and reviewed in this presentation

Medical Marijuana in Florida

Federal Law
➢ Since 1996, 31 states and Washington, DC have passed laws allowing medical marijuana
➢ These state marijuana laws do not change the fact that using marijuana continues to be an offense under Federal law

Federal Law
➢ On August 29, 2013 the Justice Department announced that the Department would not challenge state laws that allow for the medical and recreational use of marijuana
Compassionate Medical Cannabis Act of 2014
- In 2014, the Florida Legislature passed the "Compassionate Medical Cannabis Act"
- The Act authorized the DOH to establish the Office of Compassionate Use (OCU) in order to implement and manage the various aspects of the program

Right to Try Act
- 2015 - Right to Try Act, §499.0295, F.S. • Allowed terminally-ill patients (death within 1 year of diagnosis) to receive experimental medications that passed Phase 1 of a clinical trial
- 2016 – Added Low-THC cannabis and medical cannabis to Right to Try Act

Amendment 2
- The Florida Medical Marijuana Legalization Initiative
- November 8, 2016
- Approved by 71% of Florida voters

Timeline of Medical Marijuana in Florida
- 2014 • Compassionate Medical Cannabis Act
- 2015 • Right to try Act
- 2016 • Additional of Medical Marijuana to Right to Try Act
- 2016 • Medical Marijuana Legalization

The 2019 Florida Statutes
381.986 Medical use of marijuana
- Qualifying medical conditions
  - Cancer
  - Epilepsy
  - Glaucoma
  - HIV/AIDS
  - Posttraumatic stress disorder
  - Amyotrophic lateral sclerosis
  - Crohn’s disease
  - Parkinson’s disease
  - Multiple sclerosis
  - A terminal condition
  - Chronic nonmalignant pain

Medical Marijuana and Florida
True or False
➢ Medical marijuana is not the same as cannabidiol (CBD)
  a) True
  b) False

True or False
➢ Marijuana is safe because it is a plant
  a) True
  b) False

Fundamentals of Cannabis

Endocannabinoid System
➢ Endocannabinoid System Role
  • Widespread neuromodulatory system involved in:
    ▪ CNS development
    ▪ Synaptic plasticity
    ▪ Response to endogenous and environmental insults
    ▪ eCBs produced “on-demand” under stimuli due to CB1 receptor agonist activity – provide antinociception
    ▪ Homeostasis
Endocannabinoid System

Cannabis Plant Biology
Species & Strains
- Cannabis Sativa
  - Several subspecies
    - Cannabis Sativa Sativa
    - Cannabis Sativa Indica
    - Cannabis Sativa Ruderalis

Pharmacology of Cannabis

Active Compounds
Phytocannabinoids
- Primary – Tetrahydrocannabinol (THC) and Cannabidiol (CBD)
- Others – Cannabichromene (CBC), Cannabinol (CBN), Cannabigerol (CBG)

Active Compounds
Other compound classes
- Flavonoids – role in plant pigmentation
- Terpenes – role in plant aroma

Active Compounds
- Inter-strain variability in THC:CBD ratio
- C. Indica dominant strains tend to produce more CBD relative to THC
- C. Sativa dominant strains tend to produce more THC relative to CBD
Pharmacology

- Psychotropic effects
  - Both psychological stimulation and sedation
- Somatic effects
  - Analgesia, antinociception, and orexigenia
- At high doses
  - Induces anxiety, tachycardia, and hypertension

The mechanism of action of phyto-, endo-, and synthetic cannabinoids involves activation of receptors, CB1 and CB2

- CB1 is expressed in both the central and peripheral nervous system
- CB2 is expressed mainly in the peripheral nervous system

THC Pharmacology and Effect

- Interacts with CB1 and CB2 as an orthosteric agonist

Psychoactive effects (dose and route dependent)
  - Euphoria (≤ dose)
  - Anxiolytic or Anxiogenic (≥ or > dose)

CNS Depressant (≤ or ≥ doses)
  - Drowsiness, somnolence
  - Mental slowness, impaired reaction time
  - Cognitive impairment
  - Psychosis (≥ ≥ doses)
    - Visual disturbances
    - Nightmares
    - Hallucination
    - Delusions

Cardiovascular effects
  - Syncope, tachycardia, palpitation, peripheral vasodilation

GI effects
  - Dry mouth
  - Anti-emetic
  - Pro-emetic (≥ ≥ cumulative doses)
  - Increased appetite and/or weight gain
THC Pharmacology and Effect
- In younger patients (<25 years) chronic use shows decline in
  - Executive and psychomotor functioning
  - Impulse control and attention

CBD Pharmacology and Effect
- Is a negative allosteric modulator (NAM) of CB1
  - Has negligible “negative” psychoactive effects alone
  - Decreases binding and/or functional response of THC when bound to CB1

CBD Pharmacology and Effect
- Other receptors involved
  - CB2 – anti-inflammatory, Alzheimer’s disease
  - PPARy – anticancer effect, glucose and lipid metabolic effects
  - 5-HT1A receptors – anti-anxiety, anti-depressant, anti-emetic, analgesic
  - GPR – pain regulation, Parkinson’s disease?

CBD Pharmacology and Effect
- TRPV 1 – antipsychotic activity, anti-anxiety, analgesic
- TRPV 2 – anticancer activity
- Nicotinic receptors – Alzheimer’s disease?
- GABA – antiepileptic and anxiolytic

True or False
- There are zero FDA approved medications that have chemicals found in marijuana
  a) True
  b) False

Indication for Prescription
- Chemotherapy-associated nausea and vomiting
  - Marinol® (Dronabinol), Syndros® (Dronabinol) and Cesamet™ (Nabilone)

- AIDS-associated anorexia
  - Marinol® (Dronabinol), Syndros® (Dronabinol)

- Dravet syndrome and Lennox-Gastaut syndrome
  - Epidiolex® (Cannabidiol)
Epidiolex® (Cannabidiol)

Potential Indications
- CBD
  - Generalized anxiety
  - Obsessive compulsive disorder
  - Panic disorder
  - Psychosis

Pharmacokinetics of Cannabis

Pharmacokinetics
- Cannabinoids are lipophilic and can be rapidly absorbed
- Pharmacokinetic profiles of THC and CBD vary considerably:
  - Among users
  - Dose and form
  - Acute and chronic use
  - Route of administration

Routes of Administration
- Inhalation by smoking or vaporization
  - Herbal cannabis, resin, concentrates
- Oral
  - Prescription cannabinoids, edibles, tinctures
- Oro-mucosal or sublingual
  - Lollipops, lozenges
- Topical or Rectal
  - Herbal cannabis, resin, concentrates

Absorption
- Smoked and vaporized vs oral ingestion of cannabis
  - Higher blood levels
  - Quicker onset of action
  - Greater bioavailability
Absorption

- THC peaks by 10 minutes after a single puff/inhalation
- Bioavailability after inhalation:
  - THC: ~25% (range 2%-56%)
  - CBD: ~31% (range 11%-45%)

Effect of Route of Administration on Cmax/Dose

Absorption

Marked interindividual variability

- VARIATION IN PRODUCT MATRIX
- IGNITION TEMPERATURE
- INHALATION DYNAMICS

Absorption

- Oral absorption has more variability and lower bioavailability
- Factors affecting absorption
  - Concentration
  - Physical state of the product/formulation (matrix)
  - Disintegration/dissolution
  - Rate, vascularity and blood flow, gastric motility, and ambulatory status of the consumer

Distribution

- Distribution: (4-14 L/kg) and is time dependent
- Plasma protein binding: ~97%
- THC release from fat depot is slow

Elimination

- Estimates of cannabinoid elimination half-life vary
- THC has a fast initial half-life (~6 minutes) and long terminal half-life (22 hours)
- CBD has long terminal elimination half-life
  - ~31 ± 4 hours post inhalation
Metabolism

- Major metabolic routes of metabolism are:
  - Decarboxylation
  - Oxidation
  - Conjugation

Structures of THC and Major Metabolites

Drug Interactions

In Vitro and Animal Studies

Interactions with CYP450s

- High potential for first-pass marijuana-drug interactions
- Inhibition of CYPs expressed in the intestine and liver
- CBD showed a higher potential than THC

Interactions with CYP450s

- Substrate
  - CYP2C9 (THC)
  - CYP2C19 (CBD)
  - CYP3A4 (CBD and THC)

- Inhibitor
  - CYP2B6 (CBD)
  - CYP3A4 (CBD)
  - CYP2D6 (CBD)

- Inducer
  - CYP1A2 (Cannabis smoke)
  - CYP2B6 (CBD)
Interactions with (UGTs)
- Glucuronidation is a major Phase II biotransformation process
- CBD and CBN show in vitro inhibition and induction of certain uridine 5-diphospho-glucuronosyl transferases (UGT1A7/8/9)
- CBD has been reported to inhibit ethanol glucuronidation
- CBN increases ethanol glucuronidation in a concentration-dependent manner

Interactions with Transporters
- Cannabinoids are both substrates and inhibitors of drug transporters
- Currently studied drug transporters include:
  - ATP efflux transporters
  - Breast cancer resistance protein (BCRP) transporters
  - Multi-drug resistance associated protein (MRP)
  - P-glycoprotein

Interactions with Transporters
- Terpenes have also been shown to inhibit these drug transporters
- Cannabinoids can:
  - Decrease protein expression of P-gp
  - Increase protein expression of BCRP
- Flavonoid glycosides can inhibit OATP1A2 and OATP2B1

Pharmacogenomics
- Polymorphisms in either gene ABCB1 and ABCG2 that encode P-gp and BCRP respectively
- CYP2C9*2 and CYP2C9*3 polymorphisms may lead to reduced formation of 11-OH-THC

Drug Interactions
Human Clinical Drug Interactions

Epidiolex
- In patients receiving Clobazam
  - Inhibition of CYP2C19 has lead to increase plasma concentration of active metabolite Ndesmethylclobazam
  - Increased sedation reported
  - N-desmethylclobazam concentrations remained higher at eight weeks after dosage adjustment of clobazam
Epidiolex

- Assessment of ALT, AST, and total bilirubin prior to initiating treatment, with dose changes or the addition of or changes in hepatotoxic medications
- Discontinue treatment if transaminase levels >3 x ULN, bilirubin levels >2 x ULN

Dose adjustment with moderate to severe hepatic impairment
- Substrate of CYP2C19 (minor), CYP3A4 (minor), UGT1A7, UGT1A9, UGT2B7
- Inhibits CYP2C19 (moderate)

Theophylline

- Smoking Cannabis has lead to approximately 40% higher mean clearance of Theophylline due to CYP1A2 induction

Summary

- Clinically significant interactions:
  - Inhibition of hepatic CYP2C19
  - Case report suggested inhibition of hepatic CYP2C9

Summary

- In vitro-in vivo extrapolation suggested risk for interactions mediated via:
  - Inhibition of intestinal CYP3A
  - Hepatic CYP1B1, CYP2B6, CYP2C9, and CYP2C19 by THC and CBD
  - Hepatic CYP1A1, CYP1A2, CYP2A6, CYP2D6, and CYP3A by CBD

Summary

- In vitro inhibition and induction of certain UGTs
- In vitro and animal studies on efflux transporters, such as P-gp, BCRP, and MRP1
- Potential marijuana-drug interactions via inhalation of marijuana due to CYP1A1 induction
Conclusion

Marijuana-drug interactions remains challenging to study due to:

- Schedule I classification
- Diversity of marijuana strains and derivative products on the commercial market
- Variety of routes of administration

References

Immunizations Review & Concerns
Vanessa Tomm, PharmD
PGY1 Pharmacy Resident

Objectives
- Review current trends with vaccine-preventable diseases
- Identify patient populations at increased risks to communicable diseases as well as those in whom vaccinations are contraindicated
- Describe recent vaccination schedule updates and immunization legislation and how it may impact pharmacy practice

Meningitis Outbreak at UCSB
- Four cases of invasive meningococcal disease occurred in November 2013
- UCSB undergraduate students
- 
  - Serogroup B previously had not been available in the USA as a meningococcal vaccination

Meningitis Outbreak at UCSB
- UCSB student, a promising lacrosse and soccer player underwent limb amputation
- Family asked the FDA to fast track Bexsero’s approval
- Bexsero was offered to 20,000 students at UCSB

Freedom to choose and my right to be safe: Controversy in Immunizations

Review
Reasons
Concerns
Pharmacist Role
Cases
"We often fear what we do not understand. Our best defense is knowledge.”
-Tuvok

**REVIEW IMMUNIZATION BASICS**

**Immunity Types**

- Antibodies are disease-specific
- **Two types of immunity:**
  - *Active*
  - *Passive*

**Active Immunity**

- Results when exposure to a disease organism triggers the immune system to produce antibodies to that disease
- Occur through infection or introduction
- Long-lasting
Immunity Types

Passive Immunity

- Provided antibodies to a disease rather than producing own
- **Examples of Immunoglobulins:**
  - Human Hepatitis B
  - Human Rabies
  - Human Tetanus
  - Immunoglobulin G

Vaccine and Immunity

Vaccine and Boosters

Vaccine Types

<table>
<thead>
<tr>
<th>Type</th>
<th>Process</th>
</tr>
</thead>
<tbody>
<tr>
<td>Live Attenuated Vaccine</td>
<td></td>
</tr>
<tr>
<td>Inactivated Vaccine</td>
<td></td>
</tr>
<tr>
<td>Subunit/Conjugate Vaccine</td>
<td></td>
</tr>
</tbody>
</table>

Herd Immunity

- Protecting a whole community from a disease by immunizing a critical mass of its population
- Indirect and direct protection
Routes of Administration

**IM (Intramuscular)**
- DTaP, DT, Tdap, Td
- Hib
- HepB
- HepA
- HPV
- MenACWY
- MenB
- PCV & PPSV
- IPV
- Zos: Shingrix
- Combination:
  - Pediarix
  - Pentacel
  - Kinrix; Quadracel
  - Twinrix
- MMR
- PPSV
- IPV
- VAR
- Zos: Zostavax
- Combination:
  - ProQuad
- RV
- Flumist

**SQ (Subcutaneous)**
- HMM
- PPSV
- SPV
- VAX
- Zos: Zostavax
- Combination:

**PO (Oral)**
- Rota
- Nipah
- Quadracel
- Taihara

**IN (Intranasal)**
- Flu

----

Common Contraindications to Vaccines

- Family history of altered immunity
- Severe immunodeficiency
- Encephalopathy
- Severe allergic reaction
- Pregnancy

Specific Contraindications to Vaccines

<table>
<thead>
<tr>
<th>Immunization</th>
<th>Contraindication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatitis B</td>
<td>Hypersensitivity to yeast</td>
</tr>
<tr>
<td>PCV13</td>
<td></td>
</tr>
<tr>
<td>HPV</td>
<td></td>
</tr>
<tr>
<td>LAIV</td>
<td>Taken influenza antiviral medications</td>
</tr>
<tr>
<td></td>
<td>within previous 48 hours</td>
</tr>
<tr>
<td>Rotavirus</td>
<td>History of intussusception</td>
</tr>
</tbody>
</table>

Immunizations: Multiple Vaccines

- “Live-Live Rule”
  - Such vaccines must either be given:
    - Same date OR
    - Separated by at least 28 days
  - Not produce a proper immune response
  - Invalid dose

Vaccinating Adults: HALO

<table>
<thead>
<tr>
<th>Letter</th>
<th>Factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>Health</td>
</tr>
<tr>
<td>A</td>
<td>Age</td>
</tr>
<tr>
<td>L</td>
<td>Lifestyle</td>
</tr>
<tr>
<td>O</td>
<td>Occupational</td>
</tr>
</tbody>
</table>
**HALO: Specific High Risk Groups**

**Health & Age Factors**

- Adult 65 YO and Older
- Diabetes
- Pregnancy
- HIV/AIDS
- Young Children < 2 YO
- Cancer
- Asthma
- Children with Neurologic Conditions
- Heart Disease
- BMI ≥ 40

---

**Question Time**

#1 True or False: The following populations are at a higher risk for experiencing complications with influenza: those less than two years old or greater than 65 years of age, those with asthma, and those with a BMI of 35 or higher.

**ACIP & Vaccination Schedule**

- ACIP
- AAP
- AAFP

- Reviews data from clinical trials and other studies to develop recommendations
- ACIP continues to monitor vaccine safety and effectiveness post-market
- May change/update recommendations based on new data

---

**ACIP Considerations**

- How safe is the vaccine when given at specific ages?
- Does the vaccine work at specific ages?
- How serious is the disease this vaccine prevents?
- How many children would get the disease the vaccine prevents if we did not have the vaccine?

---

**Vaccine Safety Monitoring**

How a vaccine’s safety continues to be monitored

- Clinical Monitoring Safety Assessment Project (CMSAP)
- Vaccine Safety Datalink (VSD) Program
- Vaccine Safety Study (VSS)

- Reviews data from clinical trials and other studies to develop recommendations for vaccine safety monitoring.
- May change/update recommendations based on new information to ensure vaccine safety.
- Clinical monitoring safety assessment project (CMSAP) provides comprehensive data on vaccine safety.

---

**Question Time**

#1 FALSE: The following populations are at a higher risk for experiencing complications with influenza: those less than two years old or greater than 65 years of age, those with asthma, and those with a BMI of 35 or higher.
Florida Law Requirements

Public/Non-Public Preschool Entry
- DTaP
- IPV
- Hib
- Hepatitis B (Hep B)
- Varicella

Public/Non-Public Schools
Kindergarten - 12th Grade
- 4-5 doses of DTaP
- 4-5 doses of IPV
- 2 doses of MMR
- 3 doses of Hep B
- One Tdap
- 2 doses of Varicella
- Varicella vaccine not required
  *if varicella disease history documented by health care provider

Immunization Requirements: Chapter 1003 Section 22


Florida versus USA


Vaccinate Only Adults

- Effective 2/1/2015
- Florida pharmacist license active and in good standing
- Certification program of 20 hours
- Registered with Florida SHOTS
- May give immunizations listed and recommended in CDC's Adult Immunization Schedule

Vaccinate ONLY Adults: Chapter 455 Section 189

Florida Pharmacist: Vaccine Limitations

- Yellow Fever requires additional certification
- Vaccine supply shortage and limited number of IND providers
- Florida Department of Health will not be processing any new applications to certify any new yellow fever vaccine providers

CDC course available at: https://www.cdc.gov/travel/page/yellow-fever-vaccine-course

0.24 CEUs

Question Time

#2 True or False: Additional CEs are required for pharmacists to vaccinate patients/customers for Yellow Fever.

#2 TRUE Additional CEs are required for pharmacists to vaccinate patients/customers for Yellow Fever.
REASONS TO IMMUNIZE

Ten Threats to Global Health in 2019
1. Air pollution and climate change
2. Noncommunicable diseases
3. Global influenza pandemic
4. Fragile and vulnerable settings
5. Antimicrobial resistance
6. Ebola and other high threat pathogens
7. Weak primary health care
8. Vaccine hesitancy
9. Dengue
10. HIV


Vaccine Hesitancy
- Reluctance or refusal to vaccinate despite vaccine availability
- Threatens to reverse progress made in decreasing incidence of vaccine-preventable diseases

Reasons Behind Not Vaccinating
- Religious reasons
- Personal beliefs/philosophical reasons
- Safety concerns
- Parent’s desire for additional education

Impact of Vaccine Hesitancy
- Vaccination is one of the most cost-effective ways of avoiding disease:
  - 2-3 million deaths/year
  - 1.5 million deaths could be avoided if global coverage of vaccinations improved
- Measles 30% increase globally

Measles Cases in the US

### Measles & Complications

- **Subacute sclerosing panencephalitis (SSPE)**
- Generally develops 7-10 years after measles infection
- Despite full recovery
- Rare, but fatal disease

---

### Exemptions

- **Medical Exemption:** All states allow medical exemption, and certain states only allow it to be written by a physician
- **Religious Exemption:** Establish that constitutional right to elect not to receive a vaccine
- **Philosophical, Conscientious, or Personal Belief Exemption:** Individuals who hold conscientious objections to one or more vaccines

---

### Florida Exemption Forms

- **Form DH 680:**
  - Medical Exemption
  - Child's physician must state reasons for based on valid clinical reasoning/evidence
- **Form DH 681:**
  - Religious Exemption
  - Conflict with religious tenets and practices of child's parent or guardian
  - Issued by a County Health Department

---

### Why Immunize?

- High possibility of protection without infection
- Morbidity prevention
- Diseases are becoming rare due to vaccinations
  - With reducing rates epidemic can occur
- **Vaccinate to protect our future**

---

### Question Time

- **#3 True or False:** Herd immunity is a situation, in which a sufficient proportion of a population is immune to an infectious disease to make its spread from person to person unlikely. Even individuals not vaccinated are offered some protection because the disease has little opportunity to spread within the community. Also known as community immunity.
Herd immunity is a situation, in which a sufficient proportion of a population is immune to an infectious disease to make its spread from person to person unlikely. Even individuals not vaccinated are offered some protection because the disease has little opportunity to spread within the community. Also known as community immunity.

Concerns with Vaccines

Wakefield et al.


Vaccines & Autism

Brent Taylor et al.

- Relationship between receipt of MMR vaccine and development of autism (n = 498)
- Examined incidence and age at diagnosis of autism in vaccinated and unvaccinated children
  - Percentage of children vaccinated was same in children with autism as in other children in North Thames region
  - No difference in age of diagnosis of autism was found in vaccinated and unvaccinated children
  - Onset of symptoms of autism did not occur with MMR vaccine administration (multi-doses)
- Analyses did not support causal association between MMR vaccine and autism

Madsen et al.

- Relationship between receipt of MMR vaccine and development of autism (n = 537,303)
- ~82% of children had received the MMR vaccine
  - Risk of autism similar in vaccinated and unvaccinated children
  - No temporal clustering of cases of autism at any time after immunization
  - Neither autistic disorder/autistic spectrum disorder were associated with MMR vaccination
- No association between the age at the time of vaccination, the time since vaccination, or the date of vaccination and the development of autism
Vaccine & Autism Link

Centers for Disease Control and Prevention

**Vaccines Do Not Cause Autism**

**Autism is a developmental disability that is usually diagnosed in the first 3 years of life.** People with autism communicate, move, learn, and think in different ways. Many research finds CDC’s autism-related research is consistent with other large epidemiologic studies, communities across the United States. CDC’s commitment to providing accurate data on ASD, seeking for causes of and reasons that increase the risk for ASD, and developing resources that help identify children with ASD as early as possible.

There is no link between vaccines and autism.

Thimerosal & Vaccines

Today, no childhood vaccine used in the US except some formulations of flu vaccine in multi-dose vials use thimerosal as a preservative


Thimerosal in Vaccines

Today

- Significantly declined due to reformulation and development of single-dose vials
- All vaccines routinely recommended for children 6 years of age and younger in the U.S. available as thimerosal free
- Only mostly present in multi-dose vials

Ethylmercury vs. Methylmercury

**Methylmercury**
- Harm CNS
- $t_\text{1/2}:1.5$ months
- Acquired via exposure
- FDA regulated

**Ethylmercury**
- Rapidly eliminated
- $t_\text{1/2}:<1$ week

Vaccines with Thimerosal

- **Trivalent**: Fluvirin (multi and single dose)
- **Quadriant**: Afluria (multi-dose)
  - FluLaval (multi-dose)
  - Fluzone (multi-dose)
Several vaccines at same time does not cause any chronic health problems
Recommended vaccines have been shown to be as effective in combination as they are individually
Based on this information, both the ACIP and the AAP recommend getting all routine childhood vaccines on time.

**Multiple Vaccines**

- No Upper Limit per ACIP
- **Three EXCEPTIONS**: 
  - PCV13 and PPSV23
  - PCV13 and Menactra
  - Cholera and TY21a vaccine

### Immunization Specific Misperceptions

<table>
<thead>
<tr>
<th>Immunization</th>
<th>Misperceived Contraindication</th>
</tr>
</thead>
<tbody>
<tr>
<td>DPT</td>
<td>- Family history of seizures</td>
</tr>
<tr>
<td></td>
<td>- Status of neurodevelopment</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>- Pregnancy</td>
</tr>
<tr>
<td>Measles</td>
<td>- Autoimmune diseases (e.g. systemic lupus erythematosus or rheumatoid arthritis)</td>
</tr>
<tr>
<td>Rotavirus</td>
<td>- Pregnancy</td>
</tr>
<tr>
<td></td>
<td>- Immunocompromised household contacts</td>
</tr>
<tr>
<td>Zoster</td>
<td>- Therapy with low dose acyclovir (e.g. 200 mg three times daily) for treatment of herpes zoster (shingles)</td>
</tr>
<tr>
<td></td>
<td>- Low dose acyclovir (0.5 mg/kg/day) for treatment of herpes zoster (shingles)</td>
</tr>
</tbody>
</table>

### Vaccines and Pregnancy

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Indicated During Every Pregnancy</th>
<th>May Be Given During Pregnancy in Certain Populations</th>
<th>Contraindicated During Pregnancy</th>
<th>Can Be Administered Postpartum or When Breastfeeding a Baby</th>
</tr>
</thead>
<tbody>
<tr>
<td>DTaP</td>
<td>✖️</td>
<td>✖️</td>
<td>✖️</td>
<td>✖️</td>
</tr>
<tr>
<td>Tdap</td>
<td>✖️</td>
<td>✖️</td>
<td>✖️</td>
<td>✖️</td>
</tr>
<tr>
<td>Hepatitis A</td>
<td>✖️</td>
<td>✖️</td>
<td>✖️</td>
<td>✖️</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>✖️</td>
<td>✖️</td>
<td>✖️</td>
<td>✖️</td>
</tr>
<tr>
<td>HPV</td>
<td>✖️</td>
<td>✖️</td>
<td>✖️</td>
<td>✖️</td>
</tr>
<tr>
<td>MMR</td>
<td>✖️</td>
<td>✖️</td>
<td>✖️</td>
<td>✖️</td>
</tr>
<tr>
<td>VAR</td>
<td>✖️</td>
<td>✖️</td>
<td>✖️</td>
<td>✖️</td>
</tr>
</tbody>
</table>

These misperceptions result in missed opportunities to administer recommended vaccines.
FDA and Recalls

June 15, 2017:
- Recalls are publicly listed with Enforcement Report

Vaccines and Recalls

Two recalls between 2014-2019
- 2017:
  - Menveo (Meningococcal Groups A,C,Y,W)
- 2015:
  - Flulaval Quadrivalent (Influenza)

Question Time

#4 A parent presents to you that due to religious reasons that they do not wish to administer the MMR vaccine to their child who is entering Kindergarten. Under Florida regulations is this permitted?

A. Florida law only permits exemptions of vaccines due to medical reasons
B. Florida law only permits exemptions of vaccines due to religious and medical reasons. Form DH680 must be completed.
C. Florida law only permits exemptions of vaccines due to religious and medical reasons. Form DH681 must be completed.
D. Florida law does not allow exemptions of vaccines for any reason
E. This is not a required vaccine

Community Pharmacists

More than 90% of the U.S. population lives within two miles of a community pharmacy

Pharmacies present an accessible option to improve:
- Vaccination rates
- Vaccination capacity
Pharmacist Direct Impact

- Help promote public health with campaigning
- Access regularly updated credible information
- Facilitate communication between patients and other stakeholders about resources
- Lead and establish immunization programs
- Empower other pharmacists and pharmacist interns to become certified

Pharmacists: Minimize Errors

- **Patient assessment**
- **Product selection**
- **Allergies**
- **Consent & VIIR**
- **Flu Shots**
- **Egg Free Influenza Vaccines**
- **Flubok & Flucelax Quadrivalents**

Florida Imunization Bills

<table>
<thead>
<tr>
<th>Bill #</th>
<th>Date</th>
<th>Position</th>
<th>Title</th>
</tr>
</thead>
<tbody>
<tr>
<td>HB 825</td>
<td>12/10/19</td>
<td>Referred to multiple committees</td>
<td>Requires pharmacists to administer any licensed vaccine to children, any age</td>
</tr>
<tr>
<td>SB 674</td>
<td>11/6/19</td>
<td>Referred to Health Policy, Children, Families and Elder Affairs, Rules Committees on 11/6/2019</td>
<td>Requires a minimum percentage of all children enrolled in a child care facility to be vaccinated</td>
</tr>
<tr>
<td>SB 64</td>
<td>8/10/19</td>
<td>Referred to Health Policy, Education and Rules</td>
<td>Requires religious belief exemption to vaccine and creates review board for medical exemptions</td>
</tr>
<tr>
<td>SB 215</td>
<td>8/29/19</td>
<td>Enacted, 6/18/2019, Chapter No. 2019-107, Effective Date: 1/1/2021</td>
<td>Mandatory reporting and tracking of vaccines by health care practitioners in registry</td>
</tr>
</tbody>
</table>

Finding Credible Vaccine Information

- Immunization Action Coalition
- Centers for Disease Control & Prevention
- World Health Organization

Download “CDC Vaccine Schedules” free for iOS and Android

Florida Pharmacist Limitations

- Lack of mandatory reporting
  - **Will be enforced 2021**
- Restricted to adult patients
- Work flow
  - Technicians cannot administer vaccines
  - Pharmacist:pharmacist intern ratio 1:1
  - Protocol under supervisory practitioner
Case 1: Inpatient Discharge
A 10 year old patient with sickle cell anemia is being discharged from the hospital. She has not received her influenza vaccine this season and is up to date with all of her vaccinations until the age of 6 years old. What are some potential recommendations that you may advise the medical team with?
A. Influenza vaccine
B. Meningococcal ACWY vaccine
C. Tetanus, diphtheria, pertussis vaccine
D. Human papillomavirus vaccine

Case 2: School Health Fair
A 36 year old mother with her daughter attends a school fair. Her daughter is catching up on vaccinations. The mother wishes to receive the influenza vaccine. Note she has received her Td booster in the last 5 years. As a preceptor which vaccinations may the pharmacist interns recommend for the mother?
A. Influenza vaccine
B. Human papillomavirus vaccine
C. Tetanus booster
D. None of the above
HPV Vaccine Age Extension

FDA approves expanded use of Gardasil 9 to include individuals 27 through 45 years old

- Gardasil 9 prevents certain cancers and diseases caused by nine HPV types
- About 4,000 women die from cervical cancer caused by certain HPV viruses
- Cancer that affects BOTH men and women

9-14 YO: 2 doses
15-45 YO: 3 doses

Case 3: Community Pharmacy

A 65 year old customer with one dose of Zostavax presents to the pharmacy counter. You inquire if he has received his influenza vaccines for this flu season, in which he responds, “Yes.” What other vaccine recommendations may you inquire about? A. Human papillomavirus vaccine B. Tetanus booster C. Pneumococcal vaccine D. Zoster recombinant vaccine

Zostavax vs. Shingrix

- Shingrix preferred by CDC/ACIP
- Zostavax (51%) vs. Shingrix (90%)


Case 4: Community Pharmacy

You are a managed care pharmacist overseeing transactions for a hospital and receive a notification for a rejection for an influenza vaccine. The patient is a 2 year old receiving an influenza (Afluria quadrivalent) vaccine, in which the product of 0.5 mL is being selected. A previous dose of influenza vaccine was administered 4 weeks ago. How do you respond? A. Override rejection as correct B. Contact provider for product of 0.25 mL dose C. Patient is too young to receive influenza vaccine D. Incorrect for the patient to receive two influenza vaccinations in same season
Minimize Errors

- Assess age
- Assess product selection
- Assess vaccine frequency

<table>
<thead>
<tr>
<th>Age</th>
<th>Afluria Quadrivalent</th>
<th>Fluzone Quadrivalent</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 - 35 months</td>
<td>0.25 mL</td>
<td>0.25 or 0.5 mL</td>
</tr>
<tr>
<td>&gt; 35 months</td>
<td>0.5 mL</td>
<td>0.5 mL</td>
</tr>
</tbody>
</table>

Children 6 months-8 years of age 2 doses of influenza when 1st administration (at least 4 week separation)

Conclusion

- Increased communicable diseases due to vaccine hesitancy
- Pharmacists may inform the public of necessary vaccinations and must be conscientious of contraindications and comorbidities
- Several pending Florida Bills may expand pharmacist practice with immunizations
- Religious and medical exemptions are permitted in Florida

Questions?

“We often fear what we do not understand. Our best defense is knowledge.”

-Tuvok
Inborn Errors of Metabolism: It’s In the Genes

Ashley S. Cherian, PharmD
PGY2 Pediatric Pharmacy Resident
ashley.cherian@jhsmiami.org

Pharmacist Objectives

➢ Describe the pathophysiology and diagnosis of inborn errors of metabolism (IEM)
➢ Discuss agents used in the pharmacologic treatment and management of IEM
➢ Recommend an appropriate treatment and monitoring plan for patients diagnosed with IEM

Technician Objectives

➢ Discuss the pharmacologic treatment options used in IEM
➢ Differentiate between the brand name and generic name of medications used for IEM
➢ Describe the appropriate preparation, storage, and stability requirements of medications used in the management of IEM

Abbreviations

➢ BCAA - branched-chain amino acids
➢ BCKD - branched-chain α-ketoacid dehydrogenase complex
➢ BMP - basic metabolic panel
➢ CK - creatine kinase
➢ CNS - central nervous system
➢ CPS1 - carbamoyl phosphate synthetase 1
➢ DNPH test - dinitrophenylhydrazine test
➢ ECHO - echocardiography
➢ EGK - electrocardiography
➢ ERT - enzyme replacement therapy
➢ GAA - acid-α-glucosidase
➢ IEM - inborn errors of metabolism
➢ LFTs - liver function tests
➢ MRI - magnetic resonance imaging
➢ MSUD - maple syrup urine disease
➢ NAG - N-acetylglutamate
➢ NAGS - N-acetylglutamate synthetase
➢ OTC - ornithine transcarbamylase
➢ PAA - phenylacetic acid
➢ PAGN - phenylacetylglutamine
➢ TPN - total parenteral nutrition
➢ UCD - urea cycle disorders

Background

➢ Group of disorders resulting from the deficiency in activity of an enzyme in a metabolic pathway
➢ Over 500 disorders have been identified
  • Incidence is 1:1,000
➢ 25% of IEM manifest in the neonatal period
  • Signs and symptoms are non-specific
Background

- Florida Newborn Screening is done within 24 hours of birth to test for a total of 54 conditions.
- 3 major genetic centers in Florida:
  - University of Florida Genetics Institute
  - University of South Florida Health
  - Holtz Children’s Hospital – Jackson Health System

Types of Errors

- Amino acid metabolism
- Carbohydrate metabolism
- Lipid metabolism
- Citric acid cycle/electron transport chain
- Urea cycle

Errors in Amino Acid Metabolism

MAPLE SYRUP URINE DISEASE

Background

- Autosomal recessive disease characterized by deficiency in mitochondrial BCKD complex
  - Mutations in BCKDHA, BCKDHB, and DBT genes
- Affects second step in catabolic BCAA pathway
  - Metabolizes ketoacids of leucine, isoleucine, and valine
- High levels of these amino acids, primarily leucine, cause symptoms of disease
- Worldwide incidence 1:185,000 live births

Clinical Presentation

- Signs and symptoms:
  - Encephalopathy
  - Ketosis
  - Cerebral edema
  - Elevated BCAAs
  - Cerumen and urine may smell like maple syrup
- Types:
  - Classic: most common form, neonatal onset
  - Intermediate
  - Intermittent
  - Thiamine-responsive
Labs and Diagnostic Tests
- Newborn screen
- Plasma amino acid analysis
  - Elevated leucine levels
  - Plasma allo-isoleucine greater than 5 µmol/L
- Urine organic acids and ketonuria
- DNPH test
- BCKD enzyme activity
- Molecular genetic testing

Treatment Recommendations
- Acute treatment
  - IV fluids - D10% + 0.45%NS at 1.5 x maintenance
  - Intralipids
  - TPN and feeds
    - BCAA-free formula
    - Amino acid replacement
      - Isoleucine 150 mg/kg/day
      - Valine 100 mg/kg/day
- Goal leucine level
  - Age less than or equal to 5 years old: 100-200 µmol/L
  - Age greater than 5 years old: 100-300 µmol/L

Chronic treatment
- BCAA restricted diet and special formula
- Supplementation with valine and isoleucine
- Thiamine supplementation
  - 10-100 mg/day
- Regular diet and "sick" diet
  - Sick diet
    - Reduction in protein by 50-100% for 24-48 hours
    - Adequate hydration
    - Non-protein energy sources of nutrition
- Liver transplantation
  - Help to restore synthetic function in pathways or products affected by IEM
  - Considered in patients who
    - Have achieved good metabolic control through dietary management
    - Suffer from severe disease manifestation or life-threatening decompensations
  - Not considered a curative treatment option

Evidence and consensus-based guideline created through systematic review
- Addresses 5 main areas
  - Nutrition treatment
  - Optimal BCAA concentrations
  - Thiamine
  - Pregnant patients
  - Liver transplantation

Nutrition treatment
- BCAA free protein
- Fluids and electrolyte monitoring
- TPN and lipids
- Isoleucine and valine supplementation
Optimal BCAA concentrations

- Leucine
  - Age less than or equal to 5 years old: 75-200 µmol/L
  - Age greater than 5 years old: 75-300 µmol/L
- Isoleucine and valine: 200-400 µmol/L

Thiamine challenge: 50-200 mg/day x 1 month

Pregnant patients

- Insure adequate protein and BCAA requirements
- Maintain BCAA levels
- Treat any symptoms aggressively to prevent stressful states
- Increase nutrient intake in women who are breastfeeding

Liver transplantation

- Option for individuals whose MSUD is well-controlled

**Glycogen Storage Disease Type II**

**POMPE DISEASE**

Autosomal recessive trait characterized by GAA deficiency leading to accumulation of lysosomal glycogen in heart, skeletal, and smooth muscle, and the nervous system

- Inherited muscular myopathy
- Mutations in GAA1, GAA2, and GAA4

Incidence: 1:40,000

**Clinical Presentation**

- Limb-girdle syndrome, limb weakness, difficulty walking, head lag
- Dyspnea secondary to diaphragm weakness
- Infantile onset (survival less than 1 year)
  - Cardiac hypertrophy
  - Failure to thrive
  - Feeding difficulties
  - Respiratory infections
- Late-onset

**Labs and Diagnostic Tests**

- Deficiency of GAA
- Elevated serum CK
- Elevated LFTs
- Elevated urinary glucose tetrasaccharide
- Chest x-ray
- EKG and ECHO
- Pulmonary function in late onset
- Newborn screen
Treatment Recommendations

- Supportive care

- Enzyme replacement therapy
  - Alglucosidase alfa (Myozyme®)
    - Cost: $970 per 50 mg vial
    - Dose: 20 mg/kg/dose IV every 2 weeks
    - Administer over 4 hours using a 0.2 micron filter

- Gene therapy

Zhang et al

- Assess safety, effectiveness, and appropriate dosing regimens of ERT in infantile-onset Pompe disease
- Cochrane Database review of trials with ERT in children with infantile onset Pompe disease
- No trials compared effectiveness and safety of therapy to other interventions
- One trial compared Myozyme® dosing

Background

- UCD are a group of rare congenital disorders due to a complete or partial deficiency in the urea cycle
  - Autosomal recessive disorders with the exception of OTC deficiency (X-linked)
- UCD are the primary cause of hyperammonemia in newborns (plasma ammonia greater than or equal to 150 µmol/L)
  - Estimated incidence 1:35,000 births
- Inability to detoxify nitrogen leads to the accumulation of ammonia
Hepatic Encephalopathy

- Damage to liver causes shunting of blood to collateral veins
- Substances bypass metabolism and accumulate
- Accumulation of ammonia causes CNS disturbances
- Hyperammonemia can lead to hepatic encephalopathy

Clinical Presentation

- Complete deficiency typically seen in neonatal period
  - Symptom progression → irreversible cerebral edema, permanent neurologic damage, or death
- Partial deficiencies can be triggered at any time
  - Characterized by
    - Loss of appetite
    - Vomiting
    - Lethargy
    - Behavioral abnormalities
    - Sleep disorders
    - Psychosis

Labs and Diagnostic Tests

- Family history
  - 3 generation history in family members with neurologic signs and symptoms
- Newborn screen
- Hyperammonemia
- BMP and LFTs
- Anion gap less than 20
- MRI
- Plasma amino acid analysis
- Molecular genetic testing

Treatment Recommendations

- Acute Management
  - Protein restriction and reversal of catabolism
  - Fluids and nutritional support
  - Cofactor/enzyme replacement
  - Pharmacotherapy
  - Severe → hemodialysis
- Subsequent treatment is tailored to the specific UCD

- Chronic Management
  - Low protein diet
  - Amino acid supplementation
    - Arginine 100-600 mg/kg/day
    - Citrulline 170 mg/kg/day or 3.8 g/m²/day
  - Nitrogen scavenger therapy
  - Liver transplantation
    - Primarily for more severe UCD deficiencies
## Treatment Recommendations

<table>
<thead>
<tr>
<th>ACUTE MANAGEMENT</th>
<th>CHRONIC MANAGEMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Protein restriction and reversal of catabolism</strong></td>
<td>Low protein diet</td>
</tr>
<tr>
<td><strong>Fluids and nutritional support</strong></td>
<td>Amino acid supplementation</td>
</tr>
<tr>
<td><strong>Cofactor/enzyme replacement</strong></td>
<td>Vitamin and mineral supplementation</td>
</tr>
</tbody>
</table>

**Pharmacotherapy**
- Ammonul® (sodium phenylacetate/sodium benzoate)
  - 455,000 per vial
- Carbaglu® (carbamyl glutamate)
  - $238 per tablet
- Buphenyl® (sodium phenylbutyrate)
  - $14,000 per bottle
- Ravicti® (glycerol phenylbutyrate)
  - $5,755 per bottle

**Severe** → hemodialysis
**Liver transplantation**

## Survival After Treatment with Ammonul® for UCD

**PURPOSE**
- Determine if treatment with Ammonul® reduced mortality due to acute hyperammonemia

**METHODS**
- Open-label, uncontrolled, multicenter study

**RESULTS**
- Patients age greater than 30 days more likely than neonates to survive episode of hyperammonemia ($p < 0.001$)
- Patients age greater than or equal to 12 years more likely to survive than younger patients ($p < 0.001$)
- Patients age less than 30 days with peak ammonia greater than 1,000 µmol/L least likely to survive ($p < 0.001$)
- Dialysis used in 60% of neonates and 7% of patients age greater than or equal to 30 days

## Carbaglu®

- Synthetic analog of NAG which acts as an allosteric activator of CPS1 in liver mitochondria
  - CPS1 → first enzyme in urea cycle, converts ammonia to urea

**Dose**
- 100-250 mg/kg/day PO divided in 2 to 4 doses (round dose to nearest 50 mg)
- 200 mg tablet may be dissolved in 2.5 mL water to final concentration of 80 mg/mL

**贮存**
- Before opening, store CARBAGLU® at room temperature between 59°F to 86°F (15°C to 30°C).
- After opening, store CARBAGLU® at room temperature between 59°F to 86°F (15°C to 30°C).
- Do not use CARBAGLU® if the vial is cracked or if the bottle is cloudy.
- Keep CARBAGLU® tablets in a tightly closed container to protect the tablets from moisture.
- Write the date the CARBAGLU® tablet container is opened on the container label.
- Do not use CARBAGLU® tablets after the expiration date on the tablet container.
Efficacy and Role of Carbaglu® in NAGS deficiency

- Effective in treating acute hyperammonemia by avoiding need for detoxification in acute decompensation
- Doses in reports ranged from 100-250 mg/kg/day divided four times a day for acute hyperammonemia
- Effective in maintaining ammonia levels and avoiding need for additional drug therapy and protein restriction in long-term management
- Successfully used in other UCD as well as other IEM such as MSUD

Nitrogen Scavenger Therapy

- Buphenyl®
  - Weight less than 20 kg: 450-600 mg/kg/day in divided doses with feeds 3 to 6 times daily
  - Weight greater than or equal to 20 kg: 9.9-13 g/m²/day in divided doses with feeds/meals
- Ravicti®
  - Phenylbutyrate-naïve: 5-12.4 g/m²/day in divided doses with feeds/meals 3 times daily
  - Switching from sodium phenylbutyrate: daily dose of Buphenyl® (g) x 0.86

Ammonia Control in Children with UCD: Buphenyl® vs Ravicti®

<table>
<thead>
<tr>
<th>PURPOSE</th>
<th>Comparison of 24 hour ammonia profiles and correlation of drug effects of Buphenyl® vs Ravicti®</th>
</tr>
</thead>
<tbody>
<tr>
<td>METHODS</td>
<td>Phase 2, open-label, fixed sequence, switch-over study</td>
</tr>
<tr>
<td>RESULTS</td>
<td>Ammonia values 25% lower in Ravicti® vs Buphenyl® in per protocol population (p &lt; 0.05)</td>
</tr>
<tr>
<td></td>
<td>No statistically significant differences in PAA vs PAGN exposure</td>
</tr>
<tr>
<td></td>
<td>Plasma ammonia exposure lower in patients taking Ravicti®, but not statistically significant</td>
</tr>
<tr>
<td></td>
<td>Ravicti® was found to be equivalent to Buphenyl®</td>
</tr>
</tbody>
</table>

Summary

- IEM is a group of disorders in which a single gene defect causes a block in a metabolic pathway, leading to accumulation of a substrate or deficiency of a product in the pathway
- Management of IEM generally includes therapies to target specific deficiencies or manage accumulation of toxic metabolic products, in addition to dietary modifications and supplementation
- Treatment options for certain disorders have been shown to be effective and can prolong survival

Question 1

- T/F: IEM is a group of disorders in which a single gene defect causes a block in a metabolic pathway, leading to accumulation of a substrate or deficiency of a product in the pathway
Question 1
➢ T/F: IEM is a group of disorders in which a single gene defect causes a block in a metabolic pathway, leading to accumulation of a substrate or deficiency of a product in the pathway

**TRUE**

Question 2
➢ T/F: Amino acid supplementation with arginine, citrulline, carnitine, valine, or isoleucine may be indicated in the treatment and long-term management of IEM disorders

**TRUE**

Question 3
➢ T/F: Sodium phenylacetate/sodium benzoate is the generic medication name for Ravicti®, a medication used in the management of urea cycle disorders (UCD)

**FALSE**

- Ammonul® = sodium phenylacetate/sodium benzoate
- Buphenyl® = sodium phenylbutyrate
- Ravicti® = glycerol phenylbutyrate

Questions??
Inborn Errors of Metabolism: It’s In the Genes

Ashley S. Cherian, PharmD
PGY2 Pediatric Pharmacy Resident
ashley.cherian@jhsmiami.org
**Postpartum Depression! One IV and I am Back to Happy!**

Gabrielle DuBruille, PharmD  
PGY-1 Resident Pharmacist  
Boca Raton Regional Hospital  
Baptist Health South Florida

**Disclosures**

The author of this presentation has no relevant financial or non-financial relationships in the products described and reviewed in this presentation.

**Objectives**

- Discuss the epidemiology, diagnostic criteria, and pathophysiology of postpartum depression (PPD)
- Review clinical evidence for the treatment options for women suffering with PPD
- Identify treatment regimens for women suffering with PPD
- Evaluate the implication of new drug therapies on the management of PPD
- Recognize side effects and monitoring parameters associated with drugs used in the treatment of PPD

**PPD Introduction**

More intense than "baby blues"

"Baby blues" symptoms: crying spells, mood swings, anxiety, difficulty sleeping

"Baby blues" time frame: resolves around 2 weeks post delivery

**What is PPD?**

A depressive episode that can occur during pregnancy as well as after delivery

**Definitions**

Postpartum depression differs according to different resources:

- DSM-V: onset within 4 weeks
- ICD-10: onset within 6 weeks
- Clinical research and practice: onset within 1 year
Diagnostic Criteria

• Diagnostic and statistical manual for mental disorders (DSM)

Major Depressive Disorder (MDD) Diagnostic Criteria

- One or more major depressive episodes, no history of mania
- > 5 symptoms for at least 2 weeks
- Must have depressed mood or loss of interest

DSM-5 Criteria

Must have at least 5 symptoms, with one being (1) or (2)

1. Depressed mood
2. Loss of interest
3. Weight loss or weight gain
4. Insomnia or hypersomnia
5. Psychomotor agitation or retardation
6. Fatigue
7. Feelings of worthlessness
8. Diminished ability to think or concentrate
9. Recurrent thoughts of death, suicidal ideation, suicide attempt

PPD Diagnostic Criteria

• Same DSM-5 criteria as MDD, but a specifier was created:
  • Postpartum and antepartum depression
    • With peripartum onset
    • Onset of depressive episode during pregnancy or within 4 weeks postpartum

Prevalence

- Postpartum depression: 9%
- Major depressive disorder in women: 10%

PPD Onset

- Antepartum: 38%
- Postpartum: 42%

Highest incidence of postpartum depression occurs in the first 6 weeks after delivery
Pathophysiology

1. Increased hormone sensitivity
2. Altered levels of neuropeptides
3. Altered levels of neurotransmitters
4. Genetics

- Decrease in estrogen, progesterone, and cortisol
- Estrogen and progesterone are responsible for emotional processing, arousal, motivation, and cognition

Altered levels of neurotransmitters
- Allopregnanolone increases during pregnancy, then decreases after childbirth
- Fluctuations linked to depression and anxiety

Altered levels of neuropeptides
- Family history increases risk

Risk Factors
- Previous history of depression
- Family history of depression, mood disorders, or anxiety disorders
- Sexual abuse
- Negative attitude towards pregnancy
- Absence of breastfeeding
- Adolescent pregnancy
- Lack of social support
- Unhealthy lifestyle

Complications of PPD
- Prenatal onset associated with substance abuse, preeclampsia, and low birth weight
- Poor infant nutrition and health
- Weakened maternal-infant bonding time
- Delayed cognitive skills
Treatment Options for PPD

Psychosocial and psychological methods: Mild to moderate PPD

Antidepressants: Moderate to severe PPD

Hormonal therapy: Estrogen, brexanolone (Zulresso®)

When to Consider Antidepressants

- Refractory symptoms not responding to psychological treatment
- Severe symptoms requiring rapid treatment
- Patient preference

Pharmacotherapy

May improve symptoms better than non-pharmacological care

Continue treatment for at least 6 months after effective dose determined

Side effects may be increased in the postpartum period

Antidepressants may take up to 4-6 weeks for maximum effects

Pharmacotherapy

Selection based upon:
- Prior response to antidepressants
- Side effect profile
- Pregnancy category
- Infant exposure
- Patient preference

Antidepressant Options

- Selective serotonin reuptake inhibitors (SSRIs)
- Serotonin norepinephrine reuptake inhibitors (SNRIs)
- Monoamine oxidase inhibitors (MAOIs)
- Tricyclic antidepressants (TCAs)

Question #1

Select the antidepressant(s) that are considered SNRIs:

a) Citalopram (Celexa®)
b) Venlafaxine (Effexor®)
c) Paroxetine (Paxil®)
d) Duloxetine (Cymbalta®)
Assess the benefit of breastfeeding versus the risk of neonatal exposure to medication.

**Quick Review**

### SSRI
- Citalopram (Celexa®)
- Escitalopram (Lexapro®)
- Fluoxetine (Prozac®)
- Paroxetine (Paxil®)
- Sertraline (Zoloft®)

### SNRI
- Desvenlafaxine (Pristiq®)
- Duloxetine (Cymbalta®)
- Levomilnacipran (Fetzima®)
- Venlafaxine (Effexor®)

### TCA
- Amitriptyline (Elavil®)
- Desipramine (Norpramin®)
- Nortriptyline (Pamelor®)

### MAOI
- Phenelzine (Nardil®)
- Tranylcypromine (Parnate®)

**Antidepressants to Avoid**

**Pregnancy**
- Paroxetine (Paxil®): Risk of congenital cardiovascular malformations
- Clomipramine (Anafranil®): Risk of congenital cardiovascular malformations
- MAOIs: Interaction with medications and foods

**Breastfeeding**
- Doxepin (Silenor®): High passage into breastfeeding resulting in possible irritability, convulsions, and respiratory depression in the neonate
- MAOIs: Lack of breastfeeding data, interaction with medications and foods

**Side Effects**

**SSRIs**
- Nausea, vomiting, diarrhea
- Headache
- Hypertension

**SNRIs**
- Similar to SSRIs
- Seizures

**TCA**
- Nausea, vomiting, diarrhea

**Risk Factors**

- Assess the benefit of breastfeeding versus the risk of neonatal exposure to medication

**Low lactation risk**
- Sertraline (Zoloft®)*
- Paroxetine (Paxil®)
- Nortriptyline (Pamelor®)

**Moderately safe lactation risk**
- Fluoxetine (Prozac®)
- Citalopram (Celexa®)
- Venlafaxine (Effexor®)

**Hazardous lactation risk**
- Lithium

**Treatment**

**First line: SSRIs**
- Citalopram (Celexa®), escitalopram (Lexapro®), sertraline (Zoloft®)

**Second line: Switch agents instead of augmentation**
- Different SSRIs, SNRIs, bupropion (Wellburt®), mirtazapine (Remeron®)

**Additional options:**
- Trazodone (Desyrel®), Nefazodone (Serzone®)
- TCAs

**Side Effects**

**SSRIs**
- Anticholinergic side effects
- Orthostatic hypotension
- Possible fatal overdose
- Sedation

**TCA**
- Hypertensive crisis
- Headache
- Dizziness
- Insomnia
Hormonal Therapy

Estrogen Therapy

- Limited evidence supporting use
- Clinical review indicates reduction in symptoms of major depression after 12 weeks in patients with severe PPD
- Place in therapy: Severe PPD, not first line therapy

Brexanolone (Zulresso®)

Endogenous hormone: positive allosteric modulator of GABA-A receptors

Only FDA approved treatment for postpartum depression in adults

Schedule IV controlled substance

Question #2

The mechanism of action of brexanolone (Zulresso®) is related to its direct, rapid increase of serotonin and norepinephrine in the brain

a) True
b) False


Question #3

Brexanolone (Zulresso®) is administered over 60 hours as a continuous infusion

a) True
b) False

Administration

Single continuous IV infusion over 60 hours

Approved as a risk evaluation and mitigation strategy (REMS) drug due to serious adverse reactions

Adverse Reactions

Black Box Warnings (BBW)

- Excessive sedation
- Loss of consciousness

Adverse Drug Reactions

- Suicidal thoughts and behaviors
- Presyncope
- Xerostomia

Terminate infusion if:

- Excessive sedation
- Loss of consciousness
- Hypoxic

Resume infusion at the same dose or lower dose

Do NOT resume infusion

REMS Program

Healthcare settings must be certified in the ZULRESSO REMS to administer the drug

Patients must be enrolled in the ZULRESSO REMS to be able to start treatment

Pharmacies outside the healthcare setting that are preparing the drug for administration must enroll in the ZULRESSO REMS

Dosing

<table>
<thead>
<tr>
<th>Time</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 to 4 hours</td>
<td>30 mcg/kg/hour</td>
</tr>
<tr>
<td>4 to 24 hours</td>
<td>60 mcg/kg/hour</td>
</tr>
<tr>
<td>24 to 52 hours</td>
<td>90 mcg/kg/hour</td>
</tr>
<tr>
<td>52 to 56 hours</td>
<td>60 mcg/kg/hour</td>
</tr>
<tr>
<td>56 to 60 hours</td>
<td>30 mcg/kg/hour</td>
</tr>
</tbody>
</table>

- No renal impairment dose adjustment
- No hepatic impairment dose adjustment

Primary Literature

Brexanolone injection in postpartum depression: two multicenter, double-blind, randomized, placebo controlled, phase 3 trials

Methods

Objective
• Assess the efficacy of brexanolone (Zulresso®) in the treatment of moderate to severe postpartum depression
• Double-blind, randomized, placebo-controlled, phase 3 clinical trials

Design
• Double-blind, randomized, placebo-controlled, phase 3 clinical trials

Inclusion criteria
• 18-45 YO
• < 6 mo postpartum
• Qualifying HAM-D score
  • Study 1: ≥26
  • Study 2: 20-25
• Depressive episode that met DSM-IV criteria
• Negative pregnancy test

Exclusion criteria
• Renal failure requiring dialysis
• Anemia
• Known allergy to allopregnanolone or progesterone
• History of schizophrenia or bipolar disorder

Baseline Demographics

Average age: 28 YO
62% white population
Average HAM-D score: 26

History of depression:
Study 1: 43%
Study 2: 29%

Baseline antidepressant use:
Study 1: 25%
Study 2: 18%

Concomitant antidepressant use:
Study 1: 30%
Study 2: 25%

Study 1 Methods
138 patients with PPD < 6 mo post delivery
Brexanolone 90 mcg/kg/hr titration (n=45)
Brexanolone 60 mcg/kg/hr titration (n=47)
Placebo (n=46)

Study 2 Methods
108 patients with PPD < 6 mo post delivery
Brexanolone 60 mcg/kg/hr titration (n=54)
Placebo (n=54)

Primary Outcome
1° Outcome: Change from baseline in the Hamilton Depression Rating Scale (HAM-D) at 60 hours
• HAM-D determines level of depression
• 17 item scored questionnaire
• Mild depression: 10-13 points
• Mild to moderate depression: 14-17 points
• Moderate to severe depression: >17 points
HAM-D Questionnaire

HAM-D Items
- Depressed mood
- Feelings of guilt
- Suicide
- Initial insomnia
- Insomnia during the night
- Delayed insomnia
- Work and interests
- Retardation
- Agitation

Points:
- 0- Absent
- 1- Sadness
- 2- Occasional weeping
- 3- Frequent weeping
- 4- Extreme symptoms

Secondary Outcome

HAM-D score reduction at
- 0, 2, 4, 8, 12, 24, 48, 60 and 72 hours after infusion
- Follow-up days 7 and 30

Primary Outcome Results

Study 1
- **Brex 60**: 19.5 point reduction
  - (95% CI -8.8 to -2.2)
- **Brex 90**: 17.7 point reduction
  - (95% CI -6.9 to -0.5)

Study 2
- **Brex 90**: 14.6 point reduction
  - (95% CI -4.5 to -0.5)

Secondary Outcome Results

**HAM-D score reduction at 30 days**
- **Study 1 BRX 60**: -13.8 vs -19.5 (95% CI -9.5 to -1.8)
  - p=0.0044
- **Study 1 BRX 90**: -13.8 vs -17.6 (95% CI -7.6 to 0.0)
  - p=0.0481
- **Study 2 BRX 90**: -15.2 vs -14.7 (95% CI -2.0 to 3.1)
  - p=0.6710
**Adverse Drug Reactions**

### Study 1
- Treatment: 41 patients
- Placebo: 22 patients

### Study 2
- Treatment: 25 patients
- Placebo: 24 patients

**Most common**
- Headache: 22 patients
- Dizziness: 17 patients
- Somnolence: 13 patients

**Serious**
- Suicidal ideation: 1 patient
- Intentional overdose attempt during follow-up: 1 patient
- Altered state of consciousness: 1 patient
- Syncope: 1 patient

---

**Study Conclusions**

- Brexanolone (Zulresso®) administration resulted in significant and clinically meaningful reductions in HAM-D total score at 60 hours compared to placebo in women suffering with moderate to severe PPD
- Brexanolone (Zulresso®) is associated with rapid onset of action and durable treatment response
- Due to minimal concomitant antidepressant use, brexanolone (Zulresso®) should be utilized as primary therapy in PPD

---

**Brexanolone (Zulresso®) Place in Therapy**

- Guidelines do not recommend use
- Moderate to severe PPD
- Adults <6 mo postpartum

---

**Hospital Logistics**

- Sufficient budget to approve use
- Medication training for physicians, nurses, and pharmacists
- Stored in the pharmacy's controlled substance safe
- Must be administered in a hospital through a REMS program
- Increased nursing staff required for drug administration and continuous pulse oximetry monitoring

---

**Patient Logistics**

- REMS enrollment
- Drug education prior to administration
- Minimum length of stay: 2.5 days
- Must be accompanied during interaction with children
- Insurance coverage

---

*Image sources:* [Lancet](https://www.thelancet.com), [Women's Mental Health](https://www.womensmentalhealth.org)
Question #4
Brexanolone (Zulresso®) has a BBW for suicidal thoughts and behaviors

a) True
b) False

Brexanolone has a warning for suicidal thoughts and behaviors, not a BBW. It has a BBW for excessive sedation and sudden loss of consciousness.

Thank you!

Postpartum Depression!
One IV and I am Back to Happy!

Gabrielle DuBruille, PharmD
PGY-1 Resident Pharmacist
Boca Raton Regional Hospital
Baptist Health South Florida

References


LGBTQ+ Gender Identification and the Pharmacist’s Approach to Patient Care

Claire Gelin, PharmD, MBA
PGY1 Pharmacy Resident
Bruce W. Carter VA Healthcare System

Objectives
- Define LGBTQ+ inclusive terminology and provide an overview of the community
- Identify healthcare disparities and barriers to care for LGBTQ+ identifying patients
- Describe gender-affirming hormone pharmacotherapy
- Discuss the pharmacist’s role in caring for LGBTQ+ patients

Overview
- LGBTQ+ is an umbrella term coined to incorporate the entire spectrum of sexual orientation
- The “+” denotes additional sexual orientations
- Rainbow flag was popularized as a symbol of the community by San Francisco artist Gilbert Baker in 1978

Overview
- 11% of the U.S. population acknowledge same-sex attraction whereas only 3.5% openly identify as lesbian, gay, or bisexual
- Approximately 0.35% of the U.S. population identify as is transgender
- First gender reassignment surgery was performed in 1966 at Johns Hopkins University Medical Center

The Gender Unicorn

Gender Terminology
- Cisgender
  - A person whose gender identity aligns with the sex assigned to them at birth based upon external anatomy
- Transgender
  - A term for people whose gender identity and/or expression is different from cultural expectations based on the sex they were assigned at birth
- Non-binary
  - A person who does not identify exclusively as a man or a woman
Sexual Identity Terminology

- Lesbian
  - A woman attracted to other women
- Gay/Homosexual
  - A person attracted to members of the same gender
- Bisexual
  - A person attracted to more than one sex, gender or gender identity

Queer

- Fluid identities and orientations
- Often used interchangeably with “LGBTQ”

Asexual

- A person with low or lacking sexual attraction to others or desire for sexual activity

Pansexual

- A person attracted to others regardless of biological sex, gender identity, or sexual orientation

Personal Identity

Sexual Identity

- Based upon sexual preference and attraction
  - Lesbian
  - Gay
  - Bisexual
  - Asexual
  - Pansexual
  - Heterosexual

Gender Identity

- Based upon how one feels about their gender
  - Cis/transgender
    - Female
    - Male
  - Non-binary
    - Agender
    - Genderfluid
    - Genderqueer

Gender Pronouns

- Some languages, such as English, do not have a third gender pronoun available
  - Feminine: she/her/hers
  - Masculine: he/him/his
- The dichotomy of “he and she” in English does not leave room for other gender identities, which is a source of frustration to the transgender and gender queer communities
  - Neutral: they/them/their
  - Variations: ze/hir/hir

LGBTQ+ Community

- 1 in 100,000 individuals is a transwoman and 1 in 400,000 is a transman
  - Likely a conservative estimate
- In the 2017 publication, Diagnostic and Statistical Manual of Mental Disorders (DSM-5) replaced “gender identity disorder” with “gender dysphoria”
  - Applicable only when a person is significantly distressed by the mismatch between their sex assigned at birth and gender identity

U.S. LGBTQ+ Population 2015-2016
Top 10 Places with Transgender Population

<table>
<thead>
<tr>
<th>State/Territory</th>
<th>Percentage</th>
<th>Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Washington D.C.</td>
<td>2.77%</td>
<td>14,950</td>
</tr>
<tr>
<td>Hawaii</td>
<td>0.78%</td>
<td>8,490</td>
</tr>
<tr>
<td>California</td>
<td>0.76%</td>
<td>218,400</td>
</tr>
<tr>
<td>New Mexico</td>
<td>0.75%</td>
<td>11,750</td>
</tr>
<tr>
<td>Georgia</td>
<td>0.75%</td>
<td>55,050</td>
</tr>
<tr>
<td>Texas</td>
<td>0.66%</td>
<td>125,150</td>
</tr>
<tr>
<td>Florida</td>
<td>0.66%</td>
<td>100,300</td>
</tr>
<tr>
<td>Oregon</td>
<td>0.65%</td>
<td>19,750</td>
</tr>
<tr>
<td>Oklahoma</td>
<td>0.64%</td>
<td>18,350</td>
</tr>
<tr>
<td>Delaware</td>
<td>0.64%</td>
<td>4,550</td>
</tr>
</tbody>
</table>

LGBTQ+ Health Disparities

- Higher rates of depression and anxiety
- Increased alcohol use, substance abuse, and tobacco use
- More likely to be denied access to healthcare or experience harassment from providers
- Higher instances of delaying care
- Increased emergency room visits
- Higher risk of comorbidities

Lesbian and Bisexual Women Health Disparities

- HPV and subsequent cervical cancer
- Intimate partner violence
- Military sexual trauma
- Chronic stress or PTSD especially older population and those who are not open about their sexual orientation

Gay and Bisexual Men Health Disparities

- Higher rates of STIs, STDs, and HIV/AIDS
- Increased exposure risk for hepatitis viruses
- Higher rates of anal cancer and erectile dysfunction
- More likely to have an eating disorder

Transgender Health Disparities

- Twice as likely to be unemployed
- Four times as likely to earn less than $10,000 annually
- Higher incidence of obesity
- More likely to be diagnosed with hypertension and kidney disease
- Approximately 19% of patients have been refused medical care

Gender Affirming Procedures

- Primary medical intervention sought by transgender people
- Allows patients to align physical appearance with personal gender identity
- Non-pharmacological interventions
- Surgeries specific and non-specific to the transgender community
Specific Surgical Interventions
- Feminizing vaginoplasty
- Masculinizing phalloplasty or chest surgery
- Facial feminization procedures
- Voice alteration surgery

Nonspecific Surgical Interventions
- Orchietomy
- Breast augmentation
- Hysterectomy
- Oophorectomy

Nonpharmacological Gender Affirming Interventions
- Chest packing/binding
- Voice modification/therapy
- Facial hair removal
- Genital packing/tucking
- Therapy groups

Male-to-Female (MtF) Gender Affirming Pharmacotherapy
- Estrogen and/or antiandrogen therapy
- Maintain estrogen levels in the physiologic range for menstruating woman
- Target serum levels
  - Estradiol <200pg/mL
  - Testosterone <55ng/dL

Estrogen Products
<table>
<thead>
<tr>
<th>Agent</th>
<th>Formulation</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estradiol</td>
<td>PO</td>
<td>2-6mg daily</td>
</tr>
<tr>
<td></td>
<td>Transdermal patch</td>
<td>0.025-0.2mg every daily</td>
</tr>
<tr>
<td>Estradiol valve</td>
<td>IM/SC injection</td>
<td>5-30 mg every 2 weeks or</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2-10 mg every week</td>
</tr>
<tr>
<td>Estradiol cypionate</td>
<td>IM/SC injection</td>
<td>2.5mg every 2 weeks</td>
</tr>
</tbody>
</table>

Contraindications
- History of DVT/PE
- Hypertriglyceridemia
- Severe hepatic impairment
Effects of Estrogen: MtF

- Antiandrogens
  - Spironolactone
    - Formulation: PO
    - Dose: 100-300mg daily
  - Contraindications:
    - Hyperkalemia
    - Addison disease

Side Effects
- Migraines
- Mood swings
- Hot flashes
- Weight gain
- Increased CV risk
- Increased triglycerides
- Hepatotoxicity
- Gall stones
- Prolactinoma

Monitoring Parameters
- Total estrogen
- Prolactin
- Follicle-stimulating hormones
- Luteinizing hormones
- Electrolytes
- Triglycerides
- Liver function tests
- Weight
- Routine cancer screenings

Female-to-Male (FtM) Gender Affirming Pharmacotherapy
- Testosterone supplementation
- Dosing should reflect the goals of the patient
- Serum levels should within therapeutic range for a male:
  - Non-injectables: 350-1100ng/dL
  - Injectables: 350-700mg/dL

Testosterone Products
- Testosterone Enanthate or Cypionate
  - Formulation: IM injection
  - Dose: 100mg every 2 weeks or 50-100mg every week
- Testosterone Undecanoate
  - Formulation: IM injection
  - Dose: 1g every 6 weeks x 2 doses, then 1g every 12 weeks
- Testosterone Enanthate
  - Formulation: SC injection
  - Dose: 50-100mg every week
- Testosterone (Androgel)
  - Formulation: 1.62% topical gel
  - Dose: 50-100mg daily
Effects of Testosterone: FtM

- Injection site reactions
- Hyperhidrosis
- Alopecia
- Acne
- Vaginal drying
- Elevated hematocrit
- Hypertension

Monitoring Parameters

- Blood pressure at each clinic visit
- Liver function tests
- Lipid panel
- Hemoglobin
- Hematocrit
- Serum testosterone
- Glucose

Building Patient Rapport

- At the first encounter, introduce yourself to the patient
- Identify yourself as an ally
- Ask the patient which pronoun(s) they prefer or if they have changed when appropriate

Pharmacist’s Role

- Provide a safe space for patient’s to effectively communicate their health and life experiences
- Adjust necessary medications based upon sex assigned at birth
  - Creatine Clearance
  - Teratogenic medications
  - CHADS2VASc Score
- Manage co-morbidities and reduce risk

Pharmacist’s Role

- Provide patient education regarding risks associated with gender affirming medications
- Improve patient access to transition medications
- Avoid gender identity assumptions
Possible Ramifications

- Alienation
- Continued lack of care
- Worsening of co-morbidities
- Purchasing gender affirming pharmacotherapy from unlicensed sources

Provider Resources: GLMA

- Gay and Lesbian Medical Association
  - Founded in 1981
  - Includes over 1000 LGBTQ+ healthcare professionals and student allies
  - GLMA Handbook on LGBT Health ~ $100
  - Provider directory available
  - 48 providers listed in South Florida
  - www.glma.org
  - 38th Annual Conference:
    - Sept. 23-26, 2020 in Ft. Lauderdale, FL

Provider Resources: WPATH

- The World Professional Association for Transgender Health
  - Founded in 1979
  - Devoted to the understanding and treatment of gender dysphoria
  - Free Standards of Care e-book
  - www.wpath.org
  - Provider directory available
  - 4 providers listed in South Florida
  - 26th Scientific Symposium
    - Nov. 6-10, 2020 in Hong Kong

Recommendations

- Incorporate LGBTQ+ patient care lectures into healthcare professional student curriculum
- Develop specialty clinics and/or healthcare teams
- Normalize LGBTQ+ patient interaction
- Create inclusive patient forms
- Create and identify safe spaces/zones for LGBTQ+ patients

Question

- True or False:
  LGBTQ+ populations have the higher rates of tobacco, alcohol, and other substance use.

TRUE
LGBTQ+ Health Disparities

- Higher rates of depression and anxiety
- Increased alcohol use, substance abuse, and tobacco use
- More likely to be denied access to healthcare or experience harassment from providers
- Higher instances of delaying care
- Increased emergency room visits
- Higher risk of comorbidities

Question

- True or False:
  Transgendered individuals are equally susceptible to health risks and environmental stressors when compared to cis-gendered individuals.
  
  FALSE

Transgender Health Disparities

- Twice as likely to be unemployed
- Four times as likely to earn less than $10,000 annually
- Higher incidence of obesity
- More likely to be diagnosed with hypertension and kidney disease
- Approximately 19% of patients have been refused medical care

Question

- True to False:
  Pharmacists must consider appropriate dose adjustments for transitioning patients based on their biological gender.
  
  TRUE
Pharmacist’s Role

- Provide a safe space for patient’s to effectively communicate their health and life experiences
- Adjust necessary medications based upon sex assigned at birth
  - Creatine Clearance
  - Teratogenic medications
  - CHAD, VASC Score
- Manage co-morbidities and reduce risk

References

The Role of the Pharmacist in Lethal Injections

Rucha B. Acharya, Pharm.D.
PGY-2 Ambulatory Care Pharmacy Resident
Nova Southeastern University College of Pharmacy
Email: racharya@nova.edu

Objectives
- Explain the difference between euthanasia, physician assisted death, and the double effect
- Compare the pros and cons of physician-assisted death
- Discuss laws addressing lethal injections in Florida
- Describe the pharmacology and administration of lethal injections
- Compare the stance of various pharmacist and medical organizations

What is Euthanasia?

Active Euthanasia¹
- The deliberate administration of lethal drugs to end a terminally ill patient's life
- Active euthanasia remains illegal in almost all countries

Passive Euthanasia¹
- The withholding or withdrawing of treatment which is necessary for maintaining life
- Passive euthanasia is generally accepted worldwide

Euthanasia¹
- An act undertaken by a physician that intentionally ends the life of a person at his or her request
- The physician administers the lethal substance
Factors That Make Patients Seek out Euthanasia¹

- Terminally ill conditions
- Physical conditions
- Psychological factors

Patient Case 1

- DM is a 29 year old female with a diagnosis of stage 4 lung cancer
  - She is told she has 6 months to live
- Her oncologist writes prescription for a lethal dose of secobarbital
- She comes in to the pharmacy and states that she will take this when her suffering becomes too great

Patient Case 2

- WD is an 84 year old female with a diagnosis of stage 4 lung cancer
  - She is told she has 6 months to live
- Her oncologist writes prescription for a lethal dose of secobarbital
- She comes in to the pharmacy and states that she will take this when her suffering becomes too great

Who Would You Dispense the Lethal Medication For?

A. Patient 1 only (29 y/o)
B. Patient 2 only (84 y/o)
C. Both Patient 1 and Patient 2
D. Neither Patient

What is Physician-Assisted Suicide (PAS)²

- A patient self-administers a lethal substance that is prescribed by a physician
Death With Dignity Laws

- Allow **qualified** terminally-ill adults to voluntary request and receive a prescription medication to hasten their death

Qualification for PAS

- The patient must be:
  - A resident of a state that has enacted a death with dignity statute
  - At least 18 years of age
  - Mentally competent

Medications for PAS

<table>
<thead>
<tr>
<th>Medication</th>
<th>Class of Medication</th>
<th>Lethal Dose</th>
<th>Counseling</th>
</tr>
</thead>
</table>
| Secobarbital (Seconal®) | Barbiturate CII    | 9 grams in capsules | - Take on empty stomach  
                      |                     |             | - Take an antiemetic 1 hour prior to ingestion  
                      |                     |             | - Mix with sweet substance to mask bitter taste  
                      |                     |             | - Store out of reach of children and keep away from others to prevent unintentional overdose |
| Pentobarbital (Nembutal®) | Barbiturate CII    | 10 grams in liquid | - Prevent intentional overdose |

Pharmacy Association Stance

- APhA: Supports “informed decision-making based upon the professional judgement of pharmacists, rather than endorsing a particular stance on the issue”
Pharmacy Association Stance

- ASHP: “To reaffirm that pharmacists have a right to participate or decline to participate in medical aid in dying without retribution”.
- “To take a stance of studied neutrality on legislation that would permit medical aid in dying for competent, terminally ill patients”.

Pros and Cons of Physician-Assisted Suicide

Pros

- A pharmacist should dispense the medication for physician-assisted suicide because...

A Common Misconception

- PAS ≠ Suicide
  - The patient does not necessarily want to die
  - The terminal illness is already killing the patient

Pharmacist Code of Ethics

I. A pharmacist respects the covenantal relationship between the patient and pharmacist.
II. A pharmacist promotes the good of every patient in a caring, compassionate, and confidential manner.
III. A pharmacist respects the autonomy and dignity of each patient.
IV. A pharmacist acts with honesty and integrity in professional relationships.
V. A pharmacist maintains professional competence.
VI. A pharmacist respects the values and abilities of colleagues and other health professionals.
VII. A pharmacist serves individual, community, and societal needs.
VIII. A pharmacist seeks justice in the distribution of health resources.

Oath of a Pharmacist

- “I promise to devote myself to a lifetime of service to others through the profession of pharmacy. In fulfilling this vow:
  - I will consider the welfare of humanity and relief of suffering my primary concern.
  - I will apply my knowledge, experience, and skills to the best of my ability to assure optimal outcomes for my patients.
  - I will respect and protect all personal and health information entrusted to me.
  - I will accept the lifelong obligation to improve my professional knowledge and competence.
  - I will hold myself and my colleagues to the highest principles of our profession’s moral, ethical and legal conduct.
  - I will embrace and advocate changes that improve patient care.
  - I will utilize my knowledge, skills, experiences, and values to prepare the next generation of pharmacists.”
Alternative Methods

- Varian, a 68 year old woman living in NY where PAS is illegal
- Diagnosed with a brain tumor and had <6 months to live
- Attempted to die peacefully in the arms of her husband using a cocktail of diazepam, dimenhydrinate, and vodka
- Found by hospice nurse and EMS revived her despite her DNR

Consequence for Refusing to Dispense

- Patient seeks alternative methods
- Death certificate: suicide
- Potential denial of life insurance claim
- Family left with emotional and financial burden

Conclusions

- PAS ≠ Suicide
- Oath of pharmacist includes allowing for relief of suffering
- By refusing to dispense, we are denying these patients autonomy and dignity

Cons

- A pharmacist should not dispense the medication for physician-assisted suicide because...

Professional Integrity

- American Medical Association Stance on PAS:
  - “PAS is fundamentally incompatible with the physician’s role as a healer...”
  - Instead of engaging in assisted suicide, physicians:
    - Should not abandon a patient once it is determined that cure is impossible
    - Must provide appropriate comfort care and adequate pain control
Hippocratic Oath

“I will give no deadly medicine to anyone if asked, nor suggest any such counsel”

Optimization of Palliative Care

- PAS would undermine efforts to maintain and improve care for patients nearing the end of life
  - There is a need for improved pain and symptom control
  - There is a need for improved treatment of psychologic conditions that accompany terminal illnesses
- PAS may be helping few, but neglecting many

Slippery Slope

- Potential for misuse and abuse
- At risk populations may be discounted as unproductive or burdensome
- May be financial motivations by insurance companies
  
  *May lead to nonvoluntary euthanasia*

Slippery Slope

- Barbara, a 64 year old woman in Oregon where PAS is legal
- Suffered from lung cancer
  - Last hope was a $4,000 a month drug that her physician prescribed for her
  - Insurance company refused to pay
  - Instead, agreed to cover a medication for assisted death that would cost ~$50

Common Misconception: A Good Death

- Misconception that PAS is a quick, painless, and guaranteed way to die
  - Cases of patients vomiting pills
  - Cases of waking up instead of dying
  - Cases of a lengthy time to death
  - Cases of severe adverse reactions

Conclusions

- AMA does not support PAS
- Terminally ill patients deserve compassion and care
- May lead to a slippery slope of unintended negative consequences
- Real goal should be improving palliative care for the dying
Double Effect

- If doing something morally good has a morally bad side effect, it is morally OK to do so
  - Providing that the bad side effect wasn’t intended

Patient Case 1

- DM is a 29 year old female with a diagnosis of stage 4 lung cancer
  - She is told she has 6 months to live
  - Her oncologist writes prescription for a lethal dose of secobarbital
  - She comes in to the pharmacy and states that she will take this when her suffering becomes too great

Patient Case 2

- WD is an 84 year old female with a diagnosis of stage 4 lung cancer
  - She is told she has 6 months to live
  - Her oncologist writes prescription for a lethal dose of secobarbital
  - She comes in to the pharmacy and states that she will take this when her suffering becomes too great

Who Would You Dispense the Lethal Medication For?

- A. Patient 1 only (29 y/o)
- B. Patient 2 only (84 y/o)
- C. Both Patient 1 and Patient 2
- D. Neither Patient

PAS = Suicide?

- A. True
- B. False
- C. Unsure

Lethal Injections
Pharmacy Organization Stance on Execution?

A. Support  
B. Oppose  
C. Neutral  
D. Unsure

Use of Lethal Injections

- All states and the federal government use lethal injection as the primary method of execution
- Protocols vary by jurisdiction and use either a one, two, or three drug protocol

History in Florida

- 2019-2 executions
- 2018-2 executions
- 2017-3 executions
- 2016-1 execution
- 2015-2 executions
- 2014-8 executions

Lethal Injection Protocol in Florida

- Three Drug Protocol
  - Etomidate injection
  - Rocuronium injection
  - Potassium acetate injection

Lethal Injection Protocol in Florida

<table>
<thead>
<tr>
<th>Medication</th>
<th>Class</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Etomidate (Amidate®)</td>
<td>General anesthetic</td>
<td>200 mg</td>
</tr>
<tr>
<td>Rocuronium (Zemuron®)</td>
<td>Neuromuscular blocking agent</td>
<td>1000 mg</td>
</tr>
<tr>
<td>Potassium acetate</td>
<td>Electrolyte supplement</td>
<td>240 mEq</td>
</tr>
</tbody>
</table>
Botched Executions\textsuperscript{15}

- Estimated that 3% of U.S. executions from 1890 to 2010 were botched.
- Since 1890:
  - 8,776 total executions
  - 276 botched executions
  - Lethal injections: 75 (7.12%)
  - Lethal gas: 32 (5.4%)

APhA Stance on Prisoner Execution\textsuperscript{17}

"The American Pharmacists Association \textit{discourages} pharmacist participation in execution on the basis that such activities are fundamentally contrary to the role of the pharmacist as providers of health care."

ASHP Stance on Prisoner Execution\textsuperscript{18}

"To acknowledge that an individual’s opinion about capital punishment is a personal moral decision; further, to \textbf{oppose} pharmacist participation in capital punishment; further, to reaffirm that pharmacists have a right to decline to participate in capital punishment without retribution."

Conclusion

- Florida uses a 3 drug protocol for the lethal injection:
  - Etomidate
  - Rocuronium
  - Potassium acetate
- APhA and ASHP both firmly oppose the participation of pharmacists in capital punishment.

References

Introduction

Transitions of care is the process of effectively moving a patient between healthcare locations, providers, or different levels of care. This process allows for coordination and continuity of healthcare as a patient’s health conditions and care needs change. Quality transitions of care has been a major focus to improve patient outcomes and reduce hospital readmission rates.

Hospital Readmission Rates

- Approximately, 20% of Medicare patients are readmitted to the hospital within 30-days
- Estimated 20% of readmissions are caused by uncoordinated transitions of care
- A large percentage of readmissions are due to improper use of medication

Importance of Transitions of Care

- Narrows the gap of communication between healthcare personnel through complete transfer of information
- Potentially prevents adverse side effects
- Promotes safe and timely transfer of patients from one level of care to another
- Decreases hospital readmission rates

Objectives

- Define transitions of care in a community pharmacy and discuss the role of a community pharmacist
- Identify essential components for implementing transitions of care in a community pharmacy setting
- Discuss the relevancy of transitions of care and its correlation to hospital readmission rates
- Determine common barriers and potential solutions to transitions of care services provided in the community pharmacy
- Explain various intervention programs that can be offered during transitions of care in a community pharmacy setting
- Review clinical trials on the impact of community pharmacist on hospital readmission rates
Consequence of Readmission Rates

- Prior to the 2010 Affordable Care Act (ACA), Medicare was spending up to $17 billion due to high readmission rates
- Hospitals maximized their revenues by filling all their beds and billing for services
- In 2012, ACA established the Hospital Readmissions Reduction Program (HRRP)

Hospital Readmission Reduction Program

- Reduces payments to hospitals with excess readmission rates
- Percentage reduction off the entire Medicare reimbursement for the hospital, not just readmissions
- Since the launch of the program, hospitals have experienced approximately $1.9 billion in penalties, including $528 million in the 2017 fiscal year

Hospital Pharmacists Role in Decreasing Hospital Readmission Rates

- The goal is to reduce negative patient outcomes from medication-related errors
- Hospital pharmacists can assist by the following:
  - Effective medication reconciliation
  - Participation on rounds (multidisciplinary teams)
  - Patient education/discharge counseling

THE BIG PICTURE

Impact of Community Pharmacist

- Forefront of patient care
- Improve adherence
- Physician-patient communication
- Medication cost
Clinical Services Provided in Community Pharmacies

- Immunizations
- Health Screenings
- Medication Therapy Management
- Smoking Cessation
- Chronic Disease Management
- Transitions of Care

Transitions of Care in Community Pharmacy

Implementing a Transitions of Care Program

- Establish affiliations with insurance companies and local hospitals
- Advertise pharmacy services
- Qualify patients for transitions of care programs
- Accessibility to patient health records

Eligible Patients for TOC Programs

- Discharged from the hospital within the past 30 days
- Specific number of hospital admissions
- Severity of disease states and other risk factors for re-admission
- History of frequent hospitalizations or emergency department visits
- Several medications and comorbid conditions

Barriers

- Inadequate staffing of pharmacists and technicians
- Lack of time
- Lack of access to hospital data
- Poor communication between physicians and pharmacists
- Lack of physician and patient acceptance
- Lack of reimbursements
- Problems identifying the right person to speak with in regards to establishing a transitions of care program for patients
- Issues with developing a proposal

Community Pharmacy Interventions
Transitional Care Interventions

LACE Index Score

- A risk tool promoted by the Institute of Health Improvement to identify preventable readmissions
  - L: Length of Stay
  - A: Acuity of Admission
  - C: Comorbidities
  - E: Emergency Department Visits within the last 6 months

LACE score ranges from 1-19
- 0-4 Low-risk
- 5-9 Moderate-risk
- ≥ 10 High-risk

Bedside Delivery

- Bedside delivery provides the initial consultations
- Signatures of patient/caregiver and delivering technician/pharmacist obtained for proof of delivery
- Benefits include:
  - 30-day supply of medication
  - Immediate start to therapy
  - Prior authorization completed prior to discharge to avoid future break in therapy

Medication Reconciliation

- Medication Reconciliation should contain all pertinent information including:
  - Name, date of birth, and pharmacy name
  - Known drug allergies and reactions
  - List all prescribed medications, over-the-counter medications, and supplements
    - Name
    - Dose
    - Frequency
    - Indication of Use
    - Prescriber
    - Missed doses

Medication Therapy Management (MTM)

- Upon discharge, patients can be asked to participate in MTM services
- Services can be conducted via telephone or in-person
- The session can be provided within one-week post-discharge to prevent drug events that can induce readmissions
- All elements of MTM sessions should be documented in a secured pharmacy database (Medmonitor, Mirixa and Outcomes, etc.)

Follow-Up Calls

Improving Patient’s Access to Medication

- Only 40% of patients report filling their prescriptions on the day of discharge
- Another 40% wait at least 9 days, with 22% not picking up in the first 10 days after discharge
- Patients may face issues such as:
  - Prior authorizations
  - Prescription clarification
  - Drug out-of-stock

Coordination and continuity required. America’s Pharmacist website. June 2016
Follow-Up Consultations

- A community pharmacist can conduct follow-up phone calls to assess for:
  - Adherence
  - Adverse/Side effects
  - Resolve medication-related issues
  - Refill reminders
  - New-to-therapy calls

Coordination and continuity required. America’s Pharmacist website. June 2016

ADDITIONAL SERVICES

New-to-Therapy Calls

- For newly prescribed medications, pharmacist may call within a week to discuss therapeutic efficacy or issues
- Medication nonadherence is a national problem that can lead to ineffective treatment and additional healthcare expenses
- A single telephone call from a trusted community pharmacist may improve medication adherence
- Optimally, reducing hospital readmissions

Coordination and continuity required. America’s Pharmacist website. June 2016

Pill Packaging

- Medications are packaged in blisters under the supervision of a pharmacist
- Dosage times are marked and can be identified by color-coded columns
- Blister pack contains multiple pills in one blister
- May be more convenient for patients taking multiple medications

Coordination and continuity required. America’s Pharmacist website. June 2016

Clinical Study

Impact of community pharmacy post-discharge medication therapy management on hospital readmission rate

| Purpose | To determine if a community pharmacy-based transitions of care program would decrease hospital readmissions, resolve medication-related problems, and increase patient satisfaction |
| Methods | Prospective, quasi-experimental study |
| Inclusion Criteria: | • ≥ 18 years old • Discharged from two local hospitals • Diagnosed with CHF, COPD, or Pneumonia |

Impact of community pharmacy post-discharge medication therapy management on hospital readmission rate cont’d

Setting: Nine Kroger Pharmacies located in Western Cincinnati
Interventions: Pharmacist intervention vs. usual care
Outcomes: 
   Primary: 
     - 30-day readmissions
   Secondary: 
     - 30-day ED visits
     - Composite
Enrollment: 106 eligible patients, 90 patients completed the study

Study Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Usual care (n=36)</th>
<th>Pharmacists intervention (n=36)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease</td>
<td>15(25%)</td>
<td>9(50%)</td>
<td>0.05</td>
</tr>
<tr>
<td>Diabetes</td>
<td>9(25%)</td>
<td>12(33%)</td>
<td>0.14</td>
</tr>
<tr>
<td>COPD</td>
<td>10(28%)</td>
<td>12(33%)</td>
<td>0.17</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>11(30%)</td>
<td>9(25%)</td>
<td>0.09</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>13(36%)</td>
<td>14(40%)</td>
<td>0.47</td>
</tr>
<tr>
<td>Men</td>
<td>23(64%)</td>
<td>18(60%)</td>
<td>0.47</td>
</tr>
<tr>
<td>Age (years)</td>
<td>68(18%)</td>
<td>59(16%)</td>
<td>0.30</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>31(86%)</td>
<td>29(81%)</td>
<td>0.06</td>
</tr>
<tr>
<td>Black</td>
<td>5(14%)</td>
<td>7(19%)</td>
<td>0.46</td>
</tr>
<tr>
<td>Other</td>
<td>0(0%)</td>
<td>4(11%)</td>
<td>0.04</td>
</tr>
<tr>
<td>Marital Status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single</td>
<td>20(56%)</td>
<td>19(53%)</td>
<td>0.83</td>
</tr>
<tr>
<td>Married</td>
<td>13(36%)</td>
<td>16(44%)</td>
<td>0.26</td>
</tr>
<tr>
<td>Unmarried</td>
<td>5(14%)</td>
<td>1(3%)</td>
<td>0.02</td>
</tr>
<tr>
<td>Education</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High School</td>
<td>29(80%)</td>
<td>27(75%)</td>
<td>0.30</td>
</tr>
<tr>
<td>College</td>
<td>6(17%)</td>
<td>9(25%)</td>
<td>0.24</td>
</tr>
<tr>
<td>Grad School</td>
<td>0(0%)</td>
<td>0(0%)</td>
<td></td>
</tr>
<tr>
<td>Income</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; $35,000</td>
<td>13(36%)</td>
<td>14(39%)</td>
<td>0.67</td>
</tr>
<tr>
<td>$35,000-$45,000</td>
<td>10(28%)</td>
<td>7(19%)</td>
<td>0.13</td>
</tr>
<tr>
<td>&gt; $45,000</td>
<td>9(25%)</td>
<td>9(25%)</td>
<td>0.97</td>
</tr>
<tr>
<td>Insurance</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medicare</td>
<td>20(56%)</td>
<td>15(42%)</td>
<td>0.02</td>
</tr>
<tr>
<td>Medicaid</td>
<td>1(3%)</td>
<td>8(22%)</td>
<td>0.06</td>
</tr>
<tr>
<td>Other</td>
<td>7(19%)</td>
<td>18(44%)</td>
<td>0.01</td>
</tr>
<tr>
<td>Event</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cause of event</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart Disease</td>
<td>20(56%)</td>
<td>18(45%)</td>
<td>0.07</td>
</tr>
<tr>
<td>CVD</td>
<td>3(8%)</td>
<td>9(25%)</td>
<td>0.43</td>
</tr>
<tr>
<td>Stroke</td>
<td>2(6%)</td>
<td>7(19%)</td>
<td>0.06</td>
</tr>
<tr>
<td>Urinary Infections</td>
<td>2(6%)</td>
<td>5(14%)</td>
<td>0.13</td>
</tr>
<tr>
<td>Respiratory Infections</td>
<td>15(42%)</td>
<td>14(39%)</td>
<td>0.81</td>
</tr>
<tr>
<td>Other</td>
<td>4(11%)</td>
<td>9(25%)</td>
<td>0.07</td>
</tr>
<tr>
<td>Readmission</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30-day</td>
<td>7(20%)</td>
<td>16(44%)</td>
<td>0.01</td>
</tr>
<tr>
<td>1-year</td>
<td>22(61%)</td>
<td>22(61%)</td>
<td>1.00</td>
</tr>
<tr>
<td>30-day ED</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ED visits</td>
<td>18(50%)</td>
<td>24(67%)</td>
<td>0.14</td>
</tr>
<tr>
<td>30-day visit</td>
<td>18(50%)</td>
<td>24(67%)</td>
<td>0.14</td>
</tr>
</tbody>
</table>

Study Results Cont’d

Pharmacist Recommendations:
- Providers resulted action

Study Conclusion
- Community pharmacies successfully collaborated with hospitals to develop a referral process for transitions of care interventions
- Patients who received MTM services had significantly fewer readmissions than patients who received usual care
- Patient satisfaction showed no significant difference in the intervention group vs. usual care group.

TRANSITION OF CARE MODEL
SunRay Drugs Model

- SunRay Drugs, a group of 5 independent pharmacies, established affiliation with Mercy Philadelphia Hospital (MPH) for transitions of care services for both inpatient and outpatient to reduce 30-day hospital readmission.
- Provided an array of services
  - Prescription dispensing
  - Free delivery
  - Blister packing
  - Compounding
  - Medication disposal service
  - Free HIV testing
  - MTM
  - Vaccines
  - Health screenings

SunRay Drugs Initiatives

- Identified patients
- Offered patients to participate in the TOC program
- Once enrolled, case management coordinated all prescriptions sent to SunRay Drugs
- SunRay provided same-day delivery to patients’ homes or bedside
- Within 72 hours of delivery, community pharmacist called patient to assess compliance
- Offered complete medication management services
- Pharmacist communicated with patient’s physician

Challenges Faced

- Patient recruitment
- Identify high risk
- In-services
- High no-show rates
- Patient incentives
- Obtaining accurate patient information
- Lack of access to medical records
- Collaborative relationship
- Lack of access to hospital system

Question

Barriers of developing a transitions of care program in a community pharmacy consist of the following: inadequate staffing, lack of time, and lack of access to hospital system.

True or False

Question

Establishing a transitions of care program will increase healthcare costs and readmissions.

True or False

Question

All discharged patients must be enrolled in the transitions of care program.

True or False
Conclusion

- Effective transitions of care programs have been associated with reduced readmission rates, healthcare costs, and adverse events
- Community pharmacists are often underutilized in transitions of care
- Expand the role of community pharmacists by implementing transitions of care programs and overcoming barriers
- More research needs to be conducted to demonstrate the clinical impact of a community pharmacy based transitions of care program.

References