Recent Pharmacological & Therapeutic Developments in Women's Health

Satellite Conference and Live Webcast
April 16, 2021
9:00 – 12:00 p.m. Central Time

Produced by the Alabama Department of Public Health
Video Communications and Distance Learning Division

Faculty

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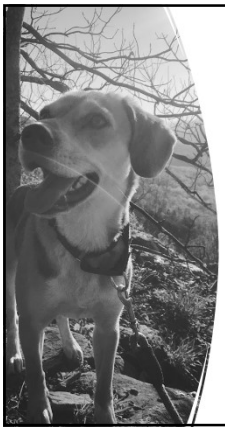
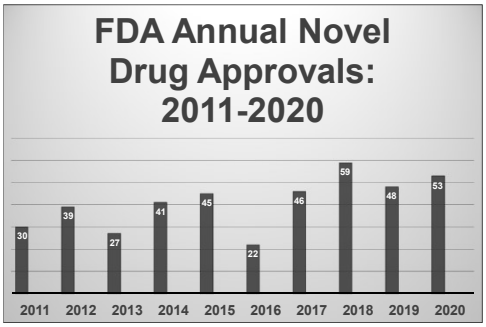
Educational Objectives

- **Outline the recent developments, guidelines and/or recommendations for pharmacological management of women's health conditions, with a focus on contraception.**
- **Identify essential information to counsel patients on the therapeutic application of these medications.**

Still Have Sugar & Spice



Edi the Grand Dog's first visit to our house



2020 Drug Approvals

- 53 Novel agents approved
  - Historical previous 10 year average = 40
    - 31 Orphan Drugs
    - 21 "First in Class"
    - 17 Fast-track
    - 22 Break-through
    - 30 Priority review
    - 12 Accelerated approval

FDA.gov

Faster FDA Drug Approvals: Good or Bad?

- Over the last 4 decades, the FDA has loosened its requirements for approving new drugs, increasingly accepting less data and more surrogate endpoints in clinical trials, and shortening its reviews. Is this good or bad?
- From 1995 to 1997, 80.6% of new drugs were approved on the basis of two pivotal trials — but that number dropped to 52.8% from 2015 to 2017. A number of programs were enacted during the study period that led to faster approvals, such as fast track and the breakthrough therapy designation.
- And with COVID, we have reinstated "Emergency Use Authorization" (EUA).

Medscape, January 28, 2020

3 Question Knowledge Assessment on Contraception

Compare your score with others taking it on Medscape.com

Medscape.com, November 21, 2019

Which of the Following is Most Accurate Regarding Recommendations for Contraceptive Use by the CDC?

A. If progestin-only pills are started more than 5 days after menstrual bleeding started, women should abstain from sexual intercourse or use an additional contraceptive method for the next 2 days.

B. Misoprostol is recommended for routine use before IUD insertion.

C. A pelvic examination and screening for obesity is recommended prior to insertion of etonogestrel (Implanon®) implant.

D. Women who are breastfeeding can begin using combined hormonal contraceptives 7-10 days after delivery.

Which of the Following is Most Accurate Regarding Recommendations for Contraceptive Use by the CDC?

A. If progestin-only pills are started more than 5 days after menstrual bleeding started, women should abstain from sexual intercourse or use an additional contraceptive method for the next 2 days. (47%)

B. Misoprostol is recommended for routine use before IUD insertion. (6%)

Which of the Following is Most Accurate Regarding Recommendations for Contraceptive Use by the CDC?

C. A pelvic examination and screening for obesity is recommended prior to insertion of etonogestrel implant. (35%)

D. Women who are breastfeeding can begin using combined hormonal contraceptives 7-10 days after delivery. (12%)

Which of the Following is Most Accurate Regarding Recommendations for Contraceptive Use by the CDC?

Rational for answers

- **A. According to CDC guidelines, if progestin-only pills are started within the first 5 days since menstrual bleeding started, no additional contraceptive protection is needed. If progestin-only pills are started more than 5 days since menstrual bleeding started, women should abstain from sexual intercourse or use additional contraceptive protection for the next 2 days.**
- **B. Regarding IUD insertion, although misoprostol may be helpful in some certain situations, CDC does not recommend routine use.**

Which of the Following is Most Accurate Regarding Recommendations for Contraceptive Use by the CDC?

Rational for answers

- **C. A pelvic examination is not necessary before initiation of etonogestrel implant because the examination would not facilitate detection of conditions with which implant use is unsafe. Obese women are able to use these implants, so screening for obesity is not necessary.**
- **D. Women who are breastfeeding should not use combined hormonal contraceptives during the first 3 weeks after delivery because of concerns about an increased risk for VTE. Also, women who are breastfeeding should avoid COCs during the 4th week postpartum because of concerns about effects on breastfeeding performance.**

Oral Contraceptive Use *Decreases* Risk for Which of the Following Conditions?

A. Migraine headaches

B. Hypertension

C. Blood clots

D. Pelvic inflammatory disease

Oral Contraceptive Use *Decreases* Risk for Which of the Following Conditions?

A. Migraine headaches (39%)

B. Hypertension (7%)

C. Blood clots (4%)

D. Pelvic inflammatory disease (50%)

Oral Contraceptive Use *Decreases* Risk for Which of the Following Conditions?

Rational for answers

- **Oral contraceptives reduce the risk for several conditions, including benign breast disease, PID and functional cysts. Oral contraceptives are also noted to lessen the risk for epithelial ovarian and endometrial carcinoma.**

Oral Contraceptive Use *Decreases* Risk for Which of the Following Conditions?

Rational for answers

- Some OCs, especially those that contain estrogen, can trigger migraine headaches, and some have also been associated with increased risk for high blood pressure. This is believed to be secondary to an estrogen-induced increase in renin substrate in susceptible individuals. The risk is higher in patients with additional risk factors, such as obesity, significant family history of hypertension, or history of smoking. For women with high blood pressure, an alternative progesterone-only method should be recommended.

Oral Contraceptive Use *Decreases* Risk for Which of the Following Conditions?

Rational for answers

- Oral contraception also increases the risk for blood clots in the legs, as the estrogen component of oral contraceptives has the capability of activating the blood clotting mechanism.

Which of the Following is Most Accurate, According to Guidelines on Emergency Contraception from the ACOG?

A. Levonorgestrel emergency contraception should be avoided in women who wish to later become pregnant, due to an increased risk for subsequent ectopic pregnancy.

B. Oral emergency contraception may be used more than once, even within the same menstrual cycle.

C. A pregnancy test is recommended prior to administration of emergency contraception to avoid unnecessary use.

D. Most emergency contraceptives are ineffective 48 hours after sexual intercourse and should only be offered within 72 hours.

Which of the Following is Most Accurate, According to Guidelines on Emergency Contraception from the ACOG?

A. Levonorgestrel emergency contraception should be avoided in women who wish to later become pregnant, due to an increased risk for subsequent ectopic pregnancy. (5%)

B. Oral emergency contraception may be used more than once, even within the same menstrual cycle. (37%)

C. A pregnancy test is recommended prior to administration of emergency contraception to avoid unnecessary use. (9%)

D. Most emergency contraceptives are ineffective 48 hours after sexual intercourse and should only be offered within 72 hours. (49%)

Which of the Following is Most Accurate, According to Guidelines on Emergency Contraception from the ACOG?

Rational for answers

- According to guidelines from ACOG, data are not available on the safety of current regimens of emergency contraception if used frequently over a long period. However, oral emergency contraception may be used more than once, even within the same menstrual cycle. Treatment with EC should be initiated as soon as possible after sexual intercourse to maximize efficacy. EC should be made available to patients who request it as long as 5 days after sexual intercourse.

Which of the Following is Most Accurate, According to Guidelines on Emergency Contraception from the ACOG?

Rational for answers

- The ACOG guidelines also indicate that existing data suggest that use of levonorgestrel EC does not increase the chance that a subsequent pregnancy will be ectopic.
- The ACOG guidelines state that no clinical examination or pregnancy testing is necessary before provision or prescription of EC.

Recent Developments in Contraception

Contraception for Women With Chronic Medical Conditions: Choosing the Right Method

- The CDC regularly updates *Medical Eligibility Criteria for Contraceptive Use* that designates medical conditions into one of four categories to guide the selection of an appropriate contraceptive method.
  - These categories range from category 1 (medical conditions for which there are no restrictions) to category 4 (a condition for which use of the contraceptive method represents an unacceptable health risk).

CDC Website

Contraception for Women With Chronic Medical Conditions: Choosing the Right Method

- The CDC eligibility criteria are available on a free app:
  - https://itunes.apple.com/us/app/contraception/id595752188?mt=8
  - https://play.google.com/store/apps/details?id=gov.cdc.ondieh.nccdphp.contraception2

CDC Website

Contraception for Women With Chronic Medical Conditions: Choosing the Right Method

- Medical conditions addressed by this bulletin include:
  - Conditions associated with an elevated risk for VTE, including postpartum status and familial thrombophilias;
  - Systemic lupus erythematosus
  - Migraine with or without aura
  - Hypertension
  - Diabetes
  - Obesity

Contraception for Women With Chronic Medical Conditions: Choosing the Right Method

- Medical conditions addressed by this bulletin include:
  - Depression
  - Family history of breast cancer or known *BRCA1* or *2* mutations
  - Personal history of breast cancer
  - Concomitant use of medications including rifampin and liver-enzyme-inducing antiepileptic and antiretroviral medications
  - Older reproductive age, including perimenopausal status
  - Prior bariatric surgery

CDC UPDATE

CDC Website

Health Indications for Non-contraceptive Use of Hormonal Contraceptives

- Treatment of menorrhagia and bleeding due to leiomyomas/adenomyosis
- Treatment of dysmenorrhea and pelvic pain from endometriosis
- Inducing amenorrhea and menstrual cycle regularity
- Treatment of PMS/PMDD
- Prevention of ovarian cysts
- Prevention of menstrual migraines (without aura)
- Chemoprevention of endometrial ovarian, and colorectal cancer
- Treatment of acne and hirsutism (hyperandrogenism)

OCs May Curb Severe Asthma Attacks

- **Researchers at the University of Gothenburg stated: "Studies have been published trying to understand why boys have a higher incidence of asthma than girls. But starting from around the time of puberty this changes, and asthma becomes more common in women than in men."**

Medscape, November 25, 2020

OCs May Curb Severe Asthma Attacks

- **An analysis of data from more than 80,000 women with asthma found a small but significant reduction in severe asthma attacks in those who had been on the pill for 3 or more years, researchers reported in *Thorax*.**

Medscape, November 25, 2020

ACOG Supports OTC Birth Control Products (Not Just Pills)

- **13 states allow pharmacists to dispense hormonal contraception without a doctor's visit or approval. Online services are also on the rise.**
  - **Globally, fewer than a third of countries require a Rx to obtain birth control.**
- **For many years, ACOG has called for OTC sales of hormonal contraceptives, and in 2019 it expanded that recommendation to contraceptive patches, vaginal rings, and depot medroxyprogesterone.**
  - **In addition, ACOG opposes age restrictions for adolescent girls who have started menstruation.**

ACOG, September 24, 2019

Annovera® - A New Contraceptive Vaginal Ring

- **Annovera®, a contraceptive vaginal ring that releases 150 mcg of segesterone acetate, a synthetic progestin, and 13 mcg of ethinyl estradiol, was approved by the FDA in August, 2018.**

The Medical Letter, December 16, 2019

Annovera® - A New Contraceptive Vaginal Ring

- **It is the first product to contain segesterone and the second vaginal ring to become available in the US.**
  - **NuvaRing®, which delivers etonogestrel and ethinyl estradiol, was the first.**
  - **It is softer and more pliable than the NuvaRing®.**

The Medical Letter, December 16, 2019

Annovera® - A New Contraceptive Vaginal Ring

- Unlike NuvaRing®, which requires use of a new ring each month, the Annovera® ring is left in place for 21 days and removed for 7 days in each cycle.
  - It provides contraceptive efficacy for up to 13 cycles (1 year) of use.

The Medical Letter, December 16, 2019

Annovera® - A New Contraceptive Vaginal Ring

- It has a Pearl Index of 2.98 (almost 3 unintended pregnancies occur per 100 women in a year compared to a Pearl Index of 80 in couples not using a contraceptive method), which is comparable to most available hormonal contraceptives.

The Medical Letter, December 16, 2019

Cost of Annovera®

- The lowest GoodRx price for Annovera® is around $1,981, 15% off the average retail price of $2,335 for one year use.
- The cost for NuvaRing vaginal ring (0.015 mg-0.12 mg/24 hours) is around $519 for a supply of 3 rings, which is ~$2076/year.

FDA.gov, May 30, 2019

Progestin-Only Contraceptive Drospirenone (Slynd®)

- In May 2019, the FDA approved Slynd®, a progestin-only ("mini-pill") oral contraceptive containing the synthetic progestin drospirenone in a 4 mg dosage strength that is given in a 24/4 dose regimen.
  - All other progestin only pills in the US contain norethindrone.

FDA.gov, May 30, 2019

Progestin-Only Contraceptive Drospirenone (Slynd®)

- Drospirenone is a spironolactone analogue with antimineralocorticoid and antiandrogenic activity.
  - Yaz® has both drospirenone and ethinyl estradiol.

FDA.gov, May 30, 2019

Continuous Combined Pill: Amethyst®

- Amethyst®, which contains levonorgestrel/ethinyl estradiol is the generic version of Lybrel®, which is no longer available.
- Lybrel® was the first extended-cycle oral contraceptive designed to supply an active dose of hormones for 365 days and have no more periods.

Black Box Warning on Amethyst®

- Levonorgestrel/ethinyl estradiol is contraindicated in women with a BMI greater than or equal to 30 kg/m(2). Compared to women with a lower BMI, women with a BMI greater than or equal to 30 kg/m(2) had reduced effectiveness and may have a higher risk for venous thromboembolism events (VTEs).

Black Box Warnings with Xulane® Transdermal Extended-Release

- Women over 35 years old who smoke should not use norelgestromin and ethinyl estradiol transdermal system.
- Cigarette smoking increases the risk of serious cardiovascular events from combination hormonal contraceptives (CHC) use.

Black Box Warnings with Xulane® Transdermal Extended-Release

- There may be an increased risk of venous thromboembolism (VTE) among women who use the norelgestromin and ethinyl estradiol transdermal system compared to women who used certain oral contraceptives.

Black Box Warnings with Xulane® Transdermal Extended-Release

- The pharmacokinetic (PK) profile of ethinyl estradiol (EE) for the norelgestromin and ethinyl estradiol transdermal system is different from the PK profile for oral contraceptives in that it has a higher areas under the time-concentration curve, steady state concentrations and lower peak concentrations.
  - Note: An FDA "Limitation of Use" for Xulane® is that it may be less effective in preventing pregnancy in women 90 kg or greater. This is ***not*** a Black Box warning as it is with Amethyst®.

FDA Approves Weekly Contraceptive Patch: Twirla®

- In February 2020, the FDA approved a new contraception for women whose BMI is < 30 kg/m2.
  - Twirla® is a transdermal system applied weekly for 3 weeks of the month to deliver a 30 mcg daily dose of ethinyl estradiol and 120 mcg daily dose of levonorgestrel.

Medscape, February 18, 2020

FDA Approves Weekly Contraceptive Patch: Twirla®

- What, if any, advantages it offers over Xulane®, which contains 150 mcg norelgestromin (which is metabolized to levonorgestrel) and 35 mcg of ethinyl estradiol per day, has not been determined.

Medscape, February 18, 2020

FDA approves Phexxi® for Use as On-Demand Contraceptive

- A contraceptive drug comprising lactic acid, citric acid, and potassium bitartrate (Phexxi®) has gained FDA approval.
- It is the first nonhormonal, on-demand vaginal pH regulator, designed to maintain vaginal pH within the range of 3.5-4.5.

FDA.gov, May 26, 2020

FDA approves Phexxi® for Use as On-Demand Contraceptive

- In an open-label multicenter trial, 1,183 women aged 18-35 years with regular menstrual cycles were intravaginally administered a 5-gram dose of the drug in gel form up to 1 hour prior to intercourse. Of the women, 101 had pregnancies during 4,769 cycles. The 7-cycle cumulative pregnancy rate was 14%.
  - Common adverse events included urinary tract infection, bacterial vaginosis, vaginal discharge, and dysuria, in addition to vulvovaginal burning sensation, pain, pruritus, and mycotic infection.
    - It was previously approved for use as a vaginal lubricant (Amphora®) but was never marketed.

FDA.gov, May 26, 2020

Recent Developments in Emergency Contraception (EC)

Pediatricians Urge Better Access to Emergency Contraception

- Pediatricians should be aware of EC methods, according to a new policy statement from the AAP that supports broader access to EC for reducing teen pregnancy.
  - Barriers to EC use among adolescents include their cost, ~$50 for EC pills, and accessibility.
    - A recent study found 64% of pharmacies stocked emergency contraceptives, with almost half keeping them on a locked shelf.

Pediatrics, November 18, 2019
https://doi.org/10.1542/peds.2019-3149

Recent Developments in EC: Preventeza®

- In 2018, FDA approved Preventeza® as the newest OTC emergency contraceptive.
- It is dosed as one levonorgestrel 1.5 mg tab, just like Plan B One-Step®, Take Action®, My Way®, etc.

Recent Developments in EC: Preventeza®

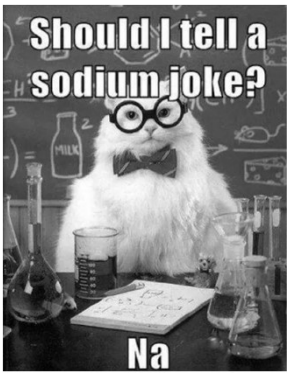
- **According to *Pharmacist's Letter*, July 2018, feel comfortable recommending OTC levonorgestrel within 3 days of unprotected sex.**
- **It can be used up to 5 days after sex...but labeling doesn't recommend it, and efficacy declines the longer the patient waits.**

Recent Addition to EC Formulary in Alabama: ellaOne®

- **In 2010, the FDA approved ulipristal (ellaOne®), a progesterone agonist/antagonist, as a prescription EC for use up to 120 hours (5 days) following unprotected sexual intercourse or contraceptive failure.**

Recent Addition to EC Formulary in Alabama: ellaOne®

- **Anti-abortion groups had urged the FDA to reject the drug, noting that it is chemically similar to RU-486, but in the review, the FDA said that it found no evidence the drug could terminate an existing pregnancy.**
  - **It is used off-label for uterine fibroids.**



Recent Miscellaneous Developments in Women's Health

Endometriosis: Elagolix (Orlissa®)

- **Treatment of moderate to severe pain from endometriosis.**
  - **Inhibiting GnRH signaling, reducing pituitary secretion of FSH and LH, and decreasing ovarian production of estradiol and progesterone.**

Pharmacology	
Class	GnRH inhibitor
Route	Oral tablet
Dosing	150 mg once daily for 24 months or 200 mg twice daily for 6 months (
Metabolism	CYP3A4 (major)
Elimination	hepatic
Half life	4-6 hours
Adverse Effects	**Mineral bone density decreases;** hot flushes and/or night sweats, headache, nausea, insomnia, mood swings, depression/depressive symptoms, anxiety, and arthralgia
Contraindications	pregnancy

Note: Both GnRH agonists and antagonists ultimately induce a hypoestrogenic state. GnRH antagonists immediately suppress release of gonadotropin and theoretically could provide a faster therapeutic effect without the symptom flare-up associated with GnRH agonists.

Management of Menorrhagia

- Heavy menstrual bleeding (HMB) or menorrhagia occurs in 9% to 14% of women.
- Traditional therapy includes NSAIDs, OCs and Hormonal IUD (Liletta®, Mirena®).

Management of Menorrhagia

- Newer therapies include:
  - Lysteda® tablets (tranexamic acid), (also available as Cyklokapron® for bleeding disorders) works by stabilizing a protein that helps blood to clot.
  - The OC Natazia® (estradiol valerate/dienogest)
  - Elagolix/Estradiol/Norethindrone acetate (Oriahnn®) capsules

FDA Approves New Option to Treat Heavy Menstrual Bleeding Associated with Fibroids

- In 2020, the FDA approved the combination product consisting of elagolix, estradiol and norethindrone acetate (Oriahnn®) capsules for the management of heavy menstrual bleeding associated with uterine leiomyomas (fibroids).
  - The most common adverse effects of Oriahnn® were hot flushes, headache, fatigue, and irregular vaginal bleeding.
  - The elagolix component may cause bone loss over time. Due to the increased risk of fractures from bone loss, women should not take Oriahnn® for more than 24 months.
  - The drug's label also includes the standard warnings of all estradiol/norethindrone products.

FDA.gov, May 29, 2020

Medical Letter's Review of Oriahnn® for Heavy Menstrual Bleeding Associated with Uterine Fibroids

- Oriahnn® is the first product to be approved in the US for this indication.
- The GnRH receptor antagonist relugolix (Orgovyx®), which is approved for treatment of prostate cancer, is being reviewed by the FDA for use in combination with estradiol and norethindrone acetate for the same indication.

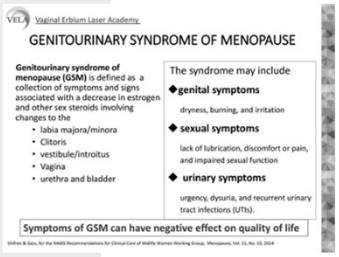
The Medical Letter, April 5, 2021

Genitourinary Syndrome of Menopause (GSM)

- Formerly known as ***atrophic vaginitis*** or ***vulvovaginal atrophy,*** genitourinary syndrome of menopause (GSM) is a new term that describes various menopausal symptoms and signs including not only genital symptoms (dryness, burning, and irritation), and sexual symptoms (lack of lubrication, discomfort or pain, and impaired function, but also urinary symptoms (urgency, dysuria, and recurrent UTI.
- The prevalence of GSM is estimated at around 40%-60%.

Medscape, February 12, 2021

Genitourinary Syndrome of Menopause (GSM)



New Nonhormonal Hot Flash Treatments on the Way

- **A new group of nonhormonal drugs currently in clinical trials shows promise for treating menopausal hot flashes as effectively as hormones,**
- **In Phase III Clinical Trials, kisspeptin/neurokinin B/dynorphin (KNDy) neuron manipulation have been up to 80% effective in the amelioration of hot flashes and improvement in other menopausal symptoms.**

North American Menopause Society (NAMS) 2020 Annual Meeting, Reported by Medscape, October 9, 2020

New Nonhormonal Hot Flash Treatments on the Way

- **While several nonhormonal drugs are already used to treat vasomotor symptoms in menopausal women with and without breast cancer, none are as effective as hormone treatments.**
  - **Presently the SSRIs, SNRIs and GABAergics, along with clonidine and oxybutynin are the most effective alternatives.**

North American Menopause Society (NAMS) 2020 Annual Meeting, Reported by Medscape, October 9, 2020

Vaginal Microbiome Transplantation in Women with Intractable Bacterial Vaginosis

- **Similar to the concept of fecal microbiome transplants (FMT) for *C. difficile*, the first exploratory study testing the use of vaginal microbiome transplantation (VMT) from healthy donors as a therapeutic alternative for patients suffering from recurrent BV has been completed. (ClinicalTrials.gov NCT02236429)**

Nature medicine 25 (Suppl. 1), October 2019

Vaginal Microbiome Transplantation in Women with Intractable Bacterial Vaginosis

- **5 patients were treated, and in 4 of them VMT was associated with full long-term remission until the end of follow-up at 5–21 months after VMT.**
  - **The authors conclude that the therapeutic efficacy of VMT in women with intractable and recurrent BV should be further determined in randomized, placebo-controlled clinical trials.**

Nature medicine 25 (Suppl. 1), October 2019

Gabapentin Not Effective for Chronic Pelvic Pain (CPP)?

- **A study published in *Lancet*, September 26, 2020, should cause us to rethink gabapentin's role in treating CPP. Researchers in Britain performed a double-blind study at 37 centers which randomized over 300 women age 18-50 years to gabapentin or placebo for 16 weeks. The gabapentin dose could be increased to a high of 2700 mg daily.**

Medscape, October 22, 2020

Gabapentin Not Effective for Chronic Pelvic Pain (CPP)?

- **At study conclusion, the primary outcomes were similar in the gabapentin and placebo groups. The proportion of women with serious adverse events was 7% in the gabapentin group and 2% in the placebo group.**
- **The findings of this trial clearly indicate that because gabapentin is not effective in treating CPP, it should not be used as a first-choice medication to treat this condition.**

Medscape, October 22, 2020

Respiratory Depression with Gabapentinoids

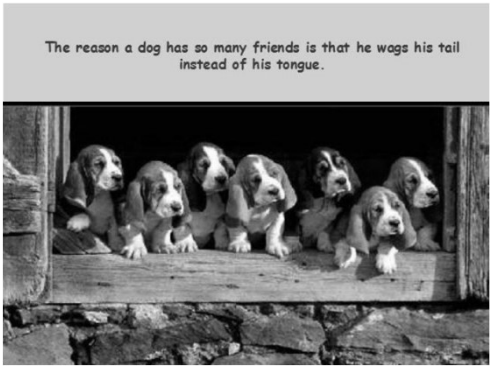
- **The FDA has required new warnings in the labels of gabapentin and pregabalin (Lyrica®) about the risk of life-threatening or fatal respiratory depression in patients with COPD and concurrent use of opioids or other CNS depressants. Elderly patients are also at increased risk.**

The Medical Letter, June 2020

Respiratory Depression with Gabapentinoids

- **They are FDA-approved to treat a variety of neurologic and neuropathic disorders and are frequently used off-label to treat non-neuropathic pain, anxiety, and insomnia, and hot flashes in women with breast cancer. Gabapentin and pregabalin have a lower potential for abuse than opioids, but physical and psychological dependence can occur.**

The Medical Letter, June 2020



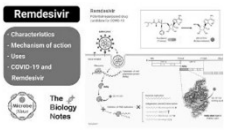
Recent Miscellaneous Developments

Drugs for the Treatment of COVID-19

- **The only drug currently approved for treatment is remdesivir, which was approved by the FDA in October 2020.**
- **There are many studies ongoing, some that have resulted in the Emergency Use Authorization (EUA) of other drugs.**

Potential Therapeutic Classes for COVID-19

- **Antiviral Therapy**
  - **Remdesivir**
    - **Interferes with the action of viral RNA-dependent RNA polymerase and evades proofreading by viral exoribonuclease (ExoN), causing a decrease in viral RNA production**
  - **Hydroxychloroquine**
  - **Protease Inhibitors**
  - **Ribavirin**



Potential Therapeutic Classes for COVID-19

- Immune-based Therapy
  - Corticosteroids (Dexamethasone)
    - Critically ill patients with COVID-19 have an overwhelming inflammation and cytokine-related lung injury, which can physiopathologically end in fibrosis. Corticosteroids could be an adjuvant therapy, and it could be useful to prevent or treat chronic lung complications derived from the disease.
  - IL-6, IL-1 inhibitors
  - Interferons
  - Kinase inhibitors

Potential Therapeutic Classes for COVID-19

- Miscellaneous Therapies
  - Vitamin C & D and Zinc
  - Famotidine (Pepcid®)
  - Iveremectin
  - Antibacterials
  - ACEIs/ARBS
  - Antithrombotics

Potential Therapeutic Classes for COVID-19

- Antibody Therapy
  - Convalescent plasma
  - IVIG
  - Polyclonal/Monoclonal Antibodies:
    - Bind to the viral surface and blocks entry to prevent infection
      - Regenergon
      - Eli Lilly

Recent EUAs

- Lilly's monoclonal antibiodies bamlanivimab and etesevimab administered together are authorized for use under an EUA for the treatment of mild to moderate (COVID-19) in with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progressing to severe COVID-19 and/or hospitalization.

Medscape, March 22, 2021

What did President Trump Receive as Treatment?

- Regeneron's polyclonal antibody
- Remdesivir
- Dexamethasone
- Zinc
- Vitamin D
- Famotidine
- Melatonin
- Daily aspirin

Key References for COVOD-19 Treatment

- NIH Guidelines
- IDSA
- WHO
  - Just search for NIH, IDSA or WHO Covid Treatment Guidelines

IDSA Updates Guidelines for COVID-19 Treatment

- **While there is still no "game-changer" for treating COVID-19, the Infectious Diseases Society of America (IDSA) continues to examine available and potential treatments as new evidence emerges.**

Medscape, March 22, 2021

A Benefit of Dark Chocolate (Cocoa): Peripheral Artery Disease?

- **Investigators randomly assigned 44 patients age 60 or above to receive a cocoa beverage or a placebo beverage. Participants who drank the cocoa 3 times daily had significantly greater improvements in 6-minute walk distance compared with the placebo group.**
- **Also, those who drank the cocoa showed improvement in perfusion to the legs and improvement in calf skeletal muscle characteristics, including improved function of the mitochondria, compared with their counterparts who drank the placebo beverage.**

Circulation Research, February 14, 2020 **(Notice the date!)**

Manufacturers Ordered to Pay Hawaii $834 Million Over Plavix® Warning Label

- **In February 2021, BMS and Sanofi were ordered to pay more than $834 million to the state of Hawaii for failing to properly warn non-white patients of health risks from Plavix® (clopidogrel).**
- **Clopidogrel is not fully active until it is metabolized, which can vary genetically. Studies have shown that about 14% of Chinese patients are unable to properly metabolize the drug, compared to 4% of black and 2% of white patients.**

Medscape, February 23, 2021

FDA Approves New Type of Cholesterol Drug

- **In 2020, the FDA approved bempedoic acid (Nexletol®), and in combination with ezetimibe (Nexlizet®).**
  - **It is approved as adjunct therapy to maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia.**
  - **It inhibits adenosine triphosphate-citrate lyase (ACL) which blocks the production of LDL-cholesterol.**

Pharmacy Today, February 24, 2020

FDA Approves New Type of Cholesterol Drug

- **In late-stage trials, bempedoic acid reduced LDL-C levels an average 18% compared with placebo in patients taking moderate- and high-dose statins, and up to 28% in patients taking low-dose or no statins.**
  - **Adverse effects include elevated uric acid levels and increased risk of ruptured tendons.**

Pharmacy Today, February 24, 2020

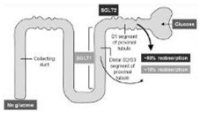
Updated Recommendations Shift Therapy Paradigm for Patients with Type 2 Diabetes

- **The GLP-1 receptor agonists and SGLT2 inhibitors are paradigm-shifting therapies in type 2 diabetes for patients with atherosclerotic vascular disease, heart failure, and chronic kidney disease.**
- **This is the conclusion of *A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD).***

Diabetes Care, December 2019

Sodium Glucose Cotransporter 2 (SGLT2) Inhibitors ("Flozins")

- **Inhibition of SGLT2 reduces resorption of glucose in the kidney, with a consequent lowering of plasma glucose levels as well as weight loss.**
  - **Canagliflozin (Invokana®)**
  - **Dapagliflozin (Farxiga®)**
  - **Empagliflozin (Jardiance®)**
  - **Ertugliflozin (Steglatro®)**



Glucagon-like polypeptide-1 (GLP-1) Agonists

- **Activation of GLP-1 receptors stimulate release of insulin. Glucagon secretion is also reduced and gastric emptying is delayed.**
  - **Exenatide (Byetta®, Bydureon®)**
  - **Liraglutide (Victoza®)**
  - **Dulaglutide (Trulicity®)**
  - **Lixisenatide (Adlyxin®)**
  - **Semaglutide (Ozempic® Injection, Rybelsus® Oral)**

SGLT2 Inhibitors Have a Breakout Year

- **The benefits from SGLT 2 inhibitors proven recently for cutting heart failure and slowing progression of chronic kidney disease, all regardless of diabetes status, have thrust this drug class into the top tier of agents for potentially treating millions of patients with cardiac or renal disease.**
  - **The SGLT2 inhibitors, first licensed for U.S. marketing in 2013 purely for glycemic control, have recently shown benefits in a range of patients reminiscent of what's been established for ACE inhibitors and angiotensin receptor blockers (ARBs).**

Medscape, 8-11-20

Semaglutide (Ozempic®) for Weight Loss

- **In recently published clinical trials, once-weekly injection of semaglutide (Ozempic®) reduced body weight significantly in patients *with and without* type 2 diabetes when given in addition to lifestyle intervention.**
  - **Liraglutide (Saxenda®), another GLP-1 receptor agonist, has been FDA-approved for weight management since 2015.**

Lorcaserin (Belviq®) Taken off the Market

- **In February 2020, Eisai Inc. voluntarily withdrew lorcaserin (Belviq®) after a safety clinical trial found an increased occurrence of cancer in patients taking it for weight loss.**
- **When the drug was approved a few years ago, the FDA noted that the risk of cardiovascular problems was low, but a range of cancer types was reported, including pancreatic, colorectal, and lung.**

FDA MedWatch, February 13, 2020

Semglee®: A New Insulin Glargine

- **The FDA recently approved Semglee®, an insulin glargine product similar to Lantus®. It is the second "follow-on" insulin glargine product to become available in the U.S.; Basaglar® was the first.**

The Medical Letter, January 25, 2021

Semglee®: A New Insulin Glargine

- **Even though all three are similar in composition, strength, and biological properties, and they appear to produce similar clinical results, the they are not considered interchangeable; pharmacists generally cannot substitute one product for the other without permission from the prescriber.**

The Medical Letter, January 25, 2021

Semglee®: A New Insulin Glargine

Table 1. Insulin Glargine Products[1]

Drug	Concentration	Some Formulations	Cost[2]
Lantus (Sanofi)	100 units/mL	10 mL vials	$283.60
		3 mL *SoloStar*[3]	85.10
Basaglar[4] (Lilly)	100 units/mL	3 mL *KwikPen*[3]	65.30
Semglee[4] (Mylan)	100 units/mL	10 mL vials	98.70
		3 mL prefilled pens[5]	29.60

1. Insulin glargine is also available in a 300 unit/mL formulation (*Toujeo*).
2. Approximate WAC for one 10-mL vial or one disposable pen. WAC = wholesaler acquisition cost or manufacturer's published price to wholesalers; WAC represents a published catalogue or list price and may not represent an actual transactional price. Source: Analysource® Monthly. January 5, 2021. Reprinted with permission by First Databank, Inc. All rights reserved. ©2021. www.fdbhealth.com/policies/drug-pricing-policy.
3. Prefilled, disposable pens. Available in boxes containing 5 pens each.
4. "Follow-on" product highly similar to Lantus; *Basaglar* and *Semglee* are not interchangeable with Lantus.
5. Available in boxes containing 1, 3, or 5 pens each.

The Medical Letter, January 25, 2021

Some Anticholinergics are Linked to 50% Greater Dementia Risk

- **According to an NIH funded study of more than 280,000 patients age 55 and older, long-term exposure to some anticholinergics is associated with a significant increase in dementia risk.**
- **Risk for dementia was significant in patients receiving the following anticholinergics:**
  - **Antidepressants: 1.29 (1.24-1.34)**
  - **Antiparkinson drugs: 1.52 (1.16-2.00)**
  - **Antipsychotics: 1.70 (1.53-1.90)**
  - **Bladder antimuscarinic drugs: 1.65 (1.56-1.75)**
  - **Antiepileptic drugs: 1.39 (1.22-1.57)**

JAMA Intern Med, June 26, 2019

FDA Orders Stronger Warnings on Benzodiazepines

- **In September 2020, the FDA requested updated boxed warnings on benzodiazepines to reflect their "serious" risks of abuse, misuse, and withdrawal reactions.**
- **According to the FDA, in 2019, an estimated 92 million benzodiazepine prescriptions were dispensed from U.S. outpatient pharmacies, most commonly alprazolam, clonazepam, and lorazepam.**

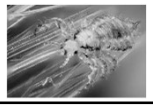
FDA.gov, September 24, 2020

FDA Approves Rx to OTC Switch

- **Diclofenac topical gel, 1% (Voltaren Arthritis Pain®)**
  - **Diclofenac was first approved in 2007 as a Rx drug for treatment of the pain of osteoarthritis of joints. It has not been shown to work for strains, sprains, bruises, or sports injuries.**
- **Olopatadine ophthalmic solution/drops (Pataday®)**
  - **Two dosage strengths were approved: 0.1% Pataday Twice Daily Relief® and 0.2% Pataday Once Daily Relief® for temporary relief of itchy and red eyes. It was first approved in 1996 under the name Patanol® as a prescription drug for treatment of allergic conjunctivitis.**

Ivermectin Topical (Sklice®) Now Available OTC

- **In October 2020, the FDA approved ivermectin (Sklice®) lotion, 0.5% for the single-use treatment of head lice infestation in individuals aged 6 months and older. It was approved as a Rx drug in 2012.**
  - **According to CDC, an estimated 6 million-12 million cases of head lice infestation occur each year among U.S. children aged 3-11 years..**



FDA.gov, October 27, 2020

FDA approves combination ibuprofen-acetaminophen: Advil Dual Action®

- **The first OTC combination drug containing both ibuprofen and acetaminophen (Advil Dual Action®) is now available. It contains 250 mg of ibuprofen and 500 mg of acetaminophen.**
- **The American Dental Association's Council, welcomed the news, citing a recent studies that found that this combination "offered the most favorable balance between benefits and harms" for treating dental pain over opioids.**

American Dental Association News, March 2, 2020

Cannabis Throughout History

- **In 1937, cannabis was a Rx drug.**
  - **Congress passed the Marijuana Tax Act, which placed prohibitive tariffs and registration requirements on physicians prescribing and pharmacists dispensing cannabis**
- **1930's CBD was isolated from the Cannabis sativa plant**
- **In 1942 → Removed from USP**
- **In 1970 → Controlled Substances Act passed**
  - **Marijuana assigned Schedule I status**

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Cannabis and Cannabinoids

- **Cannabis (marijuana) contains more than 60 pharmacologically active cannabinoids; delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) are the best known.**
  - **THC is the main psychoactive constituent of cannabis. CBD, unlike THC, does not produce intoxication or euphoria.**
- **As of November 2020, 35 states now permit some *medical* use of marijuana that contains THC. In these states, cannabis products are available with varying restrictions and requirements, such as a certification for each for each individual patient signed by a physician or another health care provider.**

The Medical Letter, November 18, 2019

Cannabis Questions Answered

- **WHAT'S THE DIFFERENCE BETWEEN CBD & CANNABIS?**
  - **Cannabis is the scientific name of the plant, while CBD, or cannabidiol, is one of the most abundant of the many active chemicals contained in the cannabis plant.**
- **WHAT'S THE DIFFERENCE BETWEEN CBD AND HEMP?**
  - **Hemp is a variety of cannabis grown specifically for fiber that is used for industrial purposes.**
  - **Hemp has very little THC, or tetrahydrocannabinol.**
  - **THC is another common chemical found in cannabis and is the chemical responsible for the plant's psychoactive effects. Hemp contains less than 0.3% THC.**

APhA Pharmacy Today, February, 2020

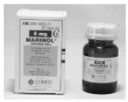
Legal Considerations

- **Under Federal Controlled Substance Act, marijuana and its derivatives are Schedule I Controlled Substances.**
  - **However, another Federal law, the *Agriculture Improvement Act of 2018 (aka "Farm Act")*, stipulates that cannabis containing no more than 0.3% THC is defined as hemp and is not a controlled substance under Federal law, but individual states may have their own regulations.**

The Medical Letter, November 18, 2019

Commercially Available Cannabis Products

- **Dronabinol (Marinol® capsules) & Syndros® oral solution)**
  - **N/V related to chemotherapy**



- **Nabilone (Cesamet®)**
  - **N/V related to chemotherapy**

- **Epidiolex® (CBD)**
  - **Epilepsy**

Variations in Potency

- **A study published in *JAMA* 2017; 318:1708, CBD products purchased on-line were examined using liquid chromatography to assess the accuracy of their labeled CBD content.**
  - **Among 84 products, 58 contained CBD concentrations that were >10% above or below their labeled content, and 18 contained potentially intoxicating concentrations of THC.**
    - **Contamination of cannabis with pesticides and heavy metals has been reported.**

The Medical Letter, November 18, 2019

Are Your Patients Taking CBD?

- **A Gallup poll from August 2019 found:**
  - **1 in 7 Americans use CBD**
  - **11% of users are 50 to 64 years of age, and that 8% are at least 65 years of age.**
  - **Pain relief, anxiety, insomnia, and arthritis are the top reasons for use.**
  - **Nearly 4 in 10 Americans think CBD oils should be legally available for adults to buy over the counter.**

Medscape, January 15, 2020

Cannabis and Driving

- **The minimal concentration of THC in the blood that will result in impairment (e.g., while driving) has not been determined.**
- **Several states currently enforce *per se* limits to determine marijuana impaired driving, typically 5 ng/ml of THC, though some states enforce a zero-tolerance policy for THC – any level of THC is prohibited.**
- **But, the time between a roadside traffic stop and subsequent blood testing could take hours, making potential impairment difficult to measure since THC levels might have declined long before testing.**

CBD Users May Test Positive for Marijuana on Urine Drug Screen

- **A small study found that THC was present in half of urine samples from individuals who had used CBD oil for a month.**
  - **"It is often assumed individuals using hemp-derived products will test negative for THC," noted Staci Gruber, PhD, of Harvard. "[Our] results indicate this may not be true, especially if assays are more sensitive than advertised, underscoring the potential for adverse consequences, including loss of employment and legal or treatment ramifications, despite the legality of hemp-derived products."**

JAMA Psychiatry. Published online November 4, 2020

FDA Warning Letters Target OTC Cannabidiol Product Claims for Pain Relief

- **In March 2021, the FDA warned two manufacturers about illegal marketing of drugs containing CBD for OTC use without an approved new drug application, for using substandard manufacturing processes, and for failure to comply with current good manufacturing practices.**

Medscape, March 25, 2021

FDA Warning Letters Target OTC Cannabidiol Product Claims for Pain Relief

- **51 previous warning letters have been issued by the FDA since 2015 to manufacturers of products containing CBD.**
- **The FDA has stated that CBD has "known pharmacologic effects on humans, with demonstrated risks, it cannot be legally marketed as an inactive ingredient in OTC drug products that are not reviewed and approved by the FDA."**

Medscape, March 25, 2021

When You Know It's Time to Retire