



Clinical Presentation – 10/23/2020

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Anticonvulsants

- Epilepsy is one of the most common disorders of the central nervous system (CNS). It affects 2.2 million Americans, with 150,000 new cases diagnosed each year. When a person has 2 or more seizures, they are considered to have epilepsy. An estimated 1.2% of the total US population have active epilepsy.
- Lennox-Gastaut syndrome is one of the most severe forms of childhood epilepsy and is one of the hardest forms to treat. It is characterized by mental retardation and multiple seizure types. Patients have seizures daily, sometimes experiencing several seizures within a day. Patients may also experience “drop attacks”, which is defined as a loss of muscle control causing the patient to fall abruptly to the floor.
- Dravet syndrome is a rare, catastrophic form of epilepsy that presents in the first year of life and is characterized by frequent, prolonged seizures. Patients may experience multiple seizure types during their lifetime. Infants with Dravet syndrome often experience multiple comorbidities over their lifetime related to the persistent seizure activity, including behavioral and developmental delay. Dravet syndrome is also associated with a 15% to 20% mortality rate due to Sudden Unexpected Death in Epilepsy (SUDEP).
- Goals of treating epilepsy are to reduce the frequency of seizure occurrence along with providing the best possible quality of life for the patient. Ideally, this would be achieved using a medication with minimal adverse effects and drug interactions. Treatment will depend on the type of seizure. Many different classes of drugs are available to treat the different forms of seizures and some patients will require more than 1 drug to control their seizures.
- Pharmacologic treatment of epilepsy includes drugs with the following mechanism of action:
 - Barbiturates that depress CNS activity by binding to the barbiturate site at the gamma aminobutyric acid (GABA) receptor complex (enhancing GABA activity), reduce monosynaptic

transmission resulting in decreased excitability of the entire nerve cell, and increase the threshold for electrical stimulation of the motor cortex.

- Hydantoin that appear to stabilize the seizure threshold and prevent the spread of seizure activity rather than abolish the primary focus of discharge.
- Succinimides that suppress the paroxysmal 3-cycles-per-second spike and wave activity associated with lapses of consciousness common in absence seizures and reduce the frequency of epileptiform attack
- Benzodiazepines that potentiate the effects of GABA suppressing the spike and wave discharge associated with absence seizures
- Carbamazepine Derivatives that either reduce the polysynaptic responses and blocks the post-tetanic potentiation or inhibit the sustained repetitive neuronal firing by blocking the voltage gated sodium channel
- Valproic Acid and derivatives that increase the brain concentration of GABA
- Other anticonvulsants with various mechanisms of action that range from binding to the synaptic vesicle protein 2A, blocking the sodium channel, inhibiting gamma-amino butyric acid transaminase, and/or interacting with the cannabinoid receptors

Hemophilia

- Hemophilia is a rare, inherited bleeding disorder where the blood does not clot properly due to an absence of 1 of the coagulation factors present in normal blood. Hemophilia is identified as an X-linked congenital bleeding disorder that has an estimated frequency of 1 in 5,000 to 10,000 births. The World Federation of Hemophilia estimates the global prevalence of hemophilia at around 400,000 persons. It is estimated there are approximately 20,000 persons in the United States afflicted with hemophilia.
- Hemophilia A is by far the most common form of hemophilia in the US (representing 80 – 85% of patients) with hemophilia B being the second most common. Hemophilia A or B are characterized as deficiencies in factor VIII (8) or IX (9), respectively. Although type A and B are the most common types of hemophilia, the term also encompasses a number of other rare factor deficiencies. These disorders include deficiencies involving the following factors: factor I (1) – fibrinogen deficiency; factor II (2) – prothrombin deficiency; factor V (5) – proconvertin deficiency; factor X (10) – Stuart-Prower deficiency; factor XI (11) – hemophilia C or plasma thromboplastin deficiency; factor XII (12) – Hageman factor deficiency; and factor XIII (13) fibrin stabilizing deficiency.
- Hemophilia, regardless of type (hemophilia A or B), is classified as mild (patient having 5% - 40% of the normal clotting factor level), moderate (1% - 5% of the normal clotting factors level), or severe (less than 1% of the normal clotting factor level) depending on the intrinsic amount of clotting factor.
- The recommended treatment of bleeding episodes is dependent on several factors, including the patient's severity level, the location, and type of the injury or trauma, as well as the patient's overall status. Providing immediate treatment reduces the risk of lasting damage, the need for additional medication, and the reduction of pain, as well as additional treatments. It is important to note that a person with a bleeding disorder will not bleed faster than anyone else; however, the bleeding will last longer if untreated.

- Von Willebrand disease (vWD) is a group of inherited bleeding disorders related to the absence or defects of von Willebrand factor, a clotting protein, needed to achieve hemostasis. Von Willebrand factor binds to factor VIII and platelets to generate a platelet plug during the clotting process. The disease leads to bleeding from impaired platelet adhesion and aggregation, which may be accompanied by reduced levels of factor VIII.
- Prophylaxis should be considered optimal therapy for individuals with severe hemophilia A or B where endogenous factor levels are found to be less than 1%. Prophylaxis therapy should be initiated early, with the goal of keeping trough values for factor VIII or factor IX levels above 1% between doses, although benefit may still be seen when trough levels fall below the target goal. The optimal dosing and frequency of administration for each individual patient should be determined by appropriate laboratory monitoring.
- The goal of episodic treatment is to raise the factor level in the blood from 40% to 100% depending on the location and level of injury.
- Products used in the treatment of hemophilia are differentiated based upon factor type, whether they are derived from pooled human plasma in the manufacturing process, as well as their level of purity or purification process.

HIV/AIDS

- Human Immunodeficiency Virus (HIV) infection is a complex disease that results in destruction of the immune system of HIV-infected individuals. There are 2 major subtypes of HIV: HIV-1 and HIV-2. The HIV-1 subtype is considered most responsible for the Acquired Immune Deficiency Syndrome (AIDS) epidemic. The HIV-2 subtype is thought to be less virulent and less transmissible; however, both are known to cause AIDS and are transmitted by sexual contact, through blood, and from mother to child. By far, HIV-1 is more common worldwide, and HIV-2 is more concentrated in West Africa.
- The HIV retrovirus establishes infection by killing the CD4 positive (CD4+) T cells that are crucial to a healthy immune system. These T cells are also called “T-helper cells” because they also signal other cells in the immune system to perform their functions. Research has shown that most infecting strains of HIV use a co-receptor molecule called CCR5, in addition to the CD4 molecule, to enter the T cells and take over the cellular machinery for viral replication. Without these CD4+ T cells, the immune system is vulnerable to infection. A healthy uninfected person usually has 800 to 1,200 CD4+T cells per cubic millimeter (mm³) of blood. Once infected, the number of T cells declines. If the T cell count falls below 200/mm³, then the condition is classified as AIDS. The individual then becomes even more vulnerable to the opportunistic infections (OIs) and cancers that are associated with this end stage of HIV disease.
- Eight therapeutic classes represent the drug treatment options for HIV/AIDS: nucleoside and nucleotide reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), integrase inhibitors (INSTIs), CCR5 antagonists, fusion inhibitors, pharmacokinetic enhancers, and a monoclonal antibody.
- Initial regimen selection should be guided by patient characteristics, including comorbidities, drug-drug interaction possibilities, toxicity risk, regimen complexity, and virologic efficacy.

- Alternative regimens may be more desirable if individual patient needs warrant it. However, although alternate regimens are deemed efficacious, they may have select disadvantages compared to the preferred regimens.
- Regimens should be selected or changed based on resistance test results, with consideration of dosing frequency, pill burden, adverse effect profiles, co-morbidities, and drug interactions. Patients receiving antiretroviral treatment should be monitored regularly and treatment failure should be detected and managed early, with the goal of therapy, even in previously treated patients, being HIV-1 RNA suppression below commercially available assay quantification limits.
- The Initial Antiretroviral Treatment of Adults (IAS) recommends an integrase inhibitor (INSTI) plus 2 NRTIs generally for initial therapy with unique patient circumstances guiding the treatment choice.

Multiple Sclerosis Agents

- Multiple sclerosis (MS) is a complex human autoimmune-type inflammatory disease of the central nervous system (CNS). Although the etiology is predominantly unknown, MS is characterized pathologically by demyelination and subsequent axonal degeneration. The nerve degeneration associated with MS can result in a wide variety of symptoms, including sensory disturbances in the limbs (e.g., numbness, paresthesias, burning, pain), optic nerve dysfunction, ataxia, fatigue, and bladder, bowel, and sexual dysfunction. Severe cases may result in partial or complete paralysis.
- MS results in significant physical disability in over 30% of patients within 20 to 25 years of onset. Cognitive dysfunction occurs in an estimated 40% to 70% of MS patients, but no correlation exists with the degree of physical disability.
- It is estimated that nearly 1 million people are living with MS in the United States. Multiple sclerosis occurs most commonly in Caucasians, with rare cases in African-Americans and Asian-Americans. Like other presumed autoimmune diseases, MS is more common in females and clinical symptoms often first manifest during young adulthood. The prevalence of MS varies widely with location; the highest prevalence is reported at higher latitudes in northern regions of Europe and North America.
- At onset of the disease, MS can be categorized as either relapsing-remitting MS (observed in 85% to 90% of patients) or primary progressive MS (observed in 10% of patients). Relapses or “attacks” typically present subacutely, with symptoms developing over hours to several days, persisting for several days or weeks, and then gradually dissipating. The attacks are likely caused by the migration of activated, myelin-reactive T cells into the CNS, resulting in acute inflammation with associated edema.
- The clinical course of MS, therefore, falls into 1 of the following categories, with the potential to progress from less severe to more serious types and cannot be predicted with certainty:
 - Clinically isolated syndromes (CIS): the first episode of neurologic symptoms due to inflammation or demyelination lasting at least 24 hours. Patients with magnetic resonance imaging (MRI)-detected brain lesions consistent with MS are at high risk of developing MS.
 - Relapsing-remitting MS (RRMS): Clearly defined, self-limited attacks of neurologic dysfunction, followed by periods of remission without disease progression. Most patients experience a recovery of function that is often, but not always, complete.

- Primary progressive MS (PPMS): Nearly continuous worsening of disease not interrupted by distinct relapses; some individuals have occasional plateaus and temporary minor improvements.
- Secondary progressive MS (SPMS): Relapsing-remitting disease course at onset, followed by progression with or without occasional relapses, minor remissions, and plateaus; most patients eventually convert to progressive MS.
- The goals of treatment are to reduce relapses and new MRI lesion activity.
 - IFN β binds to cell surface-specific receptors, initiating a cascade of signaling pathways that end with the secretion of antiviral, antiproliferative, and immunomodulatory gene products. While IFN β has no direct effects in the CNS, it rapidly (within 2 weeks) blocks blood-brain barrier leakage and resolves gadolinium (Gd)-enhanced MRI activity. Two subspecies of IFN β are indicated for use in MS: IFN β -1a (Avonex, Plegridy, Rebif) and IFN β -1b (Betaseron, Extavia). While both subspecies have similar biological effects, the extent of activity varies between the 2. Plegridy is a pegylated formulation of IFN β -1a.
 - Alemtuzumab (Lemtrada) is a CD52 directed cytolytic monoclonal antibody and is presumed to bind to CD52, a cell surface antigen present on T and B lymphocytes. Following cell surface binding to T and B lymphocytes, alemtuzumab results in antibody-dependent cellular cytotoxicity and complement mediated lysis.
 - Cladribine (Mavenclad) is a purine antimetabolite that is thought to have cytotoxic effects on B and T lymphocytes through impairment of DNA synthesis, resulting in depletion of lymphocytes.
 - Dalfampridine is a broad-spectrum potassium channel blocker and has been shown to increase conduction of action potentials in demyelinated axons through inhibition of potassium channels.
 - Dimethyl fumarate (Tecfidera) and diroximel fumarate (Vumerity) share monomethyl fumarate (MMF) as a metabolite. These have been shown to activate the Nuclear factor-like (Nrf2) pathway in animal and human studies which may be the mechanism by which it achieves its therapeutic effect, but the exact mechanism is unknown. The Nrf2 pathway is involved in the cellular response to oxidative stress.
 - Glatiramer (Copaxone), a synthetic molecule, is thought to inhibit the activation of myelin basic protein-reactive T cells and may also induce antigen-specific suppressor T cells (T cells with activity characterized by anti-inflammatory effects).
 - Natalizumab (Tysabri) inhibits α 4-mediated adhesion of leukocytes (excluding neutrophils) to their counter-receptors by binding to the α 4-subunit of α 4 β 1 and α 4 β 7 integrins that are expressed on the leukocytes cell surface. These receptors include vascular cell adhesion molecule-1 (VCAM-1) and mucosal addressin cell adhesion molecule-1 (MAdCAM-1). Ultimately, this prevents leukocytes from transmigrating across endothelium, such as the blood brain barrier.
 - Ocrelizumab (Ocrevus) is a recombinant humanized CD20 monoclonal antibody. The precise mechanism in the treatment of MS is unknown; however, it targets and binds to CD20, a cell

surface antigen present on pre-B and mature B lymphocytes. This results in antibody-dependent cellular cytotoxicity and complement-mediated lysis.

- Teriflunomide (Aubagio), the active metabolite of leflunomide, is an immunomodulator with anti-inflammatory properties that inhibits dihydro-orotate dehydrogenase, an enzyme involved in de novo pyrimidine synthesis. Although the mechanism of action of teriflunomide is not completely known, it may reduce the number of activated lymphocytes in the CNS.

Antineoplastic: Oncology, Oral – Breast

- Breast cancer is the most common site of cancer in women and is second only to lung cancer as a cause of cancer death in American women. Death rates from breast cancer have steadily decreased in women since 1989 due to improvements in both early detection and treatment. Breast cancer is most frequently diagnosed in women between the ages of 55 to 64 with the median age at diagnosis being 62 years. Other risk factors include various endocrine, genetic, environmental, and lifestyle factors.
- All invasive breast cancer tumors are analyzed for the tumor's hormone receptor status and the presence or absence of the Her2/neu (HER2) receptor protein. Hormone receptor status is used clinically as an indicator of likely response to hormonal therapy. About two-thirds of patients with primary or metastatic breast cancer have hormone receptor (HR)-positive tumors. Hormonal therapies to treat breast cancer can be beneficial in both the adjuvant and metastatic setting of HR-positive disease.
- The menopausal status of the patient and the hormone receptor status of the tumor are important considerations in the therapeutic use of these agents. The prevalence and frequency of HR-positive tumors are higher in postmenopausal patients as compared to premenopausal patients. Hormone receptor positivity is associated with a superior response to hormonal therapy.
- Treatment of breast cancer should be based upon the patient's clinical factors and should include adjuvant systemic therapy where indicated.

Antineoplastic: Oncology, Oral – Hematologic

- Hematologic cancers encompass a group of blood cancers including multiple subtypes of leukemias and lymphomas.
- The subtypes of leukemias include Acute Lymphocytic Leukemia (ALL), Philadelphia chromosome positive ALL, Acute Myeloid Leukemia (AML), Acute Promyelocytic Leukemia (APL), and Chronic Myeloid Leukemia (CML).
- The subtypes of lymphomas include Hodgkin Lymphoma (HL), Non-Hodgkin Lymphoma (NHL), Chronic Lymphocytic Leukemia (CLL), Small Lymphocytic Lymphoma (SLL), Diffuse Large B Cell Lymphoma (DLBCL), Follicular Lymphoma (FL), Mantle Cell Lymphoma (MCL), Marginal Zone Lymphoma (MZL), Cutaneous T-cell Lymphoma (CTCLs)
- Other tumors included in the review of this group include dermatofibrosarcoma protuberans, Gastrointestinal Stromal Tumors (GIST), Graft versus Host Disease (GVHD), Kaposi sarcoma (KS), Multiple Myeloma (MM), Myelodysplastic syndromes, Myelofibrosis (MF), Polycythemia Vera (PV), Systemic Mastocytosis, and Waldenström's macroglobulinemia/lymphoplasmacytic lymphoma (WM/LPL).

Antineoplastic: Oncology, Oral – Lung

- Lung cancer is the leading cause of cancer death in both men and women in the United States (US). In 2020, an estimated 228,820 new cases of lung cancer will be diagnosed and 135,720 deaths are estimated to occur. Deaths from lung cancer have been declining, however despite the decline, there are still more US lung cancer deaths annually than deaths from breast cancer, prostate cancer, colorectal cancer, and brain cancers combined.
- Depending on the stage of the disease at diagnosis and the histologic subtype, the treatment of lung cancer may involve surgery, radiation, chemotherapy, targeted therapy, immunotherapy, or a combination of these approaches. Lung cancer is divided into 2 major classes: non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC). These 2 types of lung cancer differ in their biology, treatment, and overall prognosis.
- NSCLC accounts for more than 80% of all lung cancer cases. There are 2 major histologic subtypes of NSCLC, squamous cell and nonsquamous cell. Nonsquamous cell includes adenocarcinoma, which is the most common type of lung cancer diagnosed in the US and is also the most common subtype occurring in non-smokers.
- Oral treatment of lung cancer should be based upon the characteristics of the tumor including various factors identified by genomic profiling identifying sensitivity to anaplastic lymphoma kinase tyrosine kinase inhibitors or epidermal growth factor receptor tyrosine kinase inhibitors.

Antineoplastic: Oncology, Oral – Other

- The agents in this review are indicated for the treatment of a variety of malignant solid tumors, and one is also indicated for the hematologic malignancy, follicular lymphoma (FL). Many of the drugs included in this review, particularly the ones approved within the last 5 years, are examples of precision medicine where the FDA approved indication is defined by the use of a biomarker to -drive appropriate patient selection.
- Therapy for Bladder Cancer, CNS Cancer, Cholangiocarcinoma, Colon Cancer, Epithelioid Sarcoma, Follicular Lymphoma, Gastric Cancer, Gastrointestinal Stromal Tumors (GIST), Hepatocellular Carcinoma (HCC), Neurofibromatosis type 1 (NF1), NTRK Gene Fusion, Ovarian Cancer (Including Fallopian Tube or Primary Peritoneal Cancer), Pancreatic Cancer, Prostate Cancer, Soft Tissue Sarcoma, and Thyroid Carcinoma.

Antineoplastic: Oncology, Oral – Prostate

- In the United States (US), prostate cancer is the most commonly diagnosed cancer in men (excluding non-melanoma skin cancers), with an estimated 191,930 cases projected to be diagnosed in 2020.
- While prostate cancer accounts for the largest percentage of diagnosed cases in US males (20%), it only accounts for about 10% of all cancer deaths in this population. There has been a decreasing incidence of prostate cancer diagnoses since the early 1990s, and from 2011 to 2015, the incidence of prostate cancer declined approximately 7% per year (likely due to a change in practice during that time which saw a decreased rate of routine prostate-specific antigen (PSA) screening).

- Androgens (specifically testosterone) are a known growth signal for prostate cancer, and the majority of prostate cancers are hormonally dependent. Due to the hormone responsiveness of the tumor, androgen deprivation therapy (ADT) is a cornerstone of prostate cancer treatment.
- The prognosis of patients diagnosed with prostate cancer is determined by several factors, including the tumor size, histologic grade (reported as a Gleason score), PSA level, and disease stage. While early stage disease is highly curable, advanced, metastatic disease is currently considered incurable.
- The antiandrogens included in this review work by either inhibiting the androgen receptor, inhibiting androgen uptake, blocking the effect of testosterone at the receptor, inhibiting androgen biosynthesis, or elevating total plasma concentrations of estradiol.

Antineoplastic: Oncology, Oral – Renal Cell

- Renal cell carcinoma (RCC) accounts for approximately 4% of all newly-diagnosed cancers in the United States (US). The median age at diagnosis is 64 years, with 76% of cases being diagnosed in patients ages 55 or older.
- Overall 5-year survival for patients diagnosed with RCC was 75.2% from the period of 2010 to 2016. If the disease is localized at time of diagnosis, outcomes are excellent with a 5-year survival of approximately 93%; however, patients diagnosed with advanced, metastatic disease (about 16% of diagnoses) have much poorer outcomes with only a 12% survival rate at 5 years. The incidence of RCC in men is more than twice that of women in the US. The most common presenting triad of symptoms includes hematuria, flank mass, and flank pain; however, as the use of routine imaging has become more widespread, the frequency of incidental detection of RCC has increased, and only about 30% of patients are now diagnosed on the basis of symptoms.
- Smoking, obesity, and hypertension are known environmental risk factors for the development of RCC. There are also hereditary types of RCC; von Hippel-Lindau (VHL) disease predisposes patients to the development of kidney cancer. Approximately 85% of all kidney tumors are RCC, and 70% of all RCCs have clear cell histology. Other less common histologies are usually grouped together as “non-clear cell” tumors.
- Surgery is performed in most patients with RCC, using either a partial or radical nephrectomy depending on the stage and size of the tumor. Targeted therapies utilizing tyrosine kinase inhibitors (TKIs) and immunotherapy checkpoint inhibitors, given either separately or in combination, have become the usual first-line and second-line treatment options for advanced renal cell carcinoma due to their improved efficacy and tolerability compared to the cytokines.

Antineoplastic: Oncology, Oral – Skin

- Skin cancers are largely divided into 2 groups, melanoma skin cancers and non-melanoma skin cancers (NMSCs). NMSC are also called keratinocyte carcinomas. The most common NMSCs include basal cell carcinoma (BCC) and cutaneous squamous cell carcinoma (SCC). The distinction between melanoma and non-melanoma skin cancers is generally based on the lack of propensity for NMSC to metastasize as compared to melanoma, which has a high risk of metastasis and is often fatal in advanced stages. Aside from melanoma, cutaneous SCC and BCC, there are other types of cancers involving the skin. These

include primary cutaneous B-cell lymphomas, peripheral T-cell lymphomas, and certain sarcomas, such as dermatofibrosarcoma protuberans (a sarcoma of fibroblast origin) and AIDS-related Kaposi sarcoma. In addition, Merkel cell carcinoma (MCC) is a rare, aggressive cutaneous tumor that has both a high local recurrence rate and a high risk for distant metastatic disease.

- NMSCs are the most commonly occurring type of cancer, and their prevalence is more than that of all other types of cancers combined. The number of NMSCs treated in the US in 2012 was estimated to exceed 5 million cases. BCC is the most prevalent NMSC; it is at least twice as common as SCC. NMSC rarely metastasizes but can cause extensive local tissue destruction which can lead to disfigurement and may affect surrounding areas including bone.
- Surgery is the primary modality utilized for local BCC. Approximately half of all patients with metastatic cutaneous melanoma are positive for a BRAF mutation with most BRAF mutations occur at V600E but less frequently may occur at V600K. For patients with BRAF-mutated melanoma, the BRAF inhibitors have been shown to improve response rates, progression-free survival (PFS), and overall survival (OS).
- Mitogen-activated extracellular kinases (MEK) inhibitors were shown to improve response rate, duration of response, PFS, and OS of metastatic melanoma when given in combination with BRAF inhibitors compared to BRAF monotherapy.
- Furthermore, the hedgehog pathway inhibitors selectively inhibit transmembrane protein smoothened (SMO), a key transmembrane protein involved in hedgehog signal transduction of cancerous epithelial cells.

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Androgenic Agents

- The American College of Physicians (ACP) released a new guideline for testosterone treatment in men with age-related low testosterone. ACP recommends in this population testosterone treatment only to help them improve their sexual function with the preference of IM formulations over transdermal formulations, based on cost. Symptoms should be reassessed within 12 months of starting therapy. Treatment should be discontinued if symptoms fail to improve. The ACP recommends against initiating testosterone tx in this population to improve energy, vitality, physical function, or cognition.

Antibiotics, gastrointestinal (GI)

- Dificid (fidaxomicin) is now approved for the treatment of Clostridioides difficile- associated diarrhea (CDAD) in patients as young as 6 months of age. A new 40mg/mL oral suspension was approved to allow dosing for the younger pediatric age range. Dificid was previously only approved for adults.
- Vancocin (vancomycin capsule) is now approved for the treatment of Clostridioides difficile-associated diarrhea in pediatric patients less than 18 years of age. The indication previously stated that safety and efficacy had not been established in pediatric patients.

Antibiotics, topical

- There is no recent information of significance in this class since the last time the class was reviewed.

Antibiotics, vaginal

- There is no recent information of significance in this class since the last time the class was reviewed.

Antiemetics/Antivertigo agents

- Akynzeo (fosnetupitant/palonosetron) is now available in a new single dose 20 mL vial for IV infusion (235mg fosnetupitant/0.25mg palonosetron). It was previously only available as a capsule (300mg netupitant/0.5mg palonosetron) and a lyophilized powder in a single dose vial for reconstitution (235mg fosnetupitant/0.25mg palonosetron).

Antifungals, oral

- There is no recent information of significance in this class since the last time the class was reviewed.

Antifungals, topical

- Jublia (efinaconazole) is now indicated for the treatment of patients ≥ 6 years of age for the topical treatment of onychomycosis of the toenail(s) due to *Trichophyton rubrum* and *Trichophyton mentagrophytes*. It was previously only indicated for use in adult patients.

Antihistamines - first generation

- Endo has made a business decision to permanently discontinue Semprex-D. There are no generic versions.

Antiparasitics, topical

- There is no recent information of significance in this class since the last time the class was reviewed.

Antipsychotics

- The FDA issued a Drug Safety Communication strengthening warnings regarding bowel concerns in patients taking clozapine. Constipation that may occur with clozapine can, uncommonly, progress to serious bowel complications. The FDA is advising that HCPs evaluate bowel function prior to starting clozapine, avoid prescribing with anticholinergics, counsel patients on this risk, evaluate bowel habits throughout treatment, monitor for symptoms associated with complications, and consider prophylactic laxative treatment if the patient has a history of constipation or bowel obstruction.
- Eli Lilly will discontinue Symbyax 6/50 mg and 12/50 mg capsules. Distribution will continue until the end of December 2020.

Antivirals, topical

- There is no recent information of significance in this class since the last time the class was reviewed.

Bone resorption suppression and related agents

- The Endocrine Society updated their 2019 guidance on the management of postmenopausal osteoporosis to include Evenity (romosozumab-aqqg) with the recommendation including treatment with the once-monthly romosozumab-aqqg (210 mg) for up to 1 year in postmenopausal women with osteoporosis at very high risk for fracture to reduce risk for vertebral, hip, and nonvertebral fractures. Postmenopausal women at very high risk include those with low bone density T-scores (<-2.5) or with multiple vertebral fractures. After completing a course of romosozumab-aqqg, it is recommended that patients receive treatment with antiresorptive therapies to maintain gains in bone density and reductions in fracture risk.

Colony stimulating factors

- There is no recent information of significance in this class since the last time the class was reviewed.

Epinephrine, self-injected

- There is no recent information of significance in this class since the last time the class was reviewed.

GI motility, chronic

- There is no recent information of significance in this class since the last time the class was reviewed.

Growth hormone

- There is no recent information of significance in this class since the last time the class was reviewed.

Hepatitis C agents

- The US Preventive Services Task Force has released a recommendation regarding screening for hepatitis C virus (HCV) infection in adolescents and adults. The task force is recommending screening for HCV infection in adults aged 18 to 79 years. The recommendation expands the population of patients that are recommended to be screened as it applies to all adults aged 18 to 79 years, previously adults born between 1945 and 1965 were recommended for screening as well as others who were at high risk. The new recommendation applies to asymptomatic adults, including those who are pregnant, within the recommended age range, including those without known liver disease. For the majority of adults, a one-time screening is recommended; however individuals with continued risk for HCV should be screened periodically.
- Epclusa (sofosbuvir/velpatasvir) is now approved for the treatment of HCV genotypes 1, 2, 3, 4, 5, and 6 in pediatric patients 6 years of age and older and weighing 17 kg or more. It was previously only approved for treatment in adults.

- Epclusa (sofosbuvir/velpatasvir) is now approved for the treatment of HCV genotypes 1, 2, 3, 4, 5, and 6 in treatment-naïve and treatment-experienced liver transplant recipients with cirrhosis or with compensated cirrhosis. The recommended dosage in this population is once daily for 12 weeks.
- Harvoni (ledipasvir/sofosbuvir) and Sovaldi (sofosbuvir) are now available in pellet pack formulations intended to be used in the pediatric population for the indications for which the products have previously received FDA approval.

Hypoglycemics, incretin mimetics/enhancers

- Invokamet and Invokamet XR are now approved to reduce risk of end-stage kidney disease, doubling of serum creatinine, CV death, and hospitalization for heart failure in patients with T2DM and diabetic nephropathy with albuminuria > 300mg/day. These drugs were previously approved to reduce the risk of major adverse cardiovascular events (MACE) and as an adjunct to diet and exercise to improve glycemic control in patients with T2DM.
- The American Diabetes Association (ADA) published the Standards of Medical Care in Diabetes - 2020. Key revisions include two new sections: "Migrant and Seasonal Agricultural Workers," and "Pancreatic Diabetes or Diabetes in the Context of Disease of the Exocrine Pancreas." A new recommendation was added regarding testing for prediabetes and/or T2DM in overweight/obese women who have ≥ 1 additional diabetes risk factor who are planning a pregnancy. New recommendations were added around autoimmune conditions (thyroid disease, celiac disease) and comorbid conditions (hepatitis C infection). Recently approved intranasal and SC glucagon formulations and the use of continuous glucose monitoring were added to the Hyperglycemia section. Recently approved oral semaglutide was added as a treatment option. The cardiovascular outcomes study discussion was revised and SGLT2 inhibitors and GLP-1 agonists are recommended for patients with ASCVD, heart failure, or CKD, independent of HbA1c. Recommendations around blood pressure targets during pregnancy and the use of statins have been revised. New recommendations for children and adolescents were added based on the approval of liraglutide in children ≥ 10 years old.
- Trulicity (dulaglutide) is now approved to reduce the risk of major adverse cardiovascular events (MACE; CV death, non-fatal MI, non-fatal stroke) in adults with T2DM who have established CV disease or multiple CV risk factors. It was previously approved as an adjunct to diet and exercise to improve glycemic control in adults with T2DM. The initial dosage for MACE is 0.75 mg subcutaneously once weekly. This dose may be increased to 1.5 mg once weekly if needed for glycemic control.
- American College of Cardiology published 2020 Expert Consensus Decision Pathway on Novel Therapies for Cardiovascular Risk Reduction in Patients with Type 2 Diabetes. The decision pathway provides guidance for initiating and monitoring SGLT2 inhibitors and GLP-1RAs to reduce cardiovascular disease risk in diabetic patients. The guidance provides a summary of cardiovascular and renal (if applicable) outcome trials, opportunities to consider initiation of one of these agents, and decision algorithms for which agent by considering individual preferences or priority.

Hypoglycemics, insulin and related

- Lyumjev (insulin lispro-aabc) a rapid-active human insulin analog is indicated to improve glycemic control in adults with diabetes mellitus. It is approved for IV and subcutaneous use in 100 units/mL in 10 mL multi-dose vials and 3mL single-patient use Kwikpen, Junior Kwikpen, Tempo pen, and cartridges. It is also available in 200 unit/mL 3 mL single-patient use KwikPen. Dosing is individualized. Contraindications, warnings, and adverse effects are consistent with other insulin lispro-containing products.

Hypoglycemics, meglitinides

- There is no recent information of significance in this class since the last time the class was reviewed.

Hypoglycemics, metformin

- There is no recent information of significance in this class since the last time the class was reviewed.

Hypoglycemics, sodium-glucose cotransporter-2 inhibitors (SGLT2)

- Farxiga (dapagliflozin) is now approved to reduce the risk of CV death and hospitalization for heart failure (HF) in adults with HF with reduced ejection fraction (NYHA class II-IV). Farxiga was already indicated in T2DM patients as an adjunct to diet and exercise to improve glycemic control and to reduce the risk of hospitalization for HF in adults with T2DM and established CV disease or multiple CV risk factors. The recommended dose in heart failure patients is 10 mg once daily.
- American College of Cardiology published 2020 Expert Consensus Decision Pathway on Novel Therapies for Cardiovascular Risk Reduction in Patients with Type 2 Diabetes. The decision pathway provides guidance for initiating and monitoring SGLT2 inhibitors and GLP-1RAs to reduce cardiovascular disease risk in diabetic patients. The guidance provides a summary of cardiovascular and renal (if applicable) outcome trials, opportunities to consider initiation of one of these agents, and decision algorithms for which agent by considering individual preferences or priority.
- The FDA issued a Drug Safety Communication to update an earlier communication regarding the risk of leg and foot amputations with canagliflozin-containing medications, Invokana, Invokamet, Invokamet XR. The update states that, based on review of data from 3 new clinical trials, they have removed the Boxed Warning language from package inserts of canagliflozin-containing medications. The FDA states that subsequent data have demonstrated additional clinical benefits leading to additional indication approvals, while the risk of amputation (although still present) is lower than previously described. The risk of amputation remains a warning in the labeling.

Hypoglycemics, thiazolidinedione (TZD)

- There is no recent information of significance in this class since the last time the class was reviewed.

Macrolides-Ketolides

- There is no recent information of significance in this class since the last time the class was reviewed.

Opiate dependence treatments

- The FDA has released a drug safety communication and a MedWatch for opioid pain relievers and opioid use disorder (OUD) agents recommending healthcare providers discuss and consider naloxone use with all patients at the time of prescribing. Furthermore, the FDA is requiring manufacturers for all opioid pain relievers and OUD treatments (e.g., buprenorphine, methadone and naltrexone) add recommendations on naloxone to the product labeling for healthcare providers to consider and discuss prescribing naloxone. When these meds are prescribed or renewed, the FDA is recommending the potential need for a naloxone prescription be evaluated. Corresponding updates will also be made to the Med Guides. In addition, for patients that are not receiving a prescription for an opioid analgesic or OUD treatment, consideration should be given to prescribing naloxone for them if they are at a higher risk of opioid overdose (e.g., current/prior diagnosis of OUD or prior opioid overdose). The FDA also recommends healthcare providers consider prescribing naloxone when a patient has household members (e.g., children, close contacts) who may be at risk for accidental ingestion or opioid overdose.
- BioDelivery Sciences has made a business decision to discontinue Bunavail.

Tetracyclines

- There is no recent information of significance in this class since the last time the class was reviewed.

SINGLE PRODUCT REVIEWS

- An over the counter formulation of Benzefoam foam is now available for the topical treatment of acne.
- Dupixent (dupilumab) is now available in a 300 mg/2mL single-dose prefilled pen for use in adults and adolescents 12 years of age and older which includes use in certain patients with atopic dermatitis, asthma, and chronic rhinosinusitis with nasal polyposis (CRSwNP). Previously, Dupixent was only available as a single-dose prefilled syringe approved for use in children as young as 6 years of age.
- Nexlizet (bempedoic acid and ezetimibe) has been approved as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia (HeFH) or established ASCVD who require additional LDL-C lowering. It is available as a fixed dose combination tablet containing 180 mg of bempedoic acid and 10 mg of ezetimibe. The recommended dose is 1 tablet orally once daily with or without food and should be administered at least 2 hours before or 4 hours after bile acid sequestrants. Warnings, contraindications, warnings, drug interactions, and adverse reactions are similar to bempedoic acid and ezetimibe containing products.
- An over the counter Voltaren gel (diclofenac sodium topical gel 1%) has been approved by the FDA. Previously this medication was only available only with a prescription. The product is currently not federally rebatable and therefore does not qualify for consideration for inclusion on the Preferred Drug List, however, if the rebate status changes, the medication will be considered along with the rest of the medications in the class upon the regular review of the class.
- Dayvigo (lemorexant), an orexin receptor antagonist, is indicated for the treatment of insomnia, characterized by difficulties with sleep onset and/or sleep maintenance, in adults. Dayvigo is a DEA schedule IV product and is approved as 5 mg and 10 mg tablets. The recommended dose is 5 mg taken

immediately before going to bed with at least 7 hours remaining before the planned time of awakening. The dose may be increased to a max of 10 mg based on clinical response and tolerability. The time to sleep onset may be delayed if Dayvigo is taken with or shortly following a meal. Dayvigo is contraindicated in patient with narcolepsy. Warnings include CNS depressant effects and daytime impairment, sleep paralysis and cataplexy-like symptoms, complex sleep behaviors, compromised respiratory function, worsening of depression/suicidal ideation, and need to evaluate co-morbid diagnoses if insomnia persists. The most common adverse reaction was somnolence.