New Drug Update 2022

Presentation by Daniel A. Hussar, Ph.D.
Dean Emeritus and Remington Professor Emeritus
Philadelphia College of Pharmacy

This presentation considers the properties and uses of selected new therapeutic agents. The indications and routes of administration for these new drugs are reviewed, as are the most important precautions and practical considerations regarding their use. Where possible, the properties of the new drugs are compared with those of older drugs marketed for the same indications. A New Drug Comparison Rating (NDCR) is provided for each of the new drugs considered.

Learning Objectives:

After attending this program, the participant will be able to:

1. Identify the new therapeutic agents and explain their appropriate use.
2. Identify the indications and mechanisms of action of the new drugs.
3. Identify the most important adverse events and other risks of the new drugs.
4. State the route of administration for each new drug and the most important considerations regarding dosage and administration.
5. Compare the new therapeutic agents with older medications to which they are most similar in properties and/or use, and identify the most important advantages and disadvantages of the new drugs.

New Drug Comparison Rating (NDCR) system

5 = important advance
4 = significant advantage(s) (e.g., with respect to use/effectiveness, safety, administration)
3 = no or minor advantage(s)/disadvantage(s)
2 = significant disadvantage(s) (e.g., with respect to use/effectiveness, safety, administration)
1 = important disadvantage(s)

Additional information

The Pharmacist Activist newsletter: www.pharmacistactivist.com

COVID-19 **Nirmatrelvir/ritonavir (Paxlovid – Pfizer) – 2021**

Description: A SARS-CoV-2 main protease inhibitor; with ritonavir, an HIV-1 protease inhibitor and CYP3A4 inhibitor;

Indication: Emergency Use Authorization (EUA): Administered orally for the treatment of mild to moderate COVID-19 in adults and pediatric patients (12 years of age and older and weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death;

Limitations of use: Is not authorized for initiation of treatment in patients requiring hospitalization due to severe or critical COVID-19, for pre-exposure or post-exposure prophylaxis for prevention of COVID-19, or for use longer than 5 consecutive days;

New Drug Comparison Rating (NDCR) =

Comparable drugs: Bamlanivimab/etesevimab, casirivimab/imdevimab (REGEN-COV), sotrovimab;

Advantages:
---Is the first orally-administered antiviral product to be demonstrated to be effective in the treatment of COVID-19;
---Has a different mechanism of action that may provide effectiveness against more variants of SARS-CoV-2;

Disadvantages:
---Interacts with many other drugs;
---Use is not recommended in patients with severe hepatic or severe renal impairment;
---Use is limited to patients 12 years of age and older (compared with bamlanivimab/etesevimab which may be used in patients as young as newborns);
---Authorized use is more limited (compared with bamlanivimab/etesevimab and casirivimab/imdevimab that are also authorized for use for post-exposure prophylaxis for prevention of COVID-19);

Recommended dosage: Nirmatrelvir must be co-administered with ritonavir, with which it is co-packaged; 300 mg (two 150 mg tablets) with 100 mg ritonavir (one tablet) with all three tablets taken together twice daily for 5 days; treatment should be initiated as soon as possible after diagnosis of COVID-19, and within 5 days of symptom onset; dosage of nirmatrelvir should be reduced by one-half in patients with moderate renal impairment;

Products: Co-package of nirmatrelvir film-coated tablets (150 mg) and ritonavir film-coated tablets (100 mg);

Contraindications/most important risks:
---Interactions: Concurrent use of Paxlovid is contraindicated with drugs that are highly dependent on CYP3A for clearance and for which elevated concentrations are associated with serious and/or life-threatening reactions (alfuzosin, meperidine, piroxicam, propoxyphene, ranolazine, amiodarone, dronedarone, flecainide, propafenone, quinidine, colchicine, lurasidone, pimozide, clozapine, dihydroergotamine, ergotamine, methylergonovine, lovastatin, simvastatin, sildenafil (when used for PAH), triazolam, oral midazolam);
Concurrent use of Paxlovid is contraindicated with drugs that are potent CYP3A inducers where significantly reduced nirmatrelvir or ritonavir concentrations may be associated with the potential for loss of virologic response and possible resistance (carbamazepine, phenobarbital, phenytoin, rifampin, St. John's wort, apalutamide);
EUA fact sheet should be consulted regarding additional medications with which Paxlovid may interact;
---Hepatic adverse events (e.g., transaminase elevations, jaundice);

Most common adverse events: Dysgeusia (6%), diarrhea (3%); hypertension (1%), myalgia (1%);

Comments: Nirmatrelvir inhibits the SARS-CoV-2 main protease (Mpro) and prevents viral replication. Ritonavir is **not** active against SARS-CoV-2 Mpro, but inhibits the CYP3A-mediated metabolism of nirmatrelvir, resulting in increased plasma concentrations of the latter agent. Paxlovid was evaluated in a placebo-controlled trial in non-hospitalized adults, in which COVID-19 related hospitalization or death from any cause through Day 28 was 0.8% (no deaths) in Paxlovid-treated patients (n = 1039), and 6.3% (1.1% deaths) in patients receiving placebo (n= 1046).

Migraine **Atogepant (Qulipta – AbbVie) – 2021**

Description: A calcitonin gene-related peptide (CGRP) receptor antagonist;

Indication: Administered orally for the preventive treatment of episodic migraine in adults;

New Drug Comparison Rating (NDCR) =

Comparable drug: Rimegepant (Nurtec ODT); (ubrogepant (Ubrelvy) is also an orally-administered CGRP receptor antagonist that is only indicated for the acute treatment of migraine);

Advantages:
---May be less likely to cause hypersensitivity reactions (which are identified as a warning in the labeling for rimegepant);
---May be used in an adjusted dosage with interacting medications (whereas the concomitant use of rimegepant with a strong CYP3A4 inhibitor, strong and moderate CYP3A4 inducers, or inhibitors of P-glycoprotein or breast cancer resistance protein should be avoided);

Disadvantages:
---Labeled indications are more limited (rimegepant is also indicated for the acute treatment of migraine);
---May be more likely to cause fatigue;

Recommended dosage: 10 mg, 30 mg, or 60 mg once a day;
---dosage modifications:
10 mg once a day in patients also being treated with a strong CYP3A4 inhibitor, or in patients with severe renal impairment/end-stage renal disease;
10 mg or 30 mg once a day in patients also being treated with an organic anion transporting polypeptide (OATP) inhibitor;
30 mg or 60 mg once a day in patients also being treated with a strong or moderate CYP3A4 inducer;

Products: Tablets – 10 mg, 30 mg, 60 mg;

Contraindications/most important risks:
---Pregnancy (may cause adverse developmental effects based on animal studies);
---Hepatic impairment (should be avoided in patients with severe hepatic impairment);
---Renal impairment (should be used in a lower dosage in severe renal impairment and end-stage renal disease);
---Interactions: Strong CYP3A4 inhibitors; increase activity of atogepant which should be used in a lower dosage;
Strong and moderate CYP3A4 inducers; decrease activity of atogepant which should be used in a higher dosage;
OATP inhibitors; increase activity of atogepant which should be used in a lower dosage;

Most common adverse events: Nausea (6%), constipation (6%); fatigue/somnolence (4%);

Comments: Atogepant is the third CGRP antagonist for oral administration in the management of migraine, joining rimegepant and ubrogepant. However, the labeled indications for the three agents vary, with ubrogepant indicated for the acute treatment of migraine, atogepant for the preventive treatment of episodic migraine, and rimegepant for both but in different dosage regimens. Four other CGRP antagonists are administered parenterally for the preventive treatment of episodic migraine and chronic migraine, and these agents include erenumab (Aimovig), fremanezumab (Ajovy), galcanezumab (Emgality), and eptinezumab (Vyepti). Galcanezumab also has a labeled indication for the treatment of episodic cluster headache.

Atogepant was evaluated in two 12-week placebo-controlled studies in patients with episodic migraine (4-14 monthly migraine days [MMD]), in which the primary efficacy endpoint was the change in baseline in mean MMD (7.5 – 7.9 MMD). Dosages of 10 mg, 30 mg, and 60 mg daily of atogepant reduced migraine frequency with the difference from placebo being a reduction of approximately 1 MMD.

ADHD **Viloxazine hydrochloride (Qelbree – Supernus) – 2021**

Description: A selective norepinephrine reuptake inhibitor;

Indication: Administered orally for the treatment of attention-deficit hyperactivity disorder (ADHD) in pediatric patients 6 to 17 years of age;

New Drug Comparison Rating (NDCR) =

Comparable drug: Atomoxetine (e.g., Strattera);

Advantages:
---Has fewer contraindications and warnings (but primarily involving conditions more likely to be experienced in adults [e.g., narrow-angle glaucoma, severe cardiovascular disorders, severe hepatic effects]);

Disadvantages:
---Is a strong CYP1A2 inhibitor (concurrent use is contraindicated with sensitive CYP1A2 substrates or CYP1A2 substrates with a narrow therapeutic range);
---Labeled indication does not include use in adults;
---Should not be used during pregnancy;

Recommended dosage: Children 6-11 years of age – initially 100 mg once a day and then titrated in increments of 100 mg at weekly intervals to the maximum recommended dosage of 400 mg once a day; adolescents 12-17 years of age – initially 200 mg once a day and, after 1 week, may be increased to 400 mg once a day; for patients who have difficulty swallowing, contents of a capsule may be sprinkled over a teaspoonful of applesauce, which should be consumed in its entirety without chewing, within 2 hours; dosage should be reduced in patients with severe renal impairment;

Products: Extended-release capsules – 100 mg, 150 mg, 200 mg;

Contraindications/most important risks:
---Suicidal thoughts and behaviors (boxed warning);
---Blood pressure and heart rate may be increased;
---Mania or hypomania may be activated (patients should be screened for bipolar disorder);
---Somnolence and fatigue (caution should be exercised when engaged in activities requiring mental alertness);
---Pregnancy (may cause maternal harm and should not be used);
---Hepatic impairment (use is not recommended);
---Interactions: Monoamine oxidase (MAO) inhibitors: concurrent use with, or within 2 weeks after discontinuing a MAO inhibitor, is contraindicated;
Sensitive CYP1A2 substrate (e.g., duloxetine) or CYP1A2 substrates with a narrow therapeutic range (e.g., theophylline): action may be increased by viloxazine and concurrent use is contraindicated;
CYP2D6 substrates (e.g., dextromethorphan): action may be increased by viloxazine;
CYP3A4 substrates: action may be increased by viloxazine;

Most common adverse events: Somnolence (16%), headache (11%), fatigue (6%), decreased appetite (7%), nausea (5%), vomiting (4%), insomnia (4%), irritability (3%);

Comments: Viloxazine is the second selective norepinephrine reuptake inhibitor to be approved for the treatment of ADHD, joining atomoxetine. The new agent is a less potent norepinephrine reuptake inhibitor and, unlike atomoxetine, it acts *in vitro* as a serotonin $(5\text{-HT})_{2B}$ receptor agonist and a 5-HT_{2C} receptor antagonist although the clinical significance of these differences is not known. Viloxazine was evaluated in three 6-8 week placebo-controlled clinical trials. The primary endpoint was the change from baseline to the end of the study in the ADHD Rating Scale and the secondary endpoint was the change in the Clinical Global Impression-Improvement Score. There was a statistically significant reduction (improvement) in both of these measures with viloxazine.

ADHD **Serdexmethylphenidate/dexmethylphenidate HCl (Azstarys – Corium) -2021**

Description: A central nervous system (CNS) stimulant;

Indication: Administered orally for the treatment of attention deficit activity disorder (ADHD) in patients 6 years of age and older;

New Drug Comparison Rating (NDCR) =

Comparable drug: Dexmethylphenidate (e.g., Focalin XR);

Advantages: None;

Disadvantages:
---Dosage and formulation potencies are more complex;

Recommended dosage: In patients 6-12 years of age – initially, 39.2 mg/7.8 mg once daily in the morning; may be increased after one week to 52.3 mg/10.4 mg per day, or decreased to 26.1 mg/5.2 mg per day, depending on response and tolerability: in patients 13 years of age and older – initially, 39.2mg/7.8 mg once daily in the morning; may be increased after one week to 52.3 mg/10.4 mg per day; in patients who have difficulty swallowing, contents of capsule may be sprinkled into water or over two tablespoonfuls of applesauce and consumed within 10 minutes;

Products: Capsules – 26.1 mg/5.2 mg, 39.2 mg/7.8 mg, 52.3 mg/10.4 mg; the combined molar dose of the two agents is equivalent to 20, 30, or 40 mg dexmethylphenidate hydrochloride, respectively;

Contraindications/most important risks:
---Abuse and dependence (Schedule II);
---Cardiovascular reactions (avoid use in patients with coronary artery disease, serious arrhythmias, cardiomyopathy);
---Blood pressure and heart rate increases;
---Psychiatric adverse events (may cause psychotic or manic symptoms);
---Peripheral vasculopathy including Raynaud's phenomenon (should observe for digital changes);
---Long-term suppression of growth (monitor height and weight in pediatric patients);
---Priapism;
---Interactions: Monoamine oxidase (MAO) inhibitors: concurrent use with, or within 2 weeks of discontinuation of a MAO inhibitor, is contraindicated;
Antihypertensive drugs: blood pressure should be monitored and dosage adjusted as needed;
Risperidone: risk of extrapyramidal symptoms may be increased when dosage of either agent is changed);
Halogenated anesthetics (e.g., halothane, sevoflurane): avoid use of Azstarys on day of surgery);

Most common adverse events: Reported in 5% of more and at least twice the rate of the placebo group in studies with other methylphenidate products: decreased appetite and weight, nausea, abdominal pain, vomiting, dyspepsia, insomnia, anxiety, affect lability, irritability, dizziness, increased blood pressure, tachycardia;

Comments: Methylphenidate blocks the reuptake of norepinephrine and dopamine into the presynaptic neuron and increases the release of these monoamines into the extraneuronal space. Dexmethylphenidate is the more pharmacologically active d-enantiomer, and serdexmethylphenidate is a prodrug of dexmethylphenidate that extends its action and permits once-daily dosing. Azstarys was evaluated in patients 6-12 years of age in a placebo-controlled clinical trial in which, at the end of the 1-week treatment period, raters evaluated the attention and behavior of the children in a laboratory classroom setting over a period of 13 hours using a validated 13-item teacher-rated scale that assesses manifestation of ADHD in a classroom setting. The primary efficacy endpoint was the mean change from baseline of the combined scores averaged across the test day, with assessments conducted at 0.5, 1, 2, 4, 8, 10, 12, and 13 hours post-dose. The mean change from baseline in the scores was statistically significantly lower (indicating improvement) with Azstarys compared to placebo.

Alzheimer's disease **Aducanumab-avwa (Aduhelm – Biogen) – 2021**

Description: An amyloid beta-directed antibody;

Indication: Administered intravenously for the treatment of patients with Alzheimer's disease; (indication was subsequently revised to note that treatment should be initiated in patients with mild cognitive impairment or mild dementia stage of disease, the population in which treatment was initiated in clinical trials);

New Drug Comparison Rating (NDCR) =

Comparable drugs: Cholinesterase inhibitors (e.g., donepezil) and memantine (e.g., Namenda);

Advantages:
---Has a unique mechanism of action (reduces amyloid beta plaques in the brain);

Disadvantages:
---Clinical benefit has not been established;
---Must be administered intravenously (whereas comparable drugs are administered orally);
---Treatment requires brain magnetic resonance imaging (MRI) monitoring;
---May cause amyloid related imaging abnormalities (ARIA);
---Has not been directly compared with comparable drugs in clinical trials;

Recommended dosage: Administered by intravenous infusion over approximately one hour every four weeks and at least 21 days apart; initial dosage is 1 mg/kg (infusions 1 and 2), that is increased to 3 mg/kg (infusions 3 and 4), 6 mg/kg (infusions 5 and 6), and 10 mg/kg (infusion 7 and beyond); brain MRIs should be obtained prior to initiating treatment, and prior to the 7^{th} and 12^{th} infusions;

Products: Injection: single-dose vials – 170 mg/1.7 mL, 300 mg/3 mL (should be stored in a refrigerator); solution with the appropriate dose/volume should be added to an infusion bag of 100 mL of 0.9% Sodium Chloride Injection; immediate administration following dilution is recommended using an intravenous line containing a sterile, low-protein binding, 0.2 or 0.22 micron in-line filter;

Contraindication/most important risks:
---Amyloid related imaging abnormalities (ARIA; e.g., edema, hemosiderin deposition; enhanced clinical vigilance is recommended during the first 8 doses of treatment);
---Hypersensitivity reactions (e.g., urticaria, angioedema);

Most common adverse events: ARIA-edema (35%); ARIA-H microhemorrhage (19%), ARIA-H superficial siderosis (15%), headache (21%), falls (15%);

/Comments: The accumulation of amyloid beta plaques in the brain is thought to be a factor in the development of symptoms and dementia associated with Alzheimer's disease. Aducanumab is the first treatment to be approved that is directed at the underlying pathophysiology of the disease. The drug was evaluated in two placebo-controlled studies in patients with confirmed amyloid pathology and mild cognitive impairment or mild dementia, and was determined to consistently reduce amyloid beta plaques in the brain in a dose- and time-dependent manner. The reduction is this surrogate marker is thought to predict clinical benefit but is not itself a measure of clinical benefit. In both studies patients were randomized to receive aducanumab low dose, aducanumab high dose, or placebo intravenously every 4 weeks for 18 months. At a point during the trials a "futility analysis" was conducted that appeared to indicate that aducanumab was not likely to be more effective than placebo and the company terminated both trials prior to their planned completion. Following the termination of the trials, the company continued to reanalyze the available data/results. In one of the clinical trials, no statistically significant differences on the efficacy endpoints were observed between the aducanumab-treated and the placebo-treated patients. However, in the other clinical trial the high dose (but not the low dose) of aducanumab was thought to reduce clinical decline, as reflected by a statistically significant treatment effect on the primary and secondary efficacy endpoints compared to placebo. The FDA approved the drugs under the provisions of the Accelerated Approval Program.

Contraception **Estetrol monohydrate/drospirenone (Nextstellis – Mayne) – 2021**

Description: A combination oral estrogen/progestin contraceptive;

Indication: Administered orally for use by females of reproductive potential to prevent pregnancy; may be less effective in women with a BMI of 30 kg/m^2 or higher;

New Drug Comparison Rating (NDCR) =

Comparable drugs: Other combination oral estrogen/progestin contraceptive products;

Advantages:
---Estetrol is selective for nuclear estrogen receptors alpha and beta, and has a longer half-life;
---Estetrol may have less risk than other estrogens (but comparative studies have not been conducted);

Disadvantages:
---Has not been directly compared with comparable drugs in clinical trials;

Recommended dosage: One tablet at the same time every day; product labeling and patient information should be consulted for starting use, switching from other contraceptives, and when doses are missed;

Product: Tablets – 14.2 mg estetrol (15 mg estetrol monohydrate) and 3 mg drospirenone, in blister packs containing 28 tablets with 24 active tablets and 4 inert tablets;

Contraindications/most important risks:
---Women who are over 35 and smoke (boxed warning; smoking increases the risk of serious cardiovascular events);
---Contraindicated in women with a high risk of thrombotic disease, current or history of a hormonally-sensitive malignancy (eg., breast cancer), liver disease, abnormal uterine bleeding, adrenal insufficiency, or renal impairment;
---Thromboembolic and other vascular disorders (discontinue if thrombotic or thromboembolic event occurs);
---Hypertension (blood pressure should be monitored periodically);
---Migraine (discontinue if new, recurrent, persistent or severe migraines occur);
---Liver disease (withhold or discontinue for persistent or significant elevation of liver enzymes);
---Gallbladder disease and cholestasis (consider discontinuation in women with symptomatic disease);
---Hormonally-sensitive malignancy (discontinue if such a malignancy is diagnosed);
---Bleeding irregularities and amenorrhea;
---Glucose tolerance and hypertriglyceridemia (consider another contraceptive method with hypertriglyceridemia);
---Lactation (may decrease milk production);
---Interactions: Ombitasvir/paritaprevir/ritonavir, with or without dasabuvir: concurrent use is contraindicated;
Medications that increase serum potassium concentrations: concurrent use increases risk of hyperkalemia;
CYP3A inducers: contraceptive failure and/or breakthrough bleeding may result; avoid concurrent use or, if concurrent use is necessary, use a back-up nonhormonal contraceptive method during use and up to 28 days after discontinuation of the CYP3A inducer;
Lamotrigine: exposure and effectiveness of lamotrigine may be decreased;
Systemic corticosteroids: exposure and activity of corticosteroid may be increased;

Most common adverse events: Mood disturbance (11%), bleeding irregularities (10%), breast symptoms (5%), headache (5%), dysmenorrhea (4%), increased weight (3%), acne (3%);

Comments: Estetrol is a new synthetic analog of a native estrogen present during pregnancy that is selective for nuclear estrogen receptors alpha and beta. It has a longer half-life than other estrogens, which has been suggested to reduce the likelihood of irregular bleeding. Drospirenone is a progestin and spironolactone analogue with anti-mineralocorticoid and antiandrogenic activity, and may increase serum potassium concentrations. In a clinical trial in women 16-35 years old, the primary endpoint was the Pearl Index (pregnancy rate per 100 woman-years of use). The Pearl Index was 2.65 (2.57 in women with a BMI less than 30 kg/m^2, and 2.94 in those with a BMI of 30 to less than 35 kg/m^2. These rates are generally similar to those of other newer combination oral contraceptives.

Vulvovaginal candidiasis **Ibrexafungerp citrate (Brexafemme – Scynexis) – 2021**

Description: A triterpenoid antifungal agent;

Indication: Administered orally for the treatment of adult and post-menarchal pediatric females with vulvovaginal candidiasis;

New Drug Comparison Rating (NDCR) =

Comparable drug: Fluconazole (e.g., Diflucan);

Advantages:
---May be effective in some infections caused by strains of *Candida* that are resistant to fluconazole;
---Has a unique mechanism of action (inhibits glucan synthase and exhibits fungicidal activity);

Disadvantages:
---Is contraindicated in women who are pregnant;
---May be more likely to cause gastrointestinal adverse events;
---Has not been directly compared with fluconazole in clinical trials;
---Labeled indications are more limited (whereas fluconazole is also indicated for the treatment of oropharyngeal and esophageal candidiasis and cryptococcal meningitis);

Recommended dosage: 300 mg (two tablets) twice a day for one day; dosage should be reduced to 150 mg twice a day for one day in patients also being treated with a strong CYP3A4 inhibitor;

Product: Tablets – 150 mg in a blister pack with four tablets;

Contraindications/most important risks:
---Pregnancy (may cause adverse developmental effects and use is contraindicated; women of reproductive potential should be advised to use effective contraception);
---Interactions: Strong CYP3A4 inhibitors: may increase activity of ibrexafungerp and dosage should be reduced;
Strong or moderate CYP3A4 inducers: may decrease activity and concurrent use should be avoided;

Most common adverse events: Diarrhea (17%), nausea (12%), abdominal pain (11%);

Comments: Vulvovaginal candidiasis is usually caused by *Candida albicans* but may also be caused by other *Candida* species. It is often treated with antifungal agents (azoles) that are administered vaginally or with a single oral dose of fluconazole. Ibrexafungerp is the first triterpenoid antifungal agent and has a mechanism of action that is similar to that of the echinocandin antifungal agents (e.g., caspofungin) that are only administered parenterally. However, ibrexafungerp binds to different sites on the glutan synthase enzyme that is involved in the formation of fungal cell walls.

Ibrexafungerp was evaluated in two placebo-controlled clinical trials, and it was determined to be statistically significantly more effective than placebo. A complete clinical response at the "test of cure" visit (in 8-14 days) was experienced by 50% and 64% of those treated with ibrexafungerp in the two trials, respectively, compared with 28% and 45% of those receiving placebo. A negative culture at the test of cure visit was experienced by 50% and 59% of the patients treated with the drug, compared with 19% and 29% of those receiving placebo. A complete clinical response at a follow-up visit (in 21-29 days) was experienced in 60% and 73% of those treated with the new drug, compared with 44% and 49% of those receiving placebo.

Overactive bladder **Vibegron (Gemtesa – Urovant) – 2021**

Description: A beta-3 adrenergic receptor agonist;

Indication: Administered orally for the treatment of overactive bladder (OAB) with symptoms of urge urinary incontinence, urgency, and urinary frequency in adults;

New Drug Comparison Rating (NDCR) =

Comparable drug: Mirabegron (Myrbetriq);

Advantages:
---May be more selective for beta-3 receptors;
---Is less likely to increase blood pressure;
---Is not likely to interact with CYP2D6 substrates;
---Instructions are provided in the labeling for administration in patients who can't swallow tablets;

Disadvantages:
---Labeled indications are more limited (whereas mirabegron is also indicated for concurrent use with solifenacin, and for the treatment of neurogenic detrusor overactivity in pediatric patients);

Recommended dosage: 75 mg once a day with or without food; tablets should be swallowed whole with a glass of water, or may be crushed, mixed with a tablespoonful of applesauce and administered immediately with water;

Product: Tablets - 75 mg;

Contraindications/most important risks:
---Urinary retention: risk is increased in patients with bladder outlet obstruction, and also in patients taking a muscarinic antagonist for OAB;
---Hepatic impairment: has not been studied in patients with severe hepatic impairment, and is not recommended;
---Renal impairment: has not been studied in patients with end-stage renal disease, and is not recommended;
---Interactions: Digoxin: concentration and exposure of digoxin may be increased, and concentration should be monitored before and during therapy;

Most common adverse events: Headache (4%), nasopharyngitis (3%), diarrhea (2%), nausea (2%), upper respiratory tract infection (2%);

Comments: Activation of beta-3 adrenergic receptors in the bladder results in relaxation of detrusor smooth muscle and increased bladder capacity. Vibegron is the second beta-3 adrenergic receptor agonist for the treatment of OAB, joining mirabegron, and is thought to have a more selective action than mirabegron for beta-3 receptors. Muscarinic antagonists (anticholinergics) such as tolterodine and solifenacin are the most widely used medications for treating OAB.

The effectiveness of vibegron was evaluated in a 12-week placebo-controlled, active controlled (tolterodine) clinical trial. There was a statistically significant reduction with vibegron in average daily number of micturitions (-1.8; baseline 11.3)) compared with placebo (-1.3; baseline 11.8), but not compared with tolterodine. There was also a statistically significant reduction with vibegron in the average daily number or urge urinary incontinence episodes (-2.0; baseline 3.4) compared with placebo (1.4; baseline 3.5), but not compared with tolterodine.

Acne

Clascoterone (Winlevi – Cassiopea) – 2021

Description: A topical androgen receptor inhibitor;

Indication: Applied topically for the treatment of acne vulgaris in patients 12 years of age and older;

New Drug Comparison Rating (NDCR) =

Comparable drugs: Topical retinoids (adapalene [e.g., Differin] is used for comparison);

Advantages:
---Has a unique mechanism of action (androgen receptor inhibitor for topical use);

Disadvantages:
---May cause hyperkalemia and hypothalamic-pituitary-adrenal (HPA) axis suppression:
---Is administered twice a day (whereas adapalene is administered once a day);
---Requires a prescription (whereas adapalene 0.1% gel is available without a prescription);
---Formulation options are more limited (whereas adapalene is also available in gel and lotion formulations, and in combination with benzoyl peroxide in a topical gel formulation);
---Has not been directly compared with comparable drugs in clinical trials;

Recommended dosage: Applied topically in a thin layer (approximately 1 gram) to the affected area twice a day in the morning and evening; contact with mouth, eyes, and mucous membranes should be avoided;

Product: Cream – 1% (should be stored in a refrigerator prior to dispensing); while in use product may be stored at room temperature, and unused product should be discarded 180 days after the date of dispensing or 1 month after first opening, whichever is sooner;

Contraindications/most important risks:
---Local skin reactions; concomitant use with other potentially irritating topical products (e.g., medicated or abrasive soaps, cleansers, and other products that have a strong drying effect, and products with high concentrations of alcohol, astringents, spices, or lime) should be limited;
---Hypothalamic-pituitary-adrenal (HPA) axis suppression; if HPA axis suppression occurs, the drug should be withdrawn;
---Hyperkalemia;

Most common adverse events: Erythema/redness (12%), scaling/dryness (11%), pruritus (8%);

Comments: Androgens are one of the factors in the pathogenesis of acne and can increase sebum production and inflammation. Clascoterone is designated chemically as cortexolone-17-alpha propionate, and is the first topical androgen receptor inhibitor to be approved for the treatment of acne. Clascoterone was evaluated in two 12-week vehicle-controlled clinical trials in patients with facial acne vulgaris. The Investigator's Global Assessment (IGA; score of 0–4)) was used for assessing efficacy, with efficacy defined as at least a 2-point reduction in IGA compared to baseline and an IGA score of 0 (clear) or 1 (almost clear). The absolute change and percent change from baseline in non-inflammatory lesions (open and closed comedones) and inflammatory lesions (papules, pustules, and nodules) were also determined. IGA success was experienced by 19% and 21% of patients treated with clascoterone in the two trials, respectively, compared with 9% and 7% of those treated with the vehicle. There was a mean absolute reduction in non-inflammatory lesions of 20% in clascoterone-treated patients in both trials, compared with 13% and 11% of those treated with the vehicle. The mean absolute reduction in inflammatory lesions was 19% and 20% in patients treated with clascoterone, compared with 15% and 13% of those treated with the vehicle.

Actinic keratosis **Tirbanibulin (Klisyri – Almirall) – 2021**

Description: A microtubule inhibitor;

Indication: Applied topically for the treatment of actinic keratosis of the face or scalp;

New Drug Comparison Rating (NDCR) =

Comparable drug: Topical fluorouracil (e.g., Fluoroplex);

Advantages:
---Has a unique mechanism of action (microtubule inhibitor);
---Has a shorter duration of treatment (5 days compared to 2-6 weeks);
---Is applied once a day (compared with twice a day, although some topical fluorouracil products are administered once a day);
---Is less likely to cause severe dermatologic adverse events;
---May be used with caution during pregnancy (whereas the topical use of fluorouracil is contraindicated);

Disadvantages:
---Labeled indications are more limited (some topical formulations of fluorouracil are also indicated for the treatment of superficial basal cell carcinoma);

Recommended dosage: Apply a sufficient amount to evenly cover up to 25 cm^2 treatment field on the face or scalp once daily for 5 consecutive days; avoid washing or touching the treated area for approximately 8 hours after application; following this time the area may be washed with a mild soap.

Product: Ointment – 1% in single-dose packets;

Contraindications/most important risks:
---Skin reactions: may be severe (e.g., postulation, erosion, ulceration); should not be used until skin is healed from any previous drug or surgical treatment;
---Ocular adverse events: transfer into the eyes/periocular area during or after application should be avoided;

Most common adverse events: Local skin reactions (erythema [91%], flaking/scaling [82%], crusting [46%], swelling [39%], erosion/ulceration [12%]), application site pain (10%), application site pruritus (9%);

Comments: Actinic keratosis is characterized by scaly, erythematous macules, papules, or plaques that are commonly experienced in older, lighter-skin people with an extended history of sun exposure. Most lesions are benign but they can progress to squamous cell carcinoma. Liquid nitrogen cryosurgery of the lesions is commonly employed, and topical drug treatments with fluorouracil, imiquimod, and diclofenac gel have been used.

Tirbanibulin is a microtubule inhibitor although its specific mechanism of action in the treatment of actinic keratoses is not known. Its effectiveness was evaluated in two vehicle-controlled clinical trials. At Day 57, 44% and 54% of patients treated with tirbanibulin in the two studies experienced complete (100%) clearing of lesions compared with 5% and 13%, respectively, of those treated with the vehicle. For the second endpoint of partial (at least 75%) clearance, 68% and 76% of patients treated with the new drug attained the endpoint compared with 16% and 20% of those treated with the vehicle.