New Drugs of 2015*

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Objectives:

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

1. Identify the indications and routes of administration of the new therapeutic agents.
2. Identify the important pharmacokinetic properties and the unique characteristics of the new drugs.
3. Identify the most important adverse events and precautions of the new drugs.
4. Compare the new drugs to the older therapeutic agents to which they are most similar in activity.
5. Identify information regarding the new drugs that should be communicated to patients.

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 monthly newsletter: www.pharmacistactivist.com
Suvorexant (Belsomra – Merck)  Hypnotic

2015  New Drug Comparison Rating (NDCR) =

Indication:  Treatment of patients with insomnia characterized by difficulties with sleep onset and/or sleep maintenance

Comparable drugs:  Zolpidem extended-release (e.g., Ambien CR), eszopiclone (Lunesta)

Advantages:
--Has a unique mechanism of action (orexin receptor antagonist)
--May be less likely to cause withdrawal effects when treatment is discontinued

Disadvantages:
--Has not been directly compared with comparable drugs in clinical studies
--Is more likely to cause cataplexy-like symptoms and is contraindicated in patients with narcolepsy

Most important risks/adverse events:  Risk of excessive central nervous system (CNS) actions (e.g., impaired daytime wakefulness and alertness, impaired driving; risk is increased by the concurrent use of other CNS depressants including alcohol; all patients should be cautioned regarding the CNS effects and related risks; patients treated with a dosage of 20 mg daily should be advised against next-day driving and other activities requiring complete mental alertness); nighttime “sleep-driving” and other complex behaviors while out of bed and not fully awake, with amnesia for the event; cataplexy-like symptoms (is contraindicated in patients with narcolepsy); worsening of depression or suicidal thinking; risk of abuse (is classified as a Schedule IV controlled substance); additive CNS effects result when used concurrently with other CNS depressants (consumption of alcoholic beverages is best avoided, particularly at bedtime and in the evening); action may be increased by CYP3A inhibitors (concurrent use with a strong CYP3A inhibitor [e.g., clarithromycin, itraconazole] is not recommended; dosage should be reduced in patients also taking a moderate CYP3A inhibitor [diltiazem, verapamil, grapefruit juice]); action may be reduced by the concurrent use of a strong CYP3A inducer (e.g., carbamazepine, St. John’s wort); may increase digoxin concentrations

Most common adverse events;  Somnolence (7%)

Usual dosage:  10 mg once a night within 30 minutes of going to bed, with at least 7 hours remaining before the planned time of awakening; onset of action may be delayed if taken with or soon after a meal; if the 10 mg dose is well tolerated but not effective, the dose can be increased; the maximum recommended dosage is 20 mg once daily; if it is necessary for a patient to also be taking a moderate CYP3A inhibitor, the recommended initial dosage is 5 mg once a night, and the dosage should generally not exceed 10 mg daily in these patients; a reduction in dosage may be necessary in patients taking other CNS depressants, and in obese female patients

Products:  Film-coated tablets – 5 mg, 10 mg, 15 mg, 20 mg

Comments:  The orexins are naturally occurring neuropeptides that act in a signaling system as a central promoter of wakefulness.  This wake-promoting action results, at least in part, from the binding of orexin A and orexin B to OX1R and OX2R receptors.  Suvorexant is an orexin receptor antagonist and is the first medication with this mechanism of action.  By blocking the binding of orexins to their receptors, it is thought to suppress the wake drive.  Like the extended-release formulation of zolpidem (e.g., Ambien CR) and eszopiclone, it has been approved for the treatment of patients with insomnia characterized by difficulties with sleep onset and/or sleep maintenance.  The effectiveness of suvorexant was evaluated in three placebo-controlled studies.  The new drug was determined to be superior to placebo in reducing the time to sleep onset and in increasing total sleep time.

The antagonism of orexin receptors may underlie potential adverse events such as signs of narcolepsy/cataplexy, and loss of orexin receptors has been reported in humans with narcolepsy.
Brexpiprazole (Rexulti – Otsuka) Antipsychotic Agent

2015 New Drug Comparison Rating (NDCR) =

Indications: Treatment of patients with schizophrenia, and as adjunctive treatment of patients with major depressive disorder (MDD)

Comparable drugs: Aripiprazole (e.g., Abilify)

Advantages:
--May be effective in some patients who have not experienced an adequate response with other agents
--May be less likely to cause extrapyramidal reactions

Disadvantages:
--Has not been directly compared with comparable drugs in clinical studies
--Labeled indications are more limited (aripiprazole also has labeled indications for the acute treatment of patients with manic and mixed episodes associated with bipolar I disorder, the treatment of Tourette’s disorder, and irritability associated with autistic disorder)
--Has not been evaluated in pediatric patients (whereas aripiprazole is indicated for use in pediatric patients as young as 6 years for certain conditions)
--Dosage forms are more limited (aripiprazole is also available in an oral solution formulation, and in a parenteral formulation for intramuscular injection for the treatment of agitation associated with schizophrenia or bipolar mania)
--May be more likely to cause weight gain

Most important risks/adverse events: Increased risk of death in elderly patients with dementia-related psychosis (boxed warning), and a higher incidence of cerebrovascular adverse events (e.g., stroke, transient ischemic attack) in these patients; increased risk of suicidal thoughts and behaviors in patients 24 years of age and younger (boxed warning); neuroleptic malignant syndrome; tardive dyskinesia; seizures; orthostatic hypotension and syncope; body temperature dysregulation; dysphagia; metabolic changes (e.g., hyperglycemia/diabetes, dyslipidemia, weight gain); leukopenia, neutropenia, and agranulocytosis; potential for cognitive and motor impairment (patients should be cautioned about operating hazardous machinery); is a substrate for the CYP3A4 and CYP2D6 metabolic pathways and activity is increased by the concurrent use of a strong CYP3A4 inhibitor (e.g., clarithromycin), a moderate CYP3A4 inhibitor (e.g., fluconazole), a strong CYP2D6 inhibitor (e.g., fluoxetine, paroxetine), or a moderate CYP2D6 inhibitor (e.g., duloxetine); action is reduced by the concurrent use of a strong CYP3A4 inducer (e.g., rifampin, St. John’s wort); has not been evaluated in pediatric patients (boxed warning); may cause extrapyramidal and/or withdrawal symptoms in neonates with third trimester exposure

Most common adverse events: Weight gain (4%) in patients with schizophrenia; akathisia (9%) and weight gain (7%) in patients with MDD

Usual dosage: In the treatment of patients with schizophrenia, the recommended starting dosage is 1 mg once a day on Days 1 through 4; the recommended target dosage is 2 to 4 mg once a day; the dosage should be titrated to 2 mg once a day on Days 5 through 7, then to 4 mg once a day on Day 8; the maximum recommended daily dosage is 4 mg; when used as adjunctive treatment in patients with MDD, the recommended starting dosage is 0.5 mg or 1 mg once a day; at weekly intervals the dosage should be titrated to 1 mg once a day, and then to the target dosage of 2 mg once a day; the maximum recommended daily dosage is 3 mg; the product labeling should be consulted for the recommended dosage adjustments in patient with hepatic or renal impairment, in patients also being treated with potentially interacting medications, and in CYP2D6 poor metabolizers

Products: Tablets – 0.25 mg, 0.5 mg, 1 mg, 2 mg, 3 mg, 4 mg

Comments: Brexpiprazole is an atypical antipsychotic agent with properties and uses that are most similar to those of aripiprazole. It is thought to have partial agonist activity at serotonin 5-HT1A and dopamine D2 receptors, and antagonist activity at serotonin 5-HT2A receptors. It has been demonstrated to be more effective than placebo in reducing the occurrence of symptoms of schizophrenia, and in reducing symptoms of depression.
**Sacubitril/valsartan** (Entresto – Novartis)  
**Agent for Heart Failure**

*2015 New Drug Comparison Rating (NDCR) =*

**Indication:** To reduce the risk of cardiovascular death and hospitalization for heart failure in patients with chronic heart failure (NYHA Class II-IV) and reduced ejection fraction (is usually administered in conjunction with other heart failure therapies, in place of an angiotensin-converting enzyme [ACE] inhibitor or other angiotensin receptor blocker [ARB])

**Comparable drugs:** Enalapril, as well as other ACE inhibitors and ARBs that are indicated for the treatment of patients with chronic heart failure

**Advantages:**
--Is more effective (based on a comparison with enalapril)
--Has a unique mechanism of action (sacubitril via its active metabolite inhibits neprilysin)

**Disadvantages:**
--Has a greater risk of causing angioedema
--Is more likely to cause hypotension

**Most important risks/adverse events:** Angioedema (contraindicated in patients with a history of angioedema related to previous ACE inhibitor or ARB therapy; concurrent use with an ACE inhibitor is contraindicated; concurrent use of another ARB should be avoided; incidence is higher in Black patients than in non-Black patients); concurrent use with aliskiren (Tekturna) is contraindicated in patients with diabetes, and concurrent use should be avoided in patients with renal impairment; hypotension (risk is greater in patients treated with high doses of diuretics); hyperkalemia (serum potassium concentrations should be monitored; risk is greater in patients with severe renal impairment, diabetes, and in those using a potassium-sparing diuretic [e.g., spironolactone], potassium supplement, or a salt substitute containing potassium); reduced renal function (renal function should be monitored in patients with renal artery stenosis or who develop a significant decrease in renal function); pregnancy (boxed warning; may cause harm to the unborn child; should be discontinued when pregnancy is determined); concurrent use with a nonsteroidal anti-inflammatory drug may cause a worsening of renal function in patients at risk; may increase lithium concentrations and risk of lithium toxicity

**Most common adverse events:** Hypotension (18%), hyperkalemia (12%), cough (9%), dizziness (6%), renal failure/acute renal failure (5%)

**Usual dosage:** Should not be administered within 36 hours of switching from or to an ACE inhibitor; initial dosage - 49 mg sacubitril/51 mg valsartan twice a day; after 2 to 4 weeks, the dosage should be increased to the target maintenance dosage of 97 mg/103 mg twice a day; a reduced initial dosage of 24 mg/26 mg twice a day is recommended in patients with moderate hepatic impairment, severe renal impairment, and in patients not currently taking an ACE inhibitor or ARB or who were previously being treated with a low dosage of one of these agents (the dosage should be doubled every 2 to 4 weeks to the target maintenance dosage, as tolerated by the patient)

**Products:** Film-coated tablets – 24 mg/26 mg (sacubitril/valsartan), 49 mg/51 mg, 97 mg/103 mg; an amount of 26 mg of valsartan in the combination product is equivalent to 40 mg of valsartan in other marketed tablet formulations

**Comments:** Sacubitril is a prodrug that is rapidly converted by esterases to LBQ657, its active metabolite with a unique mechanism of action as a neprilysin inhibitor. Neprilysin causes degradation of certain vasoactive peptides and, by inhibiting neprilysin, sacubitril/LBQ657 increases the concentrations of these peptides, thereby reducing vasoconstriction and sodium retention. The sacubitril/valsartan combination formulation is usually administered in conjunction with other heart failure therapies (e.g., beta-blockers, diuretics, aldosterone antagonists), in place of an ACE inhibitor or other ARB. Sacubitril/valsartan has been demonstrated to be superior to enalapril in reducing the risk of the study’s combined endpoint of cardiovascular death or hospitalization for heart failure (21.8% compared with 26.5% with enalapril). The greater effectiveness of sacubitril/valsartan provides a significant advantage that will result in its first-line use as an alternative to an ACE inhibitor or ARB.
Ivabradine hydrochloride (Corlanor – Amgen)  
Agent for Heart Failure

2015  New Drug Comparison Rating (NDCR) =

Indication:  To reduce the risk of hospitalization for worsening heart failure in patients with stable, symptomatic chronic heart failure with left ventricular ejection fraction of 35% or lower, who are in sinus rhythm with resting heart rate of at least 70 beats per minute and either are on maximally tolerated doses of beta-blockers or have a contraindication to beta-blocker use.

Comparable drugs:  Medications used in treatment regimens for patients with heart failure (e.g., an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, a beta-blocker, a diuretic, an aldosterone antagonist)

Advantages:  
--Contributes to greater effectiveness in reducing the risk of hospitalization for worsening heart failure  
--Has a unique mechanism of action (reduces heart rate by blocking the hyperpolarization-activated cyclic nucleotide-gated channel responsible for the cardiac pacemaker If current, which regulates heart rate)  
--May be used in some patients for whom a beta-blocker is contraindicated

Disadvantages:  
--Is not more effective in reducing the risk of cardiovascular death  
--Use is associated with a greater risk of bradycardia  
--Is more likely to cause visual disturbances (visual brightness)  
--May interact with more medications

Most important risks/adverse events:  Contraindicated in patients with acute decompensated heart failure, blood pressure less than 90/50 mmHg, resting heart rate less than 60 beats per minute prior to treatment, or pacemaker dependence (heart rate maintained exclusively by the pacemaker); contraindicated in patients with sick sinus syndrome, sinoatrial block, or 3rd degree AV block unless a functioning demand pacemaker is present, and use should be avoided in patients with 2nd degree AV block, unless a functioning demand pacemaker is present; risk during pregnancy (women of childbearing potential should be advised to use effective contraception); contraindicated in patients with severe hepatic impairment; activity is increased by strong CYP3A4 inhibitors (e.g., clarithromycin, itraconazole) and concurrent use is contraindicated; concurrent use with a moderate CYP3A4 inhibitor (e.g., diltiazem, verapamil, grapefruit juice) should be avoided; activity is reduced by CYP3A4 inducers (e.g., carbamazepine, rifampin, St. John’s wort) and concurrent use should be avoided; bradycardia (risk is increased by the concurrent use of other medications that slow heart rate [e.g., diltiazem, verapamil, digoxin, amiodarone]); should not be used in patients with a demand pacemaker set to a rate of 60 beats per minute or higher

Most common adverse events:  Bradycardia (10%), hypertension (9%), atrial fibrillation (8%), luminous phenomena (phosphenes, visual brightness; 3%)

Usual dosage:  Initial dosage – 5 mg twice a day with meals; patient should be assessed after 2 weeks of treatment and the dosage should be adjusted to achieve a resting heart rate between 50 and 60 beats per minute; thereafter the dosage should be adjusted based on resting heart rate and tolerability; maximum dosage is 7.5 mg twice a day; in patients with a history of conduction defects, or other patients in whom bradycardia could lead to hemodynamic compromise, treatment should be initiated with a dosage of 2.5 mg twice a day

Products:  Film-coated tablets (scored) – 5 mg, 7.5 mg

Comments:  Ivabradine causes a dose-dependent reduction in heart rate by blocking the hyperpolarization-activated cyclic nucleotide-gated channel responsible for the cardiac pacemaker If current, which regulates heart rate. Its effectiveness was evaluated in several large placebo-controlled studies. The primary endpoint in the study that provided the strongest support for its approval was a composite of the first occurrence of either hospitalization for worsening heart failure or cardiovascular death. Although ivabradine reduced the risk of the combined endpoint (25% vs. 29% of those receiving placebo), its benefit reflected only a reduction in the risk of hospitalization, and there was not a favorable effect on the mortality component of the primary endpoint.
**Alirocumab** (Praluent – Sanofi; Regeneron)  
**Lipid-regulating Agent**

2015  
**New Drug Comparison Rating (NDCR) =**

**Indication:** Administered subcutaneously as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia or clinical atherosclerotic cardiovascular disease who require additional lowering of low-density lipoprotein cholesterol (LDL-C)

**Comparable drugs:** Statins (e.g., atorvastatin); (a similar drug, evolocumab, has been subsequently approved)

**Advantages:**
--Is more effective in lowering LDL-C  
--Has a unique mechanism of action (inhibits proprotein convertase subtilisin kexin type 9 [PCSK9])  
--Less likely to cause adverse events  
--Less likely to interact with other drugs

**Disadvantages:**
--Must be administered by injection (subcutaneously)  
--Effect on cardiovascular morbidity and mortality has not been determined  
--More likely to cause allergic reactions  
--May cause injection site reactions

**Most important risks/adverse events:** Hypersensitivity reactions; potential for immunogenicity and development of anti-drug antibodies

**Most common adverse events:** Nasopharyngitis (11%), injection site reactions (7%), influenza (6%)

**Usual dosage:** Administered subcutaneously; recommended starting dosage is 75 mg once every 2 weeks; if the LDL-C response is not adequate, the dosage may be increased to the maximum dosage of 150 mg every 2 weeks; LDL-C concentrations should be determined within 4 to 8 weeks of initiating treatment or changing the dosage; if a dose is missed, the patient should administer the dose within 7 days from the missed dose, and then resume the regular dosage schedule; if the missed dose is not administered within 7 days, the patient should wait until the next dose on the original schedule

**Products:** Injection in single-dose, prefilled pens and syringes – 75 mg, 150 mg (should be stored in a refrigerator); the dosage form should be allowed to warm to room temperature for 30 to 40 minutes prior to administration; should be administered as soon as possible after it has warmed up; should not be used if it has been at room temperature for 24 hours or longer

**Comments:** Proprotein convertase subtilisin kexin type 9 (PCSK9) binds to the low-density lipoprotein receptors (LDLR) on the surface of hepatocytes to promote LDLR degradation in the liver. Because LDLR is the primary receptor that clears circulating LDL, a decrease in LDLR by PCSK9 results in higher blood concentrations of LDL-C. Alirocumab is a human monoclonal antibody that targets PCSK9, and is the first PCSK9 inhibitor to be approved for marketing in the United States (evolocumab [Repatha] was subsequently approved as the second agent in this class of agents). By inhibiting the binding of PCSK9 to LDLR, it increases the number of LDLRs available to clear LDL, thereby lowering LDL-C concentrations.

The effectiveness of alirocumab was demonstrated in five placebo-controlled studies in patients who were already being treated with a maximally tolerated dosage of a statin, with or without other lipid-modifying therapy. The addition of alirocumab to the regimen resulted in a further lowering of LDL-C concentrations by approximately 50% compared with placebo, and it represents an important addition to the options available for the treatment and prevention of cardiovascular disease. The statins have been demonstrated to reduce the risk of having a heart attack or stroke. A study to evaluate the effect of adding alirocumab to statins on reducing cardiovascular risk is ongoing.
**Evolocumab** (Repatha – Amgen)  
Lipid-regulating Agent  

2015  
New Drug Comparison Rating (NDCR) =

Indications: Administered subcutaneously as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia (HeFH) or clinical atherosclerotic cardiovascular disease (CVD), who require additional lowering of low-density lipoprotein cholesterol (LDL-C); is also indicated as an adjunct to diet and other LDL-lowering therapies (e.g., statins, ezetimibe, LDL apheresis) for the treatment of patients with homozygous familial hypercholesterolemia (HoFH) who require additional lowering of LDL-C.

Comparable drug: Alirocumab (Praluent)

Advantages:
--Labeled indications include the treatment of patients with homozygous familial hypercholesterolemia
--Dosage regimens include an option for administration once a month (whereas alirocumab is administered every 2 weeks)

Disadvantages:
--Higher dosage requires multiple (3) injections

Most important risks/adverse events: Hypersensitivity reactions; potential for immunogenicity and development of anti-drug antibodies

Most common adverse events: Nasopharyngitis (11%), upper respiratory tract infection (9%), influenza (8%), back pain (6%), injection site reactions (6%)

Usual dosage: Administered subcutaneously; 140 mg every 2 weeks or 420 mg once monthly in patients with HeFH or patients with primary hyperlipidemia with established clinical atherosclerotic CVD; to administer a dose of 420 mg, 3 injections of 140 mg should be administered consecutively within 30 minutes; 420 mg once monthly in patients with HoFH; in patients with HoFH, LDL-C concentrations should be measured 4 to 8 weeks after initiating treatment, because responses to therapy will depend on the degree of LDL-receptor function; if a dose is missed, the dose should be administered as soon as possible if there are more than 7 days until the next scheduled dose, or omit the missed dose and administer the next dose according to the original schedule

Products: Injection in single-use prefilled autoinjectors and syringes – 140 mg (should be stored in a refrigerator); the dosage form should be allowed to warm to room temperature for at least 30 minutes prior to administration; alternately, may be kept at room temperature in the original carton but must be used within 30 days

Comments: Proprotein convertase subtilisin kexin type 9 (PCSK9) binds to the low-density lipoprotein receptors (LDLR) on the surface of hepatocytes to promote LDLR degradation in the liver. Because LDLR is the primary receptor that clears circulating LDL, a decrease in LDLR by PCSK9 results in higher blood concentrations of LDL-C. Evolocumab is a human monoclonal antibody that targets PCSK9, and is the second PCSK9 inhibitor to be marketed in the United States, joining alirocumab (Praluent) that was marketed one month earlier. By inhibiting the binding of PCSK9 to LDLR, these agents increase the number of LDLRs available to clear LDL, thereby lowering LDL-C concentrations.

The effectiveness of evolocumab was demonstrated in multiple placebo-controlled studies in patients who were already being treated with a maximally tolerated dosage of a statin, with or without other lipid-modifying therapy. The addition of evolocumab to the regimen in patients with clinical atherosclerotic CVD or HeFH resulted in a further lowering of LDL-C concentrations by approximately 60% compared with placebo. In patients with HoFH, evolocumab reduced LDL-C by approximately 30% compared with placebo. The statins have been demonstrated to reduce the risk of having a heart attack or stroke. However, the effect of evolocumab (or alirocumab) on cardiovascular morbidity or mortality has not been determined.
**Edoxaban tosylate monohydrate** (Savaysa – Daiichi-Sankyo)  
**Anticoagulant**

2015  
**New Drug Comparison Rating (NDCR)**  

**Indications:** To reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation; for the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE) following 5-10 days of initial therapy with a parenteral anticoagulant

**Comparable drugs:** Apixaban (Eliquis), rivaroxaban (Xarelto), dabigatran (Pradaxa)

**Advantages:**
- Is administered once a day (compared with apixaban and dabigatran that are administered twice a day)
- Less likely to interact with other medications

**Disadvantages:**
- May be less effective (is noninferior to warfarin whereas comparable drugs are more effective for certain indications)
- Should not be used in patients with a creatinine clearance greater than 95 mL/minute
- Labeled indications are more limited (compared with apixaban and rivaroxaban that are also indicated for the prophylaxis of DVT in patients undergoing knee or hip replacement surgery)
- Treatment of DVT and PE should be preceded by parenteral anticoagulant therapy (compared with apixaban and rivaroxaban for which the recommendations do not include prior parenteral anticoagulation)

**Most important risks/adverse events:** Contraindicated in patients with active pathological bleeding; risk of bleeding (risk factors include the concomitant use of other medications that may be associated with bleeding events e.g., aspirin, antiplatelet agents, chronic use of nonsteroidal anti-inflammatory agents); risk of epidural or spinal hematomas in patients receiving neuraxial anesthesia or undergoing spinal puncture (boxed warning); discontinuation of treatment may increase the risk of thrombotic events (coverage with another anticoagulant should be strongly considered); concurrent use with rifampin should be avoided; renal function should be evaluated prior to initiating treatment (should not be used in patients with a creatinine clearance greater than 95 mL/minute)

**Most common adverse events:** Clinically relevant non-major bleeding (9%), rash (4%), abnormal liver function tests (5%)

**Usual dosage:** Patients with nonvalvular atrial fibrillation – 60 mg once a day; dosage should be reduced to 30 mg once a day in patients with a creatinine clearance of 15 to 50 mL/minute; in patients with DVT or PE, 60 mg once a day following 5 to 10 days of therapy with a parenteral anticoagulant; dosage should be reduced to 30 mg once a day in patients with a creatinine clearance of 15 to 50 mL/minute, in patients who weigh less than or equal to 60 kg, or patients who are taking certain concomitant P2Y-glycoprotein inhibitors; if treatment must be discontinued for a reason other than pathological bleeding, coverage with another anticoagulant should be considered

**Products:** Tablets – 15 mg, 30 mg, 60 mg

**Comments:** Like apixaban and rivaroxaban, edoxaban is a factor Xa inhibitor, whereas dabigatran is a direct thrombin inhibitor and warfarin is a vitamin K antagonist. Warfarin is the only one of these anticoagulants for which a specific antidote (vitamin K) is currently available. In the clinical studies, edoxaban was determined to be noninferior to warfarin in reducing the risk of stroke and systemic embolism, and noninferior to warfarin with respect to recurrent venous thromboembolic events. The incidence of major bleeding (e.g., intracranial hemorrhage) was less with edoxaban compared with warfarin. Like the other new oral anticoagulants, edoxaban has not been studied in patients with mechanical heart valves or moderate to severe mitral stenosis, and it is not recommended in these patients.
Idarucizumab (Praxbind – Boehringer Ingelheim) Reversal Agent

2015 New Drug Comparison Rating (NDCR) =

Indications: Administered intravenously in patients treated with dabigatran (Pradaxa) when reversal of the anticoagulant effects is needed for emergency surgery/urgent procedures or in life-threatening or uncontrolled bleeding

Comparable drugs: None

Advantages: --Is the first agent that reverses the action of dabigatran and neutralizes its anticoagulant activity

Disadvantages: --None

Most important risks/adverse events: Hypersensitivity reactions (administration should be immediately discontinued if anaphylactic or other serious allergic reactions occur); patients with hereditary fructose intolerance (may experience serious adverse events following the parenteral administration of sorbitol [included as an excipient in the formulation of idarucizumab]); re-elevation of coagulation parameters (if clinically relevant bleeding also reappears 12-24 hours after administration, a second dose may be considered); thromboembolic risk (to reduce the thrombotic risk of the underlying disease, resumption of anticoagulant therapy should be considered as soon as medically appropriate [at least 24 hours after use of idarucizumab])

Most common adverse events: Hypokalemia (7%), delirium (7%), constipation (7%), pyrexia (6%), pneumonia (6%)

Usual dosage: 5 grams (two vials) administered intravenously as two consecutive infusions, or bolus injections by injecting both vials consecutively one after another via syringe; a repeat dose may be considered in urgent situations, but the effectiveness and safety of repeat doses have not been established

Product: Sterile solution in single-use vials containing 2.5 grams of the drug in 50 mL (should be stored in a refrigerator); the recommended dose (2 vials) contains 4 grams of sorbitol; once the solution has been removed from the vial, administration should begin promptly or within one hour; a pre-existing intravenous line may be used for administration but it must first be flushed with 0.9% Sodium Chloride Injection

Comments: Dabigatran exhibits its anticoagulant effects by acting as a direct thrombin inhibitor. In situations in which patients experience life-threatening or uncontrolled bleeding or there is a need for emergency surgery/urgent procedures, the availability of a reversal agent is very important. Idarucizumab is a humanized monoclonal antibody fragment that binds to dabigatran and its acylglucuronide metabolites with a higher affinity than the binding affinity of dabigatran to thrombin. The new drug is a specific reversal agent for dabigatran and neutralizes its anticoagulant activity. It does not reverse the action of the factor Xa inhibitor anticoagulants apixaban (Eliquis), edoxaban (Savaysa), and rivaroxaban (Xarelto).

The approval of idarucizumab was based on a reduction in unbound dabigatran and normalization of coagulation parameters in healthy volunteers, and its effectiveness in a study of 123 patients who received the drug due to uncontrolled bleeding or because they required emergency surgery. In the latter study, the anticoagulant activity of dabigatran was fully reversed in 89% of the patients within 4 hours of receiving idarucizumab.
Cangrelor (Kengreal – The Medicines Company)  

2015  New Drug Comparison Rating (NDCR) = 

Indication: Administered intravenously as an adjunct to percutaneous coronary intervention (PCI) to reduce the risk of periprocedural myocardial infarction (MI), repeat coronary revascularization, and stent thrombosis (ST) in patients who have not been treated with a P2Y₁₂ platelet inhibitor and are not being given a glycoprotein IIb/IIIa inhibitor

Comparable drugs: Clopidogrel (e.g., Plavix); other P2Y₁₂ platelet inhibitors include prasugrel (Effient) and ticagrelor (Brilinta)

Advantages:
--Is more effective than clopidogrel in reducing the occurrence of MI and ST and the need for repeat coronary revascularization
--Has a rapid onset of action

Disadvantages:
--Is more likely than clopidogrel to cause bleeding
--Is administered intravenously (whereas the comparable drugs are administered orally)

Most important risks/adverse events: Bleeding (is contraindicated in patients with significant active bleeding); hypersensitivity; decreased renal function; dyspnea; if clopidogrel or prasugrel are administered during the cangrelor infusion, they will have no antiplatelet effect until the next dose is administered

Most common adverse events: Bleeding (15.5% - representing serious/life-threatening bleeding [0.2%], moderate bleeding events [0.4%], and mild bleeding events [14.9%])

Usual dosage: 30 mcg/kg as an intravenous bolus (administered rapidly in less than 1 minute) followed immediately by a 4 mcg/kg/minute intravenous infusion; IV bolus should be initiated prior to PCI; maintenance infusion should ordinarily be continued for at least 2 hours or for the duration of PCI, whichever is longer; following discontinuation of the infusion, platelet inhibition should be maintained using an oral P2Y₁₂ platelet inhibitor (600 mg of clopidogrel or 60 mg of prasugrel may be administered immediately after discontinuation of cangrelor; 180 mg of ticagrelor may be administered at any time during the cangrelor infusion or immediately after discontinuation)

Product: Single-use vials – 50 mg as a lyophilized powder; should be reconstituted with 5 mL of Sterile Water for Injection; reconstituted solution should be immediately diluted further by withdrawing the contents of a reconstituted vial and adding to a 250 mL saline bag; bolus volume should be administered rapidly (less than 1 minute) from the diluted bag via manual IV push or pump; bolus should be completely administered before the start of PCI and the infusion should be started immediately after discontinuation of the bolus

Comments: Cangrelor is a direct-acting P2Y₁₂ platelet receptor inhibitor that blocks adenosine diphosphate (ADP)-induced platelet activation and aggregation. It is the first P2Y₁₂ platelet inhibitor to be administered intravenously and, after administration of an IV bolus followed by an IV infusion, platelet inhibition occurs within 2 minutes. Following discontinuation of the infusion, the anti-platelet effect decreases rapidly and platelet function returns to normal within one hour. The use of cangrelor is followed with the use of an oral P2Y₁₂ platelet inhibitor. The effectiveness of cangrelor was demonstrated in a study in which it was compared with clopidogrel in more than 10,000 patients undergoing PCI who had not been previously treated with antiplatelet therapy other than aspirin. The primary outcome measure was the first occurrence of any one of the composite endpoint of all-cause mortality, MI, ST, and ischemia-driven revascularization within 48 hours of randomization. Cangrelor significantly reduced the occurrence of primary composite endpoint events compared to clopidogrel (4.7% and 5.9%, respectively), representing a relative risk reduction of 22%. Most of the effect was a reduction in post-procedural MIs. Cangrelor did not reduce the risk of death (0.3% in both groups). Bleeding occurred more frequently in patients treated with cangrelor (15.5%) compared with clopidogrel (10.9%), with severe/life-threatening bleeding events occurring in 0.2% and 0.1% of patients, respectively.
Mepolizumab (Nucala – GlaxoSmithKline) Antiasthmatic Agent

2015 New Drug Comparison Rating (NDCR) =

Indication: Administered subcutaneously for the add-on maintenance treatment of patients aged 12 years and older with severe asthma and with an eosinophilic phenotype;
Is not indicated for the treatment of other eosinophilic conditions, or for the relief of acute bronchospasm or status asthmaticus

Comparable drugs: Omalizumab (Xolair)

Advantages:
--May increase the effectiveness of treatment of patients with severe asthma and with an eosinophilic phenotype
--May permit a reduction in dosage of oral corticosteroids
--Has a unique mechanism of action (is an interleukin-5 [IL-5] antagonist)
--Less risk of anaphylaxis (labeling for omalizumab includes a boxed warning regarding this risk)
--Is not likely to be associated with the occurrence of eosinophilic conditions

Disadvantages:
--Labeled indications are more limited (indications for omalizumab include patients with moderate to severe allergic asthma, as well as chronic idiopathic urticaria)

Most important risks/adverse events: Hypersensitivity reactions (e.g., rash, pruritus, angioedema, bronchospasm; treatment should be discontinued if reactions occur); should not be used to treat acute bronchospasm or status asthmaticus; reduction in dosage or discontinuation of systemic or inhaled corticosteroids (if appropriate, dosage should be reduced gradually under the supervision of a physician, to avoid systemic withdrawal symptoms and/or unmasking of conditions previously suppressed by systemic corticosteroid therapy); opportunistic infections (risk of herpes zoster infection and, if appropriate, varicella vaccination should be considered prior to starting treatment); helminth infections (should be treated prior to starting treatment; if a helminth infection develops during treatment and does not respond to anti-helminth treatment, mepolizumab should be discontinued until the infection resolves)

Most common adverse events: Headache (19%), injection site reactions (8%), back pain (5%), fatigue (5%)

Usual dosage: 100 mg every 4 weeks administered subcutaneously into the upper arm, thigh, or abdomen

Product: Single-dose vials – 100 mg of lyophilized powder for reconstitution; should be reconstituted and administered by a healthcare professional; contents of a vial should be reconstituted with 1.2 mL of Sterile Water for Injection; reconstituted solution should not be shaken to avoid foaming and/or precipitation; product labeling should be consulted for specific recommendations for reconstitution and administration

Comments: Many patients with asthma do not experience adequate reduction of symptoms and associated complications with available treatments, and there are more than 400,000 asthma-related hospitalizations each year in the United States. Multiple cell types, including eosinophils, and mediators (e.g., cytokines) are involved in the inflammatory process that occurs in the airways of the lungs. Interleukin-5 (IL-5) is the major cytokine that is responsible for the growth and differentiation, recruitment, activation, and survival of eosinophils. Mepolizumab is an IL-5 antagonist that reduces the production and survival of eosinophils. It has been approved for use in conjunction with other maintenance treatments for patients with severe asthma and with an eosinophilic phenotype. The effectiveness of mepolizumab was demonstrated in three placebo-controlled trials in which either the new drug or placebo was added to an existing treatment regimen (e.g., oral and/or inhaled corticosteroids). In one of the studies, the primary endpoint was the percent reduction of the oral corticosteroid dose during weeks 20 to 24 compared with the baseline dose, while maintaining asthma control. Twenty-three percent of the patients treated with mepolizumab had a 90% to 100% reduction in their oral corticosteroid dose, compared with 11% in the placebo group. Additionally, 54% of patients treated with the new drug achieved at least a 50% reduction in the daily prednisone dose compared with 33% of those receiving placebo. Mepolizumab did not provide consistent improvements in mean change from baseline in mean forced expiratory volume in 1 second (FEV1).
**Lumacaftor/ivacaftor** (Orkambi – Vertex)

**Agents for Cystic Fibrosis**

2015 New Drug Comparison Rating (NDCR) =

**Indication:** Treatment of cystic fibrosis in patients age 12 years and older who are homozygous for the F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene; if the patient’s genotype is unknown, an FDA-cleared cystic fibrosis mutation test should be used to detect the presence of the F508del mutation on both alleles of the CFTR gene

**Comparable drug:** Ivacaftor (Kalydeco)

**Advantages:**
--Is effective in patients who are homozygous for the F508del mutation in the CFTR gene, the most common mutation that results in cystic fibrosis
--Lumacaftor has a unique mechanism of action (improves stability of F508del-CFTR and increases the quantity of mature protein at the cell surface)

**Disadvantages:**
--Use has not yet been evaluated in children less than 12 years of age (whereas ivacaftor is indicated in children as young as 2 years of age who have certain mutations in the CFTR gene)
--Lumacaftor has not been evaluated as a single agent

**Most important risks/adverse events:** Risk in patients with advanced liver disease (patients should be closely monitored and dosage should be reduced); transaminase (ALT; AST) and bilirubin elevations (serum ALT, AST, and bilirubin should be determined prior to initiating treatment, every 3 months during treatment, and annually thereafter; product labeling should be consulted for recommendations for more frequent monitoring or interruption of treatment in patients with elevated concentrations); respiratory adverse events (e.g., dyspnea, chest discomfort, abnormal respiration); cataracts (lens opacities/cataracts have been reported in pediatric patients treated with ivacaftor); lumacaftor is a strong inducer of CYP3A and may reduce the systemic exposure of medications that are substrates of this metabolic pathway (e.g., exposure of hormonal contraceptives may be reduced and should not be relied upon as an effective method of contraception); ivacaftor is a substrate of CYP3A (activity is reduced by strong CYP3A inducers [e.g., rifampin] and concurrent use is not recommended); concurrent use with cyclosporine, everolimus, sirolimus, or tacrolimus should be avoided, and concurrent use with midazolam or triazolam is not recommended; may reduce the action of corticosteroids (e.g., prednisone), certain antibiotics (e.g., clarithromycin), certain antifungal agents (e.g., itraconazole; concurrent use is not recommended), nonsteroidal anti-inflammatory drugs (e.g., ibuprofen), selective serotonin reuptake inhibitors (e.g., escitalopram, sertraline), sulfonylureas, and proton pump inhibitors; may alter the action of warfarin

**Most common adverse events:** Dyspnea (13%), nasopharyngitis (13%), nausea (13%), diarrhea (12%), upper respiratory tract infection (10%), fatigue (9%), abnormal respiration (9%), rash (7%), flatulence (7%)

**Usual dosage:** Two tablets (each containing lumacaftor 200 mg/ivacaftor 125 mg) every 12 hours with fat-containing food (e.g., eggs, cheese pizza, whole milk); product labeling should be consulted for dosage recommendations in patients with moderate or severe hepatic impairment, and in those taking a CYP3A inhibitor

**Product:** Tablets – 200 mg lumacaftor and 125 mg ivacaftor

**Comments:** Cystic fibrosis (CF) is caused by a mutation in a gene that encodes for the protein cystic fibrosis transmembrane conductance regulator (CFTR) that regulates ion (e.g., chloride) and water transport in the body. Children must inherit two defective CFTR genes, one from each parent, to have CF. The F508del mutation is the most common cause of CF. People who have two copies of the F508del mutation account for approximately one-half of the CF population in the US. Lumacaftor improves the stability of F508del-CFTR and increases the quantity of mature protein that reaches the cell surface. Ivacaftor is a CFTR potentiator that facilitates increased chloride transport. The combination formulation was evaluated in two placebo-controlled studies in which improved lung function was demonstrated, compared with the experience of the patients receiving placebo.
Eluxadoline (Viberzi – Allergan)  

Agent for Irritable Bowel Syndrome with Diarrhea

2015  

New Drug Comparison Rating (NDCR) =

Indication:  Treatment of adult patients with irritable bowel syndrome with diarrhea (IBS-D)

Comparable drug:  Alosetron (e.g., Lotronex)

Advantages:
--Has a unique mechanism of action (is a mu-opioid receptor agonist and a delta-opioid receptor antagonist)
--Labeled indication is not restrictive (whereas alosetron is indicated only for women with severe IBS-D)
--Less risk of serious gastrointestinal adverse events (whereas the labeling for alosetron includes a boxed warning regarding the risk of ischemic colitis and serious complications of constipation)
--Prescribing is not restricted (whereas prescribers of alosetron must be enrolled in a Prescribing Program and patients must understand and comply with the provisions of a Patient Acknowledgement Form)

Disadvantages:
--Has a greater risk of sphincter of Oddi spasm and pancreatitis
--Is a controlled substance (Schedule IV)

Most important risks/adverse events:  Contraindicated in patients with known or suspected biliary duct obstruction, or sphincter of Oddi disease or dysfunction, or a history of pancreatitis or structural diseases of the pancreas, including known or suspected pancreatic duct obstruction (with respect to the risk of sphincter of Oddi spasm and pancreatitis, patients without a gallbladder should be monitored for new or worsening abdominal pain, or acute biliary pain with liver or pancreatic enzyme elevations; treatment should be discontinued if these symptoms develop); contraindicated in patients with severe hepatic impairment, severe constipation or sequelae from constipation, or suspected mechanical GI obstruction; contraindicated in patients with alcoholism, alcohol abuse, alcohol addiction, or in those who drink more than 3 alcoholic beverages/day; potential for misuse/abuse (included in Schedule IV); is a substrate for organic anion transporter polypeptide (OATP)1B1 and dosage should be reduced when an OATP1B1 inhibitor (e.g., cyclosporine, gemfibrozil) is used concurrently; action may be increased by the concurrent use of a strong CYP inhibitor (e.g., clarithromycin, paroxetine); concurrent use with drugs that may cause constipation (e.g., alosetron, anticholinergics, opioid analgesics) should be avoided (loperamide may be used occasionally for the acute management of severe diarrhea but chronic use should be avoided); may increase the action of rosuvastatin (Crestor) and the lowest effective dose of rosuvastatin should be used; may increase the action of CYP3A substrates with a narrow therapeutic index (e.g., cyclosporine, fentanyl)

Most common adverse events:  Constipation (8%), nausea (7%), abdominal pain (7%)

Usual dosage:  100 mg twice a day with food; dosage should be reduced to 75 mg twice a day with food in patients who do not have a gallbladder, have mild or moderate hepatic impairment, are concurrently taking an OATP1B1 inhibitor (e.g., cyclosporine, gemfibrozil), or who are unable to tolerate the 100 mg dose; treatment should be discontinued in patients who develop severe constipation for more than 4 days

Products:  Tablets - 75 mg, 100 mg

Comments:  IBS-D is a functional bowel disorder that is characterized by chronic abdominal pain and frequent diarrhea (loose or watery stools at least 25% of the time). Loperamide may help control diarrhea but does not provide adequate relief of symptoms in many patients. Alosetron is a serotonin (5-HT3) receptor antagonist that may be effective, but its labeled indication is limited (i.e., women with severe IBS-D who have not responded to conventional therapy) and it may cause serious GI adverse events. Rifaximin (Xifaxan) was previously available for the treatment of certain types of travelers’ diarrhea and to reduce the risk of overt hepatic encephalopathy recurrence. Rifaximin and eluxadoline were approved for the treatment of IBS-D on the same date. Eluxadoline has mixed opioid receptor activity; it acts as an agonist at mu receptors and kappa receptors, and as an antagonist of delta receptors. Its effectiveness was demonstrated in two placebo-controlled studies in which it was more effective than placebo in reducing abdominal pain and improving stool consistency over 26 weeks of treatment.
Naloxegol oxalate (Movantik – AstraZeneca)  
Agent for Constipation

2015 New Drug Comparison Rating (NDCR) =

Indication: Treatment of opioid-induced constipation (OIC) in adults with chronic non-cancer pain

Comparable drugs: Lubiprostone (Amitiza), methylnaltrexone (Relistor)

Advantages:
-- Is administered orally (compared with methylnaltrexone that is administered subcutaneously)
-- Is administered once a day (compared with lubiprostone that is administered twice a day)

Disadvantages:
-- More likely to interact with other drugs
-- Labeled indications are more limited (lubiprostone is also indicated for the treatment of patients with chronic idiopathic constipation, as well as irritable bowel syndrome with constipation in women 18 years of age and older; methylnaltrexone is also indicated for the treatment of patients with advanced illness who are receiving palliative care when response to laxative therapy has not been sufficient)

Most important risks/adverse events: Contraindicated in patients with known or suspected gastrointestinal obstruction and at increased risk of recurrent obstruction; gastrointestinal perforation (patients should be monitored for severe, persistent, or worsening abdominal pain, and treatment should be discontinued if symptoms develop); opioid withdrawal (patients with disruption of the blood-brain barrier are at greater risk); pregnancy (could precipitate opioid withdrawal in an unborn child if used during pregnancy; should only be used during pregnancy if the anticipated benefit justifies the risk to the unborn child); action is increased by CYP3A4 inhibitors (concurrent use with a strong CYP3A4 inhibitor [e.g., clarithromycin, itraconazole] is contraindicated, and use with a moderate CYP3A4 inhibitor [e.g., diltiazem, verapamil] should be avoided whenever possible); consumption of grapefruit products should be avoided; concurrent use of a strong CYP3A4 inducer (e.g., carbamazepine, rifampin, St. John’s wort) is not recommended; concurrent use with another opioid antagonist should be avoided because of the increased risk of opioid withdrawal

Most common adverse events: Abdominal pain (21%), diarrhea (9%), nausea (8%), flatulence (6%), vomiting (5%)

Usual dosage: Maintenance laxative therapy should be discontinued prior to initiating treatment; however, if there is a suboptimal response to naloxegol after 3 days, laxatives may be used as needed: -- 25 mg once a day in the morning at least 1 hour prior to the first meal of the day or 2 hours after the meal; the dosage should be reduced to 12.5 mg once a day in patients with moderate, severe, or end-stage renal impairment, and in patients in whom the concurrent use of a moderate CYP3A4 inhibitor is unavoidable; treatment should be discontinued if therapy with the opioid analgesic is discontinued

Products: Tablets – 12.5 mg, 25 mg

Comments: Naloxegol is the third drug to be specifically approved for the treatment of opioid-induced constipation, joining lubiprostone, a chloride channel activator that acts in the gastrointestinal tract, and the opioid antagonist methylnaltrexone. Naloxegol is a pegylated derivative of naloxone that is a peripherally-acting mu-opioid receptor antagonist that is effective following oral administration (whereas methylnaltrexone is administered subcutaneously). For several reasons, including the presence of the polyethylene glycol (PEG) moiety that reduces its passive permeability as compared with naloxone, the CNS penetration of naloxegol is negligible at the recommended dosage, thereby limiting the potential for interference with centrally-mediated opioid analgesia. It is not considered to have a risk of abuse or dependency.

The effectiveness of naloxegol was evaluated in patients who had taken an opioid for at least 4 weeks. The primary endpoint of a specified increase in the number of spontaneous bowel movements was experienced by 44% of the patients treated with naloxegol compared with 29% of those receiving placebo.
Rolapitant hydrochloride (Varubi – Tesaro)  

2015 New Drug Comparison Rating (NDCR) =

Indication: In combination with other antiemetic agents in adults for the prevention of delayed nausea and vomiting associated with initial and repeat courses of emetogenic cancer chemotherapy, including, but not limited to, highly emetogenic chemotherapy

Comparable drugs: Aprepitant (Emend), netupitant (included in combination with palonosetron in Akynzeo)

Advantages:
--Has a longer duration of action
--Is a single-dose treatment (compared with aprepitant that is used as a 3-dose treatment)
--Dosage adjustment for dexamethasone is not needed when used concurrently
--Is available as a single agent (compared with netupitant that is only available in a fixed combination with palonosetron)

Disadvantages:
--Labeled indication is more limited (comparable drugs are indicated to prevent both acute and delayed nausea and vomiting; aprepitant is also indicated for the prevention of postoperative nausea and vomiting)
--Is not indicated for use in pediatric patients (whereas aprepitant is indicated for use in children as young as 6 months of age)
--Inhibits CYP2D6 and concurrent use with thioridazine (a CYP2D6 substrate) is contraindicated; use with other CYP2D6 substrates with a narrow therapeutic index should be avoided

Most important risks/adverse events: Is a CYP2D6 inhibitor and inhibitory effect of a single dose lasts for at least 7 days (concurrent use with thioridazine [a CYP2D6 substrate] is contraindicated, and concurrent use with other CYP2D6 substrates with a narrow therapeutic index [e.g., pimozide] should be avoided); is a CYP3A4 substrate and concurrent use with a strong CYP3A4 inducer (e.g., rifampin) may reduce effectiveness and should be avoided; inhibits P-glycoprotein (P-gp) and may increase the risk of adverse events with P-gp substrates with a narrow therapeutic index (e.g., digoxin); inhibits Breast-Cancer-Resistance Protein (BCRP) and may increase the risk of adverse events with BCRP substrates with a narrow therapeutic index (e.g., methotrexate)

Most common adverse events (in patients receiving cisplatin-based highly emetogenic chemotherapy [cycle 1]): Neutropenia (9%), hiccups (5%)

Usual dosage: 180 mg as a single dose approximately 1 to 2 hours prior to chemotherapy on Day 1; is co-administered with a serotonin 5-HT3 receptor antagonist (e.g., granisetron) and 20 mg of dexamethasone (30 minutes prior to chemotherapy); dexamethasone is also administered in a dosage of 8 mg twice a day on Days 2, 3, and 4 in patients treated with cisplatin-based highly emetogenic chemotherapy, but not in patients treated with moderately emetogenic chemotherapy and combinations of an anthracycline and cyclophosphamide; antiemetic regimen should be administered prior to the initiation of each chemotherapy cycle but at no less than 2-week intervals

Product: Film-coated tablets – 90 mg

Comments: Rolapitant is the third substance P/neurokinin 1 (NK1) receptor antagonist to be marketed in the United States, joining aprepitant and netupitant. The effectiveness of the new drug was demonstrated in three studies in which a regimen of rolapitant, granisetron, and dexamethasone was compared with a control therapy that included granisetron, dexamethasone, and placebo. The primary endpoint in the studies was a complete response (defined as no emetic episodes and no rescue medication) in the delayed phase (25 to 120 hours) of chemotherapy induced nausea and vomiting. Approximately 70% of the patients treated with the regimen that included rolapitant experienced a complete response, compared with approximately 60% of those receiving the control regimen. Rolapitant has not been directly compared with aprepitant or netupitant in clinical studies.
**Flibanserin** (Addyi – Sprout; Valeant)  
**Agent for Female Sexual Dysfunction**

2015  
**New Drug Comparison Rating (NDCR) =**

**Indication:** Treatment of premenopausal women with acquired, generalized hypoactive sexual desire disorder (HSDD), as characterized by low sexual desire that causes marked distress or interpersonal difficulty and is NOT due to a co-existing medical or psychiatric condition, problems within the relationship, or the effects of a medication or other drug substance; is NOT indicated for the treatment of HSDD in postmenopausal women or men, or to enhance sexual performance.

**Comparable drug:** None

**Advantages:**
-- Is the first drug to be approved for the treatment of HSDD

**Disadvantages/Limitations**
-- Risk of severe hypotension and syncope
-- Use of alcohol is contraindicated
-- Is only available through a restricted distribution program

**Most important risks/adverse events:** Hypotension and syncope (risk of serious events is increased by consumption of alcoholic beverages, concurrent use of a moderate or strong CYP3A4 inhibitor, and hepatic impairment – these increased risks are the subject of a boxed warning in the labeling, contraindications in patients with these increased risks, and availability of the drug only through a restricted distribution program); central nervous system (CNS) depressant action (e.g., sedation, somnolence; risk is increased by the concurrent use of other agents with CNS depressant activity and by situations in which concentration of flibanserin is increased; patients should avoid activity requiring full alertness until at least 6 hours after each dose and until they know how the drug affects them); action is increased by the concurrent use of oral contraceptives and other weak CYP3A4 inhibitors; action is reduced by CYP3A4 inducers and concurrent use should be avoided; action is increased in patients who are CYP2C19 poor metabolizers; may increase action of digoxin.

**Most common adverse events:** Dizziness (11%), somnolence (11%), nausea (10%), fatigue (9%), insomnia (5%)

**Usual dosage:** 100 mg once a day at bedtime; if there is no improvement after 8 weeks, treatment should be discontinued.

**Product:** Tablets – 100 mg; prescribers and pharmacists must be certified to participate in the restricted distribution program.

**Comments:** It is estimated that approximately 10% of premenopausal women experience hypoactive sexual desire disorder (HSDD). HSDD is designated as “acquired” when it develops in a patient who previously had no problems with sexual desire. HSDD is “generalized” when it occurs regardless of the type of sexual activity, the situation, or the sexual partner. Flibanserin is the first drug to be approved for the treatment of HSDD. It acts as an agonist at serotonin 5-HT1A receptors and as an antagonist at serotonin 5-HT2A receptors; however, its specific mechanism of action in treating HSDD is not known. The effectiveness of flibanserin was demonstrated in three, 24-week placebo-controlled studies that included approximately 2,400 premenopausal women. Compared with placebo, flibanserin increased the number of satisfying sexual events, increased sexual desire, and decreased the occurrence of distress. Additional analyses investigated whether the improvements with the drug were meaningful (i.e., feeling much improved or very much improved) to patients. Approximately 10% more flibanserin-treated patients than placebo-treated patients reported meaningful improvements.

Flibanserin may cause severe hypotension and syncope, the risk for which is increased by the consumption of alcoholic beverages. Alcohol is contraindicated and the healthcare provider must assess the likelihood of the patient abstaining from alcohol use. Because of this risk, the drug is only available in a restricted distribution program in which prescribers and pharmacists must be certified. In patients who require the use of a moderate or strong CYP3A4 inhibitor, flibanserin should be discontinued at least 2 days prior to starting the CYP3A4 inhibitor.
Ceftazidime pentahydrate/avibactam sodium (Avycaz – Actavis) Antibacterial Agent

2015 New Drug Comparison Rating (NDCR) =

Indications: Administered by intravenous infusion in a regimen that also includes metronidazole for the treatment of adults with complicated intra-abdominal infections (cIAI) caused by Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis, Providencia stuartii, Enterobacter cloacae, Klebsiella oxytoca, and Pseudomonas aeruginosa; also indicated for the treatment of adults with complicated urinary tract infections (cUTI) including pyelonephritis caused by Escherichia coli, Klebsiella pneumoniae, Citrobacter koseri, Enterobacter aerogenes, Enterobacter cloacae, Citrobacter freundii, Proteus species, and Pseudomonas aeruginosa; use should be reserved for patients who have limited or no alternative treatment options

Comparable drugs: Ceftolozane/tazobactam (Zerbaxa)

Advantages:
--Has activity against carbapenem-resistant Enterobacteriaceae, including bacteria that produce Klebsiella pneumoniae carbapenemase

Disadvantages:
--Has limited activity against Gram-positive bacteria and anaerobic bacteria
--Is infused intravenously over 2 hours (whereas ceftolozane/tazobactam is infused over 1 hour)

Most important risks/adverse events: Contraindicated in patients with known serious hypersensitivity to products containing avibactam, ceftazidime, or another cephalosporin; cross-hypersensitivity may occur in patients with a history of penicillin allergy; decreased efficacy in patients with a baseline creatinine clearance of 30 to 50 mL/minute (creatinine clearance should be monitored at least daily in patients with changing renal function and the dosage should be adjusted accordingly); central nervous system reactions (e.g., seizures) may occur, especially in patients with renal impairment; possibility of Clostridium difficile-associated diarrhea; elimination of avibactam may be reduced by probenecid and concurrent use is not recommended; ceftazidime may cause a false-positive reaction in certain urine glucose tests (glucose tests based on enzymatic glucose oxidase reactions should be used)

Most common adverse events (and incidence in patients with cIAI and cUTI, respectively): Vomiting (14%; 0%), nausea (10%; 2%), constipation (4%; 10%), anxiety (5%; 10%), abdominal pain (8%; 7%), dizziness (0%; 6%)

Usual dosage: 2 grams ceftazidime/0.5 grams avibactam every 8 hours by intravenous infusion over 2 hours for 5 to 14 days for the treatment of cIAI, and for 7 to 14 days for the treatment of cUTI; the dosage should be reduced to 1 gram/0.25 grams every 8 hours in patients with a creatinine clearance of 31-50 mL/minute; the product labeling should be consulted for the recommended dosage in patients with more severely impaired renal function

Product: Single-use vials – 2 grams ceftazidime/0.5 grams avibactam; contents of a vial should be constituted with 10 mL of Sterile Water for Injection, 0.9% Sodium Chloride Injection, 5% Dextrose Injection, or Lactated Ringer’s Injection; with the same diluent used for constitution of the powder (except for Sterile Water for Injection), the constituted solution should be diluted to achieve a total volume between 50 mL and 250 mL

Comments: Ceftazidime is a cephalosporin antibacterial agent that has been available as a single agent for a number of years. Avibactam is a new beta-lactamase inhibitor that protects ceftazidime against inactivation by beta-lactamase enzymes, thereby increasing the activity of the antibiotic against Gram-negative bacteria. Avibactam is a non-beta-lactam and may inhibit certain bacteria-produced beta-lactamasmes that are not inhibited by other beta-lactamase inhibitors. Of particular importance is its activity against Gram-negative bacteria that produce Klebsiella pneumoniae carbapenemase. The contribution of avibactam to the combination product was based on data from in vitro studies and animal models of infection. The effectiveness of the new combination plus metronidazole was evaluated in a study in patients with cIAI, in which it was compared with meropenem (Merrem). Both treatments provided a favorable microbiological response in more than 90% of patients. In patients with cUTI, ceftazidime/avibactam was compared with imipenem/cilastatin (Primaxin), and both treatments provided a favorable microbiological response in approximately 70% of patients.
Isavuconazonium sulfate (Cresemba – Astellas)  Antifungal Agent

2015  New Drug Comparison Rating (NDCR) = 

Indications: Administered orally or intravenously for the treatment of invasive aspergillosis or invasive mucormycosis

Comparable drug: Voriconazole (Vfend)

Advantages:
--Labeled indications include invasive mucormycosis
--Is less likely to cause prolongation of the QT interval, visual disturbances, hallucinations, and photosensitivity reactions
--Is more suitable for use in patients with impaired renal function (whereas the intravenous use of voriconazole should be avoided in patients with moderate to severe renal impairment)
--Is administered once a day for maintenance treatment (whereas voriconazole is administered every 12 hours)

Disadvantages:
--Labeled indications are more limited (voriconazole is also indicated for candidemia and disseminated candidiasis, esophageal candidiasis, and serious infections caused by Scedosporium apiospermum and Fusarium species)
--May shorten the QT interval
--Efficacy and safety in patients less than 18 years of age have not been established (whereas voriconazole is indicated for use in patients as young as 12 years)
--Insoluble particulates may form in intravenous solutions

Most important risks/adverse events: Shortens the QT interval (contraindicated in patients with familial short QT syndrome); infusion-related reactions (e.g., hypotension, dyspnea; treatment should be discontinued); potential for serious hypersensitivity and severe skin reactions (caution must be exercised in patients with hypersensitivity to other azoles); serious hepatic adverse events (liver function tests should be evaluated at the start of therapy and during the course of treatment); embryo-fetal toxicity (use is best avoided during pregnancy); action may be increased by strong CYP3A4 inhibitors (e.g., clarithromycin) and reduced by strong CYP3A4 inducers (e.g., carbamazepine), and concurrent use of such combinations is contraindicated; may increase the action of immunosuppressants (e.g., cyclosporine, tacrolimus), midazolam, atorvastatin, and digoxin, and concurrent use of the new drug may require dosage adjustment of the latter agents; may decrease the action of lopinavir/ritonavir

Most common adverse events: Nausea (26%), vomiting (25%), diarrhea (22%), headache (17%), hypokalemia (14%), constipation (13%), dyspnea (12%), cough (12%), peripheral edema (11%), back pain (10%), elevated liver function tests (16%)

Usual dosage: Loading dose – 372 mg (equivalent to 200 mg of isavuconazole) every 8 hours for 6 doses; maintenance dosage – 372 mg once a day starting 12 to 24 hours after the last loading dose

Products: Capsules – 186 mg (equivalent to 100 mg of isavuconazole); should be kept in the original container to protect from moisture, and should not be put in pill boxes or pill organizers; single-dose vials – 372 mg (should be stored in a refrigerator); powder should be reconstituted and resultant solution should be diluted by adding to an infusion bag; visible translucent or white particulates may be present which are removed by an in-line filter with a microporous membrane pore size of 0.2 to 1.2 micron

Comments: Isavuconazonium is a prodrug that is converted to isavuconazole following administration. Isavuconazole is an azole antifungal drug with an antifungal spectrum that is similar to that of voriconazole and posaconazole (Noxafil). Its effectiveness in the treatment of invasive aspergillosis was demonstrated in a clinical trial in patients who received either isavuconazonium or voriconazole. Overall success at the end of treatment was seen in 35% of the patients treated with the new drug and 39% of the patients treated with voriconazole. In patients with invasive mucormycosis, isavuconazonium was compared with the natural disease progression associated with untreated mucormycosis. The overall response success rate at the end of treatment was 31%.
**Daclatasvir dihydrochloride** (Daklinza – Bristol-Myers Squibb)  
**Antiviral Agent**

2015  
**New Drug Comparison Rating (NDCR) =**

**Indication:** For use with sofosbuvir (Sovaldi) for the treatment of patients with chronic hepatitis C virus (HCV) genotype 3 infection (regimen is less effective in patients with cirrhosis)

**Comparable drugs:** Ledipasvir (in combination with sofosbuvir in the product Harvoni), ombitasvir (in combination with paritaprevir and ritonavir as part of the Viekira Pak regimen)

**Advantages:**  
-- Is the first regimen for chronic HCV genotype 3 infection that does not require administration with interferon or ribavirin

**Disadvantages:**  
-- Is not available in a combination formulation with sofosbuvir, and use is more expensive  
-- Labeled indications do not include chronic HCV genotype 1 infection

Most important risks/adverse events: Action is reduced by strong inducers of CYP3A (carbamazepine, phenytoin, rifampin, St. John's wort) and concurrent use is contraindicated; dosage should be increased when used concurrently with a moderate inducer of CYP3A (e.g., dexamethasone, efavirenz); action is increased by strong inhibitors of CYP3A (e.g., clarithromycin, itraconazole) and dosage should be reduced when used concurrently; serious bradycardia has occurred when coadministered with sofosbuvir and amiodarone (e.g., Cordarone), particularly in patients also receiving a beta-blocker or those with underlying cardiac comorbidities and/or advanced liver disease (coadministration of amiodarone is not recommended but, if there are no alternative treatment options, cardiac monitoring is recommended); may increase the action of dabigatran (Pradaxa; concurrent use is not recommended), digoxin, and the statins

Most common adverse events (used in combination with sofosbuvir in a 12-week course of treatment): Headache (14%), fatigue (14%), nausea (8%), diarrhea (5%)

**Usual dosage:** 60 mg once a day with or without food, in a regimen with sofosbuvir 400 mg once a day, for 12 weeks; optimal duration of treatment for patients with cirrhosis has not been established; dosage should be reduced to 30 mg once a day in patients also being treated with a strong CYP3A inhibitor; dosage should be increased to 90 mg once a day in patients also being treated with a moderate CYP3A inducer.

**Products:** Tablets – 30 mg, 60 mg

**Comments:** HCV genotype 3 causes less than 10% of chronic HCV infections in the United States, although the incidence of infections caused by HCV genotype 3 in certain other countries (e.g., India) is considerably higher. Daclatasvir is the third inhibitor of the HCV NS5A protein that is required for viral replication, joining ledipasvir and ombitasvir. It is used in a treatment regimen with sofosbuvir, and is the first regimen that does not include interferon or ribavirin to be demonstrated to be effective for the treatment of chronic HCV genotype 3 infection. The effectiveness of the daclatasvir and sofosbuvir regimen was evaluated in a study in which patients were treated for 12 weeks and were monitored for 24 weeks post-treatment. In treatment-naïve patients, 98% of the patients with no cirrhosis of the liver and 58% of the patients with cirrhosis achieved a sustained virologic response (SVR). In treatment-experienced patients, 92% of those with no cirrhosis of the liver and 69% of those with cirrhosis achieved a SVR. The lower SVR in patients with cirrhosis is identified as a limitation of use in the labeling for daclatasvir.
Secukinumab (Cosentyx – Novartis)  
Agent for Psoriasis

2015  New Drug Comparison Rating (NDCR) =

Indication: Administered subcutaneously for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy; (has been subsequently approved for the treatment of patients with psoriatic arthritis and ankylosing spondylitis)

Comparable drugs: Ustekinumab (Stelara), etanercept (Enbrel)

Advantages:
--Is more effective (based on limited comparative studies)
--Has a unique mechanism of action (is an interleukin-17A antagonist)
--Is administered less frequently (compared with etanercept that is administered once a week for maintenance treatment)

Disadvantages:
--Two injections are needed for administration of the usual 300 mg dose
--Is administered more frequently (compared with ustekinumab that is administered every 12 weeks for maintenance treatment)
--Labeled indications are more limited (compared with ustekinumab that is also indicated for the treatment of patients with psoriatic arthritis, and etanercept that is also indicated for the treatment of patients with psoriatic arthritis, rheumatoid arthritis, polyarticular juvenile idiopathic arthritis, and ankylosing spondylitis)

Most important risks/adverse events: Risk of infection (if a serious infection develops during treatment the drug should be discontinued until the infection resolves; in patients with a chronic infection or history of a recurrent infection, use of secukinumab should be carefully evaluated); exacerbation of tuberculosis (patients should be evaluated for tuberculosis infection prior to initiating treatment); exacerbation of active Crohn’s disease; hypersensitivity reactions (prefilled syringes and the removable cap of the pen device contain natural rubber latex that may cause a reaction in latex-sensitive individuals); live vaccines should not be administered during treatment; non-live vaccinations administered during treatment may not elicit an immune response sufficient to prevent disease

Most common adverse events: Nasopharyngitis (11%), diarrhea (4%), upper respiratory tract infection (3%)

Usual dosage: Administered subcutaneously – 300 mg at Weeks 0, 1, 2, 3, and 4 followed by 300 mg every 4 weeks; each 300 mg dose is given as two subcutaneous injections of 150 mg

Products: Single-use prefilled syringes and single-use Sensoready pen – 150 mg/mL; single-use vial – 150 mg as a lyophilized powder requiring reconstitution (should be prepared and reconstituted by a healthcare provider; product labeling should be consulted for specific recommendations); products should be stored in a refrigerator

Comments: Interleukin-17A (IL-17A) is a naturally occurring cytokine that is involved in normal inflammatory and immune responses. It is present in elevated concentrations in psoriatic plaques. Secukinumab is a human monoclonal antibody that selectively binds to IL-17A and inhibits its interaction with IL-17 receptors, thereby inhibiting the release of proinflammatory cytokines and chemokines. Its effectiveness was demonstrated in four placebo-controlled trials that included more than 2,400 participants. The primary endpoints were a reduction in the Psoriasis Area and Severity Index (PASI) score of at least 75% (PASI 75) from baseline to week 12 and treatment success (clear or almost clear) on the Investigator’s Global Assessment after 12 weeks of treatment. In the four studies, between 75% and 87% of patients treated with 300 mg doses of secukinumab attained a PASI 75, compared with 3% or fewer of the patients who received placebo. In one study, some patients were treated with etanercept, and a significantly larger number of patients treated with secukinumab attained the endpoints. In a preliminary study, secukinumab has also been reported to be more effective than ustekinumab.
Deoxycholic acid (Kybella – Allergan) Cytolytic Agent

2015 New Drug Comparison Rating (NDCR) =

Indication: Administered subcutaneously in adults for improvement in the appearance of moderate to severe convexity or fullness associated with submental fat (double chin); use for the treatment of subcutaneous fat outside the submental region has not been evaluated and is not recommended

Comparable drugs: None

Advantages: --Is the first drug approved for the reduction of submental fat

Disadvantages: --None

Most important risks/adverse events: Contraindicated in the presence of infection at the injection sites; dysphagia (may be exacerbated in patients with pre-existing dysphagia); marginal mandibular nerve injury (asymmetric smile, facial muscle weakness; should not be injected into or in close proximity to the marginal mandibular branch of the facial nerve); injection site hematoma/bruising (should be used with caution in patients with bleeding abnormalities or who are being treated with anticoagulant or antiplatelet therapy); risk of tissue damage if injected into or in close proximity to vulnerable anatomic structures (salivary glands, lymph nodes, muscles)

Most common adverse events: Injection site reactions: edema/swelling (87%), hematoma/bruising (72%), pain (70%), numbness (66%), erythema (27%), induration (23%)

Usual dosage: Administered by injection into the subcutaneous fat tissue in the submental area using an area-adjusted dose of 2 mg/cm\(^2\); a single treatment consists of up to a maximum of 50 injections, 0.2 mL each (up to a total of 10 mL), spaced 1 cm apart; up to 6 single treatments may be administered at intervals no less than 1 month apart

Product: Vials for single patient use – 2 mL of sterile solution containing 10 mg of deoxycholic acid/mL; effective and safe use depends on the use of the correct number and locations for injections, proper needle placement, and administration techniques; the product labeling should be consulted for information regarding administration and injection technique; use of ice/cold packs, and topical and/or injectable local anesthesia (e.g., lidocaine) may enhance patient comfort

Comments: Endogenous deoxycholic acid is a bile acid that is a product of cholesterol metabolism. The deoxycholic acid in the Kybella formulation is prepared synthetically and is identical to endogenous deoxycholic acid. When injected into subcutaneous fat, it destroys the cell membrane causing lysis (i.e., a cytolytic action). The effectiveness of deoxycholic acid was evaluated in two placebo-controlled studies in adults with submental fat (i.e., grade 2 or 3 on 5-point grading scales, where 0 = none and 4 = extreme), as judged by both clinician and patient ratings. The efficacy assessments were based on at least 2-grade and at least 1-grade improvements on the composite of clinician-reported and patient-reported ratings of submental fat 12 weeks after the final treatment. A 2-grade improvement occurred in 13% and 19% of patients treated with the drug in the two studies, compared with 0% and 3% of those receiving placebo. A 1-grade improvement occurred in 70% and 66% of those treated with deoxycholic acid, compared with 19% and 22% of those receiving placebo. In a subset of patients, changes in submental fat volume were evaluated using magnetic resonance imaging; 43% of the patients treated with deoxycholic acid had at least a 10% reduction in submental fat volume, compared with 5% of those receiving placebo. The overall patient-reported satisfaction and self-perceived visual attributes showed greater improvement in the deoxycholic acid group than in the placebo group.