

Major New Drugs

Part 1

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Goals and Objectives

Goals:

To provide the pharmacist with information about recently approved major new drug entities introduced in the United States.

Objectives:

After completing this article, the pharmacist should be familiar with the:

1. Pharmacology of each new drug.
2. Pharmacokinetic profile of each new drug.
3. Major use(s) of each new drug.
4. Therapeutic efficacy of each new drug.
5. Adverse effects of each new drug.

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Varenicline – Chantix -- Pfizer

Varenicline is a partial nicotinic acetylcholine receptor agonist that has been designed to activate this system while displacing nicotine at its sites of action in the brain. Varenicline is specifically indicated for use as an aid in smoking cessation.

Varenicline is an alpha-4 beta-2 neuronal nicotinic acetylcholine receptor agonist that competitively inhibits the ability of nicotine to bind to and activate the alpha-4 beta-2 receptor. Varenicline exerts mild agonistic activity at this site, though at a level much lower than nicotine; it is presumed that this activation eases withdrawal symptoms.

Adverse effects associated with the use of varenicline include nausea, insomnia, headache, fatigue, flatulence and dry mouth.

The typical oral regimen for varenicline utilizes a 1-week dosing titration: 0.5 mg once daily on days 1-3, and 0.5 mg twice daily on days 4-7, followed by 1 mg twice daily for 12 weeks, with responders receiving an additional 12-week treatment course to promote long-term abstinence.

Tiotropium – Spiriva – Boehringer Ingelheim

Tiotropium is a long acting anticholinergic drug that is used once daily for maintenance therapy of bronchospasm associated with chronic obstructive pulmonary disease.

Tiotropium is a quaternary ammonium compound that binds with high affinity to muscarinic receptors in airway smooth muscle cells and mucus glands and inhibits the effects of acetylcholine in these areas.

Tiotropium is poorly absorbed systemically, has an onset of about 30 minutes after inhalation, reaches peak effects in about three hours, and persists for about 24 hours. Tiotropium has a cumulative effect and reaches maximum activity in about a week. The terminal elimination half-life is approximately six days.

Adverse effects associated with the use of tiotropium are attributed to its anticholinergic effects and include dry mouth, constipation, tachycardia, blurred vision, urinary retention and narrow angle glaucoma.

The usual dosage for tiotropium is the inhalation of the contents of one capsule each day (18 micrograms of the drug) using a special device (HandiHaler). Each capsule should be maintained in the sealed blister packaging until it is used and administration of the drug should be by the specific instructions.

Trospium – Sanctura – Indevus/Odyssey

Trospium is an anticholinergic drug used for treatment of overactive bladder with symptoms of urge urinary incontinency, urgency and urinary frequency. Trospium is a quaternary ammonium compound that acts mainly as a muscarinic-receptor antagonist.

Trospium is administered orally with only about ten percent of the dose absorbed. If taken with food, the absorption is reduced significantly. Serum concentrations peak

within six hours. Trospium is eliminated primarily unchanged via renal processes and has a half-life of about 18 hours.

Adverse effects associated with the use of trospium include dry mouth and other minor symptoms associated with anticholinergic drug use.

The usual oral dose is 20 milligrams twice daily.

Azacitidine – Vidaza – Pharmion

Azacitidine is a pyrimidine nucleoside analog of cytidine that is used subcutaneously for treatment of patients with myelodysplastic syndrome. Myelodysplastic syndrome is a group of conditions caused by a problem in the blood-forming cells of the bone marrow.

Azacitidine exerts its effects by causing cytotoxicity on abnormal hematopoietic cells in bone marrow and abnormal DNA. The dose required for azacitidine to exert its activity does not appear to be large enough to cause damage to normal tissues and cells.

Azacitidine has adequate bioavailability after subcutaneous administration, achieves peak plasma levels within one hour, is eliminated primarily in the urine, and has a half-life of about four hours.

Adverse effects associated with the use of azacitidine include overall low blood counts, gastrointestinal problems (e.g., nausea, diarrhea, vomiting), fever, tiredness and bruising. Azacitidine may cause harm to a fetus.

The usual initial dose for azacitidine is 75 mg/sq. meter daily for one week administered every four weeks. Patients should be premedicated for nausea and vomiting. If no benefit has occurred after two cycles, then the dose can be increased to 100 mg/sq. meter. If no major toxicity occurs, then treatments should continued for a minimum of four cycles.

Nelarabine – Arranon – Glaxosmithkline

Nelarabine is a prodrug of the deoxyguanosine analog 9-beta-D-arabinofuranosylguanine (ara-G) that is used to treat patients with T-cell acute lymphoblastic leukemia and T-cell lymphoblastic lymphoma that has not responded to at least two other chemotherapy regimens.

Nelarabine is quickly demethylated to ara-G and after conversion to an analog is incorporated into DNA. This results in cell alteration.

Adverse effects associated with the use of nelarabine include anemia, neutropenia, leukopenia and thrombocytopenia. Neurotoxicity (e.g., ataxia, coma), which can be fatal, must be monitored and is dose-limiting.

The usual adult dose for nelarabine is 1500 mg/square meter of body surface. The drug is administered intravenously over a 2-hour period on days 1, 3 and 5, then it is repeated every 21 days.

Abatacept – Orencia – Bristol-Myers Squibb

Abatacept is used to treat moderate to severe rheumatoid arthritis in patients who have not responded to other anti-rheumatic drugs.

Abatacept is an inhibitor of T-cell activation, which often is an inflammatory action that enhances rheumatoid arthritis.

Adverse effects associated with abatacept include infections, which may be serious, and enhancement of other diseases that are present (e.g., COPD).

Abatacept is administered intravenously over 30 minutes on day one and again at 2 and 4 weeks, and every four weeks thereafter. Abatacept has a half-life of almost two weeks. The dose of abatacept is based on weight (80-100 kg is 750 milligrams; over 100 kg is 1 gram). Patients should be skin-tested for tuberculosis before initiating treatment and should not receive vaccines during treatment or for a minimum of three months after ending treatment.

Lenalidomide – Revlimid – Celgene

Lenalidomide is a thalidomide analog used for treating transfusion-dependent anemia associated with myelodysplastic syndrome that has a lower risk of mortality and/or progression to leukemia based on scoring systems.

Myelodysplastic syndrome is a heterogeneous group of bone marrow disorders with a high incidence of cytogenetic abnormalities. These disorders can progress to more severe disorders (e.g., leukemia).

Adverse effects associated with the use of lenalidomide include thrombocytopenia, leucopenia, diarrhea, rash, and fatigue. Since lenalidomide is related to thalidomide, it is contraindicated in pregnant women and available only via a restricted distribution system.

Lenalidomide is administered orally with an individual dosage regimen. Lenalidomide is well and rapidly absorbed, eliminated primarily in the urine unchanged, and has a half-life of about two hours.

Insulin Glulisine – Apidra – Sanofi Aventis

Insulin glulisine is a rapid acting insulin that is used immediately before meals and often combined with a longer acting insulin.

Insulin glulisine does not form hexamer aggregates as rapidly as regular insulin; therefore, it is absorbed faster and reaches peak concentrations within an hour and has a duration of action of about four hours.

The primary adverse effect associated with insulin glulisine is hypoglycemia, which has been similar to other drugs in this group as well as regular insulin.

Insulin glulisine is equal in potency to regular human insulin and is administered 15 minutes before or after starting a meal. It can be injected subcutaneously or infused via an external pump.

Deferasirox – Exjade – Novartis

Deferasirox is an oral chelating drug approved by the FDA as an orphan drug for treatment of chronic iron overload due to blood transfusions. Deferasirox is a tridentate; therefore, two molecules of deferasirox bind to one iron molecule. Deferasirox has a very low affinity for zinc and copper.

Deferasirox has a 70% bioavailability, achieves peak levels in four hours, has a half-life of 8 to 16 hours, and is eliminated primarily via the feces.

Adverse effects associated with the use of deferasirox include gastrointestinal symptoms (e.g., vomiting, diarrhea), rash, ocular disturbances, and hearing loss. Auditory and ophthalmic exams should be done annually for patients taking deferasirox.

The usual dose for deferasirox is 20 milligrams/kilogram, which can be adjusted every 3 to 6 months to a maximum of 30 milligrams/kilogram/day. Deferasirox tablets must be dissolved in a glass of water or orange or apple juice and taken 30 minutes before eating at the same time each day. Deferasirox should not be administered with any product containing aluminum (e.g., antacid).

Anidulafungin – Eraxis – Pfizer

Anidulafungin is an echinocandin antifungal that is used to treat esophageal Candida infections and other complicated Candida infections.

Anidulafungin inhibits fungal cell wall synthesis, is used intravenously, has a slow metabolism, is eliminated in the feces, and has a half-life of more than a day.

Adverse effects associated with the use of anidulafungin include histamine-like reactions (e.g., rash, flushing), fever, nausea, vomiting, and hypokalemia.

The intravenous dosage varies with regard to the fungal infection, but is typically 100 to 200 milligrams on day one, followed by half the dose for two weeks.

Ranolazine – Ranexa – Cv Therapeutics

Ranolazine is used in combination with other drugs (e.g., amlodipine) to treat chronic angina. The anti-anginal and anti-ischemic mechanism of action of ranolazine is unknown, but it may be related to inhibition of the late inward sodium current which could reduce intracellular calcium concentrations and improve left ventricular function.

Ranolazine is well absorbed, eliminated primarily unchanged in the urine, is metabolized mainly by CYP3A4 and has a half-life of about 7 hours.

Constipation, nausea, dizziness, and headache are adverse effects that are moderately encountered with the use of ranolazine. Since ranolazine is a substrate of CYP3A4, it should not be used with strong or moderate inhibitors of the enzyme (e.g., itraconazole, diltiazem, clarithromycin). Ranolazine should not be used in patients with hepatic impairment or pre-existing QT prolongation.

The usual dose for ranolazine is 500 milligrams twice a day, which can be increased to a maximum of one gram twice daily.

Lubiprostone – Amitiza – Sucampo/Takeda

Lubiprostone is a chloride channel activator that is used for treatment of chronic constipation in adults. Lubiprostone acts locally in the gastrointestinal tract by enhancing the

intestinal fluid, which is rich in chloride, to reduce colonic transit time.

Lubiprostone acts locally and has minimal bioavailability, is metabolized in the stomach and jejunum, and is eliminated in the urine and feces.

Adverse effects associated with the use of lubiprostone include headache, nausea, and diarrhea. Lubiprostone should not be used in pregnant women and a pregnancy test should be conducted prior to administering the drug.

The usual dose is 24 micrograms twice a day with food.

Conivaptan – Vaprisol – Astellas

Conivaptan is a vasopressin antagonist used intravenously for short-term treatment of euvolemic hyponatremia, which is usually caused by inappropriate ADH secretion, hypothyroidism, or adrenal insufficiency.

Conivaptan antagonizes certain vasopressin receptors in the renal collecting duct which results in excretion of free water. Conivaptan is highly protein bound, is metabolized in the liver by CYP3A4, eliminated in the feces and has a half-life of five hours.

Adverse effects associated with the use of conivaptan include infusion site reactions, headache, thirst, hypokalemia, and gastrointestinal tract issues. Since conivaptan is a substrate for CYP3A4, it is contraindicated to use with strong CYP3A4 inhibitors (e.g., itraconazole, clarithromycin). In addition, conivaptan should not be used in pregnant women.

The usual dose of conivaptan is 20 milligrams intravenously over thirty minutes followed by a continuous infusion of 20 milligrams for 24 hours. The dose may be increased to 40 milligrams/24 hours, if needed.

Insulin Detemir – Levemir – Nova Nordisk

Insulin detemir is a long acting basal insulin analog used for type 1 and type 2 diabetes. Insulin detemir differs from human insulin by the elimination of the amino acid threonine in position B30 and the addition of a 14-carbon fatty acid chain at position B 29.

Insulin detemir is absorbed slowly from the injection site, is highly bound to albumin, is about 60% bioavailable, achieves maximum concentrations within 8 hours, and has a half-life of about 7 hours.

As with most insulins, the most common adverse effect is hypoglycemia.

Insulin detemir can be taken once or twice daily and is substituted unit-for unit with NPH insulin in most cases. Insulin detemir should not be mixed with other insulins.

Inhaled Insulin – Exubera – Pfizer

Inhaled insulin is a dry powder formulation of rapid-acting human insulin that is used in the treatment of type 1 or type 2 diabetes.

The product is packaged in blisters containing one or three milligrams of dry powder insulin, which is equivalent to 3 or 8 units of insulin, respectively. A single blister is inserted into a handheld inhaler device with a clear chamber reservoir. The handle of the device is compressed and the insulin is released into the chamber for inhalation. About 40% of the inhaled powder reaches the deep lung. Patient satisfaction with this dosage form has been very good.

The bioavailability of inhaled insulin is about 10%, but it has a rapid onset of action and a duration of action slightly shorter than regular insulin.

Adverse effects associated with the use of inhaled insulin include hypoglycemia, mild to moderate cough, pulmonary function issues, and the development of anti-insulin antibodies. Smoking may increase the effect of inhaled insulin.

The dose of inhaled insulin is determined individually on the needs of the diabetic patient.

Naltrexone – Vivitrol – Alkermes/Crphalon

Naltrexone, an opioid receptor antagonist, is used in an injectable extended-release formulation once a month in concert with psychosocial support to maintain abstinence from alcohol. Naltrexone inhibits the rewarding effects of alcohol.

This unique formulation of naltrexone achieves peak concentrations at two hours and again in about three days before declining after approximately two weeks. Naltrexone is metabolized in the liver and does not appear to accumulate.

Adverse effects of this dosage formulation of naltrexone include injection site reactions and gastrointestinal tract effects. Oral formulations of naltrexone have caused hepatic toxicity.

This special formulation of naltrexone is available only from specific requests to the manufacturer. The drug must be refrigerated until use.