

What's New in Clinical Pharmacology and Therapeutics

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ABSTRACT

The US Food and Drug Administration (FDA) has approved several new drugs in the last few years. We have summarized a few of these that should be of interest to a primary care physician. These belong to either a new class of drugs or have a better drug profile in terms of ease of administration, prolonged duration of action, or fewer side effects.

Daptomycin is a cyclic lipopeptide, active against methicillin resistant *Staphylococcus aureus* (MRSA). Telithromycin is a ketolide that can be used in place of macrolide antibiotics. Rifaximin is a semi-synthetic derivative of rifampin approved by the FDA for treatment of traveller's diarrhea.

Pramlintide is an injectable synthetic amylin useful in treating type 1 and 2 diabetes. Tiotropium is an anti-cholinergic bronchodilator that can be taken once a day for treatment of chronic obstructive pulmonary disease. Lanthanum Carbonate is useful in treatment of hyperphosphatemia in patients with end stage renal disease. Flumist is an intranasal influenza vaccine. Eszopiclone is a new hypnotic that has fewer side effects. Memantine is in a new class of drugs useful in the treatment of Alzheimer's disease. Ibandronate is a new bisphosphonate approved for once a month use for osteoporosis in postmenopausal women. Acamprosate is approved for treatment of alcohol dependence.

INFECTIOUS DISEASES

Daptomycin (Cubicin)

Daptomycin belongs to a new class of antibiotics called cyclic lipopeptides.¹ It binds to bacterial membranes causing rapid depolarization of the membrane poten-

tial that leads to inhibition of protein, RNA, and DNA synthesis and causes cell death. It has bactericidal activity against gram-positive bacteria² and has been approved for the intravenous treatment of complicated skin and soft tissue infections such as abscesses, post-surgical wound infections, infected ulcers, and severe cellulitis caused by methicillin-resistant *Staphylococcus aureus* (MRSA). It is active against MRSA, *Staphylococcus pyogenes*, *Streptococcus agalactiae*, *Streptococcus dysgalactiae* subspecies equisimilis, and *Enterococcus faecalis* (Vancomycin-susceptible strains only) and thus has a similar spectrum of activity as that of vancomycin. It is not indicated for the treatment of pneumonia as it penetrates poorly into alveolar secretions. Daptomycin is administered intravenously at 4 mg/kg once daily for 7-14 days. For patients with severe renal impairment (creatinine clearance <30 ml/min or patients on hemodialysis), it is given once every 48 hours. No dose adjustment is necessary in the elderly, obese, or those with mild to moderate hepatic dysfunction. Adverse effects include constipation, nausea, injection site reactions, headache, insomnia, fever, and rash. Rarely it can increase serum CPK levels and cause muscle discomfort and weakness, which are reversible upon discontinuation of the drug.³ It is recommended to stop statins and other agents associated with rhabdomyolysis during treatment with daptomycin. CPK levels should be monitored on a weekly basis. Daptomycin is also being studied for other indications including streptococcal bacteremia, endocarditis, and vancomycin-resistant enterococci and for treatment of osteomyelitis and diabetic foot infections.

Telithromycin (Ketek)

Telithromycin is the first of a new class of antibiotics, the ketolides.⁴ Like macrolide antibiotics, it binds to bacterial ribosome and disrupts protein synthesis. It differs from macrolides by ketone and methoxy-group substitutions that make it more acid stable and less susceptible to drug export pumps and increases the drug's ribosomal affinity, thereby overcoming the most

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frequent mechanisms of bacterial resistance to macrolides. The main advantage of telithromycin is its activity against most macrolide-resistant streptococci. It is also active against *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, *Legionella pneumophila*, *H. influenzae*, *Bordetella pertussis*, most strains of group A beta-hemolytic streptococci, erythromycin-susceptible strains of *Staphylococcus aureus*, *Helicobacter pylori*, and some anaerobes. It has been approved by the FDA for oral treatment of acute bacterial exacerbations of chronic bronchitis, acute bacterial sinusitis, and mild-to-moderate community-acquired pneumonia in patients ≥ 18 years of age.⁵ The dose is 800 mg orally once daily; it can be administered with or without food. The duration of therapy depends on the type of infection. The most common adverse effects are diarrhea, nausea, and vomiting. Other less common but serious adverse effects include visual disturbances, prolongation of the QTC interval, exacerbation of myasthenia gravis, and hepatic dysfunction. No dose adjustment is necessary for patients with mild to moderate renal impairment (creatinine clearance ≤ 30 ml/min). Telithromycin is metabolized by CYP3A4 enzymes and is a potent inhibitor of these enzymes, thereby increasing levels of drugs metabolized by these enzymes such as statins and midazolam. These drugs should be stopped while taking the antibiotic. Drugs that inhibit CYP3A4 enzymes, such as ketoconazole, can increase telithromycin levels, whereas inducers of these enzymes such as rifampin and phenytoin can decrease its levels. Telithromycin can be used as an alternative to quinolones against macrolide-resistant *Streptococcus pneumoniae*.

Rifaximin (Xifaxan)

Rifaximin is a semi-synthetic derivative of rifampin approved by the FDA for the treatment of traveller's diarrhea (TD) caused by the noninvasive strains of *Escherichia coli* in patients ≥ 12 years of age.⁶ It acts by inhibition of bacterial RNA synthesis. Traveller's diarrhea is defined as 3 or more unformed stools in a 24-hour period plus at least 1 symptom of either abdominal pain, bloating, abdominal cramps, nausea, vomiting, fever, or tenesmus. TD can occur in 20%-80% of people traveling from developed countries to developing countries. The most common cause of TD is a noninvasive strain of *E. coli*. Other causes include *C. jejuni*, Shigella, Salmonella, viruses, and parasites. Rifaximin is administered 200 mg orally 3 times daily with or without food for 3 days. No specific dosage adjustment is required for patients with hepatic insufficiency. No severe adverse effects occur with rifaximin. It is contraindicated in patients with hypersensitivity to rifamycins.

Hypersensitivity reactions including allergic dermatitis, rash, angioneurotic edema, urticaria, and pruritis have been reported. It is not effective in patients with diarrhea complicated by fever and/or blood in the stool or diarrhea caused by organisms other than *E. coli*. It is an alternative to quinolones⁷ or azithromycin for noninvasive infections as it is not absorbed systemically when taken orally and reaches high concentrations in the intestinal tract only. It is a category C drug in pregnancy (human studies are not available and animal studies are either not available or indicate possible fetal risk).

ENDOCRINE SYSTEM

Pramlintide (Symlin)

Pramlintide is the first injectable non-insulin drug approved for the treatment in patients with type 1 or type 2 diabetes who have failed to achieve desired glucose control despite optimal insulin therapy.⁸ Pramlintide is a synthetic form of human amylin that is secreted by pancreatic beta cells along with insulin in response to food intake. It slows gastric emptying, thereby reducing the initial postprandial increase in plasma glucose. It does not alter the overall absorption of nutrients. It also acts by suppressing the glucagon secretion, thus leading to suppression of endogenous glucose output from the liver in insulin-using patient with diabetes. Pramlintide also leads to decreased caloric intake and potential weight loss by its action on the satiety center in brain. It should be administered subcutaneously. Although it is metabolized by the kidneys, studies have shown that no dose adjustment is required in patients with moderate or severe renal impairment or in patients with hepatic dysfunction. No studies have been done in patients requiring dialysis. Pramlintide is associated with an increased risk of insulin-induced severe hypoglycemia in patients with type 1 diabetes within the first 3 hours of its administration. The patients should be instructed to monitor pre- and post-meal glucose levels and adjust the pre-meal insulin dose of rapid-acting insulin accordingly. Pramlintide should not be used in patients who demonstrate poor compliance with current insulin therapy or self-glucose monitoring. It should be avoided in patients who have a hemoglobin A1c $> 9\%$, recurrent severe hypoglycemia requiring treatment during the past 6 months, hypoglycemia unawareness, confirmed diagnosis of gastroparesis requiring the use of pro-motility drugs, and in pediatric patients. Pramlintide and insulin should always be administered as separate injections and should never be mixed. The adverse effects include hypoglycemia, nausea, vomiting, anorexia, headache, fatigue, and dizziness. The initial dose of pramlintide is different in patients with type 1

and type 2 diabetes. In patients with type 1 diabetes, the initial dose is 15 mg titrated to 30-60 mg as tolerated, whereas in patients with type 2 diabetes using insulin, it should be initiated at 60 mg and increased to 120 mg. The insulin dose in type 1 and type 2 patients may need to be decreased by 50%. Clinical studies have shown that pramlintide reduces post-prandial hyperglycemia, causes less fluctuations of blood glucose during the day, and has better long-term glucose control compared to patients taking insulin alone.^{9,10} It is a category C drug in pregnancy and it is unknown whether it is excreted in human milk.

RESPIRATORY SYSTEM

Tiotropium (Spiriva)

Tiotropium is the first anti-cholinergic bronchodilator to offer once-daily dosing for maintenance treatment in patients with chronic obstructive pulmonary disease (COPD) and is not indicated for rapid relief of bronchospasm. It acts by the inhibition of muscarinic receptors in smooth muscle and mucus glands resulting in bronchodilation and decreased airway secretions. It is available in a 18 mcg capsule form that is inhaled once daily using a handheld device. It is poorly absorbed systemically and no dose adjustment is required for the elderly or in patients with mild renal impairment or hepatic dysfunction. However, patients with creatinine clearance of ≤ 50 ml/min should be closely monitored. The most common anticholinergic adverse effect is dry mouth, which is mild and resolves with continued treatment. Others include constipation, tachycardia, blurred vision, urinary retention, and narrow angle glaucoma. It should be used cautiously in patients with bladder neck obstruction or prostatic hyperplasia. Studies have shown that tiotropium can improve lung function, reduce symptoms, improve quality of life, and decrease the number of exacerbations with once daily dosing, which is a major advance in the treatment of COPD.^{11,12} It is a pregnancy category C drug.

EXCRETORY SYSTEM

Lanthanum Carbonate (Fosrenol)

Lanthanum carbonate is a new option in the treatment of hyperphosphatemia in patients with end-stage renal disease.^{13,14} Lanthanum ions bind to ingested phosphate in food, which is then excreted as insoluble lanthanum-phosphate complexes. It should be chewed completely prior to swallowing and can be taken with or immediately after a meal. The dose is 750-1500 mg daily orally; it can be titrated up to 3750 mg daily based on serum phosphate level. The most common adverse effects are

nausea, vomiting, abdominal pain, and dialysis graft occlusion. Lanthanum carbonate is not metabolized by cytochrome P450 enzymes. It should be used with caution in patients with acute peptic ulcer disease, inflammatory bowel disease, and bowel obstruction. Also, the long-term effects beyond 3 years are unknown. In clinical studies, it has been shown to have similar efficacy and safety when compared to calcium carbonate in decreasing phosphate level, but it does not induce hypercalcemia, which is its main advantage. Lanthanum does not cause osteomalacia, which is seen with aluminum products used previously to treat hyperphosphatemia. It is a category C drug in pregnancy.

PREVENTIVE MEDICINE

Flumist (Influenza vaccine)

Flumist is the first intranasally administered influenza vaccine and is also the first live attenuated influenza vaccine approved by the FDA to prevent influenza A and B in healthy people age 5-49 years old.^{15,16} It is given as a nasal spray of 0.5 ml and stimulates immunity by viral replication in the naso-pharynx. It contains 2 strains of influenza A, which causes the most severe and widespread outbreaks, and 1 strain of B, which causes a more mild illness. These strains are selected annually by the US Public Health Service. These strains induce both local influenza-specific Ig A antibody and variable levels of systemic humoral and cellular immunity. Children 5-8 years old need 2 doses at least 6 weeks apart whereas individuals 9-49 years old need only 1 dose. Flumist is a "needle-free" alternative to intramuscular influenza vaccine. Clinical studies have shown it to be as effective as injected inactivated influenza vaccine in healthy children and adults and that it leads to statistically significant reductions in the number of episodes and days of severe febrile respiratory illness, and in workdays lost, physician visits, and antibiotic use due to influenza infection. The most common adverse effects associated with the vaccine are nasal congestion, runny nose, sore throat, and cough. Flumist should not be used in children < 5 years old since increased rate of asthma exacerbations within 6 weeks of vaccination were observed. For people ≥ 50 years of age, safety has not been established. Flumist should not be given to people in whom live virus vaccines are contraindicated such as pregnant women, immunocompromised patients, or those receiving immunosuppressive drugs. Flumist is grown in eggs and should not be given to patients with hypersensitivity to egg proteins. It is also contraindicated in children and adolescents on chronic aspirin therapy because of risk of Reye's syndrome. Flumist is substantially expen-

sive compared to intramuscular inactivated vaccine. It may be welcome by those eligible people who are reluctant to get a shot.

SLEEP MEDICINE

Eszopiclone (Lunesta)

Eszopiclone is a pyrrolopyrazine derivative that has been approved by the FDA for treatment of insomnia. Unlike other hypnotic drugs, it is not limited to short-term use. It is not chemically-related to other hypnotic drugs such as zolpidem (Ambien), zaleplon (Sonata) or the benzodiazepines. All of these drugs are believed to act through an agonist effect on gamma amino butyric acid (GABA). The exact mechanism of action of eszopiclone in enhancing sleep is unknown. It is rapidly absorbed when taken orally in a 1-3 mg daily dose and is extensively metabolized in the liver by CYP3A4 and CYP2E1 enzymes. The inactive metabolites are excreted mainly in urine. Elimination is slower in the elderly. Results from clinical studies have shown that it reduces sleep latency and nighttime awakenings, improves sleep maintenance, and increases total sleep time and quality of sleep.¹⁷ When compared to a placebo, it showed better next-day functioning, mental alertness, and sense of well being. These effects were maintained during a 6-month study period.¹⁸ Adverse effects include bitter taste, headache, somnolence, dizziness, and dry mouth.

GERIATRIC MEDICINE

Memantine (Namenda)

Memantine is the first drug in a new class approved by the FDA for the treatment of moderate to severe Alzheimer's disease.¹⁹ It has a different mechanism of action from the acetylcholine esterase inhibitors donepezil (Aricept), galantmine (Reminyl), rivastigmine (Exelon), and tacrine (Cognix). Memantine is an N-methyl-D-aspartate (NMDA) receptor antagonist. It inhibits the effects of glutamate, which is the principal excitatory neurotransmitter in the brain. It has been hypothesized that glutamatergic overstimulation at the NMDA receptor can be toxic to neurons and can cause neurodegenerative disorders such as Alzheimer's disease. Memantine is given orally 5-20 mg once daily with or without food. Its dose should be decreased in patients with moderate renal impairment, and it is not indicated with severe renal dysfunction. The adverse effects include dizziness, headache, constipation, confusion, hallucinations, and hypertension. It should be used cautiously in patients on other NMDA receptor antagonists such as amantadine, ketamine, etc., as it has not been evaluated with these drugs. In clinical studies, memantine has been

shown to improve cognitive and day-to-day functions compared to a placebo. The combination of memantine and donepezil appears to be more effective than placebo plus donepezil.²⁰ Memantine is better tolerated than the choline-esterase inhibitors and is associated with fewer gastrointestinal side effects. It is moderately effective for moderate-to-severe Alzheimer's disease, but its use in patients with milder forms of the disease has not been fully evaluated.

Ibandronate (Boniva)

Ibandronate is a new oral bisphosphonate approved to be taken once a month for the prevention and treatment of osteoporosis in postmenopausal women. It was first approved for daily dosing in May 2003. Like other bisphosphonates, it reduces bone resorption and turnover by inhibiting osteoclast activity and also leads to an increase in bone mass. It should be taken with 6-8 oz of water in the morning at least 60 minutes before eating to avoid esophageal irritation. The patient should avoid a supine position for 60 minutes after taking it. The adverse effects include GI disturbances such as esophagitis, gastritis, and diarrhea. With once-monthly formulation, constipation, influenza-like illness, and pain in the extremities occur more often than with once-daily dose. As with other bisphosphonates, it should not be used in patients with severe renal impairment. A once-monthly dose of 150 mg has been found to be as effective as the daily dose of 2.5 mg in increasing bone mineral density and decreasing bone turnover, thus reducing fracture risk, especially at the lumbar spine. In clinical studies, consistently higher bone mineral density increases were reported at other sites with monthly compared to daily dosing.²¹ Patients should also take calcium and vitamin D supplements while on ibandronate therapy. An injectable form of ibandronate for use once every 3 months is under investigation.²²

MISCELLANEOUS DRUGS

Acamprosate (Campral)

Acamprosate is the third drug to be approved by the FDA for the treatment of alcohol dependence.^{23,24} (The others are disulfiram and naltrexone.) Acamprosate is structurally related to gamma-amino butyric acid (GABA) and decreases glutamatergic transmission and modulates neuronal hyperexcitability during alcohol withdrawal by restoring the balance between the excitatory glutamate and inhibitory GABA neurotransmitter in the brain. Acamprosate thus reduces the negative reinforcing effects of alcohol such as anxiety, stress, and dysphoria associated with the absence of alcohol. It is indicated for the maintenance of abstinence from

Table 1. Highlights of the Drugs Discussed

Name	Class	Dose and Route	Major Side Effects	Indications
Daptomycin (Cubicin)	Cyclic Lipopeptide	4 mg/kg once daily for 7-14 days, intravenously	Constipation, nausea, injection site reactions, increased CPK	Complicated soft tissue infections
Telithromycin (Ketek)	Ketolides	800 mg once daily, orally. Duration depends on infection	GI effects, prolongation of QT interval, exacerbation of myasthenia gravis	Infection caused by Macrolide-resistant streptococci
Rifaximin (Xifaxan)	Rifampin derivative	200 mg 3 times a day for 3 days, orally	Hypersensitivity reactions	Travelers' diarrhea caused by <i>E. coli</i>
Pramlintide (Symlin)	Injectable Non-insulin	Type 1 DM – 15 mcg up to 30-60 mcg, Type 2 DM – 60 mcg up to 120 mcg, subcutaneously	Hypoglycemia, GI side effects	Type 1 and 2 DM in addition to insulin therapy
Tiotropium (Spiriva)	Anticholinergic Bronchodilator	18 mcg capsule once daily using hand-held inhaler	Anticholinergic side-effects: dry mouth, urinary retention, etc.	Maintenance treatment of COPD
Lanthanum Carbonate (Fosrenol)	Phosphate binder	750-1500 mg/day, up to 3750 mg/day orally	GI effects, dialysis graft occlusion	Treatment of hyperphosphatemia in ESRD patients
Flumist	Influenza vaccine	0.5 ml Intranasally	Nasal congestion, sore throat, cough	Influenza A and B in healthy persons 5-49 years old
Eszopiclone (Lunesta)	Pyrraloyrazine derivative	1mg once daily, up to 3 mg/day orally	Bitter taste, headache, dry mouth, dizziness	Treatment of insomnia
Memantine (Namenda)	NMDA Receptor antagonist	5 mg once daily, up to 20 mg/day orally	Dizziness, hallucinations, hypertension	Moderate to severe Alzheimers disease
Ibandronate (Boniva)	Bisphosphonate	150 mg once a month, orally	Esophagitis, gastritis, diarrhea	Prevention and treatment of osteoporosis in postmenopausal women
Acamprosate (Campral)	Gamma-amino-butyric acid agonist	666 mg 3 times a day, orally	Headache, diarrhea, flatulence	Treatment of alcohol withdrawal

alcohol in patients who have stopped drinking prior to initiation of acamprosate. Its efficacy in patients with polysubstance abuse who also drink alcohol is not known. Treatment should be started as soon as possible after alcohol withdrawal and abstinence are achieved and should be continued even if the patient relapses. The usual dose of 666 mg 3 times daily orally of acamprosate should be reduced to half in patients with moderate renal impairment (creatinine clearance of 30-50 ml/min) and should not be used if the creatinine clearance is ≤ 30 ml/min. Acamprosate is not metabolized in the liver and has no drug interactions involving cytochrome P450 enzymes. The most common adverse effects are headache, diarrhea, flatulence, and nausea. It may increase the risk of suicidal ideation and suicidal attempts; however, completed suicides have rarely oc-

curred. Acamprosate has been shown to be comparable in effectiveness to naltrexone, but the combination was found to be more effective than naltrexone alone.²⁵ It can be used in combination with naltrexone or disulfiram, or as an alternative to naltrexone in patients who can't take it due to liver dysfunction or patients who are receiving concurrent opioid therapy. All patients should also receive some type of psychosocial or behavioral support in addition to drug therapy. It is a category C drug in pregnancy.

A summary of the information presented in this article can be found in Table 1.

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