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New Drugs: Beleodaq, Belsomra, Jardiance, and Zydelig

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Goal. The goal of this lesson is to provide information on belinostat (Beleodaq®), empagliflozin (Jardiance®), idelalisib (Zydelig™) and suvorexant (Belsomra®).

Objectives. At the completion of this activity, the participant will be able to:

1. identify the new drugs by generic name, trade name and chemical name when relevant;
2. select the indication(s), pharmacologic action(s) and clinical applications for each drug;
3. recognize important therapeutic uses for the drugs and their applications in specified pathologies; and
4. demonstrate an understanding of adverse effects and toxicity, significant drug-drug interactions, and patient counseling information for these drugs.

The four new-molecular entity drugs discussed in this lesson are indicated to treat a wide variety of pathologies (Table 1). The lesson provides a brief introduction to the therapeutic agents, and its depth is not intended to extend beyond an overview of the topic. The reader is, therefore, urged to consult the products' full prescribing information leaflet (package insert), *Medication Guide* when available, and other reliable sources for detailed descriptions.

Belinostat (Beleodaq)

Belinostat is the third drug approved since 2009 for treatment of peripheral T-cell lymphoma (PTCL). FDA granted approval to pralatrexate (Folotyn) in 2009 for patients with relapsed or refractory PTCL, and romidepsin (Istodax) in 2011 for treatment of PTCL in patients who received at least one prior therapy.

Indications and Use. Beleodaq (Bē-lēo-dak) is approved for treatment of patients with relapsed or refractory PTCL. This indication was authorized under accelerated approval based on tumor response rate and duration of response. An improvement in survival or disease-related symptoms has not been established. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trial.

Relapsed or Refractory Peripheral T-cell Lymphoma. PTCL is a rare and fast-growing form of non-Hodgkin lymphoma. The neoplasms comprise a heterogeneous group of aggressive malignancies derived from mature T-cell PTCL, and natural killer T-cell lymphomas. They account for between 10 and 15 percent of non-Hodgkin lymphomas in the Western hemisphere, with a higher prevalence in Asia estimated at nearly 24 percent. The geographic and ethnic differences that confer increased risk for development of PTCL may be due to exposure to viruses, such as human T-cell lymphotrophic virus-1, implicated in the pathogenesis of adult T-cell leukemia/lymphoma, and Epstein-Barr virus, associated with natural killer T-cell lymphoma, and the underlying host susceptibility to the virus infection.

PTCL has a relatively poor prognosis compared with B-cell lymphomas as a whole. Although T-cell lymphomas vary with respect to clinical features, prognosis, and treatment response, the two-year failure-free survival for patients with intermediate-to-high risk disease is estimated at 10 percent.

Although anthracycline-based regimens (e.g., daunorubicin, doxorubicin and others) are widely used as first-line therapy, their benefit has not been established prospectively in PTCL. In the absence of randomized trials, high-dose therapy with stem cell transplantation is widely used. For relapsed or refractory PTCL, autologous (similar genetically) and allogeneic (different genetically) stem cell transplantation is the standard of care for eligible patients. However, chemotherapy-refractory patients are not good candidates for this approach. New approaches that include drugs with novel mechanisms of action are urgently needed.

Mechanism of Action. Belinostat is a potent inhibitor of histone deacetylase enzymes, which catalyze the removal of acetyl groups from the lysine residues of histones and some non-histone

Table 1
Selected new drugs

Generic (Trade Name)	Distributor	Indication	Dose*	Dosage Form	Most Common Side Effects	Medication Guide‡
Belinostat (Beleodaq)	Spectrum Pharmaceuticals	peripheral T-cell lymphoma	1,000 mg/m^2 over 30 min	500 mg single-use vial for IV infusion	(>25%): nausea, fatigue, pyrexia, anemia, vomiting	No
Empagliflozin (Jardiance)	Boehringer Ingelheim	Type 2 diabetes mellitus	10-25 mg once daily	10 mg, 25 mg oral tablets	(≥5%): urinary tract infections, female genital mycotic infections	No
Idelalisib (Zydelig)	Gilead Sciences	chronic lymphocytic leukemia, follicular B-cell non-Hodgkin lymphoma, small lymphocytic lymphoma	150 mg twice daily	100 mg, 150 mg oral tablets	(≥20%): diarrhea, pyrexia, fatigue, nausea, cough, pneumonia, abdominal pain, chills, rash	Yes
Suvorexant (Belsomra)	Merck & Co.	insomnia	10-20 mg daily	5 mg, 10 mg, 15 mg, 20 mg oral tablets	(≥5%): somnolence	Yes

*Recommended dose for most patients
‡Availability at the time of publication of this lesson

proteins. The drug shows preferential cytotoxicity toward tumor cells compared to normal cells.

Efficacy and Safety. Safety and efficacy were evaluated in a clinical study involving 129 participants with relapsed or refractory PTCL. All participants were treated with Beleodaq until their disease progressed or side effects became unacceptable. Results showed that 25.8 percent of participants experienced complete or partial response following treatment.

The most common adverse effects were nausea, fatigue, pyrexia, anemia, and vomiting.

Warnings, Precautions, and Contraindications. The following **warnings** and **precautions** are listed:

• *Thrombocytopenia, leukopenia (neutropenia and lymphopenia), and anemia*: Monitor blood counts and modify dosage for hematologic toxicities.

• *Infection*: Serious and fatal infections (e.g., pneumonia and sepsis) have been noted. Do not administer the drug to persons with active infection.

• *Hepatotoxicity*: Beleodaq may cause hepatic toxicity and liver function test abnormalities. Monitor liver function and omit or modify dosage for hepatic toxicities.

• *Tumor lysis syndrome*: Monitor patients with advanced stage disease and/or high tumor burden, and take appropriate precautions.

• *Gastrointestinal (GI) toxicity*: Nausea, vomiting, and diarrhea occur with Beleodaq and may require the use of antiemetic and antidiarrheal medications.

• *Embryo-fetal toxicity*: Beleodaq may cause fetal harm when administered to a pregnant woman. Advise women of potential harm to the fetus and to avoid pregnancy while receiving the drug.

No **contraindications** are reported.

Drug Interactions. Belinostat is primarily metabolized by hepatic UGT1A1. Evaluate risk vs. benefit before concomitant administration of Beleodaq with strong inhibitors of UGT1A1 (e.g., atazanavir, gemfibrozil, indinavir, ketoconazole, sorafenib).

Administration, Dosing, and Availability. The recommended dosage is 1,000 mg/m^2 given over 30 minutes by IV infusion once daily on days 1-5 of a 21-day cycle. Cycles can be repeated until disease progression or unacceptable toxicity. Treatment discontinuation or interruption with or without dosage reductions by 25 percent may be needed to manage adverse reactions.

Beleodaq is available in single-use vials containing 500 mg of lyophilized powder for reconstitution with Sterile Water for Injection.

Patient Counseling. Specific points for patient counseling are summarized in Table 2.

Idelalisib (Zydelig)

Considerable progress has been made in the availability of treatments for chronic lymphocytic leukemia (CLL). FDA approved

Table 2
Patient information for Beleodaq*

Inform patients:
- to read the Patient Information brochure before starting the drug and to reread it each time they receive Beleodaq;
- to report symptoms of nausea, vomiting, and diarrhea to their physician so that appropriate antiemetic and antidiarrheal medications can be administered;
- to report any symptoms of thrombocytopenia, leukopenia (neutropenia and lymphopenia), anemia, or infection to their physician right away;
- (women of childbearing age) to avoid pregnancy while receiving Beleodaq;
- to understand the importance of monitoring liver function test abnormalities and to immediately report potential symptoms of liver injury.

*A complete list of information is available in the product's Prescribing Information.

obinutuzumab (Gazyva) in November 2013, ibrutinib (Imbruvica) in February 2014, and a new use for ofatumumab (Arzerra) in April 2014 to treat CLL. Zydelig is the latest drug approved for CLL.

Indications and Use. Zydelig (Zye-DEL-ig) is approved for treatment of patients with relapsed CLL, in combination with rituximab (Rituxan), in patients for whom rituximab alone would be considered appropriate therapy due to other co-morbidities; treatment of patients with relapsed follicular B-cell non-Hodgkin lymphoma (FL) who have received at least two prior systemic therapies; and in persons with relapsed small lymphocytic lymphoma (SLL) who have received at least two prior systemic therapies. As was the case with belinostat, accelerated approval was granted for FL and SLL based on overall response rate. Improvement in patient survival or disease-related symptoms has not been established. Continued approval for these indications may be contingent upon verification of clinical benefit in confirmatory trials.

Relapsed Chronic Lymphocytic Leukemia. CLL is a neoplasm resulting from progressive accumulation of functionally incompetent monoclonal B-lymphocytes in blood, bone marrow, lymph nodes, spleen, and liver. It is the most prevalent adult leukemia in the Western world, with approximately 100,000 patients living with the disease in the United States. It was estimated that more than 15,000 men and women would be diagnosed with CLL, and approximately 4,500 would die from it in 2014. The median age of patients with CLL at diagnosis is between 67 and 72 years; two-thirds of cases are diagnosed among those aged ≥65 years. It is more common in males than females.

The clinical course of CLL is extremely heterogeneous. Some patients will live for decades and never require treatment, while others require immediate treatment. A major focus of research has been to identify those clinical and biologic factors that influence the clinical course of the neoplasm, to help determine whether patients will have indolent (slow to develop, inactive or relatively benign) disease or rapid progression, and which patients will respond best to which treatment.

Standard therapy has included combinations of purine analogues, alkylating agents, and monoclonal antibodies. In younger patients without major coexisting illnesses, these regimens can provide high response rates of durable length, but cause substantial toxicity. As a result, these treatments often have unacceptable adverse effects in older patients and those with coexisting illnesses.

Patients with relapsed CLL often have limited options because of development of resistance to, or persisting toxicity of, previous therapies. This is particularly true for elderly patients and those with coexisting illnesses. Rituximab is commonly used in such patients, although it is not approved as monotherapy. Rates of response to rituximab vary, and the duration of progression-free survival is generally short.

The phosphoinositide 3-kinase (PI3K) signal transduction pathway is highly active in tumors and is responsible for many of the hallmarks of cancer. Signaling through the B-cell receptor is mediated, in part, by activation of the delta isoform of phosphatidylinositol 3-kinase (PI3Kδ), one of four catalytic isoforms (alpha, beta, gamma, and delta) that differ in their tissue expression. The delta isoform is highly expressed in lymphoid cells and the most critical isoform involved in the malignant phenotype in CLL.

Mechanism of Action. Idelalisib is a potent, highly selective, orally bioavailable small molecule that inhibits PI3Kδ, which is expressed in normal and malignant B-cells. Idelalisib induces apoptosis (natural cell death) and inhibits proliferation in cell lines derived from malignant B-cells and in primary tumor cells. Treatment of lymphoma cells with idelalisib results in inhibition of chemotaxis and adhesion, and reduces cell viability.

Efficacy and Safety. Safety and efficacy to treat relapsed CLL were established in a clinical trial of 220 patients who were randomly assigned to receive Zydelig and rituximab, or placebo and rituximab. The trial was terminated early for efficacy following the first pre-specified interim analysis point that showed participants treated with Zydelig and rituximab had the possibility of living at least 10.7 months without disease progression, compared to about 5.5 months for participants treated with placebo and rituximab. Results from a second interim analysis continued to show a statistically significant improvement for Zydelig and rituximab over placebo plus rituximab.

Safety and efficacy to treat relapsed FL and relapsed SLL were established in a clinical trial involving 123 participants with indolent non-Hodgkin lymphoma. All participants were treated with Zydelig and evaluated for complete

Table 3
Patient information for Zydelig*

Inform patients:
- to read the FDA-approved *Medication Guide* supplied with each new and refilled prescription;
- that the drug may cause severe diarrhea or colitis and to notify their physician immediately if the number of bowel movements increases by six or more daily;
- that the drug may cause severe skin reactions, intestinal perforation, pneumonitis, neutropenia, and anaphylaxis, and to notify their physician immediately if they develop signs or symptoms of these conditions;
- (women of childbearing age) to avoid pregnancy during treatment with Zydelig and to not breastfeed while taking the drug. If contraceptive methods are being considered, advise the use of adequate contraception during therapy and for at least one month after completion of therapy;
- to take Zydelig exactly as prescribed and not to change the dose or to stop taking the drug unless told to do so by their physician;
- to swallow Zydelig tablets whole;
- that if a dose is missed by less than six hours, to take the missed dose right away and take the next dose as regularly scheduled;
- that if a dose is missed by more than six hours, wait and take the next dose as regularly scheduled.

*A complete list of information is available in the product's *Medication Guide*.

or partial disappearance of their cancer after treatment (overall response rate, or ORR). Outcomes revealed that 54 percent of participants with relapsed FL and 58 percent of participants with SLL experienced ORR.

Zydelig carries a **Boxed Warning** alerting patients and health care professionals of fatal and serious toxicities including hepatotoxicity, severe diarrhea and colitis, pneumonitis, and intestinal perforation that can occur in Zydelig-treated patients. Common adverse effects include diarrhea, pyrexia, fatigue, nausea, cough, pneumonia, abdominal pain, chills, rash, neutropenia, hypertriglyceridemia, hyperglycemia, ALT elevations, and AST elevations.

Warnings, Precautions, and Contraindications. The following **warnings** and **precautions** are listed:

- *Fatal and/or serious hepatotoxicity*: Avoid concurrent use of Zydelig with other drugs that may cause hepatotoxicity.
- *Severe diarrhea or colitis*: Avoid concurrent use of Zydelig and other drugs that cause diarrhea.
- *Fatal and serious pneumonitis*: If pneumonitis is suspected, interrupt Zydelig until the etiology of pulmonary symptoms has been determined.
- *Severe cutaneous reactions*: Monitor patients for development of severe cutaneous reactions and discontinue Zydelig.
- *Intestinal perforation*: Discontinue Zydelig permanently in patients who experience intestinal perforation.
- *Anaphylaxis*: Monitor patients for anaphylaxis and discontinue Zydelig.
- *Neutropenia*: Monitor blood counts at least every two weeks for the first three months of therapy.
- *Embryo-fetal toxicity*: The drug may cause fetal harm. Advise women of potential risk to a fetus, and to avoid pregnancy while taking it.

The only **contraindication** noted is a history of serious allergic reactions including anaphylaxis and toxic epidermal necrolysis.

Drug Interactions. The AUC of idelalisib was reduced by 75 percent when coadministered with a strong CYP3A inducer; therefore, avoid coadministration with strong CYP3A inducers such as rifampin, phenytoin, St. John's wort, or carbamazepine. The AUC of idelalisib was increased 1.8-fold when coadministered with a strong CYP3A inhibitor. Zydelig is a strong CYP3A inhibitor, so avoid coadministration of CYP3A substrates.

Administration, Dosing, and Availability. The recommended starting dose is 150 mg orally, twice daily. Zydelig is available in 100 mg and 150 mg tablets.

Patient Counseling. An FDA-approved *Medication Guide* must be dispensed with each new or refilled prescription for Zydelig. Specific points for counseling are summarized in Table 3.

Empagliflozin (Jardiance)

Type 2 diabetes mellitus (T2DM) affects approximately 26 million people, and accounts for more than 90 percent of diabetes cases diagnosed in the United States. This has resulted in an increase in T2DM drug development. While numerous categories of new drugs have been introduced that represent novel mechanisms for treating this disorder, the sodium glucose co-transporter 2 (SGLT2) inhibitors are especially prominent. Empagliflozin is the third SGLT2 inhibitor approved since March 2013, with canagliflozin (Invokana) and dapagliflozin (Farxiga) preceding it.

Indications and Use. Jardiance (jar-DEE-ans) is indicated as an adjunct to diet and exercise to improve glycemic control in adults with Type 2 diabetes mellitus. It is not approved for treatment of Type 1 diabetes mellitus or diabetic ketoacidosis.

Type 2 Diabetes Mellitus. Evidence clearly links T2DM with multisystem complications and comorbidities. These include nephropathy and peripheral neuropathy; glaucoma, cataracts, and retinopathy; bacterial and fungal infections, and other dermatologic conditions; cardiovascular and cerebrovascular disease, myocardial infarction, and stroke; digestive problems; sexual dysfunction; periodontal disease; and depression. Diet modification and physical exercise are always the first steps to lower blood glucose and, thus, reduce the incidence of these comorbidities in patients with T2DM. In the UK Prospective Diabetes Study, intensive treatment with metformin, sulfonylureas, or insulin resulted in only a limited improvement in glycemic control over 10 years, compared with

dietary modification alone, with a significant loss in glycemic control over time. Use of other therapies may also be limited by clinically significant side effects such as hypoglycemia, weight gain, and edema. These limitations clearly indicate a need for additional antihyperglycemic therapeutic options for patients with T2DM.

The SGLT2 is located in the brush border membrane of the nephron proximal convoluted tubule, and is the predominant transporter responsible for 80 to 90 percent of glucose resorption from the glomerular filtrate. Under normoglycemic conditions, glucose is completely reabsorbed by SGLT2 in the kidney. However, the reuptake capacity of the kidney is saturated at glucose concentrations of approximately 11 mmol/L, resulting in glucosuria. This threshold concentration can be decreased by inhibition of SGLT2.

Mechanism of Action. Empagliflozin is an inhibitor of SGLT2, and the drug reduces renal resorption of filtered glucose, thus lowering the renal threshold for glucose, and thereby increasing urinary glucose excretion.

Efficacy and Safety. Safety and effectiveness were evaluated in seven clinical trials totaling 4,480 patients with T2DM. The pivotal trials showed that the drug improved hemoglobin A1c levels. The drug has been studied as monotherapy and in combination with other T2DM therapies including metformin, sulfonylureas, pioglitazone, and insulin.

FDA is requiring four postmarketing studies:

- completion of an ongoing cardiovascular outcomes trial;
- a pediatric pharmacokinetic/pharmacodynamic study;
- a pediatric safety and efficacy study. As part of the safety and efficacy study, the effect on bone health and development will be evaluated; and
- a nonclinical (animal) juvenile toxicity study with a particular focus on renal development, bone development, and growth.

Empagliflozin can cause dehydration leading to hypotension that can result in dizziness and/or fainting and a decline in renal function. Elderly patients with impaired renal function, and patients on diuretics to treat other conditions, appear to be more susceptible to this risk.

Warnings, Precautions, and Contraindications. The following **warnings** and **precautions** are listed:

- *Hypotension*: Before initiating Jardiance, assess and correct volume status in patients with renal impairment, in the elderly, in patients with low systolic blood pressure, and in patients on diuretics. Monitor for signs and symptoms of hypotension during therapy.
- *Impairment in renal function*: Monitor renal function during therapy. More frequent monitoring is recommended in patients with eGFR below 60 mL/min/1.73 m^2.
- *Hypoglycemia*: Consider lowering the dose of insulin secretagogue or insulin to reduce the risk of hypoglycemia when initiating Jardiance.
- *Genital mycotic infections*: Monitor and treat as appropriate.
- *Urinary tract infections*: Monitor and treat as appropriate.
- *Increased LDL-C*: Monitor and treat as appropriate.
- *Macrovascular outcomes*: There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with Jardiance.

Two **contraindications** are listed: (1) history of serious hypersensitivity reaction to Jardiance, and (2) severe renal impairment, end-stage renal disease, or dialysis.

Drug Interactions. Coadministration of empagliflozin with diuretics may result in increased urine volume and frequency of voids, which might enhance the potential for volume depletion. Coadministration with insulin or insulin secretagogues increases the risk for hypoglycemia.

Administration, Dosing, and Availability. The recommended dose is 10 mg once daily, taken in the morning with or without food. Dosage may be increased to 25 mg once daily in patients who tolerate the drug. Assess renal function before initiating empagliflozin. Do not initiate the drug if eGFR is below 45 mL/min/1.73 m^2. Discontinue the drug if eGFR falls persistently below 45 mL/min/1.73 m^2. Jardiance is marketed in 10 mg and 25 mg tablets.

Patient Counseling. Specific points for patient counseling are summarized in Table 4.

Table 4
Patient information for Jardiance*

Inform patients:
- to read the Patient Information brochure before starting the drug and to reread it each time the prescription is refilled;
- of potential risks and benefits of Jardiance, as well as the importance of adherence to dietary instructions and regular physical activity;
- to take Jardiance only as prescribed; if a dose is missed, to take it as soon as the patient remembers. Patients should not double their next dose;
- that urinary tract infections and mycotic genital infections are the most common adverse reactions; and advise them on symptoms of those infections;
- that hypotension may occur, and to contact their physician if they experience symptoms;
- (women of childbearing age) that the use of Jardiance has not been studied in humans during pregnancy, so they should report pregnancy to their physician as soon as possible. Nursing mothers should discontinue Jardiance or nursing if possible;
- that renal function should be assessed prior to initiation of Jardiance and be monitored periodically thereafter, and that elevated glucose in urinalysis is expected when taking Jardiance.

*A complete list of information is available in the product's Prescribing Information.

Suvorexant (Belsomra)

A number of treatment options are available for insomnia. The most common interventions are

benzodiazepines and the non-benzodiazepine gamma-aminobutyric acid (GABA)-acting hypnotics such as zolpidem (Ambien), eszopiclone (Lunesta), and zaleplon (Sonata). Other less popular agents include sedating antidepressants, melatonin agonists, and antihistamines. Diminished efficacy and negative side effects restrict long-term use of these treatment options for many patients. Suvorexant is the first in a new class of pharmacologic agents aimed at treating insomnia.

Indications and Use. Belsomra (bell-SOM-rah) is indicated for the treatment of insomnia, characterized by difficulties with sleep onset and/or sleep maintenance.

Insomnia. Nearly one-third of all adults in the United States report difficulties with sleep (reported as insomnia, a condition characterized by difficulty falling asleep, maintaining sleep, waking early, or experiencing nonrestorative sleep).

Daytime consequences of insomnia include fatigue, inattention, and difficulty with school or work. Insomnia is more prevalent in women and older adults, and is common in people with depression, anxiety, dementia, substance abuse, and other psychiatric disorders.

Irregular bedtimes and heavy caffeine and alcohol use contribute to insomnia as well. It also occurs with situations that disrupt sleep such as pain, sleep apnea, restless legs syndrome, and circadian rhythm disorders in which the internal body clock is out of synchrony with the desired bedtime. In 1995, the direct costs attributable to insomnia in the United States were estimated at $14 billion per year, with $2 billion spent on medications. Costs today are likely to be much higher.

In 1998, two groups searching for new signaling molecules independently discovered the orexin neuropeptides and their receptors. One group named these peptides orexin-A and -B because they were originally believed to promote feeding (the term *orexin* comes from orexis, Greek for appetite). The other team named the peptides hypocretin-1 and -2 because they are produced in the hypothalamus and bear some similarities to the incretin family of peptides. Over the past decade, it has become clear that, although the orexin peptides have only a modest influence on feeding and appetite, their effects on arousal and sleep are profound. In fact, narcolepsy, one of the causes of excessive daytime sleepiness, is caused by a loss of the orexin-producing neurons, and this has fueled a strong interest in developing orexin antagonists as a novel approach for promoting sleep and treating insomnia.

Mechanism of Action. The means by which suvorexant exerts its therapeutic effect in insomnia is presumed to be through the antagonism of both orexin-A and -B receptors. Blocking the binding of wake-promoting neuropeptides orexin-A and orexin-B to their receptors is thought to suppress wakefulness. Antagonism of orexin receptors may also underlie potential adverse effects such as signs of narcolepsy/cataplexy.

Efficacy and Safety. Effectiveness and safety were studied in three clinical trials involving more than 500 participants. In the studies, patients taking suvorexant fell asleep faster and spent less time awake during the remainder of the night compared to those taking placebo. Belsomra was not compared to other drugs approved to treat insomnia, so it is not known if there are differences in safety or effectiveness.

Like other sleep medications, there is a risk from suvorexant of sleep-driving and other complex behaviors while not being fully awake. The chance of such activity increases if a person has consumed alcohol or taken other medications that cause drowsiness.

Abuse of suvorexant poses an increased risk of somnolence, daytime sleepiness, decreased reaction time and impaired driving skills. Patients at risk for abuse may include those with prolonged use of suvorexant, those with a history of drug abuse, and persons who use suvorexant along with alcohol or other drugs of abuse. Suvorexant is a controlled substance (Schedule IV).

Since the orexin system mainly promotes wakefulness, orexin antagonists such as suvorexant have the potential to selectively promote sleep and cause fewer side effects. Suvorexant dependence and abuse should be less of a concern, as animal studies have revealed that orexin antagonists actually reduce drug seeking. Imbalance and falls should not be a major problem, as there is no evidence that the orexin system affects balance or gait directly. Orexin antagonists should not significantly depress respiration or affect blood pressure. Moreover, because orexin antagonists have a novel mechanism of action, they have the potential to improve insomnia in patients who have found other agents ineffective.

Warnings, Precautions, and Contraindications. The following **warnings** and **precautions** are listed:

• *Daytime somnolence*: Risk of impaired alertness and motor coordination, including impaired driving; risk increases with dose; caution patients taking 20 mg about next-day driving and other activities requiring mental alertness. CNS depressant effects may persist in some patients for up to several days after discontinuing Belsomra. Individuals can be impaired even when they feel fully awake.

• *Need to evaluate for co-morbid diagnoses*: Failure of insomnia to remit after seven to 10 days of treatment may indicate the presence of a primary psychiatric and/or medical illness that should be evaluated. Re-evaluate if insomnia persists after seven to 10 days of treatment.

• *Nighttime "sleep-driving" and other complex behaviors while out of bed and not fully awake*. Risk increases with dose, with use of CNS depressants, and with alcohol. Patients taking even the lower dose (i.e., 5 mg) of Belsomra should also

Table 5
Patient information for Belsomra*

Inform patients:
- to read the FDA-approved *Medication Guide* supplied with each new or refilled prescription;
- that Belsomra can cause next-day impairment, and that this risk is increased with higher doses or if dosing instructions are not followed carefully;
- to not drive or engage in other activities requiring full alertness within 8 hours of dosing;
- to inform their families that Belsomra has been associated with getting out of bed while not being fully awake. Tell patients (and their families) to call their physician if this occurs;
- that hypnotics, like Belsomra, have been associated with "sleep-driving" and other complex behaviors while not being fully awake (e.g., preparing and eating food, making phone calls, or having sex). Tell patients and their families to call their physician if they develop any of these symptoms;
- to report any worsening of depression or suicidal thoughts immediately;
- to not drink alcohol with Belsomra;
- to take Belsomra only when preparing for or getting into bed, and only if they can stay in bed for a full night before resuming activity;
- to report all of their prescription and nonprescription medicines, vitamins and herbal supplements to their physician.

*A complete list of information is available in the product's FDA-approved *Medication Guide*.

be forewarned about the potential for this problem because there is individual variation in sensitivity to the drug.

- *Depression*: Worsening of depression or suicidal thoughts may occur. Risk increases with dose. Immediately evaluate any new behavioral changes.
- *Compromised respiratory function*: Effect on respiratory function should be considered.
- *Sleep paralysis, hypnagogic/hypnopompic hallucinations, and cataplexy-like symptoms*: Risk increases with dose.

The only **contraindication** is use in patients with narcolepsy.

Drug Interactions. Metabolism by CYP3A is the major elimination pathway for suvorexant. Concomitant use of the new drug with strong inhibitors of CYP3A (e.g., ketoconazole, itraconazole, posaconazole, clarithromycin, nefazodone, ritonavir, saquinavir, nelfinavir, indinavir, boceprevir, telaprevir, telithromycin, and conivaptan) is not recommended. The dose of Belsomra is 5 mg in subjects receiving moderate CYP3A inhibitors (e.g., amprenavir, aprepitant, atazanavir, ciprofloxacin, diltiazem, erythromycin, fluconazole, fosamprenavir, grapefruit juice, imatinib, verapamil). Dosage may be increased to 10 mg in these patients if necessary for efficacy. Suvorexant exposure can be substantially decreased when coadministered with strong CYP3A inducers (e.g., rifampin, carbamazepine, phenytoin).

Administration, Dosing, and Availability. The lowest effective dose should be used. Recommended dosage is 10 mg, no more than once per night taken within 30 minutes of going to bed, with at least seven hours remaining before the planned time of awakening. If the 10 mg dose is well-tolerated but not effective, the dose can be increased, but not to exceed 20 mg once daily. Time of onset may be delayed if taken with or soon after a meal.

Suvorexant exposure is increased in obese compared to non-obese patients, and in women compared to men. Particularly in obese women, the increased risk of exposure-related adverse effects should be considered before increasing the dose.

To assist physicians and patients in finding the best dose to treat insomnia, Belsomra tablets are available in four strengths: 5 mg, 10 mg, 15 mg, and 20 mg.

Patient Counseling. An FDA-approved *Medication Guide* must be dispensed with each new or refilled prescription for Belsomra. Specific points for counseling are summarized in Table 5.

Overview and Summary

These four newly-approved drugs, although indicated for a variety of clinical applications, share one thing in common. They all offer new therapeutic options for their respective FDA-approved indications. Clinical trial data for each of these agents have demonstrated safety and efficacy. Safe and effective use of these medications is achievable with appropriate patient counseling.

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This lesson is a knowledge-based CPE activity and is targeted to pharmacists in all practice settings.

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continuing education quiz

New Drugs: Beleodaq, Belsomra, Jardiance, and Zydelig

1. All of the following are true about PTCL neoplasms EXCEPT:
   a. they are rare and fast-growing.
   b. they account for 25% of non-Hodgkin lymphomas in the Western hemisphere.
   c. anthracyclines are widely used first-line.
   d. they have a poor prognosis compared to B-cell lymphomas.

2. Belinostat is a potent inhibitor of:
   a. CD20 antibody expression.
   b. kinase autophosphorylation.
   c. histone deacetylase enzymes.
   d. phosphatidylinositol 3-kinase.

3. All of the following are warnings/precautions for Beleodaq EXCEPT:
   a. GI toxicity.
   b. hepatotoxicity.
   c. embryo-fetal toxicity.
   d. end-stage renal disease.

4. Zydelig is approved for treatment of CLL in combination with:
   a. doxorubicin.
   b. ibrutinib.
   c. rituximab.
   d. methotrexate.

5. Which of the following is the most critical isoform of PI3K in the malignant phenotype of CLL?
   a. Alpha
   b. Beta
   c. Gamma
   d. Delta

6. The recommended starting dose for Zydelig is:
   a. 25 mg twice a day.
   b. 50 mg twice a day.
   c. 150 mg twice a day.
   d. 200 mg twice a day.

7. All of the following are true about the sodium glucose cotransporter 2 (SGLT2) EXCEPT:
   a. it is located in the proximal convoluted tubules of the nephron.
   b. it is responsible for 80-90% of glucose resorption.
   c. inhibition lowers the renal threshold for glucose.
   d. empagliflozin is the only SGLT2 inhibitor.

Completely fill in the lettered box corresponding to your answer.

1. [a] [b] [c] [d]	6. [a] [b] [c] [d]	11. [a] [b] [c] [d]
2. [a] [b] [c] [d]	7. [a] [b] [c] [d]	12. [a] [b] [c] [d]
3. [a] [b] [c] [d]	8. [a] [b] [c] [d]	13. [a] [b] [c] [d]
4. [a] [b] [c] [d]	9. [a] [b] [c] [d]	14. [a] [b] [c] [d]
5. [a] [b] [c] [d]	10. [a] [b] [c] [d]	15. [a] [b] [c] [d]

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2. Did it meet each of its objectives? ❑ yes ❑ no
   If no, list any unmet_____
3. Was the content balanced and without commercial bias?
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8. The most common adverse reactions associated with empagliflozin are:
   a. depression and suicidal thoughts.
   b. dry skin and pruritic dermatitis.
   c. elevated LDL-C and triglycerides.
   d. urinary tract infections and mycotic genital infections.

9. All of the following are true about T2DM EXCEPT:
   a. it affects approximately 36 million people in the U.S.
   b. it accounts for more than 90% of diabetes cases in the U.S.
   c. it is linked with multisystem complications and comorbidities.
   d. diet modification and physical exercise are first steps to controlling T2DM.

10. Which of the following is appropriate patient counseling for Belsomra?
   a. Do not drink alcohol with Belsomra.
   b. Avoid sunshine and fluorescent lights.
   c. Nursing mothers should not use Belsomra.
   d. Adhere to dietary and physical activity instructions.

11. Which of the following drugs can cause dehydration leading to hypotension?
   a. Belinostat
   b. Suvorexant
   c. Empagliflozin
   d. Idelalisib

12. The following drug acts by antagonizing orexin receptors.
   a. Belinostat
   b. Suvorexant
   c. Empagliflozin
   d. Idelalisib

13. Which of the following is classed as Schedule IV?
   a. Belinostat
   b. Suvorexant
   c. Empagliflozin
   d. Idelalisib

14. No contraindication is listed for:
   a. Beleodaq.
   b. Belsomra.
   c. Jardiance.
   d. Zydelig.

15. Zydelig's label includes a boxed warning for fatal and serious toxicities of all of the following EXCEPT:
   a. hepatotoxicity.
   b. intestinal perforation.
   c. pneumonitis.
   d. nephrotoxicity.

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