Depressive symptoms reduced with select adjunctive nutraceuticals

Key Point

Augmented antidepressant activity is observed with use of adjunctive nutraceuticals such as S-adenosylmethionine (SAMe), methylfolate, omega-3, and vitamin D with antidepressants, according to results of a systematic review and meta-analysis published online in the American Journal of Psychiatry.

Source URL:

Focus on Asthma Care

Advising on this article: Devra K. Dang

June 7, 2016

New first-in-class treatment effective for uncontrolled persistent asthma

Key Point

Use of the investigational agent dupilumab, an interleukin-4 and -13 inhibitor, resulted in improved lung function and reduced severe exacerbations in patients with uncontrolled persistent asthma irrespective of baseline eosinophil count, according to results of a study published online in The Lancet.

Source URL:
http://www.aphadruginfoline.com/focus-asthma-care/new-first-class-treatment-effective-uncontrolled-persistent-asthma
Focus on HIV Care

Advising on this article: Betty Dong

June 14, 2016

Updated nonoccupational HIV postexposure prophylaxis guidelines released

Key Point

CDC released an updated guideline for use of antiretrovirals in nonoccupational postexposure prophylaxis (nPEP) after sexual, injection drug use, or other nonoccupational exposure to HIV. This update incorporated information about new rapid HIV diagnostic tests and new antiretroviral medications.

Source URL:

Endocrinology

Advising on this article: Frank Pucino

June 14, 2016

Testosterone effects and duration of exposure

Key Point

Long-term exposure of testosterone replacement therapy was associated with a lower risk of death, cardiovascular (CV) events, and prostate cancer, whereas shorter durations of therapy increased the risk of death and CV events, according to results of an observational cohort study published online in The Lancet Diabetes and Endocrinology.

Source URL:

SPRINT analysis suggests lower systolic BP is better in older adults

Key Point

Results from a subgroup analysis from the SPRINT (Systolic Blood Pressure Intervention Trial) trial showed that lowering systolic blood pressure (SBP) to less than 120 mm Hg compared with less than 140 mm Hg in patients aged 75 years or older at increased cardiovascular (CV) risk resulted in a 34% reduction in risk of select CV events.

Source URL:
http://www.aphadruginfoline.com/cardiology/sprint-analysis-suggests-lower-systolic-bp-better-older-adults
In patients with chronic obstructive pulmonary disease (COPD) and a history of exacerbations in the previous year, use of inhaled indacaterol–glycopyrronium resulted in fewer exacerbations compared with salmeterol–fluticasone (Advair—GlaxoSmithKline), according to results of the FLAME (Effect of Indacaterol Glycopyrronium vs. Fluticasone Salmeterol on COPD Exacerbations) study published in the New England Journal of Medicine.

Source URL:
**Drug Interactions Corner**

Advising on this article: Daniel S. Streetman

**June 27, 2016**

**Bleeding risk increased with concurrent use of warfarin and ginkgo**

**Key Point**

Risk of bleeding increased almost 40% in patients taking concurrent warfarin and ginkgo biloba, according to an analysis of a large Veterans Administration database.

**Source URL:**

Focus on Diabetes Care

Advising on this article: Charles D. Ponte

June 27, 2016

Hypoglycemia risk increases when a DPP-4 inhibitor is given with a sulfonylurea

Key Point

The risk of hypoglycemia increases substantially when a dipeptidyl peptidase-4 (DPP-4) inhibitor is given with a sulfonylurea, emphasizing the need to reduce the sulfonylurea dose and educate patients about this increased risk when combination therapy is given.

Source URL:

### Alerts and Recalls

<table>
<thead>
<tr>
<th>Generic Name (Trade Name—Company)</th>
<th>Uses/Notes</th>
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<tbody>
<tr>
<td>June 2, 2016</td>
<td></td>
</tr>
<tr>
<td><strong>Sumatriptan iontophoretic transdermal system</strong> (Zecuity—Teva Pharmaceuticals)</td>
<td>FDA is investigating the risk of serious burns and potential permanent scarring with use of the sumatriptan iontophoretic transdermal system patch for migraine headaches.</td>
</tr>
<tr>
<td>FDA evaluating risk of burns and scars with use of patch for migraines</td>
<td>Since marketing of the patch began in September 2015, a large number of patients have reported they experienced burns or scars on the skin where the patch was worn. The reports included descriptions of severe redness, pain, skin discoloration, blistering, and cracked skin. As a result, FDA is investigating these serious adverse events to determine whether future regulatory action is needed and will update the public with new information when the review is complete. The patch contains the active ingredient sumatriptan, a prescription medication used to treat acute migraine headaches in adults. The patch delivery system is designed to deliver a dose of medicine by way of a single-use, battery-powered patch that is wrapped around the upper arm or thigh. It should remain in place for no longer than 4 hours. Health professionals should advise patients who experience moderate to severe pain at the patch site to remove it immediately to avoid possible burns or scarring, regardless of how long the patch has been worn, and contact their health professional. Patients should not bathe, shower, or swim while wearing the patch. Health professionals should consider a different formulation of sumatriptan or patients to an alternative migraine medication.</td>
</tr>
</tbody>
</table>

**Source URL:**

### Alerts and Recalls

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<tr>
<th>Generic Name (Trade Name—Company)</th>
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<tr>
<td>June 7, 2016</td>
<td><strong>Multiple generic names</strong></td>
</tr>
</tbody>
</table>

**FDA is warning consumers** about the risk of serious bleeding when using nonprescription OTC aspirin-containing antacid products to treat heartburn, sour stomach, acid indigestion, or upset stomach. Many other products for these conditions are available that do not contain aspirin.

These widely used products already contain **warnings** about this bleeding risk on their labels; however, FDA continues to receive reports of this serious safety issue. As a result, the agency will continue to evaluate this safety concern and plan to convene an advisory committee of external experts to provide input on whether additional FDA actions are needed.

OTC aspirin-antacid products are sold under various trade names, including Alka-Seltzer Original, Bromo Seltzer, Medique Medi Seltzer, Picot Plus Effervescent, Vida Mia Pain Relief, Winco Foods Effervescent Antacid and Pain Relief, and Zee-Seltzer Antacid and Pain Reliever. They are also available as generic products.

Consumers should always read the **Drug Facts label** carefully when purchasing or taking an OTC product to treat heartburn, acid indigestion, or sour or upset stomach. If the product contains aspirin, patients are urged to consider whether to choose a product without aspirin to relieve symptoms.

Patients who have one or more of the following risk factors may have a higher chance of serious bleeding when taking aspirin-containing antacid products: aged 60 years or older; have a history of stomach ulcers or bleeding problems; take a blood-thinning or steroid medicine; take other medicines containing NSAIDs, such as ibuprofen or naproxen; or drink three or more alcoholic drinks every day.

Taking more of these medicines than the amount recommended or for a longer period than recommended will increase the risk of serious bleeding.

In 2009, a **warning** about the risk of serious bleeding...
was added to the labels of all OTC products that contain NSAIDs, including aspirin-containing antacid products. However, a search of the FDA Adverse Event Reporting System (FAERS) database identified eight cases of serious bleeding events associated with these products after the warning was added. All of these patients were hospitalized. Patients had underlying conditions such as the risk factors above that put them at greater risk for developing serious bleeding events (see Data Summary). The FAERS database includes only reports submitted to FDA, so there are likely additional cases about which FDA is unaware, the agency noted.

Source URL:
Alerts and Recalls

June 7, 2016

Loperamide

(Imodium—Multiple companies)

FDA warns of serious heart problems with high doses

FDA is warning that taking higher than recommended doses of the common OTC and prescription diarrhea medication loperamide, including through abuse or misuse of the product, can cause serious heart problems that can lead to death. The risk of these serious heart problems, including abnormal heart rhythms, may also be increased when high doses of loperamide are taken with several kinds of medications that interact with loperamide (see Examples of Drugs that Can Potentially Interact with Loperamide in the FDA Drug Safety Communication).

The majority of reported serious heart problems occurred in individuals who were intentionally misusing and abusing high doses of loperamide in attempts to self-treat opioid withdrawal symptoms or to achieve a feeling of euphoria. FDA continues to evaluate this safety issue and will determine if additional FDA actions are needed.

Health professionals should be aware that use of higher than recommended doses of loperamide can result in serious cardiac adverse events. Consider loperamide as a possible cause of unexplained cardiac events including QT interval prolongation, Torsades de Pointes or other ventricular arrhythmias, syncope, and cardiac arrest.

In cases of abuse, individuals often use other drugs together with loperamide in attempts to increase its absorption and penetration across the blood–brain barrier, inhibit loperamide metabolism, and enhance its euphoric effects. If loperamide toxicity is suspected, promptly discontinue the drug and start necessary therapy. If loperamide ingestion is suspected, measure blood levels, which may require specific testing.

For some cases of Torsades de Pointes in which drug treatment is ineffective, electrical pacing or cardioversion may be required. Health professionals are encouraged to refer patients with opioid use disorders for treatment.

Source URL:
June 21, 2016

**Cholera vaccine**

*(Vaxchora—PaxVax Bermuda Ltd.)*

FDA approves vaccine to prevent cholera for travelers

FDA has approved Vaxchora, a vaccine for the prevention of cholera caused by serogroup O1, for adults aged 18 through 64 years who are traveling to cholera-affected areas. Vaxchora is the only FDA-approved vaccine for the prevention of cholera.

The live, weakened vaccine is taken as a single, oral liquid dose of approximately 3 fluid oz. at least 10 days before travel to a cholera-affected area.

The most common adverse reactions reported by vaccine participants in clinical trials were tiredness, headache, abdominal pain, nausea/vomiting, lack of appetite, and diarrhea.

Source URL:

Alerts and Recalls

Generic Name (Trade Name—Company)  
June 21, 2016

Canagliflozin, dapagliflozin  
(Multiple trade names—Multiple companies)

FDA strengthens kidney warnings for diabetes medications

Uses/Notes

FDA has strengthened the existing warning in the drug labels about the risk of acute kidney injury for the type 2 diabetes medications canagliflozin and dapagliflozin.

Health professionals should consider factors that may predispose patients to acute kidney injury before starting them on canagliflozin or dapagliflozin. These include decreased blood volume; chronic kidney insufficiency; congestive heart failure; and taking other medications, such as diuretics, blood pressure medications (angiotensin-converting enzyme inhibitors and angiotensin receptor blockers), and NSAIDs. Assess kidney function before starting canagliflozin or dapagliflozin, and monitor periodically thereafter. If acute kidney injury occurs, promptly discontinue the drug and treat the kidney impairment.

Patients should seek medical attention immediately if they experience signs and symptoms of acute kidney injury. Signs and symptoms of acute kidney injury may include decreased urine or swelling in the legs or feet. Patients should not stop taking their medication without first talking to their health professionals. Doing so can lead to uncontrolled blood glucose levels that can be harmful.

From March 2013, when canagliflozin was approved, to October 2015, FDA received reports of 101 confirmable cases of acute kidney injury, some requiring hospitalization and dialysis, with canagliflozin or dapagliflozin use. This number includes only reports submitted to FDA, so there are likely additional cases about which the agency is unaware.

In approximately one-half of the cases, the events of acute kidney injury occurred within 1 month of starting the drug, and most patients improved after stopping it. Some cases occurred in patients who were younger than 65 years. Some patients were dehydrated, had low blood pressure, or were taking other medications that can affect the kidneys.

Source URL:
Supplemental Approvals

Generic Name (Trade Name—Company)
June 22, 2016
Calcifediol
(Rayaldee—Opko Health)
Agent can now be used to treat secondary hyperparathyroidism

Uses/Notes

FDA has approved calcifediol modified-release capsules, an oral vitamin D prohormone treatment for secondary hyperparathyroidism (SHPT) in patients with stage 3 or 4 chronic kidney disease (CKD) and vitamin D insufficiency.

Approval was based on data from three randomized, double-blind, placebo-controlled studies and one open-label extension study conducted in the targeted patient population.

The modified-release formulation was designed to gradually and reliably raise serum total 25-hydroxyvitamin D (prohormone) concentrations to targeted levels (at least 30 ng/mL) while avoiding upregulation of CYP24A1, a cytochrome P450 enzyme that interferes with the desired parathyroid hormone (PTH)–lowering effect. Gradual elevation of serum total 25-hydroxyvitamin D is intended to prevent excessive elevation of serum calcium and related vascular and renal calcification.

SHPT is a condition commonly associated with CKD in which the parathyroid glands secrete excessive amounts of PTH. SHPT arises as a result of vitamin D insufficiency or impaired kidney function that prevents sufficient production of vitamin D hormone to properly regulate calcium and phosphorus metabolism, and PTH secretion. Prolonged elevation of blood PTH causes excessive calcium and phosphorus to be released from bone, leading to elevated serum calcium and phosphorus, softening of the bones and calcification of vascular and renal tissues. SHPT affects 40% to 60% of patients with moderate CKD and approximately 90% of patients with severe CKD.

Source URL:
http://www.aphadruginfoline.com/supplemental-approvals/agent-can-now-be-used-treat-secondary-hyperparathyroidism
Sofosbuvir/velpatasvir

*(Epclusa—Gilead Sciences)*

First agent to treat all six major forms of HCV receives FDA approval

**June 28, 2016**

**FDA approved** a fixed-dose combination tablet containing sofosbuvir, a drug approved in 2013, and velpatasvir, a new drug, to treat adult patients with chronic hepatitis C virus (HCV) both with and without cirrhosis.

It is the first agent to treat all six major forms of HCV.

For patients with moderate to severe cirrhosis, sofosbuvir/velpatasvir is approved for use in combination with the drug ribavirin.

Safety and efficacy of the combination agent were evaluated for 12 weeks in three Phase III clinical trials of 1,558 participants without cirrhosis or with compensated (mild) cirrhosis.

Results demonstrated that 95% to 99% of patients who received the agent had no virus detected in the blood 12 weeks after finishing treatment, suggesting the patients’ infections had been cured.

Safety and efficacy were also evaluated in a clinical trial of 267 participants with decompensated cirrhosis (moderate to severe cirrhosis), of whom 87 participants received the agent in combination with ribavirin for 12 weeks. Ninety-four percent of these patients had no virus detected in the blood 12 weeks after finishing treatment.

The agent’s most common adverse effects include headache and fatigue. The regimen for the new agent combined with ribavirin is contraindicated in patients for whom ribavirin is contraindicated.

Sofosbuvir/velpatasvir carries a warning for patients and health care providers that serious slowing of the heart rate and cases requiring pacemaker intervention have been reported when amiodarone is used with sofosbuvir in combination with another HCV direct-acting antiviral. Coadministration of amiodarone with the new agent is not recommended. The label also warns against using with certain drugs that may reduce the amount of the agent in the blood and lead to reduced efficacy.
Supplemental Approvals

Generic Name (Trade Name—Company)
June 28, 2016

Nebivolol/valsartan
(Byvalson—Allergan)

FDA approves first fixed-dose combination of beta blocker and angiotensin II receptor blocker

Uses/Notes

FDA has approved nebivolol 5-mg and valsartan 80-mg tablets, the first and only fixed-dose combination of a beta blocker and angiotensin II receptor blocker available in the United States for the treatment of hypertension.

Approval was based on a Phase III, double-blind, placebo-controlled, dose-escalating, 8-week efficacy and safety study that randomized approximately 4,100 patients with Stage 1 or 2 hypertension.

Treatment with nebivolol and valsartan for 4 weeks demonstrated statistically significant reductions from baseline in diastolic and systolic blood pressure versus either nebivolol alone or valsartan alone. The overall rate of adverse events was similar across treatment groups and placebo during this 4-week period.

Nebivolol is a beta-adrenergic receptor blocking agent that is preferentially beta-1 selective up to and including the 10-mg dose and in extensive metabolizers. While nebivolol's mechanism of action has not been definitively established, possible factors include vasodilation and decreased peripheral vascular resistance, reduced heart rate and myocardial contractility, suppression of renin, and reduced sympathetic activity.

Valsartan is an angiotensin II receptor blocker that blocks the binding of angiotensin II to the AT1 receptor in many tissues, such as vascular smooth muscle and the adrenal gland, thereby blocking its vasoconstrictor and aldosterone-secreting effects.

Allergan expects the new combination therapy to be available in the second half of 2016.

Source URL:
Gallium Ga 68 dotatate injection

Netspot, the first kit for preparation of gallium Ga 68 dotatate injection, a radioactive diagnostic agent for positron emission tomography (PET) imaging, received FDA approval on June 1, 2016. The radioactive probe helps locate somatostatin receptor–positive neuroendocrine tumors (NETs).

NETs are rare noncancerous or cancerous tumors that develop in the hormone-producing cells of the body’s neuroendocrine system. These cells are found throughout the body in organs such as the stomach, intestines, pancreas, lungs and other locations. NETs have receptors for somatostatin, a hormone that regulates the endocrine system. Ga 68 dotatate, a positron emitting analogue of somatostatin, works by binding to such receptors.

Netspot is supplied as a sterile, single-dose kit for preparation of Ga 68 dotatate injection for I.V. use. The uptake of Ga 68 dotatate reflects the level of somatostatin receptor density in NETs. This uptake can also be seen in a variety of other tumor types or other pathologic conditions or might occur as a normal variant. The uptake of Ga 68 dotatate may need to be confirmed by histopathology or other assessments.

Three studies established the safety and effectiveness of Netspot. The first compared Ga 68 dotatate images of NETs to images obtained with an approved drug, and then confirmed with computed tomography and/or magnetic resonance imaging; the second evaluated Ga 68 dotatate images using histopathology or clinical follow-up as reference standards; and the third evaluated patients with NET recurrence using Ga 68 dotatate images.

Results of all three studies confirmed the usefulness of Ga 68 dotatate images in finding the location of the neuroendocrine tumors.

Netspot contributes to overall long-term cumulative radiation exposure, and patients should drink and urinate as often as possible during the first hours following administration to help reduce this risk. No
(Netspot—Advanced Accelerator Applications USA)

New diagnostic imaging agent detects rare neuroendocrine tumors

Source URL:

Linagliptin and metformin hydrochloride extended release

(Jentadueto XR—Boehringer Ingelheim, Eli Lilly)

New once-daily combination therapy targets type 2 diabetes

A new combination agent, linagliptin and metformin hydrochloride extended-release tablets, has received FDA approval for the treatment of type 2 diabetes in adults. According to the manufacturers, the product offers adults with type 2 diabetes the convenience of a combination pill taken once a day to help lower blood glucose levels.

The product combines 2.5 mg or 5 mg of linagliptin with 1,000 mg of metformin. Linagliptin, a dipeptidyl peptidase-4 inhibitor, works by increasing hormones that stimulate the pancreas to produce more insulin and the liver to produce less glucose.

Metformin, a commonly prescribed initial treatment for type 2 diabetes, lowers glucose production by the liver and its absorption in the intestine.

It is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes when treatment with both linagliptin and metformin is appropriate. It should not be used in patients with type 1 diabetes or to treat diabetic ketoacidosis and has not been studied in people with a history of pancreatitis.

The label contains a boxed warning for the risk of lactic acidosis, a serious metabolic complication that can result from metformin accumulation during treatment.

Safety and efficacy were based on adequate and well-controlled studies of linagliptin and metformin coadministered in patients with type 2 diabetes inadequately controlled by diet and exercise and in combination with sulfonylurea.

It is the seventh new treatment from the Boehringer Ingelheim–Lilly Diabetes alliance to be approved by FDA in the past 5 years.

Source URL:
## Nitroglycerin sublingual powder

**(Gonitro—Espero Pharmaceuticals)**

Short-acting nitrate now available in single-dose packets for angina

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**Uses/Notes**

Espero Pharmaceuticals announced FDA approval of nitroglycerin sublingual powder, the first and only short-acting nitrate in a stabilized crystal granule form available in portable single-dose packets, each containing 400 mcg of nitroglycerin, to prevent or provide acute relief of an attack of angina pectoris resulting from coronary artery disease.

Clinical data indicated that sublingual absorption of nitroglycerin is higher after administration of Gonitro compared with Espero’s nitroglycerin lingual spray (Nitrolingual Pumpspray), which was launched in 1997.

Espero expects Gonitro to be available in the second half of 2016.

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**Source URL:**
