Drug & Poison Information Center—Faculty of Pharmacy—Tanata University

Drug & Poison Information Bulletin

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Inside this issue:

New prescribing guidelines for metformin

FDA revises warnings regarding use of metformin in certain patients with reduced kidney function

- **The new prescribing guidelines for metformin, just released from the US Food and Drug Administration (FDA).**
- **The headlines are as follows: You can use metformin in anyone whose estimated glomerular filtration rate (eGFR) is > 30 mL/minute/1.73 m2 and you do not have to stop metformin in someone undergoing a dye study unless their eGFR is < 60 mL/minute/1.73 m2.**
- **Use serum creatinine cut-points to determine when we should prescribe metformin in patients with any degree of renal insufficiency. Now the FDA has done away with that guideline and really expanded the number of patients that we can safely keep on metformin.**

Rules of prescribing metformin for diabetic patients

- **Test the eGFR in any patient before you start metformin. If it's > 45 mL/minute/1.73 m2, you are fine. That patient is fully eligible to be on metformin.**
- **For the most part, the FDA does not recommend starting metformin in patients with an eGFR between 30 and 45 mL/minute/1.73 m2. But they still consider metformin safe if your patient is on metformin already and seems to be deriving some benefit. So, patients down to an eGFR of 30 mL/minute/1.73 m2 can remain on their metformin.**
- **Patients with an eGFR < 30 mL/minute/1.73 m2 should not be on metformin.**

Case Report from Cairo-Involuntary movements in an adult female following a single IM dose of Metoclopramide

The regional center in Cairo received a yellow card concerning a 30 years old female who developed irritability and involuntary movements for two days following a single dose intramascular administration of Metoclopramide 10mg as anti-emetic. IM. Hyoscine was taken concomitantly as antispasmodic.

Recommendations for Healthcare Professionals:

Limited dose and duration of use:

- **Metoclopramide should only be prescribed for short-term use (up to a maximum of 5 days) at recommended doses and dose-intervals. This is in order to minimize the risks of neurological and other adverse reactions.**
- **Intravenous doses should be administered as a slow bolus (at least over 3 minutes) to minimize the risk of occurrence of adverse reactions, including cardiovascular reactions.**

Indications for use (in adult patients) are restricted as follows:

- **Metoclopramide is indicated for short-term use in the prevention and treatment of nausea and vomiting, including that associated with chemotherapy, radiotherapy, surgery and migraine.**
- **The maximum dose in 24 hours is 30mg, which can be divided into10 mg three times a day (or 0.5mg/kg body weight), by the oral, rectal, intravenous or intramuscular route.**

Source: ***Egyptian Pharmaceutical vigilance Center (EPVC),June 2016 Volume 7, Issue 6***

Guidelines for metformin in patients undergoing a radiographic dye

- **If the eGFR is > 60 mL/minute/1.73 m^2, don't worry about it. They can continue taking their metformin throughout, unless it's an intra-arterial dye study. In that case, you are going to need to hold the metformin and make sure that the renal function stays stable.**
- **If the eGFR is < 60 mL/minute/1.73 m^2 meaning between 30 and 60 then, as we did before, you stop the metformin before the patient undergoes the dye study and recheck in 48 hours to make sure that the eGFR is still in a safe range.**
- **For many of our patients undergoing radiographic dye studies who have an eGFR of > 60 mL/minute/1.73 m^2, we are not going to need to hold the metformin.**
- **These guidelines are consistent with recommendations that have been used throughout the world for many years. Health care professionals should follow the latest recommendations when prescribing metformin-containing medicines to patients with impaired kidney function.**

Facts about metformin

- **Metformin is an antihyperglycemic agent which improves glucose tolerance in patients with type 2 diabetes, lowering both basal and postprandial plasma glucose.**
- **Its pharmacologic mechanisms of action are different from other classes of oral antihyperglycemic agents. Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization.**
- **Unlike sulfonylureas, Metformin does not produce hypoglycemia in either patients with type 2 diabetes and does not cause hyperinsulinemia.**

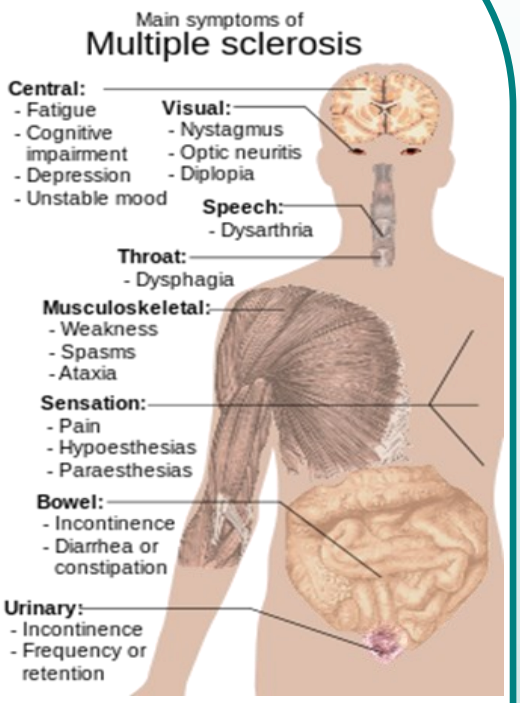
Sources:

⇒ *http://www.fda.gov/Drugs/DrugSafety/ucm493244.htm*

⇒ *http://www.medscape.com/viewarticle/864015*

New FDA approved Drug for Multiple Sclerosis

Fast facts on multiple sclerosis



- **In 2007, the World Health Organization (WHO) estimated that approximately 2.5 million people had multiple sclerosis.**
- **Multiple sclerosis rates are higher the further away you live from the equator. This leads many to believe that exposure to sunlight impacts on MS risk.**
- **It is among the most common causes of neurological disability in young adults.**
- **Women are more commonly affected by MS than men.**
- **A genetic predisposition is involved in MS.**
- **Month of birth appears to be a factor in the development of MS.**
- **Diagnosis of multiple sclerosis is still a difficult process, The Revised McDonald Criteria, and has improved the process.**
- **A person's multiple sclerosis progression can be determined by measuring how much their retina has thinned, researchers from Johns Hopkins MS Center reported in *Neurology*.**
- **There is no cure for multiple sclerosis yet. Existing treatments focus on suppressing the autoimmune response and managing symptoms.**
- **Corticosteroids *are most commonly prescribed to help MS patients*.**
- **Other drugs: Interferon Beta 1a , Copaxone (Glatiramer), Tysabri (Natalizumab), Mitoxantrone (Novantrone), Aubagio (teriflunomide), Cannabis extract, Marijuana pills and sprays ease multiple sclerosis symptoms.**

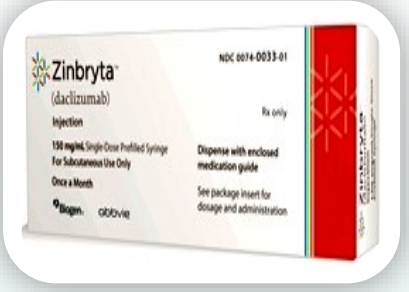
Sources:

⇒ *http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements ucm504000.htm*

⇒ *http://www.medicalnewstoday.com/articles/37556.php#what_is_ms*

New FDA approved Drug for Multiple Sclerosis

On May 27, 2016, the FDA announced the approval of Zinbryta (daclizumab) for the treatment of adults with relapsing forms of multiple sclerosis (MS). Zinbryta is a long-acting injection that is self- administered by the patient monthly.



Zinbryta should generally be used only in patients who have had an inadequate response to two or more MS drugs because Zinbryta has serious safety risks, including liver injury and immune conditions. Because of the risks.The most common adverse reactions reported by patients receiving Zinbryta in the clinical trial that compared it to Avonex include cold symptoms (nasopharyngitis), upper respiratory tract infection, rash, influenza, dermatitis, throat (oropharyngeal) pain,eczema, and enlargement of lymph nodes. The most common adverse reactions reported by patients receiving Zinbryta when compared to placebo are depression, rash, and increased alanine aminotransferase.

The boxed warning highlights other important risks of Zinbryta treatment including immune conditions, such as inflammation of the colon (non-infectious colitis), skin reactions, and enlargement of lymph nodes (lymphadenopathy).

Additional highlighted warnings include hypersensitivity reactions (anaphylaxis or angioedema), increased risk of infections, and symptoms of depression and/or suicidal ideation. The drug can cause severe liver injury, including life-threatening and fatal events. Health care professionals should perform blood tests to monitor the patient's liver function prior to starting Zinbryta, monthly before each dose, and for up to six months after the last dose.

Fast facts on multiple sclerosis

- **Multiple Sclerosis is a chronic, inflammatory, autoimmune disease of the central nervous system that disrupts communication between the brain and other parts of the body. The myelin sheath of MS patient's nerves is steadily degraded.**
- **For most people with MS, episodes of worsening function (relapses) are initially followed by recovery periods (remissions). Over time, recovery may be incomplete, leading to progressive decline in function and increased disability.**
- **Most people experience their first symptoms of MS between the ages of 20 and 40.**

What are the benefit of autophagy?

In intestinal Paneth cells, it preserves cellular function, prevents expression of damage and inflammatory markers, and prevents the development of Crohn's disease. Defects in autophagy may prevent cells from clearing away invading microbes, unwanted protein aggregates and abnormal proteins, and thereby contribute to diseases ranging from infectious disorders to neurodegeneration and cancer . By contrast, once cancer occurs, cancer cells may utilize autophagy to enhance fitness to survive with altered metabolism and in the hostile tumor microenvironment. Thus, both activation and inhibition of autophagy hold promise for improved treatment of common, devastating diseases.

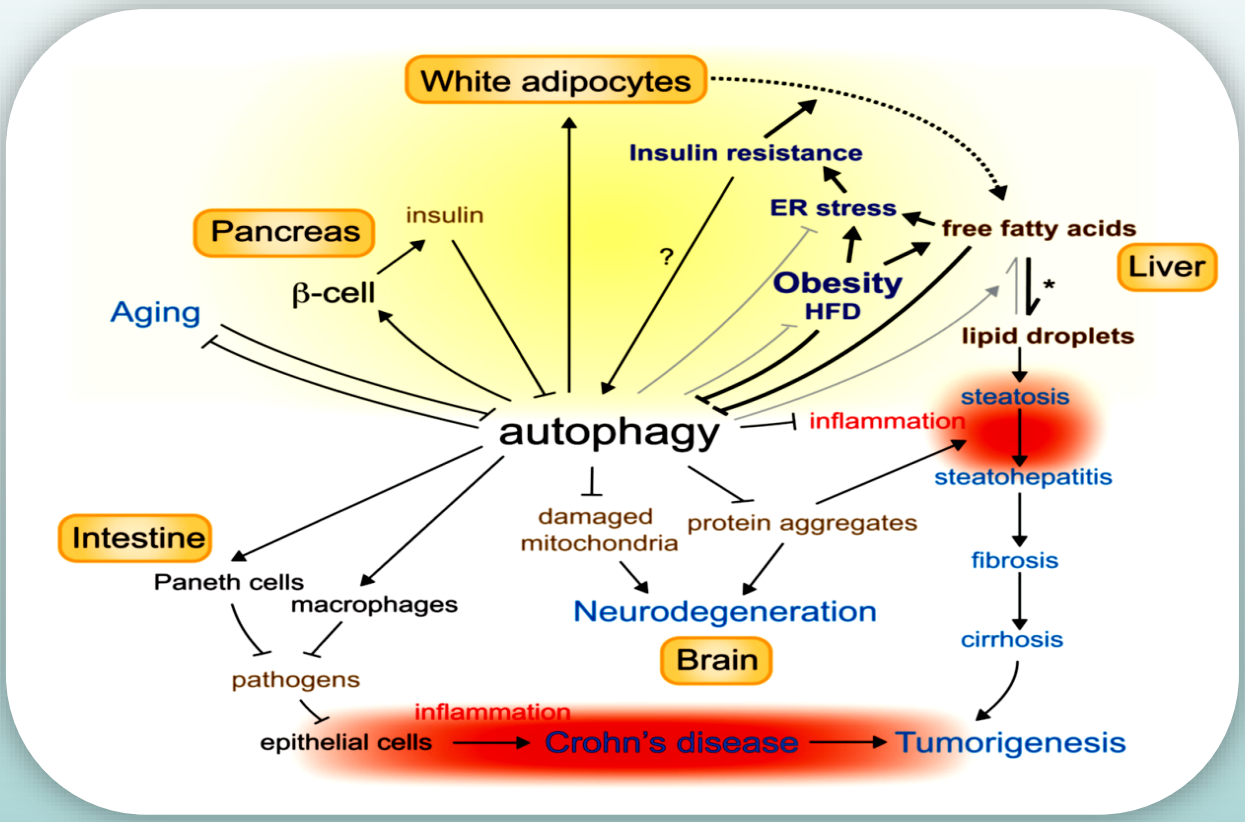


Figure 1: Role of autophagy in health and disease progression disorders are shown in blue. Lines with an arrowhead or a cross short line represent positive or negative regulation of the pathway, respectively. Bold or gray lines represent pathways up regulated or down regulated respectively during lipid homeostasis collapse. The dashed line depicts flux of fatty acids from adipocytes to liver. The asterisk indicates the abnormal deposit of fatty acids in liver when lipid homeostasis is disrupted. The question mark denotes a putative regulation. Yellow shading shows where autophagy is involved in the regulation of lipid homeostasis. Red shading shows inflammation, which promotes tumor genesis and is suppressed by autophagy. HFD: high fat diet.

Sources:

⇒ *Joshua D. Rabinowitz, Eileen White. Autophagy and Metabolism. Science. 2010 December 3; 330(6009): 1344–1348.*

⇒ *Hsin-Yi Chen, Eileen White. Role of Autophagy in Cancer Prevention. Cancer Prev Res (Phila). 2011 July ; 4(7): 973–983.*

Autophagy and Fasting!

What is autophagy (self eating) ?

Autophagy is a process of digestion of cytoplasm and worn - out organelles by the cells own lysosomes. The resulting breakdown products are inputs to cellular metabolism, through which they are used to generate energy and to build new proteins and membranes. Autophagy is the only mechanism to degrade large structures such as organelles and protein aggregates. In the absence of stress, basal autophagy serves a housekeeping function. It provides a routine "garbage disposal" service to cells, eliminating damaged components that could otherwise become toxic. Such cellular refreshing is particularly important in quiescent and terminally differentiated cells, where damaged components are not diluted by cell replication. In starvation, autophagy provides a nutrient source, promoting survival.

How autophagy is induced?

It is worth to be mentioned here that studies shows that induction of autophagy may result in the fasting rituals common in many religions as well modern cleansing rituals, producing health benefits, which means that we can simply induce this cleaning process by fasting and protect our bodies from the consequences of accumulation of cellular garbage in our bodies. Autophagy is induced by another broad range of stressors such as hypoxia, limitation of insulin, growth factors and others.

What are the benefit of autophagy?

Autophagy preserves the health of cells and tissues by replacing outdated and damaged cellular components with fresh ones. In starvation, it provides an internal source of nutrients for energy generation and thus survival, autophagy prevents degenerative diseases.

Defects in autophagy are linked to liver disease, neurodegeneration, Crohn's disease, aging, cancer, and metabolic syndrome.

Cellular garbage disposal by autophagy prevents the buildup of damaged proteins and organelles that cause chronic tissue damage and disease. Genetic inactivation of autophagy in mice revealed that the type of disease depends on the tissue type. In the brain, autophagy suppresses the accumulation of ubiquitinated proteins, disposes of aggregation-prone proteins and damaged organelles that cause Huntington's and Parkinson's diseases, and prevents neurodegeneration. In the liver, autophagy suppresses protein aggregate and lipid accumulation, oxidative stress, chronic cell death, inflammation, and cancer.

Death Risk With Off-Label Oral Ketoconazole Use, FDA Warns

- **In July 2013, the FDA removed skin and nail fungal infections as indications for ketoconazole tablets in light of possible adverse events, which also include adrenal gland problems and harmful interactions with other drugs. The agency revised the label to warn that patients with no obvious risk factors for liver disease had developed serious hepatotoxicity after taking the drug, leading to liver transplants or death in some cases.**
- **The FDA has received one report of a fatality related to oral ketoconazole since July 2013. The patient died of liver failure after taking the tablets for infected nails.**

- **"Healthcare professionals should use ketoconazole tablets only to treat serious fungal infections when no other antifungal therapies are available," the FDA said in a news release. In contrast, skin and nail fungal infections are not life-threatening, so the risks that come with oral ketoconazole outweigh the benefits. Clinicians can turn to other prescription and over-the-counter treatments for these infections.**
- **The FDA notes that topical versions of ketoconazole applied to skin or nails have not been linked to liver damage, adrenal problems, or drug interactions.**

Sources:

http://www.fda.gov/Drugs/DrugSafety/ucm500597.htm
http://www.medscape.com/viewarticle/863550

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