DEPARTMENT OF PHARMACOLOGY
ARMED FORCES MEDICAL COLLEGE, PUNE-40

The Pill Box

Issue: Fifth, Jan– Mar 2022

Dear Readers,
The purpose of this bulletin is to disseminate some important information related to drugs and medical devices likely to be of interest to everyone, involved directly or indirectly in patient care. The current issue highlights recent drug approvals, anti-obesity drugs, drug fever and few interesting potential preclinical research. Feedback and suggestions, if any, may be sent at email Id: thepillboxafmc@gmail.com .

World Obesity Day: 04 Mar 2022

Anti-obesity drugs

More than 1 billion people worldwide are obese and this number is still increasing. WHO estimates that by 2025, approximately 167 million people – adults and children – will become less healthy because they are overweight or obese. Thorough and compassionate counseling about healthy eating, physical activity, and health-seeking behavior is essential for every patient seeking weight loss, whether these lifestyle changes are used alone or in combination with anti-obesity medication or bariatric surgery. When a decision has been made to initiate pharmacologic therapy, patient comorbidities, contraindications, patient preferences, cost, and potential adverse effects are taken into account. Single agents are preferred over combination medications as initial pharmacotherapy.

Indication for drug therapy: Individuals with following body mass index (BMI) and have not met weight-loss goals (loss of at least 5 percent of total bodyweight at three to six months) with a comprehensive lifestyle intervention alone.

- BMI $\geq$30 kg/m^2
- BMI of 27 to 29.9 kg/m^2 with weight-related comorbidities

The decision to initiate drug therapy should be individualized, weighing the risks and benefits of all treatment options (lifestyle, pharmacologic, device, surgical).

Choice of agent: Pharmacologic options for the treatment of obesity include semaglutide or liraglutide (weekly or daily injection, respectively), orlistat, combination phentermine-extended release topiramate, combination extended-release bupropion-naltrexone, phentermine, benzphetamine, phendimetrazine, and diethylpropion. In meta-analyses of randomized trials comparing pharmacologic therapy with placebo, all active drug interventions are effective at reducing weight compared with placebo. Salient features of approved anti-obesity drugs along with dosing schedule, precautions/ contraindications are highlighted in subsequent pages.

Monitoring: More specific monitoring instructions depend upon the drug initiated. Phentermine-topiramate and bupropion-naltrexone may cause neuropsychiatric side effects, and patients taking these drugs should be monitored for depression or suicidal thoughts. Patient taking liraglutide or semaglutide should be monitored for symptoms of acute pancreatitis and gallbladder disease. Hyperchloremic, non-anion gap metabolic acidosis and increases in serum creatinine have been reported in patients treated with phentermine-topiramate because topiramate is a carbonic anhydrase inhibitor. Thus, serum electrolytes (including bicarbonate) and creatinine should be measured before and approximately four weeks after initiation of this combination.

Reference: National Institute of Diabetes & Digestive & Kidney Disease and UpToDate

The Pill Box Quiz: 05

Instructions:
Scan the QR code to get the questions and correct answers.

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Anti-obesity drugs: A glimpse

[Reference: National Institute of Diabetes & Digestive & Kidney Disease and UpToDate]

Drug	Usual dosing (adults)	Adverse effects and precautions
Pancreatic lipase inhibitor approved for long-term use		
Orlistat	120 mg 3 times daily with fat-containing meals. (60 mg who do not tolerate 120 mg)	Cramps, flatulence, fecal incontinence, oily spotting, absorption of fat-soluble vitamins may be reduced. Rarely reported: severe liver injury, oxalate-kidney injury. Contraindicated during pregnancy.
Combination of phentermine-topiramate approved for long-term use		
Phentermine-topiramate	Initial: 3.75 mg phentermine/23 mg topiramate once daily in the morning for 14 days, followed by 7.5 mg phentermine/46 mg topiramate daily for 12 weeks. Then titrate based upon response: 11.25 mg phentermine/69 mg topiramate daily for 14 days, and then to a maximum dose of 15 mg phentermine/92 mg topiramate once daily. Maximum dose with moderate hepatic or renal impairment (CrCl <50 mL/min) 7.5 mg phentermine/46 mg topiramate once daily. Upon discontinuation, tapering of dose over at least 1 week using every-other-day dosing is recommended.	Dry mouth, taste disturbance, constipation, paraesthesias, depression, anxiety, elevated heart rate, cognitive disturbances, insomnia (higher dose). Abuse potential due to phentermine. Topiramate is teratogenic (increased risk of oral cleft defects); negative pregnancy test prior to and during treatment and 2 forms of contraception necessary for women of child-bearing potential. Actions of topiramate component include inhibition of carbonic anhydrase; rarely metabolic acidosis and kidney stones may result from renal bicarbonate loss. Contraindicated during pregnancy, hyperthyroidism, glaucoma, patients taking MAO inhibitors.
Combination of bupropion-naltrexone approved for long-term use		
Bupropion-naltrexone	Week 1: 1 tablet (8 mg naltrexone/90 mg bupropion) once daily. Week 2: 1 tablet twice daily. Week 3: 2 tablets in morning and one tablet in evening. Week 4: 2 tablets twice daily. Maximum daily dose: 4 tablets (32 mg naltrexone/360 mg bupropion).	Nausea, constipation, headache, vomiting, dizziness, insomnia, dry mouth. Transient increase in blood pressure (1 to 2 mmHg on average) during initial 12 weeks of treatment; heart rate may also be increased. Contraindicated in patients with uncontrolled hypertension, seizure disorder, eating disorder, use of other bupropion-containing products, chronic opioid use, use within 14 days of MAO inhibitors, pregnancy, or breastfeeding.

Setmelanotide is the first FDA-approved treatment for chronic weight management (weight loss and weight maintenance for at least one year) in patients six years and older with obesity due to three rare genetic conditions: pro-opiomelanocortin (POMC) deficiency, proprotein subtilisin/kexin type 1 (PCSK1) deficiency, and leptin receptor (LEPR) deficiency confirmed by genetic testing.

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Anti-obesity drugs: A glimpse…

[Reference: National Institute of Diabetes & Digestive & Kidney Disease and UpToDate]

Drug	Usual dosing (adults)	Adverse effects and precautions
GLP-1 agonists approved for long-term use		
Liraglutide	Initial: 0.6 mg subcutaneously daily. Increase at weekly intervals (1.2, 1.8, 2.4, 3 mg) until recommended dose of 3 mg daily. If increased dose is not tolerated, consider delaying dose escalation by an additional week. [According to United States labeling, if weight loss is not ≥4% after 16 weeks or 3 mg/day is not tolerated, discontinue use. Labeling in the European Union recommends discontinuation of use if weight loss is not ≥5% after 12 weeks of 3 mg/day.]	Nausea, vomiting, diarrhea, constipation, hypoglycemia in patients with T2DM (more common if used in conjunction with diabetes medications known to cause hypoglycemia), injection site reactions, increased lipase, increased heart rate. Rarely reported: pancreatitis, gallbladder disease, renal impairment, suicidal thoughts. Causes a modest delay of gastric emptying. Advise patients to avoid dehydration in relation to GI side effects. Monitor blood glucose in diabetic patients and adjust co-administered sulfonylureas (eg, reduce dose by 50%) and other antidiabetic medications as needed to prevent potentially severe hypoglycemia. Possible increase in thyroid cancer risk based on murine model data. Contraindicated in pregnancy and in patients with a personal or family history of medullary thyroid cancer or multiple endocrine neoplasia 2A or 2B. For semaglutide, monitor patients with diabetic retinopathy for eye complications.
Semaglutide	Initial: 0.25 mg subcutaneously once weekly. Increase dose at 4-week intervals (0.5, 1, 1.7, 2.4 mg) until recommended dose of 2.4 mg weekly. If increased dose is not tolerated, consider delaying dose escalation by 4 weeks. [According to United States labeling, if 2.4 mg/week is not tolerated, discontinue use.]	
Noradrenergic sympathomimetic drugs approved for short-term use		
Benzphetamine	Initial: 25 mg once daily; may titrate up to 25 to 50 mg one to 3 times daily. Maximum dose: 50 mg 3 times daily	Due to their side effects and potential for abuse, **not preferred**. If prescribed, limit to short-term (≤12 weeks) use. Adverse effects include increase in heart rate, blood pressure, insomnia, dry mouth, constipation, nervousness. May counteract effect of blood pressure medications. Avoid in patients with heart disease, poorly controlled hypertension, pulmonary hypertension, or history of addiction or drug abuse. Contraindicated in patients with a history of CVD, hyperthyroidism, glaucoma, MAO inhibitor-therapy, agitated states, pregnancy, or breast feeding.
Diethylpropion	Immediate release: 25 mg 3 times daily, 1 hour before meals. Controlled release: 75 mg every morning.	
Phentermine	Immediate release: 15 to 37.5 mg daily or divided twice daily. Orally disintegrating tablet (ODT): 15 to 37.5 mg once daily in the morning. Immediate release (Lomaira): 8 mg 3 times daily before meals.	
Phendimetrazine	Immediate release: 17.5 to 35 mg 2 or 3 times daily, 1 hour before meals. Maximum dose: 70 mg 3 times daily. Sustained release: 105 mg daily in the morning.	

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Drug fever

Fever can be the sole manifestation in 3 to 5 percent of adverse drug reactions. Failure to recognize the etiologic relationship between a drug and fever often has undesired consequences including extra testing, unnecessary therapy, and longer hospital stays, thus increasing healthcare cost.

●**Definition** – Drug fever is a disorder characterized by fever that coincides with administration of a drug and disappears after the discontinuation of the drug, when no other cause for the fever is evident after a careful clinical history, physical examination, and laboratory investigation.

●**Mechanisms** – Mechanisms of drug fever are incompletely understood, can be classified into five broad categories:

(a) Hypersensitivity – Most common cause of drug fever; in some cases, fever is a feature of a severe cutaneous reaction. Drugs commonly associated include anticonvulsants, antimicrobials, and allopurinol.

(b) Idiosyncratic reactions – Heterogeneous category, includes malignant hyperthermia, neuroleptic malignant syndrome, and serotonin syndrome.

(c) Direct result of the pharmacologic action of the drug – Fever following chemotherapy, which results in cell damage and release of pyrogenic substances.

(d) Altered thermoregulation – Drugs such as thyroid hormone, anticholinergic agents, and sympathomimetic agents can modify thermoregulation pathways to result in fever.

(e) Reactions directly related to administration of the drug – Include contamination of parenteral fluids with endotoxin or exogenous pyrogens & intrinsic pyrogenic properties of some agents, such as amphotericin or bleomycin.

●**Evaluation** – Drug fever is a diagnosis of exclusion. After ruling out other serious causes of fever, a detailed review of the history, presenting features, and laboratory findings may reveal potential clues to the possibility of drug fever. A detailed medical history should include all current medications, including over-the-counter medications, herbal medications, supplements, and recreational substances, with a focus on drugs or drug classes that are more frequently associated with fever. The median time to onset of drug fever is about eight days after initiation of the offending agent but can range from a few hours to a few months as shown below in table.

Time to fever onset for medications commonly associated with drug fever

Drugs or drug classes	Estimated time to onset
Antimicrobial agents	1 to 5 weeks
Isoniazid	Hours to 3 weeks
Minocycline	3 weeks to 2 years
Sulfasalazine	3 weeks
Allopurinol	3 to 9 weeks
Azathioprine	1 day to 2 weeks
Antiseizure medications	
Phenytoin	1 to 8 weeks
Carbamazepine	2 days to 3 weeks
Cardiovascular agents	
Quinidine	2 weeks to 6 months
Methyldopa	11 days to 3 weeks
Chemotherapeutic agents (eg, gemcitabine)	3 days
Hydroxyurea	1 day to 6 weeks

●**Management** – Stopping the offending agent can both establish a presumptive diagnosis of drug fever and treat it. The usual approach is to sequentially discontinue drugs, beginning with the most probable offending agent. Resolution of drug fever usually occurs within 72 to 96 hours of discontinuing the culprit drug.

New Drugs Corner

Mitapivat
MOA: Pyruvate kinase activator
Indication: For the treatment of hemolytic anemia in adults with pyruvate kinase (PK) deficiency.

Sutimlimab-jome
MOA: Classical complement inhibitor
Indication: To decrease the need for red blood cell (RBC) transfusion due to hemolysis in adults with cold agglutinin disease (CAD).

Faricimab-svoa
MOA: Vascular endothelial growth factor (VEGF) and angiopoietin-2 (Ang-2) inhibitor
Indication: Neovascular (Wet) Age-Related Macular Degeneration (nAMD) and Diabetic Macular Edema (DME)

Tebentafusp-tebn
MOA: Bispecific gp100 peptide-HLA-directed CD3 T cell engager
Indication: HLA-A*02:01-positive adult patients with unrespectable or metastatic uveal melanoma.

Abrocitinib
MOA: A Janus kinase (JAK) inhibitor
Indication: Refractory, moderate-to-severe atopic dermatitis where disease is not adequately controlled with other systemic drug products, including biologics, or when use of those therapies is inadvisable.

Daridorexant
MOA: Orexin receptor antagonist
Indication: Insomnia characterized by difficulties with sleep onset and/or sleep maintenance.

Efgartigimod alfa-fcab
MOA: Neonatal Fc receptor blocker
Indication: Generalized myasthenia gravis (gMG) with anti-acetylcholine receptor (AChR) antibody positive

Inclisiran
MOA: Small interfering RNA (siRNA) directed to PCSK9 (proprotein convertase subtilisin kexin type 9) mRNA
Indication: As an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia (HeFH) or clinical atherosclerotic cardiovascular disease (ASCVD), who require additional lowering of low density lipoprotein cholesterol (LDL-C)

Tezepelumab-ekko
MOA: Thymic stromal lymphopoietin (TSLP) blocker, human monoclonal antibody (IgG2λ)
Indication: Add-on maintenance treatment of adult & pediatric patients aged 12 years & older with severe asthma.

Pafolacianine
MOA: Optical imaging agent
Indication: In ovarian cancer as an adjunct for intraoperative identification of malignant lesions.

Maribavir
MOA: Cytomegalovirus (CMV) pUL97 kinase inhibitor
Indication: For the treatment of adults and pediatric patients (12 years of age and older and weighing at least 35 kg) with post-transplant CMV infection/disease that is refractory to treatment (with or without genotypic resistance) with ganciclovir, valganciclovir, cidofovir or foscarnet.

Reference: USFDA

Pre-clinical research : Potential molecules

Experimental compound protects obese mice from diabetes-like metabolic changes

Scientist tested an experimental small-molecule compound called IXA4 and found it to activate a natural signaling pathway in both the liver and the pancreas in obese mice. It acts on a signaling pathway involving two proteins called IRE1 and XBP1s. When activated by a certain type of cellular stress, IRE1 activates XBP1s, which in turn alters the activity of a host of genes, including many metabolic genes, in an effort to reduce the cellular stress. Prior studies suggest that the activity of this pathway, at least in the short-term, can protect liver and fat cells from stresses caused by obesity. However, past research has also shown that keeping IRE1/ XBP1 switched on chronically ends up harming cells, triggering inflammation and worsening overall metabolic dysfunction. IRE1/XBP1s signaling is a response to cellular stress, and keeping it on all the time essentially tells the cell that the stress can't be resolved, so the cell in effect kills itself. IXA4 activates IRE1/XBP1s for just a few hours at a time. Because it otherwise allows IRE1 to turn off, it can in principle be given daily without triggering the deleterious signaling seen with constant IRE1 activation, making it a promising candidate to explore for human treatments. After just eight weeks of treatment with IXA4 in obese mice, the treated mice had improved glucose metabolism and insulin activity, less fat build up and inflammation in the liver, and no loss of insulin-producing cells in the pancreas, compared to untreated obese mice. IXA4 can also be explored as a potential treatment for other metabolic disorders such as fatty liver disease.

Journal Reference: Aparajita Madhavan, Bernard P. Kok, Bibiana Rius *et al*. Pharmacologic IRE1/XBP1s activation promotes systemic adaptive remodeling in obesity. *Nature Communications*, 2022; 13 (1) DOI: 10.1038/s41467-022-28271-2

An insulin patch that sticks inside a person's cheek

People primarily take insulin by injecting themselves with pens or syringes, or they have semi-permanent pumps implanted. These methods are invasive and uncomfortable, and require safe needle or biohazard disposal and sterile conditions. The membrane lining inside of the mouth is very thin, making it a potential place for drugs to easily enter the bloodstream. The researchers first soaked small squares of a nanofiber mat, made from electrospun fibers of poly (acrylic acid), β-cyclodextrin and reduced graphene oxide, in a solution with insulin for three hours. Then, applied the insulin-loaded patches onto cheek linings and corneas from pigs. Heating the material with a near-infrared laser for 10 minutes to 122-degree F activated the material and released insulin into the two types of membranes several times faster than through skin. In addition, the researchers placed the patches in vivo inside the cheeks of three insulin-dependent pigs. The cheek linings showed no irritation or visual changes from the laser's heat. As soon as the material was activated, the pigs' blood sugar levels declined. Simultaneously, the animals' plasma insulin levels increased. This study seems to be proof-of-concept that this preliminary platform is efficient at getting insulin into the bloodstream.

Journal Reference: Anna Voronova, Cristina Prieto, Maria Pardo-Figuerez *et al*. Photothermal Activatable Mucoadhesive Fiber Mats for On-Demand Delivery of Insulin via Buccal and Corneal Mucosa. *ACS Applied Bio Materials*, 2022; DOI: 10.1021/acsabm.1c01161

Diabetes, metabolic syndrome in mice treated with novel class of compounds

Researchers found that the gradual decline of protein SWELL1 (also LRRC8a) may have a central role in the development of diabetes and other aspects of metabolic syndrome. This protein helps to control insulin secretion from the pancreas and improve insulin sensitivity, including in skeletal muscle and adipose tissue. The compound SN-401 binds to SWELL1 in a manner that stabilizes the protein complex so as to enhance expression and signaling across multiple tissues, including adipose, skeletal muscle, liver, the inner lining of blood vessels, and pancreatic islet cells. This restores both insulin sensitivity across tissue types and insulin secretion in the pancreas. The study showed that the SN-401 compound improved multiple aspects of metabolic syndrome in two groups of mice that each developed diabetes from different causes, one because of a genetic predisposition and the other due to a high-fat diet. In addition to improving insulin sensitivity and secretion, treatment with the compound also improved blood sugar levels and reduced fat buildup in the liver. Most of these studies were conducted with an injected form of the compound, but the researchers showed evidence that it also could be effective if taken by mouth. The researchers further showed that the compound does not have a big impact on blood sugar in healthy mice, which is important for its potential as a future possible therapy.

Journal Reference: Susheel K. Gunasekar, Litao Xie, Ashutosh Kumar *et al*. Small molecule SWELL1 complex induction improves glycemic control and nonalcoholic fatty liver disease in murine Type 2 diabetes. *Nature Communications*, 2022; 13 (1) DOI:10.1038/s41467-022-28435-0.