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Regional Poison Control Center, Birmingham, AL

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Rybelsus™ - First Oral GLP-1 Approved by FDA for Type II Diabetes

By Paige Melton, East Tennessee State University PharmD Candidate

A new formulation in the GLP-1 receptor agonist class, Rybelsus or semaglutide (Novo Nordisk), has recently received FDA approval. The FDA approved Rybelsus in September of this year. This class of medications has steadily increased in popularity due to GLP-1's ability to dramatically lower blood glucose and relatively low danger of hypoglycemia with the promotion of weight loss. GLP-1 receptor agonists have also been shown to exhibit beneficial effects on cardiovascular outcomes and kidneys. It wasn't until recently though patients would be able to administer the medication via oral route; previously, SC injection only.

Currently, in the United States, there are approximately 114 million individuals living with prediabetes and diabetes. Additionally, Type II diabetes mellitus is responsible for an estimated 90-95% of all diagnosed cases. Although agents that lower blood glucose significantly continue to climb, a need still exists because data suggest that only a little over 50% of patients are at an A1C goal of lower than 7 percent.

GLP-1 receptor agonists lower blood sugar through multiple mechanisms. These agents increase secretion of glucose-dependent insulin on pancreatic β-cells, overcorrected glucagon secretion is suppressed in pancreatic α-cells, and satiety is enhanced because of the delay in gastric emptying. Oral semaglutide has been demonstrated in studies to probably be absorbed in the stomach rather than the small intestines where most oral drugs are absorbed. Peptide-derived agents are difficult to administer orally because of degradation via proteases in the GI tract. However, advancements utilizing absorption enhancers with semaglutide allow for oral delivery to reach the systemic circulation. The absorption enhancer used in this agent is what's referred to as SNAC or Sodium N-[8(2-hydroxylbenzoyl) amino] caprylate. In 2009, the FDA labeled SNAC as generally safe when used in dietary supplements.

The safety and efficacy of semaglutide have been demonstrated via clinical trials (10 PIONEER). These trials were placebo-controlled and compared to other agents in its class. There were 9,543 participants enrolled. Semaglutide was studied with other agents and by itself with regards to therapy. The combination therapies included sulfonylureas, metformin, insulins, thiazolidinediones, and sodium-glucose co-transporter-2 inhibitors. Following 26 weeks, a 7 mg once per day tablet resulted in 69% and 77% with the 14 mg tablet of patients with an HbA1C of below 7%. (**Continued on Page 4**)

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Special Interest Articles

- Rybelsus
- Antipsychotics
- Loperamide

Did you know?

A study was published in the *Annals of Internal Medicine* regarding US Food and Drug Administration drug disposal guidelines and pharmacist knowledge. Researchers found that only 47% of pharmacies gave correct instructions on how to dispose antibiotics and 34% provided correct information about opioid disposal. (https://www.fda.gov/consumers/consumer-updates/where-and-how-dispose-unused-medicines)

The Toxicology of Antipsychotics: Typical and Atypical

By Bryce Burkhart, Samford University PharmD Candidate

"The NMS tetrad of indicating symptoms includes hyperthermia, altered mental status, muscle rigidity and autonomic dysfunction."

Antipsychotics are a class of medications used heavily within the realm of psychiatric medicine, particularly in the treatment of schizophrenia and bipolar disorder. Antipsychotics may be separated into two distinct categories, commonly referred to as typical, or first-generation, antipsychotics and atypical, or second-generation, antipsychotics. The distinction between the two classifications is made based on a targeted approach to the symptomatology of schizophrenia and the differing receptors targeted.

The typical antipsychotics work through a mechanism of dopaminergic antagonism to achieve resolution of positive symptoms, which are derived from the mesolimbic pathway within the brain. The atypical antipsychotics, in addition to dopaminergic antagonism, work through 5-HT receptors as partial agonists (5-HT_{1A}) and antagonists (5-HT_{2A}). The addition of 5-HT selectivity allows for this class of agents to assist in the modulation of the negative symptoms associated with schizophrenia, which the typical agents are not capable of alleviating.

Due to the action of dopaminergic antagonism, many of the typical agents, and to some extent the atypical agents can manifest as signs and symptoms outside of the mesolimbic pathway, especially in overdoses. Extrapyramidal symptoms are derived from the nigrostriatal pathway, negative symptoms, which are worsened by the typical antipsychotics, are derived from the mesocortical pathway, and hyperprolactinemia is derived from the tuberoinfundibular pathway. Many of the antipsychotic agents are also capable of producing a wide variety of other signs and symptoms at therapeutic levels, and in acute overdose situations. This is related to the additional "dirty receptors" which some of the agents have a propensity for targeting. Agents are capable of inhibiting α-adrenergic receptors which produces hypotension and sedation, H_1 receptors which produces sedation and weight gain, M_1 receptors which produces anticholinergic actions, 5-HT_{2C} which produces weight gain, and X receptors which are potentially associated with insulin resistance and elevations of triglycerides. In addition to the receptor blockade, many of the agents can affect potassium channels, allowing for the development of QTc prolonging arrhythmias.

In the setting of acute overdose, antipsychotic medications exhibit a wide variety of effects distributed across various organ systems of the body; however, the most notable toxic effects will be observed in the central nervous and cardiovascular systems. Patients may exhibit a peripheral and/or central manifestation of toxicity. The ECG readings associated with both atypical and typical antipsychotic medication overdose are like the readings observed in TCA overdose. Both prolongation of the QRS interval and QTc interval may be observed in the setting of acute overdose. Peripheral manifestations may include tachycardia, flushed skin, reductions in the production of sweat and saliva, urinary retention, diminished bowel sounds, and mydriasis. Central manifestations may include agitation, delirium, dystonias, psychosis, hallucinations, or coma. Treatment includes symptomatic and supportive care, plus anticholinergics (benztropine or diphenhydramine) for dystonic reactions and benzodiazepines for agitation. (***Continued on Page 3)***

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Patients may also exhibit mild elevations of body temperature related to the impairment of sweat production and increased agitation. Hyperthermia may indicate the development of neuroleptic malignant syndrome (NMS), which is an alteration of the body's temperature "set point" within the hypothalamus. The NMS tetrad of indicating symptoms includes hyperthermia, altered mental status, muscular rigidity, and autonomic dysfunction. Treatment for the hyperthermia from NMS includes cooling blankets, ice packs placed in the groin and axillary areas, removing the patient's clothing, applying towels soaked in ice water with fans for circulation of air, and ice water immersion of the patient. Call the poison control center for further recommendations.

Typical Antipsychotics		
Butyrophenones	**Phenothiazines**	**Diphenylbutylpiperidines**
haloperidol (Haldol)	chlorpromazine (Thorazine)	pimozide (Orap)
	thioridazine (Mellaril)	
	prochlorperazine (Compro)	
	fluphenazine (Prolixin)	
	perphenazine (Trilafton)	
	trifluoperazine (Stelazine)	
Dibenzoxazepines	**Thioxanthenes**	**Dihydroindolones**
loxapine (Loxitane)	thiothixene (Navane)	molindone (Moban)
Atypical Antipsychotics		
"-pines"	**"-dones"**	**"2 pips & a rip"**
clozapine (Clozaril)	risperidone (Risperdal)	aripiprazole (Abilify)
olanzapine (Zyprexa)	paliperidone (Invega)	brexpiprazole (Rexulti)
quetiapine (Seroquel)	ziprasidone (Geodon)	cariprazine (Vraylar)
asenapine (Saphris)	iloperidone (Fanapt)	
	lurasidone (Latuda)	

References

1. Juurlink ND. Antipsychotics. In: Nelson LS, Howland M, Lewin NA, Smith SW, Goldfrank LR, Hoffman RS. eds. *Goldfrank's Toxicologic Emergencies*. 11th ed. New York, NY: McGraw-Hill; http://accesspharmacy.mhmedical.com.ezproxy.samford.edu/content.aspx?bookid=2569&sectionid=210274542. Accessed November 26, 2019.
2. Abi-Dargham A, Rodenhiser J, Printz D, et al. Increased baseline occupancy of D2 receptors by dopamine in schizophrenia. *Proc Natl Acad Sci U S A*. 2000; 97(14):8104-8109. doi: 10.1073/pnas.97.14.8104
3. Keck PE Jr, McElroy SL. Clinical pharmacodynamics and pharmacokinetics of antimanic and mood-stabilizing medications. *J Clin Psychiatry*. 2002; 63(Suppl 4): 3-11.
4. De Hert M, Detraux J, van Winkel R, et al. Metabolic and cardiovascular adverse effects associated with antipsychotic drugs. *Nat Rev Endocrinol*. 2011; 8(2): 114-126.
5. Bhanushali MJ, Tuite PJ. The evaluation and management of patients with neuroleptic malignant syndrome. *Neurol Clin*. 2004; 22(2): 389-411. doi: 10.1016/j.ncl.2003.12.006

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The information for prescribing semaglutide (Rybelsus) warns about increased potential risks of pancreatitis, diabetic retinopathy, hypoglycemia, hypersensitivity reactions, thyroid c-cell tumors, and AKI. Also, it has a boxed warning stating it's not a recommended first-line agent in the treatment of diabetes.

The most frequently observed adverse events noted with semaglutide use were GI-related. The main GI disturbances include nausea and vomiting and mild-to-moderate diarrhea; GI events appear to go away over time and less severe in dose titration. Rybelsus is recommended to start at a dose of 3 mg per day for 30 days, then 7 mg daily. Thereafter, the dose may be titrated to 14 mg per day, if needed. It is taken on an empty stomach (30 minutes before food intake) with less than 4 ounces of water. The oral availability of Rybelsus has great potential to increase the therapeutic use in its class and further options in the future with its alternative route of administration.

References

1. FDA approves first oral GLP-1 treatment for type 2 diabetes. US Food and Drug Administration. https://www.fda.gov/news-events/press-announcements/fda-approves-first-oral-glp-1-treatment-type-2-diabetes. Published September 20, 2019. (Accessed November 14, 2019).
2. FDA approves Rybelsus (semaglutide), the first GLP-1 analog treatment available in a pill for adults with type 2 diabetes. Novo Nordisk. https://222.novonordisk-us.com/media/news-releases.html?122973. Published September 20, 2019. (Accessed November 14, 2019). Gvoke™ (glucagon)—New drug approval. OptumRx. https://professionals.optumrx.com/content/dam/optum3/professional-optumrx/news/rxnews/drug-approvals/drugapproval_gvoke_2019-0910.pdf. 2019. (Accessed October 14, 2019).
3. Novo Nordisk. Novo Nordisk files for US FDA approval of oral semaglutide for blood sugar control and cardiovascular risk reduction in adults with type 2 diabetes. Available at: https://www.novonordisk-us.com/media/news-releases.html?122958. (Accessed November 14, 2019).
4. Pratley R, Amod A, Hoff ST, et al. Oral semaglutide versus subcutaneous liraglutide and placebo in type 2 diabetes (PIONEER 4): A randomised, double-blind, phase 3a trial. Lancet. 394(10192):39-50.

PharmD students, Bryce Burkhart and Paige Melton, visited Sylvan Springs Senior Center on November 20, 2019 to teach them about Medication Safety.

New Packaging for Loperamide

By Laura Read, RPh, CSPI, Regional Poison Control Center, Children's of AL

The United States Food and Drug Administration (FDA) has taken measures to address loperamide abuse and misuse. The makers of Imodium A-D, Imodium Multi-Symptom Relief and Be Health Loperamide HCl Capsules will change their package to contain no more than 48 milligrams of loperamide. Packages will also be individual, unit-dose blister packs.

The packaging changes do not apply to generic brands, store brands, or liquid products, however, the FDA will work with manufactures to support safe packaging. FDA also warned online retailers about selling loperamide in large quantities, but any changes online would be voluntary.

Loperamide is a synthetic opioid agonist used as an antidiarrheal medication. Loperamide is peripherally acting, and acts on the mu opioid receptor. The toxicity is from the direct action on the opioid receptor of loperamide. Dystonic reactions may develop after toxic doses from the portion of the molecule that is structurally like haloperidol.

Toxicity can cause severe central nervous system depression. Apnea and respiratory acidosis can be caused by respiratory depression. In patients taking large doses of loperamide, cardiac dysrhythmias (e.g., prolonged QRS and QT intervals, monomorphic and polymorphic (torsades de pointes) ventricular dysrhythmias) have been reported. Other adverse effects could include rhabdomyolysis, acute renal injury, aspiration pneumonitis, and hypotension.

References

1. Loperamide. POISINDEX® System (electronic version). IBM Watson Health, Greenwood Village, Colorado, USA. Available at: https://www.micromedexsolutions.com/ (Accessed December 12, 2019).
2. FDA limits packaging for anti-diarrhea medicine loperamide (Imodium) to encourage safe use. U.S Food and Drug. https://www.fda.gov/drugs/drug-safety-and-availability/fda-limits-packaging-anti-diarrhea-medicine-loperamide-imodium-encourage-safe-use. Sept 20, 2019. (Accessed December 5, 2019).
3. Bonner L. Loperamide will now come in limited-dose packaging. Pharmacy Today. https://www.pharmacytoday.org/article/S1042-0991(19)31359-3/fulltext. December 2019. (Accessed December 5, 2019).

Chemical structure of loperamide. Data from Gold Standard Drug Database