In This Issue

Cleveland Clinic Clinical Rx Forum

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Intranasal Glucagon for Severe Hypoglycemia

By: Molly Wheeler, Pharm.D.

Background: An estimated 30.3 million individuals in the U.S. are diabetic with 1.5 million having Type 1 diabetes (T1DM); a reported 6 million of these diabetic patients use insulin, putting them at higher risk for hypoglycemia (plasma glucose ≤70 mg/dL).[1,2] Severe hypoglycemic events can result in cognitive dysfunction, unconsciousness, and seizures which render the patient unable to self-treat with oral carbohydrates requiring assistance from a caregiver.[2,3] Currently, the treatment for severe hypoglycemic episodes is intramuscular (IM) glucagon which is available as GlucaGen® Hypokit (Novo Nordisk) and Glucagon™ Emergency Kit (Eli Lilly). Due to poor stability of glucagon in solution, both products require reconstitution immediately prior to injection by a caregiver or bystander resulting in a complex preparation and administration process.[3] On July 24, 2019, a simpler method of administration, intranasal (IN) glucagon (Baqsimi™; Eli Lilly), was approved by the Food and Drug Administration (FDA) for the treatment of severe hypoglycemia in patients with diabetes ≥4 years old.[4]

Mechanism of Action: Glucagon, the counter-regulatory hormone to insulin, activates hepatic glucagon receptors which stimulate glycogen breakdown leading to glucose release, ultimately increasing blood glucose levels.[4]

Clinical Trials: The approval of IN glucagon was based on two adult and one pediatric clinical trial.[5] The two adult trials had randomized, multicenter, open-label, two-period crossover, noninferiority designs. One adult trial only included patients with T1DM (N=66) while the other included patients with both T1DM (n=77) and Type

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Intranasal Esketamine for Treatment-Resistant Depression

By: Leti Vargas, Pharm.D.

Background: In the U.S. major depressive disorder (MDD) is the second most common psychiatric condition with a lifetime prevalence between 6% and 16%.[1] More than 50% of patients with MDD do not fully respond to initial therapy and 30-50% of those non-responders exhibit symptoms of treatment-resistant depression (TRD).[2] Treatment-resistant depression has been defined as failure to respond to two or more successive trials of medications from different pharmacologic classes given at adequate doses for a sufficient period of time.[3] Ketamine has been used successfully for TRD but requires intravenous (IV) administration.[4] Intranasal (IN) esketamine (Spravato™; Janssen Pharmaceutical), a more convenient form of ketamine, was approved in February 2019 by the Food and Drug Administration (FDA) as adjunctive therapy to an oral antidepressant for TRD in adults.[4]

Mechanism of Action: Research on mood disorders has demonstrated that

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2 diabetes (T2DM) (n=6); only the results from the T1DM cohort of the second trial are published. Each patient was randomized to either 1 mg IM or 3 mg IN glucagon on dosing visit one followed 1-4 weeks later by a second visit in a cross-over fashion to receive the opposite dosage form. During each visit, the patient's insulin therapy was discontinued (i.e., insulin pump suspended, basal insulin not given within 24 hours) following an 8 hour fast and their blood glucose was reduced to <60 mg/dL using an insulin infusion. Five minutes after the insulin infusion was discontinued, IN or IM glucagon was administered. The primary endpoint was successful treatment of hypoglycemia, defined as an increase in plasma glucose to ≥70 mg/dL or an increase ≥20 mg/dL from nadir within 30 minutes of glucagon administration. Blood levels of glucose and glucagon were measured every 5 minutes. Successful treatment was achieved in 74/75 (98.7%) of IN visits and 75/75 (100%) IM visits (unadjusted difference 1.5%, one-sided 97.5% CI 4.0%). Blood levels of both glucose and glucagon with IN glucagon administration were found to lag behind IM glucagon administration by ~5 minutes (p< 0.001). The authors concluded that IN glucagon is effective for correcting hypoglycemia and was non-inferior to IM glucagon in episode resolution. The pediatric trial enrolled 48 patients from 4 to <17 years old.[6] This phase 1 study had a crossover design and exclusion criteria similar to the adult trials. Patients were divided into cohorts by age (4 to <8 years old; 8 to <12 years old; 12 to <17 years old). Among the younger two cohorts, 2 mg and 3 mg fixed doses of IN glucagon were compared to each other and to weight-based IM dosing. Patients were randomized 2:1 to IN or IM glucagon. The IN group received glucagon 2 mg and 3 mg on two separate dosing visits, while the IM group received a weight-based dose on a single study visit. The target glucose for hypoglycemia induction was <80 mg/mL. The primary endpoint was a rise of ≥25 mg/dL above glucose nadir within 20 minutes of glucagon administration. The endpoint was achieved in 24/24 IM doses and 58/59 IN doses. Additionally, the 3 mg IN dose was found to be equally efficacious without increased adverse effects compared to the 2 mg dose. The authors concluded that a 3 mg dose of IN glucagon is appropriate for patients ≥ 4 years old regardless of body weight.

Safety: The most common adverse events reported in adult clinical trials with IN administration were gastrointestinal (GI) symptoms including nausea (26.1%) and vomiting (15%).[5] Headache and upper respiratory irritation occurred in 18.3% and 12.4%, respectively. Similar adverse events were reported in pediatric patients.

Dosing and Administration: The recommended dose of IN glucagon is 3 mg administered intranasally via a dispenser.[5] To administer the glucagon intranasally from the dispenser, the tip is inserted into one nostril and the plunger needs to be completely depressed until the green line is not showing. The plunger should not be pushed or tested prior to use and cannot be reused. Inhalation is not required as the medication is absorbed through the nasal mucosa. At the time of administration, emergency services should be summoned. Once the patient is cognitively able, treatment with oral carbohydrates should occur. If no response is seen after 15 minutes, an additional intranasal dose from a new dispenser may be administered. Of note, the pharmacokinetics of intranasal glucagon have been shown to be unchanged by nasal congestion.[3]

Availability and Cost: Intranasal glucagon is available as a powder in a ready-to-use IN dispenser.[5,7] Package sizes are as one or two single-use, 3 mg intranasal dispensers.[7] The average wholesale price (AWP) for a single dispenser is $280.80 and for the two-pack is $561.60.[8] The cost for currently available IM glucagon emergency kits is $268.73 per kit. These kits contain lyophilized glucagon powder in a vial with diluent in a prefilled syringe for reconstitution.[9, 10]

Formulary Status: Intranasal glucagon is currently not included in the CCHS Formulary.

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abnormalities in glutamatergic neural transmission involving the N-methyl-D-aspartate (NMDA) receptor can adversely affect emotional behavior.[5] Ketamine and esketamine are both noncompetitive NMDA receptor antagonists, however esketamine, the S-enantiomer of ketamine, is more potent. It is thought that their inhibition of the NMDA receptor may contribute to the resolution of TRD.

Key Clinical Trial: Fedgchin and colleagues evaluated the safety and efficacy of switching patients from current antidepressive therapies to a fixed dose of IN esketamine in addition to oral antidepressive therapy.[6] This phase 3, multicenter study included adults (N=342) with TRD who were randomized 1:1:1 to IN esketamine 56 mg (n=115) or 84 mg (n=114) plus a newly initiated antidepressant (AD) or placebo plus a newly initiated AD (n=113). The primary endpoint was the change from baseline (day 1) to the end of period 2 (day 28) in the Montgomery-Asberg Depression Rating Scale (MADRS) total score. The MADRS is a ten-item diagnostic survey that is utilized to determine the severity of depression or mood disorders. The score ranges from 0 to 60 with a score 7-19 indicating mild depression, a score of 20-34 indicating moderate depression, and a score >34 indicating severe depression. Patients receiving esketamine 56 mg or 84 mg in addition to the oral AD were more likely to attain clinically meaningful reductions in the MADRS total score compared to placebo plus oral AD therapy. The mean MADRS total score reductions (SD) from baseline to day 28 of 56 mg vs. 84 mg vs. placebo groups were as follows: -19.0 (13.86) vs. -18.8 (14.12) vs. -14.8 (15.07), respectively; however there were no statistically significant differences between groups. Additionally, the researchers noted that the response to esketamine plus AD was rapid and generally increased over time with repeat doses. The authors concluded that IN esketamine in 56 mg or 84 mg doses plus an oral AD achieved a clinically meaningful benefit in patients with TRD.

Safety and Black Box Warning : Esketamine has been shown to cause a significant increase in blood pressure (BP) regardless of the dose administered which commonly occurs within 40 minutes and lasts about 4 hours.[4] Esketamine caused dissociative syndrome in 41% and sedation in 23% of those treated in clinical trials. It has a black box warning for sedation, dissociation, abuse and misuse, and suicidal ideation and behaviors. Select common side effects associated with esketamine use (incidence ≥ 5%) include dissociation, dizziness, nausea, sedation, vertigo, hypoesthesia, anxiety, and elevated BP.

Risk Evaluation and Mitigation Strategy (REMS): Esketamine is a REMS medication requiring providers and patients be enrolled in the Spravato™ REMS Program.[4] The goal of this REMS program is to communicate the safety information for esketamine to reduce the risks of serious harm. Details about the Spravato™ REMS program can be found on this website: https://www.spravatorems.com/.

Dosing and Administration: Esketamine is delivered via a nasal spray device that administers a total of 28 mg of drug per unit.[4] In order to achieve higher doses multiple devices are needed. Details regarding dosage of IN esketamine are located in the package insert. When administering multiple doses, a 5 minute rest period between each administration is necessary to allow for adequate absorption. Unlike other intranasal sprays, esketamine should not be primed prior to administration. Patients must administer the medication in the presence of a healthcare provider and be evaluated for at least 2 hours for elevated BP and signs of dissociative syndrome after administration. Patients should avoid food and liquids for at least 2 hours prior to and for 30 minutes after administration.

Cost and Availability: Esketamine nasal spray, a Schedule III Controlled Substance, can only be dispensed by REMs enrolled pharmacies to enrolled providers.[4] It will be available as a 56 mg Dose Kit unit-dose carton which includes two 28 mg nasal spray devices (totaling to 56 mg) (NDC-50453-028-02) and an 84 mg Dose Kit unit-dose carton which includes three 28 mg nasal spray devices (totaling to 84 mg) (NDC-50458-028-03). Each 28 mg device individually packed in a sealed blister pack (NDC- 50454-028-00). The Average Wholesale Price (AWP) price is $354.00 for each device, therefore the 56 mg kit price will be $708 and the 84 mg kit price will be $1062.[7]

Formulary Status: Intranasal esketamine is currently on the CCHS Formulary restricted to Psychiatry for management of TRD in the outpatient setting at Lutheran Hospital only. All REMS requirements must be met.

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Additions to the Adult CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Restrictions/Comments**
Bevacizumab-awwb (Mvasi™)	Monoclonal Antibody	Cervical, Colorectal, Non-Small Cell Lung, Renal Cell Cancer	Restricted to the Department of Hematology and Medical Oncology for outpatients whose insurance mandates the use of bevacizumab-awwb (Mvasi™) This product is the biosimilar for Avastin®.
Brexanolone (Zulresso™)	Antidepressant	Post-partum Depression	Restricted to specific physicians at Hillcrest Hospital only (Ken Rao, MD, Lara Feldman, MD, Vrashali Jain, MD, Adele Viguera, MD) per the Brexanolone IV Infusion Time Limited Protocol (including a qualifying 17-item Hamilton Rating Scale for depression score ≥ 26). Both Psychiatry and Obstetrics will evaluate appropriateness of therapy before initiation of treatment.
Esketamine (Spravato™)	Antidepressant	TRD	Restricted to Psychiatry for management of TRD in the outpatient setting at Lutheran Hospital only. All REMS requirements must be met.
Mifepristone (Mifeprex®)	Abortifacient	Termination of intrauterine pregnancy	Restricted to Obstetrics/ Gynecology who are REMS certified
Polatuzumab vedotin (Polivy™)	Monoclonal Antibody	Diffuse large B-cell lymphoma, relapsed or refractory	Restricted to Department of Hematology and Medical Oncology for outpatient use only
Trastuzumab-anns (Kanjinti™)	Monoclonal Antibody	Breast Cancer	Restricted to the Department of Hematology and Medical Oncology for outpatients whose insurance mandates the use of trastuzumab-anns (Kanjinti™) This product is the biosimilar for Herceptin®.

IV= Intravenous TRD=Treatment Resistant Depression REMS=Risk Evaluation Mitigation Strategy

Removals from the Adult CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Comments**
Acetaminophen Intravenous (Ofirmev®)	Pain Reliever	Analgesia	Rationale: 1) A systematic literature review found that IV acetaminophen did not demonstrate benefit in regards to analgesic efficacy, opioid consumption, length of stay, or incidence of nausea and vomiting when compared to other analgesic alternatives including other dosage forms of acetaminophen (e.g., rectal, oral) 2) The cost of a single dose of IV acetaminophen is substantially higher than other formulations of acetaminophen
Select Oral Chemotherapy Agents	Chemotherapy	Cancer	Rationale: 1) Low utilization of these oral chemotherapy agents 2) May use patient's own supply when necessary 3) Rheumatology and Gastroenterology have evaluated and approved these removals Agents being removed: bexarotene, busulfan, capcitabine, chlorambucil, erlotinib, everolimus (Afinitor® only; Zortress® will remain on formulary), gefitinib, lomustine, melphalan, mitotane, temozolomide, topotecan, and venetoclax.

IV=Intravenous

Changes to Restrictions of Medications on the Adult CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Changes to Restrictions**
Albumin 25%	Blood Product Derivative	Plasma Volume Expander	Removed the 24-hour restriction (hard stop) on albumin 25% for the MICU albumin order panel only
Belatacept (Nujolix®)	Selective T-Cell Costimulation Blocker	Prophylaxis of Organ Rejection of Kidney Transplant	Restricted to Kidney Transplant for *de novo* initiation or conversion due to intolerable adverse events (including but not limited to: nephrotoxicity, neurotoxicity, and thrombotic microangiopathies) with a CNI or mTOR inhibitor
Bleomycin	Antineoplastic Agent	Hodgkin Lymphoma Testicular Cancer	Restricted to the Department of Hematology and Medical Oncology
Caplacizumab (Cablivi®)	Monoclonal Antibody	aTTP	Restricted to Benign Hematology (i.e., removed restriction of second-line therapy)
Epoetin alfa (Procrit®) and Darbepoetin alfa (Aranesp®)	Colony Stimulating Factor	Anemia	Removed MDS as an exclusion from the ESA therapeutic interchange
Filgrastim-sndz (Zarxio®)	Colony Stimulating Factor	Neutropenia	Restricted to the Department of Hematology and Medial Oncology for outpatient use only in patients whose insurance mandates Zarxio®
Ketamine	General Anesthetic	Severe Agitation Analgesia Sedation	Restricted to: Inpatient: 1) Emergency Medicine Staff physicians per guidelines/ protocols for severe agitation and sub-dissociative dosing 2) ICUs† 3) Acute Pain Management Service Outpatient: 1) Psychiatry and Chronic Pain Management
Posaconazole (Noxafil®)	Antifungal Agent	Fungal Infections	Restricted to: 1) Department of Infectious Diseases 2) Department of Hematology and Medical Oncology/ BMT 3) Lung Transplant

MICU= Medical Intensive Care Unit CNI=Calcineurin Inhibitor mTOR Inhibitor=Mammalian Target of Rapamycin
aTTP= Acquired Thrombotic Thrombocytopenic Purpura MDS=Myelodysplastic Syndrome ESA=Erythropoiesis-stimulating Agent
ICUs=Intensive Care Units BMT=Bone Marrow Transplant
†See Adult IV Guidelines for non-ICU units meeting the monitoring parameters in the subanesthetic ketamine infusion standard of practice.

Therapeutic Interchanges for the Adult CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Conversion***
Tiotropium bromide (Spiriva® Respimat®) Umeclidinium bromide (Incruse® Ellipta®) Aclidinium bromide (Tudorza® Pressair®)	LAMAs	COPD Asthma	**Orders for:** Spiriva® Respimat® Incruse® Ellipta® Tudorza® Pressair® **Will be converted to:** Glycopyrrolate (Seebri® Neohaler®) for non-mechanically ventilated patients Nebulized ipratropium for mechanically ventilated, ED, and Obs patients
Umeclidinium bromide/ Vilanterol trifenatate (Anoro® Ellipta®) Tiotropium bromide/ Olodaterol (Stiolto® Respimat®) Formoterol/ Glycopyrrolate (Bevespi® Aerosphere®)	LAMAs/ LABAs	COPD	**Orders for:** Anoro® Ellipta® Stiolto® Respimat® Bevespi® Aerosphere® **Will be converted to:** Indacaterol/Glycopyrrolate (Utibron® Neohaler®) for non-mechanically ventilated patients Nebulized albuterol and ipratropium (DuoNeb®) for mechanically ventilated, ED, and Obs patients
Fluticasone furoate, Umeclidinium bromide and Vilanterol trifenatate (Trelegy® Ellipta®)	Corticosteroid/ LAMAs/LABAs	COPD	**Orders for:** Trelegy® Ellipta®: **Will be converted to:** Mometasone furoate (Asmanex® Twisthaler®) and Indacaterol/Glycopyrrolate (Utibron® Neohaler®) for non-mechanically ventilated patients Budesonide solution for nebulization and Ipratropium/ Albuterol (DuoNeb®) for mechanically ventilated, ED, or Obs patients

LAMAs=Long-acting Muscarinic Antagonists LABAs=Long-acting Beta-Agonists COPD=Chronic Obstructive Pulmonary Disease
ED=Emergency Department Obs=Observation Status
*A dosage conversion table is available in Lexi-Comp® and the Therapeutic Interchange List on the DI SharePoint Site.

Therapeutic Interchanges for the Adult CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Conversion**
Ferric citrate Lanthanum carbonate Sevelamer carbonate packets Sevelamer hydrochloride Sucroferric oxyhydroxide	Phosphate Binders	Hyperphosphatemia	Ferric citrate Lanthanum carbonate Sevelamer carbonate Sevelamer hydrochloride Sucroferric oxyhydroxide Will be converted to: Sevelamer carbonate tablet*†
Lidocaine 5% Transdermal Patches	Topical Local Anesthetic	Pain Relief	Lidocaine 5% transdermal patches will be automatically converted to Lidocaine 4% transdermal patches (Salonpas®) Note: The Salonpas® Lidocaine 4% patches may be cut if necessary

*Sevelamer carbonate packets will be available for patients unable to swallow tablets.
†A dosage conversion table is available in Lexi-Comp® and the Therapeutic Interchange List on the DI SharePoint Site.

Product Standardizations, Policy Change, and New Order Set on the Adult CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Change/Comment**
Ambrisentan (Letairis®)	Vasodilator	PAH	Will stock the generic ambrisentan Substantial Cost Savings
Colistimethate (Coly-Mycin® M)	Antibiotic	Severe infections (e.g., pneumonia, meningitis, bronchiectasis in cystic fibrosis and non-cystic fibrosis patients)	Removal of colistimethate from dose rounding policy Allows for more accurate dosing of medication
Ferric Gluconate (Ferrlecit®)	Iron Preparation	Iron-deficiency	A ferric gluconate (Ferrlecit®) order panel was approved to assist the prescriber with appropriate use of this agent
Fosaprepitant Intravenous (IV Emend®)	Antiemetic	Prevention of chemotherapy-induced nausea and vomiting	Will stock generic IV fosaprepitant Substantial Cost Savings

PAH=Pulmonary Arterial Hypertension IV=Intravenous

Addition to the Pediatric CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Restrictions/Comments**
Bleomycin Intralesional Injection	Chemotherapeutic Agent	Removal of Venous Malformations	Restricted to the Department of Interventional Radiology

Changes to Restrictions of Medications on the Pediatric CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Restrictions/Comments**
Bleomycin	Antineoplastic Agent	Lymphoma Malignant Germ Cell Cancer	Restricted to Pediatric Hematology/Oncology
Dexmedetomidine (Precedex®)	Alpha 2-Adrenergic Agonist	Sedation	Removed restrictions to align with the Adult CCHS Formulary
Filgrastim (Neupogen®) and Sargramostim (Leukine®)	Colony Stimulating Factors	Neutropenia	Modified restrictions on filgrastim (Neupogen®) to include: Restricted to Solid Organ Transplant Services for patients with an ANC <1000 cells/mm^3 for a one-time dose within a 24-hour period. Filgrastim should not be used in combination with sargramostim (Leukine®). These restrictions do not apply for Hematology, Oncology, or BMT patients. Modified restrictions on sargramostim (Leukine®) to include: Restricted to Solid Organ Transplant Services for patients with an ANC < 1000 cells/mm^3 for a one-time dose within a 24-hour period . Sargramostim should not be used in combination with filgrastim (Neupogen®). These restrictions do not apply to Hematology, Oncology, or BMT patients.
Infliximab-abda (Renflexis®)	TNF Blocker	CD UC	Modified restrictions to include pediatric UC for patients whose insurance mandates the use of Renflexis® Note: Remicade® is still the preferred infliximab product on the CCHS Pediatric Formulary for inpatient and outpatient use.

ANC=Absolute Neutrophil Count BMT=Bone Marrow Transplant CD=Crohn's Disease UC=Ulcerative Colitis

Product Standardization and Policy Change for the Pediatric CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Restrictions/Comments**
Fosaprepitant Intravenous (IV Emend®)	Antiemetic	Prevention of chemotherapy-induced nausea and vomiting	Will stock generic IV fosaprepitant Substantial Cost Savings
Potassium Chloride Injection	Electrolyte	Hypokalemia	Dose rounding for patients ≥ 3 kg*

*Details about the dose rounding are located in the Dose Rounding Policy on the Drug Information Sharepoint Site.

Therapeutic Interchange for the Pediatric CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Comments**
Lidocaine 5% Transdermal Patches	Topical Local Anesthetic	Pain Relief	Lidocaine 5% transdermal patches will be automatically converted to Lidocaine 4% transdermal patches (Salonpas®) Note: The Salonpas® Lidocaine 4% patches may be cut if necessary