The Latest in the Management of Functional in Neuroendocrine Tumors

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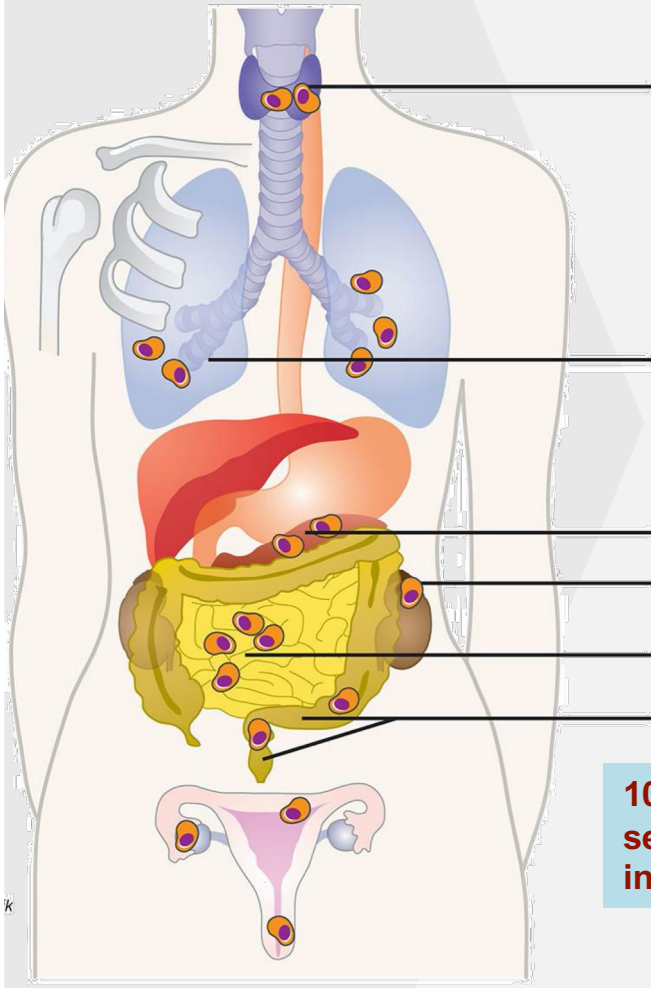
Understanding Hormones and Neuroendocrine Tumors (NETs)

What are hormones?
Hormones are **chemical messengers** made by special cells in your body. They travel through the bloodstream and tell organs what to do such as controlling digestion, blood sugar, growth, mood, and energy levels.

What are neuroendocrine tumors?
Neuroendocrine tumors (NETs) grow from **neuroendocrine cells.** Neuroendocrine cells are characterized by producing a series of molecules (neuropeptides, neuromodulators, or neurotransmitters), also called hormones.

Feature	Functional NET	Non-Functional NET
Produces hormones	Yes	No (or inactive)
Hormone symptoms	Common • Too much insulin → low blood glucose • Too much serotonin→ flushing, diarrhea • Too much gastrin → severe stomach acid and ulcers	Rare
Diagnosis timing	Often earlier	Often later
Symptoms caused by	Hormone excess	Tumor size/location

Neuroendocrine Tumors and Hormones



Thyroid → Medullary Thyroid Cancer → Calcitonin

Lung → Bronchial NET → Serotonin→5HIAA (2-5%)
Thymic NET → Ectopic ACTH syndrome (1-3%)
Ectopic production of GHRH/IGF-1

Pancreas (non-carcinoid)

Adrenal → Pheochromocytoma/Paraganglioma → Catecholamines
Metanephrines

Small Intestine → Carcinoid Sx → Serotonin→5HIAA

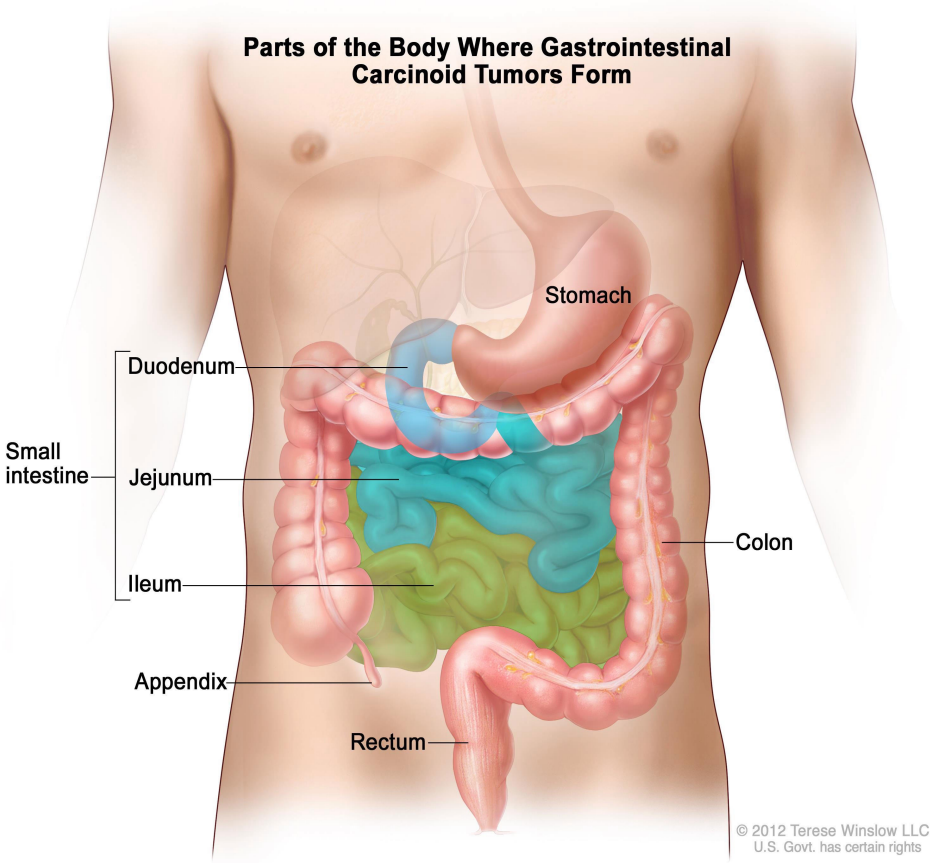
Rectum/Colon

Pancreas → Gastrinoma → Gastrin
Insulinoma → Insulin
Glucagonoma → Glucagon
VIPoma → Vasoactive Intestinal Polypeptide
Somatostatinoma → Somatostatin

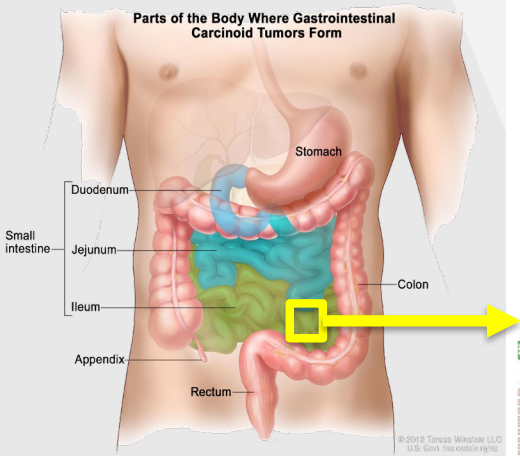
10-30% of Pancreas NETs secrete hormones resulting in clinical syndromes.

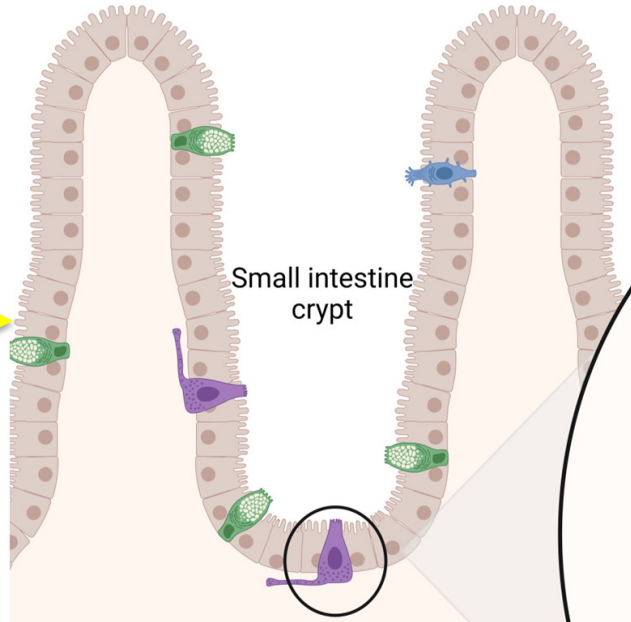
GI Neuroendocrine Tumors (GI NETs)

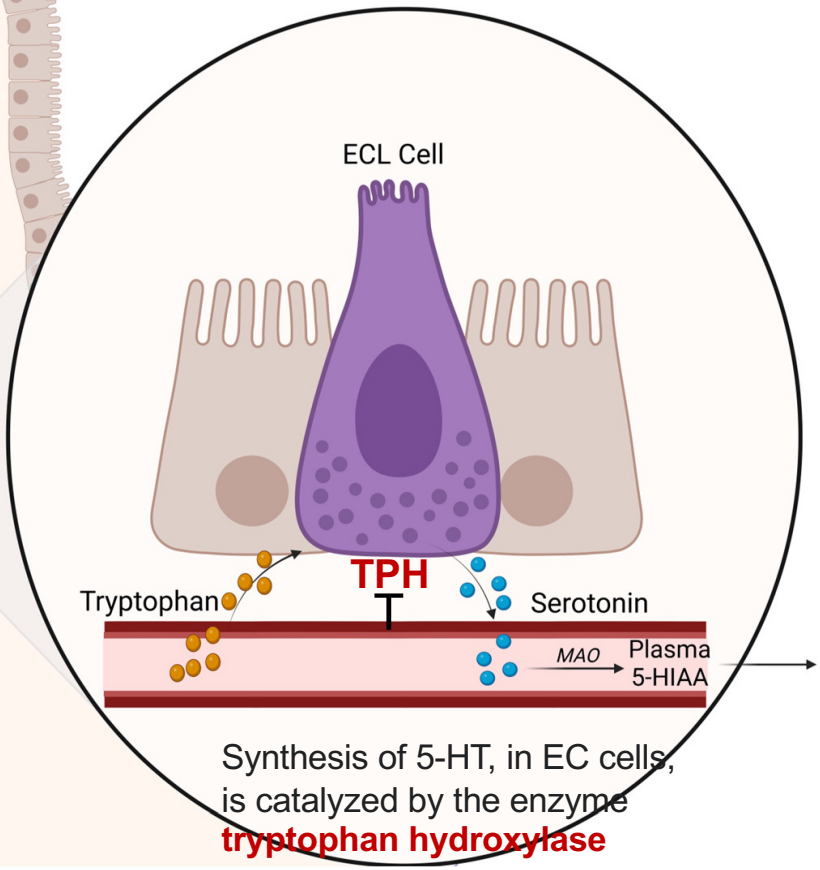
> 90 % of patients with carcinoid syndrome involve the liver with primary tumors in the distal small intestine or proximal colon.



Serotonin Pathway in the Small Intesttine







Enterochromaffin (EC) are a type of enteroendocrine cell, and neuroendocrine cell and play a crucial role in gastrointestinal regulation, particularly intestinal motility and secretion

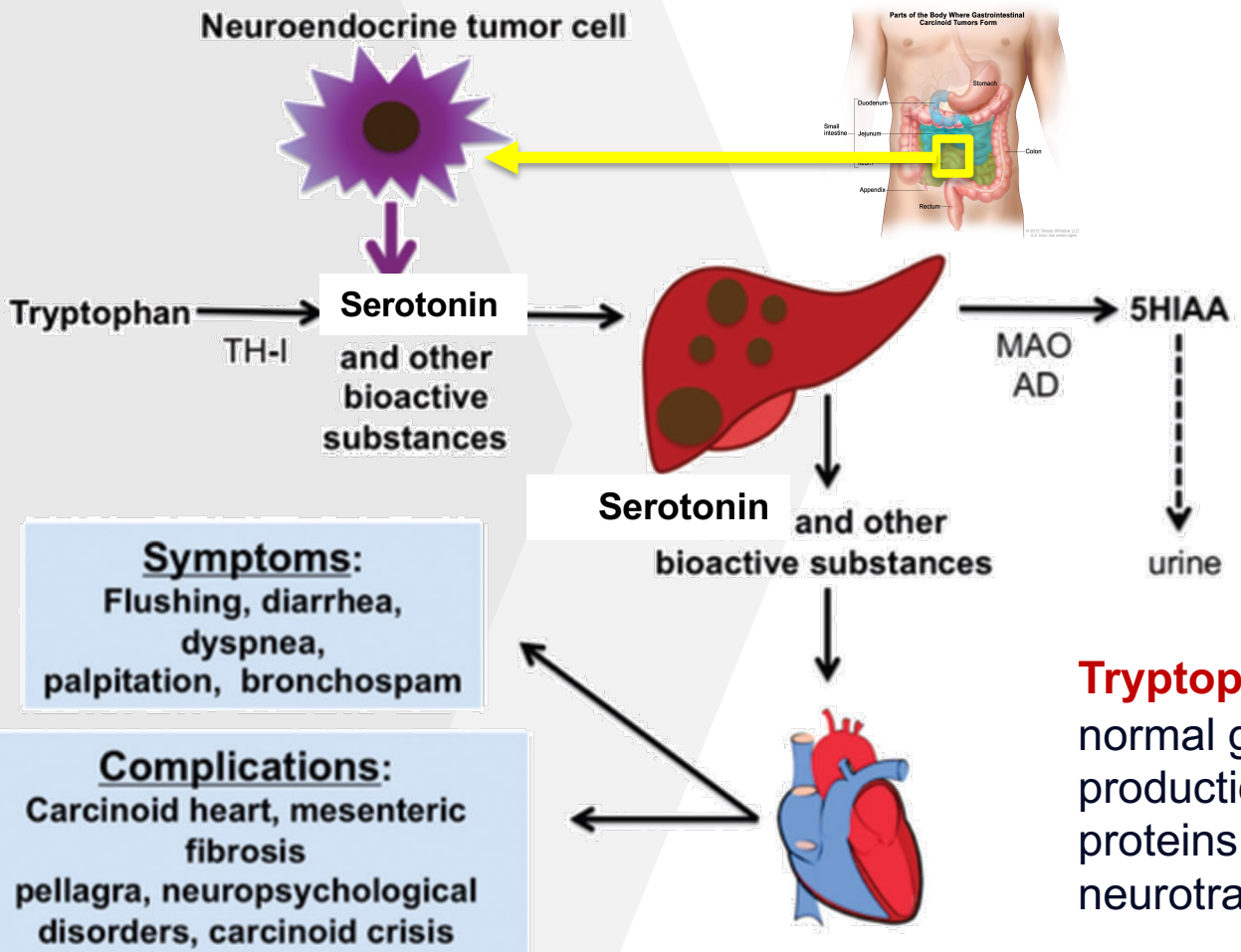
Synthesis of 5-HT, in EC cells, is catalyzed by the enzyme **tryptophan hydroxylase**

Effects of Elevated Serotonin

Carcinoid Syndrome

Tumor Growth

Serotonin and NETs

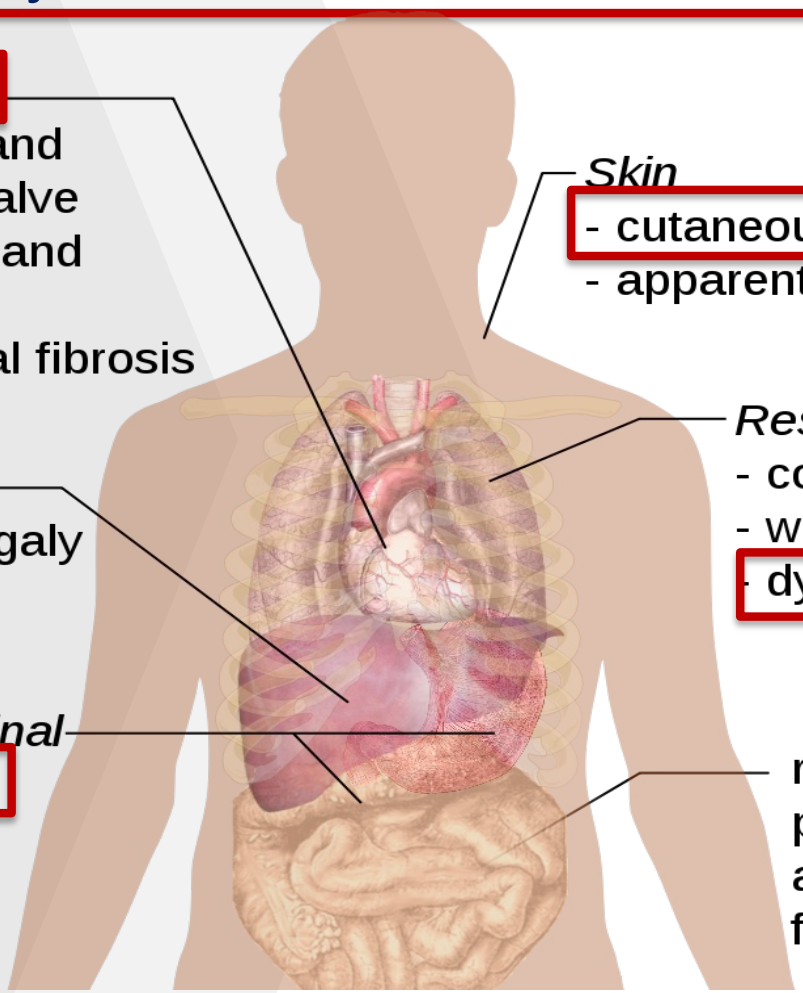


Tryptophan is an amino acid needed for normal growth in infants and for the production and maintenance of the body's proteins, muscles, enzymes, and neurotransmitters

Rubin et al. Clinics. 2018

Carcinoid Syndrome

Diarrhea → Serotonin
Flushing → Histamine/kallikrein/tachykinins



Heart
- pulmonic and tricuspid valve thickening and stenosis
- endocardial fibrosis

Skin
- cutaneous flushes
- apparent cyanosis

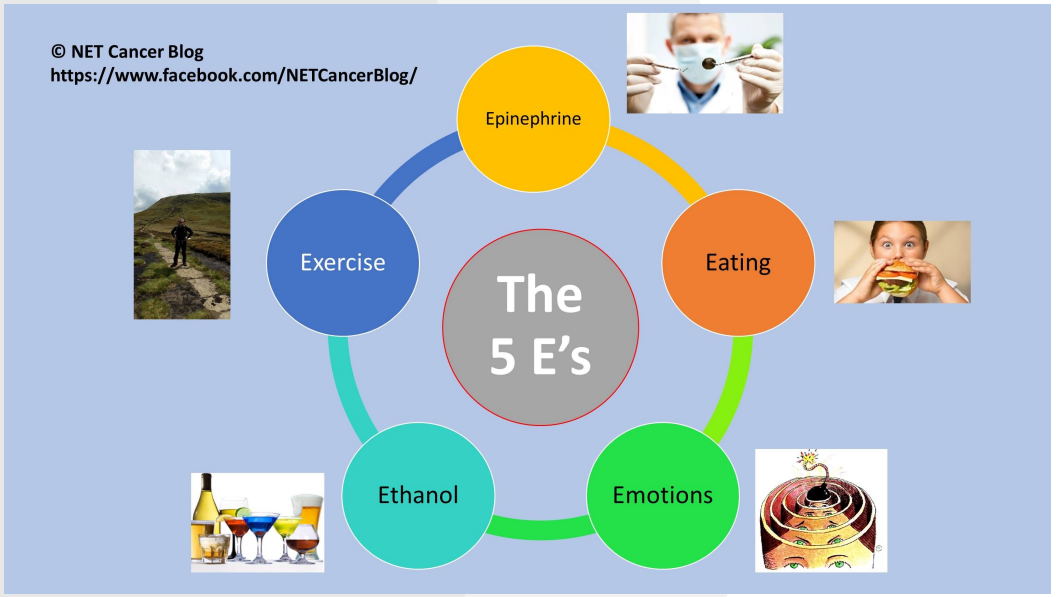
Respiratory
- cough
- wheezing
- dyspnea

Liver
- hepatomegaly

Gastrointestinal
- diarrhea
- cramps
- nausea
- vomiting

retro-peritoneal and pelvic fibrosis

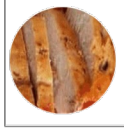
The 5 E's



Top 10 Foods Highest in Tryptophan

280mg of Tryptophan = 100% of the Recommended Daily Intake (%RDI)

1 Lean Chicken & Turkey



245% RDI (687mg)
in a 6oz chicken breast

267 calories

2 Beef (Skirt Steak)

227% RDI (636mg)
per 6oz steak

456 calories

3 Lean Pork Chops

224% RDI (627mg)
in a 6oz chop

332 calories

4 Firm Tofu

212% RDI (592mg)
per cup

363 calories

5 Fish (Salmon)

203% RDI (570mg)
per 6oz fillet

265 calories

6 Boiled Soybeans (Edamame)

149% RDI (416mg)
per cup

296 calories

7 Milk

75% RDI (211mg)
per 16oz glass

167 calories

8 Squash and Pumpkin Seeds

58% RDI (164mg)
per 1oz handful

159 calories

9 Oatmeal

33% RDI (94mg)
per cup

166 calories

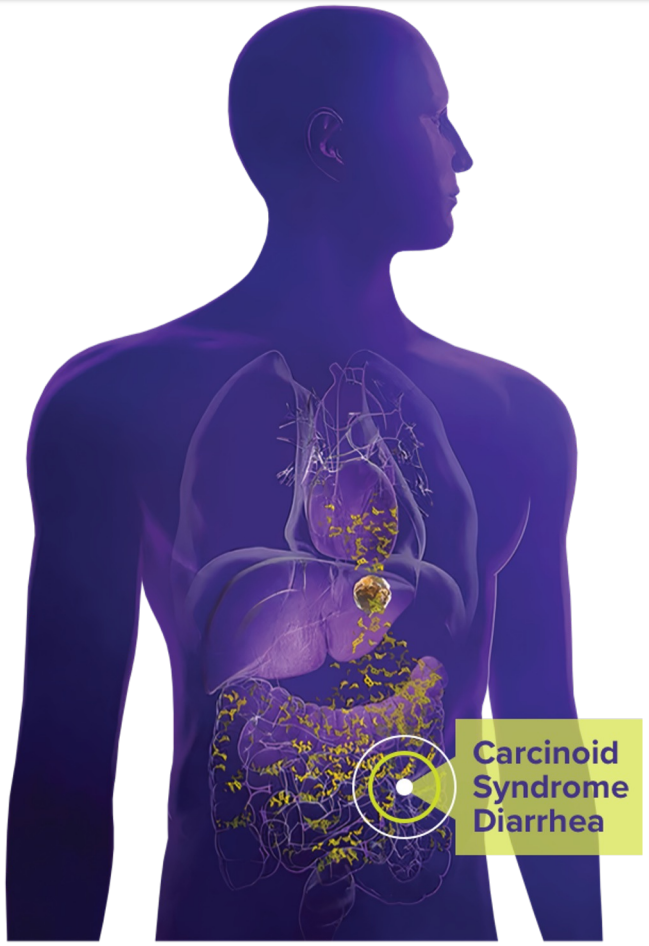
10 Eggs

27% RDI (77mg)
in 1 large egg

78 calories

Carcinoid Syndrome Diarrhea

- Occurs in 80% of patients and is often the most debilitating component of the syndrome
- Stools may vary from few to more than 30 per day, are typically watery and non-bloody, and can be explosive and accompanied by abdominal cramping
- The abdominal cramps may be a consequence of mesenteric fibrosis or intestinal blockage by the primary tumor
- The diarrhea is usually unrelated to flushing episodes

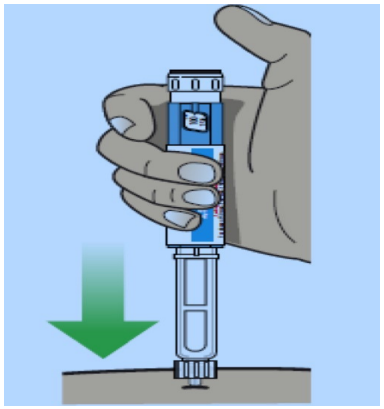


https://www.hcp/about-carcinoid-syndrome-diarrhea

Somatostatin Analog Therapy: Lanreotide or Octreotide LAR

- 80% of well-differentiated NETs express somatostatin receptors
- Somatostatin analogues have a dual role:
  - Control tumor growth
  - Control hormonal production
- Octreotide LAR and Lanreotide Autogel

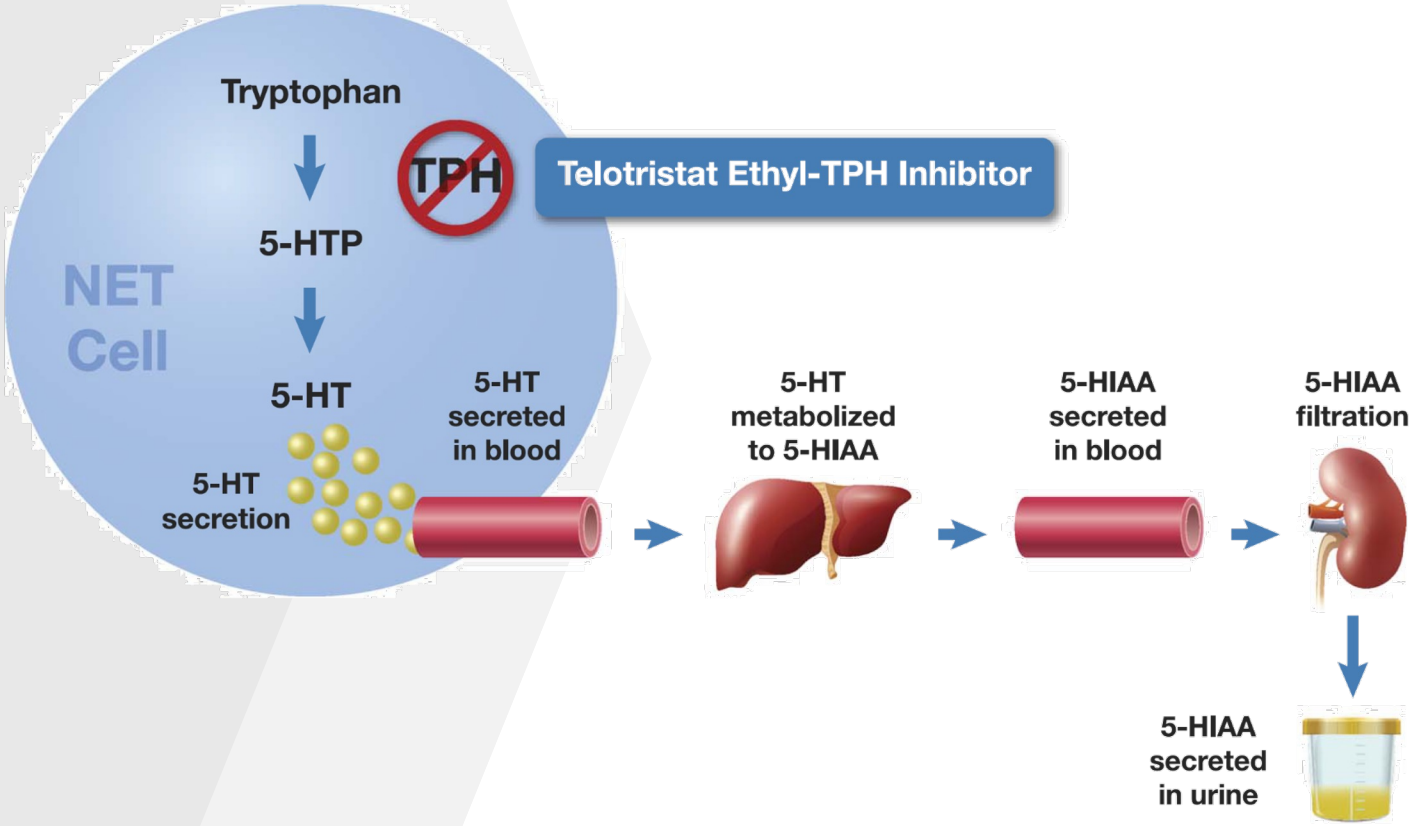
Every 28 days



A somatostatin analogue is **a man made (synthetic) version of somatostatin**. It slows down the production of hormones and growth of the NET

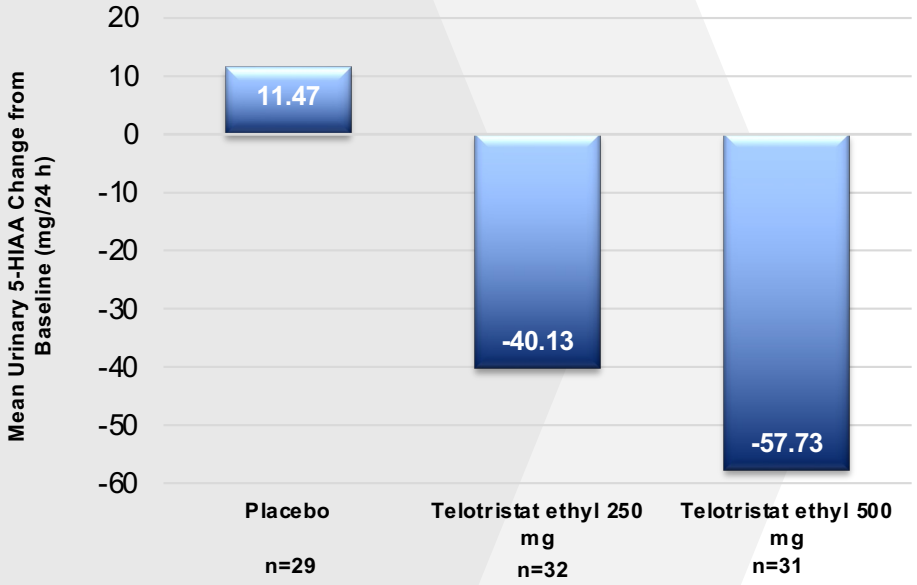
Short acting

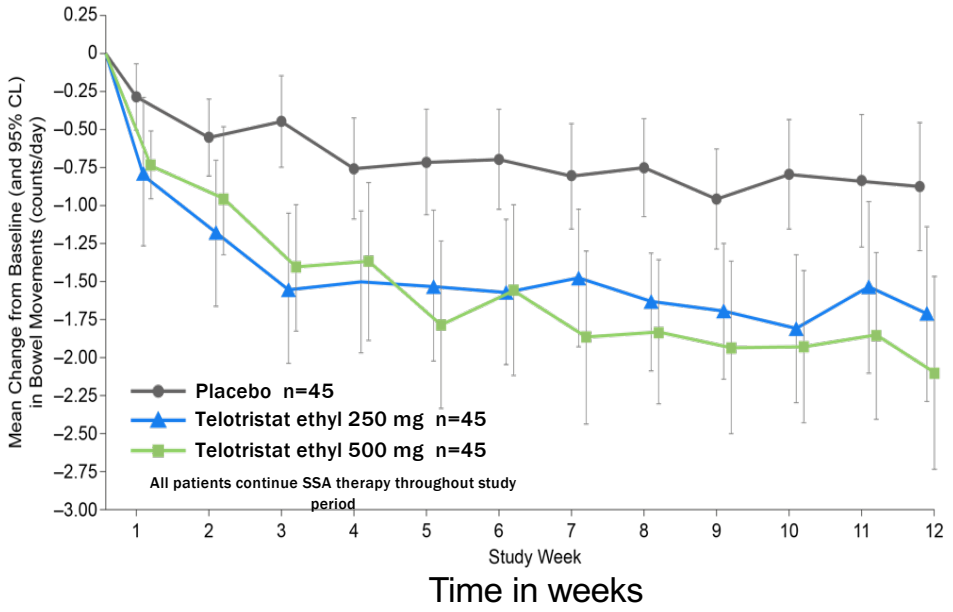
Mechanism of Action of Telotristat Ethyl in NETs



Naraev et al. Pancreas. 2019;48: 961-972

Telotristat Ethyl

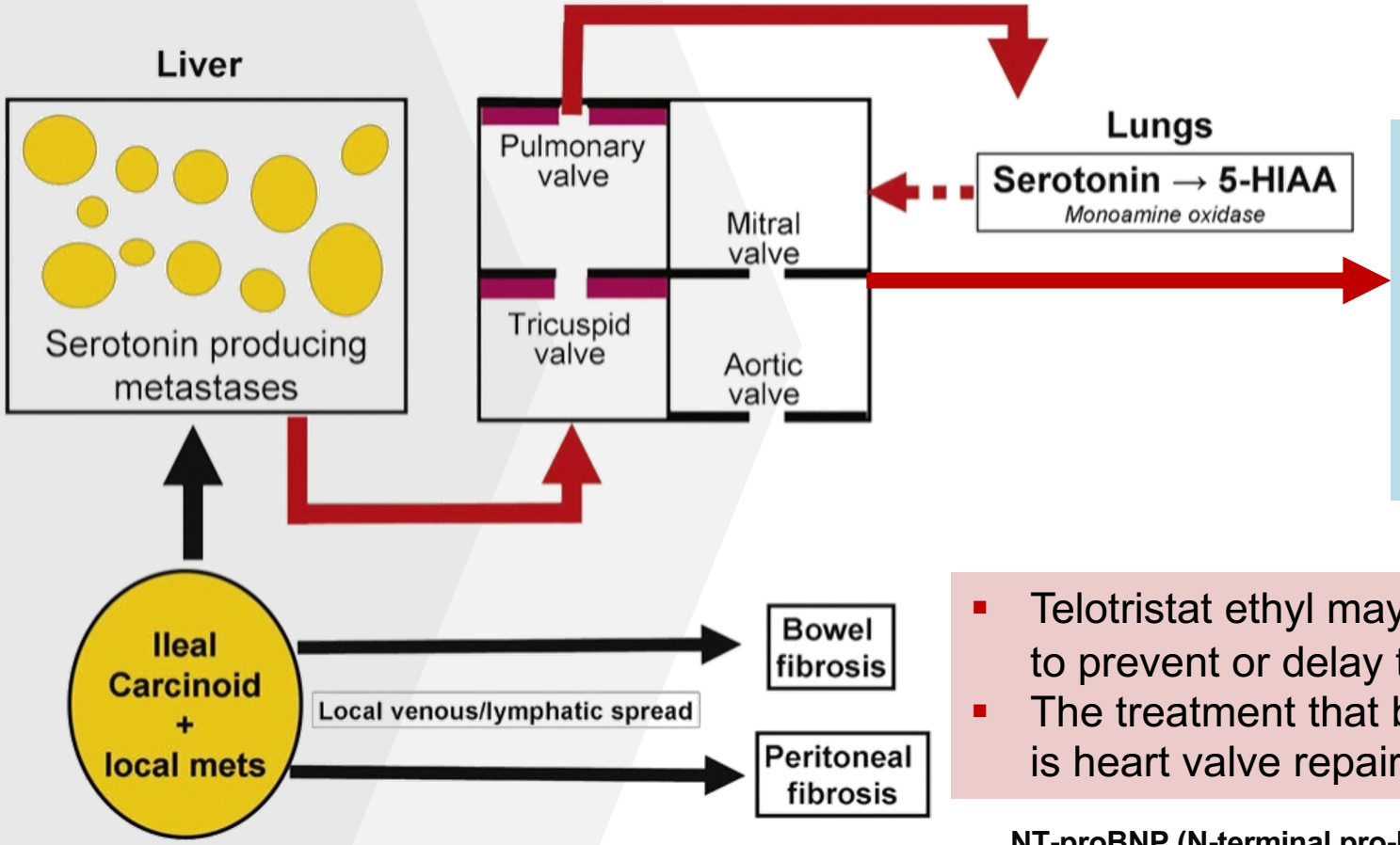




Time in weeks

Kulke M et al. *JCO.* 2017; 35 (1): 14-23

Carcinoid Heart Disease



- NT-proBNP: it is a blood test that shows how hard your heart is working
- Higher levels of NT-proBNP in your blood mean more strain on your heart

- Telotristat ethyl may be a treatment to prevent or delay the onset of CHD
- The treatment that best controls CHD is heart valve repair surgery

NT-proBNP (N-terminal pro-B-type natriuretic peptide)

Telotristat Ethyl for the Treatment of Carcinoid Heart Disease in Patients With NETs (NCT04810091)

Primary Objective:

- To estimate the percent change in N-terminal pro B-type natriuretic peptide (NT-proBNP) at 6 month visit from baseline after initiation of study drug in each arm and to compare the percent change between the two study arms.

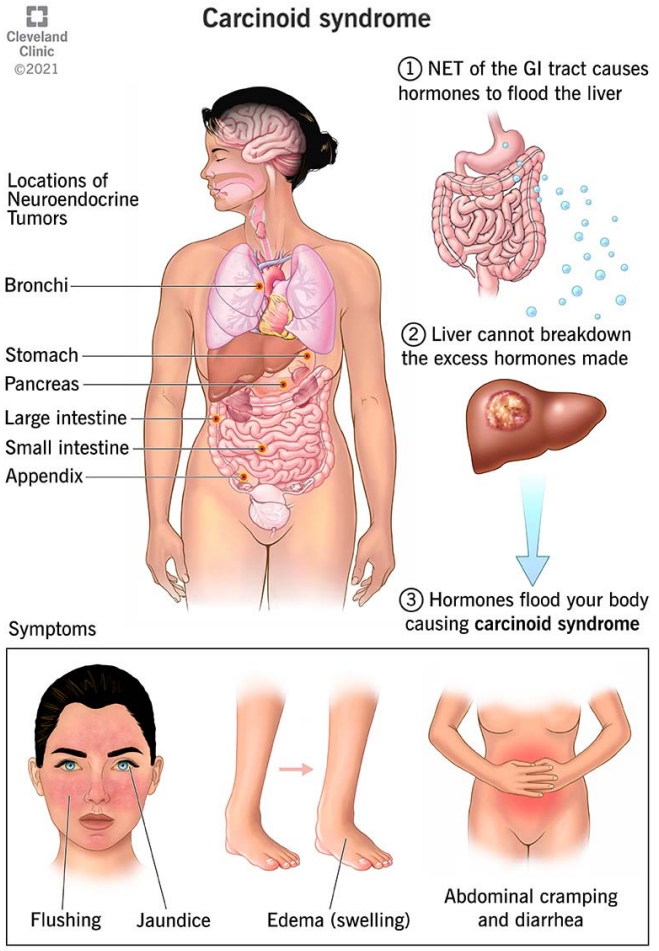
Secondary Objectives:

- To evaluate the change in functional capacity
- To evaluate changes in echocardiographic parameters
- To evaluate the change from baseline to 3 and 6 month visits in plasma 5-hydroxyindoleacetic acid (5-HIAA)

- A clinical trial comparing the effects of telotristat ethyl combined with somatostatin analog (SSA) therapy versus SSA therapy alone on specific markers of heart disease: such as NT-proBNP levels and echocardiographic parameters

What is Palsutosine?

- Paltusotine is an oral medicine designed to help control hormone-related symptoms caused by some neuroendocrine tumors (NETs). It works in a similar way to somatostatin medicines that are usually given by injection.
- Acts like somatostatin
- Attaches to somatostatin receptors on neuroendocrine tumor cells
- Signals the cells to release fewer hormones



Study to Evaluate the Safety and Dose Response of Paltusotine in Subjects With Carcinoid Syndrome

Phase II Study

- Patients with carcinoid syndrome
- Carcinoid syndrome diarrhea

40 mg Paltusotine
Two 20 mg tablets daily

Multicenter International Study

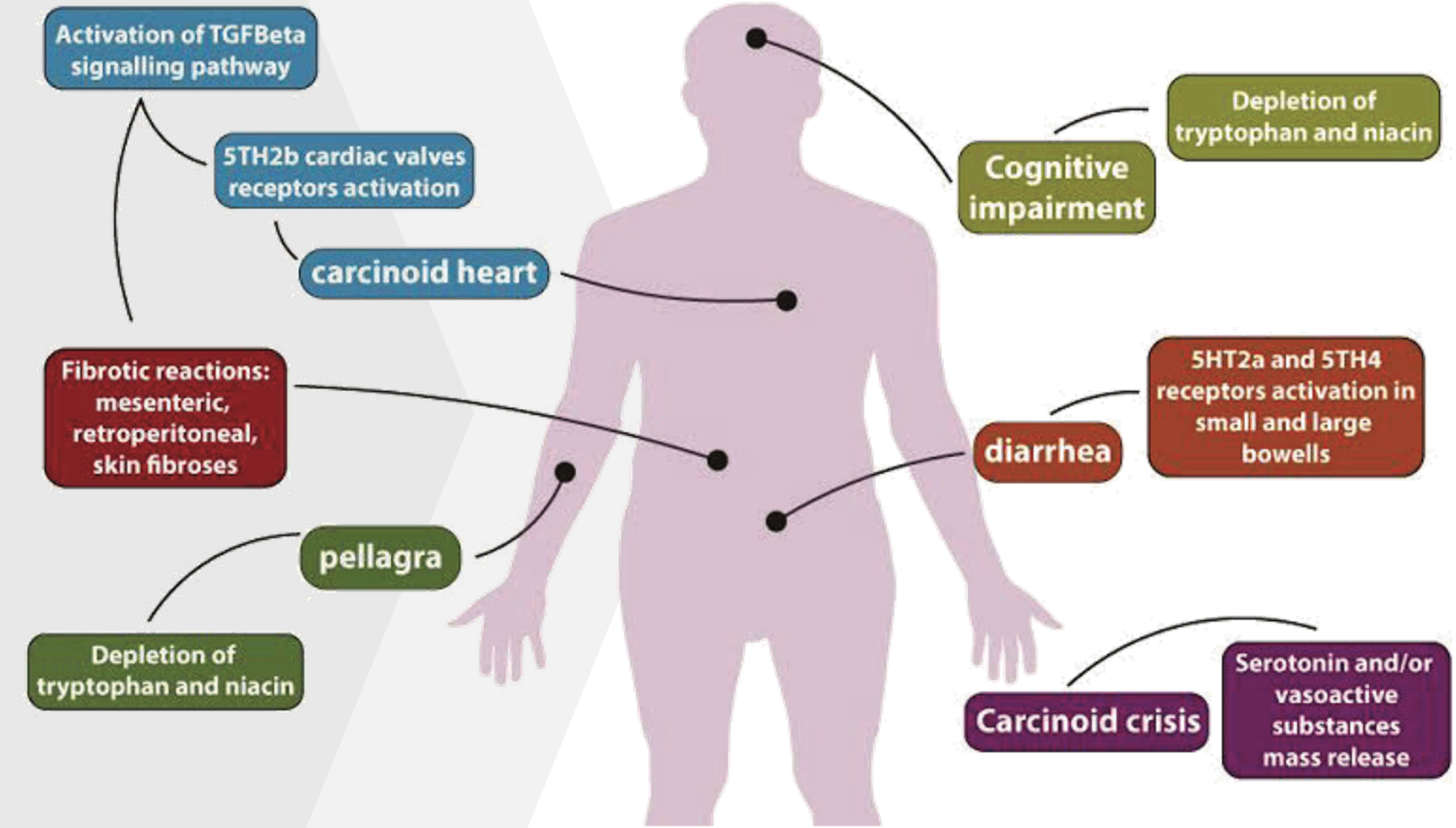
80 mg Paltusotine
Four 20 mg tablets daily

Primary Objective:
Incidence of treatment-emergent adverse events

The initial trial findings indicate that:

- **Paltusotine resulted in a 65% reduction in bowel movement frequency and 65% reduction in flushing episodes**
- **Paltusotine was generally well-tolerated**

***For more information about the paltusotine study, visit clinicaltrials.gov.**


Activation of TGFBeta signalling pathway
5TH2b cardiac valves receptors activation
carcinoid heart
Fibrotic reactions: mesenteric, retroperitoneal, skin fibroses
pellagra
Depletion of tryptophan and niacin
Cognitive impairment
Depletion of tryptophan and niacin
diarrhea
5HT2a and 5TH4 receptors activation in small and large bowells
Carcinoid crisis
Serotonin and/or vasoactive substances mass release

Summary

Serotonin overproduction is a driver of carcinoid syndrome

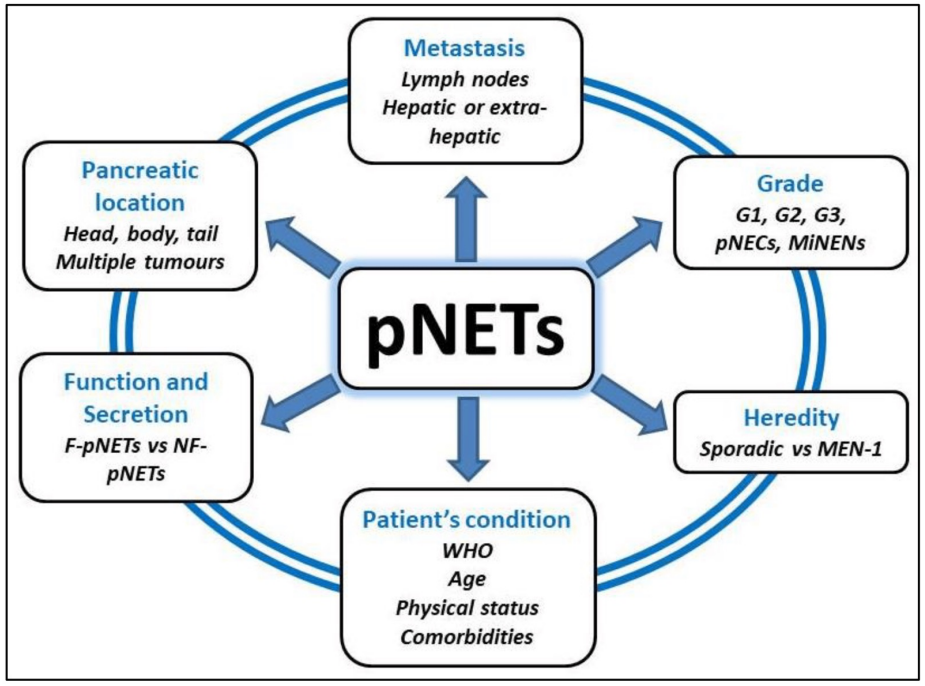
Serotonin plays important roles in development of

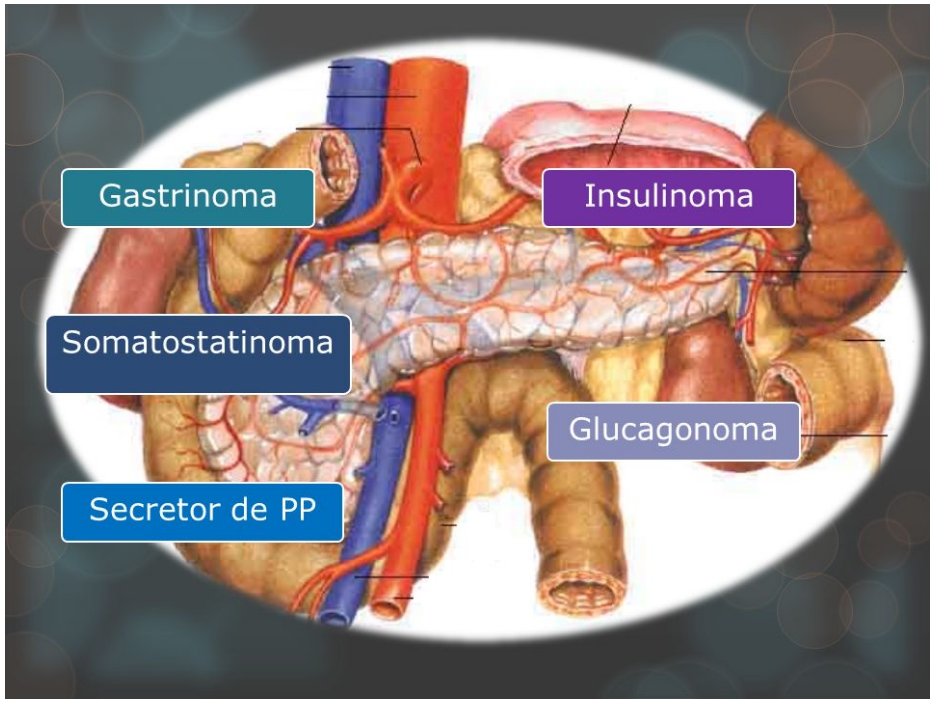
- **carcinoid heart disease**
- **mesenteric fibrosis**
- **pulmonary artery hypertension**

Serotonin has demonstrated effects on tumor growth

Control of serotonin exposure is important to improve quality of life and prognosis of patients with carcinoid syndrome

Pancreatic Neuroendocrine Tumors (PanNETs)



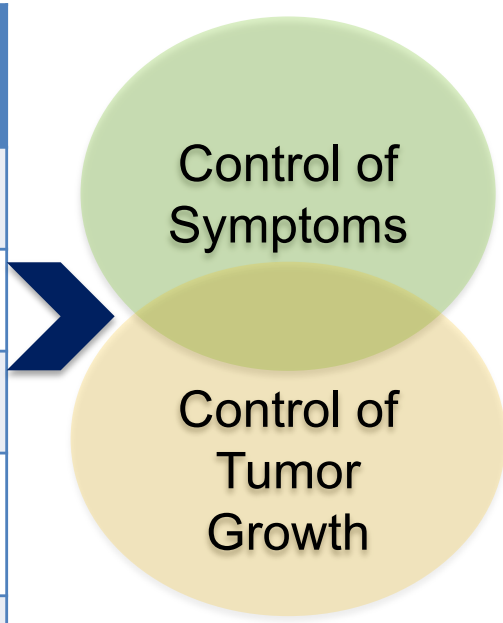


10-30% of PanNETs secrete hormones resulting in clinical syndromes

De Ponthau et al. *Cancers* **2021**, *13*, 5969.

Functional Pancreatic Neuroendocrine Tumors

Tumor	Peptide	Incidence per 10^6 persons per year	Symptoms /Syndrome
Insulinoma	Insulin	1-2	Hypoglycemia (low blood glucose)
Gastrinoma	Gastrin	0.5-1.5	Ulcers, diarrhea, Zollinger-Ellison syndrome
VIPoma	VIP	0.05-0.2	Verner-Morrison syndrome
Glucagonoma	Glucagon	0.01-0.1	Diabetes mellitus (high blood glucose), skin rashes, muscle mass loss
Somatostatinoma	Somatostatin	Very rare	Bile stones, increase fat excretion in stools, diabetes mellitus (high blood glucose)



Adapted Dr. De Herden ENDO Meeting

How Common is Low Blood Sugar in Neuroendocrine Tumors?

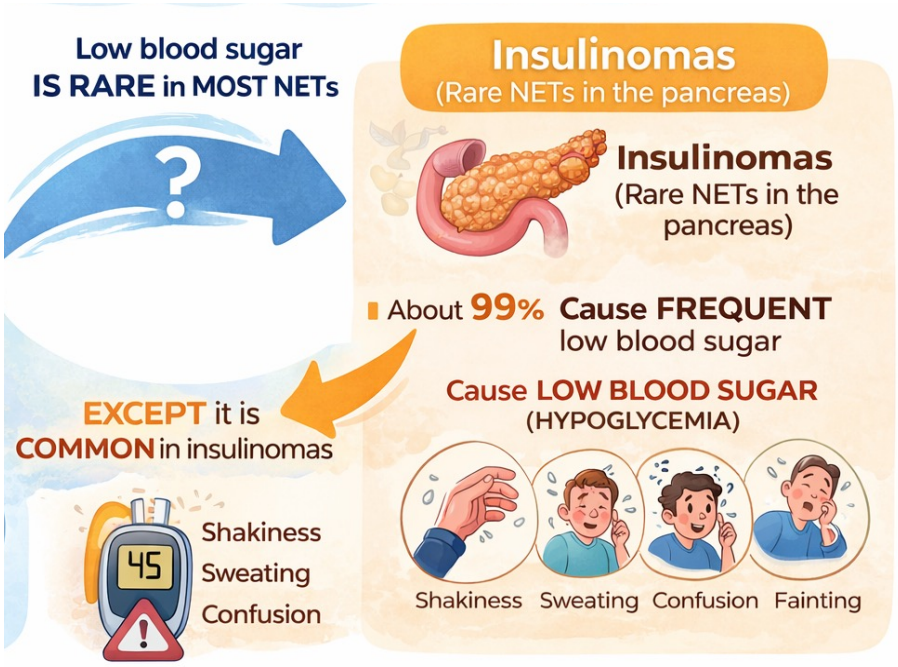
Low blood sugar is uncommon in most neuroendocrine tumors, but it is common in a specific type called an insulinoma.

Insulinomas (the main exception)

- **Insulinomas** are rare NETs of the pancreas
- They make **too much insulin**
- Insulin lowers blood sugar, so **hypoglycemia is the main symptom**

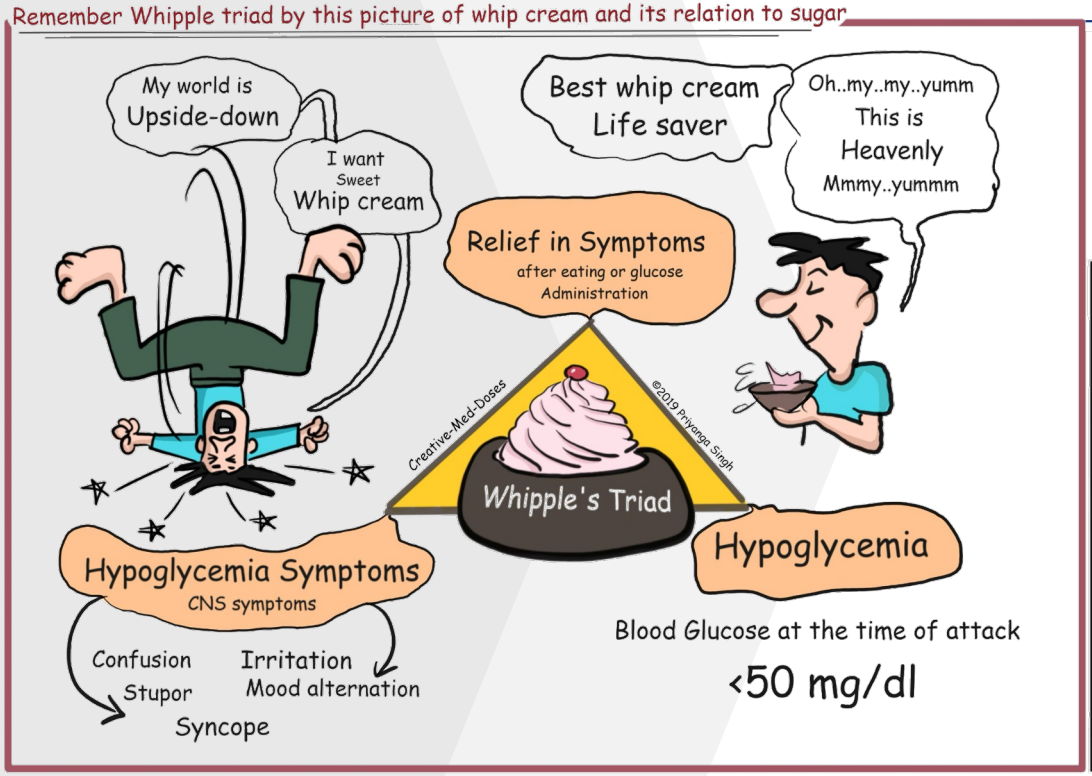
Other rare causes of hypoglycemia in NETs

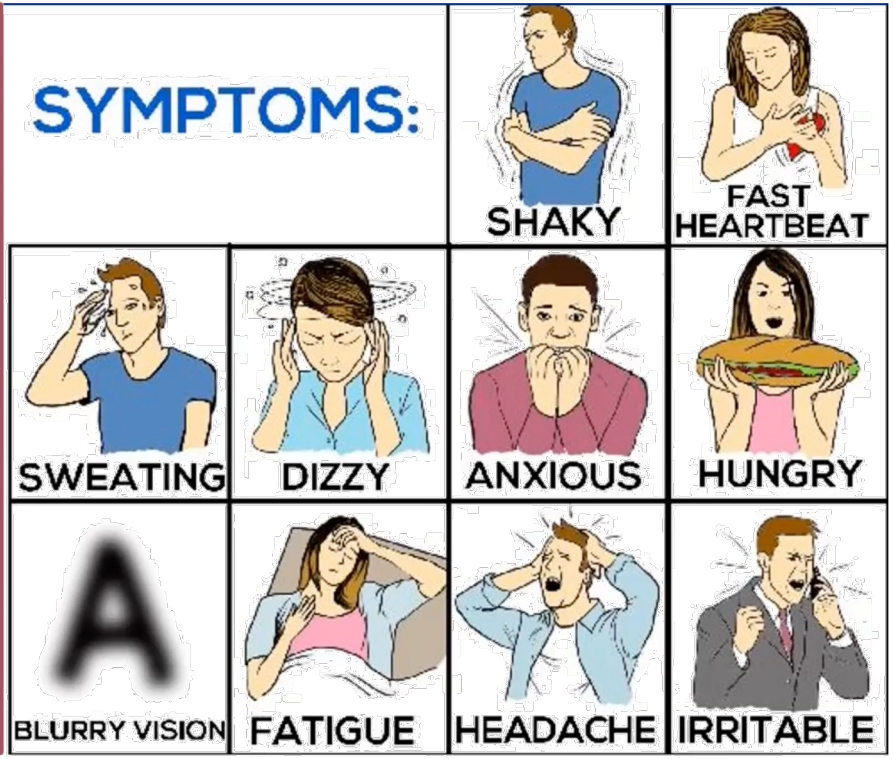
- Very rarely, low blood sugar can occur in other NET-related situations, such as:
- Tumors producing **IGF-2 or insulin-like substances**
- Very advanced disease affecting liver function
- After certain treatments or surgeries
- These situations are **less common** than insulinoma.



Insulinoma

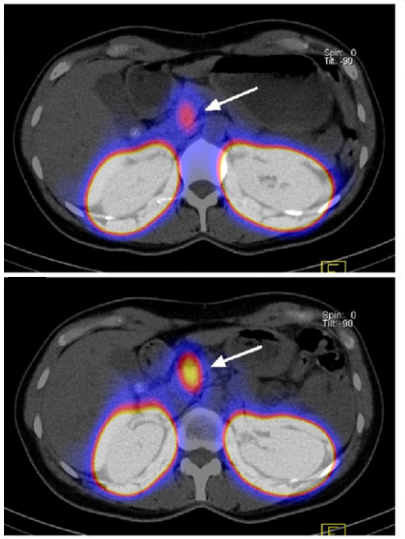
Remember Whipple triad by this picture of whip cream and its relation to sugar





Diagnosis and Tumor Localization

- **Supervised 48 hrs. fast**
  - Some hormone-producing tumors release hormones when you **haven't eaten**
  - You may be asked to fast in the hospital so doctors can:
  - Monitor your blood sugar and hormones safely
  - See how your body behaves without food
  - This is done **under close medical supervision** to keep you safe

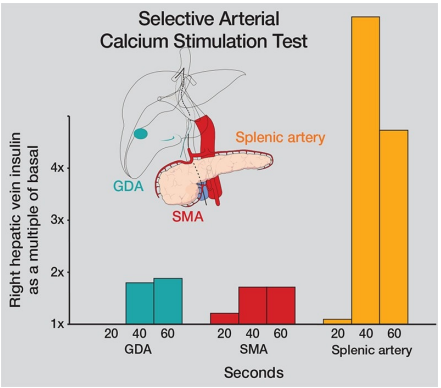


Non-Invasive tests (without surgery or scopes)

- ^{68}Ga or ^{64}Cu-DOTATATE PET Scan
- GLP-1 based scans

Invasive tests

- Endoscopic ultrasound (to look closely at the pancreas
- Selective arterial calcium stimulation
  - Used when the tumor is hard to find
  - Calcium is injected into specific blood vessels supplying the pancreas
  - Blood samples are taken to see **which area releases excess hormone**
  - Helps pinpoint **the exact location** of the tumor



Thompson SM, et al. JCEM. 2015;100:4189
Körner et al. Frontiers in Endo. 2012 : 3-158

Symptom Management of Insulinomas

Surgery (when possible)

- Surgical removal of the insulinoma is the best and preferred treatment
- Surgery can often cure the condition
- Not everyone is able to have surgery right away, or at all, so other treatments may be needed

Nutrition and glucose support

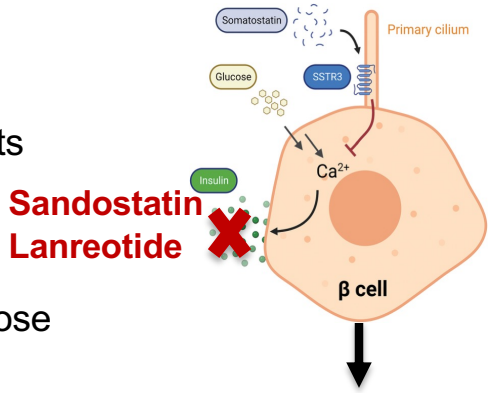
- Frequent small meals rich in complex carbohydrates, continuous oral glucose intake, IV dextrose
- Medicines that reduce insulin release

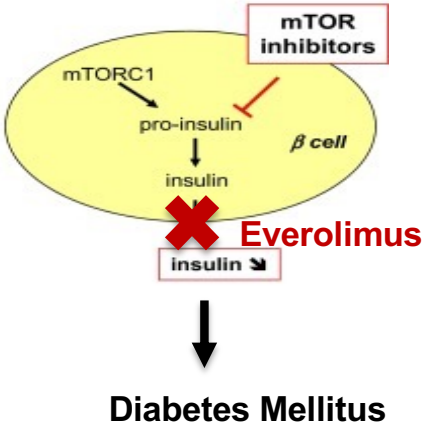
Reduce insulin secretion:

- Diazoxide: Slows down insulin release from the tumor, helps prevent blood sugar from dropping too low, commonly used when surgery is delayed or not possible
- Somatostatin analogs: Act like a natural hormone that turns down insulin release. It can help control symptoms in some patients. Given as injections (short-acting or long-acting)

Treatments for more advanced disease

- Systemic therapies: Everolimus, sunitinib, cabozantinib, CAPTEM, PRRT
- Locoregional techniques: Ablation therapy, embolization

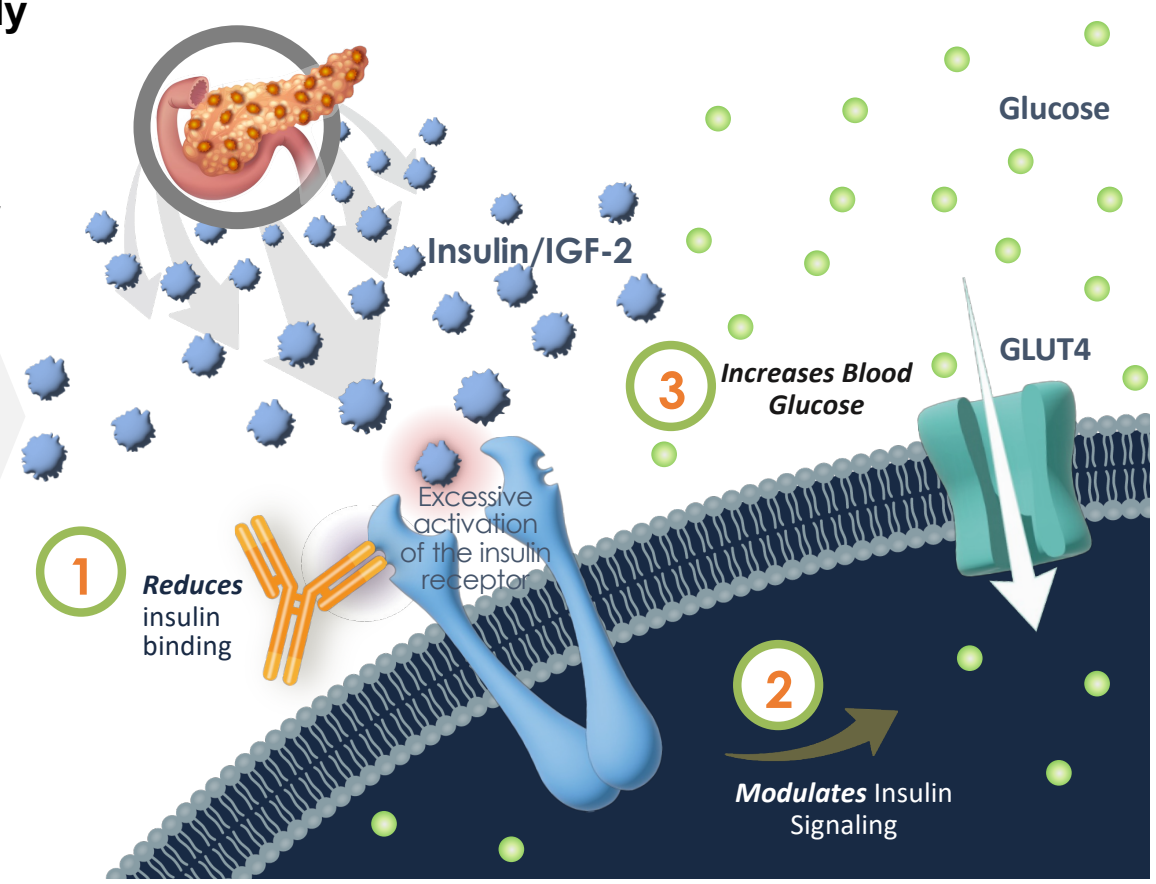




A New Treatment being Studied for Tumor-Related Low Blood Sugar

- It is a **fully human monoclonal antibody**
- Given by **IV infusion** over about **30–60 minutes**
- Designed to treat **tumor-associated hypoglycemia (insulinomas and other cancers causing low blood glucose)**

- **Reduces insulin/IGF-2 binding**
  Ersodetug partially blocks how strongly these hormones activate the insulin receptor
- **Modulates insulin signaling**
  It prevents the receptor from being "over-activated"
- **Raises blood sugar to safer levels**
  Less sugar is pulled out of the bloodstream
  Blood glucose levels increase toward normal



Real-world Patient Benefit in Expanded Access Program

15 patients total

- **14** with insulin-producing tumors (**insulinomas**)
- **1** with IGF-2–related low blood sugar
- All had **very severe hypoglycemia**
- Standard treatments **were not working well enough**

Many patients:
Were hospitalized because of dangerous low blood sugar
Needed continuous IV sugar (dextrose) or IV nutrition
Could not receive cancer treatments (like chemotherapy or radiation) because their blood sugar was too unstable
Some were very ill or receiving comfort-focused care only

Why was ersodetug considered?

Doctors requested ersodetug because:

- Low blood sugar was life-threatening
- Other medications had failed
- Controlling blood sugar was necessary before cancer treatment could continue
- This use was special permission, not routine treatment.

What happened after treatment with ersodetug?

- Blood sugar control
- Low blood sugar improved quickly
- Many patients were able to:
  - Stop IV sugar or IV nutrition
  - Leave the hospital
  - Be cared for as outpatients

Cancer care

- Once blood sugar was controlled:
  - Cancer treatments could restart
  - Care plans that were previously on hold could move forward

Quality of life

- Patients experienced:
- Fewer low blood sugar episodes
- Less time in the hospital
- Improved day-to-day functioning
- Better overall quality of life

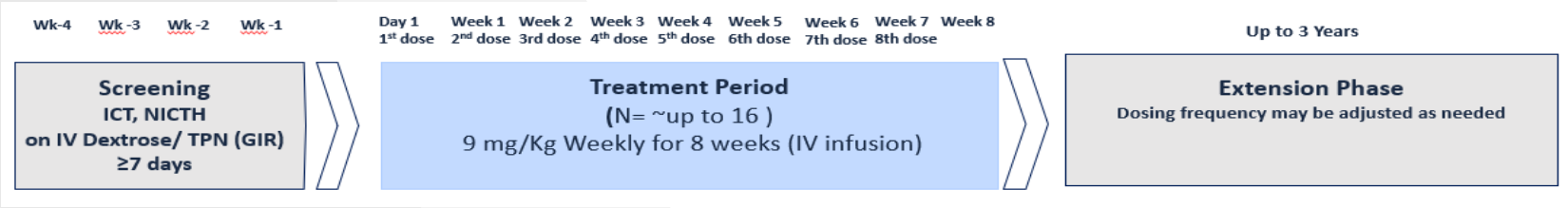
Safety

- No major medication-related side effects were reported in this group

Anti–Insulin Receptor Antibody for Malignant Insulinoma and Refractory Hypoglycemia
(Published August 23, 2023 N Engl J Med 2023;389:767-769 DOI: 10.1056/NEJMc2307576 VOL. 389 NO. 8)

Open-label, Phase 3 Study: upLIFT (RZ358-302)

A Phase 3, Single-Arm, Open-label, Pivotal Study to Evaluate the Efficacy and Safety of Ersodetug Compared to Baseline in Patients with Inadequately Controlled Hypoglycemia Due to Tumor-Associated Hyperinsulinism (tumorHI) [NCT06881992]



Inclusion

- Clinical diagnosis of tumor induced hypoglycemia with biochemical evidence of tumorHI who failed to manage hypoglycemia with usual SOC anti-hypoglycemic therapies, per investigator judgement
- Receiving IV dextrose and or parenteral nutrition for ≥7 days (prior to the 1st dose of ersodetug)

Exclusion

- Evidence of active infection including HIV, hepatitis B or C (excluding immunization patterns).
- H/o investigational therapy within 30 days or 5 half-lives (may qualify if considered safe by the PI)
- Estimated life expectancy (additional lifespan) due to underlying disease (tumor) is <8 weeks.

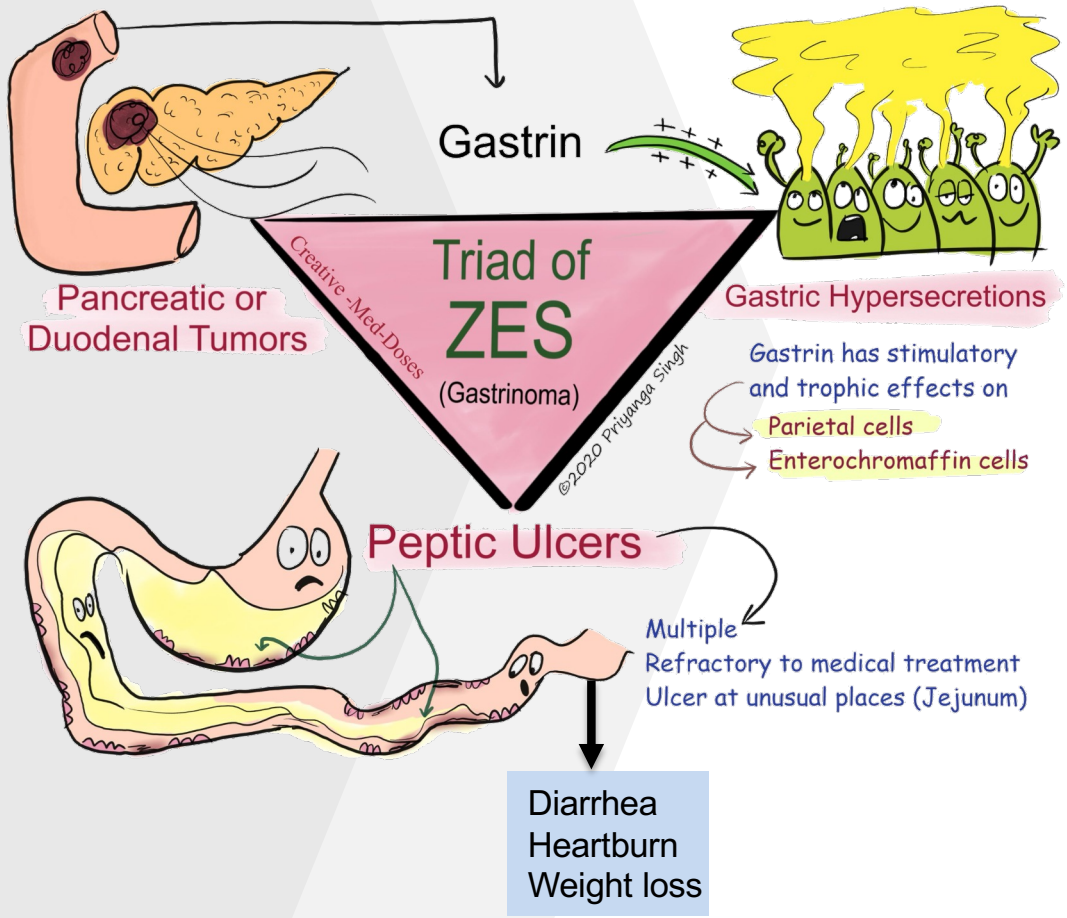
Study Duration/Dosing:

- 9 mg/kg via IV infusion: weekly for initial 8 weeks (Pivotal Phase); every 2-4 weeks up to 3 years (Extension Phase)

Endpoints:

- Clinically meaningful reduction (≥50%) in glucose infusion rate (GIR) from baseline
- Hypoglycemia assessments via SMBG and CGM; QOL, overall survival

Gastrinoma



Proton pump inhibitors

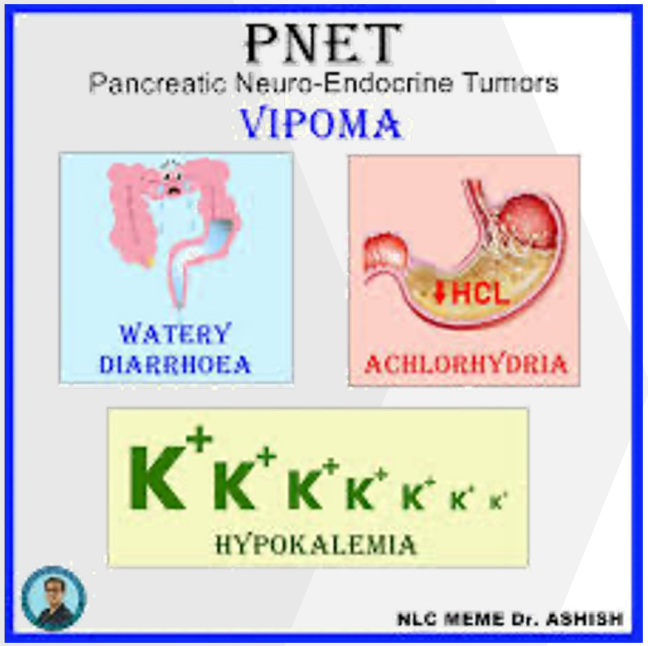
- Omeprazole (40 mg twice daily)
- Pantoprazole (80 mg twice daily)

Surgery

Management for advanced disease

- Octreotide/Lanreotide
- Liver-directed therapies: surgery, ablation, embolization
- Systemic therapies

VIPoma: Verner-Morrison syndrome



- Watery diarrhea: stools are tea-colored and odorless, stool volumes >700 mL/day-3000mL/day
- Low potassium
- Low chloride or achlorhydria
- Abdominal pain

General measures

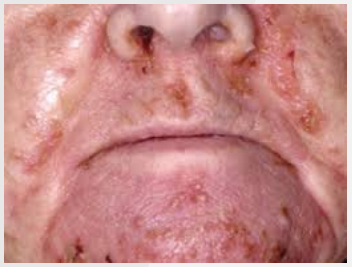
- Repletion of fluids and electrolytes
- Octreotide/Lanreotide
- Glucocorticoids: Prednisone
- Loperamide

Management for advanced disease

- Octreotide/Lanreotide
- Liver-directed therapies: surgery, ablation, embolization
- Systemic therapies

Glucagonoma

Symptoms
- Weight loss
- Skin rash (necrolytic migratory erythema)
- Glucose intolerance/diabetes
- Other symptoms:
  - Chronic diarrhea
  - Deep vein thrombosis
  - Depression, insomnia, Dementia, agitation
  - Inflammation of the tongue

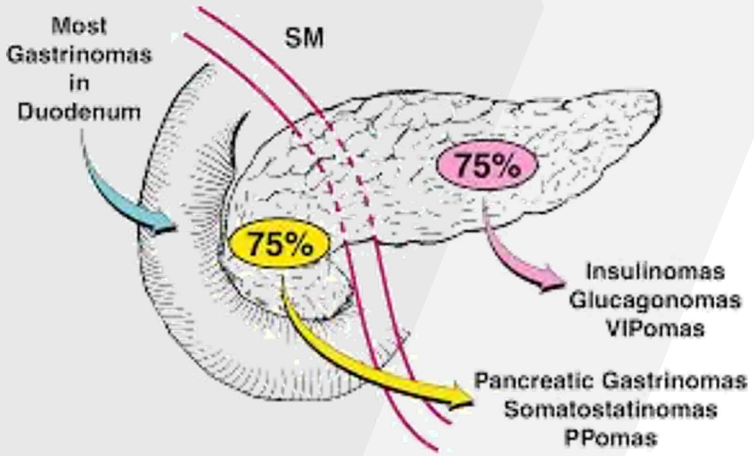


General measures
- Management of diabetes
- Nutritional support
- Infusions of aminoacids and fatty acids
- Octreotide/Lanreotide

Management for advanced disease
- Surgery
- Octreotide/Lanreotide
- Liver-directed therapies: surgery, ablation, embolization
- Systemic therapies

Somatostatinoma

Symptoms
- Diabetes Mellitus
- Cholelithiasis
- Diarrhea/fat in stools

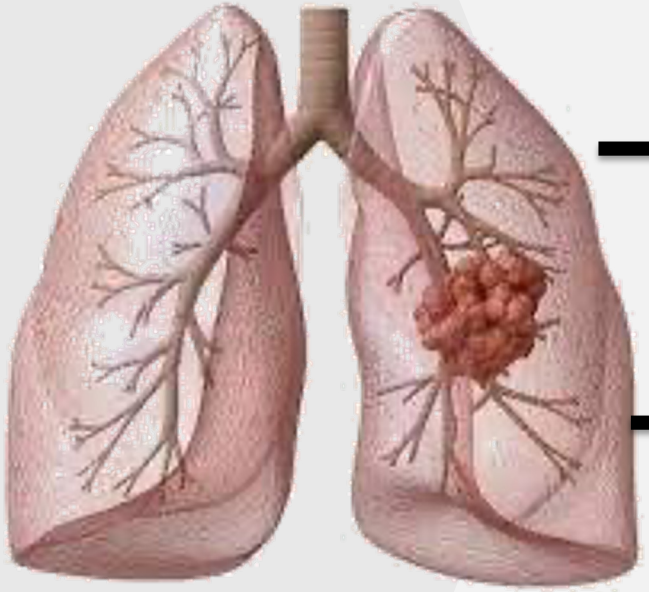


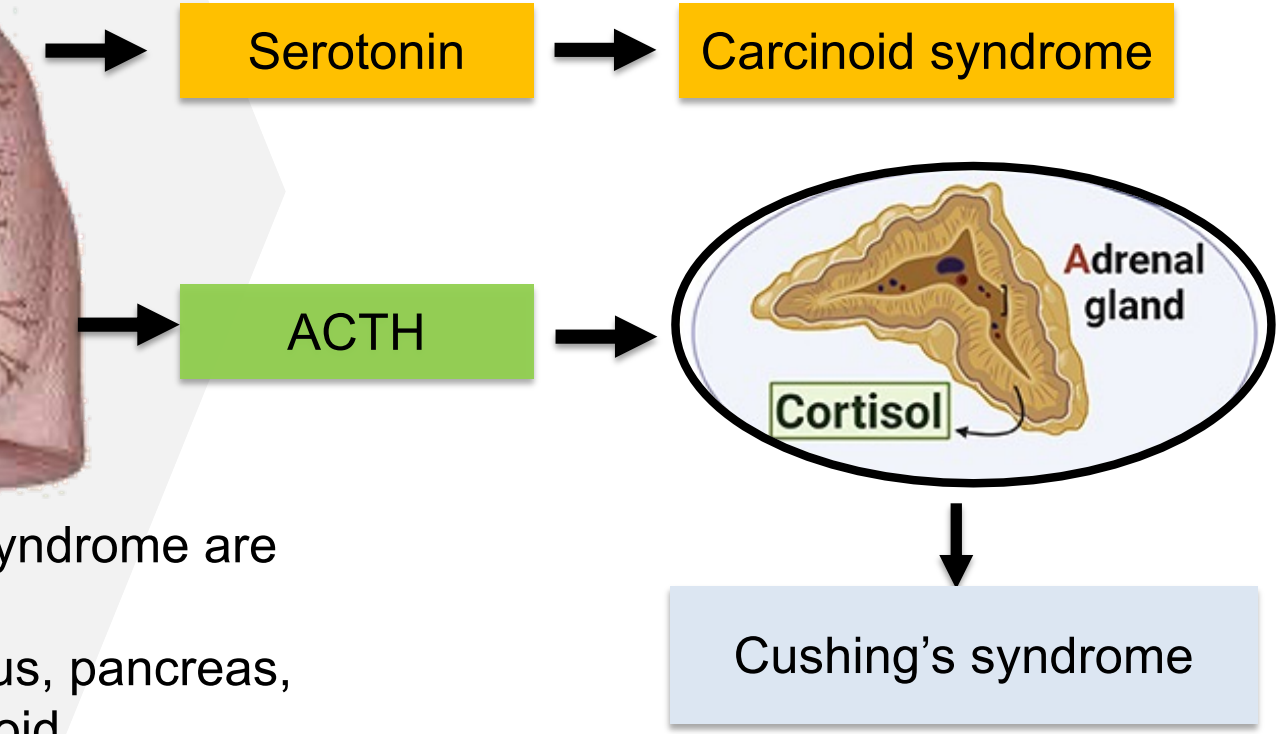
- Surgery

Management for advance disease
- Octreotide/Lanreotide
- Liver directed therapies
- Surgery
- PRRT
- Systemic therapies

Thoracic NETs

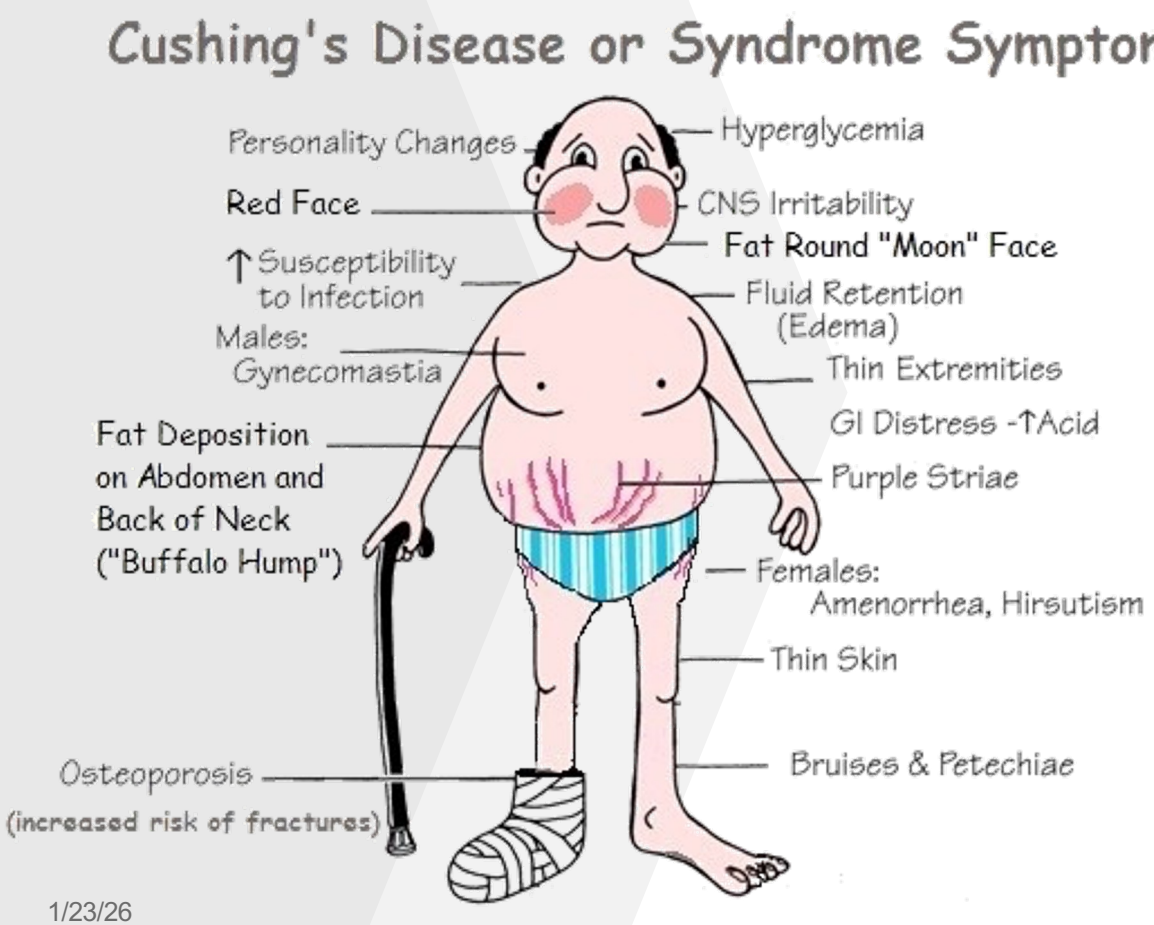
Thoracic Neuroendocrine Tumors





- 5-10% of Cushing's syndrome are paraneoplastic
- Lung (50-60%), thymus, pancreas, adrenal, ovary or thyroid

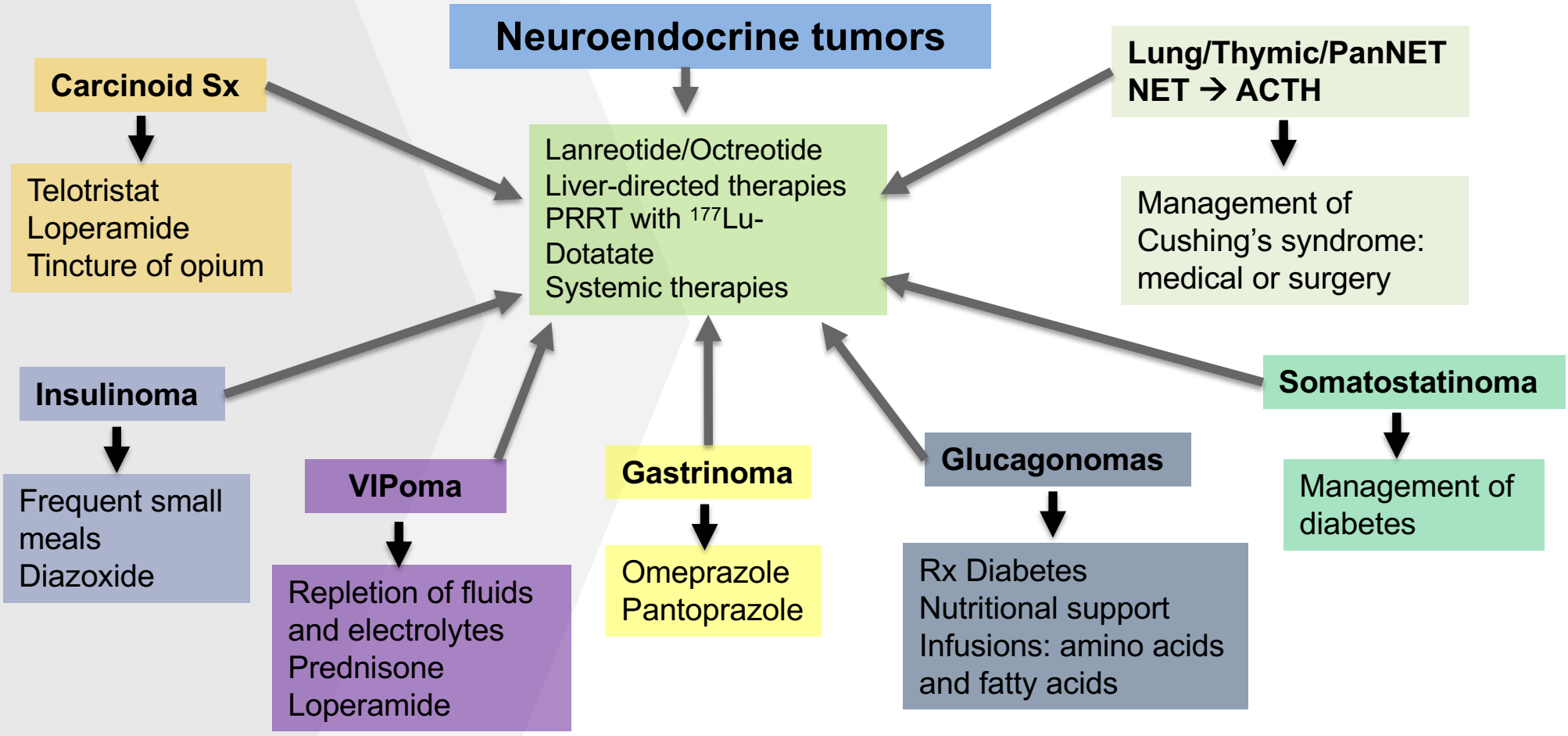
Bronchial NET Producing ACTH



Excess of cortisol

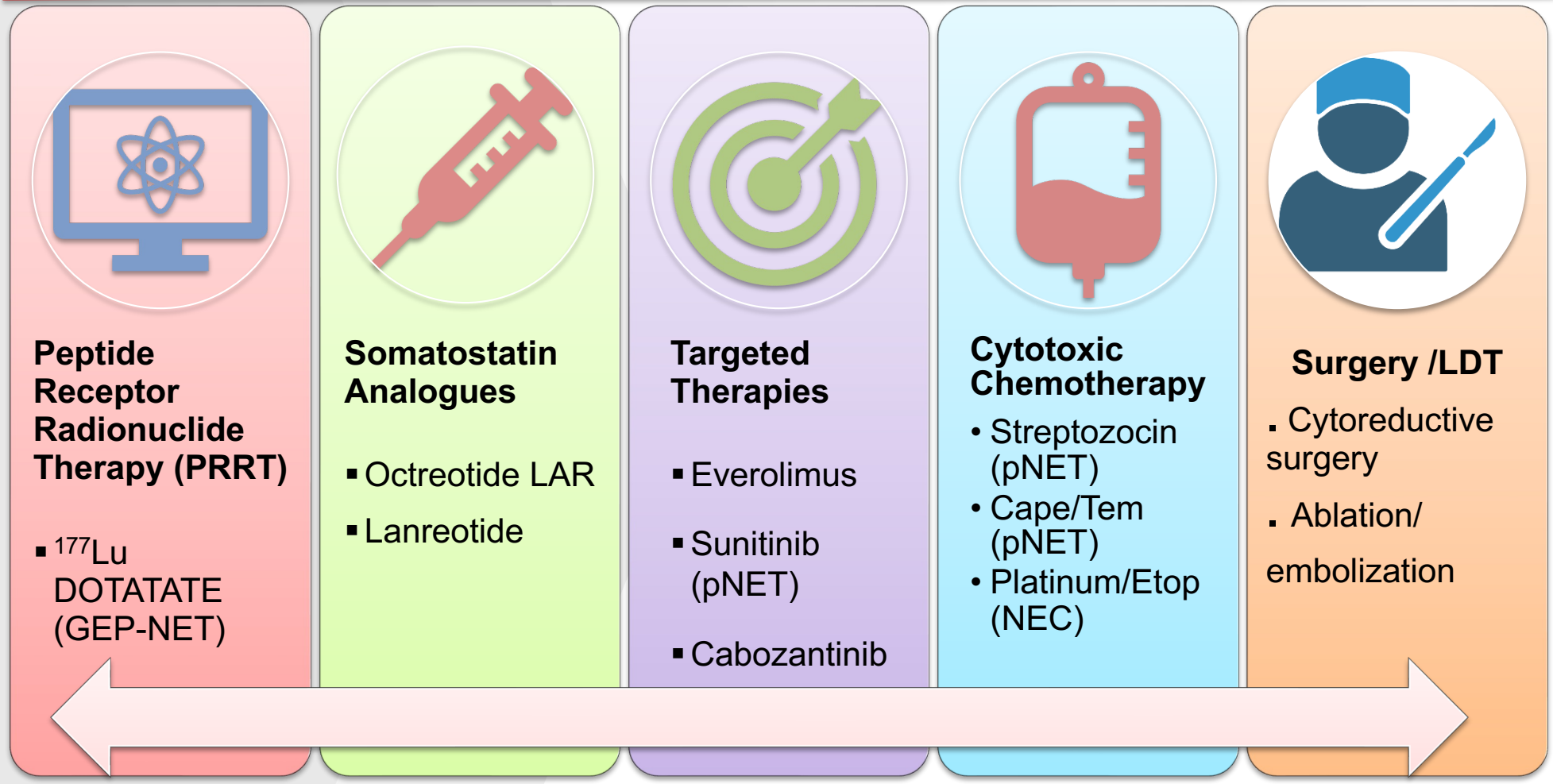
- Surgery
- Medical management: ketoconazole, metyrapone, mitotane
- Bilateral adrenalectomy

Summary - Symptom Management of Hormone Excess



Co-Chairs: Jaydira Del Rivero and Kimberly Perez Symptom Management for Well-Differentiated Gastroenteropancreatic Neuroendocrine Tumors: ASCO Guideline. 2025

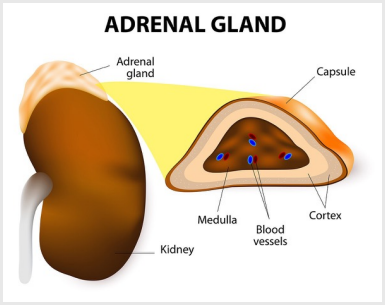
Treatments for Tumor/Hormonal Control in Advanced Disease

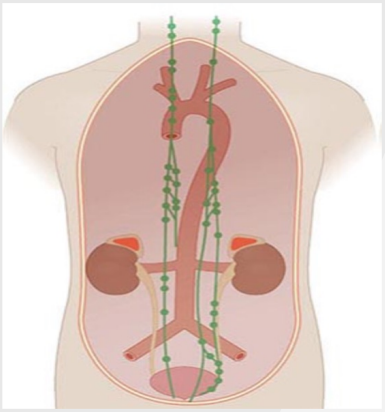


Del Rivero et at. Systemic Therapy for Tumor Control in Metastatic Well-Differentiated Gastroenteropancreatic Neuroendocrine Tumors: ASCO Guideline. JCO 2024

Pheochromocytoma and Paraganglioma (PHEO/PARA)

Pheochromocytoma and paraganglioma are rare neuroendocrine tumors and these tumors produce an excess amount of catecholamine hormone.





Pheochromocytoma: Forms in the adrenal medulla (the center of the adrenal gland)

Paragangliomas: Originates in the parasympathetic or sympathetic nervous system (nerves outside of the adrenal gland)

Common Pheochromocytoma and Paraganglioma Symptoms

Classic symptoms in 40%

- High blood pressure
- Headache
- Sweating

Other Symptoms Include:

- Flushing
- Anxiety/Panic
- Palpitation
- Abdominal pain
- Dizziness
- Blurry vision
- Diabetes symptoms
- Tachycardia
- Heart failure

Medications Commonly Used for Hemodynamic Control in Patients With PHEO/PARA

Class of Drug	Drug Name	Common Adverse Effects
α-Blockers*	Doxazosin, phenoxybenzamine, prazosin, terazosin	Low blood pressure dizziness, increase in heart rate
β-Blockers	Metoprolol, atenolol, propranolol *Labetalol	Fatigue, dizziness, asthma exacerbation
Calcium channel blockers	Amlodipine , Nifedipine	Lower extremity swealing, headaches
Tyrosine hydroxylase inhibitor	Metyrosine	Severe fatigue, neurologic adverse effects, nausea, diarrhea, anxiety

*α blockers is recommended before any procedure, surgery, ablative or systemic therapies

Pacak and Del Rivero. Endotext, 2013

Fischbein, Del Rivero…Jimenez, NANETS Consensus Guidelines 2021

Summary

- 10-30% of PanNETs secrete hormones resulting in clinical syndromes; midgut NET may develop carcinoid syndrome, bronchial/thymic NET may develop Cushing's syndrome (ACTH-dependent)
- First-line medical treatment in PHEO/PARA is alpha blockers
- Biochemical assessment in relation to the clinical presentation and adequate imaging studies
- Surgery is the cornerstone of treatment and can reduce the clinical symptoms; cytoreductive techniques in metastatic functional tumors
- Additional measurements are needed to control excess of hormone: insulinoma, gastrinoma, VIPoma, glucagonoma, alpha blockers and others
- Advanced/metastatic disease: Octreotide/Lanreotide; debulking surgery, liver ablation/embolization; PRRT with ^{177}Lu-Dotatate; chemotherapy (CAPTEM), targeted therapies (everolimus, sunitinib, cabozantinib)

Thank You for Your Attention!

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INSERT DATE