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Perspective on the Current Pharmacotherapeutic Strategies for Management of Functional Neuroendocrine Tumor Syndromes

Tetsuhide Ito[1], **Robert T. Jensen**[2]

[1]Neuroendocrine Tumor Centre, Fukuoka Sanno Hospital, International University of Health and Welfare, Fukuoka, 814-0001, Japan

[2]Digestive Diseases Branch, NIDDK, NIH, Bethesda, MD, 20892-1804, USA

Abstract

Introduction: In the past the inability to control the hormone-excess-state was the main determinant of survival in patients with Functional Neuroendocrine Neoplasm syndromes (F-NENs). This could prove especially difficult because the pharmacological armamentarium available until relatively recently was limited. In the last few years there have been a marked increase in the therapeutic strategies available which have opened new pharmacotherapeutic approaches, but have also generated some controversies, uncertainties and confusion.

Areas covered: In this perspective, the authors briefly review the different F-NENs that are established as well as those proposed; the rationale for approaching their treatment and why both an approach to controlling their hormone-excess-state and their malignant nature is required in most cases; the current recommended initial pharmacotheraputic approach to controlling the hormone-excess-state of the different F-NENs; the secondary approaches to controlling the hormone-excess-state if the initial approach fails or resistance develops; and the approach to deal with the malignant nature of the NEN per se. Also discussed are the controversies the new treatments have generated particularly related to the timing of the diagnosis of the F-NEN, as well as the sequences of secondary treatments, and the exact role of PRRT.

Expert Opinion: Unfortunately, except for patients with insulinomas(>90-95%), gastrinomas(<20-40%), a minority with the other F-panNEN syndromes and 0-<1% with Carcinoid syndrome is curative surgery possible allowing control of the hormone-excess-state and the malignant nature of most NENs(except insulinomas-being-95%). Except for insulinomas, gastrinomas and ACTHomas, long-acting somatostatin analogues are the initial pharmacological treatments for hormone-excess-state. For insulinomas prior to surgery/malignant insulinomas, diazoxide/frequent,small feedings are the initial treatments; for gastrinomas, oral PPIs need to be started as soon as possible and for ACTHomas Steroidogenesis inhibitors are generally initially used. There are now a number of secondary pharmacotherapeutic treatments for the different syndromes, including older drugs which are effective in some patients as well as newer

Correspondence to: Dr. Robert T Jensen, National Institutes of Health, Bldg. 10, Room 9C-103, Bethesda, MD 20892-1804, robertj@bdg10.niddk.nih.gov, Phone: 301-496-4201.

8. Conflicts of Interest

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therapies. These include telotristast for Carcinoid syndrome[primarily for the diarrhea, but also helps flushing in some patients]; mTor inhibitors(everolimus); pasireotide; and a number of newer agents effective in patients with ectopic Cushing syndrome. Particularly promising, is recent results with PRRT for the hormone-excess-state, independent of its anti-growth effect. The sequence to use various agents and the approach to syndrome diagnosis while taking various agents remains unclear/controversial in many cases.

Short-ABSTRACT

Introduction: In the past controlling the hormone-excess-state was the main determinant of survival in Functional-Neuroendocrine-Neoplasm-syndromes(F-NENs). This was difficult because the pharmacological-armamentarium available was limited. More recently therapeutic strategies available have increased, opening new pharmacotherapeutic-approaches,but also generated controversies/uncertainties.

Areas covered: In this perspective, the authors briefly review current established/proposed F-NENs; the rationale for treatments; the current recommended initial-pharmacotheraputic-approach to controlling F-NENs hormone-excess-state; the secondary-approaches if the initial approach fails or resistance develops; and the approach to deal with the malignant nature of the NEN per se. Also discussed are controversies/uncertainties related to the new treatments.

Expert Opinion: Unfortunately,except for patients with insulinomas(>90-95%), gastrinomas(<20-40%),a minority with the other F-panNENs and 0-<1% with Carcinoid-syndrome is curative-surgery possible. Except for insulinomas,gastrinomas and ACTHomas,long-acting somatostatin-analogues are the initial-pharmacological-treatments for hormone-excess-state. For insulinomas prior to surgery/malignant,diazoxide is initial drug-treatment; for gastrinomas,oral PPIs; and for ACTHomas Steroidogenesis inhibitors. There are now a number of secondary pharmacotherapeutic treatments for the different F-NEN-syndromes.These include telotristast(Carcinoid-syndrome; mTor- inhibitors(everolimus); pasireotide; and some newer agents in ectopic Cushing-syndrome. Particularly promising,is recent results with PRRT for the hormone-excess-state,independent of its anti-growth effect. The sequence to use various agents and the approach to syndrome diagnosis while taking various agents remains unclear/controversial in many cases.

Keywords

pancreatic neuroendocrine neoplasms; insulinoma; Zollinger-Ellison syndrome; glucagonoma; VIPoma; Carcinoid syndrome; Ectopic Cushing’s syndrome; somatostatin analogue; everolimus; PRRT

1. Introduction

Pancreatic Neuroendocrine Neoplasms(panNENs) and carcinoid tumors(GI-NEN, Lung-NEN, etc.)are now classified as Neuroendocrine Neoplasms(NENs), because of their numerous shared features and arise from the diffuse neuroendocrine system throughout the respiratory and gastrointestinal tract, and in other tissues[1–4]. These cells can synthesis and often secrete numerous peptides, amines, as well as neuron-specific enolase, synaptophysin, and chromogranins[1–3].

Both panNENs and carcinoid tumors in different locations may be associated with a specific functional syndrome(F-NEN)due to ectopic secretion of a bio-active peptide, in addition to secreting numerous substances which do not cause distinct functional syndromes(chromogranin, neuron-specific enolase, synaptophysin, ghrelin, etc.)[1,2,4]. Sixteen different F-panNEN syndromes have been described(See Table 1 for most prominent)including 9 syndromes which are well-described group(>50-100 cases): Insulinomas, gastrinomas(Zollinger-Ellison syndrome), Glucagonomas, VIPomas(Pancreatic Cholera, Verner-Morrison syndrome), somatostatinomas,(SSomas), GRFomas, ACTHomas, PTHrPomas, and panNENs associated with carcinoid syndrome[3–5]. Seven additional F-panNEN syndromes which include only small number of patients(<5 cases), but are generally accepted as causing a distinct functional syndrome have been described which include: panNENs secreting renin(Reninoma), luteinizing hormone, enteroglucagon, cholecystokinin(CCKoma),erythropoietin, GLP-1, and insulin-like growth factor II[3–6]. A number of other panNENs have been reported in some studies to cause a functional syndrome, including NENs secreting neurotensin, pancreatic polypeptide, ghrelin, calcitonin and other peptides, but which are not established to be associated with a specific syndrome, and thus generally are included in the NF-panNEN group[3–5]. Other NENs(Carcinoids)can also cause a specific functional syndrome, the carcinoid syndrome, which occurs characteristically when liver metastases are present(>95% of cases)and rarely with NENs which can drain into venous systems circumventing the liver(Bronchial, pancreatic, ovary, testis)[3,4,7–9].

The presence of a F-NEN markedly changes the clinical management because these patients now have two separate clinical aspects that need to be dealt with. Clinicians not only must deal with the potential malignant nature of the NENs, but also management of the hormone-excess-state[4,7,10]. Whereas successful surgical resection would immediately solve both problems, unfortunately this is not possible in almost all patients with Carcinoid syndrome and in 30-80% of patients with non-insulinoma panNENs(i.e. insulinomas are only malignant in <5-10% of cases)[10,11]. History has repeatedly shown us that in many cases the immediate and long-term control of the hormone-excess state is essential in these patients[4,10,12,13]. This is especially the case in patients with gastrinomas; VIPomas; some with insulinomas, especially those with malignant tumors; patients with pancreatic ACTHomas(which are malignant in >90%), and many with Carcinoid syndrome. For example, prior to the availability of histamine H_2-receptor antagonists to control the acid secretion in patients with ZES, the main cause of death was a complication of severe peptic ulcer disease such as perforation, bleeding, penetration and sepsis[12–15].

2. Approach to diagnosis and starting pharmacological management

An important aspect that is uncommonly discussed, but is quite important, is if the diagnosis is suspected, when should the diagnostic studies be performed in relation to when the pharmacological control of the hormone-excess state is begun. To make the diagnosis of F-NENs, an unphysiological secretion of the hormone must be demonstrated[3–5]. This is usually performed by demonstrating an inappropriately elevated plasma/serum level of the hormone in the presence of a prominent biologic response(i.e. hypergastrinemia in the presence of acid hypersecretion, hyperinsulinemia during marked hypoglycemia, etc.)

[3,4,16]. This can be an issue with F-NENs treated with somatostatin analogues, because they can decrease the ectopic hormone release, affecting the plasma hormone levels and control the hormone-excess state, thus complicating the diagnosis[17]. The same could occur with the use of PRRT or other medical treatments(diazoxide in insulinomas, telotristat in Carcinoid syndrome, etc.)which can decrease the hormone secretion rate. The opposite occurs in in nonZES with PPI treatment causing hypergastrinemia, as will be discussed further below, because PPI treatment leads to physiological hypergastrinemia secondary to inducing hypo/achlorhydria[16,18–20]. makes it very difficult to diagnose ZES definitively in most patients while taking these drugs[16,19–21] . A similar situation exists in referral centers because patients are invariably taking such medications when they are first referred if the diagnosis is strongly suspected, and this can complicate the subsequent diagnosis. The issue then becomes whether and when to stop the medications to firmly establish the diagnosis.

In most patients with possible carcinoid syndrome, if initially seen and the patient is untreated(not taking telotristat, long-acting somatostatin analogues)and the symptoms are not severe, urinary or plasma 5-HIAA levels can be determined prior to treatment to establish the diagnosis[7,10,22]. Most patients with insulinomas(>90%)are identified early in the disease course, without advanced disease, and can have the hypoglycemic symptoms controlled with frequent small feedings without additional medications prior to surgery, which allows time to establish the diagnosis by assessing during a 72 hr fast, the plasma insulin, proinsulin, glucose, and C-peptide levels[3,4,23]. Similarly, in most patients with glucagonomas, GRFomas, SSomas, and the other infrequent panNEN syndromes, emergent immediate treatment is not required, and time can be taken to establish the diagnosis prior to start of pharmacologic therapy.

In contrast, immediate treatment of the hormone-excess state in needed in almost all patients with ZES, who frequently have acid hypersecretion rates up to 5–10-times normal and advanced peptic disease, as well as patients with VIPomas with high volume diarrhea, hypokalemia and dehydration[4,5,24–27]. This allows little time for diagnostic studies prior to antisecretory treatment. However, if possible, in ZES patients , fasting serum gastrin levels, and gastric fluid pH at the time of a pretreatment UGI endoscopy, as well as the prominence of gastric folds during the endoscopy(which are increased in >90% of ZES patients)should be assessed[5,18,19,21,28]. Similarly, in patients with high volume diarrhea with possible VIPoma, a plasma VIP and gastrin levels, as well as 24-hour stool volume and fecal electrolytes assessed when first seen, if possible[4,5,27,29].

In patients already on antisecretory drug treatments the establishment of the diagnosis of ZES is the most difficult and controversial[16,21,30]. This occurs because stopping the PPI can be difficult and not without potential risk[20,21]. This occurs because these drugs have a long duration of action(up to one week), they induce hypo-/achlorhydria in nonZES patients and thus cause physiological hypergastrinemia to levels seen in ZES hence mimic ZES, and there are numerous reports of severe peptic complications is patients with ZES when the PPI is stopped[16,20,21]. To establish the diagnosis classically requires an elevated serum gastrin level in the presence of a gastric pH of ≤2, and thus patients may have to be off the PPI for up to a week[16,18,21]. The diagnosis of ZES is further complicated

by the fact that the use of a secretin provocative test to make the diagnosis in equivocal cases is not valid while taking PPIs and recent studies report many serum gastrin assays are not reliable[16,21,30–33]. Because of the difficulty of making the diagnosis of ZES, it is generally recommended that these patients be referred to a specialty center versed in this disease, without stopping the antisecretory drugs to confirm the diagnosis[16,21].

3. Approach initial pharmacological management(Table 1)

As is evident from Table 1, for the initial treatment of Carcinoid syndrome and all of the F-panNEN syndromes except ZES, insulinoma, and ACTHomas, the recommended pharmacological treatment is with somatostatin analogues of which two are approved(Lanreotide, octreotide)[4,7–10,17,22,23,27,34]. Long-acting preparations of each of these are now generally used(Octreotide-LAR, Lanreotide autogel) allowing monthly dosing, with the most frequent dosing being octreotide 20-30mg/mo or Lanreotide Autogel 60-120mg/mo[7–10,17]. These doses provide at least partial symptom control(diarrhea, wheezing) in most patients with Carcinoid syndrome(60-95%)and complete control in 40-70% [7–9,17]. In panNEN syndromes such as glucagonoma, GRFoma and VIPoma they provide at least partial symptomatic control in >70%[17,22,23,27,35,36]. Unfortunately, an escape phenomenon or tachyphylaxis may develop with time[7,10,17,22,23,27,36–38]and additional treatments may be required as discussed in the following section.

In patients with ZES, to control the acid hypersecretion, PPIs are the drugs of choice(Table 1), with all approved PPIs(omeprazole,lansoprazole,esomeprazole, pantoprazole, rabeprazole,dexpansoprazole)shown to be effective[4,5,26]. Because at the beginning of therapy many patients have peptic disease, frequently with ulcers[15,28], an initial dose equivalent to omeprazole 60 mg/day is recommended in patients with uncomplicated ZES(not associated with Multiple Endocrine Neoplasia-type1(MEN1), moderate/severe GERD, previous gastric acid - reducing surgery-Bilroth 2)[26,39–42]. Once the acid hypersecretion is controlled and mucosal healing occurs the dosage can be reduced in >60% to the equivalent dosage of omeprazole 20 QD[40,41]. In patients with complicated ZES an initial dose equivalent to omeprazole 40-60 BID is recommenced, which with time after symptom control and mucosal healing, can be reduced to 20 BID in most patients[40,41]. Many physicians initially start with lower omeprazole-equivalent doses, which do not control the hypersecretion in all patients[41–43], however, if careful, regular follow-up is used combined with adequate endoscopic assessment prior to treatment, this is a reasonable alternate approach. In the very rare patients who cannot take PPIs, histamine H_2 receptor antagonists can be used, but frequent(4-6 hourly), high-dosing(equivalent to ranitidine 300-600 mg/4-6 hr)is required, as well as gastric acid testing to assess efficacy, which is rarely available[44–47]. Long-term treatment with PPIs has proven safe, and efficacious, without the development of tachyplaxis[41,48]. It is important to remember that these patients, if not surgically cure(<40%), require life-long PPI treatment, and during times when oral drugs cannot be taken(GI illnesses, surgeries,etc.), parenteral PPIs should be used[4,5,11,49–51]. Of the increasing number of potential side effects being described within long term PPI treatment in nonZES patients[19], only the development of low levels of vitamin B12 have been regularly reported in some ZES patients with long-term PPI treatment[52].

In patients with insulinomas, many can have their symptoms initially, adequately controlled with frequent, small feedings and if not, then by the addition of diazoxide, which inhibits insulin release by inhibiting ATP-sensitive potassium channels on the insulinoma cells[4,23,53,54]. This is effective in 47-50%, however, its use can be associated with prominent side-effects which can limit its continued use[53–56]. Side-effects include edema due to fluid/electrolyte retention(thus, generally diazoxide is used with a diuretic), as well as hirsutism, thrombocytopenia, and renal failure[23,53–57]. In most patients this treatment is short-term, allowing time to perform tumor localization studies(see paragraph below for more detail). This is the case because >90% of insulinoma patients can be surgically cured[4,22,58].

In patients with ACTHomas, especially those with pancreatic tumors(40–90% malignant), many have severe Cushing's syndrome[5,59–66], which can be difficult to control long-term medically, and thus may require a bilaterally adrenalectomy, especially if widespread metastases to the liver,etc. prevent complete surgical resection of the primary/metastatic tumor. Pharmacological treatment to attempt to restore eucortisolemia as quickly as possible, is generally initially with steroidogenesis inhibitors(ketoconazole, metyrapone)which can have frequent side-effects, although there are some reported cases that respond to long-acting-somatostatin analogues which are generally well-tolerated[23,59,60]. PRRT may prove particularly helpful in malignant/refractory cases of Cushings syndrome[60,67–69].

4. Approach to secondary pharmacological management(Table 1)

For most patients with F-NEN syndromes, except those with ZES(gastrinomas)treated with PPIs, with time, the primary pharmacologic treatment becomes less effective[10,17,23,27,38]. Numerous approaches have been reported to be effective in different patients. For F-NEN patients treated with long-acting somatostatin analogues as their primary treatment(carcinoid syndrome, some F-panNENs, Table 1), it is reported that increasing the monthly dosage, shortening the time interval of dosing to 3 weeks or shorter and supplementing with subcutaneous shorter acting octreotide, all have value in overcoming the decreasing drug effectiveness[7,8,10,17,23]. Another approach is to switch to another drug or treatment[7,8,10,17,23]. These are summarized in Table 1 and only a few specific cases will be further discussed here.

In the case of Carcinoid syndrome , the recent approval of telotristat, a tryptophan hydroxylase 1 inhibitor that works peripherally to inhibit the synthesis of serotonin, which is important particularly in the pathogenesis of the diarrhea in these patients, and in some patients also contributes to the flushing[7–10,70]. In 40-44% of patients with Carcinoid syndrome treated with telotristat, the diarrhea is improved, and in some cases the flushing is also reduced[7,8,70]. It remains to be seen whether its use will prevent the development of carcinoid heart disease[7,8].

In the case of insulinomas, long-acting somatostatin analogues are effective in 40-50% of cases[4,17,23,36,71,72]. However, their use in insulinoma patients requires careful monitoring, because they may not only inhibit the ectopic insulin secretion, but also the release of counter-regulatory hormones, such as growth hormone secretion and

glucagon; which, in some patients, can worsen the hypoglycemia[4,10,23,72]. Fortunately, there are now an increasing number of other choices if diazoxide fails to control the hypoglycemia(Table 1)which include the mTor inhibitor, pasireotide, everolimus, beta blockers and in malignant insulinomas, PRRT(Table 1)[10,53,73–78].

Pasireotide, is a newer somatostatin receptor agonist, which has high affinity for 4 somatostatin-receptor subtypes(sst1,2,3,5), in contrast to octreotide/lanreotide which interact with high affinity with only sst2>sst5[8,78]. It is reported to be effective in F-NENs(Carcinoid syndrome, insulinomas, VIPomas, ACTHomas, GRFomas)in patients who fail treatment with Octreotide-LAR/Lanreotide-autogel[7,8,10,23,57,77–79].

PRRT has recently been approved for its antigrowth activity in patients with advanced NENs[4,80,81], and numerous recent small studies show it has beneficial potent effects in F-NENs which occurs independent of its antigrowth effects[10,53,67,73–75,80,81]. It has especially proven useful in patients failing somatostatin-analogue treatment with VIPomas, malignant insulinomas, Cushings syndrome, and Carcinoid syndrome[4,7,8,10,27,38,53,67,68,73–75,80–82]. In general PRRT treatment has been safe in these patients[80,83]although in up to 10% a hormonal crises may occur and thus additional prevent measures taken[8,84,85]. In Table 1 it is indicated, as a possible treatment in a number of F-NENs where it will likely also be effective but has not yet been reported in these patients. This approach appears highly effective and well tolerated and will likely increasingly become the most important secondary treatment in many of these syndromes.

5. Approach to NEN per se when pharmacological control effective

The only means to cure F-NENs is by surgical resection which is successful in 90-95% of insulinomas, 30-50% of ZES, <50% of other F-panNEN syndromes, and rarely in patients with Carcinoid syndrome[4,8,35,36,58]. Furthermore, with increased ability to control the hormone-excess state of F-NENs, increasingly the malignant natural history of the NEN per se is determining survival[4,86]. Therefore, all patients should undergo detailed tumor localization studies, with cross-sectional imaging(usually CT or MRI with contrast)and ^{68}Ga-DOTATOC PET/CT to determine tumor location and extent, to determine the possibility of surgical excision or plan anti-tumor therapies[22,23,87–90]. In patients with insulinomas, gastrinomas or uncommonly, with small primary F-NET, additional tumor localization studies may be needed, either pre-surgically(endoscopic ultrasound, assessment of hormonal tumor gradients, etc)[3,87,89,91–95]or at the time of surgery(duodenotomy, intra-operatiave ultrasound, duodenal transillumination, etc)[11,49,50,89,96–99].

6. Expert Opinion

Recent studies demonstrate that the incidence of NENs is increasing in all countries with a 6.4-fold increase in the US from 1973 to 2012(6.9/100,000)[100]and within this group F-NENs are not uncommon, with up to 30% of panNEN patients having a F-panNEN and 3-13% of patients with a carcinoid having a F-NEN syndrome[7,10]. This means that clinicians are going to have increased exposure to these patients.

In the past the pharmacological armamentarium available to treat patients with F-NENs was very limited. In was not until the 1970's the first effective drugs to treat F-NENs became available with diazoxide for insulinomas in 1973, and cimetidine(1977), ranitidine(1981),and famotidine(1985)for ZES[44,46,101,102]. In the 1980s the first PPI, omeprazole(1988)became available for the treatment of ZES and octreotide for the treatment of hormone-excess states(acromegaly, VIPomas). Whereas the availability of omeprazole and other PPIs largely solved the problem of the control of acid hypersecretion seen in ZES resulting in a dramatic decrease in mortality in these patients due to uncontrolled acid hypersecretion[26,41,47], this was not the case with a number of the other F-NEN syndromes. While the availability of the long acting somatostatin analogues(Octreotide-LAR,Lanreotide-autogel), in most cases initially at least partially controlled the hormone-excess in these other non-ZES,F-NEN syndromes(except insulinomas), with time resistance developed, and it became increasingly difficult to control the hormone-excess state symptoms[8,10]. More recently(since 2010)a number of new pharmacologic agents(telotristat,pasireotide,cinacalcet)as well as PRRT(2018) have become available which have proven effective in a number of these syndromes, in patients refractory to the initial treatment agent used(see Table 1, somatostatin analogues in most cases) [10,23,57,70,74–76,84,103,103–105]. The availability of these new treatment approaches combined with the increased use of surgical resection, and liver -directed therapies, has resulted in the increased ability to control symptoms long-term due to the hormone-excess state in most patients[10,23,36,84,106,107].

Although the availability of these multiple therapeutic approaches has increased the ability to control these hormone-excess states in patients with F-NENS, there still remain a number of treatment issues and a number of controverses. These include the best order of the secondary treatment regimens where multiple options are available, the long-term effectiveness of most of these secondary treatments, clear algorithms for diagnosis of the disorders when any treatment regimen is already started before the diagnosis is established, and the effectiveness of PRRT in the initial and long-term control of most F-NENs. The recent reporting of the effectiveness of PRRT in malignant insulinomas, refractory carcinoid syndrome, Cushings syndrome, and VIPomas as well as a few other F-NENs[4,7,10,34,74,75]is particularly promising, in that it is well tolerated, safe, effective, and independent of anti-growth effects[8,73,80,83,108]and thus may play and increasing role in the treatment of the hormone-excess state.

In this short article a number of issues are briefly reviewed and discussed.

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References

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1. Klimstra DS. Pathologic Classification of Neuroendocrine Neoplasms. Hematol Oncol Clin North Am 2016;30:1–19. [PubMed: 26614366]

2. Jensen RT, Norton JA, Oberg K. Neuroendocrine Tumors. In: Feldman M, Friedman LS, Brandt LJ eds. Sleisenger and Fordtran's Gastrointestinal and Liver Diseases. Philadelphia: Elsevier Saunders; 2016:501–541.

3. Jensen RT. Neuroendocrine Tumors of the Gastrointestintal Tract (GI) and Pancreas. In: Jamieson LL, Fauci AS, Kasper DL et al. eds. Harrison's Principles of Internal Medicine-ED.20. New York, New York: McGraw Hill Education Medical Publishing Division; 2018:596–615.

4••. Ito T, Jensen RT. Neuroendocrine Neoplasms and Functional Syndromes. In: Weber HC ed. Gastrointestinal Endocrinology. New York: Springer; 2020 (In press).Recent summary of all aspects of the treatment of NENs, both F-NENs and non-F-NENs.

5. Ito T, Igarashi H, Jensen RT. Pancreatic neuroendocrine tumors: clinical features, diagnosis and medical treatment: Advances. Best Pract Res Clin Gastroenterol 2012;26:737–753. [PubMed: 23582916]

6. Rehfeld JF, Federspiel B, Bardram L. A neuroendocrine tumor syndrome from cholecystokinin secretion. N Engl J Med 2013;368:1165–1166. [PubMed: 23514309]

7•. Ito T, Lee L, Jensen RT. Carcinoid-syndrome: recent advances, current status and controversies. Curr Opin Endocrinol Diabetes Obes 2018;25:22–35. [PubMed: 29120923] Review of all aspects of the Carcinoid syndrome and its management.

8•. Wolin EM, Bowen Benson III AB. Systemic Treatment Options for Carcinoid Syndrome: A Systematic Review. Oncology 2019;96:273–289. [PubMed: 31018209] Recent summary of advances in treatment of Carcinoid syndrome.

9. Oleinikov K, Avniel-Polak S, Gross DJ , et al. Carcinoid Syndrome: Updates and Review of Current Therapy. Curr Treat Options Oncol 2019;20:70. [PubMed: 31286272]

10••. Ito T, Lee L, Jensen RT. Treatment of symptomatic neuroendocrine tumor syndromes: recent advances and controversies. Expert Opin Pharmacother 2016;17:2191–2205. [PubMed: 27635672] Recent summary of treatments of refractory F-NENs syndromes.

11. Norton JA, Fraker DL, Alexander HR , et al. Surgery to cure the Zollinger-Ellison syndrome. N Engl J Med 1999;341:635–644. [PubMed: 10460814]

12. Ellison EH, Wilson SD. The Zollinger-Ellison syndrome: Re-appraisal and evaluation of 260 registered cases. Ann Surg 1964;160:512–530. [PubMed: 14206854]

13. Ito T, Igarashi H, Uehara H , et al. Causes of Death and Prognostic Factors in Multiple Endocrine Neoplasia Type 1: A Prospective Study: Comparison of 106 MEN1/Zollinger-Ellison Syndrome Patients With 1613 Literature MEN1 Patients With or Without Pancreatic Endocrine Tumors. Medicine (Baltimore) 2013;92:135–181. [PubMed: 23645327]

14. Zollinger RM, Ellison EH. Primary peptic ulcerations of the jejunum associated with islet cell tumors of the pancreas. Ann Surg 1955;142:709–728. [PubMed: 13259432]

15. Jensen RT, Gardner JD. Gastrinoma. In: Go VLW, DiMagno EP, Gardner JD et al. eds. The Pancreas: Biology, Pathobiology and Disease. New York: Raven Press Publishing Co.; 1993:931–978.

16. Ito T, Cadiot G, Jensen RT. Diagnosis of Zollinger-Ellison syndrome: Increasingly difficult. World J Gastroenterol 2012;18:5495–5503. [PubMed: 23112541]

17•. Stueven AK, Kayser A, Wetz C , et al. Somatostatin Analogues in the Treatment of Neuroendocrine Tumors: Past, Present and Future. Int J Mol Sci 2020;20:3049.Review of the roles and efficacy of somatostatin analogues in the treatment of NENs.

18. Berna MJ, Hoffmann KM, Serrano J , et al. Serum gastrin in Zollinger-Ellison syndrome: I. Prospective study of fasting serum gastrin in 309 patients from the National Institutes of Health and comparison with 2229 cases from the literature. Medicine (Baltimore) 2006;85:295–330. [PubMed: 17108778]

19. Lee L, Ito T, Jensen RT. Prognostic and predictive factors on overall survival and surgical outcomes in pancreatic neuroendocrine tumors: recent advances and controversies. Expert Rev Anticancer Ther 2019;19:1029–1050.. [PubMed: 31738624]

20. Poitras P, Gingras MH, Rehfeld JF. The Zollinger-Ellison syndrome: dangers and consequences of interrupting antisecretory treatment. Clin Gastroenterol Hepatol 2012;10:199–202 [PubMed: 21871248]

21•. Metz DC, Cadiot G, Poitras P , et al. Diagnosis of Zollinger-Ellison syndrome in the era of PPIs, faulty gastrin assays, sensitive imaging and limited access to acid secretory testing. Int J Endocr Oncol 2017;4:167–185. [PubMed: 29326808] Review of current difficult of diagnosing ZES in the era of PPI use.

22••. Pavel M, Oberg K, Falconi M , et al. Gastroenteropancreatic neuroendocrine neoplasms: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2020;31:844–860. [PubMed: 32272208] Recent paper summarizing ESMO clinical guidelines for all aspects of the management of NENs.

23•. Dimitriadis GK, Weickert MO, Randeva HS , et al. Medical management of secretory syndromes related to gastroenteropancreatic neuroendocrine tumours. Endocr Relat Cancer 2016;23:R423–R436. [PubMed: 27461388] General Review treatment of all F-NEN syndromes.

24. Roy PK, Venzon DJ, Feigenbaum KM , et al. Gastric secretion in Zollinger-Ellison syndrome: correlation with clinical expression, tumor extent and role in diagnosis - A prospective NIH study of 235 patients and review of the literature in 984 cases. Medicine(Baltimore) 2001;80:189–222. [PubMed: 11388095]

25. Jensen RT. Zollinger-Ellison syndrome. In: Podolsky DK, Camilleri M, Fitz JGKAN et al. eds. Yamada's Textbook of Gastroenterology. West Sussex. UK: John Wiley and Sons, Ltd.; 2016:1078–1102.

26. Ito T, Igarashi H, Uehara H , et al. Pharmacotherapy of Zollinger-Ellison syndrome. Expert Opin Pharmacotherapy 2013;14:307–321.

27•. Angelousi A, Koffas A, Grozinsky-Glasberg S , et al. Diagnostic and Management Challenges in Vasoactive Intestinal Peptide Secreting Tumors: A Series of 15 Patients. Pancreas 2019;48:934–942. [PubMed: 31268974] Recent review of diagnosis and in management of patients with VIPomas.

28. Roy PK, Venzon DJ, Shojamanesh H , et al. Zollinger-Ellison syndrome: clinical presentation in 261 patients. Medicine (Baltimore) 2000;79:379–411. [PubMed: 11144036]

29. Jensen RT. Overview of chronic diarrhea caused by functional neuroendocrine neoplasms. Semin Gastrointest Dis 1999;10:156–172. [PubMed: 10548409]

30. Rehfeld JF, Bardram L, Hilsted L , et al. Pitfalls in diagnostic gastrin measurements. Clin Chem 2012;58:831–836 [PubMed: 22419747]

31. Rehfeld JF, Gingras MH, Bardram L , et al. The Zollinger-Ellison Syndrome and Mismeasurement of Gastrin. Gastroenterology 2011;140:1444–1453. [PubMed: 21315717]

32. Shah P, Singh MH, Yang YX , et al. Hypochlorhydria and achlorhydria are associated with false-positive secretin stimulation testing for zollinger-ellison syndrome. Pancreas 2013;42:932–936. [PubMed: 23851430]

33. Berna MJ, Hoffmann KM, Long SH , et al. Serum gastrin in Zollinger-Ellison syndrome: II. Prospective study of gastrin provocative testing in 293 patients from the National Institutes of Health and comparison with 537 cases from the literature. evaluation of diagnostic criteria, proposal of new criteria, and correlations with clinical and tumoral features. Medicine (Baltimore) 2006;85:331–364. [PubMed: 17108779]

34•. Clement D, Ramage J, Srirajaskanthan R. Update on Pathophysiology, Treatment, and Complications of Carcinoid Syndrome. J Oncol 2020;2020:8341426. [PubMed: 32322270] Review of the roles and efficacy of somatostatin analogues in the treatment of NENs.

35. Ramage JK, Ahmed A, Ardill J , et al. Guidelines for the management of gastroenteropancreatic neuroendocrine (including carcinoid) tumours (NETs). Gut 2012;61:6–32. [PubMed: 22052063]

36. Gut P, Waligorska-Stachura J, Czarnywojtek A , et al. Management of the hormonal syndrome of neuroendocrine tumors. Arch Med Sci 2017;13:515–524. [PubMed: 28507564]

37•. Akirov A, Larouche V, Alshehri S , et al. Treatment Options for Pancreatic Neuroendocrine Tumors. Cancers (Basel) 2019;11:828.Recent Review of all aspects of the treatment of panNENs: both F-panNENs and Non-F-panNENs.

38. Bushnell DL Jr., O'Dorisio TM, O'Dorisio MS , et al. 90Y-edotreotide for metastatic carcinoid refractory to octreotide. J Clin Oncol 2010;28:1652–1659. [PubMed: 20194865]

39. Ito T, Igarashi H, Jensen RT. Zollinger-Ellison syndrome: Recent advances and controversies. Current Opinion in Gastroenterology 2013;29:650–661. [PubMed: 24100728]

40. Metz DC, Pisegna JR, Fishbeyn VA , et al. Currently used doses of omeprazole in Zollinger-Ellison syndrome are too high. Gastroenterology 1992;103:1498–1508. [PubMed: 1426868]

41. Metz DC, Strader DB, Orbuch M , et al. Use of omeprazole in Zollinger-Ellison: A prospective nine-year study of efficacy and safety. Aliment Pharmacol Ther 1993;7:597–610. [PubMed: 8161665]

42. Termanini B, Gibril F, Stewart CA , et al. A prospective study of the effectiveness of low dose omeprazole as initial therapy in Zollinger-Ellison syndrome. Aliment Pharmacol Ther 1996;10:61–71. [PubMed: 8871445]

43. Hirschowitz BI, Simmons J, Mohnen J. Long-term lansoprazole control of gastric acid and pepsin secretion in ZE and non-ZE hypersecretors: a prospective 10-year study. Aliment Pharmacol Ther 2001;15:1795–1806. [PubMed: 11683694]

44. Collen MJ, Howard JM, McArthur KE , et al. Comparison of ranitidine and cimetidine in the treatment of gastric hypersecretion. Ann Intern Med 1984;100:52–58. [PubMed: 6318628]

45. Raufman JP, Collins SM, Pandol SJ , et al. Reliability of symptoms in assessing control of gastric acid secretion in patients with Zollinger-Ellison syndrome. Gastroenterology 1983;84:108–113. [PubMed: 6128284]

46. Howard JM, Chremos AN, Collen MJ , et al. Famotidine, a new, potent, long-acting histamine H2-receptor antagonist: comparison with cimetidine and ranitidine in the treatment of Zollinger-Ellison syndrome. Gastroenterology 1985;88:1026–1033. [PubMed: 2857672]

47. Jensen RT. Use of omeprazole and other proton pump inhibitors in the Zollinger-Ellison syndrome. In: Olbe L ed. Milestones in Drug Therapy. Basel, Switzerland: Birkhauser Verlag AG Publish. Co.; 1999:205–221.

48. Hirschowitz BI, Simmons J, Mohnen J. Clinical outcome using lansoprazole in acid hypersecretors with and without Zollinger-Ellison syndrome: a 13-year prospective study. Clin Gastroenterol Hepatol 2005;3:39–48. [PubMed: 15645403]

49. Norton JA, Alexander HR, Fraker DL , et al. Does the use of routine duodenotomy (DUODX) affect rate of cure, development of liver metastases or survival in patients with Zollinger-Ellison syndrome (ZES)? Ann Surg 2004;239:617–626. [PubMed: 15082965]

50. Norton JA, Foster DS, Ito T , et al. Gastrinomas: Medical and SurgicalTreatment. Endocrinol Metab Clin North Am 2018;47:577–601. [PubMed: 30098717]

51. Fishbeyn VA, Norton JA, Benya RV , et al. Assessment and prediction of long-term cure in patients with Zollinger-Ellison syndrome: the best approach. Ann Intern Med 1993;119:199–206. [PubMed: 8323088]

52. Termanini B, Gibril F, Sutliff VE, III , et al. Effect of long-term gastric acid suppressive therapy on serum vitamin B12 levels in patients with Zollinger-Ellison syndrome. Am J Med 1998;104:422–430. [PubMed: 9626024]

53•. Veltroni A, Cosaro E, Spada F , et al. Clinico-pathological features, treatments and survival of malignant insulinomas: a multicenter study. Eur J Endocrinol 2020;182:439–446. [PubMed: 32061159] Recent review of all aspects of the management of malignant insulinomas.

54. Gill GV, Rauf O, MacFarlane IA. Diazoxide treatment for insulinoma: a national UK survey. Postgrad Med J 1997;73:640–641. [PubMed: 9497974]

55. Niitsu Y, Minami I, Izumiyama H , et al. Clinical outcomes of 20 Japanese patients with insulinoma treated with diazoxide. Endocr J 2019;66:149–155. [PubMed: 30504655]

56. Thus KA, den Boogert WJ, van der Heyden JC. Thrombocytopaenia: a serious side effect of diazoxide. BMJ Case Rep 2019;12: (in press).

57. Sileo F, Cangiano B, Cacciatore C , et al. Off-label pasireotide treatment in one insulinoma patient with an atypical presentation and intolerant to diazoxide. Endocrine 2020, (in press).

58. Falconi M, Eriksson B, Kaltsas G , et al. ENETS Consensus Guidelines Update for the Management of Patients with Functional Pancreatic Neuroendocrine Tumors and

Non-Functional Pancreatic Neuroendocrine Tumors. Neuroendocrinology 2016;103:153–171. [PubMed: 26742109]

59•. Feelders RA, Newell-Price J, Pivonello R , et al. Advances in the medical treatment of Cushing's syndrome. Lancet Diabetes Endocrinol 2019;7:300–312. [PubMed: 30033041] Recent review of newer aspects of the management of Cushing's syndrome.

60•. Young J, Haissaguerre M, Viera-Pinto O , et al. MANAGEMENT OF ENDOCRINE DISEASE: Cushing's syndrome due to ectopic ACTH secretion: an expert operational opinion. Eur J Endocrinol 2020;182:R29–R58. [PubMed: 31999619] Recent review of all aspects of the management of Ectopic Cushing's syndrome.

61. Maragliano R, Vanoli A, Albarello L , et al. ACTH-secreting pancreatic neoplasms associated with Cushing syndrome: clinicopathologic study of 11 cases and review of the literature. Am J Surg Pathol 2015;39:374–382. [PubMed: 25353285]

62. Maton PN, Gardner JD, Jensen RT. Cushing's syndrome in patients with Zollinger-Ellison syndrome. N Engl J Med 1986;315:1–5. [PubMed: 2872593]

63. Isidori AM, Kaltsas GA, Grossman AB. Ectopic ACTH syndrome. Front Horm Res 2006;35:143–156 [PubMed: 16809930]

64. Amikura K, Alexander HR, Norton JA , et al. The role of surgery in the management of ACTH-producing islet cell tumors of the pancreas. Surgery 1995;118:1125–1130. [PubMed: 7491532]

65. Zhang C, Jin J, Xie J , et al. The clinical features and molecular mechanisms of ACTH-secreting pancreatic neuroendocrine tumors. J Clin Endocrinol Metab 2020(in press).

66. Doppman JL, Nieman LK, Cutler GB Jr. , et al. Adrenocorticotropic hormone-secreting islet cell tumors: Are they always malignant? Radiology 1994;190:59–64. [PubMed: 8259429]

67. Naik C, Basu S. Peptide Receptor Radionuclide Therapy with 177Lu-DOTATATE for Metastatic Neuroendocrine Tumor Occurring in Association with Multiple Endocrine Neoplasia Type 1 and Cushing's Syndrome. World J Nucl Med 2017;16:126–132. [PubMed: 28553179]

68. Zhang J, Kulkarni HR, Baum RP. Ectopic Corticotropin-Releasing Hormone-Secreting Pancreatic Neuroendocrine Tumor: Excellent Response of Liver Metastases to Peptide Receptor Radionuclide Therapy as Demonstrated by 68Ga-DOTATOC and 18F-FDG PET/CT Imaging. Clin Nucl Med 2020;45:e125–e127. [PubMed: 31714276]

69. Hatipoglu E, Kepicoglu H, Rusen E , et al. Von Hippel Lindau disease with metastatic pancreatic neuroendocrine tumor causing ectopic Cushing's syndrome. Neuro Endocrinol Lett 2013;34:9–13. [PubMed: 23524618]

70. Lamarca A, Barriuso J, McNamara MG , et al. Telotristat ethyl: a new option for the management of carcinoid syndrome. Expert Opin Pharmacother 2016;17:2487–2498. [PubMed: 27817224]

71. Gilliaux Q, Bertrand C, Hanon F , et al. Preoperative treatment of benign insulinoma: diazoxide or somatostatin analogues? Acta Chir Belg 2020; (in press).

72. Vezzosi D, Bennet A, Rochaix P , et al. Octreotide in insulinoma patients: efficacy on hypoglycemia, relationships with Octreoscan scintigraphy and immunostaining with anti-sst2A and anti-sst5 antibodies. Eur J Endocrinol 2005;152:757–767. [PubMed: 15879362]

73•. van Schaik E, van Vliet EI, Feelders RA , et al. Improved control of severe hypoglycemia in patients with malignant insulinomas by Peptide receptor radionuclide therapy. J Clin Endocrinol Metab 2011;96:3381–3389. [PubMed: 21917872] Important study reporting successful treatment of series of patients with malignant insulinomas with PRRT.

74••. Zandee WT, Brabander T, Blazevic A , et al. Symptomatic and Radiological Response to 177Lu-DOTATATE for the Treatment of Functioning Pancreatic Neuroendocrine Tumors. J Clin Endocrinol Metab 2019;104:1336–1344. [PubMed: 30566620] Pivotal study reporting successful control of hormone excess state in a series of patients with F-NENs with PRRT.

75. Iglesias P, Martinez A, Gajate P , et al. LONG-TERM EFFECT OF (177)LU-DOTATATE ON SEVERE AND REFRACTORY HYPOGLYCEMIA ASSOCIATED WITH MALIGNANT INSULINOMA. AACE Clin Case Rep 2019;5:e330–e333. [PubMed: 31967064]

76•. Lee L, Ito T, Jensen RT. Everolimus in the treatment of neuroendocrine tumors: efficacy, side-effects, resistance, and factors affecting its place in the treatment sequence. Expert Opin Pharmacother 2018;19:909–928 [PubMed: 29757017] Recent review summarizing the results of

studies with everolimus in both F-NENS and non-F-NENs for control of both tumor growth and the hormone-excess state.

77. Tirosh A, Stemmer SM, Solomonov E , et al. Pasireotide for malignant insulinoma. Hormones (Athens) 2016;15:271–276. [PubMed: 26732164]

78•. Vitale G, Dicitore A, Sciammarella C , et al. Pasireotide in the treatment of neuroendocrine tumors: a review of the literature. Endocr Relat Cancer 2018;25:R351–R364. [PubMed: 29643113] Recent review summarizing the results of studies with Pasireotide in both F-NENs, nonF-NENs.

79. Hendren NS, Panach K, Brown TJ , et al. Pasireotide for the treatment of refractory hypoglycaemia from malignant insulinoma. Clin Endocrinol (Oxf) 2018;88:341–343. [PubMed: 29055143]

80. Kong G, Hicks RJ. Peptide Receptor Radiotherapy: Current Approaches and Future Directions. Curr Treat Options Oncol 2019;20: (in press). [PubMed: 30771020]

81. Buscombe JR. Evidence Base for the Use of PRRT. Semin Nucl Med 2020;50:399–404. [PubMed: 32768004]

82. Magalhaes D, Sampaio IL, Ferreira G , et al. Peptide receptor radionuclide therapy with (177)Lu-DOTA-TATE as a promising treatment of malignant insulinoma: a series of case reports and literature review. J Endocrinol Invest 2019;42:249–260. [PubMed: 29949120]

83. Kwekkeboom DJ, de Herder WW, Kam BL , et al. Treatment with the radiolabeled somatostatin analog [177 Lu-DOTA 0,Tyr3]octreotate: toxicity, efficacy, and survival. J Clin Oncol 2008;26:2124–2130. [PubMed: 18445841]

84•. Del Olmo-Garcia MI, Muros MA, Lopez-de-la-Torre M , et al. Prevention and Management of Hormonal Crisis during Theragnosis with LU-DOTA-TATE in Neuroendocrine Tumors. A Systematic Review and Approach Proposal. J Clin Med 2020; (in press).Recent review summarizing the treatment of PRRT induced hormonal crises in F-NENs.

85. Tapia RG, Li M, Pavlakis N , et al. Prevention and management of carcinoid crises in patients with high-risk neuroendocrine tumours undergoing peptide receptor radionuclide therapy (PRRT): Literature review and case series from two Australian tertiary medical institutions. Cancer Treat Rev 2018;66: (in press). [PubMed: 29909222]

86. Jensen RT. Natural history of digestive endocrine tumors. In: Mignon M, Colombel JF eds. Recent advances in pathophysiology and management of inflammatory bowel diseases and digestive endocrine tumors. Paris, France: John Libbey Eurotext Publishing Co.; 1999:192–219.

87. Ito T, Jensen RT. Molecular imaging in neuroendocrine tumors: recent advances, controversies, unresolved issues, and roles in management. Curr Opin Endocrinol Diabetes Obes 2017;24:15–24. [PubMed: 27875420]

88. Ito T, Igarashi H, Jensen RT. Therapy of metastatic pancreatic neuroendocrine tumors (pNETs): recent insights and advances. J Gastroenterol 2012;47:941–960. [PubMed: 22886480]

89. Lee L, Ito T, Jensen RT. Imaging of pancreatic neuroendocrine tumors: recent advances, current status and controversies. Expert Rev Anticancer Ther 2018;18:837–860. [PubMed: 29973077]

90. Ito T, Jensen RT. Imaging in multiple endocrine neoplasia type 1: recent studies show enhanced sensitivities but increased controversies. Int J Endocr Oncol 2016;3:53–66. [PubMed: 26834963]

91. Zilli A, Arcidiacono PG, Conte D , et al. Clinical impact of endoscopic ultrasonography on the management of neuroendocrine tumors: lights and shadows. Dig Liver Dis 2018;50:6–14. [PubMed: 29102525]

92. Cherner JA, Doppman JL, Norton JA , et al. Selective venous sampling for gastrin to localize gastrinomas. A prospective study. Ann Intern Med 1986;105:841–847. [PubMed: 3535602]

93. Krudy AG, Doppman JL, Jensen RT , et al. Localization of islet cell tumors by dynamic CT: Comparison with plain CT, arteriography, sonography and venous sampling. Am J Roentgenol 1984;143:585–589.. [PubMed: 6087646]

94. Doppman JL, Miller DL, Chang R , et al. Gastrinomas: localization by means of selective intraarterial injection of secretin. Radiology 1990;174:25–29 [PubMed: 2294556]

95. Frucht H, Doppman JL, Norton JA , et al. Gastrinomas: Comparison of MR Imaging with CT, angiography and US. Radiology 1989;171:713–717. [PubMed: 2655004]

96. Frucht H, Norton JA, London JF , et al. Detection of duodenal gastrinomas by operative endoscopic transillumination: a prospective study. Gastroenterology 1990;99:1622–1627. [PubMed: 2227278]

97. MacFarlane MP, Fraker DL, Alexander HR , et al. A prospective study of surgical resection of duodenal and pancreatic gastrinomas in multiple endocrine neoplasia-Type 1. Surgery 1995;118:973–980. [PubMed: 7491542]

98. Thom AK, Norton JA, Axiotis CA , et al. Location, incidence and malignant potential of duodenal gastrinomas. Surgery 1991;110:1086–1093. [PubMed: 1745977]

99. Moreno-Moreno P, Alhambra-Exposito MR, Herrera-Martinez AD , et al. Arterial Calcium Stimulation with Hepatic Venous Sampling in the Localization Diagnosis of Endogenous Hyperinsulinism. Int J Endocrinol 2016;2016:4581094. [PubMed: 27795707]

100. Dasari A, Shen C, Halperin D , et al. Trends in the Incidence, Prevalence, and Survival Outcomes in Patients With Neuroendocrine Tumors in the United States. JAMA Oncol 2017;3:1335–1342. [PubMed: 28448665]

101. McCarthy DM, Olinger EJ, May RJ , et al. H2-histamine receptor blocking agents in the Zollinger-Ellison syndrome. Experience in seven cases and implications for long-term therapy. Ann Intern Med 1977;87:668–675. [PubMed: 22304]

102. Jensen RT, Collen MJ, McArthur KE , et al. Comparison of the effectiveness of ranitidine and cimetidine in inhibiting acid secretion in patients with gastric acid hypersecretory states. Am J Med 1984;77(5B):90–105. [PubMed: 6150641]

103. Sheehan MT, Wermers RA, Jatoi A , et al. Oral cinacalcet responsiveness in non-parathyroid hormone mediated hypercalcemia of malignancy. Med Hypotheses 2020;143: (in press).

104. Tritos NA, Biller BMK. Medical Therapy for Cushing's Syndrome in the Twenty-first Century. Endocrinol Metab Clin North Am 2018;47:427–440. [PubMed: 29754642]

105••. Tsoli M, Alexandraki K, Xanthopoulos C , et al. Medical Treatment of Gastrointestinal Neuroendocrine Neoplasms. Horm Metab Res 2020;52:614–620. [PubMed: 32108932] Recent paper reviewing all aspects of the medical treatment of NENs.

106. Barat M, Cottereau AS, Kedra A , et al. The Role of Interventional Radiology for the Treatment of Hepatic Metastases from Neuroendocrine Tumor: An Updated Review. J Clin Med 2020; (in press).

107. Pavel M, O'Toole D, Costa F , et al. ENETS Consensus Guidelines Update for the Management of Distant Metastatic Disease of Intestinal, Pancreatic, Bronchial Neuroendocrine Neoplasms (NEN) and NEN of Unknown Primary Site. Neuroendocrinology 2016;103:172–185. [PubMed: 26731013]

108. Satapathy S, Mittal BR. 177Lu-DOTATATE peptide receptor radionuclide therapy versus Everolimus in advanced pancreatic neuroendocrine tumors: a systematic review and meta-analysis. Nucl Med Commun 2019;40:1195–1203. [PubMed: 31658219]

Table 1:

F-NEN syndromes, hormone-excess state symptoms and primary/secondary treatments

F-NET syndrome	Main Symptoms/sign	Initial Medical treatment	Secondary medical treatments[other treatments]
Carcinoid syndrome	Diarrhea(58-!00%)	Long-acting SS analogues	Telotristat, PRRT, interferon, serotonin receptor antagonist
	Flushing(45-96), Wheezing(3-18%) Carcinoid Heart disease(14-41%)	Long-acting SS analogues	PPRT, Interferon, telotristat [Valve replacement] [radio-embolization, hepatic embolization/chemo-embolization}
Insulinoma	Hypoglycemic-Sx= Neuropsychiatric(92%)-confusion(51%),altered consciousness((38%) Adrenergic Sx-Sweating(43%),Tremulousness (23%)	Frequent small feedings, Diazoxide	Long-acting SS analogues, PRRT(malignant insulinomas),everolimus, pasireotide, beta-blockers, calcium blockers, phenytoin [surgery as soon as possible] [radio-embolization, hepatic embolization/chemo-embolization}
Gastrinoma (Zollinger-Ellison syndrome)[ZES]	Pain (26-98%), GERD(0-56%), peptic ulcer disease(71-93%) Diarrhea(17-73%) GI bleeding(8-75%)	PPIs	Histamine H2-receptor antagonists>> Long-acting SS analogues [surgery if possible]
Glucagonoma	Diabetes (22-90%) Diarrhea (14-18%) Dermatitis(NME) (54-90%)	Long-acting SS analogues, amino acid infusion	Parenteral nutrition, ?PRRT [surgery if possible] [radio-embolization, hepatic embolization/chemo-embolization}
VIPoma(Verner-Morrison syndrome, Pancreatic cholera)	Large volume diarrhea (89-100%) Hypokalemia(67-100%)) Dehydration(44-100%) Flushing(14-33%)	Long-acting SS analogues Fluid/electrolyte replacement	PRRT, Glucocorticoids,loperamide, clonidine, sunitinib, Pasireotide,indomethacin,metoclopramide, lithium,phenothiazines [surgery if possible] [radio-embolization,hepatic embolization/chemo-embolization}
Pancreatic ACTHoma	Cushing's syndrome (100%)	Steroidogenesis inhibitors	Mitotane,Dopamine agonists, long-acting somatostatin analogues, pasireotide, PRRT [surgery of primary tumor if possible; adrenalectomy]
Less frequent panNEN syndromes			
SSoma	Diabetes, Diarrhea, Gallbladder disease, weight loss	Long-acting SS analogues	?PRRT,[surgery if possible]
GRFoma	Acromegaly		Pasireotide, ?PRRT [surgery if possible]
PTHrPoma	Hyperparathyroidism		Cinacalcet,bisphosphonates/rehydration, ?PRRT,[surgery if possible]

Abbreviations: ACTHoma (pancreatic)-Adrenocorticotropin releasing hormone ectopically in pancreas; F-NEN syndrome-distinct functional neuroendocrine neoplasm syndrome due to distinct release of biologically active hormone/amine; GI-gastrointestinal ; GERD-gastroesophageal reflux disease ; GRFoma-Growth hormone-releasing factor secreting NEN; H_2-receptor antagonists-Histamine H2-receptor

antagonists; NME-necrolytic migratory erythema; PPI-proton pump inhibitors; PTHrPoma-panNEN secreting parathromone-related peptide causing hyperparathyroidism; SS-somatostatin analogues (Long-acting forms-Octreotide-LAR, Lanreotide-Autogel); SSoma-somatostatinoma causing the somatostatinoma syndrome; sx-symptoms; VIPoma-vasoactive intestinal polypeptide secreting NEN