Optimizing the Management of Carcinoid Syndrome to Reduce the Impact of Diarrhea

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CASE STUDY

A 54-year-old male presented with complaints of periodic facial flushing and diarrhea for more than a year. He is experiencing debilitating diarrhea, with loose or watery stools accompanied by abdominal pain and fecal urgency up to 20 times per day. Medical history was significant for bowel obstruction requiring hospital admission, which eventually improved with medical management, including nasogastric decompression. Due to ongoing diarrhea, he is unable to work as a computer technician or participate in family and leisure activities.

Diagnostic workup for possible neuroendocrine tumor (NET) showed significant elevation in 24-hour urinary 5-hydroxyindoleacetic acid (5-HIAA) at 250 mg (normal: 0–6 mg/24 hr) and chromogranin A (CGA) at 525 ng/mL (normal: 0–5 ng/mL). A CT scan of the abdomen showed multiple tumors in the right lobe of the liver. Somatostatin receptor scintigraphy (octreotide scan) was strongly positive for somatostatin receptor expression within the tumors in the liver. An ultrasound-guided core needle biopsy of a tumor in the liver showed a well-differentiated metastatic grade 2 NET.

Abstract

Diarrhea is often a presenting symptom in patients with neuroendocrine tumors (NETs). Frequently diagnosed in advanced stages, carcinoid syndrome diarrhea negatively impacts patients’ well-being and quality of life. This article will review the diagnostic work-up for neuroendocrine tumors and etiology and management of NET-related carcinoid syndrome diarrhea and provide guidance for advanced practitioners, including nurse practitioners, physician assistants, pharmacists, and dieticians, focusing on their role in patient and caregiver education regarding disease, symptom monitoring and management, development of patient-specific treatment, and survivorship plans.

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Neuroendocrine tumors (NETs) are neoplasms found in neuroendocrine tissues, occurring most commonly in the bronchopulmonary system and gastrointestinal (GI) tract. The most common primary sites of GI-NETs include the small bowel, rectum, colon, pancreas, stomach, and appendix (Choti et al., 2012; Lawrence et al., 2011). Patients are often asymptomatic, and early tumor detection is usually an incidental finding. Diagnosis may be delayed for years. Small-bowel NETs present with metastases in 40% to 50% of cases, most commonly to the regional lymph nodes and liver (Bertani et al., 2015).

Epidemiology and Classification
In the United States, both the incidence and prevalence of NETs across all primary tumor sites, stages, and grades has risen (Dasari et al., 2017). Neuroendocrine tumors are identified as functioning or nonfunctioning, and characterized by symptoms or syndromes associated with hormones secreted by the tumor (Table 1; Strosberg, 2017a). Symptoms are often vague and easily mistaken for more common diagnoses, and typical overt symptoms present only with liver metastases (Molina-Cerrillo, Alonso-Gordo, Martinez-Sáez, & Grande, 2016; van der Lely & de Herder, 2005).

The Role of NETs in Carcinoid Syndrome and Carcinoid Syndrome-Related Diarrhea
Carcinoid syndrome presents in 8% to 35% of NETs in the small bowel, terminal ileum, and the appendix, and less commonly in the pancreas and lung (Halperin et al., 2017; Molina-Cerrillo et al., 2016; Phan et al., 2017; Tsoukalas et al., 2017; Zandee et al., 2017). The most common symptoms are cutaneous flushing (45%–96%), diarrhea (58%–100%), wheezing (3%–18%) and, uncommonly, carcinoid heart disease, or mesenteric or pulmonary fibrosis (Creutzfeldt, 1996; Dimitriadis, Weickert, Randeva, Kaltsas, & Grossman, 2016; Ito, Lee, & Jensen, 2018; Mota, Sousa, & Riechelmann, 2016). Diarrhea may be explosive, watery, and loose multiple times a day, adversely impacting daily life and physical, emotional, and social well-being (Fröjd, Larsson, Lampic, & von Essen, 2007; Isenberg-Grzeda, Macgregor, Matsoukas, Reidy-Lagunes, & Alici, 2017).

Pathobiology of Carcinoid Syndrome
Carcinoid syndrome is caused by the NET secretion of vasoactive compounds: serotonin, histamine, prostaglandin, tachykinins, and kallikrein (Molina-Cerrillo et al., 2016). Serotonin plays a role in the pathogenesis of carcinoid syndrome, and its measurement has been used as a biomarker of tumor activity and response to therapy. Other vasoactive compounds, such as histamine, prostaglandin E2, and tachykinins, have also been implicated in the pathophysiology of diarrheal symptoms in carcinoid syndrome. The use of somatostatin analogs, such as octreotide and lanreotide, has revolutionized the management of carcinoid syndrome, particularly in the treatment of diarrheal symptoms. These drugs act as receptor antagonists and reduce the release of vasoactive amines from NETs, thereby ameliorating diarrheal symptoms and other clinical manifestations of carcinoid syndrome. The management of carcinoid syndrome requires a multidisciplinary approach, including medical, surgical, and palliative care, with a focus on symptom control and quality of life.
central role by acting directly on the cell membrane receptors of enteric neurons enhancing peristalsis and secretory reflexes, increasing colonic mucus, and inhibiting absorption in the gastrointestinal tract, the combination of which leads to diarrhea (Lips, Lentjes, & Höppener, 2003). In the peripheral circulation, serotonin is metabolized by the liver and kidney and is converted to 5-hydroxyindoleacetic acid (5-HIAA), which is eliminated by the urine.

DIFFERENTIAL DIAGNOSIS OF NONINFECTIOUS DIARRHEA IN PATIENTS WITH NETs ON SSA s
Differential diagnosis includes ruling out pancreatic insufficiency associated with somatostatin analogs (SSAs), short gut syndrome (particularly in the case of ileocecal valve resection), biliary salt malabsorption due to surgery, administration site fibrosis, infectious diarrhea due to *Clostridium difficile*, development or worsening of diabetes due to SSA treatment, food poisoning, and poor adherence to treatment (Strosberg et al., 2017b).

THE CARCINOID SYNDROME DIARRHEA PATIENT EXPERIENCE
Carcinoid syndrome diarrhea places a significant burden on affected patients, leading to long-term suffering due to diagnosis delays and misdiagnoses. One study of 758 patients reported delay in diagnosis from symptom onset to diagnosis of 5 or more years in 37% of patients (Wolin et al., 2017).

Compared to patients without NETs and those with other cancers, patients with NETs have higher rates of mortality and hepatic and gastrointestinal morbidities (Hess et al., 2012), depression (Isenberg-Grzeda et al., 2017), and cognitive impairment (Pasięka et al., 2014), including impairment of physical function, sleep, fatigue, and more anxiety (Beaumont et al., 2012; Pearman, Beaumont, Cella, Neary, & Yao, 2016). In patients with malignant tumors, weight loss and malnutrition are linked to negative outcomes, including excess mortality and morbidity, and higher treatment costs (Weickert et al., 2017). Diarrhea appears to have an overwhelming impact on patients’ sense of well-being. In the Patient-Reported Outcomes Measurement Information System (PROMIS) survey of global health, patients with more than 4 bowel movements per day had significantly worse quality-of-life (QOL) scores across all domains, including mental health, physical health, and social role satisfaction (Pearman et al, 2016). Diarrhea, bowel movement frequency, and urgency were

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**Table 1. Sites of NETs, Associated Symptoms, and Secreted Hormones**

| Hormone | Common location | Tumor | Key symptoms |
|---------|----------------|-------|--------------|
| Serotonin | Small intestine, stomach, pancreas, duodenum, colon, appendix rectum | NET (carcinoid) | Diarrhea, cutaneous flushing, bronchospasm, valvular heart disease |
| Insulin | Pancreas | Insulinoma | Hypoglycemia, confusion, loss of consciousness, sweating or dizziness, weight increase |
| Gastrin | Duodenum, pancreas | Gastrinoma | Acid reflux, abdominal pain, diarrhea, fat malabsorption |
| Glucagon | Pancreas | Glucagonoma | Diabetes mellitus, skin lesions (necrolytic migratory erythema), glossitis, anemia, weight loss, venous thrombosis |
| VIP | Pancreas | VIPoma | Diarrhea, hypokalemia, metabolic acidosis |
| ACTH | Lung, adrenals, thyroid, pancreas | ACTHoma | Muscle weakness, hypokalemia, weight changes, truncal obesity, hypertension, diabetes |
| PTH | Lung, pancreas | PTH-like-oma | Hypercalcemia |
| Somatostatin | Pancreas, duodenum | Somatostatinoma | Abdominal pain, jaundice, gastrointestinal bleeding, gallstones, diarrhea, diabetes, weight loss, hypochlorhydria |

**Note.** NET = neuroendocrine tumor; ACTH = adrenocorticotropic hormone; PTH = parathyroid hormone; VIP = vasoactive intestinal peptide. Information from Camilleri (2015); Sandhu & Jialal (2018); Vinik et al. (2010); Zandee et al. (2017).
most frequently identified as the most important or bothersome symptoms in a smaller study (Anthony et al., 2017).

**TREATING CLINICAL SYMPTOMS OF CARCINOID SYNDROME DIARRHEA**

According to NCCN Guidelines, first-line therapy for patients with unresectable or metastatic NETs should target tumor progression and associated symptoms (Table 2; NCCN, 2018). Surgical debulking can promptly resolve symptoms of diarrhea and cutaneous flushing, and may translate to improved survival (Lee, Cheow, Teo, & Ooi, 2012).

Because the disease course of NETs can span decades, palliative care is particularly important to maintain QOL, decrease complications, and prolong life (Anthony & Freda, 2009).

First-line medical treatment of carcinoid syndrome, typically with long-acting SSAs, is aimed at activating the somatostatin receptor to stabilize tumor growth, inhibit hormonal hypersecretion of NETs, reduce circulating hormone levels, and ameliorate patient symptoms (Anthony & Freda, 2009). Both octreotide (Sandostatin LAR) and lanreotide (Somatuline Depot) long-acting SSAs are administered as either an intramuscu-

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**Table 2. National Comprehensive Cancer Network Guidelines for the Management of Symptomatic Patients With NET of the Gastrointestinal Tract**

| Disease stage   | Management                          | Guideline Recommendations                                                                 |
|-----------------|-------------------------------------|-------------------------------------------------------------------------------------------|
| First line      | Resection                           | Resection of primary tumor should be considered in locally symptomatic patients             |
|                 |                                     | Ablative techniques (radiofrequency, microwave, and cryotherapy) are options for metastases; however, prospective data for these interventions are limited |
|                 | SSAs (octreotide or lanreotide)     | Recommended for first-line control of tumor growth                                         |
|                 |                                     | Octreotide LAR is appropriate for long-term management of patients with carcinoid syndrome |
|                 |                                     | Short-acting octreotide can be added to octreotide LAR for rapid relief of symptoms or breakthrough symptoms |
|                 |                                     | SSA would better benefit patients who have positive somatostatin receptor expression on imaging (octreoscan/Ga-68 dotatate PET) |
| Progressive disease | SSAs (octreotide or lanreotide) | Treatment should be continued in patients with functional tumors and can be added to other treatment options |
|                 |                                     | May be used in patients with low-grade tumors as first-line therapy to stabilize disease    |
| Everolimus      |                                     | Option for patients with disease progression; however, the safety and effectiveness of everolimus has not been established in patients with carcinooid syndrome |
| 177Lu-DOTATATE  | Hepatic-directed therapy            | Recommended for patients with somatostatin receptor–positive imaging                       |
|                 |                                     | Appropriate for hepatic-predominant disease/hepatic progression                             |
|                 |                                     | Options include arterial embolization, hepatic chemoembolization, hepatic radioembolization, or cytoreductive surgery/ablative therapy |
| INFα            | Cytotoxic chemotherapy              | Usually only initiated after failure of SSA treatment; out of favor now                    |
|                 |                                     | Should only be considered as a last treatment option                                       |
|                 |                                     | There are no data to support a specific sequence of regional vs. systemic therapy and no data to guide sequencing of systemic options |
| Refractory disease | Telotristat ethyl + SSAs           | Recommended for persistent diarrhea that is not controlled by SSAs alone                   |
|                 | Hepatic arterial embolization ± cytoreductive surgery | Appropriate for hepatic predominant disease                                                 |
|                 | Other systemic therapy based on disease site | Cytotoxic chemotherapy can be used in patients with progressive disease and no other treatment options |

_Note._ LAR = long-acting release; PET = positron emission tomography; Lu = lutetium; SSA = somatostatin analog; INFα = interferon alpha. Information from NCCN (2018).
lar or deep subcutaneous injection. Octreotide acetate (Sandostatin) may also be administered via short-acting subcutaneous injection (Table 3; NCCN 2018).

Octreotide was the first agent used in managing NETs. Pooled data from 14 trials of approximately 400 patients reported the resolution of diarrhea in a median of 71% (range: 40%–88%) and cutaneous flushing in a median of 71% (range: 48%–100%; Modlin et al., 2006). In an 8-year study of 108 patients with symptomatic NETs, all patients showed clinical response within 3 months of initiating long-acting octreotide. The PROMID study demonstrated that long-acting octreotide significantly prolonged the median time to progression (14.3 vs. 6.0 months with placebo) or tumor-related death vs. placebo (hazard ratio [HR], 0.34; 95% confidence interval [CI] = 0.20–0.59; p < .0001; Rinke et al., 2009).

Lanreotide has also shown clinical efficacy in NETs. In the CLARINET trial (N = 204), lanreotide was associated with significantly prolonged progression-free survival vs. placebo (HR, 0.47; 95% CI = 0.30–0.73; p < .001; Caplin et al., 2014) and with significantly fewer days of octreotide rescue (-14.8%; 95% CI = -26.8% to -2.8%; p = .017) reported in the phase III, placebo-controlled trial.

### Table 3. Carcinoid Syndrome–Specific Therapies

| Agent class | MOA | Treatment | Indication | ROA | Schedule |
|-------------|-----|-----------|------------|-----|----------|
| SSAs        | Binds to somatostatin receptors to mimic somatostatin inhibition of various endocrine, neuroendocrine, exocrine, and paracrine functions | Octreotide acetate | Symptomatic treatment of severe diarrhea and cutaneous flushing episodes associated with metastatic carcinoid tumors | Subcutaneously or intravenously | First 2 weeks of treatment: 100-600 μg/d in 2–4 divided doses (mean daily dosage: 300 μg) |
| Lanreotide  | Inhibits tryptophan hydroxylase, which catalyzes the rate-limiting step in serotonin production | Telotristat ethyl | Carcinoid syndrome diarrhea in combination with SSAs in adults inadequately controlled by SSAs | Oral | 250 mg po 3 times per day with food |

Note. MOA = mechanism of action; ROA = route of administration; SSA = somatostatin analog; GEP-NETs = gastroenteropancreatic neuroendocrine tumors; PFS = progression-free survival; po = by mouth; q4wk = every 4 weeks. Information from Ipsen Pharma Biotech (2018); Novartis Pharmaceuticals Corp. (2008, 2016); Lexicon Pharmaceuticals, Inc. (2017).

*30 mg q4wk is the dose most commonly used.*
ELECT trial (Vinick et al., 2016). A post hoc analysis of the ELECT trial reported lanreotide significantly improved diarrhea and cutaneous flushing control over 48 weeks (Fisher et al., 2018a, 2018b).

There are several potential causes of diarrhea in NET patients, and identifying the root cause is essential to optimizing treatment (Table 4). Antidiarrheal medications (tincture of opium, loperamide, and diphenoxylate atropine) do not address the underlying changes in motor function and have minimal effects on symptoms (von der Ohe, Camilleri, Kvols, & Thomforde, 1993).

Dose escalation of long-acting octreotide has been shown to be clinically effective in managing diarrhea that is responsive to initial treatment. In a retrospective review, 79% of those with persistent diarrhea who received octreotide LAR reported improvement or resolution of their symptoms following dose escalation (Strosberg et al., 2014). Tachyphylaxis has been reported, and some patients may not achieve control of diarrhea despite dose escalation or shortening of the dosing schedule to every 21 days (Al-Efraij, Aljama, & Kennecke, 2015; Chadha et al., 2009; Riechelmann, Pereira, Rego, & Costa, 2017). Another option is to switch to a different SSA (Riechelmann et al., 2017). One small study of 15 patients with metastatic NETs showed that switching from lanreotide to octreotide improved symptoms in 82% of patients. The median duration of response for diarrhea, abdominal pain, or both, was 6.5 months (Ricci et al., 2000).

Since the first SSA approval, there had been no new advances in treatments specifically for carcinoid syndrome diarrhea until the approval of telotristat ethyl (Xermelo) in 2017. Telotristat ethyl was approved by the U.S. Food & Drug Administration and by the European Medicines Agency in combination with SSA therapy in adults whose disease is not adequately controlled by SSA therapy and is the only treatment currently available that directly impacts symptoms of diarrhea by inhibiting tryptophan hydroxylase, resulting in blocking peripheral serotonin synthesis (Ipsen Pharmaceuticals, 2017; Lexicon Pharmaceuticals, Inc., 2017). National Comprehensive Cancer Network Guidelines and prescribing information recommend the

| Type                          | Causes                                                                 | Symptoms                                      |
|-------------------------------|------------------------------------------------------------------------|-----------------------------------------------|
| Carcinoid syndrome            | • Overproduction of serotonin produced by neuroendocrine tumors        | • Diarrhea                                   |
|                               |                                                                         | • Cutaneous flushing                          |
|                               |                                                                         | • Wheezing/asthma-like symptoms               |
| Short gastrointestinal transit time | • Surgical resection of the small intestine for Crohn disease, trauma, malignancy, radiation, or mesenteric ischemia | • Diarrhea, loose watery stool                |
|                               | • Necrotizing enterocolitis and congenital intestinal anomalies, such as mid-gut volvulus, atresias, or gastroschisis | • Dehydration, malnutrition, weight loss      |
| Steatorrhea                   | • Pancreatic insufficiency due to chronic pancreatic inflammation and loss of acinar cells | • Bloating, cramping, gas                     |
|                               | • Bile salt deficiency due to impaired production or secretion          | • Weakness, fatigue                          |
|                               | • Malabsorption due to small intestinal disease, surgery, or medications | • Food allergies                              |
|                               | • Serotonin-induced hypermotility                                     |                                               |
|                               | • Side effect of treatment with somatostatin analogs                   |                                               |
| Bile acid diarrhea            | • Ileal dysfunction and impaired reabsorption                          | • Passage of pale, bulky, and malodorous stool|
|                               | • Small intestinal bacterial overgrowth                                 | • Usually BM right after eating, can be associated with bloating or abdominal discomfort, and with fatty foods |
|                               | • Celiac disease                                                      |                                               |
|                               | • Chronic pancreatitis                                                 |                                               |
|                               | • Excessive hepatic bile acid synthesis                                 |                                               |
| Uncontrolled blood glucose    | • Development of diabetes, or worsening of preexisting diabetes due to SSA use | • Watery stool                               |
|                               |                                                                         | • Urgency                                     |
|                               |                                                                         | • Fecal incontinence                          |
|                               |                                                                         | • Diarrhea, loose watery stools               |

Note. BM = bowel movement; SSA = somatostatin analog. Information from Camilleri (2015); Riechelmann et al. (2017); Strosberg et al. (2017b).
administration of telotristat ethyl at 250 mg orally three times per day with food to patients with carcinoid syndrome diarrhea that is unresponsive to first-line SSA therapy (NCCN, 2018).

The safety and efficacy of telotristat ethyl (250 mg or 500 mg) plus an SSA vs. placebo plus an SSA were established in the 12-week TELESTAR trial in 135 patients with four or more bowel movements per day despite stable SSA treatment (Kulke et al., 2017). Treatment was associated with significant reductions in bowel movement frequency over time in 44% and 42% of patients who received telotristat ethyl at 250 mg and 500 mg, respectively, compared to placebo, and an overall statistically significant reduction in urinary 5-HIAA levels at week 12 (\( p < .001 \)) that was sustained through 48 weeks (Kulke et al., 2017; Pavel et al., 2018). An open-label extension noted sustained improvement in diarrhea and treatment over 48 weeks, with a dose-related improvement in weight gain vs. placebo (Weickert et al., 2017). A substudy in 35 patients who underwent exit interviews described a clinically meaningful reduction in bowel movement frequency (\( \geq 30\% \) reduction in bowel movement frequency for at least 50% of the days) with telotristat ethyl treatment and satisfaction with symptom control (Anthony et al., 2017).

The overall incidence of adverse events, especially GI adverse events (nausea, abdominal pain, and vomiting), was greater among patients who received telotristat ethyl at 500 mg than 250 mg or placebo in the double-blind portion of the TELESTAR trial (Kulke et al., 2017). During the open-label portion of the study, the adverse event profile of the two doses of telotristat ethyl was generally similar to that seen in the double-blind portion of the study. Gastrointestinal events, while mild to moderate in severity, predominated (Pavel et al., 2018).

### SUPPORTING THE CARCINOID SYNDROME DIARRHEA PATIENT

Advanced practice providers (APPs) have an opportunity to improve patient care by incorporating supportive measures to complement the pharmacologic and interventional management of carcinoid syndrome symptoms. Support encompasses patient and caregiver education regarding disease, monitoring, and managing the symptoms with nonpharmacologic measures, developing patient-specific treatment and survivorship plans, and coaching patients on how to best capture and communicate their symptoms to the health-care team.

Patients should be empowered to be participants in their care through education on the importance of keeping a record or diary of diarrhea, stool consistency, frequency, and accompanying symptoms and dietary triggers in order to have more productive discussions with health-care providers. For patients receiving treatment with SSAs

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**Table 5. Questions to Assess the Impact of Carcinoid Syndrome Diarrhea on Patients' Daily Lives**

| Domain | Questions |
|--------|-----------|
| Physical | • How many bowel movements do you have per day?  
• Do you have episodes of incontinence or fecal urgency during which you are not able to make it to the toilet in time?  
• Have you experienced a change in your appetite?  
• Have you experienced weight loss? Weight gain?  
• Have you had a decrease in the number of bowel movements?  
• Have you experienced a lessening of urgency with bowel movements?  
• Have you had a decrease in the number of nocturnal bowel movements?  
• Have you had an increase in abdominal pain?  
• Have you experienced more nausea? Vomiting? Bloating?  
• Has your blood glucose been elevated or decreased? Have you had hypoglycemic episodes (shaking, sweating, etc.)? |
| Social | • Do your diarrhea symptoms limit your ability to be active and/or social?  
• Do you have energy for the activities of daily living?  
• Are you able to function throughout a full workday? |
| Emotional | • How is your overall sense of well-being?  
• Do you feel anxious or depressed due to your diarrhea? |

*Note. Information from Yadegarfar et al. (2013).*
who exhibit less relief of diarrhea, APPs should assess the preparation and administration technique.

It is important to determine the impact of symptoms on QOL, including anxiety, embarrassment, depression, and sleep disruptions due to nocturnal diarrhea (Yadegarfar et al., 2013). The negative impact of NET on a patient’s quality of life was demonstrated by the results of an anonymous, self-reported, global survey of nearly 2,000 patients with NET as reported by Singh and colleagues (2017). Questions regarding activities of daily living such as the ability to work, social interactions, and overall function help in assessing the level of QOL impact (Table 5).

Patients are often confused about the management of their NETs (Fröjd et al., 2007). Pearman and colleagues noted that more than 50% of patients desired clearer information on the long-term impact of NETs, increased access to NET specialist health-care professionals, better direction on where to find useful NET information, and more knowledgeable health-care professionals (Table 6; Pearman et al., 2016).

A collaborative approach to treatment that is patient centric and involves key stakeholders, such as family and caregivers, is particularly important in the development of a survivorship plan that manages and assesses patient expectations of treatment (Figure 1). Patients should be aware of what to expect, from imaging to lab work, and other testing that can contribute to a better sense of control and corresponding improvement in QOL. Reviewing the plan for managing breakthrough diarrhea provides the patient with a higher level of control. Finally, a patient may benefit from psychosocial assessment and support, potentially from an individual provider or patient groups, and social workers to help them navigate managing their disease (Oncology Nursing Society, 2015; Oncology Nursing Society Voice, 2018).

### SUMMARY

Managing diarrhea in patients with NETs is an important aspect of managing carcinoid syndrome and enhancing QOL. Although SSAs are considered first-line therapy and commonly used, telotristat ethyl provides an effective, safe, and well-tolerated option for carcinoid syndrome diarrhea that is not controlled by SSAs alone.

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**Table 6. Triggers for Excessive Symptoms: The Five “Es”**

| Trigger   | Response                                                                 |
|-----------|--------------------------------------------------------------------------|
| Exercise  | “Overexercise,” which could bring on excessive flushing and other symptoms |
| Emotion   | Avoid situations that evoke strong emotions, particularly anger and stress |
| Ethanol   | Small amounts of alcohol may be OK for some patients; red wine seems to be a particular trigger |
| Eating    | Avoid spicy food and “aged foods” like salami, certain cheeses, cooked tomatoes, and citrus |
| Epinephrine | Alert emergency personnel in situations such as allergic reaction or a heart problem. Ask dentist for anesthetics without epinephrine. |

*Note. Information from Northwood NETs (2012).*
Because NETs are often slow growing, chronic symptom management may be required for many years. The role of the APP in understanding the impact of carcinoid syndrome symptoms on patient QOL and oversight of care is critical. Coordination within the treatment team, patient education, monitoring of adherence to therapy, monitoring laboratory studies, and adjusting therapy based on individual response can improve the management of carcinoid syndrome diarrhea and patient QOL.

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