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Neuroendocrine Tumour Management by Somatostatin Analogues and Tryptophan Hydroxylase Inhibitors

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Background

Neuroendocrine tumours (NETs) are a family of tumours, occurring at an age adjusted rate of about 6.98 per 100,000[1]. The most common primary site of NETs are in the gastrointestinal (GI) tract (stomach, small intestine, appendix, rectum), lungs and bronchi, thymus and pancreas[2]. They can also arise in the parathyroid, thyroid, adrenal and pituitary glands[2]. Patients with well-differentiated low and intermediate grade NETs often have a relatively good prognosis, while those with poorly-differentiated, high grade NETs fare less well[3]. These tumours are often classified as functioning or nonfunctioning. Functioning NETs secrete hormones and cause a clinical syndrome[4]. Functioning NETs are often found earlier and may have a better prognosis[5].

Carcinoid syndrome is characterized as diarrhea, flushing, and bronchospasm and is related to elevated levels of serotonin when metabolized serotonin turns into 5- Hydroxyindoleacetic Acid (5-HIAA). Assessment of this is done by 24-hour urine test due to stability issues. Because of the high rate of false positives with certain diets and supplements, urine must be collected under ideal conditions (see Appendix A).

Somatostatin analogues (SSA) are commonly used in the treatment of NETs and have antisecretory and antiproliferative effects. The anti-secretory effects reduce symptoms and complications from carcinoid syndrome in patients with NET. SSAs have been shown to control the production of hormones such as growth hormone (GH) and adrenocorticotropic hormone (ACTH) [6]. SSAs have an anti-proliferative effect on gastroenteropancreatic (GEP) NETs, which was demonstrated through improved progression free survival in the landmark PROMID and CLARINET studies[7-10]. There are side effects associated with SSAs and caution is necessary when treating patients with known cholelithiasis. Please see Appendix B and the paper by Koumarianou and colleagues[11] for more information. Side effects should be managed as clinically indicated. If there is a concern regarding side effect management, the SSA should be held pending a review with the prescribing or NET physician.

Telotristat is a tryptophan hydroxylase inhibitor that can be administered in combination with SSAs, in GEP NET cases where symptoms are not controlled by SSAs alone[12-14]. The purpose of this guideline is to provide evidence-based recommendations on SSA and telotristat management for NETs in our practice setting and to define which patients are candidates for treatment with these agents. For staging, the American Joint Committee on Cancer (AJCC; 8th edition, 2017) staging for NETs[15] should be used.

Guideline Questions

1. Are long acting SSAs effective for symptom management in secretory syndromes resulting from NETs? If so, for which patients and what are the appropriate dosing regimens?
2. Which patients are candidates for adjuvant therapy with telotristat?
3. What is the role of short acting SSAs in the management of NETs?

4. Should SSAs be used in patients with carcinoid heart disease? If so, for which patients and what are the appropriate dosing regimens?
5. Are SSAs effective for the management of symptoms secondary to elevated calcitonin in medullary thyroid carcinoma? If so, for which patients and what is the appropriate dosing regimen?
6. Are SSAs effective in delaying tumour progression among patients with NETs? If so, for which patients and what are the appropriate dosing regimens?

Search Strategy

For the 2024 guideline update, the PubMed database was searched for relevant studies, guidelines and consensus documents published between 2014-2022. The specific search strategy, search terms, and search results, are presented in Appendix C. Online resources from oncology-based health organizations and guideline developers were also systematically searched, and relevant guidelines from the following organizations were considered in the development of our recommendations: the BC Cancer Agency (BCCA)[5], the National Comprehensive Cancer Network (NCCN)[2] and the North American Neuroendocrine Tumor Society (NANETS)[4].

Target Population

The recommendations in this guideline apply to patients diagnosed with NETs of the gastrointestinal tract, pancreas, lungs, thyroid, parathyroid, adrenal glands, and pituitary gland, and NETs of unknown origin.

Recommendations

Management of Functional Secretory Syndromes

1. SSAs are recommended for symptom control in patients with secretory syndromes, including but not limited to syndromes resulting from carcinoid syndrome, gastrinomas, insulinomas, somatostatinomas, glucagonomas, and VIPomas with locoregional and metastatic disease.
   a. Subcutaneous (SQ) fast acting octreotide dosing for symptom control *(Level of Evidence: I, Strength of Recommendation: A)*:
      - Optional: A trial of octreotide 100-250 µg SQ 2-3 times daily for 1-2 weeks to test for tolerability (case based) followed by introduction of long acting SSA every 4 weeks.
        - For insulinomas, the first dose of fast acting SQ octreotide should be given in a monitored setting in the case of paradoxical hypoglycemia.
      - Dose and frequency may be increased for symptom control, as needed.
      - Short-acting octreotide can be added to long acting SSA for rapid relief of symptoms or for breakthrough symptoms.
   b. Long-acting octreotide dosing for symptom control *(Level of Evidence: I, Strength of Recommendation: A)*:

- Long-acting octreotide (Sandostatin LAR or Teva-octreotide) 10-30 mg intramuscular (IM) every 4 weeks.
- Lanreotide dosing for symptom control (Somatuline Autogel) 60-120 mg SQ every 14-28 days[16-19].

c. Varying doses and intervals (i.e. increasing dose of shortening dosage interval) can improve symptomatic and biochemical control. Expert opinion from the neuroendocrine team can be requested if symptoms are not well managed.
d. Short acting octreotide is used to treat carcinoid crisis. Dosing for carcinoid crisis is a bolus of 100-500 µg IV or by infusion; urgent situations may require high doses and up to 54,000 µg has been reported *(Level of Evidence: IV, Strength of Recommendation: B)*.
    - Interoperative prevention of carcinoid crisis would be important to consider in functioning small bowel NETs with intravenous (IV) octreotide being the mainstay of management. There is debate regarding the importance of prophylactic SSA intraoperatively, but discussion amongst anesthetic and surgical teams should be encouraged[20].

Octreotide LAR and lanreotide have been shown to improve symptoms associated with hypersecretory syndromes in patients with NETs. The ELECT study demonstrated that patients with NETs and carcinoid syndrome treated with lanreotide depot 120 mg every 4 weeks had improved diarrhea and flushing both during treatment and maintenance phase compared to patients in the placebo arm of study[17-19]. All patients had access to short-acting octreotide as a rescue medication. The lanreotide group has a significantly lower number of days using the rescue medication compared to the placebo group. The PROMID study showed that patients with well-differentiated metastatic midgut NETs treated with long-acting octreotide (30 mg every 28 days) reported better control of fatigue, pain, insomnia, and diarrhea compared to patients treated with placebo[21].

Based on the available data, octreotide is recommended for symptom control in patients with secretory syndromes, resulting from gastric NETs, carcinoid syndrome, and gastrinomas, insulinomas, somatostatinomas, glucagonomas, and VIPomas with locoregional disease or metastatic disease. The use of octreotide in this setting is supported elsewhere in Canada[5, 22] and in the United States[2]. There have been no head-to-head studies comparing the two commercially available formulations of long acting octreotide, As such, either formulation can be used first line for control of hormone hypersecretion. However, Lanreotide is administered deep SQ injection and can be given by patients/caregivers at home, whereas Sandostatin LAR or Teva-octreotide must be given by a trained nurse or other healthcare professional, so this may impact treatment choice[23, 24]. A trial of SQ octreotide at a dose of 100-250 µg three times per day for 1-2 weeks followed by octreotide LAR 20-30 mg IM every 4 weeks is recommended. Similar dosing has been recommended elsewhere for use in this setting[22]. Dose and frequency may be increased for symptom control, as needed. Short-acting octreotide can be added to either long acting SSA for rapid relief of symptoms or for breakthrough symptoms[2].

2. Telotristat is used exclusively for carcinoid syndrome symptom control.
   a. Telotristat (Xermelo) is indicated for use in combination with SSAs for symptom control *(Level of Evidence: II, Strength of Recommendation: A)*:
      - Dose and Frequency: 250-500mg three times daily[12, 14, 25-31].
   b. Telotristat can be considered for primary symptom management of carcinoid syndrome if SSAs are contraindicated or not tolerated *(Level of Evidence: IV, Strength of Recommendation: C)*.

Telotristat has been demonstrated to help improve symptoms when administered in combination with SSAs in patients whose symptoms are not controlled by SSAs alone. The TELEPRO study showed that patients with carcinoid syndrome on SSA therapy had a high burden of disease before initiating telotristat. Telotristat improved bowel movement frequency, urgency, flushing and abdominal pain[13]. In the TELESTAR study, patients with metastatic NETs and uncontrolled carcinoid syndrome, treated with both 250mg and 500mg telotristat three times daily had a decrease in bowel movements per day, flushing episodes, abdominal pain and weight loss compared to placebo[14, 25, 27, 29, 32].The TELECAST and TELEPATH studies confirmed long term safety of telotristat[12, 28].

Prophylactic Action for Carcinoid Heart Disease

3. There is a lack of data on the use of octreotide for the prevention of carcinoid heart disease (CHD) in patients with carcinoid tumours. However, given the life-threatening nature of CHD and the relative safety of octreotide, use of octreotide should be considered in this setting *(Level of Evidence: III, Strength of Recommendation: C)*.
   - Patients with 5-HIAA levels greater than 50 mg/24 hours should be considered for long-acting SSA therapy, with the goal of normalizing 5-HIAA 24-hour.
   - Patients that may not tolerate the SSAs well or have risk factors for serious side effects such as cholelithiasis, uncontrolled diabetes or exocrine pancreatic insufficiency, the prophylactic use of SSAs may be started at 5-HIAA levels greater than 300 mg/24 hours.
   - A dose of octreotide 20-30 mg IM every 4 weeks or lanreotide 120mg SQ every 4 weeks is recommended for the prevention of CHD[2].

CHD results from exposure of the heart to high levels of tumour-derived vasoactive substances, such as serotonin, resulting in endocardial damage and possible ventricular failure[33]. Most patients with elevated 5-HIAA receive SSAs for functional symptom control at any level of 5-HIAA elevation. However, for asymptomatic patients that have stable disease, SSAs may be considered for CHD prophylaxis when the 5-HIAA level is greater than 50mg/24 hours. There is a subgroup of patients that may not tolerate the SSAs well or have risk factors for serious side effects such as cholelithiasis, uncontrolled diabetes or exocrine pancreatic insufficiency. For these patients the prophylactic use of SSAs may be started at a higher level. Based on data from Bhattacharyya *et al.*[34], it appears that the risk to develop CHD increases significantly at a 5-HIAA level of 300mg/24 hours.

Management of Symptoms Secondary to Elevated Calcitonin in Medullary Thyroid Carcinoma

4. SSAs have been shown to relieve symptoms associated with elevated calcitonin levels in patients with medullary thyroid carcinoma. Therefore, SSAs are recommended to manage symptoms (i.e., diarrhea) in patients with elevated calcitonin levels in medullary thyroid carcinoma. Dosing for symptoms associated with metastatic medullary thyroid cancer is octreotide 100-250 µg SQ twice daily for 1-2 weeks with subsequent introduction of long acting SSA dose and duration determined by symptom control. SSA can be given long-term without significant adverse effects *(Level of Evidence: III, Strength of Recommendation: B)*.

There have been many advances in medullary thyroid cancer management in the last 20 years, not including refractory cases or progressive disease that still require symptom management. A prospective study of 22 patients with persistent or relapsed metastatic medullary thyroid carcinoma evaluated the long-term use of SSAs; following surgery, patients had an elevated serum calcitonin level (252-69482 pg/ml). Daily octreotide (0.4-1.0 mg SQ) or monthly octreotide LAR (20-30 mg IM for 3-21 months) was given, along with systemic chemotherapy with or without external radiotherapy. Pre-existing diarrhea was improved in 8 patients (36.4% partial response) and remained stable in 10 patients. Calcitonin concentrations decreased more than 25% in 18% of patients (4 of 22)[35]. Another SSA, slow release lanreotide, was shown to improve symptoms in seven patients with advanced and symptomatic medullary thyroid carcinoma. The number and intensity of bowel movements and flushing episodes decreased in nearly all patients (7 of 8) and plasma calcitonin levels decreased significantly in nearly all patients (6 of 7); the magnitude of decrease was 50% or more in half of these patients[36]. Similar results have been reported elsewhere[37].

Antiproliferative Effect in Functioning and Nonfunctioning Tumours

5. SSAs can be used in functioning and nonfunctioning GEP NETs for their antiproliferative effect at time of progression.
    a. Octreotide LAR should be considered for its anti tumour effect in patients with locoregional unresectable or metastatic well-differentiated (low grade) mid-gut NETs whose disease is progressing regardless of functional status of the tumour[38, 39] *(Level of Evidence: I, Strength of Recommendation: A).*
        - Octreotide LAR dosing for tumour control is 30 mg IM every 4 weeks[39]. Note: therapeutic levels of octreotide would not be expected to be reached for 10-14 days after LAR injection.
    b. Lanreotide prolongs progression free survival in patients with advanced well to moderately differentiated, nonfunctioning somatostatin receptor positive enteropancreatic NETs. Lanreotide dosing for tumour control is 120 mg SQ injection every 28 days[9, 10] (KI67 up to 10) *(Level of Evidence: I, Strength of Recommendation: A)*.
    c. At progression, high dose SSAs can be used: octreotide 60mg every 4 weeks, lanreotide 120 every 2 weeks[9] *(Level of Evidence: II, Strength of Recommendation: B)*.

SSAs have been shown to slow tumour progression, as compared to placebo, in patients with locoregional unresectable or metastatic well-differentiated (low grade) NETs. The PROMID trial, comparing octreotide LAR (30 mg IM monthly) with placebo in patients with well-differentiated grade 1 NETs of the midgut. The trial demonstrated both a greater rate of stable disease at 6 months and longer progression-free survival in the octreotide-treated group, as compared to placebo[8, 38]. The RADIANT-2 study showed similar results[39]. More recently, the CLARINET trail investigated lanreotide in a randomized controlled trial of well to moderately differentiated enteropancreatic NETs (grade 1 or 2, Ki 67 <10%)[7, 10]. Lanreotide was shown to significantly prolong progression-free survival compared to placebo. Neither SSA has been compared to placebo in the phase III setting in patients with poorly differentiated mid-gut NETs or other NETs (i.e., non-mid-gut primaries) with locoregional unresectable disease or distant metastases.

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Appendix A: 5-HIAA Urine Specimen Collection Diet

Alberta Precision Laboratories
Physiologic changes in 5-HIAA excretion may be expected following ingestion of foods rich in serotonin, certain medications, as well as caffeine or other stimulants. Interpret results in the context of dietary intake or pharmacologic status.

Refer to the 24 Hour Urine Laboratory Patient Collection Instructions for instructions on collecting the specimen.

Consumption of the following foods should be avoided up to 4 days prior to testing:

- Avocado
- Banana
- Black Olives
- Broccoli
- Cantaloupe
- Cauliflower
- Chocolate
- Dates
- Eggplant
- Figs
- Grapefruit
- Honeydew
- Kiwi
- Pecan
- Pineapple
- Plantain
- Plums
- Spinach
- Tomato
- Turkey
- Walnut

DO NOT drink any fruit juices and anything containing caffeine (including coffee, tea, soft drinks containing caffeine, and energy drinks)

Appendix B: Adverse Events

Table 1: Lanreotide Adverse Events from the CLARINET trial[7]

Event*	Lanreotide	Placebo
Any adverse events	88%	90%
Any adverse event related to study treatment	50%	28%
Any adverse event according to intensity†		
Severe	26%	31%
Moderate	44%	43%
Mild	17%	17%
Any serious adverse event	25%	31%
Serious adverse event related to study treatment	3%	1%
Withdrawal from study because of any adverse events	3%	3%
Withdrawal because of adverse event related to study treatment	1%	0%
Study treatment-related adverse events in ≥5% of patients		
Diarrhea	26%	9%
Abdominal pain	14%	2%
Cholelithiasis	10%	3%
Flatulence	8%	5%
Injection-site pain	7%	3%
Nausea	7%	2%
Vomiting	7%	0%
Headache	5%	2%
Lethargy	5%	1%
Hyperglycemia	5%	0%
Decreased level of pancreatic enzymes	5%	0%

Table 2: Octreotide Adverse Events from the PROMID trial[8]

Event	Octreotide LAR	Placebo
GI Tract	14.3%	18.6%
Hematopoietic system	11.9%	2.3%
Fatigue and Fever	19.0%	4.6%
Treatment Discontinuation	12.0%%	0%
Bile stones	11.90%	2.3%

Appendix C: Search Strategy Table

Database	Date	Search Strategy	Limits	Results
PubMed	Jan. 11 2022	("lanreotid"[All Fields] OR "lanreotide"[MeSH Terms] OR "lanreotide"[All Fields] OR "lanreotides"[All Fields]) AND ("neuroendocrine tumours"[All Fields] OR "neuroendocrine tumors"[MeSH Terms] OR ("neuroendocrine"[All Fields] AND "tumors"[All Fields]) OR "neuroendocrine tumors"[All Fields])	English language, full text, humans, 2014-current, RCT, clinical trial phase II and III	29
PubMed	Jan. 13 2022	("octreotid"[All Fields] OR "octreotide"[MeSH Terms] OR "octreotide"[All Fields] OR "octreotides"[All Fields]) AND ("neuroendocrine tumours"[All Fields] OR "neuroendocrine tumors"[MeSH Terms] OR ("neuroendocrine"[All Fields] AND "tumors"[All Fields]) OR "neuroendocrine tumors"[All Fields])	English language, full text, humans, 2014-current, RCT, clinical trial phase II and III	56
PubMed	March 16, 2022	("octreotid"[All Fields] OR "octreotide"[MeSH Terms] OR "octreotide"[All Fields] OR "octreotides"[All Fields]) AND ("neuroendocrine tumours"[All Fields] OR "neuroendocrine tumors"[MeSH Terms] OR ("neuroendocrine"[All Fields] AND "tumors"[All Fields]) OR "neuroendocrine tumors"[All Fields]) AND “short acting”	English language, full text, humans, 2014-current, RCT, clinical trial phase II and III	6
PubMed	March 20, 2022	(("subcutaneous"[All Fields] OR "subcutaneously"[All Fields] OR "subcutanous"[All Fields]) AND ("octreotid"[All Fields] OR "octreotide"[MeSH Terms] OR "octreotide"[All Fields] OR "octreotides"[All Fields]) AND ("neuroendocrine tumours"[All Fields] OR "neuroendocrine tumors"[MeSH Terms] OR ("neuroendocrine"[All Fields] AND "tumors"[All Fields]) OR "neuroendocrine tumors"[All Fields]))	English language, full text, humans, 2014-current, RCT, clinical trial phase II and III	10
PubMed	March 24, 2022	(("somatostatin"[MeSH Terms] OR "somatostatin"[All Fields] OR "somatostatine"[All Fields] OR "somatostatins"[All Fields] OR "somatostatin s"[All Fields]) AND ("analog"[All Fields] OR "analoge"[All Fields] OR "analoges"[All Fields] OR "analogic"[All Fields] OR "analogical"[All Fields] OR "analogizing"[All Fields] OR "analogous"[All Fields] OR "analogously"[All Fields] OR "analogs"[All Fields] OR "analogue"[All Fields] OR "analogues"[All Fields]) AND ("condoms"[MeSH Terms] OR "condoms"[All Fields] OR "prophylactic"[All Fields] OR "prophylactically"[All Fields] OR "prophylactics"[All Fields]))	English language, full text, humans, 2014-current, RCT, clinical trial phase II and III	25
PubMed	July 15, 2022	(("telotristat"[Supplementary Concept] OR "telotristat"[All Fields]) AND ("neuroendocrine tumours"[All Fields] OR "neuroendocrine tumors"[MeSH Terms] OR ("neuroendocrine"[All Fields] AND "tumors"[All Fields]) OR "neuroendocrine tumors"[All Fields]))	English language, full text, humans, 2014-current, RCT, clinical trial phase II and III	50

Development and Revision History

This guideline was reviewed and endorsed by the Alberta Provincial Endocrine Tumour Team. Members include endocrinologists, surgical oncologists, radiation oncologists, medical oncologists, nurses, pathologists, and pharmacists. Evidence was selected and reviewed by a working group comprised of members from the Alberta Provincial Endocrine Tumour Team, and a methodologist from the Guideline Resource Unit. A detailed description of the methodology followed during the guideline development process can be found in the Guideline Resource Unit Handbook.

This guideline was originally developed in 2013 as ENDO-003 and updated in 2015 and 2024. In 2026 it was renamed NET-002 and the 5-HIAA Urine Specimen Collection Diet was updated.

Levels of Evidence

I	Evidence from at least one large randomized, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomized trials without heterogeneity
II	Small randomized trials or large randomized trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity
III	Prospective cohort studies
IV	Retrospective cohort studies or case-control studies
V	Studies without control group, case reports, expert opinion

Strength of Recommendations

A	Strong evidence for efficacy with a substantial clinical benefit; strongly recommended
B	Strong or moderate evidence for efficacy but with a limited clinical benefit; generally recommended
C	Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs, etc.); optional
D	Moderate evidence against efficacy or for adverse outcome; generally not recommended
E	Strong evidence against efficacy or for adverse outcome; never recommended

Maintenance

A formal review of the guideline will be conducted in 2025. If critical new evidence is brought forward before that time, however, the guideline working group members will revise and update the document accordingly.

Abbreviations

5-HIAA, 5- hydroxyindoleacetic acid; AJCC, American Joint Committee on Cancer; BCCA, BC Cancer Agency; GH, growth hormone; GI, gastrointestinal; IGF-1, insulin-like growth factor 1; IM, intramuscular; IV, intravenous; LAR, long acting repeatable; NCCN, National Comprehensive Cancer Network; NANETS, North American Neuroendocrine Tumor Society; NETs, neuroendocrine tumours; SSAs, Somatostatin analogues.

Disclaimer

The recommendations contained in this guideline are a consensus of the Alberta Provincial Endocrine Tumour Team and are a synthesis of currently accepted approaches to management, derived from a review of relevant scientific literature. Clinicians applying these guidelines should, in consultation with the patient, use independent medical judgment in the context of individual clinical circumstances to direct care.

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Conflict of Interest Statements

Dr. Stella Koumna reports honorarium from advisory board participation outside the submitted work.

Dr. Vicky Parkins has nothing to disclose.

Rachel Vanderploeg has nothing to disclose

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