# Evaluation of the Impact of the Burden of Carcinoid Syndrome Symptoms on Quality of Life among Treated Patients with Carcinoid Syndrome in the US Based on the PROMIS-29 Instrument

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## Background and Objectives

- Carcinoid syndrome (CS) results from the secretion of bioactive amines, peptides, and polypeptides by functional neuroendocrine tumors (NETs)[1]
  - Symptoms may include diarrhea, flushing, wheezing, and less frequently carcinoid heart disease, characterized by cyanosis and/or peripheral edema[1]
- Recent SEER data shows that among US patients with NET identified between 2000 and 2011, 19% were found to have CS at diagnosis, and over 50% of cases had CS manifesting from metastatic, well-differentiated small bowel NET[2]
- Patients with NET and CS often report reduced quality of life (QoL), particularly in areas of fatigue, general health, and physical role limitations; CS symptoms such as frequent bowel movements and flushing episodes have been shown to be significantly associated with decreased health-related QoL[3]
- The first-line systemic therapy for metastatic NET frequently includes somatostatin analogs (SSAs) such as octreotide or lanreotide[4]
  - Octreotide, approved in 1988, is indicated for the symptomatic treatment of metastatic carcinoid tumors, targeting severe diarrhea and flushing[5]; lanreotide was approved in 2014 for the treatment of patients with unresectable, well- or moderately-differentiated, locally advanced or metastatic gastroenteropancreatic NET to improve progression-free survival[6]
  - SSAs inhibit the secretion of gastrointestinal hormones and alleviate symptoms of CS associated with advanced NETs, such as diarrhea and flushing, and hormonal syndrome[4]
- The objective of this study was to assess the association between the burden of CS symptoms and QoL among patients with CS using the validated Patient-Reported Outcomes Measurement Information System (PROMIS)-29 instrument

## Methods

### Data Source

- Patients with CS symptoms in the US were recruited via Neuroendocrine Cancer Awareness Network (NCAN), a patient advocacy group, for an online, anonymous survey between July 21 and October 31, 2016
  - Eligible patients were at least 18 years old, diagnosed with NET and CS by a physician, and received either SSA or non-SSA treatment for CS symptom control
  - Examples of SSAs included lanreotide, octreotide, and pasireotide. Examples of non-SSAs included cyproheptadine, diphenoxylate-atropine, diphenhydramine, loperamide, ranitidine, and telotristat etiprate
- The survey consisted of demographic characteristics (e.g., gender, age, race), clinical characteristics (e.g., site of NET, time since NET and CS diagnoses, treatments received, CS symptoms such as flushing episodes, bowel movements, and activity levels), and QoL questions from the PROMIS-29 questionnaire
- Data were de-identified and complied with the patient confidentiality requirements of the Health Insurance Portability and Accountability Act
  - All study materials were approved by the New England Independent Review Board
  - Patients provided their informed consent prior to responding to the survey questions

### Statistical Analyses

- PROMIS-29 domain (Physical Function, Ability to Participate in Social Roles and Activities, Anxiety, Depression, Fatigue, Sleep Disturbance, and Pain Interference) T-scores were calculated according to the PROMIS profile scoring manual[7]
  - The T-score rescales the raw score into a standardized score with a mean of 50 and a standard deviation (SD) of 10, where a score of 50 is the average for the US general population
  - A higher T-score represents more of the concept being measured, i.e., better QoL for positively worded domains and worse QoL for negatively worded domains
- Descriptive analyses assessing patient demographic and clinical characteristics were conducted using means and SDs for continuous variables and frequencies and proportions for categorical variables
- Multivariable linear regression analyses, adjusting for demographic (gender, age, and race) and clinical characteristics (carcinoid/NET type, frequency or number of symptoms, and current activity level), were performed to assess the association between CS symptoms and PROMIS-29 domain T-scores
  - To illustrate the association between CS burden and QoL and to avoid multicollinearity due to the correlation between the CS burden questions, two multivariable models were assessed:
    - Model 1 examined CS symptoms through average number of bowel movements and flushing episodes per day
    - Model 2 examined CS symptoms as defined by the total number of symptoms experienced
  - Statistically significant associations were noted for *P*-values < 0.05

## Results

### Demographic and Clinical Characteristics

- Of the 117 patients who completed the online survey, the majority were female (77%) and Caucasian (91%), with a mean age of 58.0 years (**Table 1**)

**Table 1. Demographic Characteristics**

| | All Patients (N=117) | |
|---|---|---|
| Age (years), mean (SD) | 58.0 | (9.8) |
| Female, N (%) | 90 | (77%) |
| Race, N (%)[1] | | |
| Caucasian | 106 | (91%) |
| Black or African American | 6 | (5%) |
| Hispanic or Latino | 5 | (4%) |
| Asian/Pacific Islander | 0 | (0%) |
| Native American/American Indian | 1 | (1%) |
| Other | 3 | (3%) |

Abbreviations: SD, Standard Deviation.
Notes: [1]Patients were allowed to select multiple responses.

- The most common primary site of NET was ileum (47%), and the mean (SD) time from NET diagnosis to date of survey completion was 8.3 (6.0) years (**Table 2**)
- The mean time from NET diagnosis to diagnosis of CS was 1.2 years

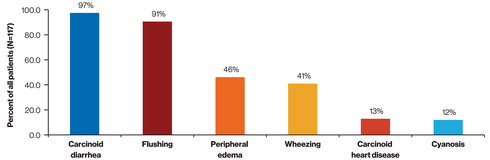
**Table 2. Clinical Characteristics**

| | All Patients (N=117) | |
|---|---|---|
| Primary site of NET, N (%)[1] | | |
| Ileum | 55 | (47%) |
| Appendix | 12 | (10%) |
| Lung | 11 | (9%) |
| Stomach | 11 | (9%) |
| Duodenum | 10 | (9%) |
| Colon | 10 | (9%) |
| Jejunum | 6 | (5%) |
| Rectum | 0 | (0%) |
| Other primary site[2] | 30 | (26%) |
| Time from NET diagnosis to survey completion date (years), mean (SD) | 8.3 | (6.0) |
| Time from CS diagnosis to survey completion date (years), mean (SD) | 7.1 | (5.5) |
| Number of CS symptoms experienced, mean (SD) | 3.0 | (1.1) |

Abbreviations: CS, Carcinoid Syndrome; NET, Neuroendocrine Tumor; SD, Standard Deviation.
Notes: [1]Patients were allowed to select multiple responses. [2]Other primary NET sites include patient-submitted mentions of: breast, cecum, intestines, liver, mesentery, pancreas, small intestine, ureter, and unknown.

- The most frequently reported CS symptoms among the six different symptoms queried in the survey included carcinoid diarrhea (97%), flushing (91%), peripheral edema (46%), and wheezing (41%) (**Figure 1**)
  - 45% of the patients reported experiencing ≥4 bowel movements and 12% experienced ≥4 flushing episodes per day in the past 2 weeks (**Figure 2**)
- At the time of the survey, 86% had CS symptoms without required bed rest or required bed rest during <50% of the waking day (**Figure 3**)

**Figure 1. CS Symptoms Experienced after NET Diagnosis**




Abbreviations: CS, Carcinoid Syndrome; NET, Neuroendocrine Tumor.

**Figure 2. Average Number of Bowel Movements and Flushing Episodes per Day in the Past 2 Weeks**

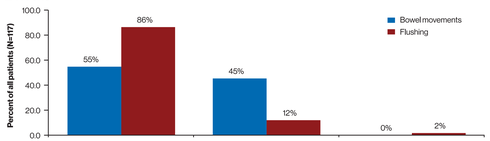
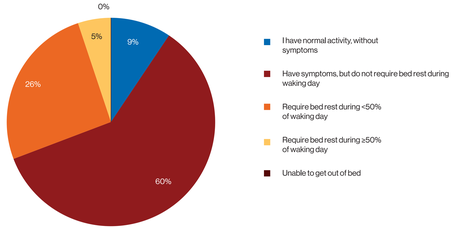



**Figure 3. Current Activity Level**




### Treatment Characteristics

- Common NET treatments that were ever received included SSAs (94%), surgical procedures (72%), and liver-directed therapy (35%) (**Table 3**)
- For CS symptom treatment, the large majority of patients reported receiving SSAs in the past month (98%)
  - A possible explanation as to why a greater percentage of patients reported SSA use for treatment of CS vs treatment of NET (98% vs 94%, respectively) may be that patients understood SSA to be prescribed for CS symptom control only
- The mean duration of CS symptom treatment with SSAs was 6.1 (SD: 4.7, range: 0.3-21.3) years, and most patients were still receiving treatment (96%) at the time of the survey
  - 43% of patients treated with SSA reported receiving SSA treatment for >5 years

**Table 3. NET and CS Treatment Characteristics**

| | All Patients (N=117) | |
|---|---|---|
| NET treatments ever received, N (%)[1] | | |
| SSAs | 110 | (94%) |
| Surgical procedures | 84 | (72%) |
| Liver-directed therapy | 41 | (35%) |
| Chemotherapy | 24 | (21%) |
| Targeted therapy | 12 | (10%) |
| Interferon | 4 | (3%) |
| Other[2] | 11 | (9%) |
| No treatment | 0 | (0%) |
| CS symptom treatments received in the past month, N (%)[1] | | |
| SSAs | 115 | (98%) |
| Non-SSAs | 12 | (10%) |
| Other treatment[3] | 15 | (13%) |
| No treatment | 0 | (0%) |
| Duration of CS symptom treatment with SSA (years)[4] | | |
| Mean (SD) | 6.1 | (4.7) |
| Still on treatment, N (%) | 111 | (96%) |
| Discontinued, N (%) | 4 | (3%) |

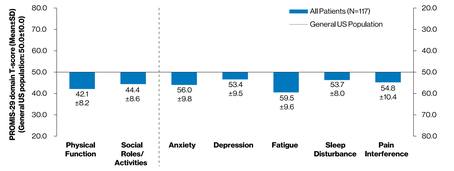
Abbreviations: CS, Carcinoid Syndrome; NET, Neuroendocrine Tumor; SD, Standard Deviation; SSA, Somatostatin Analog.
Notes: [1]Patients were allowed to select multiple responses. [2]Other NET treatments include: peptide-receptor radionuclide therapy and external beam radiation (outside of liver). [3]Other CS symptom treatments include patient-submitted mentions of: anti-nausea medication, Cap/Tem chemotherapy, chemo embolization, Creon, Fentora for pain, Lyrica diabetic neuropathy, MBG, narcotic analgesics, somatuline, surgery, Telestar, tincture of opium, and TSCE. [4]Based on patients treated with SSA (N=115).

### PROMIS-29 Quality of Life Scores

#### Descriptive Analysis

- The mean (SD) T-score for physical function and fatigue were 42.1 (8.2) and 59.5 (9.6), respectively, which were both about one SD worse than the general US population score of 50.0 (10.0)[7] (**Figure 4**)

**Figure 4. PROMIS-29 Scores, Mean ± SD[1-3]**




Abbreviations: PROMIS, Patient-Reported Outcomes Measurement Information System; SD, Standard Deviation; US, United States.
[1]T-scores reported standardized, where a score of 50 is the average for the US general population[7]. [2]Higher score in physical function and social roles/activities indicates better quality of life. [3]Higher score for anxiety, depression, fatigue, sleep disturbance, and pain interference indicates worse quality of life.

#### Multivariable Regression Analysis

- Multivariable regression analysis showed that the severity of CS symptoms experienced resulted in reduced QoL scores (**Table 4**)
  - ≥4 bowel movements/day was associated with a 3.0 point decrease in the score for Ability to Participate in Social Roles and Activities as compared with having <4 bowel movements/day (*P*=0.043)
- Similarly, the multivariable model with number of CS symptoms showed that each additional CS symptom experienced significantly worsened Physical Function, Ability to Participate in Social Roles and Activities, Fatigue, and Pain Interference (by magnitudes of 1.6 to 1.9 points in PROMIS-29 T-scores)
- Requiring any amount of bed rest during the day (compared to normal activity without CS symptoms) was also associated with decreases in the PROMIS-29 domain scores, depending on activity level

**Table 4. Multivariable Predictors of PROMIS-29 Scores**

| Total patients (N=117) | Physical Function[1] | | Social Roles/ Activities[1] | | Anxiety[2] | | Depression[2] | | Fatigue[2] | | Sleep Disturbance[1] | | Pain Interference[2] | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Patient characteristics** | **Est.** | **P-value** | **Est.** | **P-value** | **Est.** | **P-value** | **Est.** | **P-value** | **Est.** | **P-value** | **Est.** | **P-value** | **Est.** | **P-value** |
| Male | 1.4 | 0.419 | 2.5 | 0.158 | -3.4 | 0.162 | -4.2 | 0.070 | -2.3 | 0.261 | -5.9 | 0.002 * | -0.5 | 0.842 |
| Age (years) | -0.1 | 0.063 | -0.2 | 0.002 * | 0.0 | 0.927 | 0.0 | 0.928 | 0.0 | 0.978 | -0.1 | 0.491 | 0.0 | 0.949 |
| Race (ref: Caucasian) | | | | | | | | | | | | | | |
| Black or African American | 3.4 | 0.269 | 2.2 | 0.484 | -4.6 | 0.299 | -6.8 | 0.101 | 0.3 | 0.939 | -1.9 | 0.565 | -0.7 | 0.865 |
| Hispanic or Latino | 4.4 | 0.222 | 6.6 | 0.074 | -0.7 | 0.895 | 1.6 | 0.741 | -6.3 | 0.141 | -8.5 | 0.032 * | 1.9 | 0.701 |
| Other | -6.2 | 0.059 | -5.9 | 0.080 | -2.8 | 0.546 | -4.6 | 0.291 | -0.1 | 0.984 | 3.0 | 0.407 | 0.5 | 0.913 |
| **Clinical/symptom characteristics** | | | | | | | | | | | | | | |
| Carcinoid/NET type | | | | | | | | | | | | | | |
| Lung | 3.1 | 0.064 | 2.6 | 0.137 | -2.5 | 0.287 | -0.6 | 0.785 | -1.4 | 0.473 | -1.2 | 0.529 | -3.6 | 0.120 |
| Stomach | 3.9 | 0.085 | 3.6 | 0.126 | -0.7 | 0.818 | -0.3 | 0.914 | -2.7 | 0.319 | -0.1 | 0.983 | 2.9 | 0.344 |
| Duodenum | -1.2 | 0.605 | 0.4 | 0.880 | 0.6 | 0.851 | -3.5 | 0.276 | -0.2 | 0.931 | 1.5 | 0.558 | 1.1 | 0.727 |
| Jejunum | -3.6 | 0.138 | -1.2 | 0.631 | 1.1 | 0.751 | 4.0 | 0.218 | 4.1 | 0.164 | 0.9 | 0.722 | 3.0 | 0.362 |
| Ileum | 0.9 | 0.750 | 2.3 | 0.429 | -1.9 | 0.641 | -4.3 | 0.256 | -0.5 | 0.873 | -0.2 | 0.944 | 3.8 | 0.320 |
| Appendix | -7.6 | 0.005 * | -6.8 | 0.013 * | 8.6 | 0.023 * | 6.2 | 0.083 | 9.2 | 0.004 * | 2.9 | 0.320 | 6.0 | 0.095 |
| Colon | 4.6 | 0.153 | 1.4 | 0.669 | -5.3 | 0.243 | 0.0 | 0.994 | -5.4 | 0.160 | 2.8 | 0.415 | -0.4 | 0.929 |
| Other primary site[3] | 2.6 | 0.184 | 0.6 | 0.751 | -0.4 | 0.880 | 2.3 | 0.366 | -0.6 | 0.800 | -0.5 | 0.817 | -0.3 | 0.909 |
| Bowel movements per day in the past 2 weeks (ref: 0-3) | | | | | | | | | | | | | | |
| ≥4 | -1.9 | 0.194 | -3.0 | 0.043 * | 3.6 | 0.073 | 1.9 | 0.316 | 1.4 | 0.424 | 1.4 | 0.377 | 1.3 | 0.497 |
| Flushing episodes per day in the past 2 weeks (ref: 0-3) | | | | | | | | | | | | | | |
| ≥4 | -1.5 | 0.467 | -2.8 | 0.195 | 3.0 | 0.316 | 1.9 | 0.501 | 4.6 | 0.065 | 5.6 | 0.015 * | 2.7 | 0.348 |
| Not sure | -6.3 | 0.228 | -6.9 | 0.200 | 3.6 | 0.623 | 6.5 | 0.350 | 9.4 | 0.132 | 4.2 | 0.455 | -4.1 | 0.562 |
| Current activity level (ref: Normal activity without symptoms) | | | | | | | | | | | | | | |
| Have some symptoms, but do not require bed rest during the waking day | -6.1 | 0.017 * | -2.7 | 0.302 | -0.1 | 0.979 | 3.0 | 0.373 | 4.1 | 0.180 | 1.0 | 0.705 | -1.3 | 0.708 |
| Require bed rest during <50% of waking day | -10.6 | <0.001 * | -9.8 | <0.001 * | 4.5 | 0.247 | 7.4 | 0.044 * | 11.6 | <0.001 * | 3.9 | 0.194 | 9.8 | 0.009 * |
| Require bed rest during ≥50% of waking day | -16.2 | <0.001 * | -16.0 | <0.001 * | 6.0 | 0.299 | 13.9 | 0.012 * | 18.2 | <0.001 * | 5.5 | 0.218 | 5.0 | 0.361 |

Abbreviations: CS, Carcinoid Syndrome; Est, (Parameter) Estimate; NET, Neuroendocrine Tumor; PROMIS, Patient-Reported Outcomes Measurement Information System; Ref, Reference (Group).
* P<0.05.
[1]Higher score indicates better quality of life. [2]Higher score indicates worse quality of life. [3]Other primary NET sites included patient-submitted responses of: breast, cecum, intestines, liver, mesentery, pancreas, small intestine, ureter, and unknown.

## Limitations

- Recruitment was conducted primarily through NCAN, which may have resulted in a potentially biased sample not fully representative of the heterogeneous NET patient population.
- All data were self-reported and could have been subject to recall bias
- Results are based on QoL assessment at a single time point
- This study did not attempt to assess the QoL associated with any type of treatment. This would require controlling on treatment type and duration of each treatment received, which was not performed in the present analysis, but is considered in another analysis

## Conclusions

- Almost all patients (98%) who participated in this survey study reported using SSAs for CS symptom control. The mean duration of SSA use was 6.1 years. The most commonly reported CS symptoms were carcinoid diarrhea (97%) and flushing (91%)
- This study suggests that CS symptom burden as captured by more frequent flushing and bowel movements as well as a greater number of symptoms experienced and impaired activity levels are associated with lower QoL, as demonstrated by PROMIS-29. Additionally, this research indicates that benefits gained by controlling CS symptoms may lead to improvements in QoL. Future studies are needed to assess the possible impact of optimal management of CS symptoms on QoL

## References

1. Creutzfeldt W. *World J Surg* 1996;20(2):126-131.
2. Halperin D et al. *Lancet Oncol* 2017 Apr;18(4):525-534.7.
3. Beaumont J et al. *Pancreas* 2012 Apr;41(3):461-466.
4. Kulke MH. *Journal of the National Comprehensive Cancer Network* 2016 Mar;14(3):241-2.
5. Sandostatin LAR Prescribing Information. Available at https://www.pharma.us.novartis.com/sites/www.pharma.us.novartis.com/files/sandostatin_lar.pdf.
6. SOMATULINE DEPOT Prescribing Information. Available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/022074s011lbl.pdf.
7. PROMIS Profile Scoring Manual. Available at https://www.assessmentcenter.net/documents/PROMIS%20Profile%20Scoring%20Manual.pdf.

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