User Manuel for the ANMS GCSI-DD

The American Neurogastroenterology and Motility Society Gastroparesis Cardinal Symptom Index Daily Diary

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User manual developed by Henry Parkman, Michael Camilleri, Dennis Revicki for the American Neurogastroenterology and Motility Society (ANMS)

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1.0 Introduction

Gastroparesis is a symptomatic condition of delayed gastric emptying with no mechanical obstruction (Parkman 2004; Camilleri 2013). There are several etiologies of gastroparesis, including diabetic gastroparesis and postsurgical gastroparesis. In many patients, a cause cannot be found, and the condition is termed idiopathic gastroparesis. In some of these patients, a viral etiology may be suspected due to a sudden onset of symptoms associated with a viral-like prodrome.

A variety of symptoms are reported by patients with gastroparesis (Soykan 1998; Parkman 2011). These can include nausea, vomiting, early satiety, postprandial fullness, bloating, loss of appetite, abdominal distension, and abdominal pain. Patients may experience any combination of symptoms with varying degrees of severity (Parkman 2004). The symptoms are often chronic; however, patients may also have periodic exacerbations of their symptoms (Abell 2006). These symptoms reduce the patient's health-related quality of life. Many patients experience weight loss due to their symptoms.

The diagnosis of gastroparesis is made by demonstrating in a symptomatic patient delayed gastric emptying without evidence of obstruction (Parkman 2004; Camilleri 2013). Delayed gastric emptying is most commonly assessed using a validated measurement of gastric emptying. At present, the best validated, and approved method of measurement is scintigraphy of the solid phase of a meal (Camilleri 2013). Other ways to assess gastric emptying include wireless capsule motility and breath tests using stable C-13 isotopes. Absence of obstruction is most commonly determined by upper endoscopy; an alternative test is an upper gastrointestinal radiographic series, which can also assess the small intestine.

There is a need for new treatments for gastroparesis with favorable benefit risk profiles. Pharmacologic treatment of gastroparesis typically involves two classes of agents: prokinetics agents and antiemetic agents. Metoclopramide, a dopamine type 2 receptor antagonist has both prokinetics and antiemetic properties, and is the only drug currently approved by the FDA for gastroparesis, specifically for diabetic gastroparesis for up to 12 weeks of treatment.

Understanding the relevant symptoms of gastroparesis is important in treating patients with this disorder. In gastroparesis, the symptom experience and severity is obtained from the patient. Consequently, patient-reported symptom scales that capture overall gastroparesis severity are necessary for evaluating treatments for gastroparesis (FDA 2009). A well-defined patient reported outcome (PRO) instrument that measures clinically important signs and symptoms of gastroparesis would be a useful assessment tool for clinical trials to support labeling claims for treatment of gastroparesis. The ANMS GCSI-DD is a patient-reported outcome instrument that captures the daily relevant symptoms of gastroparesis.

2.0 Development of ANMS GCSI-DD

The Gastroparesis Cardinal Symptom Index (GCSI) was developed to assess the core symptoms of gastroparesis (Revicki 2003; Revicki 2004a) and represents a subset of the longer, 20-item, Patient Assessment of Upper Gastrointestinal Disorders Symptoms (PAGI-SYM) questionnaire, which was developed to assess symptoms of gastroparesis, functional dyspepsia and gastroesophageal reflux disease (Revicki 2004b; Rentz 2004).

The GCSI quantifies the severity of nine gastroparesis symptoms: nausea, retching, vomiting, stomach fullness, inability to finish a meal, excessive fullness, loss of appetite, bloating and abdominal distension (Revicki 2003; Revicki 2004a). The symptoms that comprise the GCSI

were elicited through focus groups and interviews with patients with diabetic and idiopathic gastroparesis with input from experts that care for gastroparesis patients as recommended by the FDA Guidance for PRO development (FDA 2009). In its original conception, the GCSI assessed the severity of symptoms over a prior two week period (Revicki 2003; Revicki 2004a; Revicki 2004b; Rentz 2004). A six-point Likert response scale, ranging from 0 (none) to 5 (very severe) was used to rate severity of each symptom. The nine symptom severity items may be used to calculate three symptom subscale scores: nausea/vomiting subscale (comprised of symptoms of nausea, retching, vomiting), fullness/early satiety subscale (comprised of symptoms of stomach fullness, inability to finish a meal, excessive fullness, loss of appetite), and a bloating subscale (comprised of symptoms of bloating and abdominal distension). A total GCSI composite score may also be calculated as the mean of the three subscale scores (Revicki 2003; Revicki 2004a).

The development of the ANMS GCSI-DD evolved based on several modifications to the original GCSI:

1. Symptom recall: The ANMS GCSI-DD symptom assessments are based on a 24-hour recall period. Daily symptom assessment minimizes recall bias related to the patient's symptom experience. Gastroparesis patients who participated in a GCSI cognitive debriefing study indicated that a daily symptom assessment is needed to capture fluctuations in their symptom experience (Revicki et al., 2009). As patient recall over two weeks may not be reliable, the GCSI-DD was developed to assess symptoms on a daily basis in patients with gastroparesis (Revicki 2009; Revicki 2012). The original GCSI-DD maintained the same items as the GCSI, with the only difference being the recall period.

2. Wording of symptoms: Several of the symptoms were reworded to enhance understandability. The modifications were undertaken based on feedback from the FDA and from patients with gastroparesis during cognitive debriefing interviews. This was relevant for the symptom of early satiety, postprandial fullness, bloating, and abdominal pain. The wording of early satiety was clarified to state "not able to finish a normal-sized meal (for a healthy person)". Post-prandial fullness was reworded as, "Feeling excessively full after meals", and bloating was clarified by adding the following statement: "Feeling like you need to loosen your clothes". The severity of these three symptoms is correlated to one another. Post-prandial fullness is being used instead of bloating as this symptom relates more closely with gastric emptying which is disordered in gastroparesis (Pathikonda 2012). Bloating is more often used to describe a symptom of irritable bowel syndrome which can coexist in some patients with gastroparesis (Longstreth 2006). For abdominal pain, upper abdominal pain is assessed, as this is the usual location of pain/discomfort that might occur in gastroparesis. Lower abdominal pain is more frequently seen in irritable bowel syndrome (Longstreth 2006). Upper abdominal pain was originally defined as above the naval, but recently changed to above the belly button for better patient understanding. The wording of these symptoms has been shown to be understandable to patients through cognitive debriefing (Revicki 2009; Parkman 2013; Study 1 Qualitative Report 2017).

3. Range of response options. The original response options for the GCSI/GCSI-DD (none, very mild, mild, moderate, severe, and very severe) represent the range of symptom severity seen in gastrointestinal disorders. This response scale has been used successfully in patients with gastroparesis and, based on a cognitive debriefing study and language translation related patient interviews, is well understood by patients with varying levels of education (Revicki 2004a). The recent cognitive debriefing study in

diabetic and idiopathic gastroparesis patients found that all the patients understood the response scale and could use this response scale in rating the severity of their symptoms (Revicki 2009). However, item response theory (IRT) analysis of the GCSI-DD items indicated that there were overlapping probability curves for the 'very mild' and 'mild' response categories (Revicki 2012b). In addition, very few respondents selected the very mild response. Therefore, the 'very mild' response option was removed. Subsequent IRT analyses demonstrated that the items with the revised response scale fit the graded response model and were well ordered (Revicki 2012b; Revicki 2013). Thus, 5 point likert scale is now used for the ANMS GCSI-DD with 0=none, 1=mild, 2=moderate, 3=severe, and 4=very severe.

4. Vomiting. The response scale for vomiting was changed from a severity response scale to a frequency response scale, as the severity response might not completely capture severity if more than one vomiting episodes occur (Parkman 2013). For vomiting, the number of vomiting episodes (throwing up with food or liquid coming out) is used, not the number of trips to the bathroom to throw up. This takes into account the fluid and electrolyte shifts that are related to the number of emesis episodes. Vomiting has also been suggested to be added to help capture worsening of symptoms of gastroparesis. Note that vomiting frequency and vomiting severity are well correlated (r=0.80) (Parkman 2013). In the scoring of vomiting episodes, the number of episodes of vomiting per day is used, with the episodes capped a 4, so that the scoring is similar to the symptom severity scores of the other items. Therefore, vomiting episodes are scored as 0=none; 1=one episode; 2=two episodes; 3= three episodes and 4= four or more episodes. Recent qualitative research confirmed that patients with gastroparesis understood the instructions for rating number vomiting episodes (Revicki 2009; Study 1 Qualitative Report 2017).

5. Conditions for use: The GCSI has been developed for use in both diabetic and idiopathic gastroparesis (Revicki 2003; Revicki 2004a). Studies have suggested that the type of symptoms diabetic and idiopathic gastroparesis are similar, although patients with idiopathic gastroparesis may have more severe abdominal pain, and diabetics may have more severe nausea and vomiting (Parkman 2011; Cherian 2012; Saraswathi 2013; Revicki 2013). Revicki (2013) completed a secondary analysis comparing psychometric characteristics of GCSI-DD core symptom scores in patients with idiopathic or diabetic gastroparesis. Completed confirmatory factor analyses, IRT analyses, and differential item functioning (DIF) analyses demonstrated (1) comparable and unidimensional factor structure for idiopathic and diabetic gastroparesis samples; (2) comparable item parameters and IRT model fit for idiopathic and diabetic gastroparesis samples; and (3) no evidence of uniform or non-uniform DIF for ANMS GCSI-DD items between idiopathic and diabetic gastroparesis samples.

6. Reduction of symptom items: Several of the symptoms in the original GCSI were interrelated and assessed similar types of symptoms (Saraswathi 2013). In addition, upper abdominal pain can be present in some patients with gastroparesis (Cherian 2010; Hasler 2013). The core relevant symptoms of gastroparesis were reduced to five symptoms: nausea, early satiety, postprandial fullness, upper abdominal pain, and vomiting. The symptom of bloating is included as an exploratory symptom.

7. Field testing of the ANMS GCSI-DD: This ANMS GCSI-DD instrument has been used by patients with both idiopathic and diabetic gastroparesis (Revicki 2009; Revicki 2012;

Parkman 2013; Revicki 2014). The instrument was found to be understood by patients, easily used, relevant to patients, and captures the main symptoms of gastroparesis (Revicki 2012; Parkman 2013; Study 1 Qualitative Report 2017).

3.0 Instrument: ANMS GCSI-DD

3.1 Exact Version of the ANMS GCSI-DD

The ANMS GCSI-DD is designed to assess gastrointestinal symptoms associated with idiopathic and diabetic gastroparesis. The ANMS GCSI-DD includes 5 items; item content is provided below in Table 1. The instrument asks participants to rate the severity of four symptoms: nausea, not able to finish a normal-sized meal, feeling excessively full after meals, and upper abdominal pain. The severity response is rated by the patient as the worst severity of the symptom over the previous 24 hours. The severity of symptom response scale ranges from 0 ("none"), 1 ("mild"), 2 ("moderate"), 3 ("severe") to 4 ("very severe"). For vomiting, the number of vomiting episodes (emesis) over the last 24 hours is recorded by the patient. In addition, overall severity of gastroparesis is assessed. The overall severity of gastroparesis takes into account that other symptoms might impact on a patient's condition. The ANMS GCSI-DD is designed to be administered using a paper diary, electronic diary, or by IVRS.

3.2 Prior Versions

The ANMS GCSI-DD is based on previously developed instruments: the GCSI (Revicki 2003), the GCSI-DD (Revicki 2009; Revicki 2012; Parkman 2013).

Table 1: ANMS Gastroparesis Cardinal Symptom Index Daily Diary (ANMS GCSI-DD)

Participant Number:_____ Date:_____ Time:_____

Instructions: These questions ask about symptoms you may have each day. Please complete the daily diary at about the same time every evening.

For each symptom listed below, please mark with an X the box that best describes the worst severity of each symptom during the past 24 hours. Please be sure to answer each question.

	None	Mild	Moderate	Severe	Very Severe
A. Bloating (feeling like you need to loosen your clothes)	☐	☐	☐	☐	☐
1. Nausea (feeling sick to your stomach as if you were going to vomit or throw up)	☐	☐	☐	☐	☐
2. Not able to finish a normal-sized meal (for a healthy person)	☐	☐	☐	☐	☐
3. Feeling excessively full after meals	☐	☐	☐	☐	☐
4. Upper abdominal pain (above the navel)	☐	☐	☐	☐	☐

The next question asks you to record the number of times vomiting occurred in the last 24 hours. Please record the number of vomits (throwing up with food or liquid coming out) that occurred in the last 24 hours. Record zero, if you have not vomited during the past 24 hours. If you vomited, write down the number of all vomits. If you vomited once, record one. If you vomited three times during the day, record three. If you vomited three times, whether it was during the same trip to the bathroom or three separate trips, record three as the number of episodes of vomiting.

5. During the past 24 hours, how many episodes of vomiting did you have? ____

	None	Mild	Moderate	Severe	Very Severe
6. In thinking about your gastroparesis disorder, what was the overall severity of your gastroparesis symptoms today (during the past 24 hours)?	☐	☐	☐	☐	☐

4.0. Using the ANMS GCSI-DD

4.1 Timing and Method or Mode of Questionnaire Administration

The ANMS GCSI-DD has a 24-hour recall; thus all items are designed to be self-administered on a daily basis. Although most developmental work had been performed with a paper format with one page filled out by the patient each evening, it is also amenable and has been used in studies with other methods of administration via interactive voice response systems (IVRS). The questions ask about symptoms patients may have experienced each day. It is recommended that the daily diary should be completed at about the same time every evening usually prior to bedtime to ensure that the diary captures the patient's experience after all meals.

4.2 Scoring of ANMS GCSI-DD

The severity scores of four gastroparesis-related symptoms (nausea, early satiety, postprandial fullness, upper abdominal pain) range from 0-none to 4-very severe. The vomiting score assesses the number of vomiting episodes during the day, capped at a maximum of 4; thus, the scores for vomiting range from 0 (no episodes of vomiting) to 4 (four or more episodes of vomiting). Vomiting frequency is scored as 0 episodes, 1 episode, 2 episodes, 3 episodes or 4 or more episodes (capped as 4). We will capture the number of vomiting episodes reported every day.

The ANMS GCSI-DD total gastroparesis symptom daily score is generated by summing the scores on each of the five symptom items (nausea, early satiety, postprandial fullness, upper abdominal pain, and number of vomiting episodes) and then dividing by 5, that is the number of items within the gastroparesis related symptom score. Thus, the maximum total symptom score could be (5 symptoms * maximum score 4 divided by 5); hence, the maximum score is 20/5=4. The ANMS GCSI-DD gastroparesis symptom daily score can range from 0 to 4. High scores on the ANMS GCSI-DD reflect greater symptom severity. The cognitive debriefing study found that, over a two week period, the entire response scale was observed for the items in the ANMS GCSI-DD (Revicki 2009).

5.0 Training Method/Materials

5.1 Patient Training

The instructions for completing the ANMS GCSI-DD are included in the instrument. Training for completing the daily diary is provided by the site investigator. Patients should understand their disorder: gastroparesis, where there is an abnormally delayed emptying of food from the stomach. The clinical trial that they are entering is being done to see if their symptoms of gastroparesis improve with treatment. The ANMS GCSI-DD recording sheet and instructions are reviewed with the patient prior to the patient starting the recording of daily symptoms in the diary. The symptom severity response items are reviewed: For each symptom listed below, please mark with an X the box that best describes the worst severity of each symptom during the past 24 hours. The number of vomiting episodes is defined: The next question asks you to record the number of times vomiting occurred in the last 24 hours. Please record the number of vomits (throwing up with food or liquid coming out) that occurred in the last 24 hours. Record zero, if you have not vomited during the past 24 hours. If you vomited, write down the number of all vomits. If you vomited once, record one. If you vomited three times during the day, record three. If you vomited three times, whether it was during the same trip to the bathroom or three separate trips, record three as the number of episodes of vomiting.

5.2 Investigator Training

Investigator and site staff training are provided prior to the start of clinical studies. This training is conducted at the investigator meeting or at site initiation meetings. General training on completion of the ANMS GCSI-DD should be provided, and specific training materials on the completion of the ANMS GCSI-DD should be provided to clinical investigators and clinical coordinators. Investigator training slides are not yet available; these can be provided when final version of the GCSI-DD and user manual are approved.

5.3 Other Training

No other training on the ANMS GCSI-DD is planned at this time. The developers of the ANMS-GCSI DD can help assist on training, if needed.

6.0 CONTEXT of USE

6.1 Indication – Disease/Condition and Intended Population

The target patient population for the ANMS GCSI-DD is outpatients who are 18 years or older, and who have been diagnosed with idiopathic or diabetic gastroparesis.

The diagnosis of gastroparesis is made in a symptomatic patient by demonstrating delayed gastric emptying in the absence of mechanical obstruction (Parkman 2004; Camilleri 2013). Two well validated methods for measuring gastric emptying using scintigraphy are available in the published literature:

a. Low fat egg white (EggBeaters, 300 kcal) meal protocol described initially by Tougas et al. (22Tougas 2000) and recommended by the consensus report of the Society of Nuclear Medicine and the American Neurogastroenterology and Motility Society (Abell 2008).
b. Higher fat (30%), 320 kcal egg meal protocol which has been validated including performance characteristics, coefficient of variation, robust normal values available for both males and females, and demonstrated responsiveness to prokinetic therapy (Camilleri 2012)

The clinical presentation of gastroparesis may vary, and symptoms include nausea, vomiting, early satiety, postprandial fullness, bloating, and upper abdominal pain. Based on our previous research, the ANMS GCSI-DD effectively *measures the core symptoms* of gastroparesis in patients with mild to severe disease (face validity). In a recently completed study (Revicki 2012), the instrument has been shown to *capture improvement in symptoms with treatment* (responsiveness). The *minimum clinically important difference* in the ANMS GCSI-DD score has been estimated to be 0.50 (Revicki 2012).

6.2 Clinical Trial Considerations

The ANMS GCSI-DD, or earlier versions, has been used in clinical studies assessing patients with gastroparesis (Cassilly 2008; Friedenberg 2008; Maranki 2008; Parkman 2013).

Because the response to treatment may be different with idiopathic and diabetic gastroparesis, the two conditions ordinarily should be studied in separate clinical trials. For diabetic gastroparesis, controlled stable blood glucose levels are desirable.

Gastroparesis clinical trials generally enroll outpatients with documented delayed gastric emptying and at least moderate symptom severity. Using the severity rating of the ANMS GCSI-DD symptoms, this would correspond to the average ANMS GCSI-DD score of 2.0 or greater.

Response to a drug treatment in a clinical trial could be determined using the ANMS GCSI-DD total score (e.g., as the primary endpoint) and/or one or more of the five individual symptoms that make up the total score (as secondary endpoints).
We recommend *scoring the ANMS GCSI-DD over one week blocks* both at baseline before treatment and during study treatment. The score for one week would be the average of the ANMS-GCSI-DD total score over the previous seven days, thus ranging from 0 to 4.
For clinical trials, it is helpful to record *baseline symptoms over at least one week*. A one to two week (or longer) baseline period can be used to establish the presence and persistence of symptoms and train patients in the collection of symptoms selected for the clinical trial. The baseline screening period can also be used to select for randomization those patients who fulfill specified levels of symptom severity. Responses to treatment would then be recorded in one week blocks of time using the average weekly ANMS GCSI-DD total score. For therapies that might be administered on a chronic and/or continuous basis, a treatment period of at least 8 weeks duration is suggested.
A *responder to treatment* would be defined in detail in the study protocol. Two approaches are often used:

1) assessing the difference in average score or average change in ANMS GCSI-DD total score from baseline score during treatment in the active treatment group compared to placebo group;
2) assessing the difference in responder rate between active treated and placebo treated patients; a responder would be defined as an improvement in the ANMS GCSI-DD score (e.g., >30% decrease in total symptom score, or >0.50 [the MID] decrease from baseline) in at least 50% of the days or weeks of treatment.

7.0 Clinical Claims using the ANMS GCSI-DD

Potential targeted claims are summarized below. They are based on the total score of gastroparesis-related symptoms and individual symptoms included in the ANMS GCSI-DD.

Primary endpoint:
After "n" months of treatment, Drug X significantly decreased the severity of gastroparesis related symptoms, based on the ANMS GCSI-DD total score, compared to placebo in adult patients with gastroparesis.

Secondary endpoints:
After "n" months of treatment, Drug X significantly decreased the severity of nausea compared to placebo in adult patients with gastroparesis.
After "n" months of treatment, Drug X significantly decreased the severity of early satiety compared to placebo in adult patients with gastroparesis.
After "n" months of treatment, Drug X significantly decreased the severity of postprandial fullness compared to placebo in adult patients with gastroparesis.
After "n" months of treatment, Drug X significantly decreased the severity of upper abdominal pain compared to placebo in adult patients with gastroparesis.
After "n" months of treatment, Drug X significantly decreased the number of vomiting episodes compared to placebo in adult patients with gastroparesis.
After "n" months of treatment, Drug X significantly decreased the overall severity of gastroparesis compared to placebo in adult patients with gastroparesis.

If a proposed indication is based on improvement of only one of the symptoms of gastroparesis, such as nausea or vomiting, the treatment should not worsen the other core gastroparesis symptoms or worsen the overall severity of gastroparesis as delineated by the ANMS GCSI-DD.

8.0 Summary

The ANMS GCSI-DD is designed to assess symptoms associated with idiopathic and diabetic gastroparesis. The ANMS GCSI-DD includes 5 items: nausea, vomiting, early satiety, postprandial fullness, and upper abdominal pain. Four of these (nausea, early satiety, postprandial fullness, and upper abdominal pain) are rated as none (0), mild (1), moderate (2), severe (3), very severe (4) scale on the worst severity of the symptom over the last 24 hours. Vomiting is assessed as the number of emesis episodes over the last 24 hours, with the maximum number capped at four (0 to 4 range). The ANMS GCSI-DD total score is a useful patient reported outcome for gastroparesis and as an endpoint in gastroparesis clinical trials.

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