FDA Executive Summary

Prepared for the
Fall 2020, Meeting of the
FDA's Pediatric Advisory Committee

H990014

Enterra® Therapy System

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INTRODUCTION

In accordance with the Pediatric Medical Device Safety and Improvement Act, this document provides the Pediatric Advisory Committee (PAC) with postmarketing safety information to support its annual review of the Enterra® Therapy System ("Enterra"). The purpose of this annual review is to (1) ensure that the Humanitarian Device Exemption (HDE) for this device remains appropriate for the pediatric population for which it was granted, and (2) provide the PAC an opportunity to advise FDA about any new safety concerns it has about the use of this device in pediatric patients.

This document summarizes the safety data the FDA reviewed in the year following our 2015 report to the PAC. It includes data from the manufacturer's annual report, postmarket medical device reports (MDR) of adverse events, and peer-reviewed literature.

BRIEF DEVICE DESCRIPTION

Enterra is a surgically-implanted gastric electrical stimulator (GES). The mechanism(s) by which Enterra works is not well understood but may involve indirect neuromodulation of parasympathetic nerves and/or ganglia, which regulate gastric function.

Enterra consists of the following:

1. A neurostimulator placed in a subcutaneous pocket in the abdomen, which functions like a pacemaker in delivering electrical pulses to the stimulation leads. The neurostimulator contains a sealed battery and electronic circuitry.
2. Two intramuscular leads that connect to the neurostimulator, implanted into the muscularis propria on the greater curvature at the limit of the corpus-antrum. The leads deliver electrical pulses to the stomach muscle.
3. An external clinician programmer.

Schematic diagrams of the implantable components and device placement are provided in Figure 1 and Figure 2, respectively.

FIGURE 1: Implantable components

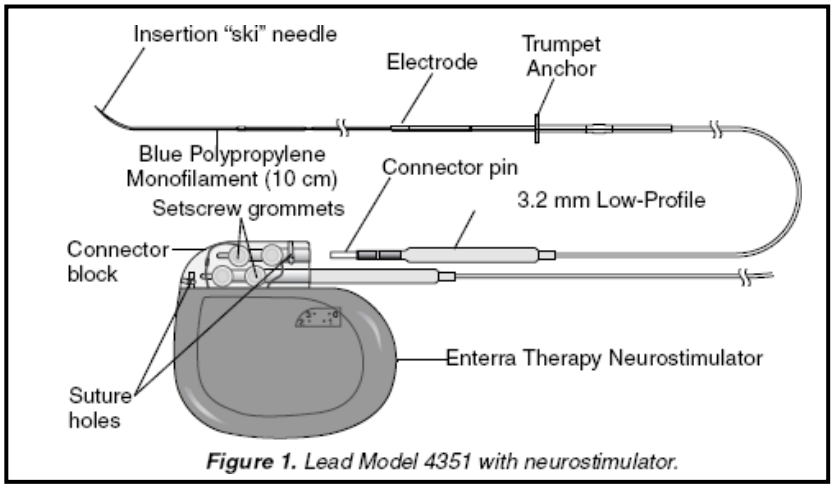
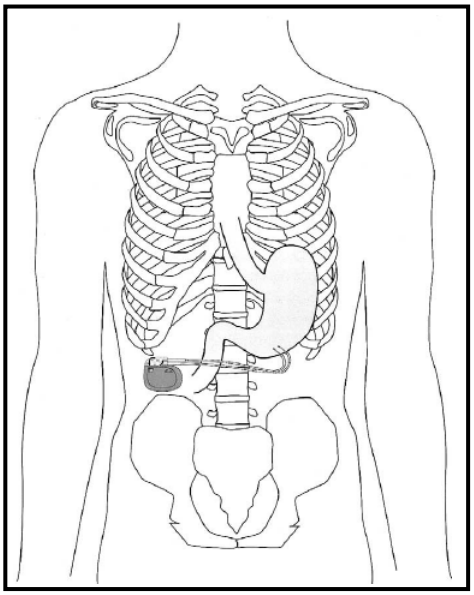


Figure 1. Lead Model 4351 with neurostimulator.

FIGURE 2: Device placement



INDICATIONS FOR USE

Medtronic Enterra Therapy is indicated for the treatment of chronic, intractable (drug-refractory) nausea and vomiting secondary to gastroparesis of diabetic or idiopathic etiology in patients aged 18 to 70 years.

REGULATORY HISTORY

September 23, 1999: Granting of Humanitarian Use Device (HUD) designation for Enterra (HUD #990014)

March 30, 2000: Approval of Enterra HDE (H990014)
March 25, 2013: Approval to profit on the sale of Enterra

DEVICE DISTRIBUTION DATA

Section 520(m)(6)(A)(ii) of The Food, Drug, and Cosmetic Act (FD&C) allows HDEs indicated for pediatric use to be sold for profit as long as the number of devices distributed in any calendar year does not exceed the annual distribution number (ADN). On December 13, 2016, the 21st Century Cures Act (Pub. L. No. 114-255) updated the definition of ADN to be the number of devices "reasonably needed to treat, diagnose, or cure a population of 8,000 individuals in the United States." Based on this definition, FDA calculates the ADN to be 8,000 multiplied by the number of devices reasonably necessary to treat an individual. However, it is to be noted that unless the sponsor requests to update their ADN based on the 21st Century Cures Act, the ADN will still be based on the previously approved ADN of 4,000. The approved ADN for Enterra is 4,000 total per year.

The total number of Enterra devices *sold* in the U.S. for the current and previous reporting periods is detailed in Table 1; the number of devices *implanted* in pediatrics is detailed in Table 2.

TABLE 1: Distribution numbers

Model Number & Component Name	Devices Sold From 02/01/19 – 01/31/20	Devices Sold From 02/01/18 – 01/31/19	Devices Sold From 02/01/17 – 01/31/18	Devices Sold from 02/01/16– 01/31/17	Devices Sold From 02/01/15 – 01/31/16	Devices Sold from 02/01/14 – 01/31/15
37800 Implantable Neurostimulator (INS)	2,053	1,951	2,017	1,865	1,611	1,391
3116 Implantable Neurostimulator	0	0	0	0	208	95
4351 Intramuscular Lead	1,988	2,106	2,535	2,462	2,151	2,151

TABLE 2: Number of devices implanted in pediatric patients

Reporting Period: 1-Feb-2019 to 31-Jan-2020	Total N (newly implanted this period)	Female			Male			Gender Unknown		
		<2	2<18	≥18<22	<2	2<18	≥18<22	<2	2<18	≥18<22
Newly implanted Pediatric patients implanted during this reporting period	31	0	9	15	1	1	3	0	1	1
Total Pediatric implant base this period	263	0	49	137	1	36	32	0	2	6

MEDICAL DEVICE REPORT REVIEW

Overview of MDR database

The MDR database is one of several important postmarket surveillance data sources used by the FDA. Each year, the FDA receives several hundred thousand medical device reports (MDRs) of suspected device-associated deaths, serious injuries, and malfunctions. The MDR database houses MDRs submitted to the FDA by mandatory reporters (manufacturers, importers and device user facilities) and voluntary reporters such as health care professionals, patients, and consumers. The FDA uses MDRs to monitor device performance, detect potential device-related safety issues, and contribute to benefit-risk assessments of these products. MDR reports can be used effectively to:

- Establish a qualitative snapshot of adverse events for a specific device or device type
- Detect actual or potential device problems in a "real world" setting/environment, including:
    - rare, serious, or unexpected adverse events
    - adverse events that occur during long-term device use
    - adverse events associated with vulnerable populations
    - off-label use
    - use error

Although MDRs are a valuable source of information, this passive surveillance system has limitations, including the potential submission of incomplete, inaccurate, untimely, unverified, or biased data. In addition, the incidence or prevalence of an event cannot be determined from this reporting system alone due to potential under-reporting of events and lack of information about frequency of device use. Because of this, MDRs comprise only one of the FDA's several important postmarket surveillance data sources.

Other limitations of MDRs include, but are not necessarily limited to:

- MDR data alone cannot be used to establish rates of events, evaluate a change in event rates over time, or compare event rates between devices. The number of reports cannot be interpreted or used in isolation to reach conclusions about the existence, severity, or frequency of problems associated with devices.

- Confirming whether a device actually caused a specific event can be difficult based solely on information provided in a given report. Establishing a cause-and-effect relationship is especially difficult if circumstances surrounding the event have not been verified or if the device in question has not been directly evaluated.

- MDR data is subjected to reporting bias, attributable to potential causes such as reporting practice, increased media attention, and/or other agency regulatory actions.

- MDR data does not represent all known safety information for a reported medical device and should be interpreted in the context of other available information when making device-related or treatment decisions.

MDRs Associated with Enterra Therapy System

MDR Search Methodology

The database was searched using the following search criteria:

A. Search 1
   - **Product Code:** LNQ
   - **Report Entered:** between May 1, 2019 and April 30, 2020

B. Search 2
   - **Brand name:** ENTERRA%
   - **Report Entered**: between May 1, 2019 and April 30, 2020

C. Search 3
   - **Premarket submission number**: H990014
   - **Report Entered**: between May 1, 2019 and April 30, 2020

The searches resulted in identifying 219 MDRs: 218 reports were submitted by the manufacturer, and one report was submitted by a user facility during this timeframe.

Thirty-four MDRs were excluded since these MDRs described "Interstim" device. Six MDRs were excluded from further analysis since these MDRs described events reported in six journal articles. Four of these article reports were excluded from the MDR analysis and the Literature Review as they were outside the defined search parameters (i.e. outside the search period, not a peer-reviewed journal, or not in English language). The two remaining journal articles are further discussed in the Literature Review section of this document. Additionally, one duplicate MDR was excluded because it was submitted from different reporting sources (Manufacturer and User facility) regarding the same event.

The remaining 178 MDRs involved MDRs received between May 1, 2019 and April 30, 2020. They included 0 death, 117 injuries, and 61 device malfunction reports. These 178 MDRs are discussed below.

Event Type by Patient Age

Table 3 below provides the distribution of the MDRs by reported event type and age grouping. Three reports identified a pediatric patient from 19.6 to 21.3 years old. These reports have been placed into age category of 18-21 years old and included two injury MDRs and one malfunction MDR.

TABLE 3: Overall event type distribution by patient age

Event Type	Total MDR Count 5/1/2018 – 4/30/2019	MDR Count by Patient Age (years)			
		Pediatric (< 18)	Pediatric (18-21)	Adult (≥ 22)	Indeterminate (Age blank)
Death*	0	0	0	0	0
Injury	117	0	2	105	10
Malfunction	61	0	1	56	4
Total MDR Count	178	3		161	14

Comparison of Current Patient Event Type Information with 2018 and 2019 Data

Table 4 below compares the Event Type distribution for this analysis to that of prior years 2018 and 2019. The current period appears to reflect about an 42% decrease of MDR submissions compared with the 2019 PAC presentation period (May 1,2018 to April 30, 2019), in the numbers of serious injury and malfunction reports. Similarly, pediatric MDR submissions decreased from nine in the previous analysis period to three in this current analysis period.

TABLE 4: Overall event type distribution by year

	Total MDR Count		
Event Type	PAC Meeting 2018 5/2017 - 4/2018	PAC Meeting 2019 5/2018 - 4/2019	PAC Meeting 2020 5/2019 - 4/2020
Death	0	1	0
Injury	285	184	117
Malfunction	150	120	61
Total MDR Count	435	305	178

Patient Gender and Age Information

In the 178 MDRs received from May 2019 to April 2020, 161 patients were noted as adult (≥22 years old) and 14 MDRs did not provide a patient age (indeterminate age reports). Three MDRs contained pediatric patients' ages that ranged from 19.6 to 21.3 years, with a mean age of 20.4 years (SD ± 0.69 years). There were also 167 MDRs, which noted the gender of the patient: 138 MDRs as female (including 2 pediatric patients), and 29 MDRs as male. The remaining 11 MDRs did not include the patient's gender (including 1 pediatric patient).

Individual review of the eleven reports narrative sections to determine gender identifiers (male or female, she or her, he or him, etc.), result in identifying one male and one female patient age indeterminate, which makes 169 MDRs noted the gender of the patient: 139 MDRs as female (including 2 pediatric patients), and 30 MDRs as male. The remaining nine MDRs did not include the patient's gender (including 1 pediatric patient).

Time to Event Occurrence

An analysis of the Time to Event Occurrence (TTEO) was performed. The TTEO is based on the implant duration and was calculated as the time between the Date of Implant and the Date of Event. For those reports without a date of event, the TTEO was calculated using the reported date of implant removal. There are total 140 MDRs (out of 178 MDRs) provided a valid event date or explant date, including all three pediatric reports.

Table 5 below provides the MDR count for the TTEO for the pediatric, adult, and indeterminate age patient populations.

TABLE 5: MDR count for the TTEO by patient age

Time to Event Occurrence (TTEO)	MDR Count by Patient Age (years)			
	Pediatric (<18)	Pediatric (18-21)	Adult (≥22)	Indeterminate (Age blank)
≤ 30 days (n=30)	0	0	28	2
31 days - ≤ 1 year (n=38)	0	1	37	0
> 1 year – ≤ 5 years (n=57)	0	2	55	0
> 5 years (n=15)	0	0	15	0
Totals (N=140)	0	3	135	2

Characterizations of the 9 MDR Narratives of Pediatric Events from May 1, 2019 – April 30, 2020 as it relates to TTEO:

A. TTEO between 31 days and ≤ 1 year of implant. (N=1)

- A 20-year old patient had shocking sensation in the stomach and decreased therapeutic effects after the device reprogramming by their doctor. The device was temporarily turned off until the patient returns to their doctor.

B. TTEO between >1 year and < 5 years of implant. (N=2)

- A 19-year-old female patient was reported having wound infection, which led to sepsis for three times. The patient was hospitalized. There was no therapeutic effect of the device, so the patient requested for device removal. There was no reported patient falls or trauma. According to her doctor, the patient has not been following up with the doctor for about one year before the report of this event.
- A 21-year-old female patient had return of symptoms of nausea and vomiting and was hospitalized. The patient planned to follow up with their managing doctor.

Characterizations of the Time to Event Occurrences (TTEO) in the adult and indeterminate age populations from May 1, 2019 – April 30, 2020

For the adult (N=135) and indeterminate age (N=2) populations with TTEO data, issues with the use of this device continue to occur most frequently from "> 1 year up to ≤ 5 years" from the date of implant, followed by issues occurring between "31 days up to ≤ 1 year", then "≤ 30 days" in the adult group; the indeterminate age group only had two cases with issues occur "≤ 30 days". In comparison to last year's analysis of reports for these TTEO groups, the same types of issues continue:

- Pain and inappropriate simulation/shocking secondary to positioning/migration of the device or battery and lead issues
- Return of symptoms of nausea and vomiting and/or loss of therapeutic effect secondary to impedance issues or battery issues
- Infection, migration and erosion issues
- Electromagnetic compatibility/interference problem

In this current analysis, the common complaint of pain continues to occur because of inappropriate stimulation/shocking as well as positioning/migration of the device or its components. The inappropriate stimulation/shocking, often caused by patient device interaction problems, such as patient losing weight after implant; device battery/lead positions; or setting of the devices. Device reposition, battery or leads revision/replacement, or turn down the voltage setting relieve the problems in most cases.

Electromagnetic compatibility interference from medical testing (MRI, smart pill endoscopy) or medical procedures (cardiac pacemaker, back surgery, colonoscopy) as well as patients encountering metal detection devices also caused abnormal shocking and unexpected decrease of therapeutic effects with the device.

Infection, migration, and erosion issues also continued to occur as in the previous years' analyses. Infection was specifically mentioned in 12 MDRs, and typically occurred within the first three years of device placement with most of them occurred in the first six months after device placement.

Infection associated with the device or component (i.e. "pocket", "lead", "INS" and "battery") was found in eight reports, while one report mentioned an infection with central line, one report noted a Methicillin-resistant Staphylococcus aureus (MRSA) infection, cause unknown and had to have their device removed, and the remaining two reports did not mention site or cause of the infection.

Six reports noted lead erosion into stomach or through the skin, and two reports noted pocket erosion through the skin. The erosion occurred between two months and nine years of implant. One lead erosion into the stomach case also reported lead erosion into the small bowel. During the surgery to remove the device, the physician found the adhesions related to the small

bowel and stomach were extremely dense and had to make multiple enterotomies to carefully peel the small bowel from the stomach and leads. After the surgery, the small bowel was examined and noted some bruising on the surface of the small bowel. The leads and gastric generator were explanted.

Migration or expulsion of device were reported in 16 MDRs. Six reports noted leads eroded into patients' stomach, one of the six reports also noted leads eroded into a patient's intestine; one report noted lead wire wrapped around a patient's intestines, which led to a bowel obstruction, a bowel resection was done, and the battery was replaced; One report noted the INS was protruding and eroding through the patient's skin. The remaining eight reports noted the devices were moving inside the pocket and the patients had to be taken back into the operation room for re-securing the device to the abdominal wall or reposition the device. The migration of device occurred between one month and nine years of implant. Pain/shocking, nausea, and decreased therapeutic effects were reported symptoms of migration, and interventions involved remove and replacement of device to address these symptoms.

As noted in previous year, adult and indeterminate age patients continue to predominantly experience nausea and vomiting with decrease in therapeutic effectiveness. Twenty-two MDRs discussed battery depletion, which lead to patient complaints of "therapy effectiveness, decreased." These continue to occur from eight months after placement to nine years, average 2.1 years with typical resolution noted as reprogramming or replacement of the battery.

Most Commonly Reported Patient Problem Codes (PPC)[1]

Table 6 below provides the most prevalent reported patient problem codes found in the MDRs reviewed during this year's analysis, differentiated by patient age. The top reported patient problem is "Pain" (n=51), compared to previous analyses to be "Vomiting and Nausea" (n=41), and is characterized as related to inappropriate stimulation/shocking as well as positioning/migration of the device or its component. In the current analysis period, there was no change in the relative ranking of the code "No known impact or consequence to patient" (n=43), "Therapeutic Response, Decreased/Paresis (n=27), "Therapeutic Effects, Unexpected" (n=20), "Infection" (n=17) and "Erosion" (n=9) as compared to prior analysis period. However, there was an increase in the use of the code "Electric Shock" (n=29) to rank the fourth, and a new patient code "Burning Sensation" (n=8) to rank the tenth compared to last year's analysis, which ranked the sixth and eleventh, respectively. On the other hand, Complaints of general "Malaise"/ "Complaint, Ill-defined (n=24) decreased from ranking the fourth to the sixth compared to last year's analysis. Overall, the top patient problems present nothing significantly new as compared to prior analysis period, and 151 out of 178 reports stating the device was not returned for evaluation. There are two reports worth noting in the current analysis period. One MDR noted the leads become entangled in the bowel of the patients that led to a bowel obstruction. A surgery was performed, and the device battery was also replaced.

[1] The total PPC does not equal the total MDR count since one MDR might have multiple patient problems. Patient problem codes indicate the effects that an event may have had on the patient, including signs, symptoms, syndromes, or diagnosis.

Another MDR noted the leads eroded into the stomach and the small bowel of the patient. The removal surgery was complicated by the extremely dense adhesions related to the small bowel and stomach, and multiple enterotomies had to be made to carefully peel the small bowel from the stomach and leads. The leads and gastric generator were explanted.

TABLE 6: Most commonly reported patient problem codes received by patient age

Patient Problem	Total Patient Problem Code in MDR	Total Patient Problem Code in MDR by Patient Age (years)			
		Pediatric (< 18)	Pediatric (18 to 21)	Adults (≥ 22)	Indeterminate (Age blank)
Pain/ Discomfort/ Pain, Abdominal	51	0	0	48	3
No known impact or consequence to patient***	43	0	0	38	5
Vomiting/ Nausea	41	0	1	39	1
Electric Shock/Nerve Stimulation, Undesired	29	0	1	24	4
Therapeutic Response, Decreased/Paresis	27	0	2	25	0
Complaint, Ill-Defined*/ Malaise	24	0	0	23	1
Therapeutic Effects, Unexpected**	20	0	1	19	0
Infection/ Wound Dehiscence	17	0	1	14	2
Erosion	9	0	0	9	0
Burning Sensation	8	0	0	7	1
Total Patient Problem Code Count	269	0	6	246	17

Note: The total MDR Occurrences does not equal the total MDR count since one MDR might have multiple patient problems.
**MDRs coded with "Complaint, Ill-Defined" often included reports of nausea and/or vomiting.*

***MDRs coded with "Therapeutic Effects, Unexpected" typically involved issues of the device not operating as the patient anticipated.*

****A code of "No Known Impact or Consequence to Patient" indicates that while a device behavior may have been identified in the report, the manufacturer or reporter did not report any patient impact or consequence because of the reported device behavior.*

Most Commonly Reported Device Problem Codes (DPC)[2]

Table 7 below provides the most commonly reported Device Problems for all MDRs differentiated by patient age. The top 2 reported device problem codes continued as in the previous analysis period with “Adverse event without identified device or use problem” (n=40) ranking the first, and “Insufficient information” (n=31) ranking the second. “Inappropriate shock” (n=29) continued to rank the third. There was an increase in the use of the code “Battery problem” to rank the fourth (n=28), and “Migration or expulsion of device/ “Unstable” (n=25) to rank the fifth, as compared to prior analysis period (ranked the seventh and sixth, respectively). There was a decrease in the use of code “High”/ “Low impedance"/ “Impedance issues” (n=15) ranking the sixth, and “Energy output problem”/ “Failure to deliver energy” (n=15) ranking the seventh compared to prior analysis period. “Patient device interaction problem” (n=7), and “Break”/ “Material deformation” (n=5) continued as in the prior analysis period to rank the ninth and tenth, respectively.

The reports with “Adverse event without identified device or use problem” related to patient issues in which the device is functioning or has no identified device problems, but the patient has complained ill-defined, pain, infection, or device intolerance issues. A review of reports found that the device problem code “Insufficient information” was commonly associated with a device not properly functioning but did not provide a detailed information of the malfunction; most of the corresponding patient problem codes are nausea, vomiting, and shocking sensation. Adjustments to the device voltage, its placement, and replacement of the leads or battery were the interventions used for the patients.

The reports of “Inappropriate Shock” typically involved the position of device, or electromagnetic compatibility/interference. The device problem codes “Battery problem”/ “Premature Discharge of battery”/ “Low battery issue”, and “High”/ “Low impedance"/ “Impedance issues”/ are associated with reports of battery problems or device high or low impedance issues. “Energy output problem”/ “Failure to deliver energy are related to nausea, vomiting, shocking, and decreased therapeutic effect issue; The reports of “Patient device interaction problem” are related to pain and positional shocking. Reprogramming, replace, or revision of device are interventions for the patients. As noted previously in the patient problem section, 151 out of 178 reports stated the device was not returned for evaluation.

[2]The total DPC does not equal the total MDR count since one MDR might have multiple patient problems. Device problem codes describe device failures or issues related to the device that are encountered during the event.

TABLE 7: Most commonly reported device problem codes received by patient age

Device Problem	Total Device Problem Code in MDR	Total Device Problem Code in MDR by Patient Age (years)			
		Pediatric (< 18)	Pediatric (18 to 21)	Adults (≥ 22)	Indeterminate (Age blank)
Adverse event without identified device or use problem	40	0	2	35	3
Insufficient information	31	0	0	26	5
Inappropriate shock	29	0	1	24	4
Battery problem/ Premature Discharge of battery /Low/Battery issue	28	0	0	28	0
Migration or expulsion of device/Unstable	25	0	0	24	1
Electromagnetic compatibility issue/ Electromagnetic interference (EMI)	16	0	0	15	1
High/Low impedance/ Impedance issues	15	0	0	14	1
Energy output problem/failure to deliver energy	15	0	0	15	0
Patient device interaction problem	7	0	0	7	0
Break/Material deformation	5	0	0	5	0
Total Device Problem Code Count	211	0	3	193	15

Note: The total MDR Occurrences does not equal the total MDR count since one MDR might have multiple device problems.

Discussion of Pediatric Patient Problem as it relates to Device Problem Information

Table 8 identifies the MDR occurrences of the top patient problems and issues in pediatric patients only, in comparison to the prior analysis period's findings.

TABLE 8: Clinical events identified with pediatric patients - year-to-year comparison*

Clinical Events	Occurrences in MDRs** 5/1/2019 – 4/30/2020	Occurrences in MDRs** 5/1/2018 – 4/30/2019	Occurrences in MDRs** 5/1/2017 – 4/30/2018
Nausea/Vomiting [Complaint ill- defined]	1	6	15
Therapeutic Response, unexpected/Paresis	3	4	3
Pain/Discomfort/ Abdominal pain/ Burning sensation	2	3	6
Electric Shock/Nerve Stimulation, Undesired/ [Inappropriate Electric Shock]	1	3	3
Infection	1	2	0

*Only the most observed patient problems and issues in pediatric MDR narratives are included.

**The total MDR Occurrences does not equal the total pediatric MDR count since one MDR might have multiple clinical events.

As in the prior analysis period, the clinical events for the three pediatric MDRs found in this analysis also involve complaints of nausea, vomiting, pain, shock, and infection, corresponding to the device issue of "Therapeutic Response, unexpected/decreased", and "inappropriate shock." These complaints and device problems are most often due to device setting, or battery and lead issues. Adjustments of the device settings, following up with treating physician, hospitalization, and request to explant the device were the noted interventions.

Re-Interventions in Pediatric Paftients from 5/1/2019 through 4/30/2020

Re-interventions addressing types of clinical events reported above are listed below in Table 9. This table summarizes the re-interventions identified in the narratives and the causal events leading to these re-interventions.

TABLE 9: Re-interventions in pediatric patients* (5/1/2019-4/30/2020)

Re-Interventions	Number of Re-Interventions	Causal Event
Replacement/Repositioning • Device or Battery	0	• Shocking/burning • Battery depletion
Explant • Device or INS	0	• Infection • Pain
Reprogramming/ Calibration	1	• Loss of therapeutic effect • Shocking/jolting/burning
Hospitalization/Emergency room	2	• Infection • Loss of therapeutic effect • Pain/discomfort • Vomiting/hematemesis
Surgery (gastrostomy) /Feeding tube	0	• Loss of therapeutic effect • Nausea/vomiting/poor intake
Office follow-up treatment	3	• Loss of therapeutic effect • Nausea/vomiting • Shocking

*Note that the total counts do not equal the number of MDRs since one MDR might have multiple noted re-interventions.

** Temporary involves the mention of temporary removal of the device and has no comment of actual replacement in the report.

Conclusions Based on MDR Review

- There have been three pediatric (out of 178) MDRs submitted for the Enterra Therapy System between May 1, 2019 and April 30, 2020. Of these, two were injury events, and one was a device malfunction event.
- The Time to Event Occurrence (TTEO) was calculated for 140 (out of 178) MDRs based on the available information contained in the reports, including all three pediatric reports.

- Review of the pediatric reports with TTEO showed:
  - One pediatric patient (age 20), had TTEO occurrence of 31 days to 1 year of implant.
    - One patient had shocking sensation in the stomach and decreased therapeutic effect after the device reprogramming by their doctor. The device was temporarily turned off until the patient returns to their doctor.
  - Two pediatric patients (ages 19 & 21), had TTEO of 1 to 5 years of implant.
    - One patient had wound infection, which led to sepsis for three times. The patient was hospitalized. There was no therapeutic effect of the device, so the patient request for device removal. There was no reported patient falls or trauma. The patient has not been following up with their doctor for one year before the report of this event.
    - One patient had return of symptoms of nausea and vomiting and was hospitalized. The patient planned to follow up with their managing doctor.

- The reported pediatric patient problems share similar complaints as identified in previous year's analyses:
  - "Nausea"/ "Vomiting".
  - "Shock"/ "Decreased Therapeutic Response".
  - "Infection"
- Device Problems in pediatric patients is also similar as the previous analysis, with the reported device problem being: "Inappropriate Shock", which was associated with complaints of "shocking sensation", and "decreased therapeutic effect". Adjustments to the device impedance settings and follow up with the patients' doctors were the solution for some of the complains.
- Reports continue to identify other underlying device functionality issues with the device lead (i.e. migration or malfunction) in addition to battery depletion issues.
- The manufacturer's evaluations of the various device issues were hindered due to devices not being returned in most cases (151 of 178 MDRs).

As in prior analysis period, complaints of return of symptoms (nausea, vomiting), decreased therapeutic effect, as well as incidences of shocking, appear to center around the position of device and/or connection/malfunction issues involving the leads or batteries.

- Overall, the Patient Problems and Device Problems observed among pediatric patients were similar to those observed in adult patients.
- The types of adverse events being seen in the current analysis period are consistent with what has been observed in prior analysis periods, with two cases worth of noting. One MDR described leads becoming entangled in the bowel of a patient and led to a bowel obstruction; a surgery was performed, and the battery of the device was replaced. Another MDR noted

leads eroded into the stomach and the small bowel of a patient. The removal surgery was complicated by the extremely dense adhesions related to the small bowel and stomach, and multiple enterotomies had to be made to carefully peel the small bowel from the stomach and leads. Bowel obstruction from leads entanglement or erosion as well as leads erosion into stomach have been addressed in the device labeling. These problems were not reported in any of the pediatric reports in this analysis period.

LITERATURE REVIEW

Purpose

A systematic literature review was conducted to evaluate the safety and probable benefit of Enterra gastric electrical stimulator (GES) in the pediatric population (<22 years old). This is an update from the literature reviews presented at the Pediatric Advisory Committee (PAC) meetings on September 23, 2014, September 16, 2015, September 14, 2016, September 12, 2017, September 23, 2018, and September 26, 2019. Specifically, the literature review was conducted to address the following questions:

1. What is the probable benefit of Enterra for the following clinical endpoints: improvement in upper GI symptoms; reduction in need for nutritional support; and improved gastric emptying time (GET)?
2. What adverse events are reported in the literature after treatment with Enterra?

The search was limited to studies published since the last PAC meeting update (May 1, 2019 and April 30, 2020), in human subjects, and in the English language. This search yielded a total of 67 citations (20 in PubMed, 41 in Embase, and 6 in MDRs). After a review of titles, abstracts, and full texts, 6 articles were selected for full review and assessment as shown in "Figure 1. Article Retrieval and Selection" below.

Methods

On July 2, 2020, searches in PubMed, Embase and from MDRs were performed using the following search terms:

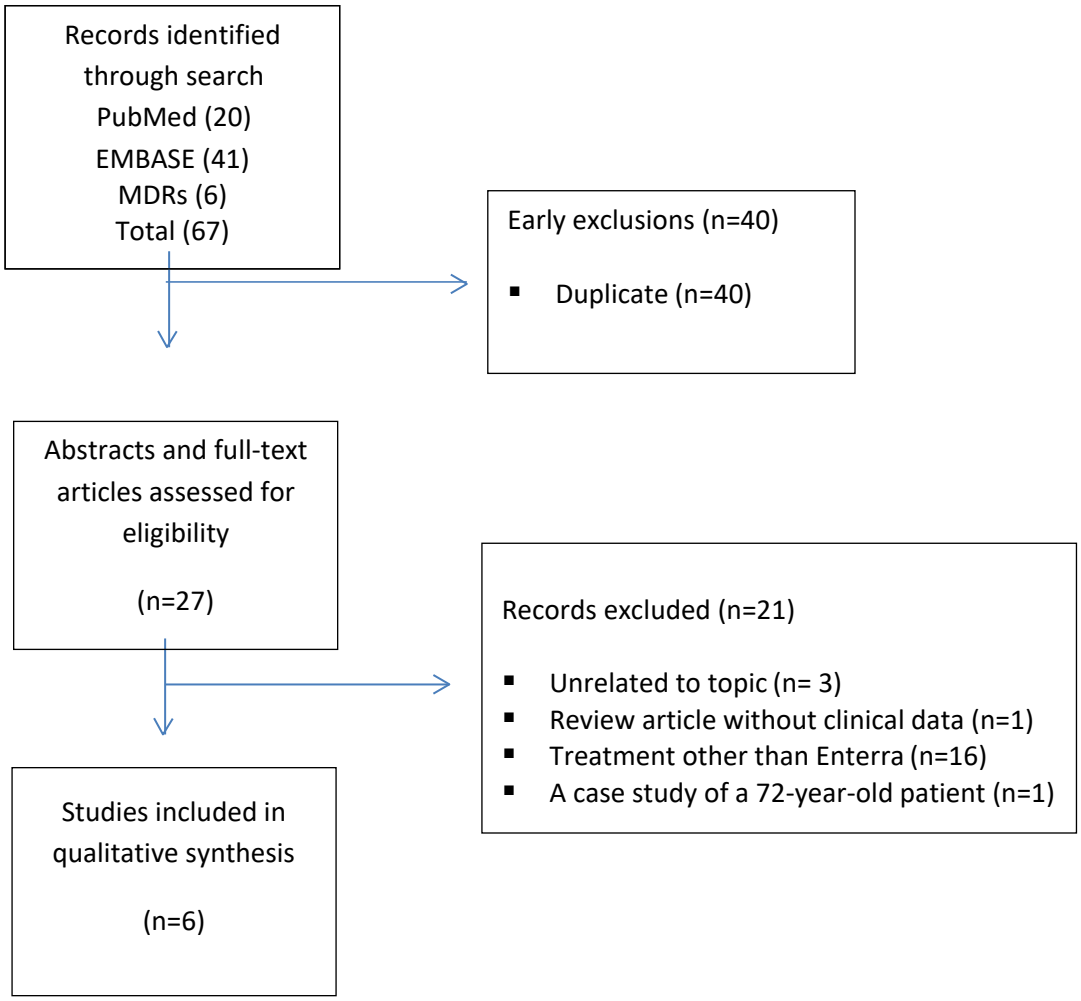
- PubMed
  "Enterra" OR "gastric electric stimulation" OR "gastric electrical stimulation" OR "gastric electrostimulation" OR "gastric pacemaker" OR "gastric pacing" OR (stimulation AND gastroparesis) OR "gastrointestinal neuromodulation"

  Filters: Publication date from 2019/05/01 to 2020/04/30; Humans; English; clinical study, clinical trial, clinical trial, Phase III, control clinical trial, randomized controlled trial.

- Embase
  ('enterra'/exp OR enterra OR 'gastric pacemaker'/exp OR 'gastric pacemaker' OR 'gastric electrical stimulation'/exp OR 'gastric electrical stimulation' OR 'gastric electric stimulation'/exp OR 'gastric electric stimulation' OR 'gastric electrostimulation' OR 'gastric pacing'/exp OR 'gastric pacing' OR '(stimulation and gastroparesis)' OR 'gastrointestinal neuromodulation') AND [humans]/lim AND [2018-2019]/py AND [english]/lim AND ([young adult]/lim OR [adult]/lim OR [aged]/lim) AND [1-5-2019]/sd NOT [1-5-2020]/sd

- MDRs
  Dr. Jian Connell, MDR Reviewer, found six titles/citations included in MDRs; one of them was excluded because it was out of date range; published before May 1, 2019 and was already included in the previous review and PAC presentation of September 26, 2019; one was excluded because it was a review article with no clinical data; another one was excluded because it was a single case study report in which it was not clear if Enterra was used and was not written in English; and the other three were duplicates already found in both PubMed and Embase. Therefore, none of these six articles were further included.

Figure 1. Article Retrieval and Selection



Summaries from Pertinent Articles

1. Hasanin M, Amin O, Hassan H, Kedar A, Griswold M, Abell TL. Temporary Gastric Stimulation in Patients with Gastroparesis Symptoms: Low-Resolution Mapping Multiple Versus Single Mucosal Lead Electrograms. Gastroenterology Res. 2019;12(2):60-66. doi:10.14740/gr1127

BACKGROUND: The authors hypothesized that using two leads will vary from a single lead by providing greater insight of gastric electrical wave propagation, through differences in measured frequency, amplitude, and frequency over amplitude ratio. They also hypothesized that a significant reduction in symptomatic vomiting score is highly predictive in a single lead temporary gastric electrical stimulation.

METHODS: A total of 111 patients with drug-refractory gastroparesis were enrolled in this non-randomized clinical trial. Forty-two patients had single lead, while 69 patients had two leads. All recordings measured mean frequency and amplitude in each lead. Patients documented symptoms using standardized symptom scores at baseline and day 5 post-procedure.

RESULTS: Single lead patients with initial low mucosal frequency showed an increase from 3.10 to 4.93 (p=0.0155), while the high frequency group decreased from 5.89 to 5.12 (p=0.135). Vomiting score decreased significantly among both groups with GES (p=0.0001). For two leads, the mucosal frequency decreased at the proximal electrode (p=0.402) and increased at the distal electrode (p=0.514), neither statistically significant (p=0.143). Mucosal electrogram amplitude values changed for both proximal, mean decrease of 0.34 mV (p=0.241), and distal, mean increase of 0.05 mV (p=0.65) with a mean difference 0.34 mV (p=0.238). However, mucosal electrogram frequency and amplitudes on day 5 were highly dependent on the baseline values (p<0.001).

Table 4

Changes, in Mean Symptom Score, as Well as Total Gastric Emptying Measured at Baseline and Post-Stimulation via Single Lead tGES

Variable	Visit 1	Visit 2	Change (CI) (P value)
Nausea	3.28	1.54	-1.7 (1.25, 2.24) (< 0.001)*
Vomiting	1.96	0.51	-1.44 (0.96, 1.93) (< 0.001)*
Anorexia	2.55	1.23	-1.32 (1.9, 0.01) (0.002)*
Bloating	2.53	1.32	-0.26 (1.72 , 1.86) (< 0.001)*
Abdominal pain	2.35	1.32	-1.03 (0.36, 1.71) (0.004)*
TSS	12.46	5.6	-6.86 (5.02, 8.71) (< 0.001)*
GET total	153.63	141.92	-11.71 (-9.32, 32.73) (0.27)

TSS: total symptom score; GET total: total gastric emptying time. All "Visit 2" values were recorded 5 days after baseline at visit 1. *The significant P values.

Table 5

Changes, in Mean Symptom Score, as Well as Total Gastric Emptying Measured at Baseline and Post-Stimulation via 2-Lead tGES

Variable	Visit 1	Visit 2	Change (CI) (P value)
Nausea	3.46	1.73	-1.73 (-2.5, -0.91) (< 0.001)*
Vomiting	2.69	1.46	-1.23 (-2.1, -0.4) (0.003)*
Anorexia	3.04	2.08	-0.96 (-1.9, -0.01) (0.047)*
Bloating	3.21	1.69	-1.52 (-2.6, -0.4) (0.006)*
Abdominal pain	2.75	1.38	-1.36 (-2.7, -0.1) (0.038)
TSS	15.38	8.27	-7.11 (-11.1, -3.1) (< 0.001)*
Frequency	6.45	5.96	-0.49 (-2.9, 1.9) (0.685)
Amplitude	0.69	0.99	0.30 (-0.3, 0.9) (0.362)
Ratio	26.43	11.49	-14.93 (-26.9, -3.0) (0.014)*
GET total	109.04	120.55	11.51 (-20.1, 43.2) (0.48)

Frequency reported as cpm and amplitude reported as mV. TSS: total symptom score; GET Total: total gastric emptying time. All "Visit 2" values were recorded 5 days after baseline at visit 1. *The significant P values.

CONCLUSIONS: As shown in the tables above, mean symptom scores including nausea, vomiting, anorexia, bloating and abdominal pain were significantly reduced ($p < 0.05$) between baseline (visit 1) and 5 days after baseline (visit 2). Total gastric emptying (GET) was slightly reduced between visits among Single Lead tGES patients, but the difference was not statistically significant ($p = 0.27$). In contrast, GET increased among 2-Lead tGES patients. However, the increment was not statistically significant ($p = 0.48$). Compared to the use of single point electrodes, the use of two low-resolution electrodes allows recording gastric electrical wave propagation with greater detail. Low resolution recording appears to be superior to single point recordings, while awaiting practical high-resolution recordings.

2. Abell T.L., Yamada G., McCallum R.W., Van Natta M.L., Tonascia J., Parkman H.P., Koch K.L., Sarosiek I., Farrugia G., Grover M., Hasler W., Nguyen L., Snape W., Kuo B., Shulman R., Hamilton F.A., Pasricha P.J. Effectiveness of gastric electrical stimulation in gastroparesis: Results from a large prospectively collected database of national gastroparesis registries. Neurogastroenterology and Motility 2019 31:12 Article Number e13714

BACKGROUND: According to the authors, GES for treating gastroparesis symptoms is controversial.

METHODS: This is a retrospective multicenter cohort study in 319 idiopathic or diabetic gastroparesis symptom patients from the Gastroparesis Clinical Research Consortium (GpCRC) observational studies including 238 patients without GES and 81 with GES (Enterra). The authors assessed the effects of GES using change in GCSI total score and nausea/vomiting subscales between baseline and 48 weeks. They used propensity score methods to control for imbalances in patient characteristics between comparison groups.

KEY RESULTS: GES patients were clinically worse (40% severe versus 18% for non-GES; $P < .001$); worse PAGI-QOL (2.2. versus 2.6; $p = 0.003$); and worse GCSI total scores (3.5 versus 2.8; $p < 0.001$). The authors observed improvements in 48-week GCSI total scores for GES versus non-GES: improvement by ≥ 1-point (RR = 1.63; 95% CI = (1.14, 2.33); $p = 0.01$) and change from enrollment

(difference = −0.5 (−0.8, −0.3); p < 0.001). When adjusting for patient characteristics, symptom scores were smaller and not statistically significant: improvement by ≥ 1-point (RR = 1.29 (0.88, 1.90); p = .20) and change from the enrollment (difference = −0.3 (−0.6, 0.0); p = .07). Of the individual items, the nausea improved by ≥ 1 point (RR = 1.31 (1.03, 1.67); p = .04). Patients with GCSI score ≥ 3.0 tended to improve more than those with score < 3.0. (Adjusted p = 0.02).

CONCLUSIONS AND INFERENCES: This study of gastroparesis patients found significant improvements in gastroparesis symptoms. Accounting for imbalances in patient characteristics, only nausea remained significant. Patients with greater symptoms at baseline improved more after GES. A much larger sample of patients is needed to fully evaluate symptomatic responses and to identify patients likely to respond to GES. Key points are shown below.

- Despite several controlled trials, GES for gastroparesis remains controversial. To address this issue, the investigators conducted a prospective controlled trial from a large database of patients with the symptoms of gastroparesis.
- The patients who received GES were clinically worse at baseline and improved in unadjusted analysis, at 48-week follow up. When adjusted by propensity scoring only nausea remained significant. Patients with higher baseline symptoms scores improved more with GES.
- Despite a large prospective cohort study, a larger sample size of patients, preferably as a randomized controlled trial, is needed to identify and predict response to GES in patients with the symptoms of gastroparesis.

3. Omer E., Kedar A., Nagarajarao H.S., Nikitina Y., Vedanarayanan V., Subramony C., Lahr C.J., Abell T.L. Cajal Cell Counts are Important Predictors of Outcomes in Drug Refractory Gastroparesis Patients with Neurostimulation. J Clin Gastroenterol 2019; Volume 53, Number 5, May/June 2019:366–372.

BACKGROUND AND AIMS: Cajal cells serve as the pacemaker cells of the gastrointestinal tract and regulates peristalsis. Based on that fact, it has been hypothesized that a decrease in Cajal cells can lead to gastroparesis and other motility issues. Treatment with medications has a limited efficacy and most resort to GES devices for symptomatic relief. The authors believe that the number of Cajal cells present is directly proportional to symptomatic relief with GES.

MATERIALS AND METHODS: Twenty-three (white female) subjects were recruited from the gastric motility clinic University of Mississippi for this cohort study with the criteria of drug refractory gastroparesis. Symptoms were measured using Likert scale and gastric emptying times were measured pre-GES and post-GES (Enterra). Serosal electrogram measurements were recorded during surgical placement of permanent electrical stimulator under various modes. Cajal cell count scoring via immunohistochemistry were performed during implantation of GES.

RESULTS: The data were grouped in two categories based on the Cajal cells that is ≥2.00 and <2.00. Subjects with higher Cajal cells reported a statistically improvement in gastroparesis symptoms. Significant differences were also noted in the first hour gastric emptying study. The mean group difference is 17.5 (95% confidence interval, 1.41-33.58; p=0.035). Serosal amplitude differences were noted being significantly higher in the group with ≥2 Cajal cells. The two groups showed a decrease in gastroparesis symptoms after GES.

CONCLUSIONS: Electrograms obtained after GES demonstrates immediate improvement in gastric electrical activity and gastroparesis symptoms in patients with relatively higher Cajal cell counts when compared with patients with extensive loss of Cajal cells.

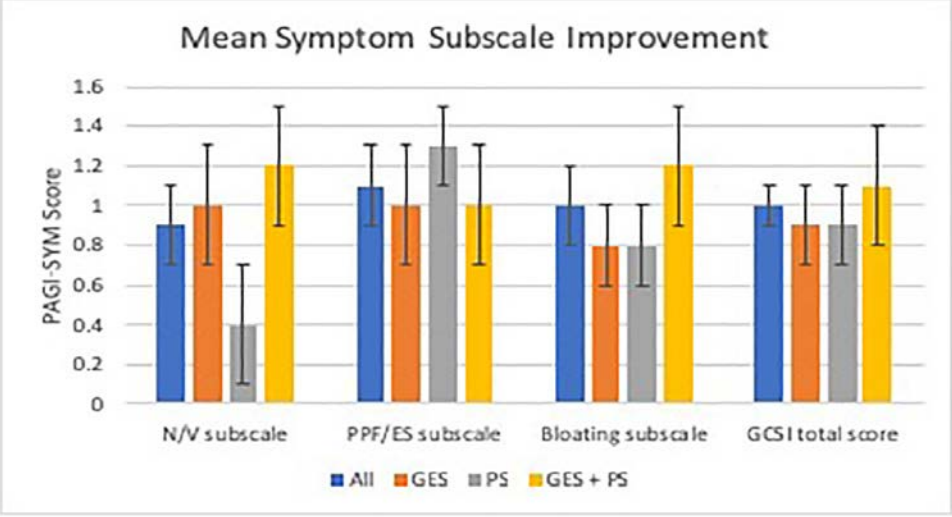
4. Zoll B., Jehangir A., Edwards M.A., Petrov R., Hughes W., Malik Z., Parkman H.P. Surgical Treatment for Refractory Gastroparesis: Stimulator, Pyloric Surgery, or Both? Journal of gastrointestinal surgery: Official Journal of the Society for Surgery of the Alimentary Tract 2019. https://doi.org/10.1007/s11605-019-04391-x.

BACKGROUND: Several surgical options exist for refractory gastroparesis including GES (Enterra) and pyloric surgery (PS) such as pyloromyotomy or pyloroplasty. Few studies exist comparing the outcomes of these surgeries.

AIM: Compare the clinical outcomes of GES, PS, and simultaneous GES+PS for refractory gastroparesis.

METHODS: In this cohort study, patients undergoing surgical intervention were given pre- and post-surgery questionnaires to assess their response to intervention: Patient Assessment of Upper Gastrointestinal Symptoms (PAGI-SYM) grading symptoms and Clinical Patient Grading Assessment Scale (CPGAS) grading response to treatment. Results are expressed as mean ± SE.

RESULTS: One hundred thirty-two patients underwent surgical intervention; Of these 132 patients, 12 were excluded, 7 had pervious histories of stimulator or pyloric surgeries, 3 did not have follow-up, and 2 had gastric stimulators removed for severe pain or infection. Therefore, 120 patients had adequate follow-up and were included in our analysis, including 74 gastric electric stimulators, 25 pyloric interventions (17G-POEM, 4 laparoscopic pyloromyotomy, and 4 laparoscopic pyloroplasty), and 21 GES+PS (5 pyloromyotomy and 16 pyloroplasty). Mean CPGAS improvement overall was 2.8 ± 0.2 ($p < 0.01$): GES+PS had CPGAS score at 3.6 ± 0.5, pyloric interventions 3.1 ± 0.5, and GES 2.5 ± 0.4 ($p > 0.05$). Mean improvement in Gastroparesis Cardinal Symptom Index (GCSI) total score was 1.0 ± 0.1 ($p < 0.01$), with improvement of 1.1 ± 0.2 for GES + PS, 0.9 ± 0.2 for GES, and 0.9 ± 0.2 for PS ($p > 0.05$). GES and GES + PS, but not PS only, significantly improved symptoms of nausea and vomiting ($p < 0.01$). Among gastroparesis subtypes, patients with diabetic gastroparesis had more improvement on nausea/vomiting subscale compared with idiopathic gastroparesis ($p = 0.028$) as shown in the figure below.



Mean GCSI symptom subscale improvement per surgical intervention. Data are expressed average ± standard error.

Comparisons were performed using student t-test with Bonferroni correction. Combined GES+PS and GES alone improved the N/V subscales than PS alone ($p = 0.028$)

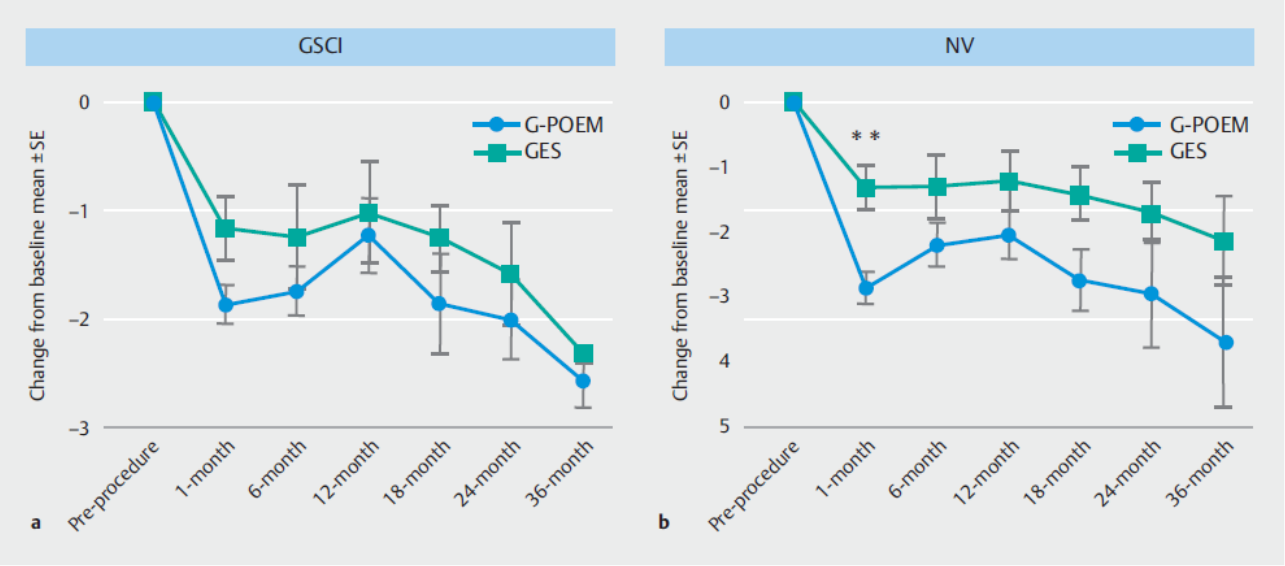
CONCLUSIONS: Patients with refractory symptoms of Gp undergoing GES, PS, or combined GES+PS each had significant improvement of their GCSI total score. GES and combined GES+PS significantly improved nausea/vomiting. These results suggest GES or combined GES+PS appears better for nausea/vomiting predominant refractory Gp.

5. Shen S., Luo H., Vachaparambil C., Mekaroonkamol P., Magdy M., Xu G., Chen H., Xia L., Shi H., Keilin S., Willingham F., Christie J., Lin E., Cai Q. Gastric peroral endoscopic pyloromyotomy versus gastric electrical stimulation in the treatment of refractory gastroparesis: a propensity score-matched analysis of long-term outcomes. Endoscopy 2020 52:5 (349-358).

BACKGROUND: Gastric peroral endoscopic pyloromyotomy (G-POEM) and GES (Enterra; Medtronic, Minneapolis, Minnesota, USA) have been reported as treatment options for refractory gastroparesis. In this study, the authors compared the long-term clinical outcomes of G-POEM versus GES in the treatment of such patients.

METHODS: In this retrospective cohort study, the authors retrospectively evaluated 111 consecutive patients with refractory gastroparesis between January 2009 and August 2018. To overcome selection bias, the authors used propensity score matching (1:1) between G-POEM and GES treatment using Enterra. The primary outcome was the duration of clinical response. The secondary end point was the incidence of adverse events. Postoperative moderate-to-severe pain requiring the use of controlled medication for at least 3 days, therapy-related (including bleeding, perforation, capnoperitoneum, and prepyloric ulcer, and infection, etc.) or device-related (including migration, erosion, shock, and dysfunction, etc.) adverse events were recorded.

RESULTS: After propensity score matching, 23 patients were included in each group. After a median follow-up of 27.7 months, G-POEM had a significantly better and longer clinical response than GES (hazard ratio [HR] for clinical recurrence 0.39, 95 % confidence interval [CI] 0.16 - 0.95; $p = 0.04$). The median duration of response was 25.4 months (95 %CI 8.7 - 42.0) in the GES group and was not reached in the G-POEM group. The Kaplan - Meier estimate of 24-month clinical response rate was 76.6 % with G-POEM versus 53.7 % with GES. GES appeared to have little effect on idiopathic gastroparesis (HR for recurrence with G-POEM versus GES 0.35, 95 %CI 0.13 - 0.95; $p = 0.05$). The incidence of adverse events was higher in the GES group (26.1 % vs. 4.3 %; $p = 0.10$). Moreover, more patients in the GES group than in the GPOEM group received analgesics for at least 3 days for postoperative pain (56.5% versus 13.0%; p=0.002). The G-POEM group had a shorter procedure time (61 versus 82 minutes; $p = 0.001$) but longer mean postoperative hospital stay (2.0 versus 0.5 days; $p < 0.001$) compared with the GES group.



▶ **Fig. 5** Changes from baseline to month 36 by treatment group. **a** Gastroparesis Cardinal Symptom Index. **b** Nausea and vomiting scores. GES, gastric electrical stimulation; G-POEM, gastric peroral endoscopic pyloromyotomy; SE, standard error. $^{**}P < 0.01$.

CONCLUSION: Among patients with refractory gastroparesis, clinical response was better and lasted longer with G-POEM than with GES (Enterra). The positive outcomes with G-POEM are likely to derive from the superior clinical response in patients with idiopathic gastroparesis. Further studies are needed to confirm these findings.

6. Ducrotte P., Coffin B., Bonaz B., Fontaine S., Bruley Des Varannes S., Zerbib F., Caiazzo R., Grimaud J.C., Mion F., Hadjadj S., Valensi P.E., Vuitton L., Charpentier G., Ropert A., Altwegg R., Pouderoux P., Dorval E., Dapoigny M., Duboc H., Benhamou P.Y., Schmidt A., Donnadieu N., Gourcerol G., Guerci B., Leroi A.M., Prevost G., Huet E., Robert M., Disse E., Denost Q., Castel B., Calabrese D., Borot S., Mathieu P., Letessier E., Vavasseur F., Reche F., Mathieu N., Borie F., Penfornis A., Hanaire H., Jeandidier N., Fontaine P. Gastric Electrical Stimulation Reduces Refractory Vomiting in a Randomized Crossover Trial. Gastroenterology 2020; Vol.158, No. 3: 506–514.e2 Clinicaltrials.gov, Number: NCT00903799.

BACKGROUND & AIMS: The authors performed a large, multicenter, randomized, double-blind trial with crossover to study the efficacy of GES in patients with refractory vomiting, with or without gastroparesis.

METHODS: For 4 months, the authors assessed symptoms in 172 patients (66% women; mean age ± standard deviation, 45 ± 12 years; 133 with gastroparesis) with chronic (>12 months) of refractory vomiting (idiopathic, associated with a type 1 or 2 diabetes, or postsurgical). A GES device (Enterra) was implanted and left inactivated until patients were randomly assigned, in a double-blind manner, to groups that received 4 months of stimulation parameters (14 Hz, 5 mA, pulses of 330 μs) or no stimulation (control); 149 patients then crossed over to the other group for 4 months.

Patients were examined at the end of each 4-month period (at 5 and 9 months after implantation).

Primary endpoints were vomiting score, ranging from 0 (daily vomiting) to 4 (no vomiting), and the quality of life, assessed by the Gastrointestinal Quality of Life Index scoring system. Secondary endpoints were changes in other digestive symptoms, nutritional status, gastric emptying, and control of diabetes.

RESULTS: During both phases of the crossover study, vomiting scores, ranging from 0 (daily vomiting) to 4 (no vomiting), were higher or better in the group with the device on (median score, 2) than the control group (median score, 1; $p < 0.001$), in diabetic and nondiabetic patients. Vomiting scores increased significantly when the device was ON in patients with delayed ($p < 0.01$) or normal gastric emptying ($p = 0.05$).

Table 3. Vomiting Frequency Score During the Crossover Phase, %

Mode	ITT population (N = 172)	Diabetic Patients (n = 72)	Nondiabetic Patients (n = 100)
ON			
≥1 vomiting episode/mo (score, 0–2)	50.3	44.4	54.7
<1 vomiting episode/mo (score, 3 or 4)	49.7	55.6	45.3
OFF			
≥1 vomiting episode/mo (score, 0–2)	64.4	60.3	67.4
<1 vomiting episode/mo (score, 3 or 4)	35.6	39.7	32.6
	P = .0006	*P* = .025	*P* = .007

Gastric emptying was not accelerated during the ON period compared with the OFF period. Having the GES turned on was not associated with increased quality of life.

ADVERSE EVENTS: A total of 101 adverse events were reported in the study, with 45 therapy or device-related events: abdominal wall pain at the implantation site (n = 28), infections at the abdominal pouch level (n = 16), hematoma (n = 1). In 3 cases, the device-related adverse events were serious enough to prompt device removal.

CONCLUSIONS: GES reduced the frequency of refractory vomiting in patients with and without diabetes, although it did not accelerate gastric emptying or improve quality of life.

Literature Review Results

In the six articles selected in this review, the studies may have included pediatric or adolescent patients. These papers were included in this review to be as inclusive as possible, given the limited literature on Enterra. Because these studies included adult subjects along with possible pediatric subjects, it is not clear if safety and probable benefits derived by the mixed cohort were experienced specifically by pediatric subjects.

a. Probable Benefit Results found in the Literature

Hasanin et al (2019), Abell et al (2019), Zoll et all (2019) and **Ducrotte et al (2020**) provide evidence of the probable benefit of Enterra reducing gastroparesis symptoms including nausea and refractory vomiting as assessed by the Gastroparesis cardinal symptom index (GCSI) and Clinical Patient Grading Assessment Scale (CPGAS). In these publications, while GES reduced the frequency of refractory vomiting, it did not accelerate gastric emptying or improve quality of life. The study published by **Omer et al (2019)** when evaluating Cajal cell counts as predictors of outcomes in drug refractory gastroparesis patients with Enterra, found an improvement in symptomatology after GES. The Study by **Shen et al (2020)** compared Gastric peroral endoscopic pyloromyotomy (G-POEM) and GES (Enterra). Although patients in both groups reduced the refractory gastroparesis symptomatology; clinical response, including nausea and vomiting, was better and lasted longer with G-POEM than with GES (Enterra). **Hasanin et al (2019)** showed that GES in addition to reducing nausea and vomiting; anorexia, bloating and abdominal pain were also significantly reduced. The need for nutritional support was not reported in any of these studies.

b. Safety Results found in the Literature

In the study by **Ducrotte et al (2020)**, out of 172 patients, 101 adverse events were reported, with 45 therapy or device-related events including abdominal wall pain at the implantation site (n = 28), infections at the abdominal pouch level (n=16), and hematoma (n = 1). In three patients, the device-related adverse events were serious enough to prompt device removal. **Abell et al (2019)** studied 81 patients treated with GES. These patients were found in need of having higher numbers of medications, including opioids (4.8 versus 4.1; p = 0.004). However, at baseline, GES patients had higher (i.e., worse) GCSI total score (3.5 versus 2.8; p < 0.001), in all the GCSI sub-scores, and in almost all the PAGI-SYM symptom severity scores. GES patients were also lower (i.e., worse) PAGI-QOL baseline score (2.2 versus 2.6; p = 0.003), but GES and non-GES patients differ in demographic, socioeconomic, behavioral indicators, and anxiety scores. **Shen et al (2020)** reported a higher incidence of adverse events in the GES group as compared to Gastric peroral endoscopic pyloromyotomy (G-POEM) group (26.1% versus 4.3 %; p = 0.10). Moreover, more patients in the GES group than in the GPOEM group received analgesics for at least 3 days for postoperative pain (56.5% versus 13.0%; p=0.002). **Zoll et al (2019)** reported that among 132 patients treated with Enterra, two had their devices removed for severe pain or infection. **Hasanin et al (2019)** and **Omer et al (2019)** did not report safety results.

c. Critical Assessment of the Literature

The current systematic literature review found six pertinent articles including a total of 618 patients treated with Enterra. All of them provide evidence of the probable benefit of Enterra reducing gastroparesis symptoms. Device-related events included abdominal wall pain at the implantation site, infections at the abdominal pouch level, and hematoma. There were 3 cases in which the device-related adverse events were serious enough to prompt device removal. Enterra patients were found in need of having higher numbers of medications, including opioids when compared to Gastric Peroral Endoscopic Pyloromyotomy (G-POEM).

The results of this systematic literature review should be interpreted considering key limitations. First, our review only identified six papers for which it could not be confirmed that these studies included pediatric patients (< 22 years-of-age) because no age ranges were reported. Hasanin et al (2019) article was published before May 1, 2019. However, the paper was included in this review to be as inclusive as possible, given the limited literature on Enterra. Secondly, there are common study limitations such as, retrospective study design in two of the studies, lack of randomization, and unknown sample size for pediatric patients.

Literature Review Conclusion

The studies found in this literature review suggest probable benefits of Enterra with respect to improvement in long-term gastroparesis symptoms. Despite the reduction of symptoms, some patients with gastroparesis who are implanted with Enterra may experience device-related adverse events that require additional surgery. The findings of this systematic literature review should be interpreted considering the insufficient evidence reported in terms of small number of papers with unknown sample size of pediatric patients. These factors limit our ability to make any firm conclusion about the probable benefits and safety of Enterra in the pediatric population.

Although it is difficult to determine if these findings are consistent with results of the Enterra systematic literature reviews presented at the previous PAC meetings, the current findings do not rise safety concerns and support the probable benefit of this device.

OVERALL SUMMARY

The FDA did not identify any new safety signals during this review of the Enterra annual report received, the MDRs received, and the peer-reviewed literature published, since our last report to the PAC.

The FDA believes that the HDE for this device remains appropriate for the pediatric population for which it was granted. The FDA will continue to implement the PAC's recommendations in addition to our routine monitoring of the safety and distribution information for this device.

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