FDA Executive Summary

Prepared for the
Fall 2022 review by 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 post-marketing 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 FDA reviewed in the year following our 2021 report to the PAC. It includes data from the manufacturer's annual report, post-market 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

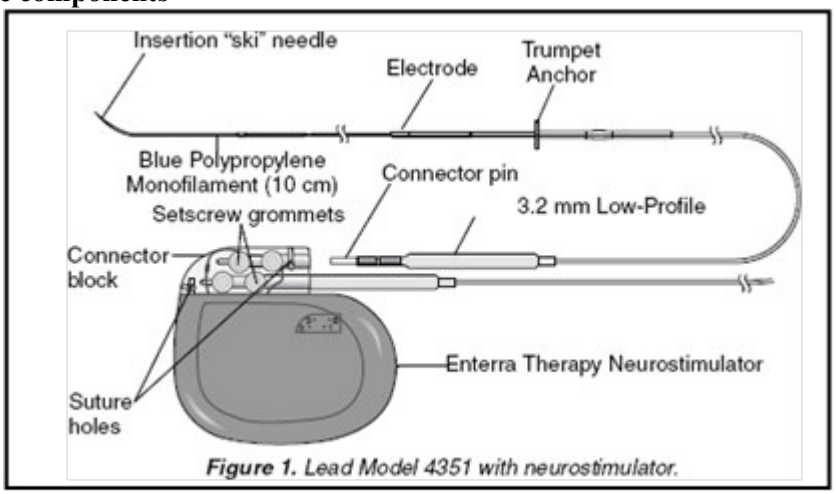
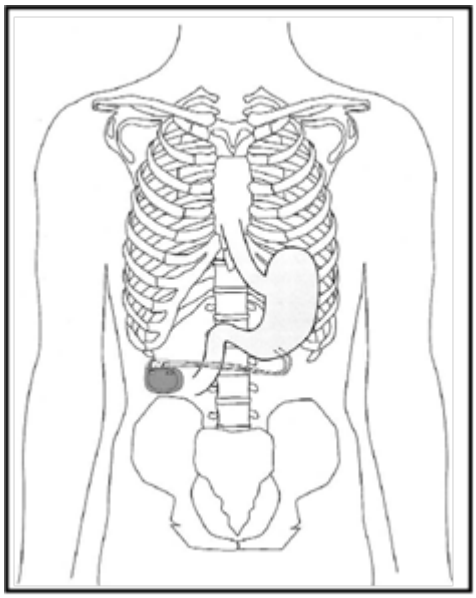


Figure 1. Lead Model 4351 with neurostimulator.

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 Act) 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. The approved ADN for Enterra is 8,000 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 02/01/21 – 01/31/22	Devices Sold From 02/01/20 – 01/31/21	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
37800 Implantable Neurostimulator	2,127	1,895	2,053	1,951	2,017	1,865	1,611
3116 Implantable Neurostimulator	0	0	0	0	0	0	208
4351 Intramuscular Lead	2,131	1,874	1,988	2,106	2,535	2,462	2,151

TABLE 2: Number of devices implanted in pediatric patients

Reporting Period: 02/01/21 – 01/31/22	Total N (newly implanted this period)	Female by age in years			Male by age in years			Gender Unknown by age in years		
		<2	2<18	≥18<22	<2	2<18	≥18<22	<2	2<18	≥18<22
Newly implanted pediatric patients during this reporting period	48	0	14	26	0	3	4	0	1	0
Total pediatric patients with active implants this reporting period	236	0	45	116	0	33	37	0	3	2

MEDICAL DEVICE REPORT REVIEW

Overview of MDR database

The MDR database is one of several important post-market surveillance data sources used by the FDA. Each year, the FDA receives several hundred thousand medical device reports 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 important post-market 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 rate 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 subject 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 MDR database was searched using the following search criteria:

A. Search 1
- Product Code: LNQ
- Report Entered: between May 1, 2021 and April 30, 2022

B. Search 2
- Brand name: ENTERRA%
- Report Entered: between May 1, 2021 and April 30, 2022

The MDR searches yielded 173 MDRs received between May 1, 2021 and April 30, 2022. The MDRs included 0 deaths, 116 injuries and 57 device malfunction reports. These 173 MDRs are discussed below. Four additional MDRs found using the search methodology were excluded from further analysis because the MDRs described events reported in seven journal articles. Four of these journal article were excluded from the MDR analysis and the literature review because the articles were outside the defined literature search parameters. The two remaining journal articles are discussed in the literature review section of this document.

Event Type by Patient Age

Table 3 provides the distribution of the MDRs by reported event type and age grouping. In this year's reporting period, there were two patients in the pediatric age category of 18-21 years old with serious injury MDR reports. There were no pediatric reports of deaths or malfunctions this reporting period.

TABLE 3: Overall event type distribution by patient age

Event Type	Total MDR Count 5/1/2021 – 4/30/2022	MDR Count by Patient Age (years)			
		Pediatric (< 18)	Pediatric (18-21)	Adult (≥ 22)	Indeterminate (Age blank)
Death	0	0	0	0	0
Injury	116	0	2	95	19
Malfunction	57	0	0	44	13
Total MDR Count	173	2		139	32

Comparison of Current Patient Event Type Information with Previous Years

Table 4 compares the event type distribution for this year's results to prior years. There was a 9% decrease in injury MDR reports this year and no change in death or malfunction reports compared to last year's PAC reporting period.

TABLE 4: Overall event type distribution by reporting year

	Total MDR Count				
Event Type	**2018 PAC Meeting 5/2017 - 4/2018**	**2019 PAC Meeting 5/2018 4/2019**	**2020 PAC Meeting 5/2019 - 4/2020**	**2021 PAC Meeting 5/2020 - 4/2021**	**2022 PAC Meeting 5/2021 - 4/2022**
Death	0	1	0	0	0
Injury	285	184	117	127	116
Malfunction	150	120	61	57	57
Total MDR Count	435	305	178	184	173

Patient Gender and Age Information

In the 173 MDRs received from May 2021 to April 2022, 139 patients were identified as adult (≥22 years old) and 32 MDRs did not provide a patient age (indeterminate age reports). Two MDRs contained pediatric subjects.

There were 158 MDRs that noted the gender of the patient: 134 MDRs were identified as female (4 reports involved the same patient) and 24 MDRs were identified as male. The remaining 15 MDRs did not include the patient gender. Review of the 15 unknown gender report narrative sections to determine gender identifiers (male or female, she or her, he or him, etc.) did not result in identifying additional female or male noted events. These reports identified the individual involved in the event only as "the 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. A total of 103 MDRs (out of 173) provided a valid event date and date of implant. 45 reports did not include a valid event or explant date. A TTEO could not be determined for these reports.

Table 5 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	0	1	21	1
31 days - ≤ 1 year	0	1	31	0
> 1 year – ≤ 5 years	0	0	39	0
> 5 years	0	0	9	0
Totals	0	2	100	1

Characterization of the MDR Narratives of the Pediatric Events

- A 19-year-old female patient had a device that migrated downward stretching the pocket. The patient had surgery on 4/20/2022 and the healthcare provider stitched the device. No further complications were reported on 5/27/2022.

- Information was received from a healthcare provider on a 20-year-old male patient that was implanted with an implantable neurostimulator for gastric stimulation on 4/15/2021. It was reported the patient experienced symptom returning 3 months post-op and 30 pounds of weight gain. Post-implant, the patient experienced loss of appetite on 7/9/2021 and return of frequent vomiting one week later. The healthcare provider (HCP) performed an impedance check and determined the impedance was out of range. On 9/9/2021 additional information was received from the HCP stating the patient was scheduled for surgery to troubleshoot the issue and potentially replace the battery and leads. On 11/1/ 2021 the HCP reported device removal/replacement was not planned. The original battery and leads are still in place. When the battery was taken out of the abdominal pocket, the impedance read within range.

Characterization of the Time to Event Occurrences in the adult and indeterminate age populations

For the adult the population with TTEO data, issues with the use of the device 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". In comparison to last year's analysis, the following issues continue to be reported:

- Pain and inappropriate simulation/shocking secondary to positioning of the device or battery and lead issues

- Symptoms of nausea and vomiting and/or loss of therapeutic effect secondary to impedance issues or battery issues

- Infection, lead, battery and erosion issues

In the 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 is often caused by patient device interaction problems, such as patient losing weight after implant; device battery/lead position; or setting of the device. Device reposition, battery or leads revision/replacement or turning down the voltage setting relieve the problems in most cases.

There were 34 reports associated with complaints of pain and 27 reports that specified shock. In one report, a patient was implanted with an implantable neurostimulator (INS) for a gastrointestinal/pelvic floor treatment. It was reported the patient had pain at the pocket site. The settings were reported to be correct and no environmental factors were listed. A physical examination was performed as well as a pocket revision to move the INS to alleviate the pain. The issue was resolved at the time of this report.

There were 50 reports of "No Clinical Signs or Symptoms or Conditions". This type of report can mean there were no health consequences or impact to the patient. These reports can also vary including reports of patients needing a physician to tighten a screw, reports of patients with batteries depleted and replaced and patients with devices out of range and requiring the voltage adjusted. This reporting year also included reports with insufficient information, reports not device related and reports with no lasting health impact to patients.

Electric shock, pain and discomfort reports continued to occur this reporting period. There were 34 reports of pain, 27 reports of electric shock and 6 reports of undesired nerve stimulation. A challenge many patients face with these painful clinical symptoms include getting relief after multiple emergency department visits. For example, one MDR stated the patient began feeling abdominal pain/cramping at the pocket site with waves of shock. A healthcare provider saw the patient in the emergency room, and the voltage was turned down from 2.5 volts to 1.2 volts. The patient returned to the emergency room and a computed tomography (CAT) scan was performed, which appeared normal. The issue was not resolved at the time of the report and no surgical intervention occurred. On 11/30/2021 additional information was received from a manufacturer representative. The representative reported the patient's doctor moved the battery to a different site due to pain on 11/2/21.

Nausea/vomiting continued to occur this reporting period. There were 37 reports of nausea/vomiting, which often lead to weight loss. One patient experienced a return of nausea and vomiting with intermittent shock. The patient did not report any falls or trauma to the device. Impedance checks were done and the healthcare provider reported normal impedance. X-rays of the stomach and esophagogastroduodenoscopy were both inconclusive. The issue was reported to be resolved with the leads being replaced and the INS still in use.

Pocket erosion and decreased therapeutic effectiveness continued to occur this reporting period. 15

MDRs reported battery depletion, which led to patient complaints of decreased therapy effectiveness. These events generally occur from 1 year after placement to 5 years, with typical resolution noted as reprogramming or replacement of the battery.

Infection was reported in 18 MDRs with 4 MDRs coming from the same patient experiencing multiple implant and explant procedures. It was reported that this patient had an infection from the previous surgery and the device was removed and replaced. No further complications were reported/anticipated at that time. On 10/14/2021 additional information was received from the patient. The patient reported that on 12/09/2021 they had been on antibiotics for months and had been in the hospital for surgery. The patient reported a weight change from 250 pounds to 190 pounds caused by or related to the device, therapy and/or implant procedure.

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

Table 6 provides the most prevalent reported patient problem codes found in the MDRs reviewed during this reporting period classified by patient age. The top reported patient problem is "Pain" (n=73), which increased from the previous year (n=65). The pain code is characterized by inappropriate stimulation/shocking/burning as well as cramping/discomfort and migration of the device or its component. "Insufficient Information" is the second most prevalent code (n=52) and "No Clinical Signs or Symptoms or Conditions " is the third most prevalent code (n=50). Overall, this year's patient problem codes do not present significantly new or increased safety concerns compared to last year.

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

Patient Problem	Total Patient Problem Code	Total Patient Problem Code by Patient Age (years)			
		Pediatric (< 18)	Pediatric (18 to 21)	Adults (≥ 22)	Indeterminate (Age blank)
Pain/ Discomfort/ Abdominal Pain/Muscle Spasms/Burning	73	0	0	68	5
Insufficient information	52	0	1	42	9
No Clinical Signs or Symptoms or Conditions	50	0	0	39	11
Electric Shock/Nerve Stimulation, Undesired	44	0	0	28	16
Vomiting/Nausea	37	0	1	35	1

[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.

Weight changes	7	0	0	7	0
Unspecified Infection/ Sepsis/Seroma	29	0	0	18	11
Erosion/ Pocket Erosion	16	0	0	4	12
Total Count	307	0	2	240	65

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

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

Table 7 provides the most prevalent reported device problems for all MDRs differentiated by patient age. The top three reported device problem codes are the same as the previous reporting period with "Adverse event without identified device or use problem" (n=47) ranking first, "Migration or expulsion of device" (n=40) ranking second, and "Impedance Problem" (n=34) ranked third this year.

The reports with "adverse event without identified device or use problem" are related to patient issues in which the device is functioning or has no identified device problems, but the patient complained of ill-defined pain, infection or device intolerance issues. Most of the corresponding patient problem codes were nausea, vomiting, and shocking sensation. Adjustments to the device voltage, device placement and replacement of the leads or battery were reported interventions in these patients. The reports of "Inappropriate Shock" typically involved the position of device, or electromagnetic compatibility/interference. "Energy output problem" and "Failure to deliver energy are related to nausea, vomiting, shocking and decreased therapeutic effect issues.

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

Device Problem	Total Device Problem Code	Total Device Problem Code by Patient Age (years)			
		Pediatric (< 18)	Pediatric (18 to 21)	Adults (≥ 22)	Indeterminate (Age blank)
Adverse Event Without Identified Device or Use Problem	47	0	1	40	6
Migration or expulsion of device	40	0	1	36	3

[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.

High impedance, Impedance Problem	34	0	1	33	0
Battery Problem, Premature Discharge of Battery	22	0	0	20	2
Inappropriate/Inadequate Shock/Stimulation	27	0	0	27	0
Energy Output Problem, Failure to Deliver Energy, Intermittent Continuity, Therapy Delivered to Incorrect Body Area	18	0	0	15	3
Break, Material Deformation, Degraded	18	0	0	15	3
Electromagnetic Compatibility Problem, Electromagnetic Interference	17	0	0	16	1
Total Device Problem Code Count	223	0	3	202	18

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 reporting periods. There were two pediatric MDRs this reporting period. Previous pediatric MDRs have involved complaints of nausea, vomiting, pain, shock and infection, corresponding to device issue related to "Therapeutic Response, unexpected/decreased", and "inappropriate shock." These complaints and device problems were most often due to device setting, battery and lead issues. Adjustments of the device settings, follow up with the treating physician, hospitalization and request to explant the device were noted interventions.

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

Clinical Events	Occurrences in MDRs** 5/1/2021- 4/30/2022	Occurrences in MDRs** 5/1/2020- 4/30/2021	Occurrences in MDRs** 5/1/2019– 4/30/2000
Nausea/Vomiting	1	1	1
Therapeutic Response, unexpected/Paresis	0	1	3

Pain/Discomfort/Abdominal pain/ Burning sensation	0	2	2
Electric Shock/Nerve Stimulation, Undesired/ [Inappropriate Electric Shock]	0	0	1
Infection	0	0	1
Therapeutic Effects, Unexpected	0	1	0
Insufficient Information/Complaint Ill-Defined	1	1	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.*

Re-Interventions in Pediatric Patients from 5/1/2020 through 4/30/2021

Re-interventions addressing clinical events are listed in Table 9. This table summarizes the re-interventions identified in the narratives and the causal events leading to these re-interventions. Re-interventions are events that required an additional procedure after the initial placement of the device. There were two pediatric MDRs this reporting period.

TABLE 9: Re-interventions in pediatric patients* (5/1/2021-4/30/2022)

Re-Interventions	Number of Re- Interventions	Causal Event
Replacement/Repositioning Device or Battery	2	• Shocking/burning • Battery depletion
Explant Device or INS	0	• Infection • Pain
Reprogramming/ Calibration	0	• Loss oftherapeutic effect • Shocking/jolting/burning
Hospitalization/Emergency room	1	• Infection • Loss oftherapeutic effect • Pain/discomfort • Vomiting/hematemesis

Surgery/impedance check	1	• Loss of therapeutic effect • Minor Injury/ Illness/ Impairment • Poor Intake
Surgery (gastrostomy) /Feeding tube	0	• Loss of therapeutic effect • Nausea/vomiting/poor intake
Office follow-up treatment	0	• 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.*

MDR Review Conclusions

- There were two pediatric MDR reports submitted for the Enterra Therapy System between May 1, 2021 and April 30, 2022.
- The number and type of pediatric MDRs this year are similar to previous reporting periods.
- The type and number of overall MDRs reported in the current reporting period are similar to the previous reporting period.
- The TTEO was calculated for 103 reports of 173 MDRs based on the available information contained in the reports. MDRs continue to occur most frequently from > 1 year up to ≤ 5 years from the date of implant.
- Patient problems observed this reporting period were similar to problem codes observed in the last reporting period. Complaints of return of symptoms (nausea, vomiting), decreased therapeutic effect, as well as incidences of shock appear to center around the position of device and/or connection/malfunction issues involving the leads or batteries.
- Device problems observed this reporting period were similar to problem codes observed in the last reporting period. Reports continue to identify device functionality issues with the device lead including migration, malfunction and battery depletion issues.

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 review is an update to the literature reviews presented at the Pediatric Advisory Committee (PAC) meetings in 2014, 2015, 2016, 2017, 2018, 2019, 2020 and 2021. 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?

Methods

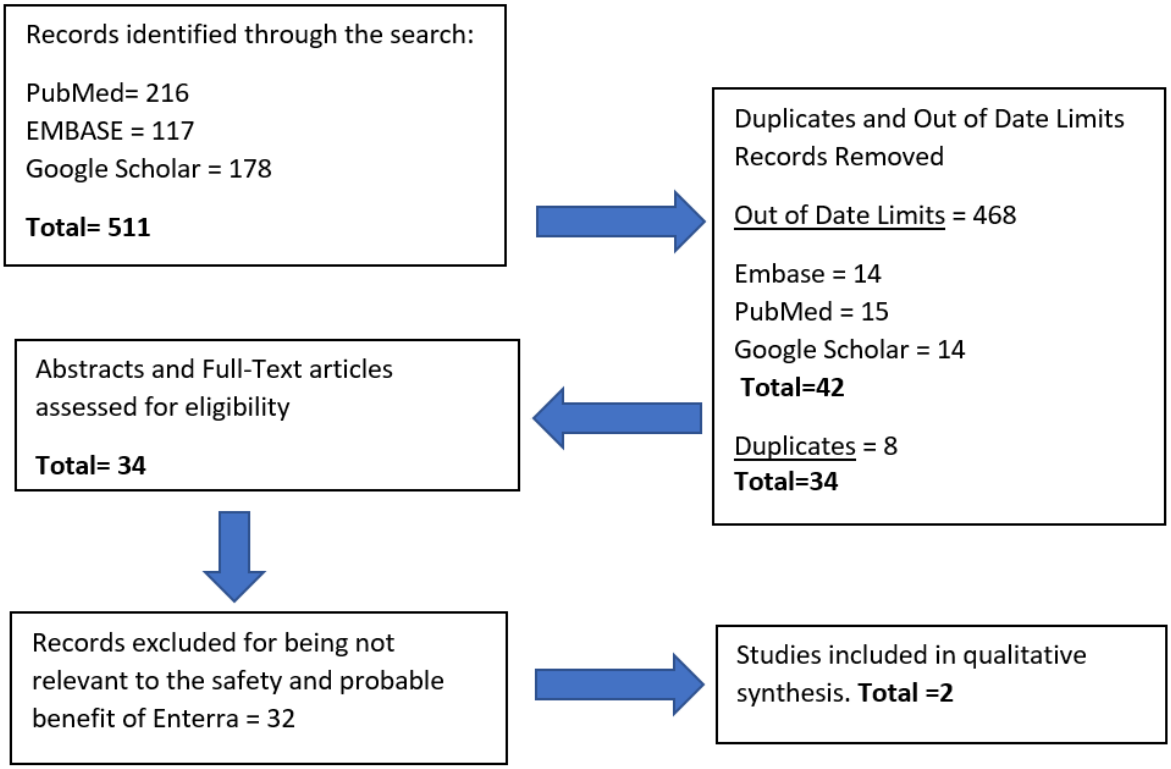
The search was limited to studies published since the last PAC meeting update (May 1, 2021 to April 30, 2022). The results were filtered for studies in human subjects, studies published in English, and excludes articles indexed to animals when not also indexed to humans. This search yielded a total of 97 citations (216 in PubMed, 217 in Embase and 187 in Google Scholar). After a review of titles, abstracts, and selected full texts, 2 articles were selected for full review and assessment as shown in "Figure 1 Article Retrieval and Selection". On May 20, 2022, 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 neuromodulat*)) AND English [la] AND ("infant, newborn" [mh] OR "infant" [mh] OR "child, preschool" [mh] OR "Child"[Mesh] OR "adolescent" [mh] OR "young adult" [mh] OR newborn* OR infant* OR child* OR preschool* OR adolescent* OR "young adult" OR pediatric* OR boy OR girl OR toddler*) AND ("2021/05/01"[Date - Create] : "2022/04/30"[Date - Create] OR "2021/05/01"[Date - Publication] : "2022/04/30"[Date - Publication])) NOT ("animals"[MeSH Terms] NOT "humans"[MeSH Terms]) =15 references

- 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 [english]/lim AND ([newborn]/lim OR [infant]/lim OR [child]/lim OR [preschool]/lim OR [adolescent]/lim OR [young adult]/lim OR newborn* OR neonat* OR infant* OR child* OR preschool* OR adolescen* OR 'young adult' OR pediatric* OR boy OR girl OR toddler*) AND [01-05-2021]/sd NOT [30-04-2022]/sd) NOT ([animals]/lim NOT [humans]/lim) =14 references

- Google Scholar
  "Enterra" AND ("gastric electrical stimulation" OR "gastric electrostimulation" OR "gastric pacemaker" OR "gastric pacing" OR gastroparesis OR "gastric neuromodulation") AND (infant OR child OR adolescent OR pediatric OR "young adult"). Limited to 2021-2022 =14 references

Figure 3. Article Retrieval and Selection



Summaries of Relevant Articles

1. Orsagh-Yentis, et al. Gastric electrical stimulation improves symptoms and need for supplemental nutrition in children with severe nausea and vomiting: A ten-year experience.

Background: The objective of this study was to evaluate the long-term efficacy and safety of gastric electrical stimulation (GES) and to evaluate patient benefit and satisfaction with the treatment.

Methods: Using a prospective registry, the investigators identified patients aged <21 years treated with GES at their institution between 2009 and 2019. Eighty-five patients (68.2% female, median age 15.8 years) completed a trial of temporary GES due to severe nausea and vomiting. Seventy-seven (90.6%) had a positive response and underwent permanent stimulator placement. The study compared symptoms, route of nutrition, and medication usage at baseline to follow-up timepoints. Factors associated with improvement were evaluated. Complications and need for battery replacement were recorded. Families were contacted to administer the Glasgow Children's Benefit Inventory (GCBI) and a parent satisfaction questionnaire.

Key Results: Seventy-seven (90.6%) subjects had a positive response and underwent permanent stimulator placement. Use of tube feeding or parenteral nutrition (PN) decreased from 72.7% at baseline to 29.9% at the most recent follow-up ($p < 0.001$). Higher baseline vomiting severity was associated with the ability to stop supplemental nutrition by 1 month ($p < 0.05$). Fourteen patients (18.2%) had complications, primarily due to stimulator-associated discomfort. Median GCBI was +52.1, indicating health-related benefit. At a median of 4.3 years after starting GES, 29 patients

(37.7%) required battery replacement. Of these 29 patients, one had seven battery replacements during a nine-year period. Fourteen (18.2%) had complications that necessitated further surgery. The most common reasons for surgery were patients experiencing an uncomfortable shocking sensation or feeling that the GES was moving or malfunctioning. Of note, the electrodes of one patient whose stimulator had been placed at an outside facility eroded through the gastric wall. That patient's stimulator was removed and permanently replaced. The stimulator was ultimately removed in ten patients (13.0%). Seven of these patients had a lack of response to stimulation. One other patient's stimulator was removed when an MRI was needed. The last three of these patients improved with GES and had their stimulators removed after a trial in which their stimulators were turned off.

Conclusions: Children with severe nausea and vomiting treated with GES experienced significant and durable improvement in symptom severity and their ability to tolerate oral nutrition.

2. Hawa K, et al. Behavioral factors and gastric electrical stimulation in children with nausea and vomiting.

Background: The objective of this study was to evaluate whether behavioral factors affect outcomes in children with chronic nausea and vomiting treated with GES.

Methods: The investigators performed a prospective cohort study and survey. The study included patients <21 years of age with chronic nausea and vomiting treated with GES from 2009-2018 referred to the Motility Clinic at Nationwide Children's Hospital in Columbus, Ohio. Demographics, medical history, and past treatment were recorded. Patients completed a Symptom Monitor Worksheet (SMW), recorded GI medications and route of nutrition at baseline and follow up visits. The investigators contacted patients in 2019-2020 to repeat a SMW and administer the Connor Davidson Resilience Scale-10 (CD-RISC-10), Life Orientation Test-Revised (LOT-R), and a mental health and school/activity survey. The investigators evaluated whether behavioral factors were associated with improvement in SMW or ability to stop supplemental nutrition.

Results: A total of 34 patients (median age 14 years, range 2-19; 70.6% female) were included in the study. At baseline, 23 (67.6%) needed supplemental nutrition (22 tube feeding and 5 parenteral nutrition), 13 (38.2%) had an anxiety disorder and 10 (29.4%) had depression. Sixteen patients (47.1%) were attending school full time but the majority were missing school most or all of the time. Most patients (61.8%) had an Individualized Education Plan (IEP). Nearly all (97%) reported missing activities some of the time or more. Patients were contacted at a median of 5.2 years after starting GES. Patients attending school full time had better SMW scores (average 30.5) than those with partial or no attendance (41.3 and 40.0 respectively). Higher LOT-R scores, indicating a more optimistic outlook, were associated with better SMW as well (correlation coefficient -0.60). After 1 year of GES, SMW scores improved by 14.7+/-15.8 and 13 of 23 patients (57%) no longer needed supplemental nutrition. Older age and not having an IEP were associated with improvement in SMW ($p=0.02$, 0.06 respectively). Anxiety, depression, and CD-RISC-10 were not associated with improvement in SMW or no longer needing supplemental nutrition.

Conclusions: In this cohort of children treated with GES, older age, optimism and ability to participate in school were associated with symptomatic improvement. The presence of anxiety or depression did not affect the likelihood of improvement.

Probable Benefit from Literature

Orsagh-Yentis et al. (2021): single arm prospective cohort study with 12 months follow-up in 85 children with severe nausea and vomiting reported 77 (90.6%) with a positive response and permanent stimulator placement. The investigators found that patients treated with GES experienced

significant and durable improvement in symptom severity and their ability to tolerate oral nutrition. Use of tube feeding or parenteral nutrition decreased from 72.7% at baseline to 29.9% at the most recent follow-up ($p < 0.001$). Median Glasgow Children's Benefit Inventory (GCBI) was +52.1, indicating health-related benefit.

Hawa et al (2021): single arm prospective cohort study in 34 children evaluated the impact of behavioral factors in children receiving GES for the treatment of nausea and vomiting with a 5.2 years median follow-up after starting GES. Children treated with GES, older age, optimism, and ability to participate in school were associated with symptomatic improvement.

Safety from Literature

Orsagh-Yentis et al (2021) reported 14 patients (18.2%) with complications, primarily due to stimulator-associated discomfort and 29 (37.7%) required battery replacement. The most common reasons for surgery were patients experiencing an uncomfortable shocking sensation or feeling that the GES was moving or malfunctioning. Of note, the electrodes of one patient whose stimulator had been placed at an outside facility eroded through the gastric wall. Although it does not seem to be more frequent than previous reporting years, device migration continues to be reported as an important adverse event that needs to be resolved with surgery. FDA will continue monitoring these adverse events.

Hawa et al (2021) did not report safety results.

Critical Assessment of the Literature

The current systematic literature review found two relevant articles, out of 511 publications including a total of 119 patients. Both articles provide evidence of the probable benefit of Enterra reducing gastroparesis symptoms. Device-related adverse events included complications primarily due to stimulator-associated discomfort, device migration and battery replacement. The results of this systematic literature review should be interpreted with consideration of its key limitations. First, our review only identified two articles, and it could not be confirmed that one of these studies included only Enterra or other types of GES devices. Secondly, there are study design limitations such as no control groups, lack of randomization and small sample size. The report from Hawa et al (2021) is a meeting abstract that does not include any details regarding the safety and effectiveness results. FDA was not able to obtain additional information on this study.

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 were implanted with Enterra experienced device migration and other device-related adverse events that required additional surgery. The limitations of the literature review prevent making firm conclusions about the probable benefits and safety of Enterra in the pediatric population. However, the current findings do not raise significant safety concerns and the results continue to support the probable benefit of Enterra.

OVERALL SUMMARY

FDA did not identify any new safety signals during this year's review of the Enterra annual report, MDRs or the peer-reviewed literature published since the last report to the PAC. FDA concludes the HDE for this device remains appropriate for the pediatric population for which it was granted. FDA will continue routine surveillance including MDR and literature reviews. FDA will report the following to the PAC in 2022: Annual distribution number, Literature review and MDR review.

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