FDA Executive Summary

Prepared for the
March 24, 2015 meeting of the
FDA's Pediatric Advisory Committee

H020007

Medtronic Activa Neurostimulator for Dystonia Treatment

I. INTRODUCTION

In accordance with the Pediatric Medical Device Safety and Improvement Act, this review provides a safety update based on the post-marketing experience with the use of the Medtronic Activa® Dystonia Therapy in pediatric patients since approval in 2003. The purpose of this review is to provide the Pediatric Advisory Committee (PAC) with post-marketing safety data so the committee can advise the Food and Drug Administration (FDA) on whether they have any new safety concerns and whether they believe that the HDE remains appropriately approved for pediatric use?

The Medtronic Activa® Dystonia Therapy system is indicated for unilateral or bilateral stimulation of the internal globus pallidus (GPi) or the subthalamic nucleus (STN) to aid in the management of chronic, intractable (drug refractory) primary dystonia, including generalized and/or segmental dystonia, hemidystonia, and cervical dystonia (torticollis) in patients seven years of age or above.

This memorandum summarizes the safety data regarding H020007 through the present day including pre-market clinical data, post-market medical device reporting (MDR) for adverse events, and peer-reviewed literature regarding safety data associated with the device.

II. ANNUAL DISTRIBUTION NUMBER (ADN) AND US DEVICE DISTRIBUTION DATA

The Food and Drug Administration Safety and Innovation Act (FDASIA) amended section 520(m) of the Federal Food, Drug, and Cosmetic Act (FD&C) and allowed 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). The ADN was defined to be the number of devices "reasonably needed to treat, diagnose, or cure a population of 4,000 individuals in the United States." FDA has interpreted that to imply that the calculation of the ADN should be 4,000 multiplied by the number of devices reasonably necessary to treat an individual. The number of devices implanted in the U.S. in 2014: 776 implants (Note that there is also one dystonia implant registered in CY 2014 without an implant date) Number of devices implanted in pediatric patients in the U.S. in 2014 (<22 years): 148 implants (Note that there are also 10 Dystonia implants registered during CY 2014 without age information)

III. POSTMARKET DATA: MEDICAL DEVICE REPORTS (MDRs)

Overview of Manufacturer and User Facility Device Experience (MAUDE) Database

Each year, the FDA receives several hundred thousand medical device reports (MDRs) of suspected device-associated deaths, serious injuries and malfunctions. The MAUDE 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 used in a "real world" setting, including
  - rare, serious, or unexpected adverse events
  - adverse events that occur during long-term device use
  - adverse events associated with vulnerable populations
  - 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.

- 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.
- MAUDE data is subjected to reporting bias, attributable to potential causes such as reporting practice, increased media attention, and/or other agency regulatory actions.
- MAUDE 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 the Medtronic Activa Neurostimulator for Dystonia Treatment

The Agency conducted queries of the MAUDE database and of the CDRH Ad Hoc Reporting System (CARS) for all MDRs associated with the Medtronic Activa Neurostimulator for Dystonia Treatment received September 28, 2013 – September 27, 2014. The queries resulted in the identification of 176 unique MDR reports. All of the reports were submitted by the manufacturer. Patient gender information was provided in 150 of the reports in which 79 were female and 71 were male patients.

Pediatric MDR Review

Patient age was able to be determined in 138 of the MDRs, which included 23 pediatric reports and 115 adult reports. The patient age was unknown in 38 reports. Pediatric patient age ranged from 9 to 21 years of age. The average age of the known pediatric patients was 15.13 years. The reporting country was available in all of the pediatric MDRs and includes the United States (n = 22) and Argentina (n = 1). There were 15 female and eight male pediatric reports.

Table 1 shows the top reported device and patient problem codes as provided in the pediatric MDRs. These codes are useful in obtaining a general overview of what is being seen in the MDRs; however they do not provide the full picture of the events occurring. Numbers from the previous analysis presented at the 2014 PAC, which included all pediatric MDRs received April 15, 2003 – September 28, 2013, are listed in parentheses in Table 1 for the ease of comparison.

Table 1. Top reported patient and device problem codes for pediatric reports received September 28, 2013 – September 27, 2014*.

Patient Problem	Number of MDRs**	Device Problem	Number of MDRs**
Unexpected therapeutic effects	7 (3)	Impedance issues	11 (11)
No known impact or consequence to patient	6 (9)	Break/fracture	5 (4)
Ill-defined complaint	6 (1)	Battery/charging issue	4 (6)
Decreased therapeutic response	4 (15)	Inappropriate shock	4 (4)
Ambulation difficulties	4 (1)	Device operates differently than expected	3 (8)
Neurological deficit/dysfunction	3 (1)	Failure to deliver energy	3 (0)
Electric shock	3 (4)	No Known Device Problem	2 (10)
Infection	2 (6)	Device displays error message	2 (3)
Muscular rigidity	2 (0)	Communication or transmission issue	1 (1)
Muscle spasm(s)	1 (1)	Material deformation	1 (0)

* The number of pediatric MDRs from the 2014 PAC (received April 15, 2003 – September 28, 2013) are listed in parentheses in Table 1 for the ease of comparison.
** A single MDR may be associated with more than one problem code.

Time to Event (TTE)

In an effort to separate reports for events that occurred zero to 30 days post implant from those that occurred greater than 30 days post implant, an analysis of the time to event (TTE) was conducted. The TTE was calculated based on implant and explant dates provided, date of event provided, and the event text for each report. The TTE was only able to be conclusively determined for nine of the pediatric reports received. There was one report in which it was confirmed that the event occurred between zero and 30 days post-implantation and eight reports in which the event occurred greater than 30 days post implantation. The sole adverse event that occurred within a month involved a lead break/fracture during implantation. Six of the adverse events that occurred 30 days post-implantation resulted in the device being replaced due to premature battery depletion (n = 2), lead break/fracture (n = 1), extended recharge time (n = 1), normal battery depletion (n = 1), and an impedance issue (n = 1). The remaining two reports involved lead breakage (n = 1) and a material deformation (n = 1).

All pediatric reports were individually reviewed to identify events that were previously determined to be clinically significant or concerning by CDRH clinicians, and to be consistent with the prior MDR analysis. The specific adverse events are illustrated in Table 2 and explained in detail in the appropriate subsections below.

Table 2. Clinically concerning pediatric reports received September 28, 2013 – September 27, 2014.

Adverse Event	Number of MDRs*
Device replaced	9
Return or worsening of symptoms	9
Lead break/fracture	5
Battery/charging issue	4
Infection	2
Device explanted	1

* A single MDR may be associated with more than one type of adverse event.

Device Replaced (n = 9)

A total of nine pediatric MDRs referenced the Activa system being replaced either in whole or in part. The time to replacement, which could be calculated in 8 of the 9 reports, ranged from 131 – 3,298 days with an average of 1,031 days (2.82 years). Device replacement occurred due to battery/charging issues, impedance issues, lead breakage, electrical shocks, a sizing issue, and an open circuit on a lead/extension.

- Battery/charging issues (n = 4): The four reports of battery/charging issues are discussed in more detail below.
- Impedance issues (n = 1): An implantable neurostimulator (INS) was replaced due to high impedance 253 days after implantation, which resolved the issue. The cause of the impedance issue was not determined.
- Lead break/fracture (n = 1): A lead breakage was found above the lead/extension connection, resulting in less than 50% therapeutic relief. The device was replaced 295 days after implantation and connected to the existing extension and battery. The patient outcome was not specified.
- Electrical shocks (n = 1): The patient experienced electrical shocks and jolting pain 3 – 5 times per day concentrated near the wire tunneled through the neck. Botox injections helped treat the pain, and the lead was replaced 3.44 years post-implantation. The patient's parents suspected that significant patient growth and several concussions contributed to the event, but their suspicions were not confirmed. The patient outcome was not specified.
- Open circuit (n = 1): The right lead and extension were replaced after 9.01 and 9.04 years, respectively, due to an open circuit. The adverse event resulted in a dystonic crisis, which will be discussed in more detail below.
- Sizing issue (n = 1): The patient's single-channel INS was replaced with a dual-channel model with new extensions because the adaptors would be too large.

Return or Worsening of Symptoms (n = 9)

An abrupt loss of stimulation was responsible for the majority of MDRs that reported the return or worsening of dystonic symptoms in pediatric patients. There were a variety of reasons cited for the loss of stimulation, including intermittent device shut off, a broken lead, and an open circuit. Two reports did

not specify a reason for the loss of stimulation. In contrast, there was one report of overstimulation that caused increased dystonic symptoms.

- Intermittent device shut off (n = 3): Electromagnetic interference (EMI) from a school security system possibly caused one report of intermittent device shut off, but the patient's outcome was unknown. The second instance was due to poor coupling while charging the device. The patient recovered without sequela once the device was turned back on. Intermittent shut off resulted in acute dystonic issues in the third patient, which were reported as a neurological deficit or dysfunction. The device issue and patient symptoms resolved when the device was replaced due to the extended time required for charging, as discussed below.
- Lead break/fracture (n = 2): There were two MDRs in which separate electrodes were broken on the same lead in a single patient. The first lead fracture was discovered after the initial implantation surgery, but the electrode remained implanted. Approximately one year later, the patient fell, hit their head and broke the second electrode on the same lead. The device was reprogrammed the following month; however there was still a loss of therapeutic effect. The return of dystonic symptoms caused the patient to experience neurological deficit/dysfunction and ambulation problems. Information regarding that patient's outcome was not provided.
- Open circuit (n = 1): An open circuit on a lead/extension resulted in a severe, life-threatening dystonic crisis and was therefore reported as a neurological deficit or dysfunction. Both the lead and extension were replaced, as mentioned previously. Severe scarring was observed over both the extension and lead during the replacement surgery, and part of the lead was fused to the patient's skull. The patient recovered without sequela following device replacement. No other information was provided.
- Unknown reason (n = 2): One patient underwent botox injections to relieve acute dystonic muscle spasms after the loss of stimulation, however no further information was provided. The other patient that experienced loss of stimulation for an unknown reason had their device reprogrammed, resulting in a decrease in dystonic symptom severity and frequency.
- Overstimulation (n = 1): One adverse event involved the patient's stimulation settings being intentionally increased by approximately 20%, resulting in electrical shocks/jolts 4 – 5 times per hour and the return of dystonic symptoms. Neither the cause for the programming change nor the patient outcome were reported.

Lead break/fracture (n = 5)

There were five MDRs that involved lead breakage or fracture. One event occurred on the day of implantation, but it is unknown if the lead was explanted or replaced. The issue was not resolved and the patient outcome was not specified. Another MDR cited lead fracture as the cause of a short circuit and impedance issues. The break, which occurred at the lead/extension connection, was discovered during surgical exploration. A future revision surgery was planned but the patient outcome was not specified. The remaining three reports of lead break/fracture were discussed previously under the subheadings "*Device replaced*" and "*Return or worsening of symptoms*".

Battery and Charging Issues (n = 4)

There were four pediatric adverse events involving battery and/or charging issues, all of which resulted in the device being replaced, as mentioned previously.

- Premature battery depletion (n = 2): One MDR stated that a full charge lasted a maximum of 12 hours, causing the patient to charge the battery several times per day. Diagnostic testing showed that the INS was not charging properly. The INS was replaced 246 days post-implantation, allowing the patient to receive therapy for 15 days between charges. In the second report, the premature battery depletion was resolved by replacement of the INS and lead extension after being implanted for 131 days.
- Delayed charge time (n = 1): There was one report of extended battery charging time (six hours per day), which the patient disliked. The rechargeable INS was replaced with two non-rechargeable devices 256 days after implantation to resolve the issue.
- Normal battery depletion (n = 1): The INS was replaced after 253 days because it was at the end of service due to normal battery depletion.

Infection (n = 2)

While only one pediatric report was coded for infection, a total of two reports of infection were identified by individual MDR review and included in Table 2. In the correctly-coded MDR, the entire system on the right side was explanted due to an infection at an unspecified time and location. Neither the cause of the infection nor the patient outcome were reported. The other report of infection was due to a broken sterilization machine in the operating room, and was unrelated to the device itself. The patient, who had pneumonia prior to implantation and was therefore at high risk for infection, tested positive for pseudomonas organism two days post-implantation and ultimately died.

Device Explanted (n = 1)

Reports in which an explant was stated to have occurred are unique from reports of a replacement, which involve the original device being explanted and a new one implanted in its place. As mentioned previously, there was one report of an entire system on one side being explanted due to an infection. Neither the causative pathogen of the infection nor the patient outcome were reported.

MDR Conclusions

A total of 23 MDRs have been identified for the Dystonia indication of the Medtronic Activa neurostimulator in pediatric patients. MDRs related to a return or worsening of symptoms (loss of therapeutic effect) accounted for 39.13% of all of the pediatric adverse events reported. These types of reports are often indicative of an issue that can be resolved. The labeling does address the issue of symptom return/worsening and these types of events are known to occur in other neurostimulators. Other patient problem types occurring within the MDRs are noted in either the device labeling or clinical summary. In contrast to the prior analysis, there were no reports of CVAs or device revisions due to patient growth. The top mechanical problem reported was impedance issues (47.83% of reports), which is a condition typically seen at the lead/device connection. The labeling states that issues with open circuits (high impedance) can occur without warning and impedance issues are also known to occur in other neurostimulators. Other device/mechanical problem types occurring within the MDRs are either noted in the device labeling or are known device issues with neurostimulator devices in general.

IV. POSTMARKET DATA: LITERATURE REVIEW WITH FOCUS ON SAFETY DATA

Purpose:

The intent of this systematic literature review is to provide an update of adverse events associated with the use of the Medtronic Activa neurostimulator since the previous literature review for the 2014 PAC meeting. The events were grouped into several categories with little overlap with the exception of power/battery issues vs. revision, which frequently occur in tandem. The categories include: general device malfunction and adverse events (nearly all events), infections, effectiveness, electromagnetic interference (EMI), depression/suicide, power/battery life/battery failure, perioperative adverse events, and revisions.

The literature review was conducted to address the following questions:

1) What adverse events (safety) are reported in the literature for Medtronic neurostimulators in the treatment of movement disorders?
2) What is the safety of these devices in the target population of pediatrics treated for dystonia?

Methods:

A systematic search of the published peer-reviewed literature in the PubMed and EMBASE databases was conducted on November 10, 2014. The review team agreed on the search terms prior to the conducting the search. The search strategy, inclusion, and exclusion criteria are detailed below.

The search was conducted in the databases using the following search string:

(medtronic dystonia) OR (medtronic activa deep brain stimulation) OR (medtronic dbs) OR (medtronic activa) OR activa OR (dbs AND pediatric AND Dystonia)

The limits utilized were articles published in English from November 26, 2013 to November 10, 2014 (previous literature review to present). The rationale for the limits was to query as widely as possible to maximize the number of relevant results. This search string yielded a total of **172** articles that were then subjected to a first pass review, consisting of assessment of title and abstract. One hundred forty five (**145)** articles were excluded based on the following: conference abstracts (n=28), duplicates (n=11), no clinical endpoints (n=8), non-pediatrics (n=30), non-humans (n=6), non-movement disorders (n=11), non-English (n=7), non-systematic reviews (n=4), unavailable articles (n=1), and unrelated topics (n=39). Therefore, 27 articles remained for the second pass assessment which consisted of full text article review. Of the 27 articles subjected to full text review, 14 articles were excluded during the second pass for the following reasons: non-pediatrics (n=10), unavailable articles (n=1), duplicates (n=2), and no clinical endpoints (n=1). Adjudication of all articles included in the final review for data synthesis was by consensus of the review team. Thirteen (13)[1-13] articles were retained for the final review. See Figure 1 below for a detailed illustration of the selection process.

Results:

Four (4) case reports[1,4,6,12] and nine (9) observational studies[2,3,5,7-11,13] were identified in the literature update. Of the identified studies, six (6) were based in the US[2,6-8,10,13], and the remaining seven (7) were OUS[1,3-5,9,11,12]. The sample sizes ranged from 1 to 368, with a mean of 38 patients. Seven studies (7) had less than10 patients[1,4,6-8,12,13], three (3) studies had 10 to 25 patients[2,10,11], two (2) studies had 25 to 100 patients[5,9], and one study (1) had more than 100 patients[3]. Of the selected 13 studies, eight (8) focused solely on pediatric patients[1,2,4,6,8-10,13], four (4) had a mixed adult-pediatric patients[3,5,7,11], and one (1) did not report patient age[12]. In papers with available age information, patients ranged from 5 to 76 years old. The indications for treatment in the subject articles included primary dystonia[2,5,9,10,12,13], secondary

dystonia[1,2,4,8-10], TS[11], and posttraumatic tremor[6,7] All of the papers in this review used some Medtronic hardware, either a Medtronic internal pulse generator (IPG), Medtronic leads, or other components. All reported that a Medtronic internal pulse generator (IPG), Medtronic leads, or other components were used.

The focus of our literature review is on primary dystonia in pediatric patients (less than the age of 22 years). As described previously, the device has a humanitarian device exemption (HDE) for the indication of long-term primary dystonia refractory to drug therapy (meaning that the device may be used in fewer than 4,000 US individuals over the age of 7 annually for dystonia). When articles identified are limited to those which consisted of primarily pediatric patients, at least some Medtronic hardware, and an indication for use including primary dystonia, four papers were retained[2,9,10,13]. These four papers evaluating the use of Medtronic Activa Dystonia Therapy in pediatrics with dystonia are discussed briefly on their own below:

Articles with a Primary Focus of Pediatric Patients

Bhanpuri[2]: A 2014 US based observational trial was conducted in 11 children. The mean age was 13.7 ± 4.5 years (range: 9-21 years). All patients within the cohort underwent bilateral *globus pallidus interus* (GPi) DBS. Of these patients, 1 patient underwent an additional surgery to add leads to the subthalamic nucleus (STN). Mean follow-up time was 4.7 years (range: 0.5-8 years). The authors reported that there were no adverse events and did not discuss any device malfunctions.

Lumsden[9]: A 2013 UK based observational trial was conducted in 42 children with a median age of 10.1 years (range: 3.3-20 years). The cohort included 14 patients with primary dystonia. All patients underwent bilateral GPi DBS. The authors did not report malfunctions or adverse events. A follow up CT of the patients was conducted just post-operatively and then at 1 year, patients were assessed with the Burke-Fahn-Marsden Dystonia Rating Scale.

Petrossian[10]: A 2013 US based observational trial was conducted in 13 children and one 25 year old female adult with a mean age of 14.5 years (range: 9-25 years). The cohort was 71% male (10/14), and 79% (11/14) of the total cohort suffered from primary dystonia. All patients underwent bilateral Gpi DBS. Mean follow-up time was 50.8 months (range: 16-84 months). The investigators identified seven (7) hardware related adverse events across five (5) patients. These included 4 lead fractures (in 2 patients, timeframes not reported), 2 infections (1 at 7 months postoperatively, and one not reported for timeframe), and 1 lead migration (7 years postoperatively). Adverse events included infection with subsequent revision and one case of complex partial seizures due to lead migration at 7 years postop.

Starr[13]: A 2014 US based observational trial was conducted in 6 pediatrics, all of whom had a diagnosis of primary dystonia. The mean age at surgery was 11.0 ± 2.8 years of age. The cohort was 67% (4/6) male, and 83% (5/6) of the patients were implanted with bilateral leads in the Gpi. The remaining patient had leads implanted into the STN. The only device malfunction reported was an open circuit on one contact of one lead. This open circuit did not trigger a revision and its resolution is not well described. There were five (5) adverse events noted among an unknown number of subjects; these included single episodes of transient slurred speech, transient dyskinesia, unexplained nausea and dizziness, right knee pain, and left shoulder pain. The authors stated that none of these adverse events was deemed serious.

Articles with Pediatric and Adult Patients

General Device Malfunction

Device malfunctions were described in six (6) of the thirteen selected papers[5-7,10,11,13]. Wire breakage was noted in 1/27 (3.7%) of patients in one study[5] due to body growth of the patient. Wire breakage was also present in 4/17 (23.5%) patients of the study conducted by Sachdev et al[11]. The reasons included a motor accident, movement from tics, and in one instance, the breakage had no obvious cause. In a case study by Carvalho et al[6], the patient's device accidently switched off through airport security attributed to electromagnetic interference. Cao et al[5] reported 2/27 (7.4%) patients experienced electrode displacement due to prolonged unhealed skin erosions. Electrode displacement 7 years postoperatively was also seen in 1/14 (7.1%) patients by Petrossian et al[10]. Lead fracture was reported in 2/14 (14.3%) patients by Petrossian et al[10]. Isaar et al[7] reported 2/5 (40%) of patients had faulty extension wires. Undefined hardware malfunction arose in 3/17 (17.6%) patients in Sachdev et al[11]. The malfunctions were detected by a recurrence of symptoms. The cases of hardware malfunction included one instance of device battery failure manifested as a severe tic recurrence and an increase in substance abuse. The other instances of hardware failure were not described further. Lastly, Starr et al[13] noted an open circuit on one contact of a lead in 1/6 (16.7%) patients. Of the device malfunctions reported, at least eight patients across all thirteen papers had a revision surgery performed to rectify problematic hardware[5,7,10,11]. Overall, the adverse events associated with the device usage is comparable to FDA's expectations. No new mechanical events or device failures were identified that give cause for concern.

Infection

Infection was the most common complication in the literature update, occurring in 38 patients (7.6%) across all 13 papers[3,8,10,11]. An example of a typical course of an infection was one caused by a *Staphylococci* agent[3]. Infections developed in the areas of lead implantation, pulse generator pouch, or extension tract[3,8,10,11]. Bjerknes et al[3] calculated a 5.6% infection rate of all patients implanted with DBS in the Oslo University Hospital from 2001-2010, utilizing a sample size of 368 patients. Of these patients, the most common site of infection was the IPG, occurring in 28/33 (84.8%) infections. As for the timing of infection, 17 occurred within the first month, 26 within the first three months, and 2 after the first year[3]. Patients of other studies developed infections between 3-4 months[8,11]. In a few instances, the timing of the infection relative to the implantation surgery was not stated[10]. For all patients, treatment consisted of a course of antibiotics, and in many cases, surgical explantation of hardware[3,8,10,11]. In some instances, the hardware was not reimplanted due to parental or patient concern[8,10]. Otherwise, the patients underwent revision surgery to replace the electrodes[11], or the remaining hardware was reprogrammed for unilateral stimulation[10].

Adverse events (AE)

The literature update identified two serious AE which have not been previously encountered in the literature review: one AE was complex partial seizures (n =1 patient)[10] and the other was status dystonicus (n =1 patient)[12]. The complex partial seizures began in a patient whose leads had migrated to the bilateral temporal lobes 7 years after implantation as described previously. This migration led to epileptiform abnormalities that resulted in complex partial seizures. The seizures ceased when the stimulation was turned off. The hardware was replaced[10].

The case of severe status dystonicus was prompted by battery end of life that subsequently caused a cessation of stimulation. Sobstyl et al[12] reported a patient that began to experience severe retrocollis and mild right dystonia due to left IPG depletion. After replacement of the left battery, the patient's symptoms improved. However, when the right IPG battery depleted, the patient experienced rapid aggravation of

dystonic symptoms which triggered rhabdomyolysis. This breakdown of muscle further elicited severe liver and renal failure. The patient was rushed for emergency surgery and the right IPG battery was replaced. Following this revision, the dystonic spasms stopped. It was unclear if the cessation of stimulation was due to standard end of life of the battery or an abnormal battery. Other cases noted instances in which battery depletion caused a recurrence of symptoms within 24-48 hours[5].

Four adverse events were reported that were transient in nature. These adverse events occurred over a brief time period but the exact length of time was not given. Sachdev et al[11] reported 2/17 (11.8%) patients felt transient anxiety. Transient depression was noted by 2/27 (7.4%) patients by Cao et al[5]. Starr et al[13] found 1/6 (16.7%) patients underwent transient dyskinesia, and there was another case (16.7%) of transient slurred speech. It is unknown if this is a report of a unique patient or one patient with multiple transient AEs.

Other AEs described in the literature relate to those provoked by adjustment of stimulation parameters at initial optimization. Although the length of time that these stimulation-induced AEs were experienced was not clear, Sachdev et al[11] stated that stimulation-related AEs were "mostly temporary and attenuated with adjustment of stimulation parameters". In a case report by Bob et al[4], the patient experienced feelings of pleasure, aggravation of posture, and feelings of fear at incorrect parameters. Isaar et al[7] reported dystonic movements of upper extremities, ataxia while walking, balance difficulty, paresthesia, and slurred speech that occurred as a direct result of stimulation. The incidence rate and duration of time was not stated for these AEs; however, the dystonic movements of hands during fine motor movements was retained in 1/5 (20%) patients and one case of paresthesia (20%) continued in a different patient even after the appropriate therapeutic parameters were set. Poor balance was seen in 2/17 (11.8%) patients by Sachdev et al[11]. Other stimulation-related effects noted in this study were agitation in 2 patients (11.8%), dizziness in 1 (5.9%), and worsening of pre-existing stutters in 1 (5.9%). Starr et al[13] found single episodes of unexplained nausea and dizziness, left shoulder pain, and right knee pain, although the duration and cause of these AEs were not reported.

In one instance, an incorrect target produced AEs. Isaar et al[7] attempted placement of a second lead in the *zona incerta* intraoperatively, but found that it produced disruptions of the pyramidal tract that resulted in pulling and pain in the left foot, dizziness, apprehension, and facial contracture. The lead was removed from this site and the patient's symptoms disappeared.

Ineffectiveness

The issue of ineffectiveness is concerning since it may necessitate surgical revision to fix the issue, adding additional exposure to general anesthetics, and surgery risks. Ineffectiveness was reported by 3 authors[2,10,11]. Although there were reports of the level of symptom reduction varying widely amongst patients in other studies[2], the following cases were the only instances in which it was stated that the device did not alleviate the movement disorder at all. Petrossian et al[10] found no improvement in the dystonic symptoms of 2 pediatric patients. For one of these patients, the cause of the secondary dystonia was a mutation in the *PANK2* gene. The etiology of the dystonia for the other nonresponsive patient was unknown. Sachdev et al[11] recounted one non-pediatric patient who suffered from worsening of tics after stimulation. Bhanpuri et al[2] reported that 10/11 patients had mild to moderate improvement, but did not elaborate on the details of the non-responder.

Conclusions Based on Literature Review:

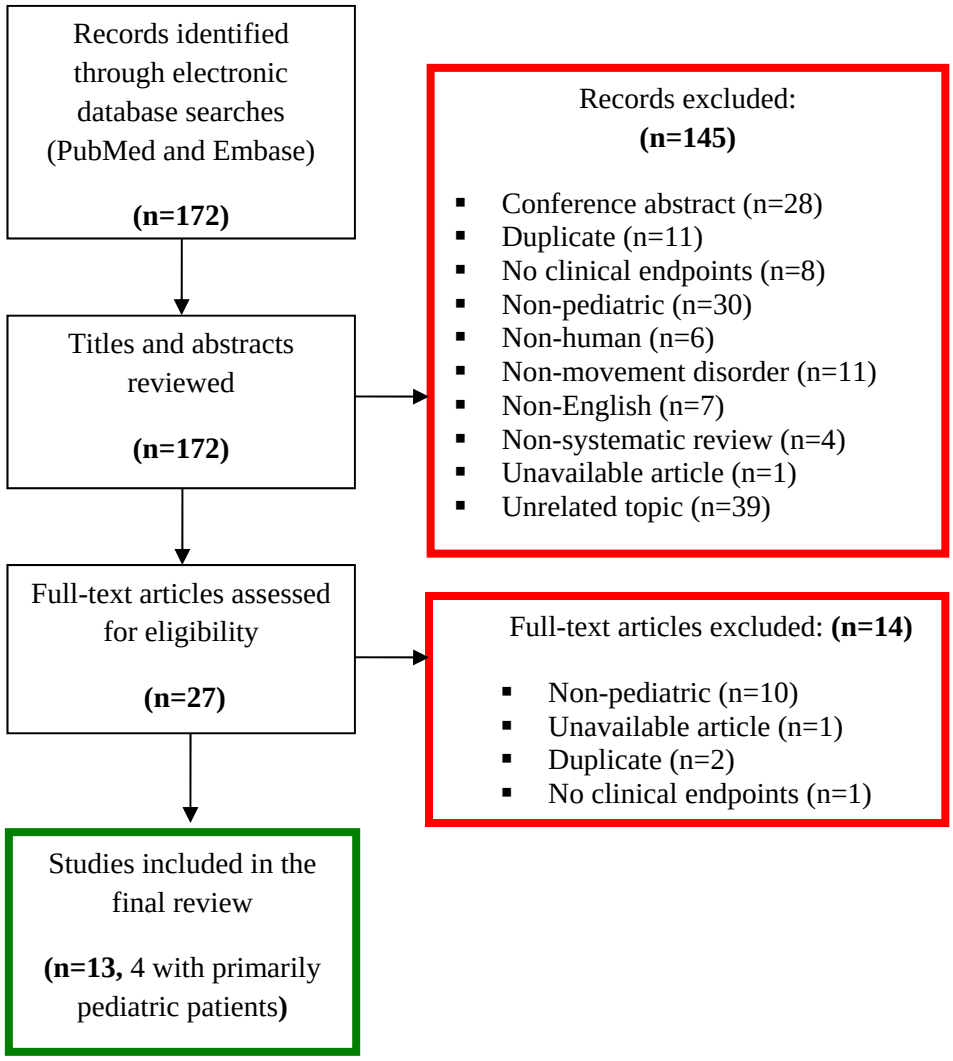
Consistent with previous literature review, infection was the most frequent adverse event following device implant. Several patients with infections needed a revision surgery, and in some instances the entire system was explanted and not reimplanted[3,8]. Severe adverse events may occur due to lead migration after the device was implanted for long periods of time, or when the battery is depleted. Other

adverse events may occur when stimulation parameters are incorrect. These expected transient side effects occur briefly during the testing phase while parameters are being optimized during the initial power up. There were also a few instances in which DBS was unable to alleviate symptoms in patients[4,10,11]. The device malfunctions identified from the update are consistent with previous literature review and no new device malfunction is identified.

Petrossian et al identified seven hardware-related adverse events in five pediatric patients. Device malfunctions included 4 lead fractures (in 2 patients), 2 infections, and 1 lead migration which lead to complex partial seizures at 7 years post-implant. Infection was also reported in this patient group.[10] The premarket review had already identified that potential lead strains or fractures related to elongation of the trunk of the patient (due to normal growth) while the length of implanted conductor (from the neurostimulator to the burr hole) remains fixed could occur. The premarket review also identified the risk of lead migration due to patient head growth resulting in ineffective stimulation and the added risk of children being engaged in active play and sports activities that could damage components of the implanted system. Information on how to mitigate this risk is detailed within the current labeling.

There are limitations to this literature assessment. Firstly, several of these articles were small observational studies or case reports. Secondly, no studies utilized control group, thus, the results reported are not as robust as in a gold standard study such as an RCT. Thirdly, no articles reported correction for medication use or changes over the course of study which could introduce bias into the observed effects. Finally, because only four out of thirteen papers specifically discussed primary dystonia in pediatrics, the literature is limited in providing generalizable safety information for this population.

Figure 1. Systematic Literature Review Workflow (Selection Process)



SUMMARY

Since HDE approval, FDA has received 23 pediatric MDRs. The most common reason for the reports was a return or worsening of symptoms. The types of reports seen in the MDRs are consistent with the adverse events noted in the literature review and are identified in the device labeling. Neither the MDRs nor the literature review identified any new significant safety signals.

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