Medtronic's
Activa® Neurostimulator for Dystonia Treatment
Humanitarian Device Exemption (HDE) H020007

Andrew Miller, M.S.
Adverse Event Analyst
Division of Postmarket Surveillance
Office of Surveillance and Biometrics
Center for Devices & Radiological Health
Food and Drug Administration

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Device Description

Source: Adapted from Medgadget.com

Dystonia Indications for Use

The Medtronic Activa® Dystonia Therapy 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 older.

Annual Distribution Number (ADN)

- The humanitarian Device Exemption (HDE) was approved with an ADN = 4,000
- Number of devices implanted in the US in 2016: 836 implants (139 in pediatric patients)
- Number of active implants in the US during CY 2016: 3440 active implants (581 in pediatric patients)

Medical Device Reports (MDRs)

Limitations of MDRs

- Under-reporting
- Data quality issues
- Biased information
- Inability to determine rate
- Cannot definitively determine causality/relationship to device

Methods

FDA Medical Device Adverse Event Database

MDR Search Inclusion Criterion:

- *Date Entered*: September 28, 2015 – September 27, 2016
- Any of the following criterion:
  - *Brand Name*: Activa
  - *Product Codes*: MRU (dystonia), MHY (Parkinsonian tremor)
  - *Premarket Submission Number*: H020007

Search Results: 324 pertinent MDRs

Overview of MDRs for the 2014, 2015, 2016 and 2017 PAC Reporting Periods

	PAC 2014			PAC 2015			PAC 2016			PAC 2017		
Event Type	**Pediatric**	**Adult**	**Unknown**	**Pediatric**	**Adult**	**Unknown**	**Pediatric**	**Adult**	**Unknown**	**Pediatric**	**Adult**	**Unknown**
Malfunction	14	46	11	19	91	26	22	101	22	27	107	35
Injury	35	101	65	22	84	38	34	122	29	31	90	33
Death	0	2	0	1	1	0	0	0	3	0	1	0
Total	49	149	76	42	176	64	56	223	54	58	198	68

PAC reporting period date ranges:

- 2014 PAC: date report entered prior to 9/27/13
- 2015 PAC: date report entered 9/28/13-9/27/14
- 2016 PAC: date report entered 9/28/14-9/27/15
- 2017 PAC: date report entered 9/28/15-9/27/16

Overview of MDRs Entered
September 28, 2015 – September 27, 2016

Reporting Country	Pediatric	Adult	Unknown	Total
US*	47	159	45	251
OUS**	6	21	15	42
Unknown	5	18	8	31

*United States (US), **Outside the United States (OUS)

Clinically Significant Pediatric MDRs Entered September 28, 2015 – September 27, 2016

Adverse Event	Number of MDRs *
Device explanted	24
Return or worsening of symptoms	15
Battery/charging issue	14
Device replaced	12
Infection	8
Potential Electromagnetic Interference (EMI)	8
Growth related issues	5
Lead break/fracture	5
Stroke	0
Cognitive Issues	0

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

Clinically Significant Pediatric MDRs Entered September 28, 2015 – September 27, 2016

Device Explanted and Replaced (N=12)

- Battery/charging issues (age range 16-18 years)
- Lead fracture (age range 14-21 years)
- Impedance issues (age 16 years)
- Infection (age 9 years)
- Patient growth (age 12 years)

Clinically Significant Pediatric MDRs Entered September 28, 2015 – September 27, 2016

Device Explanted without Replacement (N=12)

- Infection (age range 6-14 years)
- Battery/charging issues (age range 14-21 years)
- Skin erosion (age 21 years)
- Decubitus ulcer (age 5 years)
- Lack of therapeutic benefit (age 21 years)

Clinically Significant Pediatric MDRs Entered September 28, 2015 – September 27, 2016

Worsening or Return of Dystonia Symptoms (N=15)

- Battery/charging issues (ages range 16-21 years)
- Impedance issues (ages 9-18 range years)
- Device reset due to potential electromagnetic interference (age 17 years)
- Issues potentially due to patient growth (age 12 years)
- Skin erosion (age 21 years)
- Intermittent device shut off (age 17 years)

Clinically Significant Pediatric MDRs Entered September 28, 2015 – September 27, 2016

Battery/charging issues (N=14)

- Recharging issue (age range 14-21 years)
- Premature battery depletion (age range 16-18 years)
- Normal battery depletion (age 11 years)
- Overstimulation (age range 14-20 years)
- Intermittent continuity (age range 16-21 years)
- Unknown battery issue (age 14 years)

Clinically Significant Pediatric MDRs Entered September 28, 2015 – September 27, 2016

Infection (N=8)

- The organisms associated with the patient infections included:
  - *Staphylococcus aureus* (age range 9-12 years)
  - Not reported (age range 6-14 years)

- The location of the infections was reported in five of the eight MDRs:
  - three pocket site/pulse generator infections
  - two lead site infections

- All of the infections resulted in full or partial device explant, with two replacements.

Clinically Significant Pediatric MDRs Entered September 28, 2015 – September 27, 2016

Electromagnetic Interference (EMI) (N=8)

- Exposure to a computer tablet on a wheel chair (age 20 years)
- "Using software with a digital imaging system that puts out ultrasonic waves" as part of a "class" (age 17 years)
- Security gates at a school library (age 17 years)
- Security gate at an unknown location (age 12 years)
- "Working with magnets at school" (age 17 years)
- Unknown sources (age 10 years)

Clinically Significant Pediatric MDRs Entered September 28, 2015 – September 27, 2016

Potential Patient Growth Related Issues (N=5)

- "Scar tissue wrapped around the extension" requiring device replacement (age 12 years)
- Patient discomfort (tingling, burning, shocking sensations, "wires pulling" (age range 9-12 years)

Lead break/fracture (N=5)

- Intraoperative lead fracture (age range 12-21 years)
- Lead fracture due to the patient's torticollis (age 14 years)
- Lead fracture with unknown cause (age 10 years)

PAC 2017: Summary of MDRs

There were 58 MDRs reporting 43 unique events associated with use of the Activa neurostimulator in pediatric patients.

Infection and a return or worsening of dystonia symptoms (loss of therapeutic effect) were the most frequently reported pediatric patient problems.

The most frequently reported device problems were battery/charging issues and impedance issues.

No MDRs associated with pediatric stroke or cognitive changes were reported.

No new device or patient problems were identified.

Literature Review

Systematic review of the published literature to evaluate adverse events following use of the Medtronic Activa Neurostimulator for primary dystonia in pediatric patients.

Methods

- **Search Terms:** *(medtronic dystonia) OR (medtronic activa deep brain stimulation) OR (medtronic dbs) OR (medtronic activa) OR (activa) OR (dbs) AND (pediatric) AND (Dystonia)*

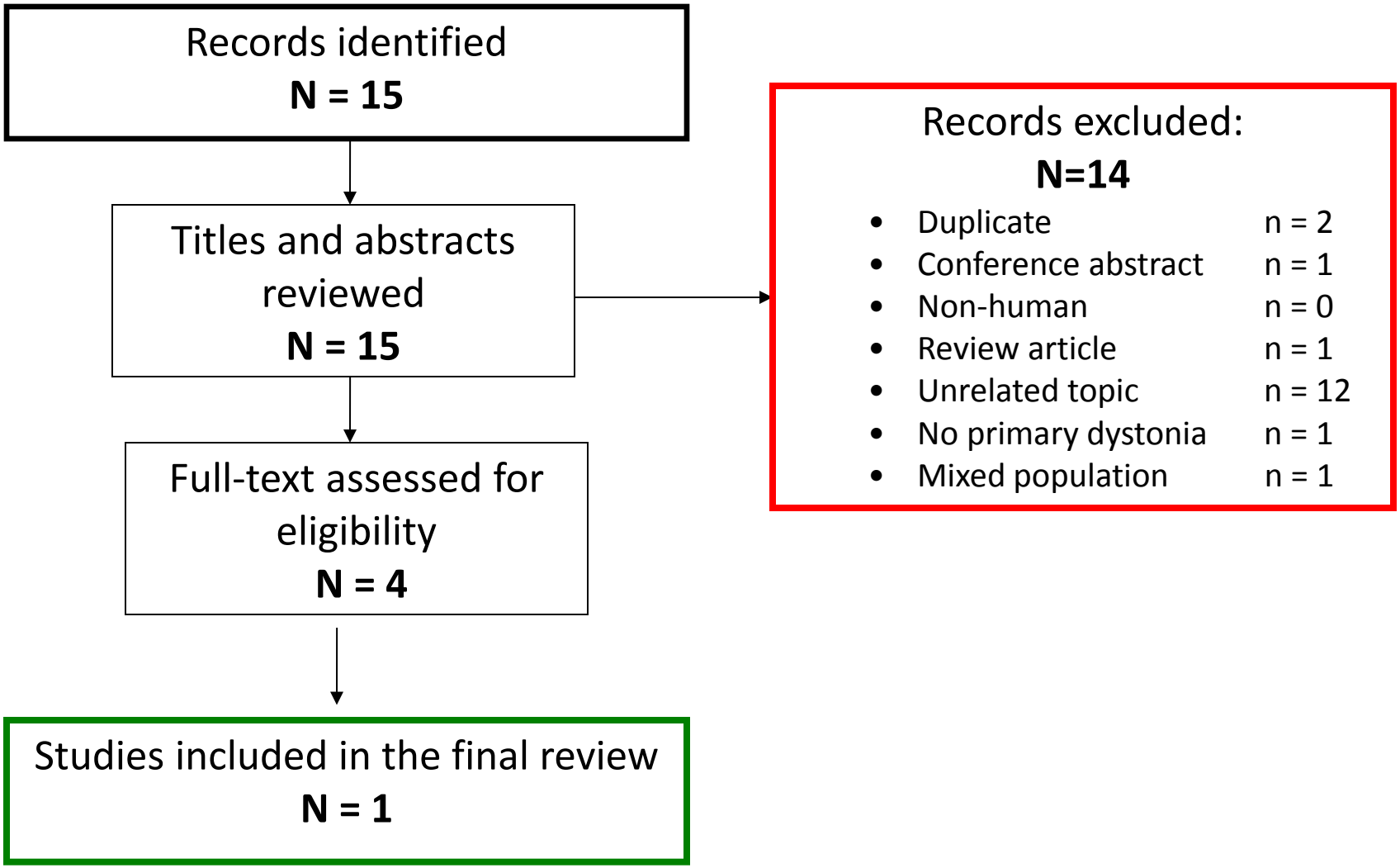
- **Database:** PubMed & EMBASE

- **Date of Search:** November 6, 2016

- **Time Period:** November 5, 2015-November 5, 2016

Papers published since the last search

Results


Records identified
N = 15
Titles and abstracts reviewed
N = 15
Full-text assessed for eligibility
N = 4
Studies included in the final review
N = 1
Records excluded:
N=14
Duplicate n = 2
Conference abstract n = 1
Non-human n = 0
Review article n = 1
Unrelated topic n = 12
No primary dystonia n = 1
Mixed population n = 1

Krause et al. (2016)

- *Retrospective chart review*
- *8 pediatric patients with generalized idiopathic or hereditary isolated dystonia:*
  - *5 males / 3 females*
  - *mean (± standard deviation) age at surgery 12.5 (± 3.5) years*
  - *long-term safety (up to 13 years) of pallidal DBS*

Adverse event	No. of patients
Revision after successful implantation for replacement of IPG after battery expiry, necessitating 10 replacements	4
Revision of the IPG due to dislocation 11 years after the initial electrode implantation	1
Bilateral electrode revision 3 years after the initial DBS	1
Stimulation-induced dysarthria limiting increase of stimulation amplitude	2
Bradykinesia induced by DBS with high stimulation amplitudes	1
Several orthopedic surgeries due to severe contractures and musculoskeletal deformities resulting from longer disease duration before DBS surgery	1

Conclusions

- No novel safety event detected in literature published since the last PAC

- These findings are consistent with the conclusions from the systematic review conducted for the previous PAC meetings

FDA Recommendations and FDA Question to the PAC

- FDA recommends continued surveillance and will report the following to the PAC in 2018:
  - Annual distribution number
  - Literature review
  - MDR review

Question: Does the Committee agree with the FDA's conclusions and recommendations?