Deep Brain Stimulation for Dystonia Final Labeling

PMA-S: Amendment

Volume 1 of 1

Medtronic

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Medtronic

Neuromodulation and Pelvic Health
7000 Central Ave. N.E.
Minneapolis, MN 55432
USA

www.medtronic.com

December 16, 2025

U.S. Food and Drug Administration
Center for Devices and Radiological Health
Document Mail Center – WO66-G609
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

Re: Final Labeling Amendment (P960009/S482/Axxx)

Dear Sir or Madam:

Please find the final labeling amendment as requested in the approval letter dated November 22, 2025, for P960009/S482 for Deep Brain Stimulation for Dystonia.

The applicable PMA/HDE submission numbers and affected products are as follows:

PMA/HDE Number (Product Code) and Trade Name	Model Numbers
P960009 (MBX, MHY, NHL, PJS) Activa™ Deep Brain Stimulation Therapy System, Percept™ PC BrainSense™	Implantable Neurostimulators: 37601, 37602, 37603, 7426, B35200, B35300 Leads: 3387S, 3389S, B33005, B33015 Extensions: 37085, 37086, 7482/7482A, 7483, B34000 Accessories: 3550-05, 3550-25, 3550-45, 3550-67, 3550-68, 37022, 64001, 64002, B31000, B31010, B31020, B31040, B31050, B31060, B31061, B32000 Clinician programmers: 8840, 8870, 8880T2, A610 Patient programmers / rechargers: 37092, 37642, A620, A90300, CD9000, RS6230, TH90, TH91, WR9230

This submission contains confidential and trade secret information, and Medtronic hereby requests that it be given the maximum protection provided by law.

The Medtronic business unit (applicant) for this submission is as follows:

Medtronic Neuromodulation
7000 Central Ave., N.E.
Minneapolis, MN 55432

If you have any questions or correspondence regarding this submission, please feel free to direct them to the correspondent below.

Sincerely,

Signed by:

Carolyn Shepler

Signer Name: Carolyn Shepler
Signing Reason: I approve this document
Signing Time: 16 December 2025 | 10:02 CST

E6AB7F051E9C4B79B83AEFD0EC9BE7F2

Primary Contact
Carolyn Shepler
Principal Regulatory Affairs Specialist
Medtronic Neuromodulation
7000 Central Ave., N.E.
MS RCE480
Minneapolis, MN 55432
Email: carolyn.shepler@medtronic.com

Alternate Contact
Eleanor Palm
Senior Regulatory Affairs Manager
Medtronic Neuromodulation
7000 Central Ave., N.E.
MS RCE480
Minneapolis, MN 55432
Email: eleanor.m.palm@medtronic.com

Deep Brain Stimulation for Dystonia Final Labeling

Deep Brain Stimulation for Dystonia was approved on November 22, 2025 in P960009/S482.

Table 1 provides a summary of all labeling submitted as part of the original PMA-S and a comparison to the final labeling. All labeling is identical to the draft labeling reviewed by FDA during review of P960009/S482 except as noted below. The changes are being made to address editorial items such as formatting, add minor clarifications, and correct minor errors.

Table 1. Final Labeling

Appendix Number	Labeling Description	Part Number in P960009/482	Final Part Number	Comparison of original and final labeling
Appendix A	Indications – Medtronic DBS Therapy for Dystonia	M944227A009 rev A REDLINE	M944227A009 rev A (clean copy)	Redlines implemented
Appendix B	Medtronic Deep Brain Stimulation Therapy for Dystonia – Information for Prescribers Addendum	M944434A008 rev A REDLINE	M944434A008 rev A (clean copy)	Redlines implemented
Appendix C	Medtronic DBS Therapy for Dystonia – Clinical Summary	M944810A003 rev A	M944810A003 rev A	Content changes made – see Table 2 for description of changes
Appendix D	Purpose of Medtronic Deep Brain Stimulation (DBS) Therapy for Dystonia	M944228A003 rev A REDLINE	M944228A003 rev A (clean copy)	Redlines implemented
Appendix E	Your Medtronic Deep Brain Stimulation Therapy for Dystonia – Patient Manual	M060407C001 rev A REDLINE	M060407C001 rev A (clean copy)	Redlines implemented

Labeling Changes After Submission

This section summarizes the substance of the updates from the DBS Therapy for Dystonia Clinical Summary that were updated compared to what was submitted to FDA.

DBS Therapy for Dystonia Clinical Summary

Part Number: M944810A003 rev A

Changes to the DBS Therapy for Dystonia Clinical Summary included updating the formatting to appear clearer and more professional. The updated format did not impact the content except for the edits as noted in Table 2 below. Text in red font (strikeout) indicates content that was deleted. Text in blue font indicates newly added content.

Table 2. Updates to DBS Therapy for Dystonia Clinical Summary

Item	Page	Change Description	Rationale for Change
1	Throughout	Updated formatting throughout and added footer and page numbers.	Updated formatting to appear clearer and more professional, and for consistency with other Medtronic DBS labeling.
2	1-2	Added cover page and brand statement	Added for consistency with other Medtronic DBS labeling.
3	5	**Medtronic Deep Brain Stimulation (DBS) Therapy for Dystonia –** Generic name for a medical treatment developed by Medtronic in collaboration with medical researchers as an aid in the management of chronic, intractable (~~drug~~ medication refractory) primary dystonia, including generalized dystonia, segmental dystonia of the head and neck, and cervical dystonia (torticollis) in adult patients, and primary generalized dystonia in pediatric patients ~~seven~~ twelve years of age or above. The therapy uses an implantable medical device to deliver electrical stimulation to the internal globus pallidus.	Updated definition to align with indication statement.
4	11	The primary clinical evidence of safety and effectiveness for Medtronic Deep Brain Stimulation (DBS) Therapy for Dystonia was compiled from a systematic review of published scientific literature, an analysis of a subset of clinical data purchased from a published randomized controlled trial (RCT) by Kupsch (2006)[2] and its long-term follow-up study by Volkman (2012),[15] collectively referred to as the "Investigator Study"[17] and data from the Medtronic Product Surveillance Registry (PSR).	Updated to clarify that evidence also included data from the Investigator Study.
5	11	Safety and effectiveness outcomes are presented separately for generalized, segmental and cervical dystonia in adult patients (> 21 years) and for generalized dystonia in pediatric patients (~~≥ 12 years of age but~~ ≤ 21 years of age). These categorizations are based on the average age reported in each publication or age of patients enrolled in the PSR registry.	Removed "≥12 years of age" in this instance to better reflect how analysis was completed. Analysis was completed based on pediatric age of 21 years or below, and some data included pediatric patients less than 12 years of age, although adequate

Item	Page	Change Description	Rationale for Change
			data to support the indication only existed for 12 and above.
6	12	Study Specific Data An analysis was performed on a subset of clinical data from a RCT that was published in Kupsch (2006).[2] Medtronic purchased the actual clinical data for 30 out of 40 studied patients directly from the authors and performed analysis of that data. Follow-up data from the same study that was published in Volkman (2012)[15] was also used. This data is referred to as the Investigator Study.[17] The Investigator Study[17] was used to support for the safety and effectiveness of bilateral GPi DBS in primary generalized and segmental dystonia in adults. The corresponding data in the primary generalized dystonia are also considered as supportive evidence for bilateral GPi DBS in primary generalized dystonia in pediatric patients ≤ 21 years of age ~~12 years of age and above~~.	Updated "12 years of age and above" to "≤ 21 years of age" in this instance to better align with the study. Per study inclusion criteria, pediatric patients 14 years of age and above were included.
7	12	Meta Analysis from Systematic Literature Review The systematic literature review involved a comprehensive search of the MEDLINE and Embase databases, as well as PubMed ahead-of-print and in-process records, over more than 10-year period covering November 1, 2012, through August 31, 2024. It included a key ~~randomized controlled trial (~~RCT~~)~~ by Kupsch (2006)[2] and its long-term follow-up,[15] both published outside this period. Other relevant studies were found by cross-referencing, with an emphasis on evidence related to particular dystonia types. The focus was on primary data sources for bilateral GPi DBS in adult patients with primary generalized, segmental, and cervical dystonia, without other neurological features or pathological abnormalities and in pediatric patients ~~12 years of age and above~~ with primary generalized dystonia, without other neurological features or pathological abnormalities. Published studies were included in the analysis if at least 80% of the study population aligned with the indication or individual patient data could be extracted for analysis.	Removed definition of acronym that was previously defined. Removed "12 years of age and above" in this instance to better reflect how analysis was completed. Analysis was completed based on pediatric age of 21 years or below, and some data included pediatric patients less than 12 years of age, although adequate data to support the indication only existed for 12 and above.
8	14	Effectiveness Objectives The overall effectiveness objective was to characterize the clinical benefits related to reduction in movement symptoms. The effectiveness of the Medtronic DBS Dystonia system was demonstrated through analysis of Study Specific Data (see Above) and results from a meta-analysis of the systematic review of published scientific literature. The average Burke-Fahn-Marsden Dystonia Rating Scale (BFMDRS) motor score was used in the analysis for primary generalized dystonia in both adults and pediatric patients ~~12 years of age and above~~ and segmental dystonia in adults. The average Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) severity score was used in the analysis for primary cervical dystonia in adults. The European Quality of Life 5-Dimension	Removed "12 years of age and above" in this instance to better reflect how analysis was completed. Analysis was completed based on pediatric age of 21 years or below, and some data included pediatric patients less than 12 years of age, although adequate data to support the indication only existed for 12 and above.

Item	Page	Change Description	Rationale for Change
		Questionnaire (EQ-5D) information at baseline and follow-up in the PSR was used in the analysis for health-related quality of life for all types of dystonia in adults.	
9	14	The Investigator Study[17] provided the main evidence to support the GPi DBS therapy in primary generalized and segmental dystonia in adults.	Updated to clarify that the Investigator Study also included segmental dystonia.
10	14	The study design of Kupsch (2006)[2] was not conducted by Medtronic but partially funded ~~sponsored~~ by Medtronic.	Updated to clarify that the Kupsch study had partial funding from Medtronic.
11	15	Kupsch (2006)[2] was a two arm, double-blind, randomized and placebo-controlled study design to demonstrate the effectiveness of GPi stimulation in subjects with primary generalized or ~~generalized idiopathic~~ segmental dystonia who were severely handicapped, in spite of optimal conservative therapy.	Updated to clarify that the Kupsch study also included segmental dystonia.
12	15	To participate, a center must have successfully treated 8 subjects with DBS Therapy, at least 2 with the target ~~Globus Pallidus internus (~~GPi~~)~~.	Removed definition of acronym that was previously defined.
13	15	*Exclusion Criteria* ▪ Mattis Score ~~<~~ ≤ 120	Corrected exclusion criteria to include less than or equal to symbol.
14	17	***Safety Objectives*** ▪ Systematic recording of the side-effects and adverse events (AEs). ▪ To characterize ~~adverse events (~~AEs~~)~~ for all subjects, including a tabulation of the profiles of the neurostimulation and sham stimulation group subjects through the 3-month blinded phase.	Updated to define acronym on first use and use acronym on subsequent use.
15	17	To demonstrate that the improvement in the movement score in the ~~Burke-Fahn-Marsden-Dystonia-Rating-Scale (~~BFMDRS~~)~~ for subjects in the ~~Deep Brain Stimulation (~~DBS~~)~~ treatment group (neurostimulation) is greater than for subjects in the control group (sham stimulation) after 3 months of therapy. The primary endpoint was a change from baseline to three months in severity of symptoms assessed with the ~~Burke-Fahn-Marsden-Dystonia-Rating-Scale (~~BFMDRS~~)~~ movement score. Data from all of the investigational sites (30/40 patients) were pooled for analysis.	Removed definition of acronyms that were previously defined.
16	17	Volkmann ~~J~~ (2014)[16]	Updated to align with other literature citations.
17	18	Safety	

Item	Page	Change Description	Rationale for Change
		A meta-analysis was conducted to compare rates of therapy-relevant safety events (excluding suicide and suicide attempt because of no reported occurrence in the patient populations evaluated), system revisions, and explants among adult patients based on the type of dystonia. Additionally, the analysis compared these rates between adult and pediatric patients ~~12 years of age and above~~ with primary generalized dystonia.	Removed "12 years of age and above" in these instances to better reflect how analysis was completed. Analysis was completed based on pediatric age of 21 years or below, and some data included pediatric patients less than 12 years of age, although adequate data to support the indication only existed for 12 and above.
18	18	Effectiveness The meta-analysis was conducted to evaluate effectiveness outcomes in adult patients with primary generalized, segmental and cervical dystonia, and in pediatric patients with primary generalized dystonia. Additionally, a comparative analysis was conducted to evaluate differences in adults versus pediatric patients ~~12 years of age and above~~ with primary generalized dystonia.	
19	19	▪ For effectiveness outcomes, the average ~~Burke-Fahn-Marsden Dystonia Rating Scale (~~BFMDRS~~)~~ motor score was used in the analysis for generalized dystonia and segmental dystonia. The average ~~Toronto Western Spasmodic Torticollis Rating Scale (~~TWSTRS~~)~~ severity score was used in the analysis for cervical dystonia.	Removed definition of acronyms that were previously defined.
20	19	Subgroup analyses by dystonia distribution or adult vs pediatric were performed using stratified meta-analysis based on dystonia body distribution or patient population (adult vs pediatric) by utilizing the option of subgroup in *metaprop* function in R. ~~d~~Dystonia subtype differences were statistically tested using the Chi-square (χ^2) test for group differences, with significance defined as $p < 0.05$.[18–20,22]	Corrected capitalization error.
21	20	The registry began as the Implantable Systems Performance Registry (ISPR) and started collecting data on ~~deep brain stimulation (~~DBS~~)~~ patients in 2009. Medtronic has continually worked to develop systems and processes to monitor product performance following market release more effectively and launched the global ~~Product Surveillance Registry (~~PSR~~)~~ in 2011.	Removed definition of acronyms that were previously defined.
22	20	▪ Primary purpose for device use is dystonia as indicated by the physician	Clarified that primary purpose for device use is as indicated by physicians.
23	21	**Safety and Effectiveness Results** Safety and effectiveness outcomes are presented separately for primary generalized, segmental and cervical dystonia in adult patients (> 21 years) and for primary generalized dystonia in pediatric patients (~~≥ 12 years of age but~~ ≤ 21 years of age). These	Removed "12 years of age and above" in these instances to better reflect how analysis was completed. Analysis was completed based on pediatric age of 21 years or below, and some data included pediatric

Item	Page	Change Description	Rationale for Change
		categorizations are based on the dystonia type, and average age reported in each publication or age of patients enrolled in the PSR registry. Safety Results Safety outcomes are presented separately for primary generalized, segmental and cervical dystonia for adult patients, and pediatric patients ~~12 years of age and above~~. Comparisons of therapy-relevant safety events between adult and pediatric patients with primary generalized dystonia by study designs are also provided below to add more detailed information on the safety profile of bilateral GPi DBS in pediatric patients ~~12 years of age and above~~.	patients less than 12 years of age, although adequate data to support the indication only existed for 12 and above.
24	21	Of the 7 events, two (neurostimulation: 1/9 and sham stimulation: 1/9) were considered serious adverse events (SAEs). During the randomization period, a total of two adverse device effects (ADEs) were reported in 2 patients (neurostimulation: 1/9 and sham stimulation: 1/9) with generalized dystonia. The overall ~~adverse event~~ AE and ~~serious adverse event~~ SAE occurrence rates were 22.2% and 11.1% in the 3-month blinded phase in the DBS group, and 72.2% and 55.6% in the open label phase, respectively.	Updated to define acronym on first use and use acronyms that were previously defined.
25	22	Among the publications for generalized dystonia, dystonia severity was characterized by severe or marked disability, impaired function in performance of activities of daily living or poor symptom control in spite of medical management.[17,23,24,26–29] Average age at surgery ranged from 22 to 38 years.[17,24–28] Duration of generalized dystonia before surgery ranged from 8 to 22 years, including Investigator Study.[17,24–26,28]	Added clarification that range includes Investigator Study.
26	22	Across six other published studies, the reported incidence rates for AE and SAE ranged from 25% to 58%,[24–28] and 8 to 18%,[24–26,28] respectively, over a follow-up periods spanning 6 months to up to 8 ~~7~~ years of follow-up in adult patients with generalized dystonia.	Corrected value, consistent with data in the corresponding table.
27	24	Table 5 summarizes overall results of the meta-analysis of therapy-relevant safety outcomes in adult patients with GPi DBS for ~~G~~generalized ~~D~~dystonia using random effects model.	Minor editorial update for consistency with the rest of the document.
28	24	For adult patients with generalized dystonia, device complications (22%), infections (12%), and intracerebral hemorrhage (symptomatic: 3%, asymptomatic: ~~0~~3%) are the main therapy-related safety events. Device revisions (19%) and explants (13%) are the most common other safety events. These rates are based on pooled data from multiple publications.	Corrected values, consistent with data presented in P960009/S482/A001 and response to interactive questions from 10-Oct-2025.

<table>
<tr><th>Item</th><th>Page</th><th>Change Description</th><th>Rationale for Change</th></tr>
<tr><td>29</td><td>24</td><td>Table 5. Pooled Safety Event Rates in adult patients with GPi DBS for Generalized Dystonia using Random Effects Model
<table>
<tr><th>Safety Event</th><th>Pooled Event Rate (95% CI)</th><th>No. of Publications</th><th>References</th></tr>
<tr><td colspan="4">Therapy-Relevant Safety Events</td></tr>
<tr><td>Device complications</td><td>22% (10-44%)</td><td>7</td><td>17,23–28</td></tr>
<tr><td>Infection</td><td>12% (8-18%)</td><td>6</td><td>17,23–27</td></tr>
<tr><td>Symptomatic ICH</td><td>3% (1-9%)</td><td>5</td><td>17,23,24,27,28</td></tr>
<tr><td>Asymptomatic ICH</td><td>~~0~~3% (~~0 26~~ 1-11%)</td><td>4</td><td>17,23,27,28</td></tr>
<tr><td colspan="4">Other Safety Events</td></tr>
<tr><td>Device revisions</td><td>19% (8-40%)</td><td>6</td><td>17,24–28</td></tr>
<tr><td>Explants</td><td>13% (8-20%)</td><td>4</td><td>17,24–26</td></tr>
</table></td><td></td></tr>
<tr><td>30</td><td>26</td><td>Among the publications for segmental dystonia, severity was characterized by severe symptoms, marked disability or functional impairment, or failed or discontinued medications or botulinum neurotoxin due to no or slight effect.[17,30–37] Average age at surgery ranged from 47 to 67 years.[17,30–37] Duration of segmental dystonia before surgery ranged from 3 to 20 years, including Investigator Study.[17,30–37]</td><td>Added clarification that range includes Investigator Study.</td></tr>
<tr><td>31</td><td>26</td><td>Across eight other published studies, the reported incidence rates for AE and SAE ranged from 8.3% to 100%,[30–36] and 0 to 25%,[36,37] respectively, over a follow-up period of 6 months to 5.6 years in adult patients with segmental dystonia of the head and neck.</td><td>Minor editorial update.</td></tr>
<tr><td>32</td><td>29</td><td>In addition to Volkmann (2014)[16], the analysis of safety of bilateral GPi DBS for the treatment of cervical dystonia in adult patients also include data from 8 published studies with a total of ~~183~~ 238 patients contributing safety outcomes.</td><td>Corrected value consistent with data in corresponding table.</td></tr>
<tr><td>33</td><td>29</td><td>Across eight ~~nine~~ other published studies, the reported incidence rates for AE and SAE ranged from 3.8% to 80%[36,38–40,42–45] and 0 to 14.3%,[36,38,39,45,48] respectively, over a follow-up period of 1 year to up to 10 years in adult patients with cervical dystonia.</td><td>Corrected value consistent with data in corresponding table and made minor editorial updates.</td></tr>
</table>

Item	Page	Change Description	Rationale for Change
34	32	Average age at surgery ranged from ~~10~~ 12 to 17 years across the studies reviewed,[25,49,51–53,55–58] with the exception of one study reporting an average age of 10.2 years.[50] Duration of dystonia symptoms before surgery ranged from 3 to 10 years.[25,49–58]	Clarified average age of surgery was 12 of older for all but one study.
35	33	Across 12 published studies, the reported incidence rates for AE and SAE ranged from 0% to 100%[23,25,49–53,55–58] and 0 to 60%,[25,50,51,53] respectively, over a follow-up period of 6 months to up to 8.5 ~~10~~ years in pediatric patients with generalized dystonia.	Corrected average value consistent with data in corresponding table and made minor editorial updates.
36	35	Petrossian ~~MT~~ (2013)[56] Ramezani ~~Ghamsari M~~ (2021)[57]	Updated to align with other literature citations.
37	36-37	The combined device complication rate across both dystonia types was 14% (95% CI: 5–34%) with ~~high~~ substantial heterogeneity across both groups (p=0.0502).	Corrected characterization of heterogeneity.
38	43	There were 166 ~~adverse events (~~AEs~~)~~ reported in 87 (28.2%) of the 308 dystonia patients. Within these adverse events, 58 were considered serious and occurred in 39 (12.7%) dystonia patients. By age group, ~~serious adverse events (~~SAEs~~)~~ occurred in 3 of 27 (11.1%) pediatric patients and 36 of 279 (12.9%) adult patients (Table 15).	Removed definition of acronyms that were previously defined.
39	46	The 37 PPEs for adult and pediatric patients are summarized in Table 18 ~~22~~ by MedDRA Preferred Term.	Corrected table reference.
40	48-49	Effectiveness Results Effectiveness outcomes comprised changes in average BFMDRS motor scores for generalized and segmental (head and neck) dystonia and average TWSTRS severity scores for cervical dystonia. Outcomes are presented separately for primary generalized, segmental (head and neck) and cervical dystonia for adult patients, and pediatric patients ~~12 years of age or above~~ with primary generalized dystonia. Comparisons of effectiveness outcomes between adult and pediatric patients with primary generalized dystonia by study designs are also included to provide additional information on the effectiveness of bilateral GPi DBS by study design in pediatric patients ~~12 years of age or above~~ with primary generalized dystonia.	Removed "12 years of age or above" in these instances to better reflect how analysis was completed. Analysis was completed based on pediatric age of 21 years or below, and some data included pediatric patients less than 12 years of age, although adequate data to support the indication only existed for 12 and above.
41	49	The highest level of available evidence is the Investigator Study,[17] a subset data of 30 patients (18 with generalized dystonia, 11 with segmental dystonia, one additional patient with multifocal dystonia is excluded from this subgroup analysis) from the Kupsch (2006)[2] ~~randomized controlled trial (~~RCT~~)~~ study and Volkmann (2012)[15] study. ~~[16,23–27]~~	Removed definition of acronym that was previously defined. Deleted typo, as citations originally corresponded to content that was deleted.

Item	Page	Change Description	Rationale for Change
42	49	Similar results were reported in the published article from the same clinical study with the full study cohort (n=40), where the motor score was improved by 44.8% at 6 months (n=24), 70.6% at 3 years (n=20) and 67.0% at 5 years (n=20), compared ~~with~~ to baseline.[15]	Minor editorial update.
43	51	*Effectiveness Outcome from the Publications* In addition to the Investigator's Study,[17] the analysis of effectiveness of bilateral GPi DBS for the treatment of primary generalized dystonia in adult patients also includes data from 5 published studies with a total of 118 patients contributing effectiveness outcomes. The 5 publications consist of 3 prospective studies and 2 retrospective studies. These total of six (6) studies (including Investigator Study) for primary generalized dystonia in adult patients include 130 patients with follow-ups ranging from 1 year to 7 years; and average baseline BFMDRS motor scores from 44 to 61 out of a possible score of 120. Across five other prospective and retrospective ~~published~~ studies, the average improvement in BFMDRS motor scores ranged from 43.5% to 79.6% at 1 year,[17,23–27] 49.9% to 82.5% at 2 years,[17,23,26,27] and 56.4% to 85.5% at 3 years.[17,25,27] Table 23 below reports effectiveness outcomes from the six publications (1 RCT, 3 prospective and 2 retrospective studies) on adult patients with GPi DBS for generalized dystonia and reflects the latest follow-up data used in the meta-analysis.	Added minor clarifications to text.
44	52	To address the possibility that effect estimates from different study designs may not represent the same inferential target, a meta-analysis of effectiveness outcomes by study designs in adult patients was conducted for generalized dystonia, focusing on the BFMDRS ~~(Burke-Fahn-Marsden Dystonia Rating Scale)~~ motor score improvements measured by standardized scales across various study designs.	Removed definition of acronym that was previously defined.
45	52	Figure 8 presents forest plots of the BFMDRS motor score at the latest follow-up in adult patients with GPi DBS for generalized dystonia, with data pooled from the prospective studies (a), retrospective studies (b) and RCT~~s~~ (c). The pooled BFMDRS motor score improvement for the three prospective studies was 58.08% (95% CI: 33.02% - 83.13%) under the random effects model with Hartung-Knapp (HK) method applied to adjust the confidence interval, shown in Figure ~~9~~8a~~)~~. In comparison, the pooled BFMDRS motor score improvement for the two retrospective studies was 65.18% (95% CI: 33.65% - 96.70%), indicated in Figure ~~9~~8b~~)~~. There was only one RCT study, and the point estimate is 60.80% with a 95% CI of 46.26% - 75.34%, shown in Figure ~~9~~8c~~)~~.	Corrected typos and updated numbering scheme for figure components.
46	53	The highest level of available evidence is the Kupsch (2006)[2] study, the ~~i~~Investigator Study,[17] a subset of data from the Kupsch (2006)[2] and Volkmann (2012).[15]	Minor editorial update for consistency with the rest of the document.

Item	Page	Change Description	Rationale for Change
47	55	Table 26 below reports effectiveness outcomes from the eight (8) publications (2 prospective and 6 retrospective studies) on adult patients with segmental dystonia and reflects the latest follow-up data used in the meta-analysis.	Added minor clarification to text
48	57	A meta-analysis of effectiveness outcomes by study designs in adult patients was conducted for segmental dystonia, focusing on the BFMDRS ~~(Burke-Fahn-Marsden Dystonia Rating Scale)~~ motor score improvements measured by standardized scales across various study designs.	Removed definition of acronym that was previously defined.
49	57	Figure 10 presents forest plots of the BFMDRS motor score at the latest follow-up for segmental dystonia in adult patients, with data pooled from the prospective studies (a), retrospective studies (b) and RCT~~s~~ (c). The pooled BFMDRS motor score improvement for the two prospective studies was 65.08% (95% CI: 53.46% - 76.70%) under the random effects model with Hartung-Knapp (HK) method applied to adjust the confidence interval, shown in Figure 10a~~)~~. In comparison, the pooled BFMDRS motor score improvement for the six retrospective studies was 61.15% (95% CI: 53.11% - 69.20%), indicated in Figure 10b~~)~~. There was only one RCT study, and the point estimate is 59.60% with a 95% CI of 45.80% - 73.40%, shown in Figure 10c~~)~~. Each study contributes roughly equally to the overall results.	Corrected typo, updated numbering scheme for figure components, and added clarification to text.
50	60	Across nine prospective and retrospective ~~other published~~ studies, the average improvement in TWSTRS severity scores ranged from 32% to 75% at 3 to 12 months,[36,39,41,44] 49% to 73% at 2 to 4 years[40,41,43,48] and one study reported an improvement range of 29% to ~~75%~~ 31%[42] ~~at follow-up time points ranging from 3 months to 7.8~~ after 10 years of follow-up. These values trended higher than the average improvement of 28% in Volkmann (2014)[16] which may have been impacted by the short follow-up of 6 months. Table 28 below reports effectiveness outcomes from the nine (9) other publications (1 prospective and 8 retrospective studies) in adult patients with cervical dystonia and reflects the latest follow-up data used in the meta-analysis.	Updated to include greater specificity of severity scores at certain follow-up periods, consistent with sections for other dystonia sub-types (e.g., generalized, segmental of the head and neck), and added minor clarification to text.
51	62	The pooled TWSTRS severity score improvement for the eight retrospective studies was 62.04% (95% CI: 54.93% - 69.15%) under the random effects model with Hartung-Knapp (HK) method applied to adjust the confidence interval, shown in Figure 12b~~)~~. There was only one RCT study, and the point estimate is 28.00% with a 95% CI of 22.26% - 33.74%, shown in Figure 12c~~)~~.	Updated numbering scheme for figure components.
52	63	Average age at surgery ranged from ~~10~~ 12 to 17 years across the studies reviewed,[25,49,51–53,55–58] with the exception of one study reporting an average age of 10.2 years.[50]	Clarified average age of surgery was 12 of older for all but one study.

Item	Page	Change Description	Rationale for Change
53	63	Table 29 below reports effectiveness outcomes from the 11 publications (4 prospective and 7 retrospective studies) on pediatric patients with generalized dystonia and reflects the latest follow-up data used in the meta-analysis.	Added minor clarification to text.
54	65	The pooled BFMDRS motor score improvement for the four prospective studies was 75.24% (95% CI: 56.85% - 93.62%) under the random effects model with Hartung-Knapp (HK) method applied to adjust the confidence interval, shown in Figure 14a~~)~~. In comparison, the pooled BFMDRS motor score improvement for the seven retrospective studies was 69.85% (95% CI: 54.34% - 85.37%), indicated in Figure 14b~~)~~.	Updated numbering scheme for figure components.
55	66	Average age at surgery in pediatric patients ranged from 10 to 17 years[25,49–53,55–58,60] and 22 to 38 years for adult patients.[17,24–28] ~~Duration of generalized dystonia before surgery ranged from 8 to 22 years.[17,24–26,28]~~ Duration of dystonia symptoms before surgery ranged from 3 to 10 years in ~~pedaitrics~~ pediatrics[25,49–53,55–58,60] and 8 to 22 years for adult patients.[17,24–26,28] Average baseline BFMDRS motor scores across the data sources ranged from 38 to 60 in pediatric population out of a possible score of 120,[23,25,49–53,55–58,60] which is comparable to the range of 42 to 64 reported in the adult population.[17,23–25,27,28]	Deleted duplicative information, corrected typo, and added clarification about data relating to the pediatric population.
56	66	There was high heterogeneity within both the adult and pediatric patient groups. This phenomenon has been reported in the published literature ~~in adult populations~~. ~~Heterogeneity also has been reported in pediatric studies.~~	Deleted duplicative information.
57	67	Additionally, a conservative assessment identified 11 cognitive-related ~~adverse events~~ AEs in additional scientific articles[62–64] and PSR, including cognitive deficits or worsening (3), depression (2), psychiatric comorbidity (2), aggression (1), agitation (1), anxiety (1), and low mood (abulia and ebullience) (1).	Updated to use acronym that was previously defined.
58	68	Additional literature review of cognitive, mood, and behavioral-related ~~adverse events~~ AEs reported three events of cognitive deficits and eight other ~~adverse events~~ AEs in three published studies[62–64].	Updated to use acronyms that were previously defined.
59	68	Xu (2020)[64] retrospectively studied nine pediatric patients treated with bilateral stimulation of the subthalamic nucleus (mean age 15.9) over 10 years, reporting cognitive deficits, depression, and anxiety as ~~adverse events~~ AEs; some symptoms improved with stimulation adjustment, though details were unspecified.	Added clarification about stimulation target of patients in Xu (2020) and updated to use acronym that was previously defined.
60	68	Additional analysis of the PSR adverse events related to cognition, mood, and behavior ~~included~~ identified only one ~~specific AEs in one~~ SAE of aggression in a pediatric patient after 6 years of device use, which~~. This patient experienced a serious adverse event of aggression and~~ was treated with medication.	Minor editorial update.

Item	Page	Change Description	Rationale for Change
61	70	Effectiveness was assessed using standardized scales to assess dystonia severity: ~~Burke-Fahn-Marsden Dystonia Rating Scale (~~BFMDRS~~)~~ for generalized/segmental dystonia and ~~Toronto Western Spasmodic Torticollis Rating Scale (~~TWSTRS~~)~~ for cervical dystonia.	Removed definition of acronyms that were previously defined.
62	71	Across nine other published studies, the average improvement in TWSTRS severity scores ranged from 32% to 75% at 3 to 12 months,[36,39,41,44] 49% to 73% at 2 to 4 years[40,41,43,48] and one study reported an improvement range of 29% to ~~75%~~ 31%[42] ~~at follow-up time points ranging from 3 months to 7.8~~ after 10 years of follow-up. These values trended higher than the average improvement of 28% in Volkmann (2014)[16] which may have been impacted by the short follow-up of 6 months.	Updated to include greater specificity of severity scores at certain follow-up periods, consistent with sections for other dystonia sub-types (e.g., generalized, segmental of the head and neck), consistent with update on page 60 of Clinical Summary (Item 50).
63	71-72	Average age at surgery ranged from ~~10~~ 12 to 17 years across the studies reviewed,[25,49,51–53,55–58] with the exception of one study reporting an average age of 10.2 years[50], and duration of dystonia symptoms before surgery ranged from 3 to 10 years.	Clarified average age of surgery was 12 or older for all but one study.
64	72	The Investigator Study[17] reported overall ~~adverse event~~ AE and ~~serious adverse event~~ SAE occurrence rates of 22.2% and 11.1% in the 3-month blinded phase, and 72.2% and 55.6% in the open label 5 year follow-up phase, respectively.	Updated to use acronyms that were previously defined.
65	72	Meta-analysis of therapy-relevant safety events across the 7 total studies showed that device complications (22%), revisions (19%), and explants (13%) were the most frequent safety events, followed by infections (12%). Intracerebral hemorrhage (symptomatic: 3% and asymptomatic: ~~0~~ 3%) were less common.	Corrected value, consistent with updates on page 24 of Clinical Summary (Items 28-29).
66	73	Across eight other published studies, the reported incidence rates for AE and SAE ranged from 8.3% to 100%,[30–36] and 0 to 25%,[36,37] respectively, over a follow-up period of 6 months to 5.6 years in adult patients with segmental dystonia of the head and neck.	Minor editorial update.
67	73	Across nine other published studies, the reported incidence rates for AE and SAE ranged from 3.8% to 80%[36,38–40,42–45] and 0 to 14.3%,[36,38,39,45,48] respectively, over a follow-up period of 1 year to 10 years in adult patients with cervical dystonia.	Minor editorial update.
68	73	There are no RCTs and few large case series evaluating DBS for pediatric dystonia. The safety analysis included 202 pediatric patients with generalized dystonia from 12 published literature studies (4 prospective and 8 retrospective studies) with an average follow-up ~~ranged~~ ranging from 6 months to 10 years. Average age at surgery ranged from 12 to 17 years across the studies reviewed,[25,49,51–53,55–58] with the exception of one study reporting an average age of 10.2 years[50] and duration of dystonia symptoms before surgery ranged from 3 to 10 years.	Added average age at surgery information to pediatric safety conclusion, and made minor editorial updates.

Item	Page	Change Description	Rationale for Change
		Across 12 published studies, the reported incidence rates for AE and SAE ranged from 0% to 100%[23,25,49–53,55–58] and 0 to 60%,[25,50,51,53] respectively, over a follow-up period of 6 months to 10 years in pediatric patients with generalized dystonia.	
69	74	A total of 166 ~~adverse events~~ AEs (related to device, therapy, or procedure) were recorded in 87 patients (28.2%).	Updated to use acronym that was previously defined.
70	75	Data to support the benefits of bilateral GPi DBS as an effective intervention for primary cervical dystonia in adults include the RCT by Volkmann (2014~~7~~)[16], which demonstrated improvement in TWSTRS severity score by 26% in the neurostimulation group compared to 6% in the sham stimulation group at 3 months and 28% at 6 months after DBS.	Corrected citation reference
71	75	Therapy-related safety event rates included device complications (8.1%), device revisions (3.2%), ~~and~~ explants (1.6%)~~.~~, infections (4.8%), and intracranial hemorrhage (symptomatic: 1.6%, asymptomatic: NR).	Minor editorial update.
72	76	Patient Perspective ~~This submission~~ The clinical data did not include specific information on patient perspectives for this device. Overall, the data ~~in this application~~ support the reasonable assurance of safety and effectiveness of this device when used in accordance with the indications for use.	Removed reference to "this submission" and "this application" from the Clinical Summary.
73	77	▪ Follow-up durations with substantial variation ranging from 6 months (Volkmann 2014~~,~~[16], Ostrem 2007[31]) to over 10 years (Walsh 2013[44]: 4.9-10.7 years; Jacksch 2022[42]: 10 years; Ramezani ~~Ghamsari~~ 2021[57]: 7-10 years) across studies, with most studies falling between 1-5 years of follow-up; and	Added citations and updated to align with other literature citations.
74	77	▪ The PSR was primarily used to provide device safety information. Patient disposition information in the PSR indicates high lost-to-follow-up (LTFU) rates (20.5%, 52.9%, 61.4%, and 68.2% for years 2-5, respectively), which likely results in underreporting of ~~adverse events~~ AEs and ~~serious adverse events~~ SAEs and introduces bias in ~~adverse event~~ AE and ~~serious adverse event~~ SAE rate assessments.	Updated to use acronyms that were previously defined.
75	79	The evidence presented ~~in this application~~ supports the reasonable assurance of effectiveness of this device when used in accordance with the indications for use.	Removed reference to "this application" from the Clinical Summary.
76	86	Added back cover	Added for consistency with other Medtronic DBS labeling.

Indications

Medtronic DBS Therapy for Dystonia

Bilateral stimulation of the internal globus pallidus (GPi) using Medtronic DBS Therapy for Dystonia is indicated as an aid in the management of chronic, intractable (oral and/or injectable medication refractory) primary dystonia, including:

- generalized dystonia, segmental dystonia of the head and neck, and cervical dystonia (torticollis) in adult patients.
- generalized dystonia in pediatric patients twelve years of age or above.

GPi target system components:

- Model B35200 Percept™ PC neurostimulator
- Model B35300 Percept RC neurostimulator
- Model 37601 Activa™ PC, Model 37602 Activa SC, or Model 37603 Activa SC neurostimulator
- Model 37086 extension
- Model 3387 or Model 3389 lead
- Model B33005 or Model B33015 SenSight™ directional lead
- Model B34000 SenSight extension

Refer to the appropriate information for prescribers booklet for contraindications, warnings, precautions, adverse events summary, individualization of treatment, patient selection, use in specific populations, resterilization, and component disposal.

Medtronic

Manufacturer
Medtronic, Inc.
710 Medtronic Parkway
Minneapolis, MN 55432
USA
www.medtronic.com
Tel. 1-763-505-5000
Toll-free 1-800-328-0810

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Medtronic Deep Brain Stimulation Therapy for Dystonia

Indication-specific information for implantable neurostimulators

Information for prescribers addendum

Rx only

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Information available for the Deep Brain Stimulation Therapies:

The information for prescribers manual provides information about contraindications, warnings, precautions, adverse events, sterilization, and component disposal. The information for prescribers addendums contain indication-specific information. For customers in Japan, the appropriate package insert provides information about safety, contraindications, warnings, precautions, and adverse events.

The indications sheet provides information about indications and related information. For customers in Japan, the appropriate package insert provides information about indications.

The system eligibility and battery longevity manual describes programming considerations and provides battery longevity information to aid in the appropriate neurostimulator selection.

MRI guidelines provide information about any MRI conditions and MRI-specific contraindications, warnings, and precautions for MRI scans with the neurostimulation system.

Product manuals, such as programming guides, recharging guides, and implant manuals provide device descriptions, package contents, device specifications, product-specific warnings and precautions, and instructions for use.

! USA **The clinical summary provides information about the clinical study results for the neurostimulation system.**

Contraindications

There are no therapy-specific contraindications for Medtronic DBS Therapy for Dystonia. Refer to the primary DBS Information for Prescribers manual for common DBS contraindications.

Warnings

Refer to the "Warnings" sections in the primary DBS Information for Prescribers manual.

Status dystonicus - Severe, life-threatening dystonia symptoms, including status dystonicus (also known as dystonic crisis or dystonic storm), during ongoing or loss of DBS Therapy may result in respiratory compromise and rhabdomyolysis. In rare cases, rhabdomyolysis may progress to multi-organ failure and death.

Monitor patients receiving DBS Therapy for these symptoms. Emphasize the importance of contacting the patient's clinician if they experience increased severity of symptoms.

Risk of depression, suicidal ideations, and suicide - Depression, suicidal ideations and suicide have been reported in patients receiving Medtronic DBS Therapy, although no direct cause and effect relationship has been established. Preoperatively, assess patients for suicide risk and carefully balance this risk with the potential clinical benefit. Postoperatively, monitor patients for the presence of depression, suicidal thoughts or behaviors, changes in mood and/or impulse control and manage these symptoms appropriately. Emphasize the importance of sustained follow-up and support with all patients, their caregivers, and family members.

Importance of regular recharging (rechargeable neurostimulator only) - Inform patients and their caregivers that it is important to maintain a regular schedule of recharging.

Return of symptoms and rebound effect - Inform patients and their caregivers that abrupt cessation of stimulation for any reason, including failure to maintain adequate battery charge in rechargeable neurostimulators, will probably cause a return of disease symptoms. In some cases, symptoms may return with an intensity greater than was experienced prior to system implant (rebound effect). This can in rare cases constitute a medical emergency. For patients with rechargeable neurostimulators, it is important that the clinician emphasize the following:

- Patients must be willing and able to perform battery status checks and battery recharge activities on a frequent basis.
- The device charge level should be maintained such that symptoms are controlled.
- The recharge warnings from the patient control device must be understood and heeded by the patient and caregiver.
- Medication may aid in symptom control during short periods of time following depletion of the device before a recharge session.

If symptoms worsen or do not abate following recharge, the patient should contact his or her clinician immediately so the status of the system can be assessed and the condition of the patient can be monitored.

Precautions

Refer to the "Precautions" sections in the primary DBS Information for Prescribers manual.

Programming with SenSight™ Directional Leads - If programming with segmented electrode levels, it is recommended that clinicians begin programming with all segments activated on the electrode level. If there are undesirable side effects or therapy is not optimal with all segments activated, it is recommended to switch to programming with directional stimulation.

Clinician training

Prescribing clinicians - Prescribing clinicians should be experienced in the diagnosis and treatment of dystonia and should be familiar with the use of the Medtronic DBS System for Dystonia.

Implanting clinicians - Implanting clinicians should have expertise with functional stereotactic neurosurgical treatment of dystonia. Such expertise should include knowledge of the anatomical and neurophysiological characteristics of the targeted nucleus, surgical and/or implantation techniques for the Medtronic DBS System for Dystonia, operational and functional characteristics of the Medtronic DBS System for Dystonia, and experience in the continued management of patients by stimulation parameter adjustment. Clinicians may contact Medtronic before prescribing or implanting a Medtronic DBS System for Dystonia for the first time and request a referral to a clinician experienced in the use of Medtronic DBS Therapy for Dystonia.

Prescribing and implanting clinicians of rechargeable neurostimulation systems should be aware of the patient requirements for a rechargeable neurostimulator. Refer to the primary DBS Information for prescribers manual for the patient requirements for rechargeable neurostimulators.

All programming of the Medtronic DBS System for Dystonia should be performed by or under the supervision of a clinician or other experienced medical personnel familiar with the use of the programming software and equipment. Clinicians should be thoroughly familiar with the supporting material for the Medtronic DBS System for Dystonia, including all product labeling and education and training materials.

Special considerations for pediatric patients

Dual system implant - If two neurostimulators are implanted, they should be implanted at least 20 cm (8 inches) apart to minimize cross-programming interference. In smaller patients, consider placing one neurostimulator in the abdomen and one in the chest region. In this case, route both lead-extension assemblies and implant both neurostimulators on the same side of the body to minimize potential electromagnetic

interference. A 95 cm extension is recommended to connect the lead to the abdominal neurostimulator. Verify final programmed parameters by reviewing both devices at the conclusion of any programming session.

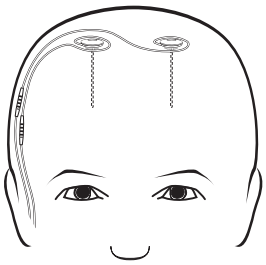

Figure 1. *Lead-extension assembly routing with a dual system implant.*

Patient growth and lead-extension length - Evaluate the patient's implanted lead-extension assembly for sufficient strain relief (for example, consider patient comfort, range of motion, x-ray visualization of the extension) at regular post-implant follow-up sessions. This monitoring is especially important for patients whose growth is not complete at implant. Consideration should be given to replacement of the extension with one of greater length during other elective surgery procedures, such as during the regular changeout of neurostimulators that must occur because of battery depletion.

Patient brain growth and lead migration - In cases where growth of the brain and/or skull is not complete at time of implant, the distance from the lead anchor point (burr hole) to the target site increases with time and growth of the individual. As a result, lead migration relative to the target site may occur.

If significant patient growth and potential resultant lead migration are anticipated, consider positioning lead electrodes as follows at the time of initial lead placement: Position the lead so that the center bipole electrodes (for example, electrodes 1 and 2) will be active. If lead migration occurs, effective stimulation may be regained through programming adjustments instead of surgical repositioning.

The need for frequent programming or the inability to control dystonic symptoms may indicate lead migration. Consider assessing system performance and potential modifications to the therapeutic settings (neurostimulator settings and/or electrode configurations). These factors should be considered in the establishment of long-term care and follow-up schedules for individuals who receive a Medtronic DBS System at an early age.

Patient brain development - The impact of DBS on overall cognitive and neurological development and behavioral changes in pediatric patients is unknown.

Important patient counseling information

Refer to the “Patient counseling information” section in the primary DBS Information for Prescribers manual for general patient counseling information for deep brain stimulation therapies.

Medtronic DBS Therapy for Dystonia is an active therapy that requires both clinician and patient involvement to be successful. Ensure the patient understands this will be a long-term relationship between physician, medical staff, patient, and family.

Show the patient and family the device before implant. This may be particularly beneficial when counseling pediatric patients.

After the Medtronic DBS System is implanted, advise the patient or caregiver to read the DBS Therapy-specific Patient manual for dystonia.

Symptom suppression

Dystonia patients may not experience immediate symptom suppression from the therapy. The patient should be advised that frequent, non-invasive adjustments to the stimulation parameters may be required to achieve optimal symptom suppression. This adjustment period may take weeks or months.

Rebound effect

Patients need to be aware that dystonia symptoms may return following accidental system turn-off, battery depletion, or system failure. It is important that the clinician discuss the predicted time of battery replacement with the patient and that the battery condition be closely monitored. It is also important that the patient and caregiver know how to use the patient control device in case the neurostimulator is accidentally turned off. If symptoms return, the patient should contact his or her clinician immediately so the status of the system can be assessed, and the condition of the patient can be monitored.

Pediatric considerations

The following issues should be included in clinician discussions with the patient and the patient’s family or caregiver(s):

- Children are often engaged in active play and sports activities that could damage components of the implanted system. While some degree of rough play may be unavoidable, children should be advised to avoid games, sports, and other pastimes where a strain to the lead-connector assembly or a percussive injury to system components may be likely to occur (for example, soccer, football, or rugby).

- Various medical or environmental (home, occupational, and other) devices may generate enough electromagnetic interference (EMI) to change the parameters of a neurostimulator, turn a neurostimulator off and on, or cause a neurostimulator to surge, shock, or jolt the patient. Ensure the patient and parents/caregivers are clear on why EMI is a potential concern, and where information on this issue can be found in their patient manuals. EMI is addressed in the “Warnings” section and the “Electromagnetic Interference” section in the DBS Patient Therapy Guide. EMI is also addressed in the “Precautions” section of the primary DBS Information for Prescribers manual.

Adverse events

For potential adverse events related to DBS therapy, refer to the primary DBS Information for Prescribers manual.

In addition to the adverse events related to DBS therapy, the following potential adverse events can occur with DBS Therapy for Dystonia.

Risks (potential adverse events) after implantation of the lead(s), extension(s), or neurostimulator(s):

- Hemiplegia or hemiparesis

Note: Pediatric patients may have increased risks of infections, device-related complications (for example, hardware breakage), revisions, and explants compared to adults due to continued growth, increased physical activity, and potential for longer duration of use.

For adverse events reported in dystonia clinical studies, refer to the clinical summary.

Medtronic

Manufacturer
Medtronic, Inc.
710 Medtronic Parkway
Minneapolis, MN 55432
USA
www.medtronic.com
Tel. 1-763-505-5000
Toll-free 1-800-328-0810

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Deep Brain Stimulation

Therapy for Dystonia

Clinical summary

Rx only

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Definition of Terms

Medtronic Deep Brain Stimulation (DBS) Therapy for Dystonia – Generic name for a medical treatment developed by Medtronic in collaboration with medical researchers as an aid in the management of chronic, intractable (medication refractory) primary dystonia, including generalized dystonia, segmental dystonia of the head and neck, and cervical dystonia (torticollis) in adult patients, and primary generalized dystonia in pediatric patients twelve years of age or above. The therapy uses an implantable medical device to deliver electrical stimulation to the internal globus pallidus.

Anatomy

Globus pallidus (GPi, GPe) – An anatomical structure of the brain which lies between the thalamus and the insular cortex. It is divided into two regions called the internal segment (GPi) and the external segment (GPe). The GPi and the GPe are part of a sub-circuit of the brain called the Basal Ganglia which constitutes a feedback loop from the cortex back to the cortex through the Thalamus, and projects to the Brain Stem. The GPi is considered an output circuit of the Basal Ganglia with cells projecting to the Thalamus and Peduncular Pontine Nucleus.

Clinical Rating Scales

These are two common rating scales that physicians use for evaluating dystonia symptoms:

Burke-Fahn-Marsden Dystonia Rating Scale (BFMDRS) -The BFMDRS is the standard for assessing primary generalized dystonia and other forms of non-generalized dystonia. It captures information about dystonic involvement in all body regions. The BFMDRS is composed of a clinical (or motor or severity) subscale which measures dystonia in nine body regions (maximum 120 = worst score) and a functional (or disability) subscale which quantifies that patients' abilities in daily life and reflects his/her quality of life (maximum 30 = worst condition). A combined score of the two subscales has a maximum or worst condition of 150. Improvement is calculated as a percent of maximum possible gain; that is, (baseline – follow-up)/baseline.[1]

A clinically meaningful improvement is ≥20% reduction in BFMDRS severity score from baseline in adult and pediatric patients.[2–4]

Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) – Cervical dystonia is often assessed with TWSTRS. TWSTRS is comprised of three parts: a clinical or severity score (maximum 35 = worst condition), a functional or disability score (maximum 32 = worst condition), and a pain score (maximum 20 = worst). Improvement is calculated as (baseline – follow-up)/baseline.[5]

A clinically meaningful improvement is ≥25% reduction in TWSTRS total and severity scores from baseline.[6]

Quality of Life (QOL)

European Quality of Life 5-Dimension Questionnaire (EQ-5D) – The EQ-5D is a five-dimensional generic preference-based measure of health-related quality of life (HRQoL) developed by the EuroQoL Group. It is comprised of five dimensions: 1) mobility, 2) self-

care, 3) usual activities, 4) pain/discomfort, and 5) anxiety/ depression. Each dimension is rated by each patient with five possible levels: level 1 response represents "no problems", level 2 "slight problems", level 3 "moderate problems", level 4 "severe problems", and level 5 "extreme problems" or "unable to perform".

The EQ-5D scoring generates an index score, with higher scores representing better health-related quality of life. The EQ-5D Index Score minimally important difference for EQ-5D has been described as a range of 0.037 to 0.069 points.[7,8]

Short Form-36 (SF-36) – The SF-36 is a self-reported quality of life instrument to measure general health status. It measures eight domains of health status: physical functioning (PF), role-physical (RP), role-emotional (RE), bodily pain (BP), vitality (VT), mental health (MH), social functioning (SF), and general health (GH). Scoring of the questions is generally based on a scale of 0-100 and the lower the score, the more disability.[9]

There are distinct concepts measured by the SF-36: a physical dimension, represented by the Physical Component Summary (PCS), and a mental dimension, represented by the Mental Component Summary (MCS). A single measure of health-related quality of life derived from SF-36 has been increasingly reported as a global, total or overall score over the past two decades.[10]

Minimal clinically important differences (MCID) have been defined for the physical component of SF-36 (improvement or worsening of 5.5 points), mental component (improvement of 6.5 points or worsening of 7.5 points), and the total score (improvement of 7.5 points or worsening of 8.5 points) with higher scores reflecting improved quality of life.[4]

Programmable Parameters

Amplitude – A measure of the electrical intensity delivered in a stimulating pulse, measured either in volts (V) or current (mA).

Anode – The positive pole of an electrical circuit. For Medtronic DBS Therapy, any one or more of the lead electrodes or the neurostimulator case can be programmed as an anode.

Bipolar stimulation system – A system in which the current flows between two or more electrodes of the lead, where the lead has both positive and negative poles. Stimulation effectiveness is greater near the negative pole than the positive pole.

Cathode – The negative pole of an electrical circuit. For Medtronic DBS Therapy, any one or more of the lead electrodes can be programmed negative and function as a cathode.

Electrode – The exposed end of a conducting wire (lead) where electrical current is transferred to the brain.

Parameter, programmable – A specific function with an operating range of selectable values (i.e., amplitude, rate, pulse width) that enables the tailoring of a therapeutic modality for a patient.

Polarity – Electrical charge of an object which is either positive or negative.

Pulse width – A measure, in microseconds, of the duration of each stimulating pulse.

Rate – A measure, in pulses per second, that provides the numbers of times stimulating pulses are delivered each second.

Telemetry – Refers to the process of transmitting and receiving data to confirm or adjust programming information from the physician programmer to the neurostimulator.

Unipolar stimulation – A system in which the electrical current flows between the electrode(s) of the lead and the neurostimulator case, which serve respectively as the negative and positive poles.

Disease Terms, Symptoms and Side Effects

Cervical dystonia – Type of focal dystonia that affects the neck and shoulder regions.

Dysarthria – Slurred speech.

Dyskinesia – Abnormal involuntary movements.

Dystonia – Dystonia is a movement disorder characterized by sustained or intermittent abnormal movements, postures, or both. Dystonic movements and postures are typically patterned and repetitive and may be tremulous or jerky. They are often initiated or worsened by voluntary action, and frequently associated with overflow movements.[11]

Dystonic tremor – Tremor-like muscle spasms or tremulous movements.

Focal dystonia – Type of dystonia that affects a single body part in isolation.

Generalized dystonia – Type of dystonia that affects the trunk and at least two or more body segments of the entire body.

Idiopathic dystonia – Type of dystonia with an unknown cause.

Inherited dystonia – Type of dystonia with a genetic origin. For example, DYT-TOR1A (formerly called DYT1) is caused by mutation of the TOR1A gene and typically occurs in childhood and results in generalized dystonia. DYT-THAP1 (formerly DYT6) is caused by a mutation of the THAP1 gene and typically occurs in adolescents or young adults and results in generalized or segmental dystonia of the head, neck and larynx.

Isolated dystonia – Type of dystonia where dystonia is the only motor symptom. Some patients with isolated dystonia also have tremor.

Meige Syndrome – A form of segmental dystonia characterized by progressive worsening of blepharospasm and spread of symptoms to oromandibular, cervical, and limb muscles.[12]

Primary dystonia – Term previously used to describe a type of dystonia where dystonia is the only motor symptom.

Secondary dystonia – Term previously used to describe a type of dystonia due to a known cause.

Segmental dystonia – Type of dystonia that affects two or three adjacent body parts.

Status dystonicus - Severe, life-threatening dystonia symptoms, including status dystonicus (also known as dystonic crisis or dystonic storm), during ongoing or loss of DBS Therapy may result in respiratory compromise and rhabdomyolysis. In rare cases, rhabdomyolysis may progress to multi-organ failure and death.

Terms Used in Clinical Studies and Analysis

Adverse event – An undesirable experience which may or may not be associated with use of a medical product.

Device event – An issue with any of the implantable or external system components.

Explant – Any component of the system removed and not replaced.

Laterality – Side or sides of the brain in which a lead is implanted or in which a procedure or procedures are attempted (unilateral = 1 side; bilateral = 2 sides).

Meta-analysis – A study design that analyzes the combined results from multiple research studies to answer a research question.

Minimal clinically important difference (MCID) – The smallest meaningful improvement or change in the clinical rating scales used by physicians.[13] Similar terms include clinically important difference or minimally important difference (MID).[10]

Product performance event – An event that is possibly due to a device-related issue.

Prospective study – A study design that enrolls a patient group before treatment and collects patient outcomes over time.

Randomized controlled trial (RCT) – A study design that randomly assigns participants into an experimental group or a control group.

Replacement – Any component of the system removed and replaced regardless of the time interval between explant and replacement (e.g., device explanted and subsequently replaced 2 months later).

Retrospective study – A study design that enrolls a patient group after treatment and analyzes data from patient records or patient recall.

Serious adverse event – Serious adverse event definitions varied across published literature. In general, any adverse event that:

- Results in death
- Is life threatening, or places the participant at immediate risk of death from the event as it occurred
- Requires or prolongs hospitalization
- Causes persistent or significant disability or incapacity
- Results in congenital anomalies or birth defects
- Is another condition which investigators judge to represent significant hazards

Sham stimulation – An inactive stimulation system designed to mimic as closely as possible to active stimulation.

Simultaneous lead implant procedures – Bilateral lead implant procedures performed in a single operative session.

System explant – A complete system (lead, neurostimulator, and extension) removed and

not replaced.

System organ class (SOC) – Medical terms which are grouped by etiology, manifestation site, and purpose. Additional groups pertain to products and social circumstances.[a]

System replacement – A system removed and replaced with another complete system regardless of the time interval between system explant and subsequent system replacement.

Systematic review – A study design that involves a comprehensive plan and search strategy to identify, appraise, and synthesize published clinical studies on a topic.

Therapy-relevant safety event – Labeled potential risks which are associated with DBS-related surgical procedures or with use of DBS Therapy after implantation; events include hemorrhage (cerebral or intracranial, symptomatic or asymptomatic), infection, device complications (lead migration, device failure, etc.), and suicide and suicide attempt.

[a] Medical Dictionary for Regulatory Activities. MedDRA Hierarchy. https://www.meddra.org/how-to-use/basics/hierarchy. Accessed April 25, 2024.

Introduction

Dystonia is a movement disorder characterized by sustained or intermittent abnormal movements, postures, or both. Dystonic movements and postures are typically patterned and repetitive and may be tremulous or jerky. They are often initiated or worsened by voluntary action, and frequently associated with overflow movements.[11] There are many different presentations of dystonia, with varied clinical features and a range of etiologies. Causes range from genetic to non-genetic or unknown origins.[b] Patients are at risk for significant disability and, in rare cases, life-threatening complications. Current treatments are symptomatic and limited. Medtronic DBS Therapy, utilizing bilateral stimulation of the internal globus pallidus (GPi), may help adults and children whose dystonia is disabling and unresponsive to other treatments.

[b] National Organization for Rare Disorders (NORD). Dystonia. Riboldi GM and Frucht SJ. Last updated April 16, 2020. At https://rarediseases.org/rare-diseases/dystonia/. Accessed April 6, 2023.

Overview of Clinical Evidence

The primary clinical evidence of safety and effectiveness for Medtronic Deep Brain Stimulation (DBS) Therapy for Dystonia was compiled from a systematic review of published scientific literature, an analysis of a subset of clinical data purchased from a published randomized controlled trial (RCT) by Kupsch (2006)[2] and its long-term follow-up study by Volkman (2012),[15] collectively referred to as the "Investigator Study"[17] and data from the Medtronic Product Surveillance Registry (PSR).

The systematic review involved a comprehensive search of the MEDLINE and Embase databases, as well as PubMed ahead-of-print and in-process records, over more than 10-year period covering November 1, 2012 through August 31, 2024. It included a key RCT by Kupsch (2006)[2] and its long-term follow-up,[14] both published outside this period. Other relevant studies were found by cross-referencing, with an emphasis on evidence related to particular dystonia types. The focus was on primary data sources for bilateral GPi DBS in adult patients with primary generalized, segmental, and cervical dystonia, and in pediatric patients 12 years of age and above with primary generalized dystonia, without other neurological features or pathological abnormalities. Published studies were included in the analysis if at least 80% of the study population aligned with the indication or individual patient data could be extracted for analysis. Foundational evidence included two randomized, controlled trials (RCTs) in adult patients: Kupsch (2006)[2] for generalized and segmental dystonia (including its long-term follow up study Volkmann (2012)[15] and Volkmann (2014)[16] for cervical dystonia). Data from an Investigator Study[17], a subset of the Kupsch (2006)[2] RCT, was included to report safety and effectiveness results separately for generalized and segmental dystonia.

Real-world data from the PSR is summarized for patients receiving DBS Therapy for primary dystonia. The PSR is a prospective, non-randomized, multi-center, global registry that enrolls patients on a rolling basis without specified limits on the number of patients or end dates. Patients from active PSR sites worldwide are followed prospectively in alignment with routine care practices throughout the lifetime of their devices or until they exit the registry.

Safety and effectiveness outcomes are presented separately for generalized, segmental, and cervical dystonia in adult patients (> 21 years) and for generalized dystonia in pediatric patients (≤ 21 years of age). These categorizations are based on the average age reported in each publication or age of patients enrolled in the PSR registry.

Study Design

Data Sources

Information was employed from multiple data sources to establish a reasonable assurance of safety and effectiveness of the Medtronic DBS Therapy system in the US as an aid in the management of chronic, intractable (oral and/or injectable medication refractory) primary dystonia, including:

- generalized dystonia, segmental dystonia of the head and neck, and cervical dystonia (torticollis) in adult patients
- generalized dystonia in pediatric patients twelve years of age or above.

These data sources included an analysis of a subset of clinical data purchased from a published randomized controlled trial (RCT) by Kupsch (2006)[2] and its long-term follow-up study by Volkman (2012),[15] collectively referred to as the "Investigator Study"[17] in this document; an additional RCT conducted by Volkman (2014)[16]; a meta-analysis of published literature; and data from the Medtronic Product Surveillance Registry (PSR).

The following clinical data sources were used:

Study Specific Data

An analysis was performed on a subset of clinical data from a RCT that was published in Kupsch (2006).[2] Medtronic purchased the actual clinical data for 30 out of 40 studied patients directly from the authors and performed analysis of that data. Follow-up data from the same study that was published in Volkman (2012)[15] was also used. This data is referred to as the Investigator Study.[17] The Investigator Study[17] was used to support for the safety and effectiveness of bilateral GPi DBS in primary generalized and segmental dystonia in adults. The corresponding data in the primary generalized dystonia are also considered as supportive evidence for bilateral GPi DBS in primary generalized dystonia in pediatric patients ≤ 21 years of age.

A RCT Study from Volkman (2014)[16] was used to support for the safety and effectiveness of bilateral GPi DBS in primary cervical dystonia in adults.

Meta Analysis from Systematic Literature Review

The systematic literature review involved a comprehensive search of the MEDLINE and Embase databases, as well as PubMed ahead-of-print and in-process records, over more than 10-year period covering November 1, 2012, through August 31, 2024. It included a key RCT by Kupsch (2006)[2] and its long-term follow-up,[15] both published outside this period. Other relevant studies were found by cross-referencing, with an emphasis on evidence related to particular dystonia types. The focus was on primary data sources for bilateral GPi DBS in adult patients with primary generalized, segmental, and cervical dystonia, without other neurological features or pathological abnormalities and in pediatric patients with primary generalized dystonia, without other neurological features or pathological abnormalities. Published studies were included in the analysis if at least 80% of the study population aligned with the indication or individual patient data could be extracted for analysis.

Medtronic Product Surveillance Registry (PSR)

Real-world data from the PSR is summarized for patients receiving Medtronic DBS Therapy for primary dystonia. The PSR is a prospective, non-randomized, multi-center, global registry that enrolls patients on a rolling basis without specified limits on the number of patients or end dates. Patients from active PSR sites worldwide are followed prospectively in alignment with routine care practices throughout the lifetime of their devices or until they exit the registry. These data were mainly used to support safety.

Study Objectives

Safety Objectives

The overall safety objective was to summarize current safety information for Medtronic DBS Therapy for Dystonia through analysis of current data from the systematic review of published scientific literature and the PSR. The analysis focused on the following therapy-relevant safety events, which are already labeled as potential risks associated with DBS-related surgical procedures or with use of DBS therapy after implantation, and are commonly reported in published scientific literature for DBS Therapy for Movement Disorders:

- Hemorrhage (cerebral or intracranial, symptomatic or asymptomatic)
- Infection
- Device complications (lead migration, device failures, etc.)
- Suicide and suicide attempt

The rates of therapy-relevant safety events were pooled separately for adult and pediatric populations and summarized using descriptive statistics. Surgical interventions including system revision (e.g., device repositioning or replacement) and complete system explant were summarized.

Effectiveness Objectives

The overall effectiveness objective was to characterize the clinical benefits related to reduction in movement symptoms. The effectiveness of the Medtronic DBS Dystonia system was demonstrated through analysis of Study Specific Data (see Above) and results from a meta-analysis of the systematic review of published scientific literature. The average Burke-Fahn-Marsden Dystonia Rating Scale (BFMDRS) motor score was used in the analysis for primary generalized dystonia in both adults and pediatric patients and segmental dystonia in adults. The average Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) severity score was used in the analysis for primary cervical dystonia in adults. The European Quality of Life 5-Dimension Questionnaire (EQ-5D) information at baseline and follow-up in the PSR was used in the analysis for health-related quality of life for all types of dystonia in adults.

Study Design: Study Specific Data

The Investigator Study[17] provided the main evidence to support the GPi DBS therapy in primary generalized and segmental dystonia in adults. The study contains a subset of data purchased by Medtronic from the Kupsch (2006).[2] Data from long-term follow-up were also used from Volkmann (2012).[15] The main purpose of the analysis was to demonstrate the effectiveness of bilateral GPi DBS in patients with primary generalized or segmental dystonia who were oral and/or injectable medication refractory. Kupsch (2006)[2] study contains 40 patients (full study cohort), of which only 30 patients signed an Informed Consent Form agreeing to have their data released to Medtronic (MDT). As such, the results and associated conclusions from the Study Specific Data only contain data from those 30 patients. The study design of Kupsch (2006)[2] was not conducted by Medtronic but partially funded by Medtronic.

Kupsch (2006)[2] RCT Study

Kupsch (2006)[2] was a two arm, double-blind, randomized, and placebo-controlled study design to demonstrate the effectiveness of GPi stimulation in subjects with primary generalized or segmental dystonia who were severely handicapped, in spite of optimal conservative therapy. Two treatment arms were studied. Patients were randomized in a 1:1 manner to receive either neurostimulation or sham stimulation for the 3-month blinded phase. The subjects in both groups were given the same operation to implant stimulation electrodes in the GPi, together with a subcutaneous stimulation system. During a 3-month follow-up period, the neurostimulation group was administered effective pallidum stimulation (frequency 130 Hz; pulse width 120 µs; amplitude 0.5 V below adverse event threshold). In the sham stimulation group, the stimulator was set at 0 volts (V), so that there would be only placebo or apparent stimulation for 3 months. Drug therapy was freely adjusted to the subjects' requirements in both groups. The groups were unblinded after 3 months and the stimulation system in the sham stimulation group was then switched to the same parameters as the neurostimulation group. This was followed by an open follow-up observation phase, with subsequent final evaluation (in comparison to the pre-operative status of both groups) after 6 months of continuous pallidum stimulation, i.e. 6 months post-operatively in the neurostimulation group and 9 months postoperatively in the sham stimulation group. After 6 months of follow-up, patients were assessed annually for 5 years in Volkmann (2012)[15] for the long-term device effect.

Study Population

The intended study population was subjects with idiopathic segmental, multifocal, or generalized dystonia, who benefit inadequately from drug treatment and who are seriously handicapped by the disease.

There were 8 study centers participating in the study: 7 centers in Germany and 1 center in Austria. The centers were chosen based on their experience with DBS Therapy. To participate, a center must have successfully treated 8 subjects with DBS Therapy, at least 2 with the target GPi. In addition, centers were required to have a projected implant rate of 10 patients per year.

Inclusion Criteria

- Presence of idiopathic multifocal segmental or generalized dystonia
- Duration of disease > 5 years
- Age between 14 and 75 years
- Relevant handicap in daily life, in spite of optimal drug therapy
- Presence of subject's written informed consent
- For adolescents between 14 and 18 years: additional written consent from parent or guardian

Exclusion Criteria

- Mattis Score ≤ 120
- Beck depression inventory (BDI) > 25
- Prior stereotactic brain operations
- Marked cerebral atrophy
- Raised bleeding tendency
- Reduced resistance to infection
- Relevant cerebrovascular disease

- Psychiatric disease which could impair cooperation in the study
- Other contraindications

Study Device

Table 1 below describes the Medtronic DBS System components used in the Kupsch (2006)[2] study.

Table 1. Description of Dystonia DBS System Components

Device Component	Model
Neurostimulator	Model 7424 Itrel II Neurostimulator Model 7428 Kinetra Neurostimulator
DBS Lead	Model 3387 DBS Lead Model 3389 DBS Lead
Extensions	Model 7482/7483 DBS Extension Model 37085/37086 DBS Extension with Universal Port Plug
Accessories	Model 8840 N'Vision Clinician Programmer Model 8870 N'Vision Application Card Model 7438 Access Review Therapy Controller Model 7436 Access Therapy Controller Model 37642 Patient Programmer w/ optional 37092 antenna Models 64001 and 64002 Pocket Adaptor

Statistical Analysis

In Kupsch (2006)[2], the primary null hypothesis was an outcome of no significant difference in the change in the movement score (an average of the two scores recorded by observers who were unaware of the group assignments) from baseline to 3 months between patients receiving active neurostimulation and those receiving sham stimulation. Sample Size: 40 patients were needed to provide the study with 90% power to detect a 25% difference between treatment groups while allowing for an overall dropout rate of 10%, with a 5% probability of a type I error on the basis of a two-sided Mann–Whitney test. Data from all patients who underwent randomization were analyzed; missing values were imputed with the last observation carried forward.

Because not all patients were reconsented for use by Medtronic, only 30 of the 40 implanted patients are available for analysis. If the original power calculation was redone using the number of patients reconsented in each group (17 active and 13 sham), the estimated power for the primary analysis of the study remains over 80%. This reinforces the fact that 30 patients truly are enough to show significant benefit with this therapy. In the Investigator's Study,[17] missing values were not imputed with the last observation carried forward. The analyses include only those patients who were reconsented for use by Medtronic.

Analyses by Dystonia Type

In addition, subgroup analysis of effectiveness was completed by dystonia type. This analysis represents data from 18 patients with generalized dystonia and 11 patients with segmental dystonia. One additional patient with multifocal dystonia is excluded from this subgroup analysis.

Safety Objectives

- Systematic recording of the side-effects and adverse events (AEs).
- To characterize AEs for all subjects, including a tabulation of the profiles of the neurostimulation and sham stimulation group subjects through the 3-month blinded phase.

Primary Objectives

To demonstrate that the improvement in the movement score in the BFMDRS for subjects in the DBS treatment group (neurostimulation) is greater than for subjects in the control group (sham stimulation) after 3 months of therapy.

The primary endpoint was a change from baseline to three months in severity of symptoms assessed with the BFMDRS movement score. Data from all of the investigational sites (30/40 patients) were pooled for analysis.

Secondary endpoints included the effect of neurostimulation on activities of daily living, the disability score on the BFMDRS, and quality of life (as assessed with the SF-36).

Kupsch (2006)[2] trial is registered with ClinicalTrials.gov number, NCT00142259.

Volkmann (2012)[15]

Volkmann (2012)[15] assessed the safety and effectiveness of bilateral GPi DBS in patients with primary generalized or segmental dystonia prospectively followed up for 5 years in the Kupsch (2006)[2] trial. 38 patients agreed to be followed up annually after the activation of neurostimulation, including assessments of dystonia severity, pain, disability, and quality of life. The primary endpoint of the 5-year follow-up study extension was the change in dystonia severity at 3 years and 5 years as assessed by open-label ratings of the BFMDRS motor score compared with the preoperative baseline and the 6-month visit. The primary endpoint was analyzed on an intention-to-treat basis.

Volkmann (2014)[16]

Volkmann (2014)[16] was used as evidence to support the Medtronic DBS Dystonia system in bilateral GPi DBS therapy in primary cervical dystonia. Volkmann (2014)[16] used similar study design as that in Kupsch (2006).[2] In brief, Volkmann (2014)[16] is a two-arm, double-blind, randomized, and placebo-controlled study design to demonstrate the safety and effectiveness of bilateral GPi DBS stimulation in patients with medication-refractory cervical dystonia.

Eligibility Criteria

Aged 18–75 years, disease duration ≥3 years, TWSTRS severity score ≥15 points. 62 Patients were enrolled from 10 academic centers in Germany, Norway, and Austria.

Protocol

Patients were randomized in a 1:1 manner to receive either neurostimulation or sham (amplitude 0 V) stimulation by computer-generated randomization lists with randomly permuted block lengths stratified by center. All patients, masked to treatment assignment, were implanted with a deep brain stimulation device and received their assigned treatment for 3 months, during which, the neurostimulation group was administered pallidum stimulation (frequency 180 Hz; pulse width 120 μs; amplitude 0·5 V below adverse event threshold). In the sham stimulation group, the stimulator was set at 0 volts (V), so that there would be only placebo or apparent stimulation for 3 months. Drug therapy was freely

adjusted to the subjects' requirements in both groups. The groups were unblinded after 3 months and the stimulation system in the sham stimulation group was then switched to the same parameters as the neurostimulation group. This was followed by an open follow-up observation phase, with subsequent final evaluation (in comparison to the pre-operative status of both groups) after 6 months of continuous pallidum stimulation, i.e. 6 months post-operatively in the neurostimulation group and 9 months postoperatively in the sham stimulation group.

Statistical Analysis

The primary null hypothesis was an outcome of no difference in the change of the TWSTRS severity score (mean of the two observer-blinded scores) from baseline to 3 months between patients receiving active neurostimulation and those receiving sham stimulation. It was estimated that a sample size of 60 patients, i.e., 30 per group would power the study at 80% with a 5% probability of a type I error (two-sided Mann-Whitney U test of the primary null hypothesis). This design allows detection of a 20% difference between treatment groups with respect to the primary outcome criterion (percentage change in TWSTRS severity score) assuming an SD of 25%, while making provision for an overall dropout rate of 10%. The primary endpoint was the change in the TWSTRS severity score from baseline to 3 months, assessed by two masked dystonia experts using standardized videos, analyzed by intention to treat. The key secondary outcome included change in TWSTRS disability. TWSTRS total score was one of the exploratory effectiveness endpoints.

This trial is registered with ClinicalTrials.gov, number NCT00148889.

Study Design: Meta-Analyses of Literature

Safety

A meta-analysis was conducted to compare rates of therapy-relevant safety events (excluding suicide and suicide attempt because of no reported occurrence in the patient populations evaluated), system revisions, and explants among adult patients based on the type of dystonia. Additionally, the analysis compared these rates between adult and pediatric patients with primary generalized dystonia.

To avoid the possibility that the quantities estimated with different study designs (e.g., randomized controlled trials, prospective studies, retrospective studies/case controls) may not represent the same target of inference (e.g., estimates from randomized trials may be for unconditional treatment effects, while estimates from observational studies may represent treatment effects conditional on covariates), meta-analyses of safety were also conducted in both adult and pediatric patients with primary dystonia stratified by study design.

Effectiveness

The meta-analysis was conducted to evaluate effectiveness outcomes in adult patients with primary generalized, segmental and cervical dystonia, and in pediatric patients with primary generalized dystonia. Additionally, a comparative analysis was conducted to evaluate differences in adults versus pediatric patients with primary generalized dystonia.

To avoid the possibility that the quantities estimated with different study designs may not represent the same target of inference, meta-analyses of effectiveness outcomes in both adult and pediatric patients were also conducted with different types of dystonia stratified by study design. Only one RCT for each dystonia type was included in the meta-analysis; therefore, only point estimate was provided for the RCT.

Data Extraction

- For safety outcomes, the proportion of patients with safety events was extracted from the publication or calculated by dividing the reported number of events by the number of patients enrolled in the study. If the authors specifically stated a type of event did not occur, the rates were reported as 0 (0%). If the authors did not comment on a type of event, not reported (NR) is shown.
- For effectiveness outcomes, the average BFMDRS motor score was used in the analysis for generalized dystonia and segmental dystonia. The average TWSTRS severity score was used in the analysis for cervical dystonia.

Statistical Methods

Meta-analysis of dystonia effectiveness and safety were implemented using random-effects modeling with inverse variance weighting. All analyses were completed using the 'meta' package in R software which enabled the use of both fixed-effect and random effects models, depending on the level of heterogeneity observed among the studies. The random effects model was preferred in cases of significant heterogeneity, quantified using the I^2 statistic and Cochran's Q-test. The precision of pooled estimates was represented by 95% confidence intervals, ensuring a comprehensive understanding of variability within and across studies.[18,19]

- Effectiveness assessment**:** Dystonia rating scale improvement (BFMDRS and TWSTRS) was measured as percentage change from baseline for effectiveness assessment. The pooled effect sizes were derived using the *metagen* function from the 'meta' package in R. Standard errors were computed from reported or imputed standard deviations to reflect score variability accurately. Confidence intervals were calculated using standard normal critical values to quantify estimate precision.
- Safety assessment**:** The pooled proportions of therapy-relevant safety events were calculated separately for each dystonia type with the *metaprop* function from the 'meta' package in R. The individual proportion from each study was logit transformed before being pooled for overall proportion estimation. A continuity correction of 0.5 was applied to studies with zero events. Confidence intervals for individual studies used the Clopper-Pearson method, and random-effects models accounted for between-study heterogeneity.[20,21]

All effectiveness and safety meta-analyses were also conducted with stratification by study design (e.g., randomized controlled trials, prospective studies, retrospective studies/case controls). Within each stratum, a random-effects model (REML estimator with Hartung–Knapp adjustment) was applied to appropriately account for between-study variability across study designs. When only a single study was available for a design stratum, the individual study was estimated and 95% confidence interval along with a narrative discussion of precision and risk of bias.

Subgroup analyses by dystonia distribution or adult vs pediatric were performed using stratified meta-analysis based on dystonia body distribution or patient population (adult vs pediatric) by utilizing the option of subgroup in *metaprop* function in R. Dystonia subtype differences were statistically tested using the Chi-square (χ^2) test for group differences, with significance defined as $p < 0.05$.[18–20,22]

Study Design: Product Surveillance Registry (PSR)

The PSR (the Registry) is comprised of a global network of hospitals, clinics and clinicians from which "real-world" product safety and patient clinical outcome information is generated. The purpose of the Registry is to provide continuing evaluation and periodic reporting of safety and effectiveness of market-released products for their intended use.

The PSR is a prospective, non-randomized, multi-center, global registry with an extensible design allowing new products to be easily added following market release. Patients are enrolled on a rolling basis without specified limits on the number of patients or end dates. Patients from all geographies where there are active PSR sites are followed prospectively in accordance with the routine care practices over the lifetime of their devices or upon exit from the registry. In addition to event collection, patients enrolled under the PSR protocol collect quality of life (EQ-5D) data at baseline and follow-up. The EQ-5D scoring generates an index score, with higher scores representing better health-related quality of life.

The primary objective of the PSR is continuing evaluation of safety and effectiveness of Medtronic market-released products for their intended use. Patients are followed prospectively for events related to the device, procedure, and/or therapy, as well as negative changes in behavior from baseline (e.g., depression, suicidal ideation). Events are further categorized as product performance events (PPE) or non-PPE.

The registry began as the Implantable Systems Performance Registry (ISPR) and started collecting data on DBS patients in 2009. Medtronic has continually worked to develop systems and processes to monitor product performance following market release more effectively and launched the global PSR in 2011. This analysis represents the data collected through October 31, 2022.

The PSR is registered with ClinicalTrials.gov number, NCT01524276.

Data Collection

Patients were identified as receiving DBS for the treatment of dystonia if they met the following criteria:

- Primary purpose for device use is dystonia as indicated by the physician
- Patients were consented
- Patients were implanted with a DBS system

Events that occurred on or after implant are included in analysis. All device/therapy/procedure related adverse events are included in the adverse event summaries. All device events are included in the device event summaries, regardless of the associated device (i.e., neurostimulator, lead, extension).

Patients were categorized as Pediatric (21 years of age or less) or Adult (older than 21 years of age).

Safety and Effectiveness Results

Safety and effectiveness outcomes are presented separately for primary generalized, segmental, and cervical dystonia in adult patients (> 21 years) and for primary generalized dystonia in pediatric patients (≤ 21 years of age). These categorizations are based on the dystonia type and average age reported in each publication or age of patients enrolled in the PSR registry.

Safety Results

Safety outcomes are presented separately for primary generalized, segmental, and cervical dystonia for adult patients and pediatric patients. Comparisons of therapy-relevant safety events between adult and pediatric patients with primary generalized dystonia by study designs are also provided below to add more detailed information on the safety profile of bilateral GPi DBS in pediatric patients.

Safety Outcomes for Bilateral GPi DBS in Adult Patients

Primary Generalized Dystonia

Study Specific Data

The analysis of safety of bilateral GPi DBS for the treatment of primary generalized dystonia in adult patients was based on data from 18 patients with generalized dystonia in the Investigator Study.[17] A summary of AEs is presented in Table 2 below. During the randomization period, a total of seven events were reported in 4 patients (neurostimulation: 2/9 and sham stimulation: 2/9) with generalized dystonia. Of the 7 events, two (neurostimulation: 1/9 and sham stimulation: 1/9) were considered serious adverse events (SAEs). During the randomization period, a total of two adverse device effects (ADEs) were reported in 2 patients (neurostimulation: 1/9 and sham stimulation: 1/9) with generalized dystonia. The overall AE and SAE occurrence rates were 22.2% and 11.1% in the 3-month blinded phase in the DBS group, and 72.2% and 55.6% in the open label phase, respectively.

Adverse events from baseline to 5 years are summarized in Table 3 below.

Table 2. Adverse Event Summary – Generalized Dystonia in Adults

	Blinded Phase				Open Label Phase	
	Neurostimulation		Sham Stimulation		All Patients	
Event Type	**Events**	**Patients % (n/N)**	**Events**	**Patients % (n/N)**	**Events**	**Patients % (n/N)**
All Events	4	22.2% (2/9)	3	22.2% (2/9)	29	72.2% (13/18)
By seriousness						
SAE	1	11.1% (1/9)	1	11.1% (1/9)	23	55.6% (10/18)
Non-SAE	1	11.1% (1/9)	1	11.1% (1/9)	5	22.2% (4/18)
Not assessed	2	22.2% (2/9)	1	11.1% (1/9)	1	5.6% (1/18)
By relatedness						
ADE	1	11.1% (1/9)	1	11.1% (1/9)	20	61.1% (11/18)

	Blinded Phase				Open Label Phase	
	Neurostimulation		Sham Stimulation		All Patients	
Event Type	Events	Patients % (n/N)	Events	Patients % (n/N)	Events	Patients % (n/N)
Non-ADE	1	11.1% (1/9)	1	11.1% (1/9)	7	27.8% (5/18)
Not assessed	2	22.2% (2/9)	1	11.1% (1/9)	2	11.1% (2/18)

Adverse events with missing date will be classified as blinded phase.

Table 3. Adverse Event Summary – Baseline to 5 years

	Serious		Non-Serious		Not assessed		Total	
Event Type	Events	Patients (%) with an Event	Events	Patients (%) with an Event	Events	Patients (%) with an Event	Events	Patients (%) with an Event
Loss of effect	5	27.8% (5/18)	0	0% (0/18)	0	0% (0/18)	5	27.8% (5/18)
Subcutaneous infection	5	16.7% (3/18)	0	0% (0/18)	0	0% (0/18)	5	16.7% (3/18)
No stimulation	4	22.2% (4/18)	2	5.6% (1/18)	1	5.6% (1/18)	7	27.8% (5/18)
Dystonia	3	11.1% (2/18)	1	5.6% (1/18)	0	0% (0/18)	4	16.7% (3/18)
Other	3	16.7% (3/18)	1	5.6% (1/18)	0	0% (0/18)	4	16.7% (3/18)
Dysarthria	2	11.1% (2/18)	0	0% (0/18)	0	0% (0/18)	2	11.1% (2/18)
Electrode fracture	1	5.6% (1/18)	0	0% (0/18)	0	0% (0/18)	1	5.6% (1/18)
Sensory disturbances	1	5.6% (1/18)	1	5.6% (1/18)	0	0% (0/18)	2	11.1% (2/18)
Stimulator malfunction	1	5.6% (1/18)	0	0% (0/18)	0	0% (0/18)	1	5.6% (1/18)
NA	0	0% (0/18)	0	0% (0/18)	3	16.7% (3/18)	3	16.7% (3/18)
Facial weakness	0	0% (0/18)	1	5.6% (1/18)	0	0% (0/18)	1	5.6% (1/18)
Interrupted stimulation	0	0% (0/18)	1	5.6% (1/18)	0	0% (0/18)	1	5.6% (1/18)
Total	25	55.6% (10/18)	7	33.3% (6/18)	4	16.7% (3/18)	36	72.2% (13/18)

NA = Not available.

Safety Outcomes from the Publications

In addition to the Investigator Study,[17] the analysis of safety of bilateral GPi DBS for the treatment of primary generalized dystonia in adult patients also include data from 6 publications representing a total of 173 patients contributing safety outcomes. These 6 publications consist of 3 prospective studies[23–25] and 3 retrospective studies.[26–28]

Among the publications for generalized dystonia, dystonia severity was characterized by severe or marked disability, impaired function in performance of activities of daily living, or poor symptom control in spite of medical management.[17,23,24,26–29] Average age at surgery ranged from 22 to 38 years.[17,24–28] Duration of generalized dystonia before surgery ranged from 8 to 22 years, including Investigator Study.[17,24–26,28]

Across six other published studies, the reported incidence rates for AE and SAE ranged from 25% to 58%[24–28] and 8 to 18%,[24–26,28] respectively, over a follow-up periods spanning 6 months to up to 8 years of follow-up in adult patients with generalized dystonia.

Table 4 lists the reported occurrence of one or more therapy-relevant safety events in adult patients with generalized dystonia in each publication.

Table 4. Therapy-Relevant Safety Events in Adult Patients with GPi DBS for Generalized Dystonia[a]

First author (Year)	Total pts. enrolled	Mean Age at surgery – yrs	Follow-up	Symptomatic ICH (n, %)	Asymptomatic ICH (n, %)	Infection (n, %)	Device complications (n, %)	Suicide, suicide attempt (n, %)	Device revisions (n, %)	Explants (n, %)
RCT (n=1)										
Investigator-Sponsored Clinical Study[17]	18	DBS: 38.2 ± 12.9 Sham: 38.1 ± 8.7	6 mos. - 5 yrs.	0 (0%)	0 (0%)	3/18 (16.7%)	11/18 (61.1%)	NR	10/18 (55.6%)	4/18 (22.2%: 2 subcutaneous infections, 1 dystonia, 1 loss of effect)
Prospective Studies (n=3)										
Coubes (2004)[23]	12	NR	42.1 ±14.8 mos.	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	NR	NR
Valldeoriola (2010)[24]	24	30 ± 14	12 mos.	1/24 (4.2%)	NR	1/24 (4.2%)	1/24 (4.2%: 1 fracture of the cable)	NR	1/24 (4.2%: 1 fracture of the cable)	2/24 (8.3%: 1 infection, 1 skin allergic reaction)
Vidailhet (2007)[25]	17	36.3[b] (range: 22-53)	3 yrs.	NR	NR	1/17 (5.9%)	2/17 (11.8%: 1 lead fractures)	NR	1/17 (5.9%: 1 lead fracture)	1/17 (5.9%: 1 infection)
Retrospective Studies (n=3)										
Fitzgerald (2014)[26]	60	33.5	5 yrs.	NR	NR	8/60 (13.3%)	11/60 (18.3%, 6 lead revisions due to suboptimal placement, 3 lead fracture, 1 lead erosion, 1 wound granuloma)	NR	8/60 (33.3%; 6 lead revisions, 2 extensions and INS replaced due to infection)	7/60 (11.7%; 7 device removals due to infection)
Isaias (2009)[27]	30	28 ± 17	Up to 8 yrs.	0 (0%)	0 (0%)	4/30 (13.3%)	6/30 (20%: 2 fractured extension cables, 1 scalp erosion, 1 IPG malfunction, 2 lack of benefit)	NR	6/30 (20%)	NR
Sobstyl (2014)[28b]	12	DYT-1 positive: 21.7 DYT-1 negative: 23.1	Up to 5 yrs.	0 (0%)	0 (0%)	NR	7/12 (58.3%, 7 pts. total: 4 electrode breakages, 2 unexpected rapid battery depletions, 2 erosions, 1 suboptimal lead position, 1 seroma)	NR	7/12 (58.3%)	NR

[a] If the authors specifically stated a type of event did not occur the rates were reported as 0 (0%). If the authors did not comment on a type of event, not reported (NR) is shown.

[b] Estimated from individual patient data reported in the publication.

Table 5 summarizes overall results of the meta-analysis of therapy-relevant safety outcomes in adult patients with GPi DBS for generalized dystonia using random effects model.

For adult patients with generalized dystonia, device complications (22%), infections (12%), and intracerebral hemorrhage (symptomatic: 3%, asymptomatic: 3%) are the main therapy-related safety events. Device revisions (19%) and explants (13%) are the most common other safety events. These rates are based on pooled data from multiple publications.

Device complications and revisions are the most frequent safety events, followed by infections. Symptomatic and asymptomatic ICH are less common. Substantial heterogeneity was observed for both device complication rates and device revision rates. The reasons for the variability may be multifactorial and influenced by experience gained over time with DBS implant surgery and differences in reporting device complications and revisions.

Table 5. Pooled Safety Event Rates in adult patients with GPi DBS for Generalized Dystonia using Random Effects Model

Safety Event	Pooled Event Rate (95% CI)	No. of Publications	References
Therapy-Relevant Safety Events			
Device complications	22% (10-44%)	7	17,23-28
Infection	12% (8-18%)	6	17,23-27
Symptomatic ICH	3% (1-9%)	5	17,23,24,27,28
Asymptomatic ICH	3% (1-11%)	4	17,23,27,28
Other Safety Events			
Device revisions	19% (8-40%)	6	17,24-28
Explants	13% (8-20%)	4	17,24-26

Primary Segmental Dystonia of the Head and Neck

Study Specific Data

The analysis of safety of bilateral GPi DBS for the treatment of primary segmental dystonia in adult patients was based on data from 11 patients with primary segmental dystonia in the Investigator Study[17].

The analysis of safety of bilateral GPi DBS for the treatment of primary generalized dystonia in adult patients was based on data from 11 patients with segmental dystonia in the Investigator Study[17]. A summary of AEs is presented in Table 6 below. There were nine events reported in 7 patients (neurostimulation: 4/7 and sham stimulation: 3/4) with segmental dystonia and four were considered SAEs in three patients (neurostimulation: 2/7 and sham stimulation: 1/4). During the open label phase after 6 months of continuous stimulation, 16 AEs were reported in 8 (72.7%) patients with segmental dystonia. During the randomization period, five ADEs were reported in 4 patients (neurostimulation: 3/7 and sham stimulation: 1/4) with segmental dystonia. The overall AE and SAE occurrence rates were reported as 57.1% and 28.6% in the 3-month blinded phase in the DBS group and 72.7% and 63.6% in the open label phase, respectively.

Adverse events from baseline to 5 years are summarized in Table 7 below.

Table 6. Adverse Event Summary – Segmental Dystonia in Adults

Event Type	Blinded Phase				Open Label Phase	
	Neurostimulation		Sham Stimulation		All Patients	
	Events	Patients % (n/N)	Events	Patients % (n/N)	Events	Patients % (n/N)
All Events	6	57.1% (4/7)	3	75.0% (3/4)	16	72.7% (8/11)
By seriousness						
SAE	3	28.6% (2/7)	1	25.0% (1/4)	12	63.6% (7/11)
Non-SAE	2	28.6% (2/7)	0	0 % (0 /4)	3	27.3% (3/11)
Not assessed	1	14.3% (1/7)	2	50.0% (2/4)	1	9.1% (1/11)
By relatedness						
ADE	4	42.9% (3/7)	1	25.0% (1/4)	13	54.5% (6/11)
Non-ADE	1	14.3% (1/7)	0	0 % (0 /4)	2	18.2% (2/11)
Not assessed	1	14.3% (1/7)	2	50.0% (2/4)	1	9.1% (1/11)

Adverse events with missing date will be classified as blinded phase.

Table 7. Adverse Event Summary - Baseline to 5 years- Segmental Dystonia

Event Type	Serious		Non-Serious		Not assessed		Total	
	Events	Patients (%) with an Event	Events	Patients (%) with an Event	Events	Patients (%) with an Event	Events	Patients (%) with an Event
Dysarthria	6	18.2% (2/11)	3	27.3% (3/11)	0	0% (0/11)	9	45.5% (5/11)
Loss of effect	2	18.2% (2/11)	1	9.1% (1/11)	0	0% (0/11)	3	27.3% (3/11)
Other	2	18.2% (2/11)	1	9.1% (1/11)	0	0% (0/11)	3	18.2% (2/11)
Depression	1	9.1% (1/11)	0	0% (0/11)	0	0% (0/11)	1	9.1% (1/11)
Dystonia	1	9.1% (1/11)	0	0% (0/11)	0	0% (0/11)	1	9.1% (1/11)
Electrode fracture	1	9.1% (1/11)	0	0% (0/11)	0	0% (0/11)	1	9.1% (1/11)
Gait disturbances	1	9.1% (1/11)	0	0% (0/11)	0	0% (0/11)	1	9.1% (1/11)
Interrupted stimulation	1	9.1% (1/11)	0	0% (0/11)	0	0% (0/11)	1	9.1% (1/11)
Stimulator malfunction	1	9.1% (1/11)	0	0% (0/11)	0	0% (0/11)	1	9.1% (1/11)
NA	0	0% (0/11)	0	0% (0/11)	3	27.3% (3/11)	3	27.3% (3/11)
Rebound	0	0% (0/11)	0	0% (0/11)	1	9.1% (1/11)	1	9.1% (1/11)
Total	16	72.7% (8/11)	5	45.5% (5/11)	4	36.4% (4/11)	25	90.9% (10/11)

NA = Not available.

Safety Outcomes from the Publications

In addition to the Investigator Study,[17] the analysis of safety of bilateral GPi DBS for the treatment of segmental dystonia in adult patients also include data from 8 published studies

with a total of 101 patients contributing safety outcomes. The 8 publications consist of 2 prospective studies[30,31] and 6 retrospective studies.[32-37]

Among the publications for segmental dystonia, severity was characterized by severe symptoms, marked disability or functional impairment, or failed or discontinued medications, or botulinum neurotoxin due to no or slight effect.[17,30-37] Average age at surgery ranged from 47 to 67 years.[17,30-37] Duration of segmental dystonia before surgery ranged from 3 to 20 years, including Investigator Study.[17,30-37]

Across eight other published studies, the reported incidence rates for AE and SAE ranged from 8.3% to 100%[30-36] and 0 to 25%,[36,37] respectively, over a follow-up period of 6 months to 5.6 years in adult patients with segmental dystonia of the head and neck.

Table 8 lists the reported occurrence of one or more therapy-relevant safety events in adult patients with GPi DBS for segmental dystonia in each publication.

Table 8. Therapy-Relevant Safety Events in Adult Patients with GPi DBS for Segmental Dystonia

First author (Year)	Total pts. enrolled	Mean Age at surgery – yrs	Follow-up	Symptomatic ICH (n, %)	Asymptomatic ICH (n, %)	Infection (n, %)	Device complications (n, %)	Suicide, suicide attempt (n, %)	Device revisions (n, %)	Explants (n, %)
RCT (n=1)										
Investigator-Sponsored Clinical Study[17]	11	DBS: 51.3 ± 12.8 Sham: 50.8 ± 15.3	5 yrs.	0 (0%)	0 (0%)	0 (0%)	6/11 (54.5%)	NR	6/11 (54.5%)	1/11 (9.1%)
Prospective Studies (n=2)										
Blahak (2008)[30]	10	57.4 ± 15.0	17 mos.	0 (0%)	0 (0%)	0 (0%)	1/10 (10%: 1 small superficial skin granuloma above the stimulation lead)	NR	0 (0%)	0 (0%)
Ostrem (2007)[31]	6	62.6	6 mos.	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Retrospective Studies (n=7)										
Fu (2024)[32]	23	52.4 ± 7.4	38.3 mos.	0 (0%)	0 (0%)	0 (0%)	0 (0%)	NR	NR	NR
Horisawa (2019)[33]	16	51.4	66.6 ± 40.7 mos. (range 13–150)	NR	NR	1/16 (6.3%)	1/16 (13.5%, 1 lead breakage)	NR	NR	1/16 (6.3%: 1 infection and lead breakage in same patient)
Reese (2011)[34]	12	64.5 ± 4.4	38.8 ± 21.7 mos.	0 (0%)	0 (0%)	1/12 (8.3%)	0 (0%)	NR	1/12 (8.3%: 1 infection)	NR
Ren (2022)[35]	13	46.9 ± 7.2	36.6 ± 11.0 mos. (range 18–55)	0 (0%)	0 (0%)	1/13 (7.7%)	NR	NR	1/13 (7.7%: 1 pouch position changed after infection)	NR
Sharma (2020)[36]	4	66.5 (range 54 – 79)[b]	1 yr.	1/4 (25%)	NR	1/4 (25%)	1/4 (25%: 1 lead fracture)	NR	NR	1/4 (25%: 1 infection & lead fracture)
Tian (2021)[37]	6	61.2 (range 53 – 71)[b]	43.7	0 (0%)	0 (0%)	0 (0%)	NR	NR	NR	NR

[a] If the authors specifically stated a type of event did not occur the rates were reported as 0 (0%). If the authors did not comment on a type of event, not reported (NR) is shown.

[b] Estimated from individual patient data reported in the publication.

Table 9 summarizes overall results of the meta-analysis of therapy-relevant safety outcomes in adult patients with GPi DBS for segmental dystonia using random effects model.

For adult patients with segmental dystonia, device complications (13%), infections (7%), and intracerebral hemorrhage (symptomatic: 6%, asymptomatic: 4%) are the main therapy-related safety events. Device revisions (14%) and explants (9%) are the most common other safety events. These rates are based on pooled data from multiple publications.

High heterogeneity was observed in device complications and device revision rates, likely influenced by clinical factors such as surgical experience and reporting practices.

Table 9. Pooled Safety Event Rates in Adult Patients with GPi DBS for Segmental Dystonia Using Random Effects Model

Safety Event	Pooled Event Rate (95% CI)	No. of Publications	References
Therapy-Relevant Safety Events			
Device complications	13% (4-32%)	7	17,30–34,36
Infection	7% (3-15%)	9	17,30–37
Symptomatic ICH	6% (2-15%)	8	17,30–32,34–37
Asymptomatic ICH	4% (2-12%)	7	17,30–32,34,35,37
Other Safety Events			
Device revisions	14% (4-41%)	5	17,30,31,34,35
Explants	9% (3-22%)	5	17,30,31,33,36

Cervical Dystonia

Study Specific Data

The analysis of safety of bilateral GPi DBS for the treatment of primary cervical dystonia in adult patients was based on primary source data from 62 patients with cervical dystonia in the Volkmann (2014)[16] RCT. The neurostimulation group reported 5 SAEs (16%, 5/32) compared to 11 SAEs (37%, 11/30) in the sham group, with 69% (11/16) resolving without sequelae (Table 10).

Table 10. Adverse Event Summary for Cervical Dystonia in Adults (Volkmann 2014)

Event Type	Open Label Phase					
	Neurostimulation (n=32)		Sham Stimulation (n=30)		All Patients (n=62)	
	Events	Patients % (n/N)	Events	Patients % (n/N)	Events	Patients % (n/N)
SAE	5	15.6% (5/32)	11	36.7% (11/30)	16	25.8% (16/62)
Non-SAE (AEs)	21	65.6% (21/32)	20	66.7% (20 /30)	41	66.1% (41/62)

Safety Outcomes from the Publications

In addition to Volkmann (2014)[16], the analysis of safety of bilateral GPi DBS for the treatment of cervical dystonia in adult patients also include data from 8 published studies with a total of 238 patients contributing safety outcomes. Among the publications on cervical dystonia, 7 studies[38–44] reported average age at surgery in the 50s to low 60s. [16] Two studies[45,46] reported an average age of surgery in the 40s, 1 study[36] in the low 70s, and 1 study[47] did not report age at surgery. Volkmann (2014)[16] reported a duration of disease of 15 years. Duration of disease trended shorter in 6 studies[38,40,41,45–47] published since 2015, ranging from 3 to 6 years. One study[36] published in 2020 had a disease duration of 17 years before surgery.

Across eight other published studies, the reported incidence rates for AE and SAE ranged from 3.8% to 80%[36,38–40,42–45] and 0 to 14.3%,[36,38,39,45,48] respectively, over a follow-up period of 1 year to up to 10 years in adult patients with cervical dystonia.

Table 11 lists the reported occurrence of one or more therapy-relevant safety events in adult dystonia patients with GPi DBS for cervical dystonia in each publication.

Table 11.Therapy-Relevant Safety Events in Adult Patients with GPi DBS for Cervical Dystonia[a]

First author (Year)	Total pts. enrolled	Mean Age at surgery – yrs	Follow-up	ICH (symptomatic) (n, %)	ICH (asymptomatic) (n, %)	Infection (n, %)	Device complications (n, %)	Suicide, suicide attempt (n, %)	Device revisions (n, %)	Explants (n, %)
RCT of GPi for Cervical Dystonia (n=1)										
Volkmann J (2014)[16]	62	DBS: 57.1 ± 9.82 Sham: 56.6 ± 11.33	6 mos.	1/62 (1.6%, 1 hemiparesis or stroke)	NR	3/62 (4.8%)	5/62 (8.1%, 1 tethering of extension cable, 2 electrode dislocations, 1 electrode misplacement, 1 IPG dislocation)	NR	2/62 (3.2%): 2 surgical exchange of device components	1/62 (1.6%)
Prospective Study of GPi for Cervical Dystonia (n=1)										
Walsh RA (2013)[44]	10	55.5 ± 12.8	7.8 yrs. (range 4.9–10.7)	NR	NR	2/10 (20%)	1/10 (10%, 1 suboptimal lead placement)	NR	4/10 (40%): 2 lead removals, 1 lead replacement, 1 lead repositioned	1/10 (10%): 1 infection
Retrospective Studies of GPi for Cervical Dystonia (n=6)										
Chung M (2015)[38]	25	52.2 ± 9.6	19.9 ± 11.5 mos.	2/25 (8.0%)	NR	1/25 (4.0%)	2/25 (8.0%, 1 electrode reposition, 1 extension line revision)	NR	2/25 (8.0%): 1 electrode reposition, 1 extension line revision	NR
Contarino MF (2014)[39]	15	56.5 ± 14.8 (range: 29-77)	2.3 ± 0.9 mos. (range 1–4)	1/15 (7%)	NR	NR	5/15 (33%, 1 tight extension, 1 painful moving IPG, 1 lead fracture and contralateral lead migration, 1 electrode fixation replacement, 1 electrode repositioning)	NR	5/15 (33%): 1 tight extension, 1 painful moving IPG, 1 lead fracture and contralateral lead migration, 1 electrode fixation replacement, 1 electrode repositioning	NR
Cui Z (2022)[45]	53	44.79 ± 12.88	40.49 ± 19.82 mos.	2/53 (3.8%)	NR	NR	0 (0%)	NR	NR	NR
Jacksch C (2022)[42]	15	61.5	10 yrs.	NR	NR	1/15 (6.7%)	2/15 (13.3%, 2 cable tractions)	NR	3/15 (20.0%): 2 revisions for cable traction, 1	NR

First author (Year)	Total pts. enrolled	Mean Age at surgery – yrs	Follow-up	ICH (symptomatic) (n, %)	ICH (asymptomatic) (n, %)	Infection (n, %)	Device complications (n, %)	Suicide, suicide attempt (n, %)	Device revisions (n, %)	Explants (n, %)
									pulse generator replacement for infection	
Sharma (2020)[36]	7	72.6 ± 16.5 (range: 51-98)[b]	1 yr.	1/7 (14.3%)	NR	NR	1/7 (14.3%: 1 tethering of extension wire)	NR	NR	NR
Wang X (2020)[46]	23	41.13 ± 13.49 (range: 16-70)	19.04 ± 16.30 mos. (range 3–74)	0/23 (0%)	0/23 (0%)	NR	NR	NR	0/23 (0%)	NR
Witt JL (2013)[43]	28	56.0 ± 10.4 (range: 33-70)	33.7 ± 25.0 mos. (range 4–97)	NR	3/28 (10.7%)	1/28 (3.6%)	2/28 (7.1%, 2 suboptimal lead placement)	NR	3/28 (10.7%): 2 lead replacement, 1 system reimplantation	1/28 (3.6%)

[a] If the authors specifically stated a type of event did not occur, the rates were reported as 0 (0%). If the authors did not comment on a type of event, not reported (NR) is shown.

[b] Estimated from individual patient data reported in the publication.

Table 12 summarizes overall results of the meta-analysis of therapy-relevant safety outcomes in adult patients with GPi DBS for cervical dystonia using random effects model.

For adult patients with cervical dystonia, device complications (11%), infections (7%), and intracerebral hemorrhage (symptomatic: 5%) are the main therapy-related safety events. Device revisions (14%) and explants (4%) are the most common other safety events. The event rates are based on pooled data from multiple publications, providing robust estimates for these outcomes.

Device complications and revisions are the most frequent safety events in cervical dystonia for adult patients with moderate to high heterogeneity, likely influenced by clinical factors such as surgical experience and reporting practices.

Table 12. Pooled Safety Event Rates in Adult Patients with GPi DBS for Cervical Dystonia Using Random Effects Model

Safety Event	Pooled Event Rate (95% CI)	No. of Publications	References
Therapy-Relevant Safety Events			
Device complications	11% (6-19%)	8	16,36,38,39,42-45
Infection	7% (3-13%)	5	16,38,42-44
Symptomatic ICH	5% (2-10%)	6	16,36,38,39,45,46
Asymptomatic ICH	NR	NA	NA
Other Safety Events			
Device revisions	14% (6-28%)	7	16,38,39,42-44,46
Explants	4% (1-11%)	3	16,43,44

Safety Outcomes for Bilateral GPi DBS in Pediatric Population with Primary Generalized Dystonia

The analysis of safety of GPi DBS for the treatment of primary generalized dystonia in pediatric patients 12 years of age and above was based on data from 12 publications evaluating 202 pediatric patients contributing safety outcomes. The published studies consist of 4 prospective[23,25,49,50] and 8 retrospective studies.[51-58]

The published studies compared reasonably well in baseline patient characteristics. Most pediatric patients received bilateral GPi DBS for primary generalized dystonia. Dystonia severity was characterized as severe or significant disability or impairment in daily activities despite medical management.[23,25,49-51,53,56-58] Average age at surgery ranged from 12 to 17 years across the studies reviewed,[25,49,51–53,55-58] with the exception of one study reporting an average age of 10.2 years.[50] Duration of dystonia symptoms before surgery ranged from 3 to 10 years.[25,49-58]

Across 12 published studies, the reported incidence rates for AE and SAE ranged from 0% to 100%[23,25,49-53,55-58] and 0 to 60%,[25,50,51,53] respectively, over a follow-up period of 6 months to up to 8.5 years in pediatric patients with generalized dystonia.

Table 13 lists the reported occurrence of one or more therapy-relevant safety events in pediatric dystonia patients with GPi DBS for generalized dystonia in each publication.

Table 13. Therapy-Relevant Safety Events in Pediatric Populations with GPi DBS Generalized Dystonia[a]

First author (Year)	Total pts. enrolled	Mean Age at surgery – yrs	Follow-up	ICH (symptomatic) (n, %)	ICH (asymptomatic) (n, %)	Infection (n, %)	Device complications (n, %)	Suicide, suicide attempt (n, %)	Revisions (n, %)	Explants (n, %)
Prospective Studies (n=4)										
Borggraefe (2010)[49]	24	14.2 ± 3.4 (range: 9-20)	12.0 ± 4.8 mos.	NR	NR	3/24 (12.5%)	9/24 (37.5%: 6 unexplained switching off the stimulator, 2 electrode migration, 1 cable perforation)	NR	4/24 (16.7%: 3 exchange of electrodes for infection, 1 abdominal pouch revision)	NR
Coubes (2004)[23]	19	≤ 17	42.1 ±14.8 mos.	0 (0%)	0 (0%)	1/19 (5.3%)	NR	NR	1/19 (5.3%)	NR
Starr (2014)[50]	6	10.2 (range: 7-13)[b]	12 mos.	0 (0%)	0 (0%)	NR	1/6 (16.7%: 1 open circuit on lead)	NR	NR	NR
Vidailhet (2007)[25]	5	17.2 (range: 15-19)[b]	3 yrs.	NR	NR	NR	NR	NR	NR	NR
Retrospective Studies (n=8)										
Ghosh (2012)[51]	6	13.2 (range: 8-21)[b]	5.8 ± 1.4 yrs. (range 4–8) primary dystonia)	0 (0%)	0 (0%)	0 (0%)	2/6 (33.3%: 1 electrode dislocation, 1 extension breakage)	NR	2/6 (33.3%: 1 electrode dislocation, 1 extension breakage)	NR
Haridas (2011)[52]	22	13.4 ± 2.7 (range: 9-21)	2 yrs.	0 (0%)	0 (0%)	3/22 (13.6%)	5/22 (22.7%: 2 desire to improve clinical response, 1 lead fracture, 1 extension cable fracture, 1 suboptimal lead position)	NR	8/22 (36.4%: 3 infection, 2 desire to improve clinical response, 1 lead fracture, 1 suboptimal lead position, 1 extension cable fracture)	NR
Krause (2016)[53]	8	12.5 ± 3.5 (range: 7-17)	58.5 ± 18.0 mos. (range 20–156)	NR	NR	NR	2/8 (25%: 1 IPG dislocation, 1 electrode revision)	NR	2/8 (25%; 1 IPG dislocation, 1 bilateral electrode revision)	NR

First author (Year)	Total pts. enrolled	Mean Age at surgery – yrs	Follow-up	ICH (symptomatic) (n, %)	ICH (asymptomatic) (n, %)	Infection (n, %)	Device complications (n, %)	Suicide, suicide attempt (n, %)	Revisions (n, %)	Explants (n, %)
Lumsden (2013)[54]	70 (63 after excluding 7 patients)	12.8 (range: 4.6-17.5)[b]	12 mos.	NR	NR	5/70 (7.1%)	NR	NR	NR	5/70 (7.1%; removal of part of the implanted stimulating system within first 6 mos. following surgery)
Markun (2012)[55]	14	15.5 ± 5.7 (range: 10-27)	32.2±17.9 (7-77) mos.	NR	1/14 (7.1%)	NR	3/14 (21.4%: 2 lead extender fractures, 1 lead repositioning)	NR	3/14 (21.4%: 2 lead extender fractures, 1 lead repositioning)	NR
Marotta (2020)[58]	9	16.0 (range: 14-17)	13 mos.	NR	1/9 (11.1%)	NR	0 (0%)	NR	0 (0%)	0 (0%)
Petrossian (2013)[56]	8	13.3 range: (9-17)[b]	50.8 mos. (median 52.5 mos., range 16–84)	0 (0%)	0 (0%)	2/8 (25%)	2/8 (25%: 2 lead fractures)	NR	0 (0%)	1/8 (12.5%: 1 infection)
Ramezani (2021)[57]	11	14.72 ± 3.71 (range: 9-20)	8.5 ± 6.9 yrs. (range 7–10)	NR	NR	0 (0%)	0 (0%)	NR	NR	NR

[a] If the authors specifically stated a type of event did not occur; the rates were reported as 0 (0%). If the authors did not comment on a type of event, not reported (NR) is shown.

[b] Estimated from individual patient data reported in the publication.

Table 14 summarizes overall results of the meta-analysis of therapy-relevant safety outcomes in pediatric patients with GPi DBS for generalized dystonia using random effects model.

For pediatric patients with generalized dystonia, device complications (26%), infections (16%), and intracerebral hemorrhage (symptomatic: 4%, asymptomatic: 6%) are the main therapy-related safety events. Device revisions (21%) and explants (20%) are the most common other safety events. The event rates are based on pooled data from multiple publications, providing robust estimates for these outcomes.

Device complications, device revisions, and explants are the most frequent safety events in pediatric patients. Clinical factors (e.g., surgical experience, reporting practices) may drive this the high device-related events.

Table 14. Pooled Safety Event Rates in Pediatric Patients with GPi DBS for Generalized Dystonia Using Random Effects Model

Safety Event	Pooled Event Rate (95% CI)	No. of Publications	References
Therapy-Relevant Safety Events			
Device complications	26% (18-35%)	9	49–53,55-58
Infection	16% (9-25%)	7	23,49,51,52,54,56,57
Symptomatic ICH	4% (1-14%)	5	23,50–52,56
Asymptomatic ICH	6% (2-14%)	7	23,50–52,55,56,58
Other Safety Events			
Device revisions	21% (13-22%)	8	23,49,51–53,55,56,58
Explants	20% (7-43%)	3	54,56,58

Comparison of Therapy-Relevant Safety Events Between Adult and Pediatric Patients with Generalized Dystonia by Study Designs

A safety meta-analysis compared adult and pediatric patients with generalized dystonia using prospective and retrospective studies, as no randomized trials existed for pediatric patients. There were no RCTs included in the pediatric analysis; therefore, the safety meta-analysis for adult vs pediatrics by study design is limited to prospective and retrospective studies only. Summary of safety events by study design comparing adult and pediatric patients with primary generalized dystonia is provided below.

Device Complications

Figure 1 presents a forest plot and detailed comparison of device complication rates between adult and pediatric patients with generalized dystonia by study design, with data pooled from the prospective studies (a) and retrospective studies (b) using random effects model.

Prospective Studies: Using a random effects model, the pooled device complication rate was 7% (95% CI: 3–19%) for adult patients and 34% (95% CI: 19–53%) for pediatric patients, with no heterogeneity among studies. The combined device complication rate across both

dystonia types was 14% (95% CI: 5–34%) with substantial heterogeneity across both groups (p=0.0502).

Retrospective Studies: Using a random effects model, the pooled device complication rate was 30% (95% CI: 4–83%) for adult patients and 21% (95% CI: 14–32%) for pediatric patients. No heterogeneity was observed in pediatric studies but high heterogeneity was observed in adult studies (I^2 = 75.7%, τ^2 = 0.6925, p=0.0165). The combined device complication rate was 24% (95% CI: 16–35%) with low heterogeneity across both groups (p=0.2083).

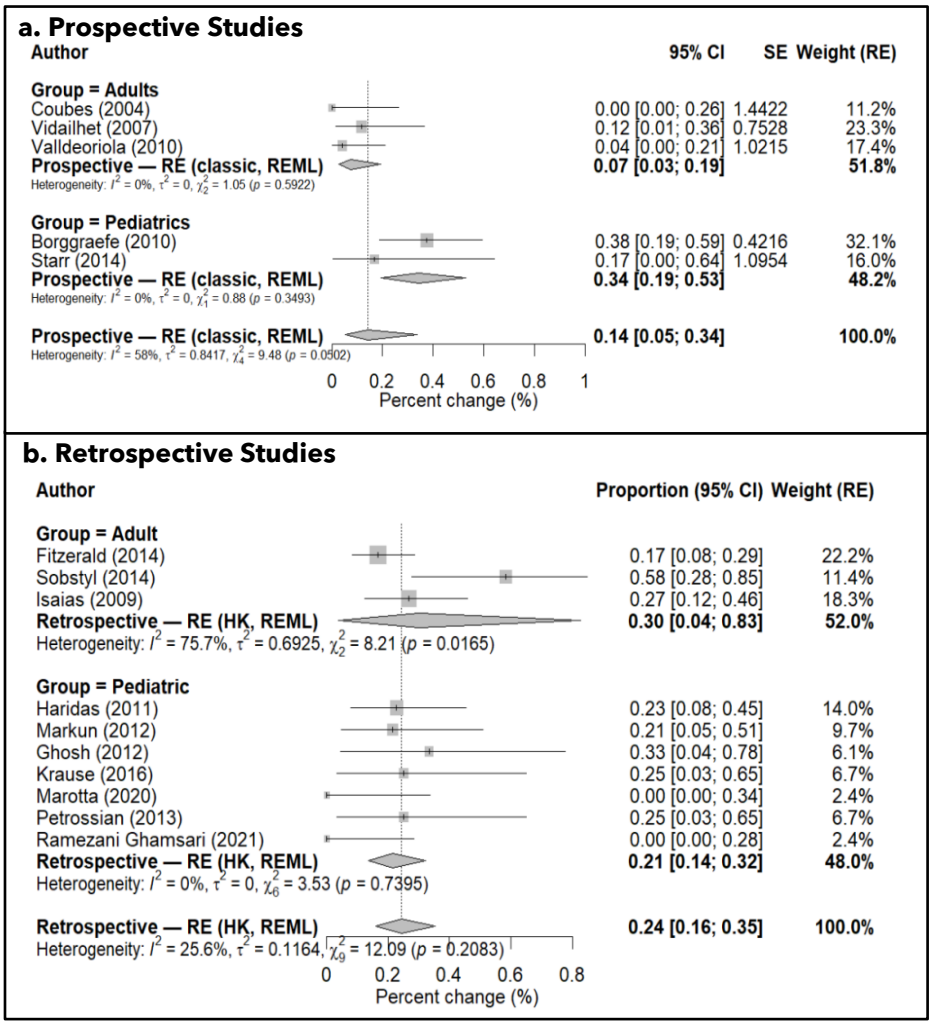

Figure 1. Forest Plot of Device Complication Rates in Adult and Pediatric Patients with Generalized Dystonia by Study Designs, a) Prospective, b) Retrospective.

Infection

Figure 2 presents a forest plot and detailed comparison of device infection rates between adult and pediatric patients with generalized dystonia by study design, with data pooled from the prospective studies (a) and retrospective studies (b) using random effects model.

Prospective Studies: Using a random effects model, the pooled infection rate was 5% (95% CI: 1–15%) for adult patients and 10% (95% CI: 4–24%) for pediatric patients, with no heterogeneity among studies. The combined infection rate for both dystonia types was 7% (95% CI: 3–15%) with no heterogeneity across both groups (p=0.7992).

Retrospective Studies: Using a random effects model, the pooled infection rate was 15% (95% CI: 9–23%) for adult patients and 19% (95% CI: 11–32%) for pediatric patients, with no heterogeneity among studies. The combined infection rate was 16% (95% CI: 11–24%) with no heterogeneity across both groups (p=0.6158).

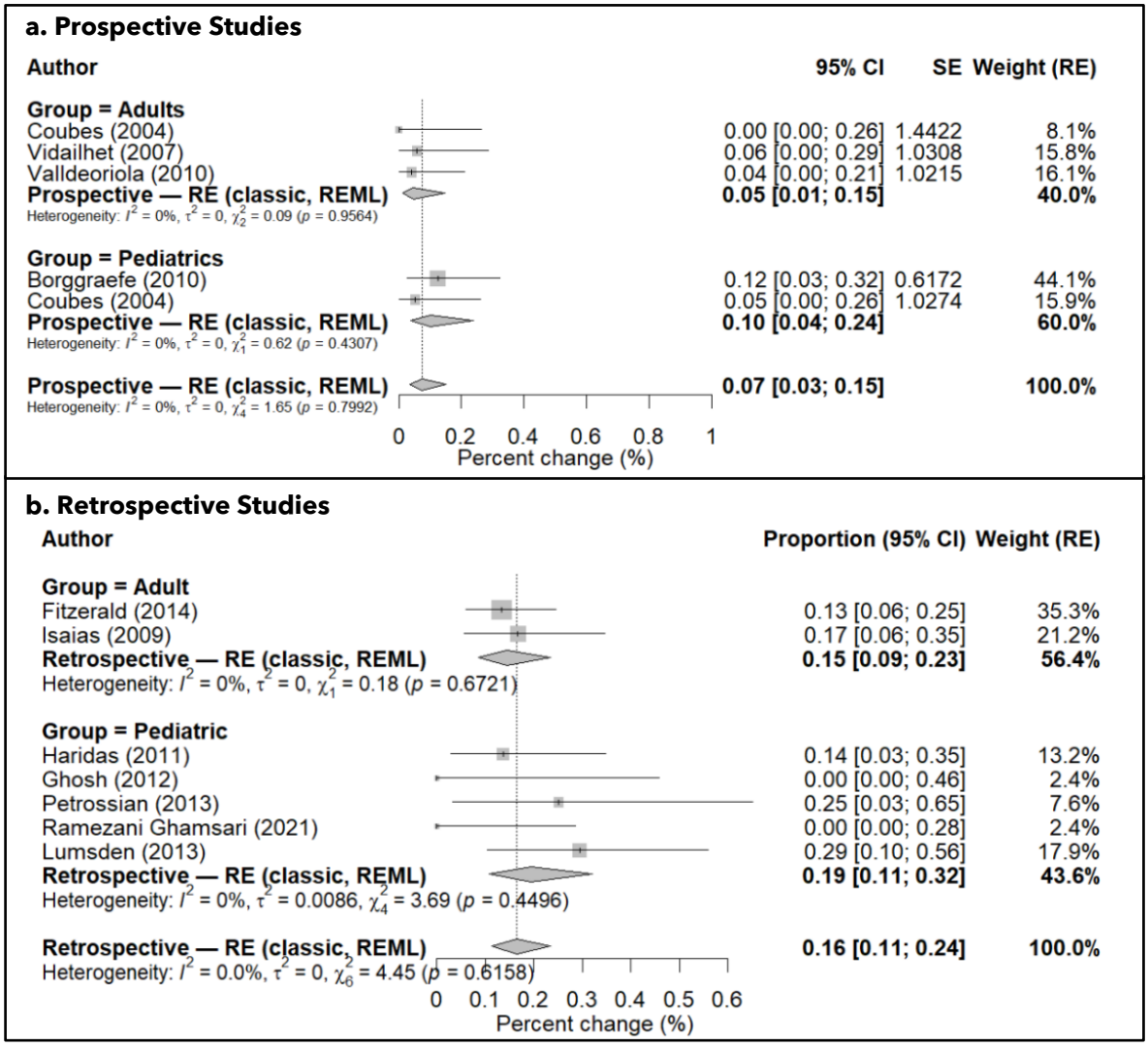

Figure 2. Forest Plot of Infection Rates in Adult and Pediatric Patients with Generalized Dystonia by Study Designs, a) Prospective, b) Retrospective.

Symptomatic ICH

Figure 3 presents a forest plot and detailed comparison of symptomatic ICH rates between adult and pediatric patients with generalized dystonia by study design, with data pooled from the prospective studies (a) and retrospective studies (b) using random effects model.

Prospective Studies: Using a random effects model, the pooled symptomatic ICH rate was 4% (95% CI: 1–18%) for adult patients and 4% (95% CI: 1–25%) for pediatric patients, with no heterogeneity among studies. The combined symptomatic ICH rate was 4% (95% CI: 1–13%) with no heterogeneity across both groups (p=0.9619).

Retrospective Studies: Using a random effects model, the pooled symptomatic ICH rate was 2% (95% CI: 0–16%) for adult patients and 4% (95% CI: 1–19%) for pediatric patients, with no heterogeneity among studies. The combined symptomatic ICH rate was 3% (95% CI: 1–11%) with no heterogeneity across both groups (p=0.9378).

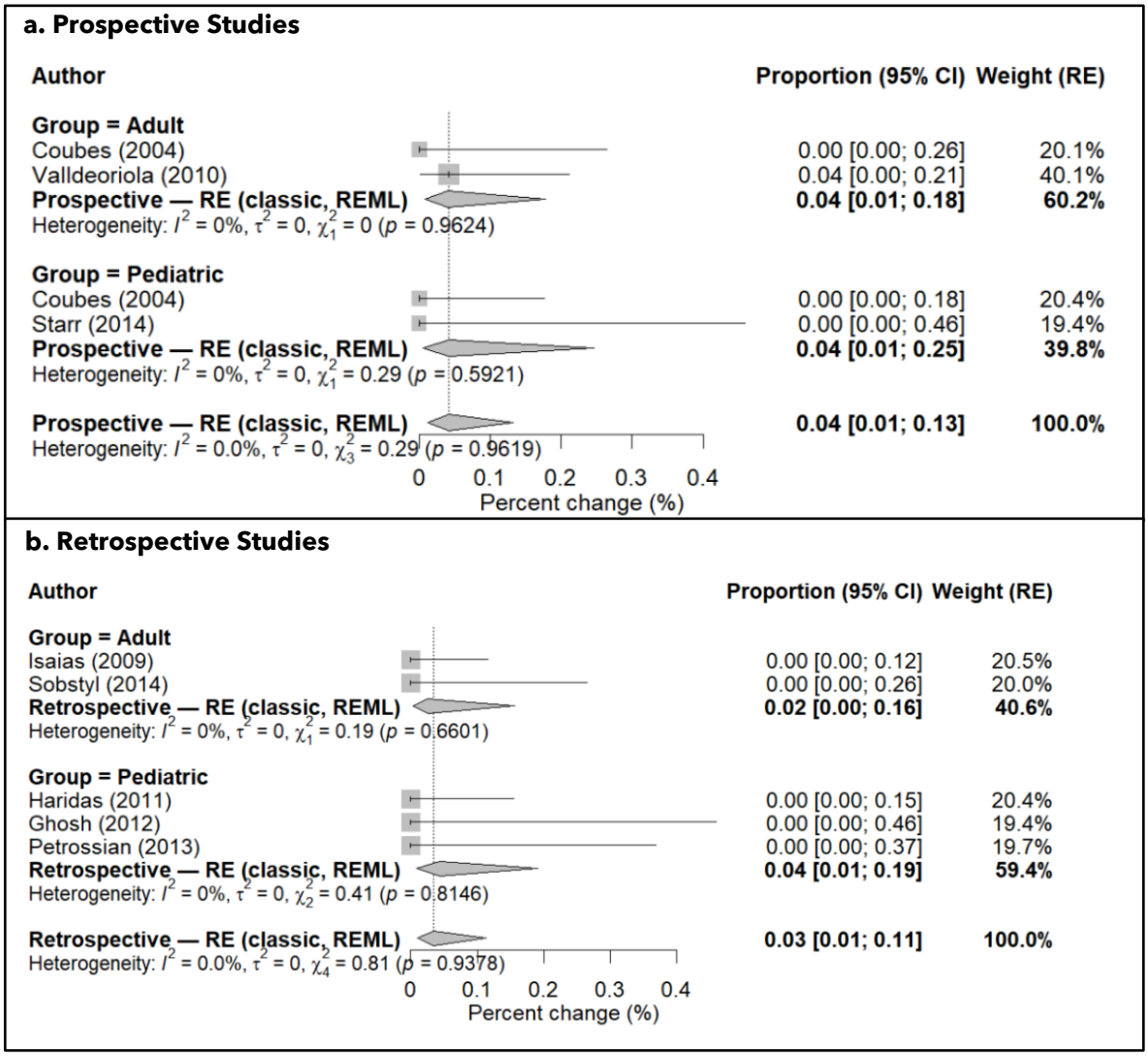

Figure 3. Forest Plot of Symptomatic Intracranial Hemorrhage Rates in Adult and Pediatric Patients with Generalized Dystonia by Study Designs, a) Prospective, b) Retrospective.

Asymptomatic ICH

Figure 4 presents a forest plot and detailed comparison of asymptomatic ICH rates between adult and pediatric patients with generalized dystonia by study design, with data pooled from the prospective studies (a) and retrospective studies (b) using random effects model.

Prospective Studies: Only one prospective study in adult cohort reported of asymptomatic ICH rates. The point estimate of asymptomatic ICH rates for this study for adult patients was 0% (95% CI: 0–26%) and pooled estimate of asymptomatic ICH rate for two studies for pediatric patients was 4% (95% CI: 1–25%), with no heterogeneity among studies. The combined asymptomatic ICH rate was 4% (95% CI: 1–18%) with no heterogeneity across both groups (p=0.8652).

Retrospective Studies: Using a random effects model, the pooled asymptomatic ICH rate was 2% (95% CI: 0–16%) for adult patients and 7% (95% CI: 2–17%) for pediatric patients, with no heterogeneity among studies. The combined asymptomatic ICH rate was 5% (95% CI: 2–13%) with no heterogeneity across both groups (p=0.9261).

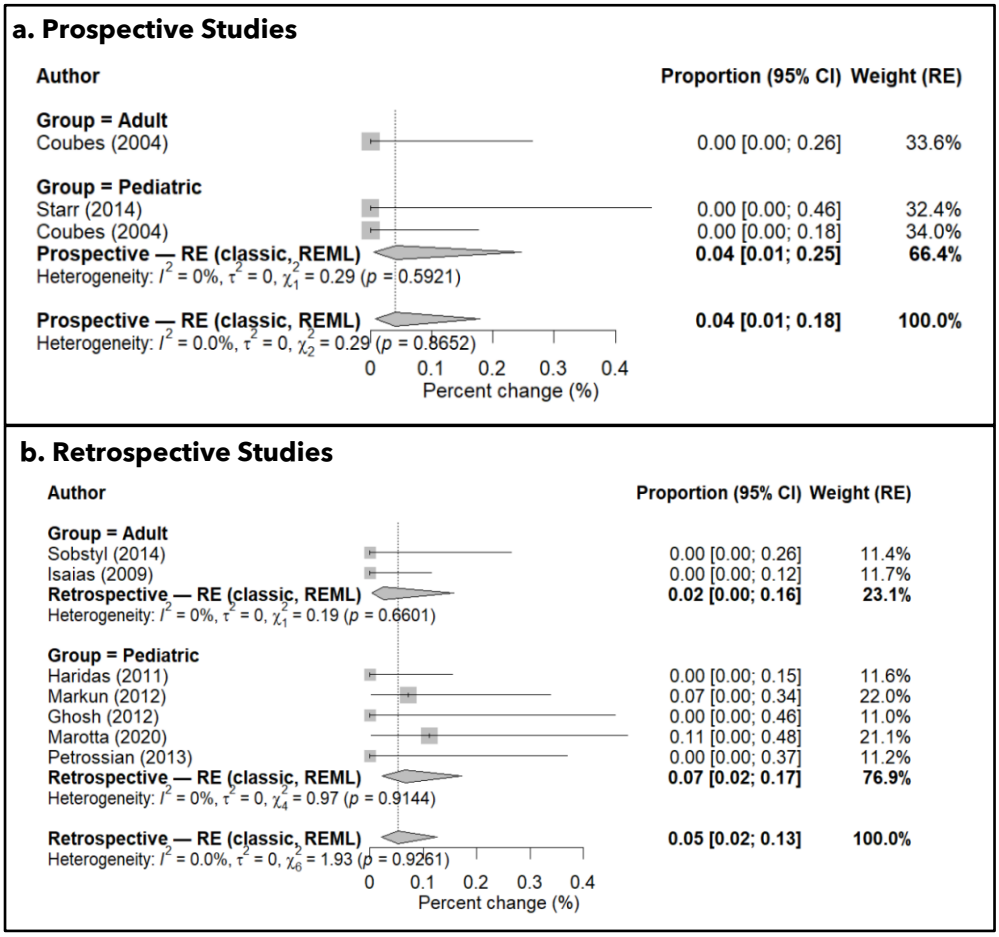

Figure 4. Forest Plot of Asymptomatic Intracranial Hemorrhage Rates in Adult and Pediatric Patients with Generalized Dystonia by Study Designs, a) Prospective, b) Retrospective.

Device Revisions

Figure 5 presents a forest plot and detailed comparison of device revisions rates between adult and pediatric patients with generalized dystonia by study design, with data pooled from the prospective studies (a) and retrospective studies (b) using random effects model.

Prospective Studies: Using a random effects model, the pooled device revision rate was 5% (95% CI: 1–18%) for adult patients and 12% (95% CI: 4–30%) for pediatric patients, with no heterogeneity among studies. The combined device revisions rate was 9% (95% CI: 4–20%) with no heterogeneity across both groups (p=0.4303).

Retrospective Studies: Using a random effects model, the pooled device revisions rate was 26% (95% CI: 2–86%) for adult patients and 27% (95% CI: 15–44%) for pediatric patients. Substantial heterogeneity was observed in included studies for adult patients (I^2 = 80.2%, τ^2 = 1.0284, p=0.0064) but no heterogeneity was observed among pediatric studies. The combined device revisions rate was 24% (95% CI: 14–39%) with moderate heterogeneity across both groups (p=0.0535), primarily driven by the substantial heterogeneity observed in adult patients.

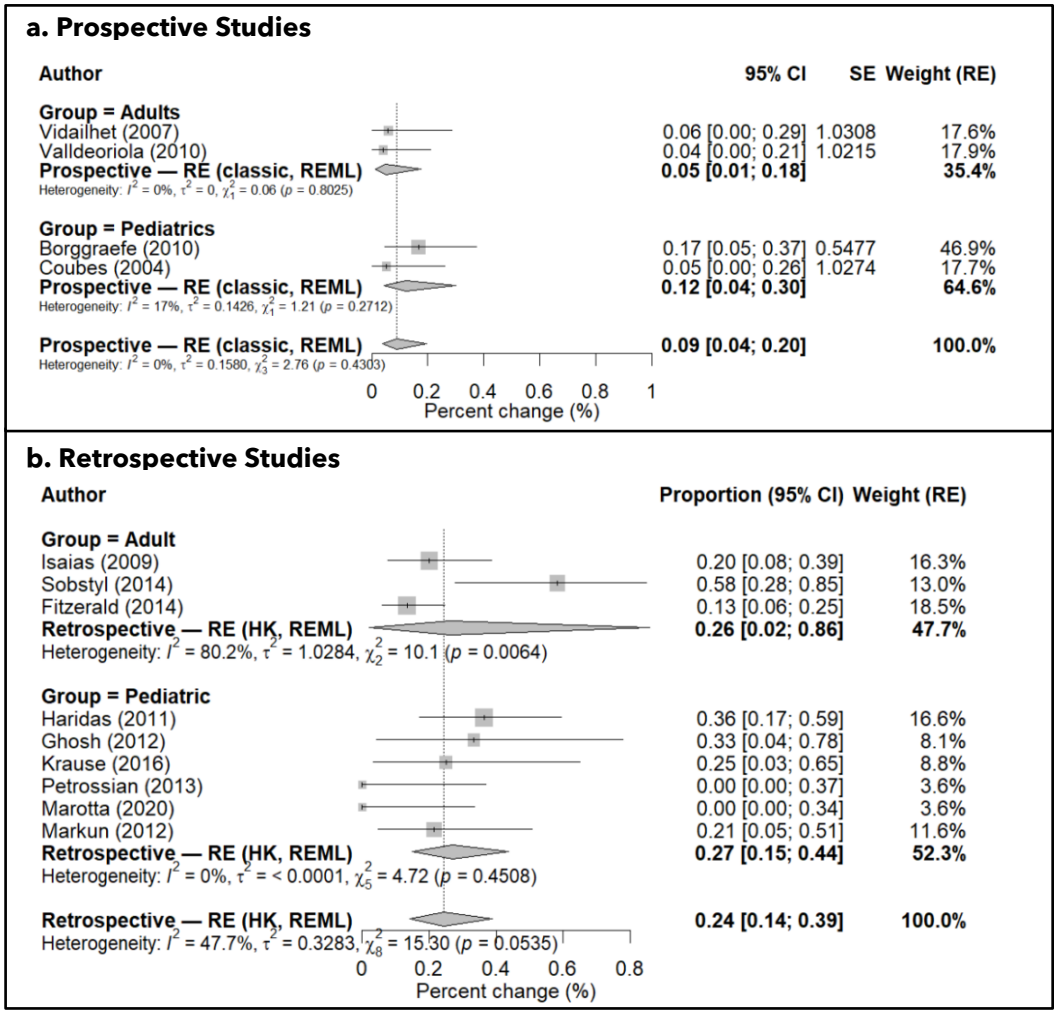

Figure 5. Forest Plot of Device Revision Rates in Adult and Pediatric Patients with Generalized Dystonia by Study Designs, a) Prospective, b) Retrospective.

Explants

Table 6 presents a forest plot and detailed comparison of explant rates between adult and pediatric patients with generalized dystonia by study design using random effects model. No explant rate was reported from the included studies for pediatric patients in prospective studies; therefore, data pooled from the retrospective studies only is presented for explants. Only one study presented the explant rate for adult patients and the point estimate for explant rate was 12% (95% CI: 5–23%) for adult patients and pooled estimate from three studies for pediatric patients was 20% (95% CI: 7–43%) for pediatric patients, with low heterogeneity among studies. The combined explant rate was 16% (95% CI: 8–29%) with low heterogeneity across both groups (p=0.2795).

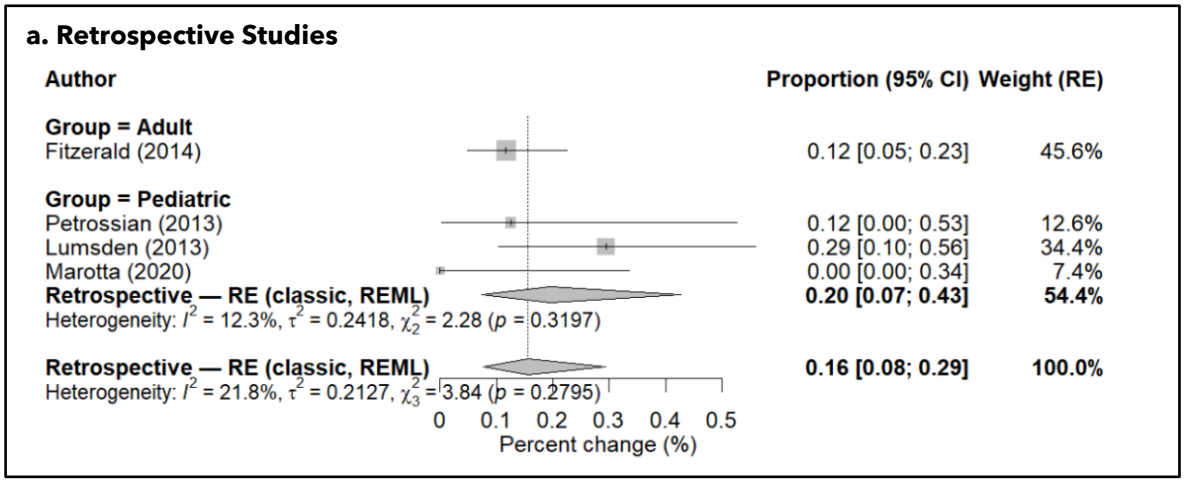

Figure 6. Forest Plot of Explant Rates in Adult and Pediatric Patients with Generalized Dystonia in Retrospective Studies

Product Surveillance Registry (PSR)

The PSR began collecting data on DBS patients in 2009. Safety data was available for 308 DBS patients with primary dystonia from 12 different countries enrolled in the registry. This analysis represents the data collected between 2009 and October 31, 2022. The majority of dystonia patients were adult (279/308; 90.6%). There were 27 (27/308; 8.8%) pediatric patients and two patients with missing age information.

The majority of patients (250/273, 91.6%) had leads implanted in the GPi region with bilateral stimulation (255/273, 93.4%). Mean age of adult and pediatric patients is 53 ± 14.4 years (range 22-88 years) and 16 ± 3.9 years (range 8-21 years), respectively. The average duration of device exposure for implanted dystonia patients was 38.2 ± 32.6 months for adult and 35.9 ± 30.9 months for pediatric patients, respectively.

Adverse Event Summary

Events currently collected include all events that appear or worsen during the registry and are a result of implanted or external components (device related), implant or modification procedures (procedure related), or stimulation therapy (therapy related).

There were 166 AEs reported in 87 (28.2%) of the 308 dystonia patients. Within these adverse events, 58 were considered serious and occurred in 39 (12.7%) dystonia patients. By age group, SAEs occurred in 3 of 27 (11.1%) pediatric patients and 36 of 279 (12.9%) adult patients (Table 15). The 2 patients with unknown age did not experience any SAEs. The 58 SAEs by System Organ Class (SOC) are summarized in Table 16.

Table 15. Adverse Event and Serious Adverse Event Summary

Age Group	Number at risk	Adverse Events			Serious Adverse Events		
		Number of AEs	Patients with AEs	% of patients with AEs	Number of SAEs	Patients with SAEs	% of patients with SAEs
Adult	279	156	78	28.0%	54	36	12.9%
Pediatric	27	8	7	25.9%	4	3	11.1%
Unknown	2	2	2	100.0%	0	0	0.0%
Total	**308**	**166**	**87**	**28.2%**	**58**	**39**	**12.7%**

Table 16. Serious Adverse Event Summary by System Organ Class (SOC) and Preferred Term (PT)

Adverse Event SOC and PT	Adult (N = 279)	Pediatric (N = 27)	Total* (N = 308)
All Adverse Events	**54 (36, 12.9%)**	**4 (3, 11.1%)**	**58 (39, 12.7%)**
Infections and infestations	**14 (9, 3.2%)**	**1 (1, 3.7%)**	**15 (10, 3.2%)**
Medical Device Site Infection	8 (4, 1.4%)	1 (1, 3.7%)	9 (5, 1.6%)
Wound Infection	4 (4, 1.4%)	0 (0, 0.0%)	4 (4, 1.3%)
Meningitis Bacterial	1 (1, 0.4%)	0 (0, 0.0%)	1 (1, 0.3%)
Staphylococcal Infection	1 (1, 0.4%)	0 (0, 0.0%)	1 (1, 0.3%)
Psychiatric disorders	**1 (1, 0.4%)**	**1 (1, 3.7%)**	**2 (2, 0.6%)**
Aggression	0 (0, 0.0%)	1 (1, 3.7%)	1 (1, 0.3%)
Depression	1 (1, 0.4%)	0 (0, 0.0%)	1 (1, 0.3%)
Nervous system disorders	**18 (13, 4.7%)**	**0 (0, 0.0%)**	**18 (13, 4.2%)**
Dystonia	10 (7, 2.5%)	0 (0, 0.0%)	10 (7, 2.3%)
Dyskinesia	2 (2, 0.7%)	0 (0, 0.0%)	2 (2, 0.6%)
Basal Ganglia Haemorrhage	1 (1, 0.4%)	0 (0, 0.0%)	1 (1, 0.3%)
Cerebral Haemorrhage	1 (1, 0.4%)	0 (0, 0.0%)	1 (1, 0.3%)
Cerebrovascular Accident	1 (1, 0.4%)	0 (0, 0.0%)	1 (1, 0.3%)
Generalised Tonic-Clonic Seizure	1 (1, 0.4%)	0 (0, 0.0%)	1 (1, 0.3%)
Haemorrhage Intracranial	1 (1, 0.4%)	0 (0, 0.0%)	1 (1, 0.3%)
Spinal Cord Disorder	1 (1, 0.4%)	0 (0, 0.0%)	1 (1, 0.3%)
Gastrointestinal disorders	**1 (1, 0.4%)**	**0 (0, 0.0%)**	**1 (1, 0.3%)**

Adverse Event SOC and PT	Adult (N = 279)	Pediatric (N = 27)	Total* (N = 308)
Dysphagia	1 (1, 0.4%)	0 (0, 0.0%)	1 (1, 0.3%)
Skin and subcutaneous tissue disorders	**1 (1, 0.4%)**	**0 (0, 0.0%)**	**1 (1, 0.3%)**
Blister	1 (1, 0.4%)	0 (0, 0.0%)	1 (1, 0.3%)
Musculoskeletal and connective tissue disorders	**4 (3, 1.1%)**	**0 (0, 0.0%)**	**4 (3, 1.0%)**
Muscle Tightness	3 (2, 0.7%)	0 (0, 0.0%)	3 (2, 0.6%)
Neck Pain	1 (1, 0.4%)	0 (0, 0.0%)	1 (1, 0.3%)
Renal and urinary disorders	**1 (1, 0.4%)**	**0 (0, 0.0%)**	**1 (1, 0.3%)**
Acute Kidney Injury	1 (1, 0.4%)	0 (0, 0.0%)	1 (1, 0.3%)
General disorders and administration site conditions	**8 (7, 2.5%)**	**0 (0, 0.0%)**	**8 (7, 2.3%)**
Medical Device Site Pain	4 (4, 1.4%)	0 (0, 0.0%)	4 (4, 1.3%)
Medical Device Site Fistula	2 (1, 0.4%)	0 (0, 0.0%)	2 (1, 0.3%)
Gait Disturbance	1 (1, 0.4%)	0 (0, 0.0%)	1 (1, 0.3%)
Medical Device Site Discomfort	1 (1, 0.4%)	0 (0, 0.0%)	1 (1, 0.3%)
Injury, poisoning and procedural complications	**4 (4, 1.4%)**	**1 (1, 3.7%)**	**5 (5, 1.6%)**
Wound Dehiscence	1 (1, 0.4%)	1 (1, 3.7%)	2 (2, 0.6%)
Pneumocephalus	1 (1, 0.4%)	0 (0, 0.0%)	1 (1, 0.3%)
Seroma	1 (1, 0.4%)	0 (0, 0.0%)	1 (1, 0.3%)
Subdural Haematoma	1 (1, 0.4%)	0 (0, 0.0%)	1 (1, 0.3%)
Product issues	**2 (2, 0.7%)**	**1 (1, 3.7%)**	**3 (3, 1.0%)**
Device Extrusion	1 (1, 0.4%)	1 (1, 3.7%)	2 (2, 0.6%)
Device Lead Damage	1 (1, 0.4%)	0 (0, 0.0%)	1 (1, 0.3%)

Note: Sum of patients experiencing each event may not add to total as patients may have experienced more than 1 event. SOC = MedDRA System Organ Class. PT = MedDRA Preferred Term.

*Two patients with unknown age.

Device Event Summary

Device events (DE) could be related to the neurostimulator, lead, extension, and/or external device (such as the recharger). Product performance-related events (PPE) are a subset of device events determined to be product performance-related and may or may not be related to a corresponding adverse event.

There were 53 device events (DEs) reported in 37 (37/308; 12.0%) patients, including 11.8% (33/279) in adult patients and 11.1% (3/27) in pediatric patients. Of the 53 DEs, 38 were product performance-related events that occurred in 30 (30/308; 9.7%) dystonia patients,

including 9.3% (26/279) in adult patients and 11.1% (3/27) in pediatric patients (Table 17). The 37 PPEs for adult and pediatric patients are summarized in Table 18 by MedDRA Preferred Term. One patient of unknown age with an event (neurostimulator unable to recharge) with one PPE is not included within the Table 18.

Table 17. Device Event Summary

Age Group	Number at risk	All Device Events			Product Performance-Related Events		
		Number of DEs	Patients with DEs	% of patients with DEs	Number of PPEs	Patients with PPEs	% of patients with PPEs
Adult	279	49	33	11.8%	34	26	9.3%
Pediatric	27	3	3	11.1%	3	3	11.1%
Unknown	2	1	1	50.0%	1	1	50.0%
Total	**308**	**53**	**37**	**12.0%**	**38**	**30**	**9.7%**

Table 18. Product Performance Events Summary[a]

Device Event	Adults N=279			Pediatric N=27		
	No. of Events	No. of Patients	% of Patients	No. of Events	No. of Patients	% of Patients
High Impedance[b]	13	11	3.9%	0	0	0.0%
Extension Migration	5	4	1.4%	0	0	0.0%
Lead Migration/Dislodgement[b]	5	4	1.4%	0	0	0.0%
Device Malfunction	3	3	1.1%	0	0	0.0%
Low Impedance[b]	2	2	0.7%	1	1	3.7%
Neurostimulator Unable To Recharge	1	1	0.4%	1	1	3.7%
Lead Fracture	2	2	0.7%	0	0	0.0%
Device Connection Issue	1	1	0.4%	0	0	0.0%
Device Electrical Finding	1	1	0.4%	0	0	0.0%
Device End of Life	1	1	0.4%	0	0	0.0%
Medical Device Complication[c]	0	0	0.0%	1	1	3.7%
Total	**34**	**26**	**9.3%**	**3**	**3**	**11.1%**

[a] One patient with unknown age with an event (neurostimulator unable to recharge) is not presented in this table.

[b] One event each of High Impedance, Lead Migration/Dislodgement, and Low Impedance was serious without a corresponding clinical diagnosis (i.e., AE) reported on the Event CRF. Because no AE was reported, these events are not included in the SAE summaries. The high impedance event was serious due to in- patient or prolonged hospitalization and medical or surgical intervention to prevent life threatening illness or injury or permanent impairment to a body structure or a body function. The lead migration/dislodgement and low impedance events were serious due to medical or surgical intervention to prevent life threatening illness or injury or permanent impairment to a body structure or a body function.

[c] Reported as "Suspicion of heating of the antenna 5 minutes after starting the first recharge".

System Modifications

A system modification is any change to the implanted DBS system following the initial implant within the registry. This includes explant with or without replacement, repositioning, the addition of another extension and/or lead, or any other type of surgical intervention on the system. Overall, 29.5% (91/308) of dystonia patients had at least one system modification procedure (Table 19).

Out of the 91 patients with at least one system modification, 72.5% (66/91) experienced their system modification due to battery depletion without an event, 5.5% (5/91) experienced their system modification due to battery depletion with an event, and 35.2% (32/91) experienced their system modification due to an event. Patients may have experienced separate system modifications due to battery depletion and due to an event.

Overall, 25.9% (7/27) of pediatric dystonia patients had at least one system modification procedure. Table 20 below shows the reasons for all system modifications.

Within adult patients, 2.2% (6/279) had a permanent neurostimulator explant, and within pediatric patients, 3.7% (1/27) had a permanent neurostimulator explant.

Table 19. System Modifications Summary

Age Category	Number of Patients	% of Patients
Adult (N=279)	84	30.1%
Pediatric (N=27)	7	25.9%
***Total (N=308)**	**91**	**29.5%**
*Two patients with unknown age.		

Table 20. Reasons for System Modifications

Age category	Modification Reason	Number of procedures	Number of patients with a system modification
Adult	Battery depletion	105	62
Adult	Battery depletion; Event	6	5
Adult	Event	56	31
Adult	Other	5	3
Adult	**Total**	**172**	**84**
Pediatric	Battery depletion	4	4
Pediatric	Event	1	1
Pediatric	Other	2	2
Pediatric	**Total**	**7**	**7**

Patient Deaths

All deaths were collected regardless of their relatedness to the device, implant procedure, and/or therapy. There were 15 deaths: 12 deaths occurred in adult patients and 3 deaths occurred in pediatric patients. Twelve deaths in adult patients were attributed to cardiac arrest (1), heart attack/heart failure (2), Huntington's Chorea (1), advanced dystonia (1), liver cancer (1), and unknown causes (6). Three deaths in pediatric patients were attributed to respiratory system infection (1), worsened dystonia (1), and unknown cause (1). Eleven of the deaths were reported as not related to the device or procedure. Four deaths due to unknown causes had an unknown relationship to the device or procedure. None of these deaths were reported as a direct result of a product performance event.

Effectiveness Results

Effectiveness outcomes comprised changes in average BFMDRS motor scores for generalized and segmental (head and neck) dystonia and average TWSTRS severity scores

for cervical dystonia. Outcomes are presented separately for primary generalized, segmental (head and neck) and cervical dystonia for adult patients, and pediatric patients with primary generalized dystonia. Comparisons of effectiveness outcomes between adult and pediatric patients with primary generalized dystonia by study designs are also included to provide additional information on the effectiveness of bilateral GPi DBS by study design in pediatric patients with primary generalized dystonia.

Effectiveness Outcomes in Adult Population

Generalized Dystonia

The analysis of effectiveness of bilateral GPi DBS for the treatment of primary generalized dystonia in adult patients was based on data from the Investigator's Study[17] and 5 publications (3 prospective and 2 retrospective) representing a total of 130 patients contributing device effectiveness outcomes. The highest level of available evidence is the Investigator Study,[17] a subset data of 30 patients (18 with generalized dystonia, 11 with segmental dystonia, one additional patient with multifocal dystonia is excluded from this subgroup analysis) from the Kupsch (2006)[2] RCT study and Volkmann (2012)[15] study.

Study Specific Data

The Investigator Study[17] included 18 patients with generalized dystonia, randomly assigned 9 patients to neurostimulation group and 9 to the sham stimulation group. Baseline characteristics were similar between the neurostimulation group and the sham stimulation group. During the randomization period, the BFMDRS motor score improved significantly in the neurostimulation group compared to the sham stimulation group (42.3% vs 2.5%; p=0.005). During the open-label phase, the BFMDRS motor score was improved by 50.1% at 6 months (n=18), 69.9% at 3 years (n=16), and 60.8% at 5 years (n=12), compared to baseline. Similar results were reported in the published article from the same clinical study with the full study cohort (n=40), where the motor score was improved by 44.8% at 6 months (n=24), 70.6% at 3 years (n=20), and 67.0% at 5 years (n=20), compared to baseline.[15]

Similar improvement was also observed for BFMDRS disability score, 35.6% for the neurostimulation group compared to 7.1% for the sham stimulation group at 3 months (p=0.005). The improvement in BFMDRS disability score as compared to baseline was significant and sustained at the 5-year follow-up for patients.

Table 21 and Table 22 present the BFMDRS motor score and the BFMDRS disability score by each follow-up for generalized dystonia.

Table 21. BFMDRS Motor Score Improvement by Visit for Generalized Dystonia

			BFMDRS Movement Score		Change from baseline			
BFMDRS (Movement)	**Range of possible scores**	**Visit**	**N**	**Mean ± SD**	**N**	**Absolute Change Mean ± SD**	**Percent Change Mean ± SD**	**P-value**
Total	0 – 120	Baseline (Neurostimulation)	9	61.4 ± 27.5	9	NA	NA	NA
		Baseline (Sham Stimulation)	9	50.0 ± 29.1	9	NA	NA	NA

			BFMDRS Movement Score		Change from baseline			
BFMDRS (Movement)	**Range of possible scores**	**Visit**	**N**	**Mean ± SD**	**N**	**Absolute Change Mean ± SD**	**Percent Change Mean ± SD**	**P-value**
		3 Month (Neurostimulation)	9	32.7 ± 18.3	9	-28.7 ± 22.2	-42.3 ± 24.8	0.005[a]
		3 Month (Sham Stimulation)	8	52.0 ± 27.8	8	-0.5 ± 7.7	2.5 ± 23.2	
		6 Month	18	27.8 ± 20.9	18	-27.9 ± 17.7	-50.1 ± 22.0	<0.001[b]
		1 Year	12	27.5 ± 24.3	12	-29.0 ± 14.4	-55.6 ± 25.2	<0.001[b]
		2 Year	16	25.5 ± 22.7	16	-29.9 ± 18.1	-57.2 ± 25.6	<0.001[b]
		3 Year	16	19.3 ± 20.8	16	-37.0 ± 19.3	-69.9 ± 20.1	<0.001[b]
		4 Year	13	21.1 ± 22.1	13	-34.4 ± 24.6	-63.9 ± 24.2	<0.001[b]
		5 Year	12	25.5 ± 22.2	12	-35.4 ± 21.3	-60.8 ± 25.7	<0.001[b]

[a] Two-sided Mann-Whitney Test

[b] Two-sided Wilcoxon signed-rank Test

Table 22. BFMDRS Disability Score Improvement by Visit for Generalized Dystonia

			BFMDRS Disability Score		Change from baseline			
BFMDRS (Disability)	**Range of possible scores**	**Visit**	**N**	**Mean ± SD**	**N**	**Absolute Change Mean ± SD**	**Percent Change Mean ± SD**	**P-value**
Total	0 - 30	Baseline (Neurostimulation)	9	14.1 ± 6.1	9	NA	NA	NA
		Baseline (Sham Stimulation)	9	12.0 ± 7.2	9	NA	NA	NA
		3 Month (Neurostimulation)	9	9.6 ± 6.0	9	-4.6 ± 2.6	-35.6 ± 22.1	0.005[a]
		3 Month (Sham Stimulation)	8	11.0 ± 7.4	8	-0.9 ± 0.8	-7.1 ± 8.3	
		6 Month	18	8.3 ± 6.6	18	-4.8 ± 3.7	-40.8 ± 25.8	<0.001[b]
		1 Year	11	9.6 ± 8.0	11	-4.9 ± 4.1	-40.0 ± 31.2	0.008[b]
		2 Year	15	7.7 ± 6.9	15	-5.6 ± 5.1	-46.0 ± 28.1	<0.001[b]
		3 Year	14	8.6 ± 7.4	14	-5.1 ± 3.9	-42.4 ± 25.1	<0.001[b]
		4 Year	13	7.8 ± 7.3	13	-5.2 ± 4.7	-43.1 ± 30.5	0.002[b]
		5 Year	12	8.8 ± 7.3	12	-5.7 ± 3.8	-44.8 ± 28.3	0.002[b]

[a] Two-sided Mann-Whitney Test

[b] Two-sided Wilcoxon signed-rank Test

Effectiveness Outcome from the Publications

In addition to the Investigator's Study,[17] the analysis of effectiveness of bilateral GPi DBS for the treatment of primary generalized dystonia in adult patients also includes data from 5 published studies with a total of 118 patients contributing effectiveness outcomes. The 5 publications consist of 3 prospective studies and 2 retrospective studies. These total of six (6) studies (including Investigator Study) for primary generalized dystonia in adult patients include 130 patients with follow-ups ranging from 1 year to 7 years; and average baseline BFMDRS motor scores from 44 to 61 out of a possible score of 120.

Across five other prospective and retrospective studies, the average improvement in BFMDRS motor scores ranged from 43.5% to 79.6% at 1 year,[17,23–27] 49.9% to 82.5% at 2 years,[17,23,26,27] and 56.4% to 85.5% at 3 years.[17,25,27]

Table 23 below reports effectiveness outcomes from the six publications (1 RCT, 3 prospective and 2 retrospective studies) on adult patients with GPi DBS for generalized dystonia and reflects the latest follow-up data used in the meta-analysis.

Table 23. BFMDRS Motor Scores at the Latest Follow-up in Adult Patients with GPi DBS for Generalized Dystonia

Publication	Study Type	Age at Surgery	BFMDRS Motor Score				
			Last Follow-up (years)	N*	Baseline Score	% Improvement ± SD	p-value
Investigator-sponsored study[17]	RCT	38.2 ± 12.9	5.0	12	DBS: 61.4 ± 27.5 Sham:50.0 ± 29.1	60.80±25.7 %	<0.01
Coubes (2004)[23]	Prospective	NR	2.0	12	57.9 ± 28.5	70.10±23.6%	0.0003
Valldeoriola (2010)[24]	Prospective (blinded)	30 ± 14	1.0	24	46.4 ± 21.4	50.22±NR%	<0.05
**Vidailhet (2007)[25]	Prospective	36.3 ± 9.8	3.0	17	48.4	56.40±25.2%	NR
Fitzgerald (2014)[26]	Retrospective	33.5	5.0	60	NR	49.80±NR%	<0.001
Isaias (2009)[59]	Retrospective	28 ± 17	7.0	5	44 ± 23.3	82.00±16.8%	0.068

* Sample size indicates the number of patients with data available at the most recent follow-up.

**Data estimated from the individual patient data.

A meta-analysis was conducted, comprising of 130 patients with follow-ups ranging from 1 year to 7 years.

Figure 7 presents a forest plot of BFMDRS motor scores at the latest follow-up for generalized dystonia in adult patients, with data pooled from the selected studies. The

pooled BFMDRS motor scores improvement calculated using the random effects model was 60.51% (95% CI: 50.69-70.32%) and 56.02% (95% CI: 51.89–60.15%) under the common effect model. High heterogeneity was observed among the included studies (I^2 = 77.2%, τ^2 = 114.1195, p=0.0005).

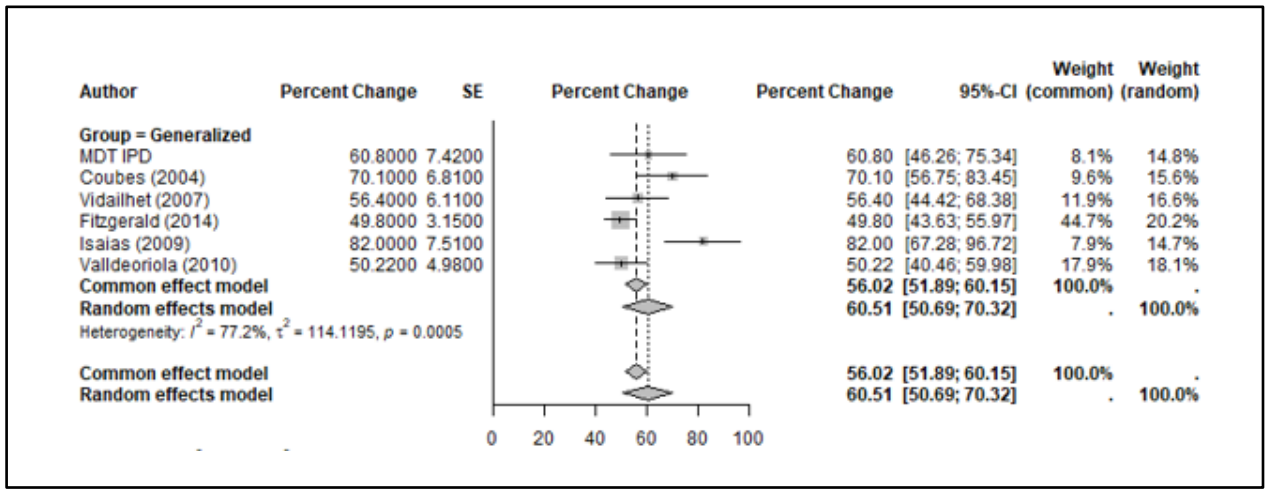

Figure 7. Forest Plot of Percent Improvement in BFMDRS Motor Scores in Adult Patients with Generalized Dystonia at the Latest Follow-up Reported in Each Study

Meta-analysis Stratified by Study Design on Generalized Dystonia in Adult Patients

To address the possibility that effect estimates from different study designs may not represent the same inferential target, a meta-analysis of effectiveness outcomes by study designs in adult patients was conducted for generalized dystonia, focusing on the BFMDRS motor score improvements measured by standardized scales across various study designs. Only one RCT was included in the meta-analysis; therefore, only the point estimate was provided for the RCT.

Figure 8 presents forest plots of the BFMDRS motor score at the latest follow-up in adult patients with GPi DBS for generalized dystonia, with data pooled from the prospective studies (a), retrospective studies (b), and RCT (c). The pooled BFMDRS motor score improvement for the three prospective studies was 58.08% (95% CI: 33.02% - 83.13%) under the random effects model with Hartung-Knapp (HK) method applied to adjust the confidence interval, shown in Figure 8a. In comparison, the pooled BFMDRS motor score improvement for the two retrospective studies was 65.18% (95% CI: 33.65% - 96.70%), indicated in Figure 8b. There was only one RCT study and the point estimate is 60.80% with a 95% CI of 46.26% - 75.34%, shown in Figure 8c. Each study contributes roughly equally to the overall results. Notably, the retrospective studies demonstrated greater heterogeneity (I^2 = 93.6%, τ^2 = 485.2587, p < 0.0001) than the prospective studies (I^2 = 64.1%, τ^2 = 64.3561, p = 0.0615).

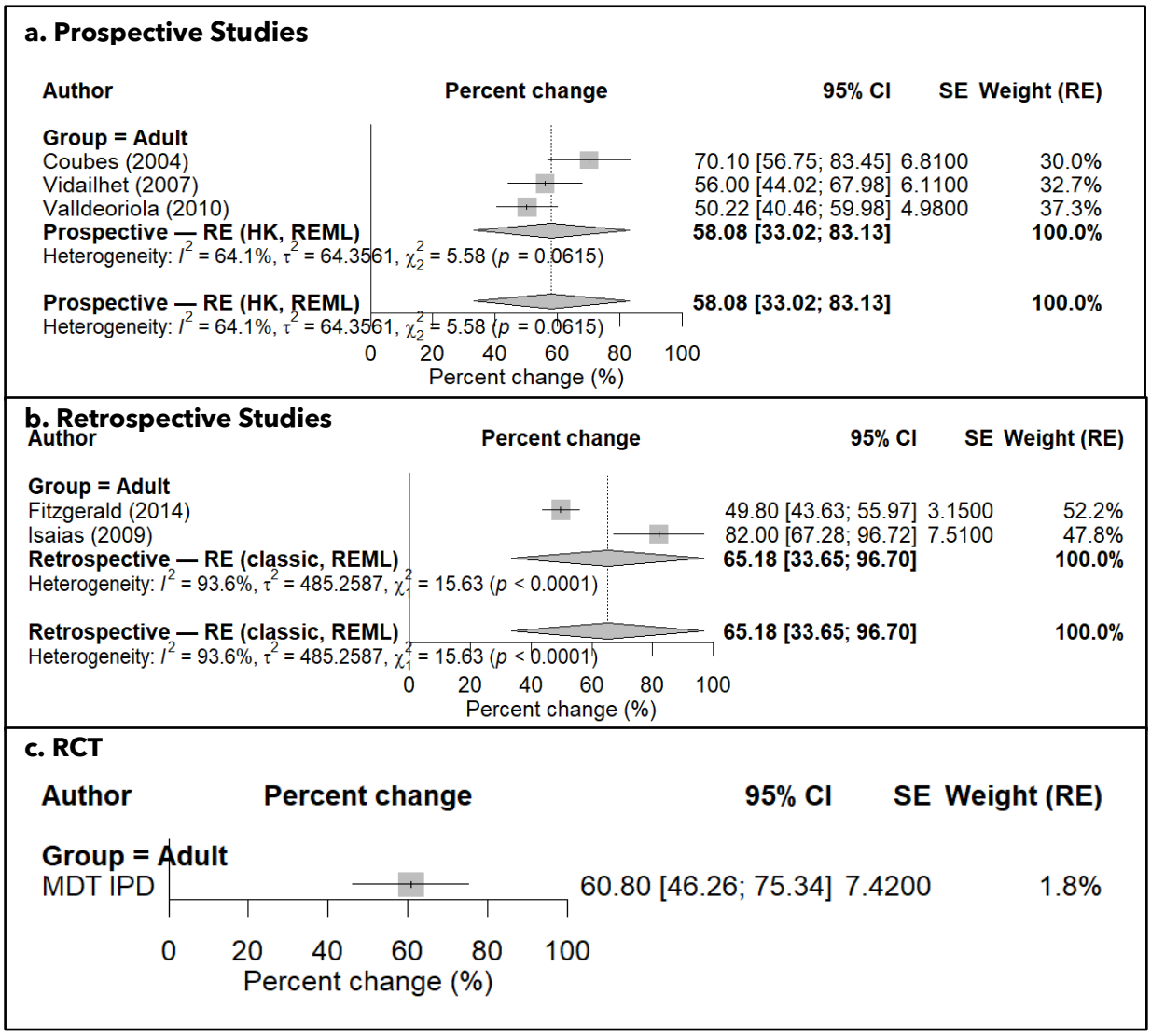

Figure 8. Forest Plots of Percent Improvement in BFMDRS Motor Scores in Adult Patients with GPi DBS for Generalized Dystonia at the Latest Follow-up by Study Designs, a) Prospective, b) Retrospective, c) RCTs.

Segmental Dystonia of the Head and Neck

The analysis of effectiveness of bilateral GPi DBS for the treatment of primary segmental dystonia of the head and neck in adult patients includes data from the Investigator Study[17] and 8 published studies with a total of 94 patients contributing effectiveness outcomes. The highest level of available evidence is the Kupsch (2006)[2] study, the Investigator Study,[17] a subset of data from the Kupsch (2006)[2] and Volkmann (2012).[15]

Study Specific Data

The Investigator Study[17] included 11 patients with segmental dystonia, randomly assigned 7 patients to neurostimulation group and 4 to the sham stimulation group. Baseline characteristics were similar between the neurostimulation group and the sham stimulation group. During the randomization period, the BFMDRS motor score improved significantly in the neurostimulation group compared to the sham stimulation group (61.2% vs 0.9%; p=0.011). During the open-label phase, the BFMDRS motor score was improved by 60.0% at 6 months (n=11), 64.5% at 3 years (n=8) and 59.6% at 5 years (n=5), compared to baseline. Similar results were reported in the published article from the same clinical study with the full study cohort (n=40), where the motor score was improved by 54.5% (n=16) at 6 months, 60.5% (n=11) at 3 years, and 49.4% (n=12) at 5 years, compared with baseline.[15]

Similar improvement was also observed for BFMDRS disability score, 60.3% for the neurostimulation group compared to 8.3% for the sham stimulation group at 3 months (p=0.021). The improvement in BFMDRS disability score as compared to baseline was significant and sustained at the 5-year follow-up but improvement was not statistically significant beyond 6 months.

Table 24 and Table 25 present the BFMDRS motor score and the BFMDRS disability score by each follow-up for segmental dystonia.

Table 24. BFMDRS Motor Score Improvement by Visit for Segmental Dystonia

			BFMDRS Movement Score		Change from baseline			
BFMDRS (Movement)	**Range of possible scores**	**Visit**	**N**	**Mean ± SD**	**N**	**Absolute Change Mean ± SD**	**Percent Change Mean ± SD**	**P-value**
Total	0 – 120	Baseline (Neurostimulation)	7	27.7 ± 16.2	7	NA	NA	NA
		Baseline (Sham Stimulation)	4	18.5 ± 6.9	4	NA	NA	NA
		3 Month (Neurostimulation)	7	11.6 ± 9.2	7	-16.1 ± 8.2	-61.2 ± 13.6	0.011[a]
		3 Month (Sham Stimulation)	4	18.1 ± 6.1	4	-0.4 ± 2.3	-0.9 ± 9.4	
		6 Month	11	9.5 ± 7.2	11	-14.9 ± 12.0	-60.0 ± 28.7	<0.001[b]
		1 Year	8	6.7 ± 5.9	8	-16.4 ± 12.6	-71.6 ± 20.3	0.008[b]
		2 Year	7	11.3 ± 11.5	7	-17.7 ± 15.4	-62.3 ± 33.2	0.016[b]
		3 Year	8	10.5 ± 9.9	8	-16.8 ± 11.5	-64.5 ± 23.6	0.008[b]
		4 Year	7	9.4 ± 9.3	7	-19.1 ± 11.6	-70.6 ± 22.5	0.016[b]
		5 Year	5	12.5 ± 9.1	5	-18.8 ± 14.0	-59.6 ± 24.4	0.063[b]

[a] Two-sided Mann-Whitney Test

[b] Two-sided Wilcoxon signed-rank Test

Table 25. BFMDRS Disability Score Improvement by Visit for Segmental Dystonia

			BFMDRS Disability Score		Change from baseline			
BFMDRS (Disability)	**Range of possible scores**	**Visit**	**N**	**Mean ± SD**	**N**	**Absolute Change Mean ± SD**	**Percent Change Mean ± SD**	**P-value**
Total	0 - 30	Baseline (Neurostimulation)	7	6.7 ± 3.4	7	NA	NA	NA
		Baseline (Sham Stimulation)	4	4.3 ± 1.3	4	NA	NA	NA
		3 Month (Neurostimulation)	7	2.6 ± 2.1	7	-4.1 ± 2.9	-60.3 ± 23.8	0.021[a]
		3 Month (Sham Stimulation)	4	3.8 ± 0.5	4	-0.5 ± 1.0	-8.3 ± 16.7	
		6 Month	8	3.3 ± 1.3	8	-2.3 ± 1.7	-38.6 ± 11.6	0.008[b]
		1 Year	7	2.6 ± 2.4	7	-2.1 ± 2.6	-45.8 ± 37.7	0.109[b]
		2 Year	6	5.7 ± 3.5	6	-0.8 ± 2.6	-11.9 ± 49.9	0.688[b]
		3 Year	7	5.1 ± 3.4	7	-1.0 ± 2.9	-13.9 ± 61.4	0.375[b]
		4 Year	5	5.0 ± 3.5	5	-2.0 ± 3.5	-21.1 ± 72.3	0.375[b]
		5 Year	4	4.5 ± 4.4	4	-2.8 ± 2.6	-42.7 ± 37.3	0.250[b]

[a] Two-sided Mann-Whitney Test

[b] Two-sided Wilcoxon signed-rank Test

Effectiveness Outcome from Publications

In addition to the Investigator's Study,[17] the analysis of effectiveness of bilateral GPi DBS for the treatment of primary segmental dystonia in adult patients also includes data from 8 published studies with a total of 89 patients contributing effectiveness outcomes. The 8 publications consist of 2 prospective studies and 6 retrospective studies. A total of nine (9) studies were included for segmental dystonia in adult patients with follow-up ranging from 0.5 year to 5.6 years. Average baseline BFMDRS motor scores for segmental dystonia ranged from 13 to 37 out of a possible score of 120, which trends lower than baseline scores for generalized dystonia (range of 44 to 61) due to fewer body regions affected by symptoms.

Across eight other published studies, the average improvement in BFMDRS motor scores ranged from 45% to 72% at 3 to 8 months[30-35] and 53% to 72% at 2 to 4 years.[32,34,35,37]

Table 26 below reports effectiveness outcomes from the eight (8) publications (2 prospective and 6 retrospective studies) on adult patients with segmental dystonia and reflects the latest follow-up data used in the meta-analysis.

Table 26. Summary of Studies of Bilateral GPi DBS for Segmental Dystonia in Adult Patients

Publication	Study Type	Age at Surgery in years Mean± SD	BFMDRS Motor Score				
			Last Follow-up (years)	N*	Baseline Score Mean±SD	% improvement Mean±SD	p-value
Investigator-sponsored study[17]	RCT	51.3 ± 12.8	5.0	5	DBS: 27.7 ± 16.2 Sham: 18.5 ± 6.9	59.60±24.4%	0.063
Blahak (2008)[30]	Prospective	57.4 ± 15.0	0.6	10	37.3 ± 20.1	60.00±NR%	<0.01
Ostrem (2007)[31]	Prospective	62.2	0.5	6	22.0 ± 8.3	72.00± NR %	<0.028
Fu (2024) [32]	Retrospective	52.4 ± 7.4	3.2	23	13.1 ± 5.3	58.30±NR%	NR
Horisawa (2019)[33]	Retrospective	51.4**	5.6	16	15.5	58.90±38.1%	<0.001
Reese (2011)[34]	Retrospective	64.5 ± 4.4	3.2	11	21.4 ± 3.2	53.00± NR %	<0.001
Ren (2022)[35]	Retrospective	46.9 ± 7.2	3.1	13	16.3 ± 2.4	54.60± NR %	NR
Sharma (2020)[36]	Retrospective	66.5**	1.0	4	17.8**	65.00±12.0%	<0.05
Tian (2021)[37]	Retrospective	61.2**	3.6	6	22.6**	71.70±3.6%	NR

* Sample size indicates the number of patients with data available at the most recent follow-up.

** Estimated from individual patient data reported in the publication.

A meta-analysis was conducted, comprising of 94 patients with follow-ups ranging from 0.5 year to 5.6 years. Figure 9 presents a forest plot of BFMDRS motor scores at the latest follow-up for segmental dystonia in adult patients, with data pooled from the selected studies. The pooled BFMDRS motor score improvement calculated using the random effects model was 62.03% (95% CI: 56.56–67.51%) and 67.42% (95% CI: 65.07–69.76%) under the common effect model. High heterogeneity was observed among the included studies (I^2 = 74.3%, τ^2 = 37.3580, p=0.0001).

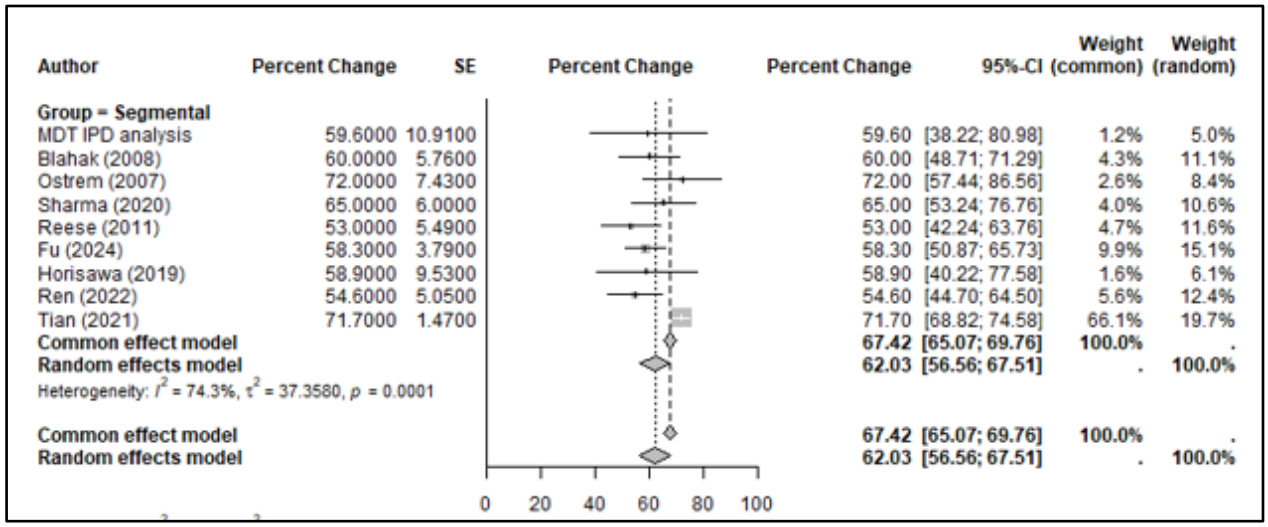

Figure 9. Forest Plot of Percent Improvement in BFMDRS Motor Scores in Adult Patients with GPi DBS for Segmental Dystonia at the Latest Follow-up Reported in Each Study

Meta-analysis Stratified by Study Design on Segmental Dystonia of Head and Neck in Adult Patients

A meta-analysis of effectiveness outcomes by study designs in adult patients was conducted for segmental dystonia, focusing on the BFMDRS motor score improvements measured by standardized scales across various study designs. Only one RCT was included in the meta-analysis; therefore, only the point estimate was provided for the RCT.

Figure 10 presents forest plots of the BFMDRS motor score at the latest follow-up for segmental dystonia in adult patients, with data pooled from the prospective studies (a), retrospective studies (b), and RCT (c). The pooled BFMDRS motor score improvement for the two prospective studies was 65.08% (95% CI: 53.46% - 76.70%) under the random effects model with Hartung-Knapp (HK) method applied to adjust the confidence interval, shown in Figure 10a. In comparison, the pooled BFMDRS motor score improvement for the six retrospective studies was 61.15% (95% CI: 53.11% - 69.20%), indicated in Figure 10b. There was only one RCT study, and the point estimate is 59.60% with a 95% CI of 45.80% - 73.40%, shown in Figure 10c. Each study contributes roughly equally to the overall results. Notably, the retrospective studies demonstrated greater heterogeneity (I^2 = 82.5%, τ^2 = 48.5080, $p < 0.0001$) than the prospective studies (I^2 = 38.6%, τ^2 = 27.8087, p = 0.2018) but heterogeneity in prospective studies was not statistically significant.

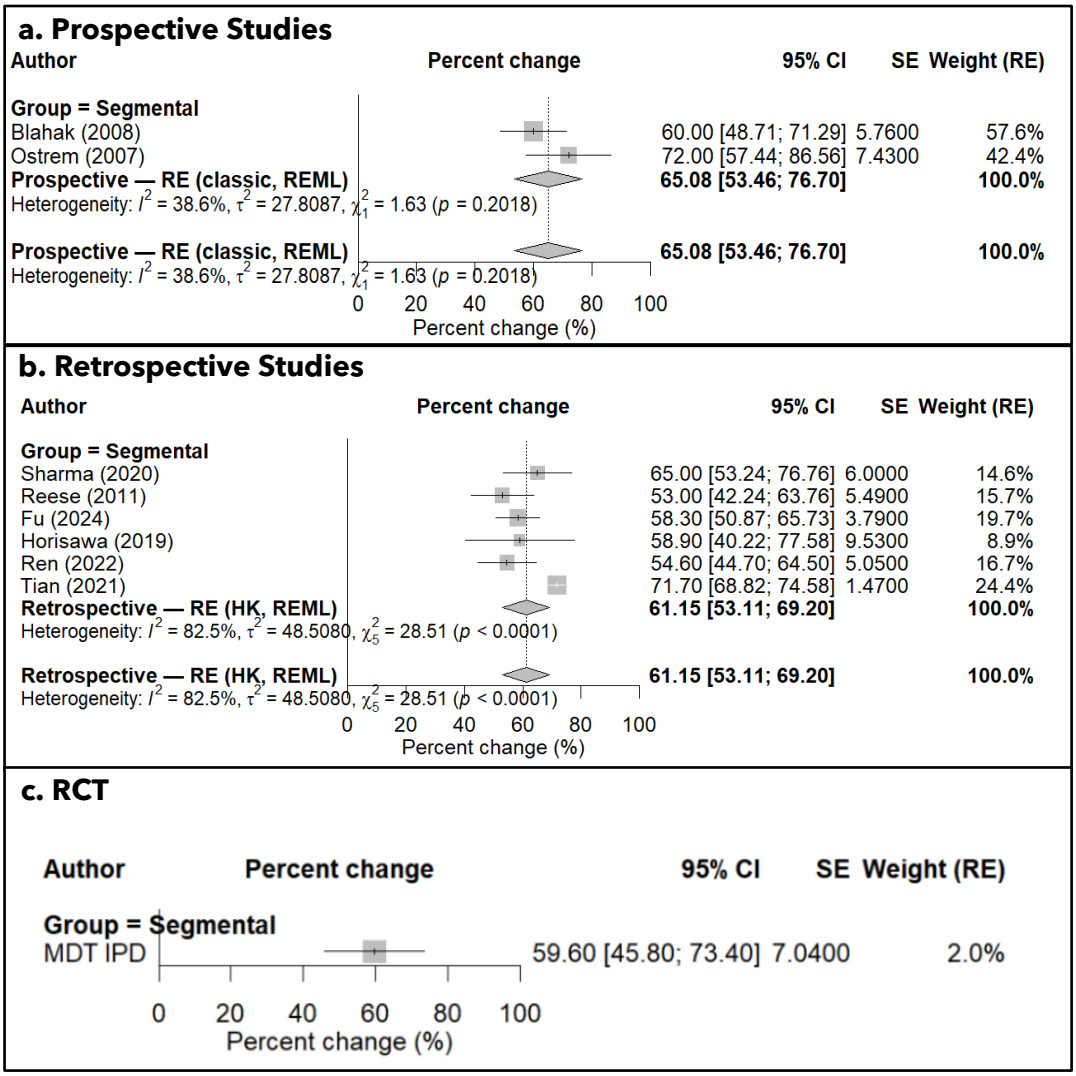

Figure 10. Forest Plots of Percent Improvement in BFMDRS Motor Scores in Adult Patients with GPi DBS for Segmental Dystonia at the Latest Follow-up by Study Designs, a) Prospective, b) Retrospective, c) RCTs.

Cervical Dystonia

The analysis of effectiveness of bilateral GPi DBS for the treatment of primary cervical dystonia in adult patients includes data from the Volkmann (2014)[16] study and 9 published studies with a total of 245 patients contributing effectiveness outcomes. The 10 publications consist of 1 RCT, 1 prospective study, and 8 retrospective studies. The highest level of available evidence is from the Volkmann (2014)[16] study.

Effectiveness Results from the Volkmann (2014) Study

The study randomized 62 patients to DBS (n=32) or sham-stimulation (n=30). The study population was approximately 57 years of age in both groups (57.1 ± 9.82 years for DBS and 56.6 ± 11.33 years for sham) with similar disease duration (14.9 ± 7.95 years for DBS and

14.8 ± 6.41 years for sham). The average baseline TWSTRS total score was 48.7 which represents motor impairment and associated disability. The average baseline TWSTRS severity score was 19.9 ± 3.7 for the DBS group and 20.9 ± 3.3 for the sham stimulation group. Three months after randomization, dystonia severity improved by 5.1 ± 5.1 points (26% improvement; 95% CI 3.5 to 7.0) in the DBS group compared with 1.3 ± 2.4 points in sham stimulation group (6% improvement; 95% CI 0.4 to 2.2) (p=0.0024; Table 27).

Analysis of secondary outcomes showed that the TWSTRS disability score improved by 5.6 ± 5.6 points in the DBS group compared with 1.8 ± 3.8 points in the sham stimulation group (p=0.007). Additionally, the Bain Tremor Score improved by 2.0 ± 2.3 points in the DBS group compared with 0.4 ± 2.1 points in the sham stimulation group (p=0.02). There were no significant differences between treatment groups in the TWSTRS pain score or the Craniocervical Dystonia Questionnaire, a quality of life measurement.

After all patients had received six months of DBS, there were highly significant improvements in all of the secondary outcomes compared with baseline (p<0.0001). The TWSTRS severity score improved by a mean of 5.8 ± 5.31 points (28%), TWSTRS disability score by 46%, TWSTRS pain score by 51%, Bain Tremor Score by 66% and Craniocervical Dystonia Questionnaire by 28%.

Table 27. Summary of TWSTRS Severity and Disability Scores (Volkmann 2014)[16]

		TWSTRS Score		Change from baseline			
Range of possible scores	**Visit**	**N**	**Mean ± SD**	**N**	**Absolute Change Mean ± SD**	**Percent Change Mean ± SD**	**P-value**
TWSTRS Severity Score							
0 – 35	Baseline (Neurostimulation)	32	19.9 ± 3.7	32	NA	NA	NA
	Baseline (Sham Stimulation)	30	20.9 ± 3.3	30	NA	NA	NA
	3 Month (Neurostimulation)	32	14.7 ± 5.0	32	−5.1 ± 5.1	-26%	0.0024
	3 Month (Sham Stimulation)	30	19.6 ± 3.9	30	−1.3 ± 2.4	-6%	
	6 Months	62	14.6 ± 5.18	62	-5.8 ± 5.3	-28%	<0.0001
TWSTRS Disability Score							
0 – 20	Baseline (Neurostimulation)	32	13.8 ± 5.3	32	NA	NA	NA
	Baseline (Sham Stimulation)	30	15.7 ± 5.1	30	NA	NA	NA
	3 Month (Neurostimulation)	32	8.1 ± 5.7	32	−5.6 ± 5.6	-41%	0.007
	3 Month (Sham Stimulation)	30	13.9 ± 6.1	30	−1.8 ± 3.8	-11%	
	6 Months	62	8.1 ± 6.28	62	-6.7 ± 7.26	-46%	<0.0001

Effectiveness Outcome from Publications

In addition to Volkmann (2014),[16] the analysis of effectiveness of bilateral GPi DBS for the treatment of primary cervical dystonia in adult patients also includes data from 9 published studies with a total of 183 patients contributing effectiveness outcomes. The 9 publications consist of 1 prospective study and 8 retrospective studies. These total of ten (10) studies were included for cervical dystonia in adult patients with follow-up ranging from 0.5 year to 7.8 years. Average baseline TWSTRS severity scores ranged from 16 to 23 in 8 studies.[36,38,43-47]

Across nine prospective and retrospective studies, the average improvement in TWSTRS severity scores ranged from 32% to 75% at 3 to 12 months,[36,39,41,44] 49% to 73% at 2 to 4 years[40,41,43,48], and one study reported an improvement range of 29% to 31%[42] after 10 years of follow-up. These values trended higher than the average improvement of 28% in Volkmann (2014)[16] which may have been impacted by the short follow-up of 6 months.

Table 28 below reports effectiveness outcomes from the nine (9) other publications (1 prospective and 8 retrospective studies) in adult patients with cervical dystonia and reflects the latest follow-up data used in the meta-analysis.

Table 28. Summary of Studies of Bilateral GPi DBS for Cervical Dystonia in Adult Patients

Publication	Study Type	Age at Surgery in years Mean±SD	TWSTRS Severity Score				
			Last Follow-up (years)	N*	Baseline Score Mean±SD	% improvement Mean±SD	p-value
Volkmann (2014)[16]	RCT	DBS: 57.1 ± 9.82 Sham: 56.6 ± 11.3	0.5	62	DBS: 19.9 ± 3.7 Sham: 20.9 ± 3.3	28.00±NR%	0.0001
Walsh (2013)[44]	Prospective	55.5 ± 12.8	7.8	10	21.5 ± 4.6	51.40±27.7%	<0.05
Chung (2015)[38]	Retrospective	52.2 ± 9.6	1.7	21	11.8 ± 2.1	62.40±18.5%	NR
Chung (2016)[47]	Retrospective	NR	1.6	4 (Phasic)	20.8 ± 5.1	75.00±NR%	0.008
				8 (Tonic)		67.00±NR%	
Cui (2022)[45]	Retrospective	44.79 ± 12.88	3.4	53	NR	61.08±NR%	0.000
Honaken (2021)[40]	Retrospective	50.1±7.3	2.8	12	15.8 ± 7.6	67.00±39.0%	<0.001
Huh (2019)[41]	Retrospective	51.7±10.2	4.4	4 (AM)	AM: 19	73.10±4.7%	NR
				13 (UM)	UM: 23	51.60±5.6%	
Sharma (2020)[36]	Retrospective	72.6 ± 16.5**	1.0	7	20.0 ± 6.0**	75.30±19.6%	NR
Wang (2020)[46]	Retrospective	41.13 ± 13.49	1.6	23	22.52 ± 3.78	48.75±33.7%	<0.001

Publication	Study Type	Age at Surgery in years Mean±SD	TWSTRS Severity Score				
			Last Follow-up (years)	N*	Baseline Score Mean±SD	% improvement Mean±SD	p-value
Witt (2013)[43]	Retrospective	56.0 ± 10.4	2.8	28	22 ± 4.18	50.80±27.6%	<0.0001

* Sample size indicates the number of patients with data available at the most recent follow-up.

** Estimated from individual patient data reported in the publication.

A meta-analysis was conducted, comprising of 245 patients with follow-ups ranging from 0.5 year to 7.8 years. Figure 11 presents a forest plot of BFMDRS motor scores at the latest follow-up for cervical dystonia in adult patients, with data pooled from the selected studies.

The pooled TWSTRS severity score improvement calculated using the random effects model was 58.32% (95% CI: 50.04–66.61%) and 55.25% (95% CI: 53.28–57.21%) under the common effect model. High heterogeneity was observed among the included studies (I^2 = 93.6%, τ^2 = 173.7703, p<0.0001).

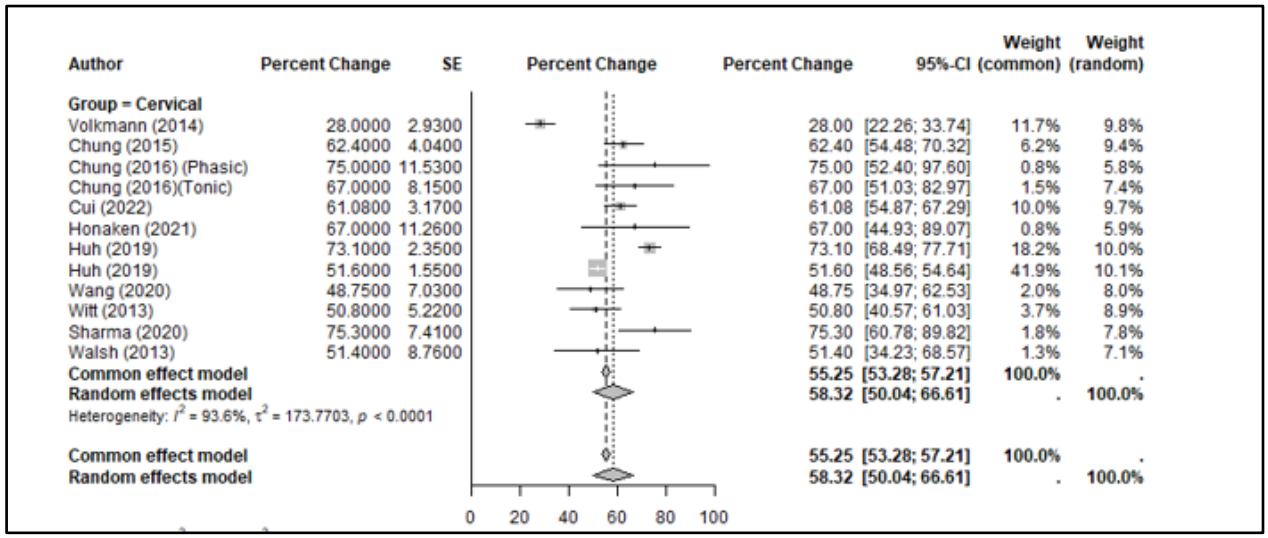

Figure 11. Forest Plot of Percent Improvement in TWSTRS Severity Scores in Adult Patients with GPi DBS for Cervical Dystonia at the Latest Follow-up Reported in Each Study

Meta-analysis Stratified by Study Design on Cervical Dystonia in Adult Patients

A meta-analysis of effectiveness outcomes by study designs in adult patients was conducted for cervical dystonia, focusing on the TWSTRS severity score improvements measured by standardized scales across various study designs. Only one RCT was included in the meta-analysis; therefore, only the point estimate was provided for the RCT.

Figure 12 presents forest plots of the TWSTRS severity score at the latest follow-up for cervical dystonia in adult patients, with data presented from the prospective study (a) retrospective studies (b), and RCT (c).

There was only one prospective study and the point estimate is 51.40% with a 95% CI of 34.23-68.57% (Figure 12a). The pooled TWSTRS severity score improvement for the eight retrospective studies was 62.04% (95% CI: 54.93% - 69.15%) under the random effects model with Hartung-Knapp (HK) method applied to adjust the confidence interval, shown in Figure 12b. There was only one RCT study, and the point estimate is 28.00% with a 95% CI of 22.26% - 33.74%, shown in Figure 12c. The retrospective studies demonstrated substantial heterogeneity (I^2 = 88%, τ^2 = 70.8406, p <0.0001).

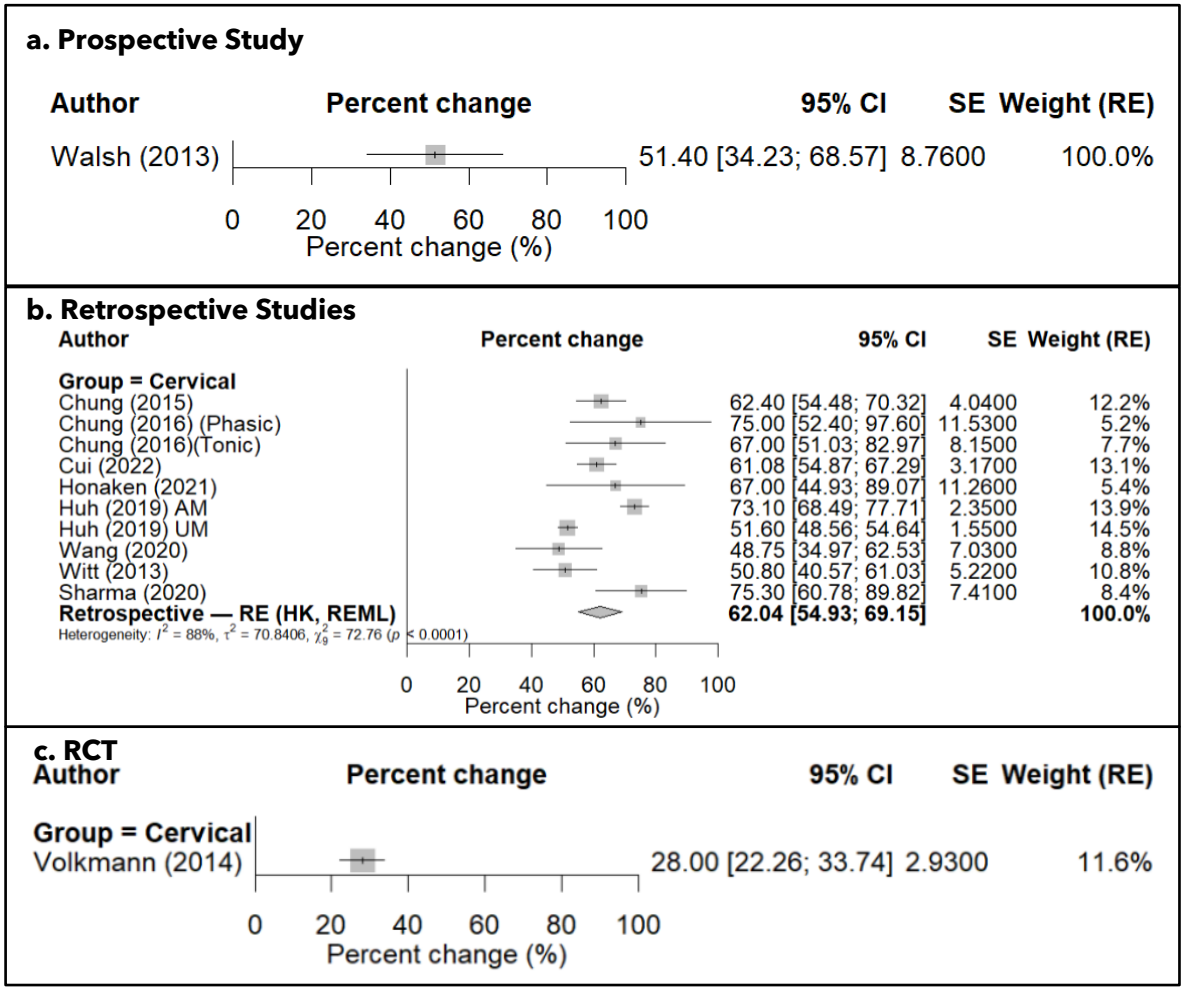

Figure 12. Forest Plots of Percent Improvement in TWSTRS Severity Scores in Adult Patients with Cervical Dystonia at the Latest Follow-up by Study Designs, a) Prospective, (b) Retrospective b) RCT.

Effectiveness Outcomes in Pediatric Population (12 years of age and above) with Primary Generalized Dystonia

Effectiveness Outcome from Publications

There are no RCTs and few large case series evaluating DBS for pediatric population 12 years of age and above with Primary Generalized Dystonia. The dataset for this population is derived from 4 prospective[23,25,49,50] and 7 retrospective[51-56,58] studies comprised of 143 patients for effectiveness analysis. Average age at surgery ranged from 12 to 17 years across the studies reviewed,[25,49,51-53,55-58] with the exception of one study reporting an average age of 10.2 years.[50] Duration of dystonia symptoms before surgery ranged from 3 to 10 years.[25,49-53,55-58,60]

Overall, improvements in average BFMDRS motor scores across all included studies ranged from 35% to 82% at 6 months,[23,51,56,58,60] 54% to 85% at 1 year,[23,25,49-53,55,58,60] 64% to 93% at 2 years,[23,52,55] and 43% to 94% when assessed at 2.7 years and beyond.[25,51-53,55,56]

Table 29 below reports effectiveness outcomes from the 11 publications (4 prospective and 7 retrospective studies) on pediatric patients with generalized dystonia and reflects the latest follow-up data used in the meta-analysis.

Table 29. Summary of Studies of Bilateral GPi DBS for Generalized Dystonia in Pediatric Patients

Publication	Study Type	Age at Surgery in years Mean± SD	BFMDRS Motor Score				
			Last Follow-up (years)	N*	Baseline Score Mean±SD	% improvement Mean±SD	p-value
Borggraefe (2010)[49]	Prospective	14.2 ± 3.4	1.0	44	56.9 ± 22.7	63.70±31.7%	<0.001
Coubes (2004)[23]	Prospective	≤ 17	2.0	19	59.8 ± 25.8	84.70±13.6%	<0.0001
Starr (2014)[50]	Prospective	10.2**	1.0	5	42.9**	82.40±20.6%	NR
Vidailhet (2007)[25]	Prospective	17.2**	3.0	5	38.4	63.60±37.6%	NR
Haridas (2011)[52]	Retrospective	13.4 ± 2.7	3.0	11	39.9 ± 19.5	94.00±NR%	0.003
Ghosh (2012)[51]	Retrospective	13.2**	5.8	6	55 ± 33.2	62.60±16.4%	NR
Krause (2016)[53]	Retrospective	12.5 ± 3.5	4.9	8	45.4±7.5	42.90±11.6%	NR
Lumsden (2013)[54]	Retrospective	12.8**	1.0	14	57.0	62.20±NR%	0.001
Markun (2012)[55]	Retrospective	15.5 ± 5.7	2.7	14	54.6 ± 22.9	70.30±NR%	<0.001

Publication	Study Type	Age at Surgery in years Mean± SD	BFMDRS Motor Score				
			Last Follow -up (years)	N*	Baseline Score Mean±SD	% improvement Mean±SD	p-value
Marotta (2020)[58]	Retrospective	16.0	1.0	9	48	82.00±NR%	NR
Petrossian (2013)[56]	Retrospective	13.3**	4.0	8	45.6*	78.30±23.0%	NR

* Sample size indicates the number of patients with data available at the most recent follow-up.

** Estimated from individual patient data reported in the publication.

A total of 11 studies comprised of 143 pediatric patients were included for generalized dystonia with follow up ranging from 1 year to 5.8 years.

Figure 13 presents a forest plot of the BFMDRS motor score at the latest follow-up for generalized dystonia in pediatric patients, with data pooled from the selected studies.

The pooled BFMDRS motor score improvement calculated was 71.46% (95% CI: 62.28–80.63%) under the random effects model and 70.90% (95% CI: 67.69–74.12%) under the common effect model. High heterogeneity was observed among the selected studies (I^2 = 89.1%, τ^2 = 192.4010, $p < 0.0001$).

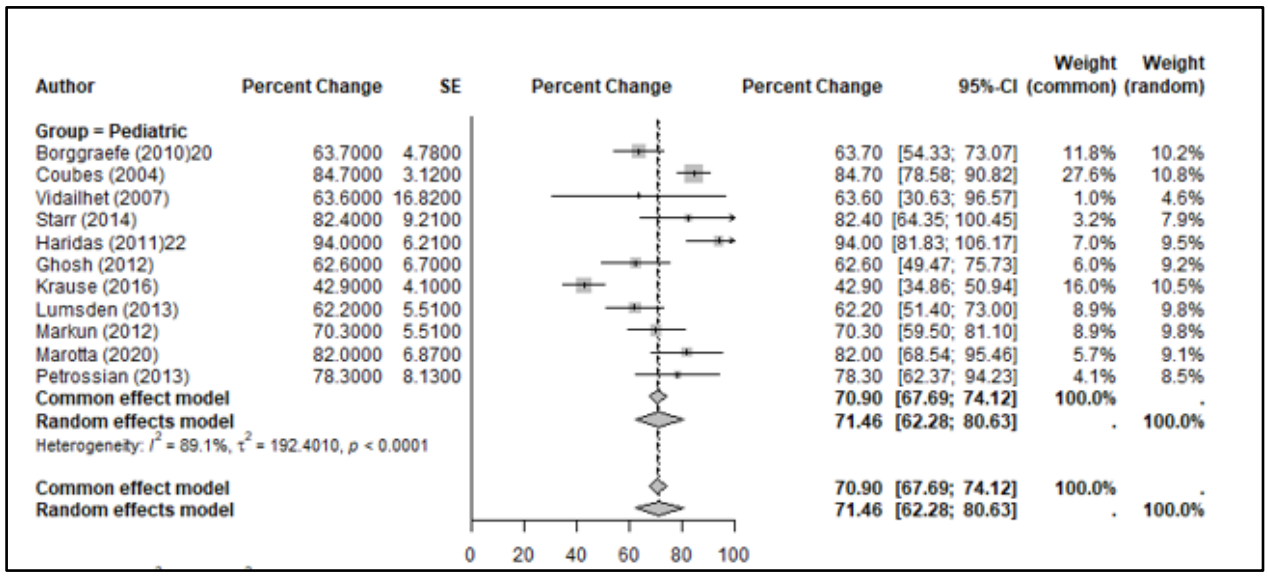

Figure 13. Forest Plot of Percent Improvement in BFMDRS Motor Scores in Pediatric Patients with GPi DBS for Generalized Dystonia at the Latest Follow-up Reported in Each Study

Meta-analysis Stratified by Study Design on Generalized Dystonia in Pediatric Patients 12 years of age or above

A meta-analysis of effectiveness outcomes by study designs was conducted in pediatric patients with generalized dystonia, focusing on the BFMDRS motor improvements measured by standardized scales across various study designs.

Figure 14 presents forest plots of the BFMDRS motor score at the latest follow-up for generalized dystonia in pediatric patients, with data pooled from the prospective studies (a) and retrospective studies (b). No RCT was reported in the pediatric patient population.

The pooled BFMDRS motor score improvement for the four prospective studies was 75.24% (95% CI: 56.85% - 93.62%) under the random effects model with Hartung-Knapp (HK) method applied to adjust the confidence interval, shown in Figure 14a. In comparison, the pooled BFMDRS motor score improvement for the seven retrospective studies was 69.85% (95% CI: 54.34% - 85.37%), indicated in Figure 14b. Notably, the retrospective studies demonstrated greater heterogeneity (I^2 = 90.2%, τ^2 = 251.9920, p < 0.0001) than the prospective studies (I^2 = 79.3%, τ^2 = 104.4817, p=0.0023).

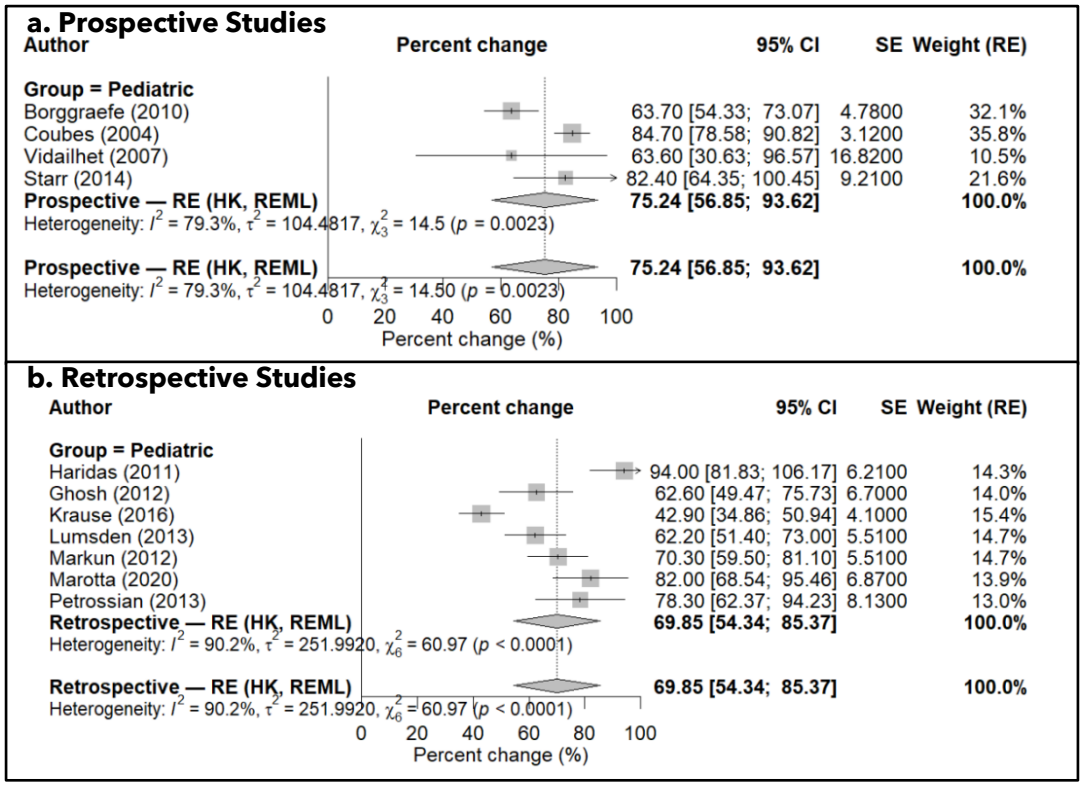

Figure 14. Forest Plots of Percent Improvement in BFMDRS Motor Scores in Pediatric Patients with Generalized Dystonia at the Latest Follow-up by Study Designs, a) Prospective, b) Retrospective.

Comparative Analysis of Adult vs Pediatric with Generalized Dystonia at Last Follow-up

A comparative meta-analysis was conducted using the random effects model to evaluate percent improvement in BFMDRS motor scores in adult patients and pediatric patients with generalized dystonia.

Average age at surgery in pediatric patients ranged from 10 to 17 years[25,49–53,55–58,60] and 22 to 38 years for adult patients.[17,24–28] Duration of dystonia symptoms before surgery ranged from 3 to 10 years in pediatrics[25,49–53,55–58,60] and 8 to 22 years for adult patients.[17,24–26,28] Average baseline BFMDRS motor scores across the data sources ranged from 38 to 60 in pediatric population out of a possible score of 120,[23,25,49–53,55–58,60] which is comparable to the range of 42 to 64 reported in the adult population.[17,23–25,27,28]

Figure 15 presents a forest plot and detailed comparison of BFMDRS scores between adult and pediatric patients with generalized dystonia at last follow-up, with data pooled from multiple studies. Six studies involving a total of 130 patients were analyzed in the adult population and 11 studies with a total of 143 patients were included in the pediatric patient population. The effectiveness data used in the analysis are listed Table 23 for adult patients and Table 29 for pediatric patients with generalized dystonia.

The pooled BFMDRS motor scores improvement for adult patients with generalized dystonia was 60.51% (95% CI: 50.69-70.32%) and 71.46% (95% CI: 62.28–80.63%) for pediatric patients under the random effects model. The overall pooled BFMDRS motor scores improvement across both patient populations was 67.58% (95% CI: 60.41-74.76%).

There was high heterogeneity within both the adult and pediatric patient groups. This phenomenon has been reported in the published literature. For example, Borggraefe (2010)[49] evaluated effectiveness outcomes by DYT1 status. Patients testing positive for DYT1 had significantly greater improvement than patients testing negative for DYT1. Markun (2012)[55] reported that patients without fixed orthopedic deformities at baseline had significantly greater improvement than patients with fixed deformities. Additionally, shorter duration of disease at time of surgery was also associated with better outcomes.[55]

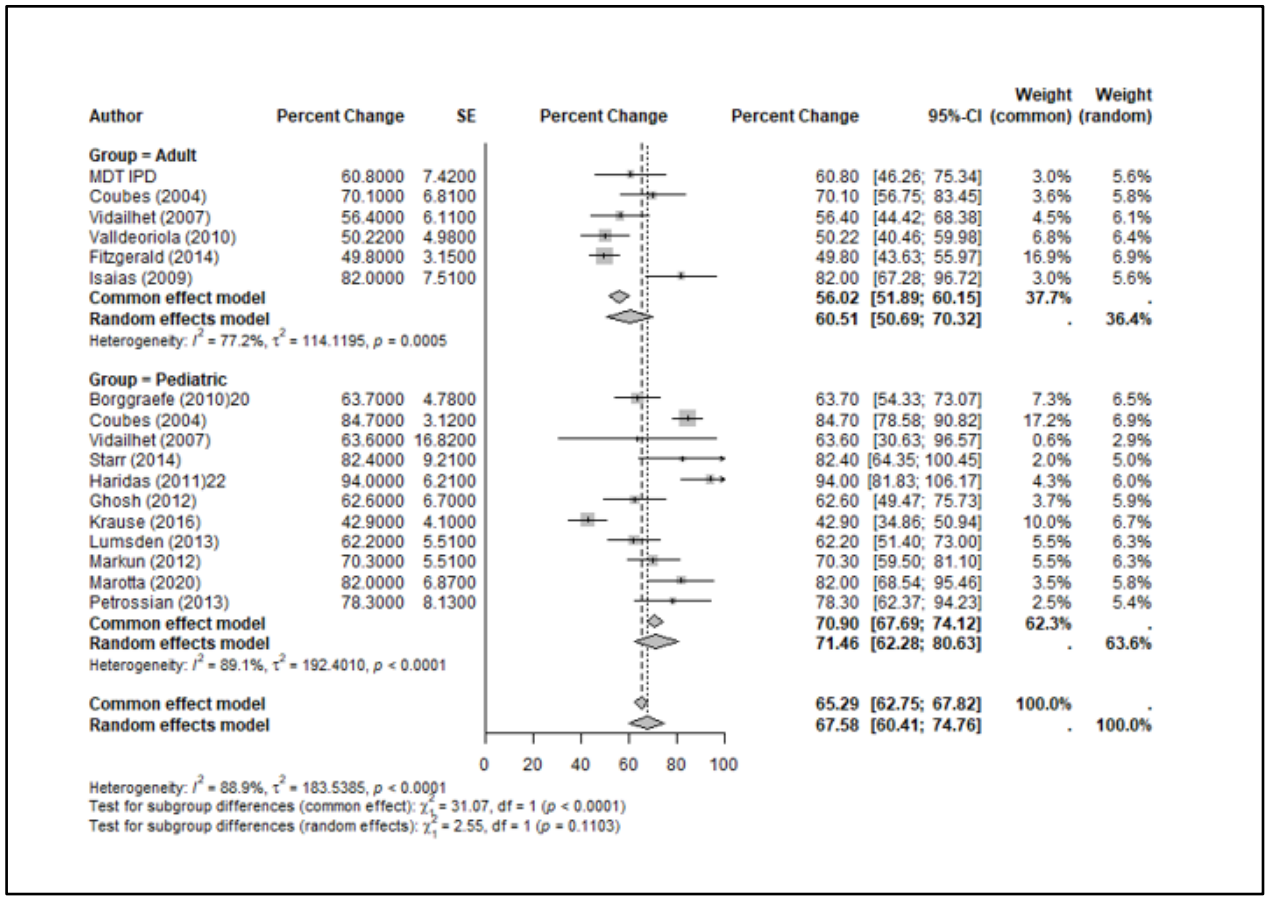

Figure 15. Forest Plot of Percent Improvement in BFMDRS Motor Scores in Adult vs Pediatric Patients with Generalized Dystonia at the Last Follow-Up

Impact of DBS on Cognitive Function in Pediatric Patients

Evidence from two small retrospective studies suggests that DBS does not adversely affect cognitive function in pediatric patients. These studies, involving a total of 22 pediatric patients followed for approximately one year, focused on the effects of GPi DBS on cognition. Marotta (2020)[58] studied nine patients, six with primary dystonia and three with secondary dystonia, over 13 months. Cognitive function, assessed using the Wechsler Intelligence Scale for Children, showed no deterioration. Additionally, two patients implanted with directional electrodes demonstrated mild improvements in executive functions. Owen (2015)[61] studied 13 children with primary dystonia with at least one year follow up and found that cognitive scores remained stable or improved in 10 patients, while three patients experienced score deterioration, possibly influenced by fatigue or distractions during testing. The authors concluded that cognition remained stable within this small cohort.

Additionally, a conservative assessment identified 11 cognitive-related AEs in additional scientific articles[62-64] and PSR, including cognitive deficits or worsening (3), depression (2), psychiatric comorbidity (2), aggression (1), agitation (1), anxiety (1), and low mood (abulia and ebullience) (1).

Additional literature review of cognitive, mood, and behavioral-related AEs reported three events of cognitive deficits and eight other AEs in three published studies[62-64]. Kaminska (2017)[62] reported complications in 129 pediatric patients with various forms of dystonia, average age 10.8 years and at least six months of follow-up. One patient experienced low mood (abulia and ebullience), which was considered an intolerable side effect of stimulation; DBS was discontinued for this patient. Koy (2019)[63] studied 72 pediatric patients with dystonia over 4.6 years, including 16 with isolated inherited or idiopathic dystonia. In the perioperative period, one reversible case of agitation was linked to anesthesia. Long-term, two transient psychiatric events were associated with stimulation, and one reversible cognitive decline was unrelated to DBS. Xu (2020)[64] retrospectively studied nine pediatric patients treated with bilateral stimulation of the subthalamic nucleus (mean age 15.9) over 10 years, reporting cognitive deficits, depression, and anxiety as AEs; some symptoms improved with stimulation adjustment, though details were unspecified.

Additional analysis of the PSR adverse events related to cognition, mood, and behavior identified only one Specific AE of aggression in a pediatric patient after 6 years of device use, which was treated with medication.

The above data is limited overall by small sample size and lack of long-term data to fully assess the impact of DBS on cognition, mood, and behavior in pediatric patients.

Quality of Life Outcomes

Product Surveillance Registry

Patients enrolled under the current PSR protocol report quality of life (EQ-5D) data at baseline and follow-up, with changes summarized in Table 30. The change in EQ-5D score was calculated from baseline to the 6- or 12- and 24-month visits.

A total of 132 therapy-naïve adult dystonia patients and 13 pediatric dystonia patients had EQ-5D assessments at both baseline and follow-up. In adults, EQ-5D scores showed statistically significant improvement at all follow-up visits ($p<0.05$) at 6, 12, and 24 months. For pediatric patients, statistical testing was not performed due to the small sample size.

Table 30. Change in EQ-5D Index from Baseline to Follow-up in Therapy-Naïve Dystonia Patients

Visit	N	Baseline mean ± SD	Follow-up mean ± SD	Change mean ± SD	P-Value
Adult Patient Population					
6 Month	71	0.588 ± 0.237	0.725 ± 0.211	0.139 ± 0.283	<0.001
12 Month	65	0.601 ± 0.234	0.711 ± 0.254	0.110 ± 0.321	0.010
24 Month	52	0.608 ± 0.270	0.757 ± 0.219	0.149 ± 0.307	0.002
Pediatric Patient Population					
6 Month	10	0.451 ± 0.348	0.658 ± 0.242	0.207 ± 0.236	NA[a]
12 Month	7	0.411 ± 0.290	0.643 ± 0.252	0.232 ± 0.435	NA[a]
24 Month	8	0.480 ± 0.336	0.804 ± 0.197	0.323 ± 0.316	NA[a]

[a] p-values are not reported due to small sample size.

Systematic Literature Review: Quality of Life

A total of seven publications reported quality of life (QoL) data related to GPi DBS. Three secondary prospective publications following the Kupsch (2006)[2] RCT demonstrated sustained QoL improvements in adults with generalized and segmental dystonia, showing 10.6 point improvement in the SF-36 physical component at six months and five years.[15,65] At 10 years of follow-up compared to baseline, the same patient group showed significant improvements in pain (Visual Analog Scale: 4.6 ± 2.7 to 3.1 ± 2.4, P = 0.007). In cervical dystonia, Volkmann (2014)[16] found no significant QoL differences at three months between DBS and sham stimulation groups but noted a significant 28% improvement in CDQ-24 scores by six months (mean reduction of 19.4 points, P<0.0001).

Four other studies assessed QoL in adult and pediatric populations:

- Valldeoriola (2010)[24]: In 22 adults with generalized dystonia, SF-36 physical scores improved from 36.08 to 62.37 (P<0.01) at one year, alongside EQ-5D and pain scale improvements.
- Blahak (2008)[30]: Adult patients with segmental dystonia experienced a 40% and 51% increase in SF-36 scores at 7.5 and 17 months, respectively. Similar improvements were observed in the physical and mental health summary subscores.
- Vidailhet (2007)[25]: Adult and pediatric patients with generalized dystonia exhibited sustained SF-36 improvements in general health, physical functioning, and pain over three years (P≤0.05).
- Starr (2014)[50]: Six pediatric patients with generalized dystonia showed a 52.6% QoL improvement (SF-36) at 12 months (P=0.027).

Prospective studies represented the highest level of clinical evidence. GPi DBS in adults with generalized and segmental dystonia demonstrated a 10.6 point improvement in the SF-36 physical component at six months which was sustained to five years.[15,65] QoL improvements are accompanied by significant improvements in pain, anxiety and depression.[14] A small prospective study of DBS in pediatric patients showed an approximate 52.6% improvement in total SF-36 scores at 12 months.[50] Additionally, evidence from other retrospective studies favors a positive impact of DBS on QoL.

Conclusions Drawn from Preclinical and Clinical Studies

Effectiveness Conclusions

Deep Brain Stimulation (DBS) targeting the globus pallidus internus (GPi) is an established therapy for primary dystonia. Effectiveness was assessed using standardized scales to assess dystonia severity: BFMDRS for generalized/segmental dystonia and TWSTRS for cervical dystonia.

Primary Generalized Dystonia in Adult Patients

The analysis included 6 studies of 130 patients with primary generalized dystonia to evaluate effectiveness at the last follow-up (1 RCT, 3 prospective studies, and 2 retrospective studies). Among the publications for generalized dystonia, dystonia severity was characterized by severe or marked disability, impaired function in performance of activities of daily living, or poor symptom control despite medical management. The highest level of available evidence is the Investigator Study,[17] which included 18 generalized dystonia subjects from the Kupsch (2006)[2] RCT and Volkmann (2012)[15] study. The BFMDRS motor score improved significantly by 42.3% in the neurostimulation group (n=9) compared to worsening by 2.5% in the sham stimulation group (n=8) at 3 months (p=0.005).[17]

Across five other published studies, the average improvement in BFMDRS motor scores ranged from 43.5% to 79.6% at 1 year,[6,14–18] 49.9% to 82.5% at 2 years,[6,14,17,18] and 56.4% to 85.5% at 3 years.[6,16,18]

Meta-analysis of the Investigator Study and published literature showed a pooled rate of improvement in BFMDRS motor scores of 60.51% (95% CI: 50.69-70.32%) in 130 patients across the 6 total studies at follow-up time points ranging from 1 to 7 years with high heterogeneity. Similar pooled improvement rates were seen when the meta-analysis was stratified by study design (i.e., RCT, prospective, and retrospective studies.)

Primary Segmental Dystonia of the Head and Neck in Adult Patients

The analysis included 94 adult patients with segmental dystonia to evaluate effectiveness at the last follow-up (1 RCT, 2 prospective, and 6 retrospective studies). Among the publications for segmental dystonia, severity was characterized by severe symptoms, marked disability or functional impairment, or failed or discontinued medications or botulinum neurotoxin due to no or slight effect. The highest level of available evidence is the Investigator Study,[17] which included 11 subjects with segmental dystonia of the head and neck from the Kupsch RCT[2] and Volkmann (2012)[15] study. The BFMDRS motor improved significantly by 61.2% in the neurostimulation group (n=7) compared to 0.9% in the sham stimulation group (n=4) at 3 months (p = 0.011). There were significant improvements in motor scores at each follow-up through 4 years (70.6%) (n=7), however, a comparable improvement at 5 years (59.6%) was not statistically significant, likely due to small sample size (n=5).

Across eight other published studies, the average improvement in BFMDRS motor scores ranged from 45% to 72% at 3 to 8 months[30-35] and 53% to 72% at 2 to 4 years.[32,34,35,37]

Meta-analysis of the Investigator Study and published literature showed a pooled rate of improvement in BFMDRS motor scores of 62.03% (95% CI: 56.56-67.51%) in 94 patients across the 9 total studies at follow-up time points ranging from 0.5 to 5.6 years with high heterogeneity. Similar pooled improvement rates were seen when the meta-analysis was stratified by study design (i.e., RCT, prospective, and retrospective studies.)

Primary Cervical Dystonia in Adult Patients

The analysis included 245 adult patients with cervical dystonia to evaluate effectiveness at the last follow-up (1 RCT, 1 prospective, 8 retrospective studies). The highest level of available evidence is the Volkmann (2014)[16] RCT for cervical dystonia in 62 patients. The TWSTRS severity score improved by 5.1 ± 5.1 points (26% improvement) in the neurostimulation group (n=32) compared to 1.3 ± 2.4 points (6% improvement) in the sham stimulation group (n=30) at 3 months (p=0.0024.). Significant differences between the neurostimulation group and the sham stimulation group were also observed in the TWSTRS disability score (41% vs. 11% improvement, p=0.007)) at 3 months. The scores were maintained after 6 months of follow-up in the open-label phase (28% improvement in TWSTRS severity and 46% in TWSTRS disability score, p<0.0001).

Across nine other published studies, the average improvement in TWSTRS severity scores ranged from 32% to 75% at 3 to 12 months,[36,39,41,44] 49% to 73% at 2 to 4 years[40,41,43,48] and one study reported an improvement range of 29% to 31%[42] after 10 years of follow-up. These values trended higher than the average improvement of 28% in Volkmann (2014)[16] which may have been impacted by the short follow-up of 6 months.

Meta-analysis of the published literature showed a pooled improvement in TWSTRS severity score of 58.32% (95% CI: 50.04–66.61%) in 245 adult patients across the 10 total studies at follow-up time points ranging from 0.5 to 7.8 years with high heterogeneity. The improvement rates were higher for the pooled retrospective studies (62.04%) compared to the point estimate for the one prospective study (51.4%) and the one RCT (28.0%) when stratified by study design.

Bilateral GPi DBS showed a more modest improvement in the RCT trial for primary cervical dystonia (TWSTRS severity score improved 26% at 3 months in the Volkman (2014)[16] study). However, the overall improvements from the published literature and meta-analysis offer additional supportive evidence of effectiveness and appear reasonably comparable between cervical and generalized and segmental dystonia, although formal statistical comparison was not conducted. In addition, while primary cervical dystonia is classified as a focal dystonia when symptoms are isolated to the neck muscles, cervical dystonia may also present as a component of a more widespread segmental or generalized dystonia. Given this symptomatic overlap, the demonstrated effectiveness of bilateral GPi DBS in primary generalized and segmental dystonia of the head and neck was considered when evaluating the potential effectiveness of bilateral GPi DBS for primary cervical dystonia that remains inadequately controlled by oral and/or injectable medications.

Primary Generalized Dystonia in Pediatric Patients (12 years of age or above)

There were no RCTs and few large case series evaluating DBS for pediatric dystonia. The analysis included 143 pediatric patients with primary generalized dystonia to evaluate effectiveness at the last follow-up (0 RCTs, 4 prospective, and 7 retrospective studies). The data sources compared reasonably well in baseline patient characteristics. Average age at surgery ranged from 12 to 17 years across the studies reviewed,[25,49,51–53,55-58] with the

exception of one study reporting an average age of 10.2 years[50], and duration of dystonia symptoms before surgery ranged from 3 to 10 years.

Overall, improvements in average BFMDRS motor scores across all included studies ranged from 35% to 82% at 6 months,[23,51,56,58,60] 54% to 85% at 1 year,[23,25,49–53,55,58,60] 64% to 93% at 2 years,[23,52,55] and 43% to 94% when assessed at 2.7 years and beyond.[25,51–53,55,56]

Meta-analysis showed a pooled improvement in BFMDRS motor score of 71.46% (95% CI: 62.28–80.63%) in 143 pediatric patients in 11 studies at follow-up time points ranging from 1.0 to 5.8 years with high heterogeneity. Similar pooled improvement rates were seen when meta-analysis was stratified by study design (75.24% prospective compared to 69.85% retrospective studies.)

Additional comparative meta-analyses of percent improvement in BFMDRS motor scores at last follow-up between adult and pediatric patients with primary generalized dystonia was conducted using the random effects model. Pooled rates of percent improvements in BFMDRS motor scores were 60.51% for adult patients with follow-up ranging from 1 to 7 years and 71.46% for pediatric patients with follow-up ranging from 1 to 5.8 years, with no significant difference between the two groups and high heterogeneity.

In summary, the data from these studies demonstrated the effectiveness of Medtronic DBS Therapy for Dystonia targeting the GPi as an aid in the management of chronic, intractable (oral and/or injectable medication refractory) primary dystonia, including generalized dystonia, segmental dystonia of the head and neck, and cervical dystonia (torticollis) in adult patients, and generalized dystonia in pediatric patients twelve years of age or above.

Safety Conclusions

Primary Generalized Dystonia in Adult Patients

The analysis included 173 patients with generalized dystonia to evaluate safety including 18 patients in the Investigator Study and 155 patients in 6 published literature studies (3 prospective and 3 retrospective studies). The Investigator Study[17] reported overall AE and SAE occurrence rates of 22.2% and 11.1% in the 3-month blinded phase, and 72.2% and 55.6% in the open label 5 year follow-up phase, respectively. Therapy-related safety events during the 5-year follow-up phase of the Investigator Study included: device complications (61.1%), device revisions (55.6%), explants (22.2%), infections (16.7%), and intracranial hemorrhage (symptomatic: 0%, asymptomatic: 0%).

Across six other published studies, the reported incidence rates for AE and SAE ranged from 25% to 58%,[24–28] and 8 to 18%,[24–26,28] respectively, over follow-up periods spanning 6 months to 7 years of follow-up in adult patients with generalized dystonia.

Meta-analysis of therapy-relevant safety events across the 7 total studies showed that device complications (22%), revisions (19%), and explants (13%) were the most frequent safety events, followed by infections (12%). Intracerebral hemorrhage (symptomatic: 3% and asymptomatic: 3%) were less common. Substantial heterogeneity was observed for both device complication rates and device revision rates, which could be multifactorial and are likely influenced by clinical factors such as surgical experience and reporting practices.

Primary Segmental Dystonia of the Head and Neck in Adult Patients

The analysis included 101 patients with segmental dystonia to evaluate safety, including 11 patients in the Investigator Study and 90 patients in 8 published literature studies (2

prospective and 6 retrospective studies). The Investigator Study[17] reported overall AE and SAE occurrence rates of 57.1% and 28.6% in the 3-month blinded phase, and 72.7% and 63.6% in the open label phase through five years, respectively. Therapy-related safety events during the 5-year follow-up phase of the Investigator Study included: device complications (54.5%), device revisions (54.5%), explants (9.1%). infections (0%), and intracranial hemorrhage (symptomatic: 0%, asymptomatic: 0%).

Across eight other published studies, the reported incidence rates for AE and SAE ranged from 8.3% to 100%,[30-36] and 0 to 25%,[36,37] respectively, over a follow-up period of 6 months to 5.6 years in adult patients with segmental dystonia of the head and neck.

Meta-analysis of therapy-relevant safety events across the 9 total studies showed similar trends in segmental dystonia compared to generalized dystonia: device complications (13%), revisions (14%), explants (9%), infections (7%), and intracranial hemorrhage (symptomatic: 6%, asymptomatic: 4%). High heterogeneity was observed for both device complication rates and device revision rates, likely influenced by clinical factors such as surgical experience and reporting practices.

Primary Cervical Dystonia in Adult Patients

The safety analysis included 238 patients with cervical dystonia from 9 published literature studies (1 RCT, 1 prospective, and 7 retrospective studies). The RCT reported 5 SAEs (16%, 5/32) in the neurostimulation group compared to 11 SAEs (37%, 11/30) in the sham group, with 69% (11/16) resolving without sequelae. Most SAEs within 6 months of follow-up were related to surgery, device or stimulation, and resolved without sequelae. Therapy-related safety event rates included device complications (8.1%), device revisions (3.2%), and explants (1.6%), infections (4.8%), intracranial hemorrhage (symptomatic: 1.6%, asymptomatic: NR).

Across nine other published studies, the reported incidence rates for AE and SAE ranged from 3.8% to 80%[36,38-40,42-45] and 0 to 14.3%,[36,38,39,45,48] respectively, over a follow-up period of 1 year to 10 years in adult patients with cervical dystonia.

A meta-analysis of therapy-relevant safety events, device revisions and explants in adult patients with cervical dystonia showed similar trends to generalized dystonia (device complications (11%), device revisions (14%), explants (4%), infections (7%), intracranial hemorrhage (symptomatic: 5%, asymptomatic: NR)) with moderate to high heterogeneity for device complications and device revision rates.

Primary Generalized Dystonia in Pediatric Patients (12 years of age and above)

There are no RCTs and few large case series evaluating DBS for pediatric dystonia. The safety analysis included 202 pediatric patients with generalized dystonia from 12 published literature studies (4 prospective and 8 retrospective studies) with an average follow-up ranging from 6 months to 10 years. Average age at surgery ranged from 12 to 17 years across the studies reviewed,[25,49,51-53,55-58] with the exception of one study reporting an average age of 10.2 years[50], and duration of dystonia symptoms before surgery ranged from 3 to 10 years.

Across 12 published studies, the reported incidence rates for AE and SAE ranged from 0% to 100%[23,25,49-53,55-58] and 0 to 60%,[25,50,51,53] respectively, over a follow-up period of 6 months to 10 years in pediatric patients with generalized dystonia.

Meta-analysis of therapy-relevant safety events for pediatric patients with generalized dystonia showed device complications (26%), device revisions (21%), explants (20%), infections (16%), and intracerebral hemorrhage (symptomatic: 4%, asymptomatic: 6%).

Safety Conclusions from Medtronic Product Surveillance Registry Data (PSR)

In addition to published literature, safety was analyzed using Medtronic PSR data. The safety analysis included 308 patients with primary dystonia, including 279 adults (90.6%) with a mean age of 53 ± 14.4 years and 27 pediatric patients (8.8%) with a mean age of 16 ± 3.9 years. Average duration of device exposure was 38.2 ± 32.6 months for adults and 35.9 ± 30.9 months for pediatric patients. A total of 166 AEs (related to device, therapy, or procedure) were recorded in 87 patients (28.2%). Serious adverse events occurred in 39 patients (12.7%), including 3 pediatric and 36 adult patients. Notable SAEs included intracranial hemorrhage (1.0% adults, 0% pediatric), infections (3.2% adults, 3.7% pediatric), procedural complications (1.4% adults, 3.7% pediatric), and psychiatric disorders (0.4% adults, 3.7% pediatric). Product performance events occurred in 9.3% of adults and 11.1% of pediatric patients. System explants occurred in 2.2% (6/279) of adult dystonia patients and 3.7% (1/27) of pediatric patients for various reasons including, infection, battery depletion, programming needs, or device protrusion. Fifteen deaths occurred in 12 adults and 3 pediatric patients. Although no deaths were directly attributed to a product performance event, four deaths were due to unknown causes with an unknown relationship to the device or procedure. There were no reported suicides or suicide attempts.

In summary, the clinical evidence compiled from the randomized controlled trials (Investigator Study)[17] and Volkmann (2014),[16] systematic review of published scientific literature, and the Medtronic PSR is consistent with the known risks in other FDA approved indications for DBS and supports the overall safety profile of Medtronic DBS Therapy for Dystonia stimulating the GPi in adult patients with primary dystonia, including generalized dystonia, segmental dystonia of the head and neck, and cervical dystonia (torticollis), and in pediatric patients with generalized dystonia twelve years of age or above.

Benefit-Risk Determination

The probable benefits of the device are based on data submitted for PMA approval as described above.

Benefits

The probable benefits of the device are based on data provided in this application to support PMA approval as described above.

Primary Generalized and Segmental Dystonia of the Head and Neck in Adult Patients

Data to support the benefits of bilateral GPi DBS as an effective intervention for primary generalized and segmental dystonia in adults include the Investigator Study,[17] which demonstrated improvement in BFMDRS motor score by 42.3% in the neurostimulation group compared to worsening by 2.5% in the sham stimulation group in generalized dystonia and 61.2% in the neurostimulation group compared to 0.9% in the sham stimulation group in segmental dystonia at 3 months after DBS. Improvements in motor scores were maintained at follow-up intervals up to 5 years. Meta-analyses of GPi DBS including 130 patients with primary generalized dystonia across 6 studies and 94 patients with segmental dystonia across 9 studies demonstrated consistent results, with motor score

improvements of 60.51% for generalized dystonia and 62.03% for segmental dystonia over follow-up periods ranging from 1 to 7 years and 6 months to 5.6 years, respectively.

Primary Cervical Dystonia in Adult Patients

Data to support the benefits of bilateral GPi DBS as an effective intervention for primary cervical dystonia in adults include the RCT by Volkmann (2014)[16], which demonstrated improvement in TWSTRS severity score by 26% in the neurostimulation group compared to 6% in the sham stimulation group at 3 months and 28% at 6 months after DBS. Improvements were also noted in TWSTRS disability scores. A meta-analysis of GPi DBS including 245 patients with primary cervical dystonia across 10 studies found a pooled improvement in TWSTRS severity of 58.32% over follow-up periods ranging from 6 months to 7.8 years.

Primary Generalized Dystonia in Pediatric Patients 12 years of age and above

Data to support the benefits of bilateral GPi DBS as an effective intervention for primary generalized dystonia in pediatric patients include a meta-analysis of GPi DBS including 143 pediatric patients with primary generalized dystonia across 11 studies, which found a pooled improvement in BFMDRS motor scores of 71.46% over follow-up periods ranging from 1 to 5.8 years.

Comparative analysis by Medtronic revealed pooled motor score improvements of 71.46% in pediatric patients versus 60.51% in adults, albeit with high heterogeneity.

Risks

The probable risks of the device are based on data provided in this application to support PMA approval as described above.

Data to support the safety of bilateral GPi DBS for primary generalized, segmental (head and neck), and cervical dystonia in adult patients and primary generalized dystonia in pediatric patients ages 12 and above include AEs, SAEs, and therapy-relevant safety events reported in the Investigator Study[17] for adult generalized and segmental dystonia, the Volkmann (2014)[16] RCT for adult cervical dystonia, and meta-analyses of therapy-relevant safety event rates reported in published literature studies for each type of dystonia.

The Investigator Study[17] reported the overall AE and SAE occurrence rates as 22.2% and 11.1% in the 3-month blinded phase in the DBS group, and 72.2% and 55.6% in the open label phase, respectively, in adult patients with generalized dystonia. Therapy-relevant safety events over 5 years for adult generalized dystonia included: infections 16.7%, and symptomatic intracranial hemorrhages 0%. The Investigator Study[17] reported the overall AE and SAE occurrence rates as 57.1% and 28.6% in the 3-month blinded phase in the DBS group, and 72.7% and 63.6% in the open label phase, respectively, in adult patients with segmental dystonia of the head and neck. Therapy-related safety events over 5 years for adult segmental dystonia included: device complications (54.5%), device revisions (54.5%), explants (9.1%), infections (0%), and intracranial hemorrhage (symptomatic: 0%, asymptomatic: 0%). The Volkmann (2014)[16] RCT reported 16% SAEs in neurostimulation group compared to 37% in the sham group, with 69% resolving without sequelae. Most SAEs within 6 months of follow-up were related to surgery, device or stimulation, and resolved without sequelae. Therapy-related safety event rates included device complications (8.1%), device revisions (3.2%), explants (1.6%), infections (4.8%), and intracranial hemorrhage (symptomatic: 1.6%, asymptomatic: NR).

Meta-analyses of therapy-relevant safety events showed device complication rates of 22% in adult generalized, 13% in adult segmental, 11% in adult cervical, and 26% in pediatric generalized dystonia. Device revision rates were 19% in adult generalized, 14% in adult segmental, 14% in adult cervical, and 21% in pediatric generalized dystonia. Explant rates were 13% in adult generalized, 9% in adult segmental, 4% in adult cervical, and 20% in pediatric generalized dystonia. Infection rates were 12% in adult generalized, 7% in adult segmental, 7% in adult cervical, and 16% in pediatric generalized dystonia. Intracranial hemorrhages were less common (⩽6%) across all groups.

While device-related safety event rates in the meta-analyses appear higher in pediatric patients with generalized dystonia compared to adult patients with generalized dystonia, the rates were more comparable to the Investigator Study of adult generalized dystonia, with similar rates of explants (20% vs 22.2%) and infections (16% vs 16.7%) and lower rates of device complications (26% vs 61.1%) and revisions (21% vs 55.6%) over a 5 year follow-up period, although formal statistical analysis was not conducted.

Additional data to support the safety of bilateral GPi DBS for primary generalized, segmental (head and neck), and cervical dystonia in adult patients and primary generalized dystonia in pediatric patients ages 12 and above include data from the Medtronic Product Surveillance Registry including 308 patients with primary dystonia (279 adult, 27 pediatric) with an average device exposure of approximately 3 years. Adverse events occurred in 28.2% of patients, with serious adverse events occurring in 12.9% of adults and 11.1% of pediatric patients. Notable SAEs included intracranial hemorrhage (1.0% adults, 0% pediatric), infections (3.2% adults, 3.7% pediatric), and procedural complications (1.4% adults, 3.7% pediatric). System explants occurred in 2.2% of adults and 3.7% of pediatric patients.

Additional factors considered in determining probable risks and benefits for the Medtronic DBS Therapy for Dystonia System included:

- Limited alternative treatments are available for chronic, intractable (oral and/or injectable medication refractory) primary dystonia that is often progressive and can lead to contractures and severe disability.
- Patients may accept higher surgical and device-related risks to achieve symptom relief when facing severe, intractable (oral and/or injectable medication refractory) dystonia.
- For pediatric patients at 12 years of age and above, with severe, intractable (oral and/or injectable medication refractory) primary generalized dystonia, early and aggressive DBS intervention may help prevent or minimize the progression of secondary musculoskeletal complications, including joint contractures and fixed postural deformities that can significantly impact long-term functional outcomes.
- By 12 years of age and above, the basic anatomical structures targeted in DBS, e.g., the GPi, have largely reached adult-like organization and size, and patients can typically tolerate the surgical procedures and device implantation similarly to adults.
- Limiting pediatric indication to ages 12 and above allows patients to have sufficient time to carefully monitor symptom development and have opportunity to better participate in treatment decisions.
- Adequate risk mitigation strategies can be implemented through patient selection, monitoring, and management of potential stimulation-related adverse events. Device labeling is implemented to implement these mitigations.

Patient Perspective

The clinical data did not include specific information on patient perspectives for this device. Overall, the data support the reasonable assurance of safety and effectiveness of this device when used in accordance with the indications for use. The probable benefit to health from the use of the device outweighs the probable risk of injury or illness from such use.

Limitations

Limitations of Results from RCT Studies

Data derived from the two randomized studies included the following limitations:

- Medication adjustments were allowed as needed with limited analyses of the impact to treatment outcomes. While treatment success with DBS possibly could be confounded by changes in medication, patients resort to surgical interventions such as DBS because of refractory dystonia symptoms or poorly tolerated side effects of medication.
- The following could affect the generalizability of results:
  - The duration of the randomized period was short,
  - Small sample size, and
  - Open-label design of follow-up reports which may result in an overestimation of the treatment effect.
  - There have been no randomized studies to evaluate the use of GPi DBS for pediatric patients twelve to 21 years of age.

Data derived from the systematic literature review included the following limitations:

- Meta-analyses of published literature revealed substantial heterogeneity. Substantial heterogeneity in the meta-analyses suggests publication bias and may underestimate risks of DBS and overestimate treatment success. The sources of heterogeneity include:
  - Studies differed in research methods and scientific rigor in terms of variable study designs, patient selection criteria, sample sizes, duration of follow-up, and reporting of safety and effectiveness outcomes;
  - DBS programming parameters with different stimulation settings, optimization protocols, and follow-up programming approaches;
  - Outcome measures with varying rater training and measurement timing;
  - Follow-up durations with substantial variation ranging from 6 months (Volkmann 2014[16], Ostrem 2007[31]) to over 10 years (Walsh 2013[44]: 4.9-10.7 years; Jacksch 2022[42]: 10 years; Ramezani 2021[57]: 7-10 years) across studies, with most studies falling between 1-5 years of follow-up; and
  - Variability in defining and reporting adverse events in publications limits the accuracy of safety information that can be extracted from the published literature. The published literature provides limited access to primary source data such as individual dystonia motor scores and detailed adverse event descriptions. In the absence of primary source data, analyses of associated variables (e.g., body distribution and etiology of dystonia, baseline symptom scores, relevant co-morbidities, etc.) are not possible. While some published reports of studies of DBS to treat dystonia symptoms provided covariate analyses, data included in these publications do not allow for verification of the analyses.

Data derived from Medtronic Product Surveillance Registry (PSR) included the following limitations:

- The PSR was primarily used to provide device safety information. Patient disposition information in the PSR indicates high lost-to-follow-up (LTFU) rates (20.5%, 52.9%, 61.4%, and 68.2% for years 2-5, respectively), which likely results in underreporting of AEs and SAEs and introduces bias in AE and SAE rate assessments. The significant missing data due to LTFU also can impact the reliability of treatment effect assessment. PSRs may preferentially capture data from patients who remain in care, potentially missing safety events that lead to treatment discontinuation or loss to follow-up.

- The PSR registry does not collect data for covariates (e.g., medical history, patient and clinical characteristics) that may affect the post-device exposure outcomes. The covariates can be used in multiple variable analysis or stratified analysis to establish association between covariates and outcomes or to adjust/control for potential confounding bias. This limitation can potentially impact the accuracy and reliability of the RWE based on the registry data due to potential confounding bias.

Overall Conclusion

The evidence presented supports the reasonable assurance of effectiveness of this device when used in accordance with the indications for use. The Investigator Study showed clinical meaningful improvements in BFMDRS motor scores for both generalized and segmental dystonia with sustained benefits through 5 years, supported by the meta-analysis showing consistent pooled BFMDRS motor scores improvement based on published literature. While the Volkmann (2014) RCT showed more modest improvements in BFMDRS for patients with cervical dystonia, the meta-analysis showed higher pooled improvement over longer follow-up periods. For generalized dystonia in pediatric patients twelve years of age or above, meta-analysis data demonstrated pooled BFMDRS motor score improvements; descriptively, these improvements appeared comparable to those reported in adult populations.

The evidence presented in this application supports the reasonable assurance of safety of this device when used in accordance with the indications for use. While device-related complications, including infections, revisions, and explants appeared numerically higher in pediatric patients at 12 years of age and above with primary generalized dystonia compared to adults with primary generalized dystonia based on the meta-analysis data, these rates were similar to those reported in the Investigator Study for adults with generalized dystonia. Although pediatric patients may experience a higher incidence of device-related safety events and long-term neurodevelopmental effects remain unknown, risks can be mitigated through careful patient selection, clinical monitoring, and device labeling.

In conclusion, the data in this application support that the probable benefits of using the Medtronic DBS Therapy for Dystonia outweigh the probable risks for bilateral stimulation of the internal globus pallidus (GPi) as an aid in the management of chronic, intractable (oral and/or injectable medication refractory) primary dystonia, including:

- generalized dystonia, segmental dystonia of the head and neck, and cervical dystonia (torticollis) in adult patients
- generalized dystonia in pediatric patients twelve years of age and above.

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Medtronic

Manufacturer
Medtronic, Inc.
710 Medtronic Parkway
Minneapolis, MN 55432
USA
www.medtronic.com
Tel. 1-763-505-5000
Toll-free 1-800-328-0810

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For the patient—Rx only

Purpose of Medtronic Deep Brain Stimulation (DBS) Therapy for Dystonia

Medtronic DBS Therapy for Dystonia delivers electrical stimulation to areas of your brain to help control symptoms of various movement disorders.

You may be a candidate for Medtronic DBS Therapy for Dystonia if you have been diagnosed with chronic, intractable (oral and/or injectable medication refractory) primary dystonia, including:

- generalized dystonia, segmental dystonia of the head and neck, and cervical dystonia (torticollis) in adult patients.
- generalized dystonia in pediatric patients twelve years of age or above.

Medtronic

Manufacturer
Medtronic, Inc.
710 Medtronic Parkway
Minneapolis, MN 55432
USA
www.medtronic.com
Tel. 1-763-505-5000
Toll-free 1-800-328-0810

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Your Medtronic Deep Brain Stimulation Therapy for Dystonia

Therapy-specific Patient Manual

! USA Rx only

Information for family members or caregivers

Read this patient manual thoroughly so you can assist the patient living with Deep Brain Stimulation (DBS) Therapy.

In addition to this manual, the patient should have a patient therapy guide.

If you do not have these manuals, contact the patient's doctor.

If you are living in certain countries, you may also receive additional patient information.

Always tell any medical personnel that the patient has an implanted neurostimulator and tell them where it is located. If medical personnel have any questions, they should contact Medtronic. Refer to the Medtronic contacts at the end of this manual.

! USA For assistance in the US, call Medtronic patient services at: 1-800-510-6735.

Have the name and telephone number of the patient’s doctor easily accessible for when you have any questions or problems.

Label symbols

The following symbols appear within the manual.

 Manufacturer

! USA For USA audiences only

Table of contents

Glossary

Battery - A part of the neurostimulator that provides the power for your brain stimulation system.

Caution - A statement that describes an action or situation which could harm you or damage the device.

Cervical dystonia (torticollis) - A localized dystonia characterized by neck muscles contracting involuntarily, causing abnormal movements and posture of the head and neck.

Contraindications - A medical term meaning that a procedure, device, or drug, etc. should always be avoided because the risk is greater than any possible benefit.

Dystonia - A neurological syndrome characterized by involuntary, sustained, patterned, and often repetitive muscle contractions of opposing muscles.

Dystonic crisis - A condition of frequent or continuous severe muscle contractions that may become life-threatening (also called status dystonicus or dystonic storm). These symptoms require immediate medical treatment.

Electromagnetic interference (EMI) - Electrical or magnetic energy that is strong enough to interfere with or disrupt your therapy.

Extension - A thin wire covered with a protective coating that connects the neurostimulator to a lead.

Generalized dystonia - Characterized by symptoms that begin in the arm or leg and advance to involve the trunk and rest of the body (affects all or most of the body).

Lead - A thin wire with protective coating that has metal electrodes on one end and a connector on the other.

Medication refractory - Not yielding or responding to oral or injectable medication therapy.

Neurostimulator - The neurostimulator is the implanted device that generates and controls your DBS therapy.

Patient control device - A hand-held device (for example, patient programmer) that allows you to turn your therapy on and off. It may also be used to adjust some therapy settings.

Precaution - See Caution.

Segmental dystonia - Involves two adjacent areas of the body (head and neck).

Stimulation - The delivery of electrical signals to the brain cells. The electrical signals may block some of the incorrect messages processed by the brain in areas that control movement.

Warning - A statement that describes an action or situation which could seriously harm you.

Medtronic DBS Patient Manual for Dystonia

This patient manual provides important DBS therapy information specific to your medical condition. It supplements the information in the DBS patient therapy guide.

You should also receive a manual instructing you how to operate your patient control device. Keep all of your patient information together.

If you are living in certain countries, you may also receive additional patient information.

DBS Therapy for Dystonia

Some of your symptoms are caused by abnormal messages sent by your brain. Your brain stimulation system delivers electrical stimulation to an area in the brain that controls movement. This may relieve the symptoms of your disease.

Benefits

Medtronic DBS Therapy for Dystonia may help control your symptoms, but it is not a cure. When you turn on the brain stimulation system, it will deliver stimulation that may decrease some or all of your symptoms. Your symptoms will return when the system is turned off.

Description of the device

Depending upon your medical condition, you may have 1 or 2 neurostimulators implanted.

Treating both sides of your body

To receive stimulation for both sides of your body, you may have 1 neurostimulator or 2 neurostimulators implanted.

You may have 2 neurostimulators, 2 leads, and 2 extensions implanted (Figure 1) or you may have 1 neurostimulator, 2 leads, and 2 extensions implanted (Figure 2).

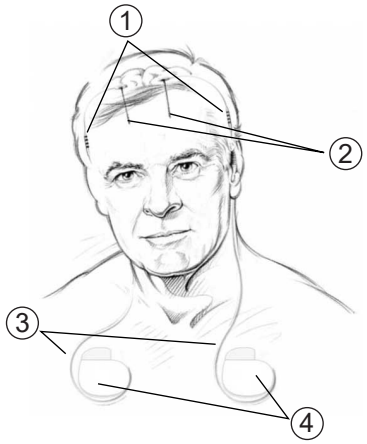

Figure 1. Implanted system for treating symptoms on both sides of your body with 2 neurostimulators.

① Lead-extension connections
② 2 leads
③ 2 extensions
④ 2 neurostimulators

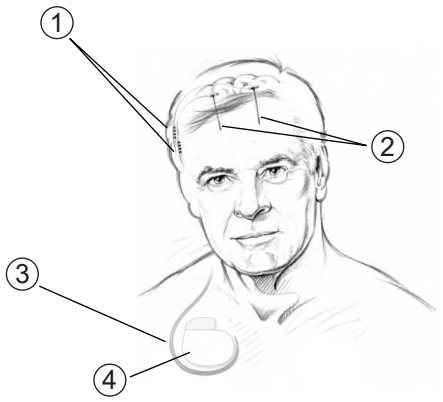

Figure 2. Implanted system for treating symptoms on both sides of your body with 1 neurostimulator.

① Lead-extension connections
② 2 leads
③ 2 extensions
④ 1 neurostimulator

What to expect from your Medtronic DBS Therapy for Dystonia

Medtronic DBS Therapy for Dystonia is a long-term therapy that requires both physician and patient involvement to be successful.

You may not experience immediate symptom suppression from the therapy. Frequent, noninvasive adjustments to the stimulation parameters may be required to achieve optimal symptom suppression. This adjustment period may take weeks or months.

Your doctor may require regular checkups to ensure the proper operation of the neurostimulator system. During these checkups, your doctor may evaluate your comfort and range of motion in the area of the neurostimulator and extension and possibly conduct x-ray evaluation of the neurostimulation system.

For pediatric patients, these evaluations are used to check if the length of the system needs to be changed due to growth since the system was placed. Your doctor may decide that a longer extension needs to be placed as your body grows, to allow the system to continue to function. Placing a longer extension requires another surgical procedure. Your doctor will also check the programming of your neurostimulator. As you grow, your doctor may need to adjust the settings of the stimulation or reprogram the electrodes that are used to deliver stimulation. These programming changes can be done during a visit to your doctor's office, and do not require additional surgery. The impact of DBS on overall brain development and behavioral changes in pediatric patients is unknown.

Contraindications

There are no therapy-specific contraindications for Medtronic DBS Therapy for Dystonia. Refer to the DBS Primary

Patient Therapy Guide for common DBS contraindications.

Warnings

Risk of depression, suicidal thoughts, and suicide—Depression, suicidal thoughts, and suicide have been reported in patients receiving DBS therapy. The factors responsible for these adverse events have not yet been established, ie, a direct cause and effect relationship to DBS has not been established. However, the seriousness of these adverse events requires attention from patients and caregivers. When considering DBS therapy be sure to discuss any history of depression or suicidal thoughts or behaviors with your physician to determine if this therapy is an appropriate option for you. If you have an implanted DBS system, it is important to attend on-going follow-up visits and to immediately notify your physician of any episodes of depression or suicidal thoughts or behaviors or changes in mood

and/or impulse control so that they can help manage these symptoms appropriately.

Risk of dystonic crisis—Loss of DBS therapy may potentially lead to severe, life-threatening dystonia symptoms. Dystonic crisis may result in breathing difficulties requiring life-support measures and severe muscle contractions that may damage the body, and in rare cases, lead to death. Contact your doctor immediately if your symptoms return or get worse.

Rebound effect—If your DBS system ceases to function for any reason (for example, battery depletion or exposure to EMI sources that may shut off the system), your symptoms may return.

In some cases, your symptoms may return at a greater intensity than before your implant. In rare situations, this could result in a medical emergency.

If your DBS system ceases to function, contact your physician immediately so the

status of your system can be assessed and your therapy restored.

Please follow your doctor's advice regarding other treatment when your neurostimulator is not working.

If your neurostimulator has a rechargeable battery, it is very important to check every day that your neurostimulator battery is charged. If the therapy provided by your neurostimulator should stop due to the battery not being charged, this could cause your symptoms to return. It is important for you to recharge your battery on a regular, frequent basis as recommended by your doctor (for example weekly or daily), to avoid your battery not being charged. If you have technical problems while charging your battery, contact your clinician or Medtronic customer support.

Rigorous activities—Normal activities, including active play and sports, could potentially result in damage of the components of the implanted system. If this occurs, the level of symptom suppression will

decrease. Consult with your physician before participating in any rigorous activities, such as sports.

Precautions

There are no DBS therapy precautions that are specific to dystonia.

Note: Refer to the DBS Patient Therapy Guide for a list of precautions related to DBS therapy.

Possible side effects after surgery

For potential risks and side effects related to DBS therapy, refer to the DBS Patient Therapy Guide.

In addition to the risks and side effects related to DBS therapy, the following side effects can occur with DBS Therapy for Dystonia.

- Muscle weakness or partial paralysis (paresis) affecting one side of the body

Note: Pediatric patients may have increased risks of infections, device-related complications, revisions, and explants compared to adults.

Expected battery life of your neurostimulator

The expected battery life for an implanted neurostimulator is different for rechargeable and non-rechargeable models.

The rechargeable battery - The Percept™ RC rechargeable battery can last for 15 years.

The non-rechargeable batteries - used by Percept PC, Activa™ PC, and Activa SC models are influenced by the programmed therapy settings of the neurostimulator.

Depending on your individual therapy settings, the non-rechargeable battery will typically last between 1 to 5 years. Consult with your clinician for exact information as it relates to your medical condition.

What to expect from your implant procedure

The following is general information about how the Medtronic DBS System will be implanted.

Your doctor will decide if one or two neurostimulator systems are needed to control your symptoms. If two systems are required, your doctor will need to place them at least 20 cm (8 inches) apart to assure they can each be properly programmed. Your doctor may place the neurostimulators either near your collarbones, within your abdomen, or both as needed to allow the proper distance between the neurostimulators.

Your doctor can provide greater detail about your implant procedure; however, the procedure normally includes the following stages.

Before surgery

You will be admitted to the hospital either the night before or the morning of your surgery. You may have your head shaved prior to surgery.

During surgery

During the surgery to implant your DBS System for dystonia, your doctor will use the following techniques to determine the area in your brain where the leads will be placed.

- You will receive local or general anesthesia before this procedure.
- Your surgeon may test stimulate areas of your brain to determine the best placement for the lead.
- When the best target in the brain is located, the lead is then passed into the brain.

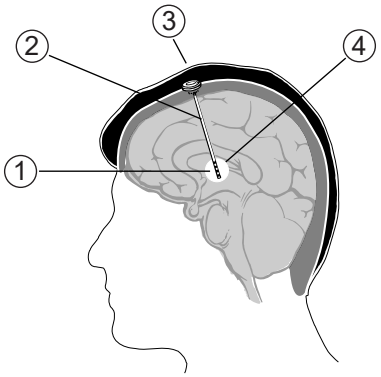

Figure 3. The location of the lead in your brain.

① Electrodes
② Lead
③ Hole cap
④ Stimulation target

Changes in therapy

There may be changes in the level of your symptom suppression over time. These changes may include:

- Less relief or no symptom relief
- Loss of effective stimulation

In many cases, your doctor can correct these changes by programming the brain stimulation system again. However, surgery may be required to reposition or replace the lead, replace the system, or remove the system.

Because your disease changes with time, your condition may improve, may worsen, or may remain unchanged with stimulation.

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Medtronic

Manufacturer
Medtronic, Inc.
710 Medtronic Parkway
Minneapolis, MN 55432
USA
www.medtronic.com
Tel. 1-763-505-5000
Toll-free 1-800-328-0810

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