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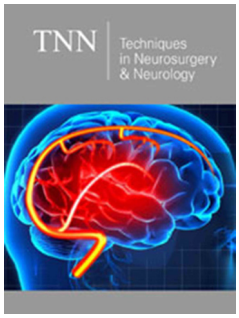
Research Article

Deep Brain Stimulation for Management of Refractory Cranial Neuralgias: A Literature Review

ISSN: 2637-7748



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Abstract

Deep Brain Stimulation [DBS] is a neuromodulatory approach of treatment brain diseases by inserting electrodes intracranially for delivering electrical impulses to targeted brain deep nuclei and structures. This method of neurostimulation is well established and evidence based for management of patients with movement disorders and approved by Food and Drag Agency of USA. After initial introduction of DBS as a feasible treatment option for patient with intractable neuropathic pain conditions, this electrical stimulation modality has gained widespread acceptance in modern management of movement disorders. Recently, Neuromodulation Appropriateness Consensus Committee, an expert panel of the International Neuromodulation Society, found that the evidence to support the use of DBS therapy for facial pain is limited and a current clinical use of intracranial stimulation for facial pain management should be seen as investigational. Several recent studies have demonstrated the benefit of DBS in controlling medically resistant facial pain conditions. With progress of understanding of neural circuitry involved in pain processing and advances in electrostimulation technology, DBS therapy appears to be clinically reasonable option for patients with various cranial neuralgias, however, no consensus exists yet as to what is optimal treatment target and nosology of facial pain. The intention of this narrative review is to critically reassess current evidence of DBS efficacy for management of patient with cranial neuralgias.

Keywords: Deep brain stimulation; Cranial neuralgias; Facial pain; Cranial neuralgias; Bilateral facial

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Submission: July 02, 2024
Published: August 28, 2024

Volume 5 - Issue 5

How to cite this article: Serge Rasskazoff*. Deep Brain Stimulation for Management of Refractory Cranial Neuralgias: A Literature Review. Tech Neurosurg Neurol. 5(5). TNN. 000624. 2024. DOI: 10.31031/TNN.2024.04.000624

Introduction

Deep Brain Stimulation (DBS) is a form of electro-neuromodulation invasive therapeutic modality by surgically implantation of intracranial electrodes into subcortical deep brain structures for use of electrical impulses to alter function of targeted brain structures. DBS has been extensively evaluated as a therapeutic option for management of patients with movement disorders and is currently used as a standard evidence-based treatment option. However initially exploration of DBS in the 1950's was used for intractable pain syndromes treatment and in fact has been considered as a method of choice for management chronic resistant pain conditions. However, due to poorly conducted clinical trials in USA the DBS was not approved by FDA as a mode of treatment for patients with various chronic neuropathic pain. The Task Force of European Federation of Neurological Societies published guidelines on neurostimulation therapy for neuropathic pain, showing a weak positive evidence for DBS use in facial pain (long term success is 38% for trigeminopathic facial pain and 36% for post-herpetic neuralgia) and concluded that DBS should be restricted to supraspecialist neurosurgical centers actively practicing DBS application for management refractory pain disorders, collecting and studying treatment outcome and publishing their results [1]. National Institute for Health and Clinical Excellence (NICE) made the recommendation for the safety and efficacy of DBS treatment for refractory chronic pain syndromes without specific information on facial pain [2]. Based on expert opinion and patient-reported outcomes the NICE approves

the DBS application in patient with intractable face pain. However, current published surgical treatment algorithm of face pains does not include DBS therapy as a surgical procedure option [3]. Neuromodulation Appropriateness Consensus Committee (NACC), the expert panel of the International Neuromodulation Society, after evaluation of current literature and clinical experience found that the evidence of current use of intracranial stimulation for face pain should be seen as investigational [4]. Therefore, at the moment the evidence-based clinical guidelines that may help to determine which patient with chronic refractory face pain is surgical candidate for DBS trial are absent. Despite available publications in clinical literature on DBS application for face pain management there is no consensus regarding patient selection for this treatment option. The purpose of the present review is to summarize the current evidence on DBS efficacy as method of neuromodulation therapy and to provide the information to support clinical decision-making for clinicians treating patients with intractable cranial neuralgias.

Methods

An electronic search was performed manually by author from PubMed of all available articles published in English language from all countries. The following keywords were selected: "DBS", "deep brain stimulation", "face pain", "cranial neuralgias", "efficacy". Only reports of patients with DBS implanted electrodes for control of chronic refractory face pain were included. During the data collection, articles reporting DBS for central post-stroke pain were excluded due to fact that facial pain was being as a part of hemi body pain. All bibliographies of obtained publications were additionally searched for any relevant reference. Additional historical references from the bibliographies of indexed publication and reviews has been researched also. The institutions from which the patients originated was recorded to avoid duplicating patient data when several publications from the same group were published. In case of multiple papers from the same center data was extracted from article with larges sample and longest outcome. The variables collected included patient demography, study publication date, first author, institution, city, country, type of publication, sample size, cranial neuralgia diagnosis, side and trigeminal branch of facial pain, previous surgical and interventional pain management treatments, DBS targets, duration of follow up and reported pain control outcomes. Electrode type, use of microelectrode intraoperative recordings, number of trials, failures and reported complications were not collected. In case of any missing data no attempt to contact corresponding authors to obtain the missing items was made. The data extraction form was completed by the same reviewer. Author in an unblinded, standardized manner, using a pre-constructed spreadsheet extracted data from identified published reports and all relevant information is summarized. Changes in pain score and response rates were considered as primary outcome of interest.

Relief from pain was assessed by 10-point pain scales used by investigators. Few publications provided incomplete information since DBS neuromodulation for face pain control was a part of bigger study on DBS application for chronic pain of various parts of human body. The efficacy of DBS was assessed on face pain of different nosology based on the third edition of the International Classification on Headache Disorders (only Part 13 Painful lesions of the cranial nerves and other facial pain) [5]. Changes in pain severity between pre- and post-DBS therapy in each diagnostic category according to ICH-3 were analyzed. Technical and surgical aspects of DBS techniques, coordinates of DBS targets, mechanism of action, safety and complications, history of DBS for chronic intractable face pain, patient selection and indications for treatment are well described elsewhere [6,7]. This narrative review provides a brief clinical summary of published evidence for different facial pain syndromes and has been structured according to the diagnoses of ICHD 3. Statistical Analysis. Due to the heterogeneous data quality and structure of the publications, the aggregate data analysis was not performed.

Result

The current literature on DBS neurostimulation in the treatment of chronic refractory facial pain is collected (Table 1). Twenty-six publications from 1980 till 2023 years were reviewed, most of them were case reports or small retrospective case series; half of the articles were part of bigger study on chronic pain of various locations and not exclusively on painful face syndromes; many of them did not provide data for individual patient. All reports represent non-blinding and non-randomized, single-arm uncontrolled studies. Data for a longer follow-up period were limited. All articles were from developed countries and all centers reporting their results were academic medical institutions: Belgium-1, Canada-5, Germany-5, Italy -1, Japan -2, Poland-1, Spain-1, Switzerland-2, UK-2, USA-4 centers. Literature search identified a total number of patients with refractory facial pain who underwent DBS neuromodulation was 175 with the biggest number of patients was collected in University Hospital Zurich from Switzerland -55. Only few centers are providing reports continuously over time with a majority of other institutions never publishing new articles on this topic again [30-32].

Table 1: Published literature on DBS for treatment of facial pain.

S. No	First Author and Year	City / Country	Institution	Publication Type	Face Pain Only	N of patients with DBS and IPG Implants	Individual Patient Data Availability
1	Turnbull IM [8]	Vancouver, Canada	University of British Columbia	Case series	No	1	Yes
2	Roldan P [9]	Valencia, Spain	University Hospital	Case series	Yes	2	Yes
3	Dieckmann G [10]	Gottingen, Germany	University of Gottingen	Case series	No	11	No

4	Hosobichi Y [11]	San Francisco, USA	University of California	Case series	No	18	No
5	Gybels J [12]	Leuven, Belgium	University of Leuven	Case series	No	11	No
6	Siegfried J [13]	ZurichS, Switzerland	University Hospital	Case series	No	55	No
7	Kumar Kx [14]	Regina, Canada	University of Saskatchewan	Case series	No	7	No
8	Taira T [15]	Tokyo, Japan	Tokyo Women's Medical College	Case report	Yes	1	Yes
9	Marchand S [16]	Sherbrooke, Canada	Universite of Sherbrooke	Case series	No	4	No
10	Constantoyannis S [17]	Vancouver, Canada	University of British Columbia	Case series	Yes	2	Yes
11	Green AL [18,19]	Oxford, UK	University of Oxford	Case series	No	5	No
12	Hamani C [20]	Toronto, Canada	University of Toronto	Case series	No	4	No
13	Rasche D [21]	Lubeck, Germany	University Hospital Schleswig-Holstein	Case series	No	8	Yes
14	Franzini A [22]	Milan, Italy	Instituto Nazionale Neurological	Case series	No	3	Yes
15	Samura K [23]	Fukuoka, Japan	Kyushu University	Case report	Yes	1	Yes
16	Coenen VA [24]	Freiburg, Germany	Freiburg University Medical Center	Case report	Yes	1	Yes
17	Cordella R [25]	Milan, Italy	Instituto Nazionale Neurological	Case series	Yes	5	Yes
18	Levine A.B [26]	London, Canada	University of Western Ontario	Case report	Yes	1	Yes
19	Yamgoue Y [27]	Lausanne, Switzerland	Centre hospitalier iniversitaire Vaudois (CHUV)	Case report	Yes	1	yes
20	Sims-Williams HP [28]	Bristol, UK	University of Bristol	Case series	Yes	3	Yes
21	Hollingworth M [29]	Bristol, UK	University of Bristol	Case series	No	1	Yes
22	Ben-Haim S [30]	San-Diego, USA	University of California	Case series	Yes	7	Yes
23	Kashanian A [31]	Los Angeles, USA	University of California	Case series	Yes	9	Yes
24	Abdallat M [32]	Hannover, Germany	Hannover Medical School	Case series	No	6	Yes
25	Saway BF [33]	Charleston, USA	Medical University of South Carolina	Case report	Yes	1	Yes
26	Mandat V [34]	Warsaw, Poland	National Research Institute of Oncology	Case series	Yes	7	Yes
Total						175	

Trigeminal Neuralgia (Table 2)

Description: A disorder characterized by recurrent unilateral brief electric shock-like pains, abrupt in onset and termination, limited to the distribution of the trigeminal nerve and triggered by innocuous stimuli. Only 3 patients with recurrent and persistent face pain due unclassified trigeminal neuralgia who underwent DBS implantation in sensory thalamus and periventricular gray matter reported in 2 publications; in two of them achieved mean pain reduction of 50% [33,34].

Table 2: Trigeminal neuralgia.

Year	Author	N pts w DBS	Age/ Gender	Pain Location	Pain Etiology	Previous Invasive Procedures	DBS target	F/U period	Pain Outcome
2003	Marchand S	2	NR	NR	Trigeminal neuralgia of unknown origin	NR	Sensory thalamus	2.5 years	Mean 53.3% pain reduction
2005	Green A.L.	1	41M	Left V1	Trigeminal neuralgia	NR	Right PVG and VPM	18 months	VAS pre-op = 63 VAS post-op =48 (23.8% pain reduction)
	Total:	3							

Trigeminal neuralgia attributed to multiple sclerosis (Table 3): Description: Trigeminal neuralgia caused by a multiple sclerosis plaque or plaques in the pons or trigeminal nerve root entry zone, and associated with other symptoms and/or clinical signs or laboratory findings of MS. A group from Italy studied DBS modality for the treatment of paroxysmal trigeminal pain in 5 patients (3 males and 2 females age ranging from 49 to 65 years) with long history of multiple sclerosis by stimulating posterior hypothalamic as a stereotactic target. Patient follow-up period was from 11 to 51 months after permanent implantation of DBS devices. Pain outcome was measured by reduction on Barrow Pain Scale. Provided evidence showed controversial efficacy results since face pain arising from the first trigeminal branch was controlled at follow up, however, all patients experienced recurrence of pain in the second and third trigeminal branches and two of them required repeated thermorhizotomies for pain control.

Table 3: Trigeminal Neuralgia attributed to multiple sclerosis.

Year	Author	N pts with DBS	Age/ Gender	Pain Location	Pain Etiology	Previous Invasive Procedures	DBS target	F/U period	Pain Outcome (Barrow Scale Pain Reduction/Time to Pain Recurrent)
2009	Gardella R	5	56F	Right V1V2V3	MS 32 years TN 21 years	4	Posterior hypothalamus	48 months	from V to IIIa 12 months
			65M	Right V1V2	MS 13 years TN 13 years	4	Posterior hypothalamus	48 months	from V to IIIa 28 months
			55M	Right V1V2	MS 14 years TN 9 years	5	Posterior hypothalamus	46 months	from V to IIIa 14 months
			56M	Left V1V2	MS 34 years TN 14 years	4	Posterior hypothalamus	51 months	from V to I 12 months
			49F	Left V1V2V3	MS 24 years TN 4 years	3	Posterior hypothalamus	11 months	from V to IIIa 11 months
	Total:	5							

Trigeminal post-herpetic neuralgia (Table 4): Description: Unilateral facial pain persisting or recurring for at least 3 months in the distribution(s) of one or more branches of the trigeminal nerve, with variable sensory changes, caused by herpes zoster. Forty-six patients with trigeminal post-herpetic neuralgia underwent DBS implantation surgery of various brain targets and collectively reported by 9 authors. Pain control outcome ranged from a clear failure to complete pain control, with half of patients achieving at least 50% pain relief during long term follow up. In 2 patients 100% of pain relief was achieved.

Table 4: Trigeminal post-herpetic neuralgia.

Year	Author	N pts w DBS	Age/ Gender	Pain Location	Pain Etiology	Previous Invasive Procedures	DBS target	F/U period	Pain Outcome
1981	Dieckmann G.	3	NR	NR	Herpes zoster	NR	VPM and PVG	Long term	2 pts success
1986	Hosobuchi Y.	5	NR	V1	Herpes zoster	NR	VPM and PAG	Long term	2 pts success

1990	Gybels J.	5	NR	NR	Herpes zoster	NR	VPL and VPM	Long term	0 pts
1991	Siegfried J.	25	NR	NR	Herpes zoster	NR	Sensory thalamus	Long term	13 pts very good 6 pts good
1997	Kumar K.	3	NR	NR	Herpes zoster	NR	PVG and sensory thalamus	Long term	0 pts
2005	Green AL	1	30F	Right V1	Herpes zoster	None	Left PVG and VPL	36 months	VAS pre-op = 6.9/10 VAS post-op = 0/10 (100% pain relief)
2006	Rasche D.	1	71M	NR	Herpes zoster	NR	VPL and PVG	1 year	50-75% pain relief
2020	Kashanian A.	2	81M	Left V1	Herpes zoster	DBS centromedial SS nucleous	Right VPM and PVG	46 months	No change in pain score (8/10) Following SRS x 2 and Radiofrequency ablation (30% pain relief)
			54M	Left V3>V2	Herpes zoster	Balloon compression	Right VPM	24 months	VAS pre-op = 10 VAS post-op = 7
2021	Abdallat M.	1	73M	Right face	Herpes zoster	NR	CM--Pf	48 months	VAS pre-op = 6 Vas post-op = 0 (100% pain relief)
	Total:	46							

Painful post-traumatic trigeminal neuropathy (Table 5): Description: Unilateral or bilateral facial pain or oral pain following and caused by trauma to the trigeminal nerve(s), with other symptoms and/or clinical signs of trigeminal nerve dysfunction. Pain duration ranges widely from paroxysmal to constant and may be mixed. The traumatic event may be mechanical, chemical, thermal or caused by radiation. Neuroablative procedures for trigeminal neuralgia, aimed at the trigeminal ganglion or nerve root, may result in neuropathic pain involving one or more trigeminal divisions; this should be considered as post-traumatic and coded here. Burchiel proposed a patient-oriented classification scheme for facial pains commonly encountered in neurosurgical practice [35]. He defined Trigeminal Neuropathic Pain (TNP) as result from unintentional injury to the fifth cranial nerve from trauma or surgery, whereas Trigeminal Differentiation Pain (TDP) results from injury to the trigeminal nerve by a lesioning procedure in an intentional attempt to treat trigeminal neuralgia. Most likely the difference between TNP and TDP is not trauma intention per se but the injury to naïve, healthy or diseased, abnormal trigeminal nerve. Patients with painful post-traumatic trigeminal neuropathy are most prevalent DBS group in literature. Out 96 patients in this group 71 satisfy criteria of TDP (anesthesia dolorosa) and 25 patients fall into TNP cohort. Only in 2 patients DBS target was posterior hypothalamus with the rest of the patients targets for implantable electric stimulation were different nuclei of sensory thalamus and/or periaqueductal gray matter. Pain reduction of more than 50% was achieved in 53% and 72% of TDP and TNP patients respectfully. DBS neurostimulation of the posterior hypothalamus completely failed to control facial pain in patients with TNP diagnoses. One patient with intractable left facial pain and severe hyperkinesia of the left arm which was developed after ablation lesioning by previous surgical treatment was successfully treated by implantation of stimulating electrode through a single stereotactic trajectory controlling both pain in face and involuntary arm moments. Another patient underwent successful DBS targeting ventroposteromedial thalamic nucleus after 10 years of VPM thalamotomy.

Table 5: Painful post-traumatic trigeminal neuropathy.

Year	Author	N pts w DBS	Age/Gender	Pain Location	Pain Etiology Burcheil Classification	Previous Invasive Procedures	DBS target
1980	Turnbull IM	1	38 M	V1	TNP	Supraorbital neurectomy	Thalamic nucleus ventrocaudalis
1981	Dieckmann G.	7	NR	NR	TDP	NR	Sensory thalamus
1982	Roldan P.	2	60 F	Right V1	TDP	Frazier technique trigeminal surgery + Right eye enucleation	VPM

			63 F	Right V1V2	TDP	Selective thermorhyzotomy	VPM
1986	Hosobuchi Y.	12	NR	NR	TDP	Sectioning of branch of trigeminal nerve or radiofrequency coagulation of the Gasserian ganglion	VPM and PAG
1990	Gybels J.	6	NR	NR	TDP	NR	VPL and VPM
1991	Siegfried J.	24	NR	NR	TDP	NR	Sensory thalamus
		6	NR	NR	TNP/ Face cancer	NR	Sensory thalamus
1997	Kumar K.	4	NR	NR	3 pts TNP 1 pt TDP	1 pt – glycerol injection	VPL and PVG
1998	Taira T.	1	52 M	Left V1V2 + left arm coarse intention tremor and dystonic posture of hand	TDP	Lesioning medullary trigeminal nucleus	VPM and Vim
2003	Marchand S.	2			TNP/ Left mandible Ameloblastoma	Surgical excision	Sensory thalamus
				Left eye and orbit	TNP/ Left optic nerve glioma	Surgical Ablation	Sensory thalamus
2004	Constantoyannis C.	1	52 M	V2	TNP/accidental trauma with multiple facial fractures	NR	Left VPM
2005	Green AL.	3	64 F	Right V2V3	TDP	Glycerol injection x 3; MVD; V3 tractotomy	Sensory thalamus
			59 M	Bilateral lower face	TNP/Tonsillar Carcinoma	Surgical resection	Bilateral PVG
			46 M	Right supraorbital	TNP/ Frontal meningioma	Surgical resection	Left PVG and VPM
2006	Rasche D.	5	36 M	NR	TDP	NR	VPM and PVG
			64 M	NR	TDP	NR	VPM and PVG
			68 F	NR	TDP	NR	VPM and PVG
			45 F	NR	TDP	NR	VPM and PVG
			26 F	NR	TDP	NR	VPM and PVG
2007	Franzini A.	2	47 M	Right V2V3	TNP/ Mandibular carcinoma	Radical transmandibular tumor resection	Posterior hypothalamus
			55 M	Right V1V2	TNP/ Nasopharyngeal carcinoma	Radiotherapy	Posterior hypothalamus
2015	Coenen V.	1	NR	NR	TNP/Epidermoid tumor involving trigeminal ganglion	Surgical tumor resection; MTS; Intrathecal drug; DBS PVG/PAG + sensory thalamus	VPM and PVG/ PAG
2016	Yamgoe Y.	1	62 F	Right V1V2	TDP	VPM thalamotomy	Left VPM
2016	Levine A	1	27 F	V2	TDP	MVD (no NVC)	Left PVG and Vc
2016	Sims-Williams	3	50 F	V1V2V3	TDP	Glycerol injection	CmPf PAG
			31 M	Left V2	TNP/Face trauma	Neuroma excision of maxillary sinus	CmPf PAG
			52 F	V2	TDP	MVD/partial sensory rhyzotomy	CmPf PAG
2018	Ben-Haim S.	4	69 M	NR	TDP	Radiofrequency ablation; balloon compression; failed PNFS trial	Right VPM and PAG

			71 F	NR	TDP	MVD with selective rhizotomy; balloon compression	Right PAG
			34 M	NR	TNP/ eye injury with metallic object	PNFS failed	Right VPM and PAG
			40 F	NR	TNP/brainstem glioma	Surgical resection of glioma	Right VPM and PAG
2020	Kashanian A	3	45 F	Left face	TDP	MVD; SRSx2	Right VPM and PVG
			39 F	Left V1	TNP	Supraorbital nerve decompression surgery	Right VPM and PVG
			42 F	Left face V2 and V3 > V1	TDP	NR	Right VPM
2021	Abdallat M.	3	48 F	Right face	TDP	Trigeminal nerve surgery	CN-Pf
			72 F	Right face	TDP	Trigeminal nerve surgery	VPM
			47 M	Left face	TNP/ Maxillary sinus surgery	NR	VPL
2022	Saway BF	1	59 M	Left Face, V1-V3, V1-2 < V3	TDP	MVD, Radiofrequency trigeminal rhizotomy	VPM + MCS
2023	Mandat V	3	NR	NR	TDP	MVD, Radiofrequency Trigeminal rhizotomy	PVG/PAG
			36 F	NR	TNP, 12 years after trauma	Thalamic DBS	PVG/PAG
			48 F	NR	TNP, 2 years after trauma	Thalamic DBS	PVG/PAG
	Total:	96					

Painful trigeminal neuropathy attributed to other disorder (Table 6): Description: Unilateral or bilateral facial or oral pain in the distribution(s) of one or more branches of the trigeminal nerve, caused by a disorder other than those described above, with other symptoms and/or clinical signs of trigeminal nerve dysfunction. This is a very rare nosology and only 2 cases have been published in literature. One is case of Parkinson's disease patient who developed intractable facial pain with allodynia as a result of long-term levodopa replacement therapy, which was alleviated by subthalamic nucleus deep brain stimulation. Another patient presented with a 2 years' history of progressive left-sided facial pain secondary to Lyme's disease contracted during field work. Patient was treated with single electrode dual target surgery (Centromedian Intra-Laminar Parafascicular Complex (CMPF) and periaqueductal grey and periventricular grey (PAG/PVG)). At 3 years' outcome results revealed only minimal symptoms in patient with full return to her daily living activities using gabapentin therapy 1.8g daily.

Table 6: Painful trigeminal neuropathy attributed to other disorders.

Year	Author	N pts w DBS	Age/ Gender	Pain Location	Pain Etiology	Previous Invasive Procedures	DBS Target	F/U Period	Pain Outcome
2008	Samura K.	1	55 F	Whole face	Parkinson Disease	NR	Bilateral STN	1 year	No pain
2017	Hollingworth M.	1	52 F	NR	Lyme disease	Pulsed radiofrequency therapy of the trigeminal ganglion	CmPf and PAG/PVG	3 years	VAS post-op = 5
	Total:	2							

Persistent Idiopathic Facial Pain (PIFP) (Table 7): Description:

Persistent facial and/or oral pain, with varying presentations but recurring daily for more than two hours/day over more than three months, in the absence of clinical neurological deficit. It is most often depicted as dull, nagging or aching, either deep or superficial. PIFP may originate from a minor operation or injury to the face, maxillae, teeth or gum, but persists after healing of the initial noxious event without any demonstrable local cause. Thalamic and/or periaqueductal grey stimulation provided significant pain relief in half of eleven PIFP patients. Neurostimulation of posterior hypothalamus of PIFP patient was absolutely unsuccessful.

Table 7: Persistent Idiopathic Facial Pain (PIFP).

Year	Author	N pts with DBS	Age/ Gender	Pain Location	Pain Etiology	Previous Invasive Procedures	DBS target	F/U period	Pain Outcome
1981	Dieckmann G.	1	NR	NR	NR	NR	NR	Long term	Success
1986	Hosobuchi Y.	1	NR	NR	NR	NR	VPM and PAG	Long term	Success
2004	Constantoyannis C.	1	NR	Left V2	Dental procedure	NR	Right VPM	7 years	Adequate pain control
2006	Hamani C.	3	75 F	Hemiface	NR	NR	Vc	5 months	Failed
			46 M	V2	NR	NR	Vc	3 months	Failed
			63 F	V1	NR	NR	Vc and PAG/ PVG	5 years	VAS pre-op = 9 VAS post-op =2 (78% pain reduction)
2007	Franzini A.	1	52 F	V2 V3	Dental procedure	NR	Posteromedial Hypothalamus	4 months	Failed (no change in pain score)
2008	Ben-Haim S	1	49 F	Left facial pain	NR	NR	Right VPM and PAG	1 year	VAS pre-op = 8 VAS post-op =5 (38% pain reduction)
2020	Kashianian A.	1	62 M	Right eye and forehead	Surgical correction of retinal detachment	Sphenopalatine ganglion x1 and Stellate ganglion x 2 blocks	Left VPM and PVG	9 months	Failed (no change in pain score)
2021	Abdallat M.	2	56 F	Right face	Dental Surgery	NR	CM-Pf	48 months	VAS pre-op = 5 VAS post-op = 1 (80% pain relief)
			43 F	Left face	Dental surgery	NR	CM-Pf	48 months	VAS pre-op = 6 VAS post-op = 6 (0% pain relief)
	Total:	11							

Study Limitation

The principal limitation of this study is that only small case series and case reports were available for data extraction and analysis with a relatively small number of participants. Evidence supporting the efficacy of DBS which has been collected makes the dataset subject to limited interpretation. The significant heterogeneity among the investigated patients was observed in collected dataset. The primary source of this heterogeneity is the fact that DBS was used for the treatment of chronic facial pain in variety of cranial neuralgias diagnoses. Moreover, variation in the stimulation brain targets and parameters, difference among old and modern electrode design, and the specifics surgical implantations setting, and trial period contribute to the increased heterogeneity. These shortcomings of data quality do not diminish the value of published results or positive clinical experiences of face pain control in patients. Variable published results of DBS for control of resistant face pain do not mean that the treatment is ineffective; however, they reveal the need of change new data acquisition and quality of publishing in order to gain meaningful information for clinical use. In the future any study on DBS for facial pain should require cranial neuralgia diagnosis according to 3rd edition of HIS classification by neurologist with specialized training in headache and face pain as an entry criterion in order to improve quality of research data in this area.

Discussion

Cranial neuralgias such as primary and secondary trigeminal neuralgia, post-traumatic trigeminal neuropathy, trigeminal post-herpetic neuralgia and persistent idiopathic facial pain syndrome are characterized by severe, disabling, typically unilateral, burning or stabbing pain. An estimated 100 per million people in the United States suffer from these disorders, and for those patients with refractory course, the impact on their quality of life can be extremely debilitating [36]. Despite being available, wide-accepted by clinicians medical and surgical treatment, intractable and therapy cranial neuralgias of different origins still poses a management challenge in patients with therapy refractory facial pain syndromes. In circumstances where there is insufficient responsiveness to pharmacological/ surgical therapies, invasive neuromodulation option, including DBS, should have considered as a potential effective treatment option.

After the introduction of human stereotactic surgery in early 1950s and in parallel to ablative surgery clinical use of brain electrical stimulation was developed. Application of DBS as a tool for control of severe pain conditions preceded it used for management of movement disorder, since refractory chronic pain was among the first studied indications for brain stimulation over 50 years ago [37]. Now deep brain stimulation is an established, FDA approved, neurosurgical technique for treatment of movement disorders and currently, it is estimated that 160,000 DBS implant procedures have been performed worldwide. The first modern use of DBS in the US occurred in early 1970's for the treatment of facial pain in patients with cranial neuralgias [38]. The exact mechanism by which DBS exerts its action on underlying pathophysiology of facial pain is still not clear. One of research hypothesis is that electrical stimulation modulates abnormal circuits toward a more physiological state [39].

DBS treatment for face pain is based on plausible physiological hypotheses and data from experiments in laboratory animals and clinical research of human subjects. The results of those experiments conducted in the 1950s and 1960s led pioneers of functional neurosurgery to stimulate the ventral posterolateral and posteromedial sensory thalamic nuclei and/or PAG and PVG in patient with chronic intractable face pain. It has been postulated that PAG stimulation is better suited to nociceptive pain, whereas sensory thalamic targets are more effective in neuropathic pain [40,41]. Both opioid and non-opioid mechanisms seem to be involved in DBS-induced analgesia. Contemporary and older case series publications on DBS application for resistant facial pain control have been restricted to only handful academic superspecialized, dedicated neurosurgical centers, located in North America, Western Europe and Japan, using this technology to relief suffering of patients with vast chronic pain conditions. There are around 2000 patients with chronic pain syndromes who underwent placement DBS system (188 patients with intractable face pain) and nearly 100 patients with cluster headache. Several factors explain this geographical and economic inequality for this method: 1) DBS is expensive neuromodulation therapy requiring significant capital investment in stereotactic and navigation equipment; high cost of implantables (IPG and electrodes) 2) existence of experienced, well-trained and qualified chronic pain multidisciplinary team for patient selection, assessment and long-term monitoring and adjustment stimulations programs. This pose an ethical issue of DBS significant financial and organizational costs and its availability to all classes of society. The expensive DBS hardware costs, high surgical and hospital fees along with lack of clinician expertise in area of functional neurosurgery for management intractable pain conditions are the issues which limiting widespread adoption of this invasive neuromodulation modalities in the developing world.

The main targets of DBS for face pain control are sensory thalamus and periventricular and periaqueductal gray matter. Selection of deep brain stimulation targets is usually based on the surgeon's judgment, his previous operative experience with DBS targets for chronic pain control and the patient symptoms and diagnosis of face pain condition. The published data suggest that posterior hypothalamus should not be used as DBS target for management of the painful lesions of the cranial nerves due to that the pathophysiological mechanisms of neuropathic trigeminal pain do not involve the hypothalamus, since acute hypothalamic stimulation in ongoing cluster headache attacks remain ineffective. The rigorous evaluation of published literature showed significant limitations in the quality of reported data. There was a wide range in age, gender, etiology, mean durations of pain, interval between onset of pain and treatment with DBS, previous invasive interventional pain modalities, deep brain sites stimulated, and duration follow up. Additionally, the lack of standardized outcomes and outcomes measures used to contribute to heterogeneity of data and the growing inability to compare study results.

Multiple reports of the same patient cohort frequently did not track individual cases through the series of publications. Deep brain stimulation yielded mixed results in different face pain syndromes: best results were achieved in patient with painful post-traumatic neuropathy, while patients with trigeminal neuralgia, trigeminal post-herpetic neuralgia and persistent idiopathic facial pain had less benefit. Findings of this study are in line with data from a meta-analysis of individual participant data of patients that were treated with DBS for chronic facial pain with total of seven DBS reported small trials consisting of 54 screened patients: DBS provide facial pain control in safe manner across different neurostimulation targets without clear superiority of specific brain nuclei, and in many patients a combination of different DBS targets were used [42]. No statistical results can be derived since results seem to vary dramatically in clinical practice and therefore, data has to be interpreted in the light of what evidence is available. The therapeutic efficacy of DBS in some of patients could be maintained long-term with over 50% pain improvement at 4-year follow-up and more, although DBS does not reduce pain in all patients with successful trials.

Analysis of available DBS data on cranial neuralgias management showed serious lack of consistency and heterogeneity in face pain diagnoses. The assignment of diagnoses or face pain was inconsistent among medical institutions and sometimes among reports of the same center. Evidence supporting application of DBS for pain control of various facial painful diagnoses is based solely on case reports and uncontrolled retrospective small studies and therefore there is a difficult challenge to interpret and to draw conclusion from current dataset. Prospective randomized, double-blinded clinical trials are often cited as highest-grade clinical evidence. In reality, several attempts of conducting the large-scales clinical DBS pain trials had obvious problems: insufficient organizational and financial support, institutional review board approval, registration requirements for clinical trials, inadequate time, lack of control groups due to ethical concerns about potential patient harm. These factors are relevant to functional neurosurgeons as limited time and resources to support meaningful outcome research are commonplace in cash-strapped health care system. The blanket call for double-blinding and randomization of clinical trials in DBS for cranial neuralgias may be untenable due to the cost of DBS therapy and the rarity of patients with refractory facial pain. Modern innovations in DBS pain surgery were started by investigator practicing functional pain neurosurgery where

outcome are almost always reported as case reports or retrospective case series. Those published opinions suffer from various forms of bias. The latter may be the highest achievable today grade of clinical evidence in an experience and skill-based specialty such as functional neurosurgery. Instead to relay on population statistics used in randomized control clinical trials, it is more appropriate to use DBS patient registry to obtain high-quality systemic data from more patients with long term follow-up.

The DBS registry is an organized method of collecting data as a systematic multicenter investigation to assess treatment efficacy based on study protocol, which should be developed by specialist in face pain management and functional neurosurgeons utilizing DBS surgery in daily practice. A minimal data set on clinical status, DBS targets, complication and outcome must be reported by each participating center by using an on-line Case Report Form as documentation method. Diagnosis of facial pain condition should be done and reported according to the criteria of the International Headache Society, a classification which intended to provide a systematic framework to better diagnose and treat face pain conditions. Patients must receive all appropriate ICHD diagnoses, meaning some patients will have more than one diagnosis (e.g. anesthesia dolorosa is trigeminal neuralgia and trigeminal post-traumatic neuropathy). Clinicians performing DBS for all patients with facial pain in experienced centers should collect data of the 2-year, 5-year and 10-year actuarial pain-free rates similar to studies on efficacy of open surgical and interventional pain management treatments of patients with trigeminal neuralgia. Development of DBS registry should be based on the general principles for registry planning, governance, data collection, quality assurance, human subjects and data protections and sharing established by a panel of authors from International Headache Society [43]. Analysis of published results has been difficult to compare treatment efficacy of between different centers due to lack of standardized outcomes. That lack of standardized outcomes and outcomes measures used to contribute to heterogeneity of data and leads the growing inability to arrive to clinical meaningful conclusion. Recently consensus meeting has been held under auspices of the Trigeminal Neuralgia Association UK and Rosetrees Trust to define the core outcome set for trigeminal neuralgia clinical trials [44]. The TN Core Outcome set (TRINCOS) agreement was reached during consensus meeting on 10 outcomes across six domains (pain, side effects, social impact, quality of life, global improvement, and satisfaction with treatment). TRINCOS is providing researchers not only with the "what to measure" information but also with "how to measure" details.

TRINCOS criteria may be applied to other cranial neuralgias. The establishing of DBS registry by professional medical societies would lead to ultimate improvement of the management of patients with intractable cranial neuralgias by providing systemic evidence into disease classification and heterogeneity, longitudinal outcomes and their predictors, treatment efficacy and safety and quality of care. Clinical DBS investigators can collect "big data" from such professional society registry to evaluate bigger cohorts than individual medical centers and may lead to recommendations based on current best evidence. Modern clinical decision-making is guided by evidence-based medicine standards formulated as practice guidelines. Determination that a requested surgical intervention (DBS) is not supported by evidence-based medicine is only helpful if an alternative treatment can be recommended with strong evidence-based medicine support. Therefore, until arrival of high-quality evidence from professional society registries, clinical practitioners should use a very low quality of evidence with high confidence obtained from published clinical experience. Practice of medicine is often defined as an 'art based on science'.

The art of medicine should be a clinical practice by customizing treatment for a particular patient utilizing best available level of clinical evidence in circumstances when there is no data from prospective randomized controlled studies available. Customizing a treatment plan to individual patient may require expert opinion and common sense, both are considered Level V clinical evidence. The lack of information on outcomes fails to provide patients with adequate answers about the prognosis of the treatment options available and just adds to the misuse of research results. However, Level V evidence, little or no systematic empirical evidence is not absence of clinical evidence. It is representing a grade D practice recommendation, where clinicians should consider all options in their decision making and be alert to new published evidence that clarifies the balance of benefit versus harm; patient preference should have a substantial influencing role [45]. Everyone has access to the current literature and this literature review could guide clinician treating patient suffering from refractory and intractable cranial neuralgias when to consider DBS surgery as a management option.

Conclusion

The DBS application as the treatment of refractory cranial neuralgias should be considered clinically established and justified to use such implantable neuromodulation technique in clinical practice. Results of recent studies at various centers have made progress in confirming DBS validity as a legitimate technology for management severe facial pain patients with cranial neuralgias. The DBS is effective therapeutic modality in clinical settings when used in appropriately selected patients, however, this invasive neuromodulation method should be only used in few centers with dedicated research program for pain disorders neuromodulation and strong DBS clinical practice and expertise. Its reversibility and safety profile during chronic continuous invasive electrostimulation made this technology ethically acceptable in those otherwise untreatable patients whose intractable facial pain achieved pain relief after this neuromodulation technique. DBS is the most expensive and invasive option of electrical stimulation approaches and should be reserved for extremely difficult-to-treat patients. Improvement of quality data reporting in future DBS studies and establishment a web-based data collection center under auspices of World Society for Stereotactic and Functional Neurosurgery, International Neuromodulation Society and International Headache Society could provide real-world contemporary data on clinical DBS efficacy and help to guide the practitioners regarding the procedural effectiveness and long-term outcome and the patient's

expectations.

The author concluded that DBS could be performed safely and successfully for medically refractory facial pain in carefully selected patients with following indications:

a) Painful post-traumatic trigeminal neuropathy-DBS as first choice for TDP and second choice for TNP if a trial of peripheral nerve stimulation of trigeminal nerve branch is unsuccessful.

b) Trigeminal neuralgia and Trigeminal post-herpetic neuralgia-DBS should be used as, last option therapy when other invasive neuromodulation approaches are failed.

c) DBS is a first choice of neuromodulation treatment using single electrode with dual target in patients with face pain and movement disorder.

d) DBS should be considered a rescue treatment in patients who underwent previous thalamotomy for face pain control and developed a tolerance.

e) Hypothalamus nuclei should not be used as the neurostimulation targets for DBS therapy of cranial neuralgias.

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