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Ablative surgery for Parkinson's disease: Is there still a role for pallidotomy in the deep brain stimulation era?

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ABSTRACT

Posteroventral pallidotomy has already been considered the surgical procedure of choice for Parkinson's disease patients with motor complications. Recently, however, several factors led to its replacement by deep brain stimulation. Nevertheless, pallidotomy has a well-documented efficacy and safety evidence regarding the reduction of parkinsonian motor symptoms. Yet, there may be manysituations where it may be considered as a better option than neuromodulation. Herein we review those possible conditions, giving emphasis to the costs, which we found to be the most limiting factor. Importantly, a cost comparison between deep brain stimulation and pallidotomy was also provided.

1. Introduction

Parkinson's disease (PD) is the second most prevalent neurodegenerative disease and movement disorder, just after Alzheimer disease and essential tremor, respectively. It is rare before the age of 50, but the prevalence after 60 can range from 1 to 4% in the highest age groups [1], being typically a disease of the elderly. In Brazil, the prevalence in a community-based study was 3.3% above the age of 64 [2].

As such, Parkinson's disease brings a significant burden to the patient and their family [3,4]. Not only it causes a functional incapacity due to the classical motor symptoms, the frequent falls, autonomic disturbances and eventually dementia, but it is also responsible for the low quality of life and increased mortality [5]. Despite the variety of treatments available, none is capable of slowing the progression of the disease, though there has been a considerable effort in seeking neuroprotective therapies [6].

1.1. History of pallidotomy

Surgical treatments for Parkinson's disease was first described in 1939 when Bucy and Case excised part of the motor cortex aiming to treat the tremor associated with the illness [7]. After several attempts to find the best target, the corticospinal tract was switched by the globus pallidus internus (GPi) and thalamus as the preferred targets to ameliorate the symptoms of Parkinson's disease. It was realized that lesions in the basal ganglia were capable of treating tremor and rigidity without producing paralysis [8,9] leading to the development of the chemopallidectomy by Cooper et al. in 1954 [10].

These surgeries, however, carried out a high mortality rate, considering the unavailability of advanced imaging technology at the time. After the great results with the introduction of L-dopa in the mid-sixties, surgery was rarely performed and it remained abandoned for years [11,12].

The return of surgical therapy for Parkinson's disease came with the observation that L-dopa treatment becomes less effective over time, along with side effects such as dyskinesias and motor fluctuations. Due to the improvement of imaging technologies and stereotactic procedures in the late eighties, Laitinen et al. explored the work of Leksell and colleagues concluding that lesions in the posteroventral segment of GPi were effective in improving the motor symptoms of PD [13]. The significant results obtained by Laitinen on improving parkinsonian signs [14,15], led to the resurgence of surgical treatment of Parkinson's

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disease, with posteroventral pallidotomy (PVP) as the procedure of choice [11,12]. That scenario remained until 1996, with the description of deep brain stimulation (DBS) for PD by Benabid et al. [16]. Since then, the popularization of the DBS brought as a consequence a diminishment of pallidotomy for the treatment of this condition.

1.2. Should the procedure be abandoned?

The abandoning of pallidotomy as a therapeutic option for Parkinson's disease was already questioned by several authors [17–22]. Firstly, its efficiency in the motor control of PD is classified as level of evidence A (proven by class I studies) [23,24]. Secondly, when performed unilaterally, posteroventral pallidotomy has the same efficacy of unilateral STN [17,25–27] and GPi [28,29] stimulation in improving parkinsonian symptoms. Finally, DBS implantation is far more expensive than pallidotomy [30] and has more selective inclusion and exclusion criteria [31,95], meaning that the first may be unavailable for some patients in developing countries, while the latest may not.

Posteroventral pallidotomy is, therefore, a historically established, evidence-based efficient procedure in improving motor symptoms of Parkinson's disease, including the motor complications of L-dopa treatment [17,23,32]. As discussed later, however, DBS has proven to be better than pallidotomy, probably because of its reversibility and safety to be performed bilaterally [33,34]. Still, when performed, DBS are usually done bilaterally, in contrast to pallidotomy, typically performed unilaterally. Plus, the surgeon may come across some situations in which an ablative procedure can be the best therapeutic option for the patient when considering its secondary conditions and social context [21].

Here one discusses the main indications for pallidotomy over DBS, along with situations in which lesion therapy might be regarded as the first option for the treatment of PD. Some of the topics that we point out are HIV and immunocompromised patients, difficulty in maintaining the follow-up after surgery, contraindications for general anesthesia, major clinical comorbidities, and the costs involved in the whole procedure. Doing so, we analyze and compare the costs between DBS and pallidotomy, emphasizing how pallidotomy can be a cost-effective method, especially in sceneries where cost-reduction is mandatory.

2. Efficacy and safety of pallidotomy vs. DBS

Although ablative procedures have been continuously replaced by stimulation as the surgical treatment of the choice for Parkinson disease, one must recognize that it is not due to a lack of efficiency or safety of posteroventral pallidotomy. The first randomized and single-blinded studyto evaluate its effectiveness on PD's motor symptoms, performed by de Bie et al. [23], compared a group of 18 patients submitted to unilateral PVP with the best medical treatment, which determined a reduction of 30,8% in “off” phase motor Unified Parkinson's Disease Rating Scale (UPDRS-III) score and a significant improvement in levodopa-induced dyskinesia in a 6 months follow-up, whereas the control group had a worsening of the symptoms.This result was then reassured in another prospective study by Vitek et al. [24], with a similar consequence of a 33,5% decrease in “off” UDPRS-III score in 6-months, which remained at 25% after 2 years.

The symptoms that improved and remained better on a long-term basis after pallidotomy were mainly dyskinesias and tremor, as indicated in an review of long-term outcomes of surgical treatments for Parkinson's disease [35]. After 5 years, mean tremor reduction remained at 65%, while dyskinesias reduction persisted at 70–75% [36,37]. In a 12 year follow-up study, this latest symptom was the one that better sustained the improvement [35]. However, a less consistent result was found for contralateral rigidity and bradykinesia, tending to a gradual recurrence after 10 years [38].

When compared to unilateral GPi stimulation in a prospective randomized study, pallidotomy was equally effective [29], showing a reduction in UPDRS-III score of 29,7% and 28,8% for ablation and stimulation, respectively. Although there is no study directly comparing unilateral STN-DBS implantation with unilateral PVP, the studies comparing it with pallidal stimulation [26] or medical therapy alone [25,27,39] have shown a reduction between 25% to 37% of UPDRS-III, which is very similar to the average reduction following a PVP surgery.

The lack of safety when performed bilaterally [40–42], however, makes pallidotomy less efficient than bilateral DBS implantation of STN or GPi. Another disadvantage of pallidotomy is the inability of improving axial symptoms, such as gait instability and freezing. Not to mention, many times it is impossible to taper or withdraw medications, as frequently achieved with STN-DBS. Conversely, the hallmark of pallidotomy regarding the management of drugs is to allow the increasing the levodopa dosage without causing side effects, such as dyskinesias [34,43,44].

Regarding the target for ablation, posteroventral pallidotomy remains the preferred one. Ventral intermedius (VIM) thalamotomy, while being the most used target in the past [12], has been abandoned due to its almost unique effect on improving tremor [35,45]. For this reason, it has been used in very particular cases in which tremor is the most predominant symptom, and bilateral DBS implantation is not feasible.

The subthalamic nucleus, being the most used target for stimulation, is no longer considered a target for ablative procedures [46]. Even though it shows similar efficacy and possible benefits over pallidotomy [47,48], there is a well-known chance of permanent hemiballism as a consequence of the surgery. In this regard, Alvarez et al. demonstrated in their series that 15% of the patients developed postoperative hemichorea-ballism [49].

Concerning the procedure's safety, there is no study so far that demonstrated a lower rate of surgical complications of pallidal or subthalamic stimulation in comparison with pallidotomy [50]. Besides, DBS implantation has exclusive complications related to the indwelling material, such as lead fracture and infection, hardware-related complications by which may end in reoperation and device explantation. This, in turn, results in additional costs and an increase in morbidity [51–53].

The most frequent complications after unilateral PVP are fatigue, hypersomnia, speech disorders and dysphagia. Major complications are unusual and include cerebral hemorrhage (4%), visual field deficits and contralateral weakness [32,42,50]. Although the rate of adverse effects following the surgery may range between 20 and 22%, about half of them are transient and improve after 1 year.

Additionally, in a review performed by Alkhani and Lozano, out of 1510 cases, the rate of major complications and mortality following the procedure were 5,3% and 0,4%, respectively [32], which is acceptable considering the benefits of surgery. Hence, even if the side effects of pallidotomy may not be reversed as with DBS does, this fact does not make the procedure unviable, since the majority of patients obtain some benefit from pallidotomy, meaning a significant improvement in their quality of life.

The ideal time to indicate a surgical therapy for PD remains highly controversial [99,100]. When pallidotomy is concerned, the majority of the studies, including all of those with a better level of evidence [23,24,33], included only patients with advanced PD and a mean duration of the disease of 10–15 years. That is reasonable, considering that the benefits of surgery are in great part related to the motor complications of levodopa treatment. Still, Schuepbach et al. [101] showed a benefit of bilateral STN-DBS compared to best medical treatment in 251 patients with mean duration of 7,5 years since the beginning of symptoms. Therefore, despite the controversies that remain regarding this subject, surgery may play a role in early-stage Parkinson's disease.

3. Situation-specific advantages of pallidotomy

3.1. HIV and immunocompromised patients

After the introduction of the highly active antiretroviral therapy (HAART), the rise of life expectancy in HIV-infected patients has been leading to an increase in the number of people with the concomitant diagnosis of PD that can live through the whole course of the disease. Reports of adverse effects, such as dyskinesias, induced by the interaction of levodopa and antiretroviral drugs have also been published [54]. Thus, the number of patients requiring surgical treatment has been increasing.

There is, however, doubt on which surgical technique may be the most appropriate for those patients. Only a small number of case reports were published on this subject [55–59], and although some patients have already been submitted to DBS surgery with good results in mid to long term, additional studies are demanding to compare the safety of both methods in immunocompromised patients.

A case series reported by Hopper et al. described 4 cases by which lesion was chosen over DBS implantation. Two of those patients were HIV-infected with a low CD4 count, and there was a significant clinical improvement after surgery, which remained after a 12 months follow-up [57]. Since infection is considered to be the most frequent hardware-related complication of DBS surgery, with rates that might be as high as 15,2% [52,60], care must be taken with such vulnerable patients. For this reason, pallidotomy remains as a good option, being even the first choice if the patient has a low CD4 count.

3.2. Difficulty in maintaining the follow-up

The inability of the patient to continue an appropriate follow-up after the surgery is a well-accepted indication to perform a lesion procedure [17,18,20,22]. That is reasonable, considering that DBS demands continuous care related to settings programming and battery replacement. In order to do that, people technically capable of performing such procedures, as well as reachable for the patients are in demand.

In middle and low-income countries where Parkinson's disease surgery is performed, it is restricted to few centers in the most populated areas [61]. Knowing that Brazil is a country with a continental dimension and many parts around the country do not have a specialized functional neurosurgery center, it seems reasonable to consider the dislocation costs of those who come from distant places from where medical assistance is performed. In addition to this, as previously mentioned, the lack of well-trained people to program and manage DBS therapy creates difficulties in implementing any neuromodulation treatment for those areas. Hence, posteroventral pallidotomy remains a good surgical option for those patients.

However, there may be a paradigm shift in the reality of the follow-up for DBS implanted patient. With the advent of software that allows us to make videoconferences and so on, it might be possible to reduce the need for dislocation and face-to-face consultations with specialized personnel [62–64]. Nonetheless, there is no way to predict how long this will become a reality, especially in places where the public health-care system lacks in funding and internal organization.

3.3. General anesthesia and major comorbidities

The selection criteria for a patient to perform Parkinson surgery must consider the presence and the degree of control of secondary diseases such as systemic hypertension, diabetes, renal impairment and other chronic comorbidities. Besides affecting primarily the elders, who are prone to have associated diseases, Parkinson's disease itself requires particular attention by the anesthesiologist, because of the drug interactions of levodopa treatment and related disturbances of the disease, such as gastric stasis, autonomic instability and respiratory dysfunction [65,66]. Hence, patients with poor clinical control and that cannot stand or do not wish to be submitted to a general anesthesia procedure, which is necessary for battery and cables placement in DBS surgery, a pallidotomy can be safely performed with local anesthesia.

Diabetes is a well-established risk factor for surgical infections and is often of the neurosurgeon's concern considering that hardware infection is the most common serious complication of DBS surgery, frequently leading to the explantation of the device [60]. Bathia et al. reported in his review that 84% of infected patients suffered comorbidities including diabetes, obesity, and smoking [67].

The studies about this subject, however, have not proven so far that diabetes is an isolated risk factor for device infection [51–53,68–70]. No large prospective study concerning that has been done so far. Therefore, diabetic patients can still be considered to be at risk for a hardware infection, especially when other comorbidities are also present, justifying the choice for PVP in diabetic patients, mainly when not stable from the glycemia standpoint.

Even though it is not clear if isolated comorbidities could be considered risk factors for complications after DBS implantation, the overall clinical status of the patient has proven to impact the rate of electrode revisions and removal. In a multiple database analysis performed by Rolston et al. [102], it was observed that in a total of 28370 DBS procedures, 15,4% were for removal or revision of previously implanted electrodes. Furthermore, it was found that a higher ASA classification, which indicates the surgical risk based on the patient's clinical status, positively correlated with a chance of having an electrode revision or removal surgery (OR 2.41; 95% CI: 1.22, 4.7).

3.4. Costs

It is complex to calculate the economic values related to Parkinson's disease. Most of the studies that focus on pharmacoeconomics do not evaluate the costs of other comorbidities and are performed in tertiary care centers. However, the financial impacts of non-pharmacological treatments are often neglected, resulting in limited studies. The overall expenditure for diagnostic procedures and hospitalization are not always available or are not evaluated along with other issues. It is worth mentioning that it is very likely that there are differences between different cultures and countries around the world concerning all types of costs, adding an extra difficulty in calculating costs in PD [71,103,104].

Aiming to evaluate the economic impact of Parkinson's disease on both healthcare provider and on individual basis, the costs can be divided into direct (health care resource use and drugs) and indirect (mortality costs, lost productivity and care replacement costs) [71]. When analyzing studies from six different countries (Germany, Austria, Portugal, Italy, Russia and Czech Republic), it is possible to observe that all of them resulted in high costs of the illness, with mean values of the total costs that ranged from €2620 (Russia) to €9820 (Austria) in a 6-months period [72–76]. Although there is a wide variation in these values, they all showed a direct relation between the severity of the disease and the costs generated by it.

In Brazil, the only study to describe in greater detail the expenses related to PD was conducted between 2003 and 2005 at two tertiary centers (Brasilia and Belo Horizonte) and it evaluated transversely 144 patients [105]. In consonance with the other studies, there was a higher cost of treatment in stages 3 and 4 Hoehn & Yahr (average expenditure of $207.1 per patient per month), while the lower was observed in steps 1 and 2 (on average $130.7 per patient per month). After the addition of pramipexole or entacapone to levodopa therapy, the monthly expenditure increased significantly ($ 224.4 and $277.9 respectively). The higher price of these products was the reason for the abandonment of treatment in 51% of patients with Parkinson's disease. The drugs used alone or in combination, have been levodopa (87, 5%) followed by amantadine (23.6%), pramipexole (20.8%) and non-antiparkinsonian drugs such as tricyclic antidepressants (18.8%). Along with the direct

costs, the study pointed several impacts to the economic and familial environment of the patients, including: retirement (72.9%) or momentary disconnection from the job (37,5%); moving to the house of relatives (7,6%); home adaptations to support disability (11,8%), and family members that temporarily left work to take care of the patient (16%).

In a different study, Findley et al. evaluated 428 patients in a prospective cohort study performed in the UK, correlating the direct costs of the disease with the Hoehn and Yahr scale (H & Y). Doing so, they were able to show a significant economic difference of mean annual costs between the initial and advanced patient, which ranged from to £2,971 (H & Y − 0 and I) to £18,358 (H & Y − V) (costs obtained in 1998) [77]. These values do not include the ones related to surgical procedures for PD, which can be considerably high.

Still, Green et al. analyzed the costs of bilateral and unilateral pallidotomy and concluded that both procedures are cost-effective [81]. Using the relationship between the H & Y stage of the patients and the direct costs of the illness, as stated by Findley et al. [77], they estimated the savings generated by reducing the severity of the disease and concluded that it would need less than 6 years for the procedure to pay itself. Moreover, in those patients with a higher H & Y scale, this time could be even shorter (less than 4 years for H & Y-V).

Considering that no large study has been conducted directly comparing the expenses of pallidotomy versus DBS for Parkinson's disease, we try here to give an insight of the initial costs of both procedures and correlate it with the impact of each procedure in the reduction of the motor symptoms of the disease.

The surgical materials used in PD's surgery include those from unilateral pallidotomy, unilateral and bilateral DBS (both rechargeable and non-rechargeable) − Table 1. Considering all the costs, for each bilateral rechargeable DBS implanted, it would be possible to buy material for 12 unilateral pallidotomies. Many variables are considered in this regard, such as the ones related to the healthcare professionals, complementary exams, and hospitalization as if they were the same for all of these procedures.

After comparing the improvement in the UPDRS-III score in *off* (without medication) between unilateral PVP and bilateral STN-DBS with the prices shown in Table 1, we determined the average costs of a 1% reduction in the score for each procedure (Table 3). In order to obtain the maximum and minimum value for a 1% *off*-phase UPDRS-III reduction by pallidotomy, the price of the material was divided by the percentage of the reduction found in the studies in Table 2a after 12–24 months' follow-up. The studies were selected based on the criteria: controlled clinical trial, prospective, randomized and blinded(single or double) [23,24,34,92–94]. Thus, we obtained a cost range from $89 to $110 (mean = $99,5) for 1% UPDRS-III decrease in *off*. In regard to STN-DBS, as there were two possibilities of materials (rechargeable and non-rechargeable), we found reasonable to include both as “STN-DBS”, and applied the same method used for pallidotomy for each material, with the percentage of motor symptoms reduction of the studies displayed in Table 2b. Since the values overlap each other, the cost range for a 1% reduction in *off*-phase UPDRS-III following STN-DBS was $561 to $1185 (mean = $873).

Doing so, we found that posteroventral pallidotomy is about 8,7 times ($873 from DBS divided by $99,5 from PVP) cheaper than STN-DBS on reducing the motor symptoms of PD. Therefore, despite the fact that DBS therapy has shown greater efficacy than PVP, this one also improves the patient's quality of life, not only reducing the motor symptoms but also improving the mood, functional and social disabilities generated by the disease, under lesser cost than DBS surgery [78–80].

Although STN-DBS is also considered to be a cost-effective procedure by several studies, most of them showed high initial costs, with values around $29,000 dollars in the first year [82–87]. Even though it may pay itself in the future, especially by reducing medication doses, patients who are not covered by private insurance or treated by a public health care system may not be able to get access to the DBS therapy due to the reasons mentioned above.

Table 1
Surgical material costs of unilateral pallidotomy, unilateral DBS implantation (rechargeable and nonrechargeable) and bilateral DBS implantation (rechargeable and nonrechargeable).*

Type of surgery	Total material costs (US Dollars)**	Materials included
Unilateral pallidotomy	$ 2,753 (R$ 11,100)	-Disposable DBS electrode kit with implanter
Unilateral DBS implantation (non-rechargeable)	$ 19,215 (R$ 77,479)	-Nonrechargeable Generator -Remote control -Cables -DBS electrode
Unilateral DBS implantation (rechargeable)	$ 31,243 (R$ 125,979)	-Rechargeable Generator -Remote control -Cables -DBS electrode -Recharge system
Bilateral DBS implantation (non-rechargeable)	$ 29,711 (R$ 119,804)	-Nonrechargeable Generator -Remote control -Cables -DBS electrode
Bilateral DBS implantation (rechargeable)	$ 35,553 (R$ 143,359)	-Rechargeable Generator -Remote control -Cables -DBS electrode -Recharge system

* Data provided by Zeiki Medical company.
** Local currency (Brazilian Real) was converted to US dollars at a rate of 1R$: $0,248 in 2015, with rounded-up values.

4. Discussion

An international survey done by Jourdain et al. [61] showed the discrepancy between what is published by the few centers specialized in Parkinson surgery from what is performed by the services worldwide. The results demonstrated that, by the year of 2009, 63% of the neurosurgeons still performed ablative procedures, even though only 7% of publications in that year were related to ablation techniques. It was also revealed that the most common source of surgery financing was the public health system. That is especially significant because they usually demand productivity and affordability from the procedures. Not to mention, being Parkinson's disease a common and prevalent disease, many countries are not able to finance their health care systems by using neuromodulation therapies, such as DBS surgery.

The results of this survey are possibly the scientific representation of concern already stated by Gross [17], De Long [18] and Hariz et al. [22], that pallidotomy is no longer being taught in functional neurosurgery specialization centers, meaning that the technique will eventually fall into oblivion. That would be reasonable if deep brain stimulation covered all the situations in which pallidotomy could be used, although we do know that this hypothetical scenario does not exist. Another possible consequence of the reduction of scientific interest in ablative procedures is that, with the continuous improvements in imaging and electrophysiological monitoring, the procedure itself could be improved.

Social factors also play a significant role in treatment received by PD patients. In a retrospective cohort study of 657,000 Medicare beneficiaries affected by the disease, Willis et al. found that blacks, Asians and those treated in minority-serving PD practices had significantly lower chances to receive a DBS treatment (blacks: AOR = 0.20, 95% CI = 0.16–0.25/Asians: AOR 0.55, 95% CI 0.44–0.7/minority-serving PD practices: AOR 0.76, 95% CI 0.66–0.87).

Inversely, patients living in a neighborhood with a high socioeconomic status (SES) index had a greater chance of receiving DBS

Table 2a
Randomized, single-blinded studies results of motor outcomes following unilateral posteroventral pallidotomy, measured by off phase UPDRS-III scale.

Author, year	Number of patients	Baseline off phase mean UPDRS III score	Off phase UPDRS III score in 6 months after PVP (% of reduction)*	Off phase UPDRS III score (% of reduction)/years of follow-up after PVP*
deBie et al. [23]	37	47	32,5 (30,8%)	no late follow-up
Vitek et al. [24]	36	43,3	28,7 (33,5%)	29,4 (25%) at 2 years*
Esselink et at. [34]	33	46,5	37 (20,4%)	32 (31,1%) at 1 year

* The percentage of reduction was calculated from a mean baseline value of 39,2 on the UPDRS III scale, recalculated according to the patients that remained in the follow-up period.

Table 2b
Randomized, single-blinded studies results of motor outcomes following bilateral STN-DBS, measured by off phase UPDRS III scale.

Author, year	Number of patients (intervention group)	Baseline off phase mean UPDRS III score	Off phase UPDRS III score in 6 months after PVP (% of reduction)	Off phase UPDRS III score (% of reduction)/ months of follow-up after PVP
Anderson et al. [94]	20	51	Not reported	27 (47%) at 12 months
Esselink et at. [34]	33	51,1	26,5 (47%)	24 (53%) at 12 months
Follet et al. [92]	299	43	29,9 (30,4%)	30,1 (30%) at 24 months
Odekerken et al. [93]	125	44,4	Not reported	24,1 (45%) at 12 months

Table 3
Comparison of the effectiveness of motor symptoms improvement and the surgical material costs between unilateral PVP and bilateral STN-DBS.

Type of procedure	Mean reduction in the off-UPDRS III score (%) in 12–24 months	Cost range per 1% reduction in the off-UPDRS III motor score ($) and mean value
Unilateral PVP [23,24,34]	25–31%	$89–$110 ($99,5)
Bilateral STN-DBS [34,92–94]	30–53%	$561–$1185 ($873)

(AOR 1.42, 95% CI 1.33–1.53) [88]. Although the reasons for these disparities could not be elucidated by the study, it is possible to conclude that DBS is not available to all patients that could benefit from it.

The public healthcare system in Brazil, contrasting with high-income countries, does not finance DBS implantation; therefore, the majority of our patients are limited to lesion therapy. When we compare the price of the procedures versus the functional outcome achieved, however, it is possible to realize that pallidotomy remains an efficient and safe therapeutic option. It is true not only for those patients that cannot afford health insurance or surgery but also for the ones that are unsuitable to perform a DBS surgery, such as HIV and immunocompromised patients, in the presence of major comorbidities, and those who are not able to be followed up on.

Furthermore, over the last decade, novel therapies have emerged using non-invasive stereotactic ablation of the basal ganglia, such as focused ultrasound [89,90] and stereotactic radiosurgery [91]. This modality of treatment is more established for essential tremor, with prospective studies showing symptomatic improvement in both techniques [95,96]. For PD, however, better results are being reported for focused ultrasound [97,98], with an additional safety of performing a pre-lesioning of the targeted area before thethermal coagulation is done, therefore reducing the risks of undesired side-effects. Although we have no clear data on the effectiveness of this method, the results of the on-going prospective studies may provide us the possibility of life-quality improvements similarly to open surgery techniques, but without its inextricable morbidity. That been said, one question that arises is: are the lesion therapies coming back? If so, why not indicate posteroventral pallidotomy anymore? If focused ultrasound and stereotactic radiosurgery have been used, why do we not use pallidotomy, an ablative procedure as the former ones? As previously mentioned,PVP is efficient, less time demanding than DBS surgery and less expensive.

It is important to mention that we are not saying that pallidotomy is superior than DBS surgery, but instead it represents more costs and it is not as feasible for all the patients around the world. Differently, we claim that we should try to adapt the type of surgical therapy to each country or place's reality and not to abandon PVP only because it represents a lesion and irreversible therapy. Instead, we should consider the decision making based on individual cases without abandoning a procedure with a real evidence level which is well established in medical literature.

5. Conclusion

DBS surgery is the surgical treatment of choice for Parkinson's disease. However, pallidotomy should not be abandoned as a therapeutic option for advanced PD. It relies majorly on the fact that it is a cost-effective, efficient and safe procedure that does not need a strict follow-up as DBS surgery does. Additionally, posteroventral pallidotomy carries lesser risks when certain comorbidities are also present, in comparison to DBS surgery. Altogether, we should still consider PVP as an available option in selected cases of Parkinson's disease.

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References

[1] L.M. de Lau, M.M. Breteler, Epidemiology of parkinson's disease, Lancet Neurol. 5 (6) (2006) 525–535, http://dx.doi.org/10.1016/S1474-4422(06)70471-9.
[2] M.T. Barbosa, P. Caramelli, D.P. Maia, M.C.Q. Cunningham, H.L. Guerra, M.F. Lima-Costa, et al., Parkinsonism and Parkinson's disease in the elderly: a community-based survey in Brazil (the Bambuí study), Mov. Disord. 21 (6) (2006) 800–808, http://dx.doi.org/10.1002/mds.20806.
[3] K. Whetten-Goldstein, F. Sloan, E. Kulas, T. Cutson, M. Schenkman, The burden of Parkinson's disease on society, family, and the individual, J. Am. Geriatr. Soc. 45 (7) (1997) 844–849, http://dx.doi.org/10.1111/j.1532-5415.1997.tb01512.x.
[4] E.A. Chrischilles, L.M. Rubenstein, M.D. Voelker, R.B. Wallace, R.L. Rodnitzky, The health burdens of Parkinson's disease, Mov. Disord. 13 (3) (1998) 406–413, http://dx.doi.org/10.1002/mds.870130306.
[5] M. Coelho, M.J. Marti, E. Tolosa, J.J. Ferreira, F. Valldeoriola, M. Rosa, et al., Late-stage parkinson's disease: the Barcelona and Lisbon cohort, J. Neurol. 257 (9) (2010) 1524–1532, http://dx.doi.org/10.1007/s00415-010-5566-8.
[6] A. Park, M. Stacy, Disease-modifying drugs in parkinson's disease, Drugs 75 (18) (2015) 2065–2071, http://dx.doi.org/10.1007/s40265-015-0497-4.
[7] P.C. Bucy, T.J. Case, Tremor physiologic mechanism and abolition by surgical means, Arch. Neurol. Psychiatry 41 (4) (1939) 721.
[8] R. Meyers, The modification of alternating tremors, rigidity and festination by surgery of the basal ganglia, Res. Publ. Assoc. Res. Nerv. Ment. Dis. 21 (6) (1942)

02–665.
[9] I.S. Cooper, Ligation of the anterior choroidal artery for involuntary movements-parkinsonism, Psychiatr. Q. 27 (1–4) (1953) 317–319, http://dx.doi.org/10.1007/BF01562492.
[10] I.S. Cooper, Intracerebral injection of procaine into the globus pallidus in hyperkinetic disorders, Science 119 (3091) (1954) 417–418, http://dx.doi.org/10.1126/science.119.3091.417.
[11] J. Guridi, A.M. Lozano, A brief history of pallidotomy, Neurosurgery 41 (5) (1997) 1169–1183, http://dx.doi.org/10.1097/00006123-199711000-00029.
[12] M.S. Okun, J.L. Vitek, Lesion therapy for Parkinson's disease and other movement disorders: update and controversies, Mov. Disord. 19 (4) (2004) 375–389, http://dx.doi.org/10.1002/mds.20037.
[13] E. Svennilson, A. Torvik, R. Lowe, L. Leksell, Treatment of parkinsonism by stereotactic thermolesions in the pallidal region. A clinical evaluation of 81 cases, Acta Psychiatr. Scand. 35 (3) (1960) 358–377, http://dx.doi.org/10.1111/j.1600-0447.1960.tb07606.x.
[14] L.V. Laitinen, A.T. Bergenheim, M.I. Hariz, Leksell's posteroventral pallidotomy in the treatment of Parkinson's disease, J. Neurosurg. 76 (1) (1992) 53–61, http://dx.doi.org/10.3171/jns.1992.76.1.0053.
[15] L. Laitinen, A. Bergenheim, M. Hariz, Ventroposterolateral pallidotomy can abolish all parkinsonian symptoms, Stereotact. Funct. Neurosurg. 58 (1–4) (1992) 14–21, http://dx.doi.org/10.1159/000098965.
[16] A.L. Benabid, P. Pollak, D. Gao, D. Hoffmann, P. Limousin, E. Gay, et al., Chronic electrical stimulation of the ventralis intermedius nucleus of the thalamus as a treatment of movement disorders, J. Neurosurg. 84 (2) (1996) 203–214, http://dx.doi.org/10.3171/jns.1996.84.2.0203.
[17] R.E. Gross, What happened to posteroventral pallidotomy for Parkinson's disease and dystonia? Neurotherapeutics 5 (2) (2008) 281–293, http://dx.doi.org/10.1016/j.nurt.2008.02.001.
[18] M. Delong, Why pallidotomy should not be abandoned, Mov. Along 3 (2001) 3.
[19] A. Benabid, Why should we abandon pallidotomy, Mov. Along 3 (2001) 3–5.
[20] M.I. Hariz, Pallidotomy for Parkinson's disease, in: A.M. Lozano, P.L. Gildenberg, R.R. Tasker (Eds.), Textbook of Stereotactic and Functional Neurosurgery, Springer, Berlin, Heidelberg, 2009, pp. 1539–1548.
[21] D.E. Lumsden, Pallidotomy in the 21st century, Dev. Med. Child Neurol. 56 (7) (2014) 607–608, http://dx.doi.org/10.1111/dmcn.12414.
[22] M.I. Hariz, G.-M. Hariz, Therapeutic stimulation versus ablation, Handb. Clin. Neurol. 116 (2013) 63–71, http://dx.doi.org/10.1016/B978-0-444-53497-2.
[23] R.M. de Bie, R.J. de Haan, P.C. Nijssen, A.W.F. Rutgers, G.N. Beute, D.A. Bosch, et al., Unilateral pallidotomy in Parkinson's disease: a randomised, single-blind, multicentre trial, Lancet 354 (9191) (1999) 1665–1669, http://dx.doi.org/10.1016/S0140-6736(99)03556-4.
[24] J.L. Vitek, R.A. Bakay, A. Freeman, M. Evatt, J. Green, W. McDonald, et al., Randomized trial of pallidotomy versus medical therapy for Parkinson's disease, Ann. Neurol. 53 (5) (2003) 558–569, http://dx.doi.org/10.1002/ana.10517.
[25] I.M. Germano, J.-M. Gracies, D.J. Weisz, W. Tse, W.C. Koller, C.W. Olanow, Unilateral stimulation of the subthalamic nucleus in Parkinson disease: a double-blind 12-month evaluation study, J. Neurosurg. 101 (1) (2004) 36–42, http://dx.doi.org/10.3171/jns.2004.101.1.0036.
[26] K. Nakamura, C.W. Christine, P.A. Starr, W.J. Marks, Effects of unilateral subthalamic and pallidal deep brain stimulation on fine motor functions in Parkinson's disease, Mov. Disord. 22 (5) (2007) 619–626, http://dx.doi.org/10.1002/mds.21300.
[27] J.L. Slowinski, J.D. Putzke, R.J. Uitti, J.A. Lucas, M.F. Turk, B.A. Kall, et al., Unilateral deep brain stimulation of the subthalamic nucleus for Parkinson disease, J. Neurosurg. 106 (4) (2007) 626–632, http://dx.doi.org/10.3171/jns.2007.106.4.626.
[28] F. Jiménez, F. Velasco, J.D. Carrillo-Ruiz, L. Garcia, A. Madrigal, A.L. Velasco, et al., Comparative evaluation of the effects of unilateral lesion versus electrical stimulation of the globus pallidus internus in advanced Parkinson's disease, Stereotact. Funct. Neurosurg. 84 (2–3) (2006) 64–71, http://dx.doi.org/10.1159/000094034.
[29] M. Merello, M.I. Nouzeilles, G. Kuzis, A. Cammarota, L. Sabe, O. Betti, et al., Unilateral radiofrequency lesion versus electrostimulation of posteroventral pallidum: a prospective randomized comparison, Mov. Disord. 14 (1) (1999) 50–56, http://dx.doi.org/10.1002/1531-8257(199901)14:13.0.CO;2-6.
[30] X. Zhu, D.T. Chan, C.K. Lau, W.S. Poon, V.C. Mok, A.Y. Chan, et al., Cost-effectiveness of subthalmic nucleus deep brain stimulation for the treatment of advanced Parkinson disease in Hong Kong: a prospective study, World Neurosurg. 82 (6) (2014) 987–993, http://dx.doi.org/10.1016/j.wneu.2014.08.051.
[31] P. Pollak, Deep brain stimulation for Parkinson's disease – patient selection, Handb. Clin. Neurol. 116 (2013) 97–105, http://dx.doi.org/10.1016/B978-0-444-53497-2.00009-7.
[32] A. Alkhani, A.M. Lozano, Pallidotomy for Parkinson disease: a review of contemporary literature, J. Neurosurg. 94 (1) (2001) 43–49, http://dx.doi.org/10.3171/jns.2001.94.1.0043.
[33] R. Esselink, R. De Bie, R. De Haan, M. Lenders, P. Nijssen, M. Staal, et al., Unilateral pallidotomy versus bilateral subthalamic nucleus stimulation in PD A randomizedtrial, Neurology 62 (2) (2004) 201–207, http://dx.doi.org/10.1212/01.WNL.0000103235.12621.C3.
[34] R. Esselink, R. de Bie, R. De Haan, E. Steur, G. Beute, A. Portman, et al., Unilateral pallidotomy versus bilateral subthalamic nucleus stimulation in Parkinson's disease: one year follow-up of a randomised observer-blind multi centre trial, Acta Neurochir. 148 (12) (2006) 1247–1255, http://dx.doi.org/10.1007/s00701-006-0907-1.
[35] M.C. Rodriguez-Oroz, E. Moro, P. Krack, Long-term outcomes of surgical therapies for Parkinson's disease, Mov. Disord. 27 (14) (2012) 1718–1728, http://dx.doi.org/10.1002/mds.25214.
[36] J. Fine, J. Duff, R. Chen, W. Hutchison, A.M. Lozano, A.E. Lang, Long-term follow-up of unilateral pallidotomy in advanced Parkinson's disease, N. Engl. J. Med. 342 (23) (2000) 1708–1714, http://dx.doi.org/10.1056/NEJM200006083422304.
[37] A.M. Strutt, E.C. Lai, J. Jankovic, F. Atassi, E.M. Soety, H.S. Levin, et al., Five-year follow-up of unilateral posteroventral pallidotomy in Parkinson's disease, Surg. Neurol. 71 (5) (2009) 551–558, http://dx.doi.org/10.1016/j.surneu.2008.03.039.
[38] M.I. Hariz, A.T. Bergenheim, A 10-year follow-up review of patients who underwent Leksell's posteroventral pallidotomy for Parkinson disease, J. Neurosurg. 94 (4) (2001) 552–558, http://dx.doi.org/10.3171/jns.2001.94.4.0552.
[39] A. Samii, V.E. Kelly, J.C. Slimp, A. Shumway-Cook, R. Goodkin, Staged unilateral versus bilateral subthalamic nucleus stimulator implantation in Parkinson disease, Mov. Disord. 22 (10) (2007) 1476–1481, http://dx.doi.org/10.1002/mds.21554.
[40] M. Merello, S. Starkstein, M. Nouzeilles, G. Kuzis, R. Leiguarda, Bilateral pallidotomy for treatment of Parkinson's disease induced corticobulbar syndrome and psychic akinesia avoidable by globus pallidus lesion combined with contralateral stimulation, J. Neurol. Neurosurg. Psychiatry 71 (5) (2001) 611–614, http://dx.doi.org/10.1136/jnnp.71.5.611.
[41] M.K. York, E. Lai, J. Jankovic, A. Macias, F. Atassi, H. Levin, et al., Short and long-term motor and cognitive outcome of staged bilateral pallidotomy: a retrospective analysis, Acta Neurochir. 149 (9) (2007) 857–866, http://dx.doi.org/10.1007/s00701-007-1242-x.
[42] Z. Hua, G. Guodong, L. Qinchuan, Z. Yaqun, W. Qinfen, W. Xuelian, Analysis of complications of radiofrequency pallidotomy, Neurosurgery 52 (1) (2003) 89–101, http://dx.doi.org/10.1097/00006123-200301000-00011.
[43] A. Castrioto, A.M. Lozano, Y.-Y. Poon, A.E. Lang, M. Fallis, E. Moro, Ten-year outcome of subthalamic stimulation in Parkinson disease: a blinded evaluation, Arch. Neurol. 68 (12) (2011) 1550–1556, http://dx.doi.org/10.1001/archneurol.2011.182.
[44] M. Zibetti, A. Merola, L. Rizzi, V. Ricchi, S. Angrisano, C. Azzaro, et al., Beyond nine years of continuous subthalamic nucleus deep brain stimulation in Parkinson's disease, Mov. Disord. 26 (13) (2011) 2327–2334, http://dx.doi.org/10.1002/mds.23903.
[45] P.R. Schuurman, D.A. Bosch, M.P. Merkus, J.D. Speelman, Long-term follow-up of thalamic stimulation versus thalamotomy for tremor suppression, Mov. Disord. 23 (8) (2008) 1146–1153, http://dx.doi.org/10.1002/mds.22059.
[46] S.H. Fox, R. Katzenschlager, S.Y. Lim, B. Ravina, K. Seppi, M. Coelho, et al., The movement disorder society evidence-based medicine review update: treatments for the motor symptoms of parkinson's disease, Mov. Disord. 26 (S 3) (2011) S2–S41, http://dx.doi.org/10.1002/mds.23829.
[47] V.A. Jourdain, G. Schechtmann, T. Di Paolo, Subthalamotomy in the treatment of Parkinson's disease: clinical aspects and mechanisms of action: a review, J. Neurosurg. 120 (1) (2014) 140–151, http://dx.doi.org/10.3171/2013.10.JNS13332.
[48] A. Coban, H. Hanagasi, S. Karamursel, O. Barlas, Comparison of unilateral pallidotomy and subthalamotomy findings in advanced idiopathic Parkinson's disease, Br. J. Neurosurg. 23 (1) (2009) 23–29, http://dx.doi.org/10.1080/02688690802507775.
[49] L. Alvarez, R. Macias, N. Pavon, G. López, M.C. Rodríguez-Oroz, R. Rodríguez, et al., Therapeutic efficacy of unilateral subthalamotomy in Parkinson's disease: results in 89 patients followed for up to 36 months, J. Neurol. Neurosurg. Psychiatry 80 (9) (2009) 979–985, http://dx.doi.org/10.1136/jnnp.2008.154948.
[50] P. Blomstedt, M.I. Hariz, Are complications less common in deep brain stimulation than in ablative procedures for movement disorders? Stereotact. Funct. Neurosurg. 84 (2–3) (2006) 72–81, http://dx.doi.org/10.1159/000094035.
[51] P. Doshi, Long-term surgical and hardware-related complications of deep brain stimulation, Stereotact. Funct. Neurosurg. 89 (2) (2011) 89–95, http://dx.doi.org/10.1159/000323372.
[52] M.Y. Oh, A. Abosch, S.H. Kim, A.E. Lang, A.M. Lozano, Long-term hardware-related complications of deep brain stimulation, Neurosurgery 50 (6) (2002) 1268–1276, http://dx.doi.org/10.1159/000323372.
[53] J. Voges, Y. Waerzeggers, M. Maarouf, R. Lehrke, A. Koulousakis, D. Lenartz, et al., Deep-brain stimulation: long-term analysis of complications caused by hardware and surgery—experiences from a single centre, J. Neurol. Neurosurg. Psychiatry 77 (7) (2006) 868–872, http://dx.doi.org/10.1136/jnnp.2005.081232.
[54] D. Caparros-Lefebvre, A. Lannuzel, F. Tiberghien, M. Strobel, Protease inhibitors enhance levodopa effects in Parkinson's disease, Mov. Disord. 14 (3) (1999), http://dx.doi.org/10.1002/1531-8257(199905)14:3<535:AID-MDS1034>3.0.CO;2-S.
[55] M.F. Gago, M.J. Rosas, P. Linhares, J. Massano, A. Sarmento, R. Vaz, Deep brain stimulation of the subthalamic nucleus for Parkinson's disease in a patient with HIV infection: dual clinical benefit, Case Rep. Neurol. 3 (3) (2011) 219–222, http://dx.doi.org/10.1159/000332610.
[56] S. Hettige, M. Samuel, C. Clough, N. Hulse, K. Ashkan, Deep brain stimulation for Parkinson's disease when HIV coexists, Mov. Disord. 24 (14) (2009) 2169–2171, http://dx.doi.org/10.1002/mds.22766.
[57] A.K. Hooper, M.S. Okun, K.D. Foote, H.H. Fernandez, C. Jacobson, P. Zeilman, et al., Clinical cases where lesion therapy was chosen over deep brain stimulation, Stereotact. Funct. Neurosurg. 86 (3) (2008) 147–152, http://dx.doi.org/10.1159/000120426.
[58] F.P.G. Messina, M.R.A. Franzini, DBS for Parkinson's disease in a HIV-positive patient: long-term follow-up, Acta Neurochir. 156 (2014) 1513–1514, http://dx.doi.org/10.1007/s00701-014-2091-z.
[59] A. Samii, J.C. Slimp, P.J. Hogan Iii, R. Goodkin, Deep brain stimulation in a patient on immunosuppressive therapy after renal transplant, Parkinsonism Relat. Disord. 11 (4) (2005) 259–260, http://dx.doi.org/10.1016/j.parkreldis.2004.11.002.
[60] J.M. Bronstein, M. Tagliati, R.L. Alterman, A.M. Lozano, J. Volkmann, A. Stefani, et al., Deep brain stimulation for Parkinson disease: an expert consensus and review of key issues, Arch. Neurol. 68 (2) (2011) 165-, http://dx.doi.org/10.1001/archneurol.2010.260.
[61] V.A. Jourdain, G. Schechtmann, Health economics and surgical treatment for Parkinson's disease in a world perspective: results from an international survey, Stereotact. Funct. Neurosurg. 92 (2) (2014) 71–79, http://dx.doi.org/10.1159/000355215.

[62] Y. Chen, H. Hao, H. Chen, L. Li, The study on a telemedicine interaction mode for Deep Brain Stimulation postoperative follow-up, 2015 37th Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC) [Internet], IEEE (2015) 186–189. [cited 2016 Oct 16] Available from: http://ieeexplore.ieee.org/xpls/abs_all.jsp?arnumber=7318331. 10.1109/EMBC. 2015.7318331.
[63] S. Marceglia, E. Rossi, M. Rosa, F. Cogiamanian, L. Rossi, L. Bertolasi, et al., Web-based telemonitoring and delivery of caregiver support for patients with Parkinson disease after deep brain stimulation: protocol, JMIR Res. Protoc. 4 (1) (2015) e30, http://dx.doi.org/10.2196/resprot.4044.
[64] A. Priori, Technology for deep brain stimulation at a gallop, Mov. Disord. 30 (9) (2015) 1206–1212, http://dx.doi.org/10.1002/mds.26253.
[65] S.I. Shaikh, H. Verma, Parkinson's disease and anaesthesia, Indian J. Anaesth. 55 (3) (2011) 228, http://dx.doi.org/10.4103/0019-5049.82658.
[66] L.J. Mason, T.T. Cojocaru, D.J. Cole, Surgical intervention and anesthetic management of the patient with Parkinson's disease, Int. Anesthesiol. Clin. 34 (4) (1996) 133–150, http://dx.doi.org/10.1097/00004311-199603440-00010.
[67] S. Bhatia, K. Zhang, M. Oh, C. Angle, D. Whiting, Infections and hardware salvage after deep brain stimulation surgery: a single-center study and review of the literature, Stereotact. Funct. Neurosurg. 88 (3) (2010) 147–155, http://dx.doi.org/10.1159/000303528.
[68] P. Kalakoti, O. Ahmed, P. Bollam, S. Missios, J. Wilden, A. Nanda, Predictors of unfavorable outcomes following deep brain stimulation for movement disorders and the effect of hospital case volume on outcomes: an analysis of 33, 642 patients across 234 US hospitals using the National (Nationwide) Inpatient Sample from 2002 to 2011, Neurosurg. Focus 38 (6) (2015) E4, http://dx.doi.org/10.3171/2015.3.FOCUS1547.
[69] K.A. Sillay, P.S. Larson, P.A. Starr, Deep brain stimulator hardware-related infections: incidence and management in a large series, Neurosurgery 62 (2) (2008) 360–367, http://dx.doi.org/10.1227/01.neu.0000316002.03765.33.
[70] F. Sixel-Döring, C. Trenkwalder, C. Kappus, D. Hellwig, Skin complications in deep brain stimulation for Parkinson's disease: frequency, time course, and risk factors, Acta Neurochir. 152 (2) (2010) 195–200, http://dx.doi.org/10.1007/s00701-009-0490-3.
[71] L.J. Findley, The economic impact of Parkinson's disease, Parkinsonism Relat. Disord. 13 (2007) S8–S12, http://dx.doi.org/10.1016/j.parkreldis.2007.06.003.
[72] Y. Winter, S. Von Campenhausen, J.P. Reese, M. Balzer-Geldsetzer, K. Longo, G. Spiga, et al., Costs of Parkinson's disease and antiparkinsonian pharmacotherapy: an Italian cohort study, Neurodegener. Dis. 7 (6) (2010) 365–372, http://dx.doi.org/10.1159/000302644.
[73] A.E. Spottke, M. Reuter, O. Machat, B. Bornschein, S. von Campenhausen, K. Berger, et al., Cost of illness and its predictors for Parkinson's disease in Germany, Pharmacoeconomics 23 (8) (2005) 817–836, http://dx.doi.org/10.2165/00019053-200523080-00007.
[74] Y. Winter, S. von Campenhausen, G. Popov, J.P. Reese, J. Klotsche, K. Bötzel, et al., Costs of illness in a Russian cohort of patients with Parkinsonös disease, Pharmacoeconomics 27 (7) (2009) 571–584, http://dx.doi.org/10.2165/11310160-000000000-00000.
[75] Y. Winter, S. von Campenhausen, H. Brozova, J. Skoupa, J.P. Reese, K. Bötzel, et al., Costs of Parkinson's disease in eastern Europe: a Czech cohort study, Parkinsonism Relat. Disord. 16 (1) (2010) 51–56, http://dx.doi.org/10.1016/j.parkreldis.2009.07.005.
[76] S. von Campenhausen, Y. Winter, A.R. e Silva, C. Sampaio, E. Ruzicka, P. Barone, et al., Costs of illness and care in Parkinson's disease: an evaluation in six countries, Eur. Neuropsychopharmacol. 21 (2) (2011) 180–191, http://dx.doi.org/10.1016/j.euroneuro.2010.08.002.
[77] L. Findley, M. Aujla, P.G. Bain, M. Baker, C. Beech, C. Bowman, et al., Direct economic impact of Parkinson's disease: a research survey in the United Kingdom, Mov. Disord. 18 (10) (2003) 1139–1145, http://dx.doi.org/10.1002/mds.10507.
[78] K. Straits-Tröster, J.A. Fields, S.B. Wilkinson, R. Pahwa, K.E. Lyons, W.C. Koller, et al., Health-related quality of life in Parkinson's disease after pallidotomy and deep brain stimulation, Brain Cogn. 42 (3) (2000) 399–416, http://dx.doi.org/10.1006/brcg.1999.1112.
[79] G. Zimmerman, L. D'Antonio, R. Iacono, Health related quality of life in patients with Parkinson's disease two years following posteroventral pallidotomy, Acta Neurochir. 146 (12) (2004) 1293–1299, http://dx.doi.org/10.1007/s00701-004-0385-2.
[80] P. Martinez-Martin, G. Deuschl, Effect of medical and surgical interventions on health-related quality of life in Parkinson's disease, Mov. Disord. 22 (6) (2007) 757–765, http://dx.doi.org/10.1002/mds.21407.
[81] A. Green, C. Joint, H. Sethi, P. Bain, T. Aziz, Cost analysis of unilateral and bilateral pallidotomy for Parkinson's disease, J. Clin. Neurosci. 11 (8) (2004) 829–834, http://dx.doi.org/10.1016/j.jocn.2004.03.007.
[82] J.E. Becerra, O. Zorro, R. Ruiz-Gaviria, C. Castañeda-Cardona, M. Otálora-Esteban, S. Henao, et al., Economic analysis of deep brain stimulation in parkinson disease: systematic review of the literature, World Neurosurg. 93 (September) (2016) 44–49, http://dx.doi.org/10.1016/j.wneu.2016.05.028.
[83] F. Valldeoriola, J. Puig-Junoy, R. Puig-Peiró, Cost analysis of the treatments for patients with advanced Parkinson's disease: SCOPE study, J. Med. Econ. 16 (2) (2013) 191–201, http://dx.doi.org/10.3111/13696998.2012.737392.
[84] E. McIntosh, A. Gray, J. Daniels, S. Gill, N. Ives, C. Jenkinson, et al., Cost-utility analysis of deep brain stimulation surgery plus best medical therapy versus best medical therapy in patients with Parkinson's: economic evaluation alongside the PD SURG trial: economic Evaluation Alongside The PD Surg Trial, Mov. Disord. 31 (August (8)) (2016) 1173–1182, http://dx.doi.org/10.1002/mds.26423.
[85] K.T. Stroupe, F.M. Weaver, L. Cao, D. Ippolito, B.R. Barton, I.E. Burnett-Zeigler, et al., Cost of deep brain stimulation for the treatment of Parkinson's disease by surgical stimulation sites, Mov. Disord. 29 (13) (2014) 1666–1674, http://dx.doi.org/10.1002/mds.26029.
[86] S. Eggington, F. Valldeoriola, K.R. Chaudhuri, K. Ashkan, E. Annoni, G. Deuschl, The cost-effectiveness of deep brain stimulation in combination with best medical therapy, versus best medical therapy alone, in advanced Parkinson's disease, J. Neurol. 261 (1) (2014) 106–116, http://dx.doi.org/10.1007/s00415-013-7148-z.
[87] J. Dams, U. Siebert, B. Bornschein, J. Volkmann, G. Deuschl, W.H. Oertel, et al., Cost-effectiveness of deep brain stimulation in patients with Parkinson's disease, Mov. Disord. 28 (6) (2013) 763–771, http://dx.doi.org/10.1002/mds.25407.
[88] A.W. Willis, M. Schootman, N. Kung, X.-Y. Wang, J.S. Perlmutter, B.A. Racette, Disparities in deep brain stimulation surgery among insured elders with Parkinson disease, Neurology 82 (2) (2014) 163–171, http://dx.doi.org/10.1212/WNL.0000000000000974.
[89] P.P. Dobrakowski, A.K. Machowska-Majchrzak, B. Łabuz-Roszak, K.G. Majchrzak, E. Kluczewska, K.B. Pierzchała, MR-guided focused ultrasound: a new generation treatment of Parkinson's disease, essential tremor and neuropathic pain, Interv. Neuroradiol. 20 (3) (2014) 275–282, http://dx.doi.org/10.15274/INR-2014-10033.
[90] D. Weintraub, W.J. Elias, The emerging role of transcranial magnetic resonance imaging-guided focused ultrasound in functional neurosurgery: MRI-Guided Focused Ultrasound, Mov. Disord. 32 (1) (2017) 20–27, http://dx.doi.org/10.1002/mds.26599.
[91] G.M. Friehs, M.C. Park, M.A. Goldman, V.A. Zerris, G. Norén, P. Sampath, Stereotactic radiosurgery for functional disorders, Neurosug. Focus 23 (6) (2007) E3, http://dx.doi.org/10.3171/FOC-07/12/E3.
[92] K.A. Follett, F.M. Weaver, M. Stern, K. Hur, C.L. Harris, P. Luo, et al., Pallidal versus subthalamic deep-brain stimulation for Parkinson's disease, N. Engl. J. Med. 362 (22) (2010), http://dx.doi.org/10.1056/NEJMoa0907083 2077-91.94.
[93] V.J. Odekerken, T. van Laar, M.J. Staal, et al., Subthalamic nucleus versus globus pallidus bilateral deep brain stimulation for advanced Parkinson's disease (NSTAPS study): a randomised controlled trial, Lancet Neurol. 12 (1) (2013) 37–44, http://dx.doi.org/10.1016/S1474-4422(12)70264-8.
[94] V.C. Anderson, K.J. Burchiel, P. Hogarth, J. Favre, J.P. Hammerstad, Pallidal vs subthalamic nucleus deep brain stimulation in Parkinson disease, Arch. Neurol. 62 (4) (2005) 554–560, http://dx.doi.org/10.1001/archneur.62.4.554.
[95] W.J. Elias, N. Lipsman, W.G. Ondo, P. Ghanouni, Y.G. Kim, W. Lee, et al., A randomized trial of focused ultrasound thalamotomy for essential tremor, N. Engl. J. Med. 375 (8) (2016) 730–739, http://dx.doi.org/10.1056/NEJMoa1600159.
[96] T. Witjas, R. Carron, P. Krack, A. Eusebio, M. Vaugoyeau, M. Hariz, et al., A prospective single-blind study of Gamma Knife thalamotomy for tremor, Neurology 85 (18) (2015) 1562–1568, http://dx.doi.org/10.1212/WNL.0000000000002087.
[97] A. Magara, R. Bühler, D. Moser, M. Kowalski, P. Pourtehrani, D. Jeanmonod, First experience with MR-guided focused ultrasound in the treatment of Parkinson's disease, J. Ther. Ultrasound 2 (1) (2014) 11, http://dx.doi.org/10.1186/2050-5736-2-11.
[98] Y.C. Na, W.S. Chang, H.H. Jung, E.J. Kweon, J.W. Chang, Unilateral magnetic resonance–guided focused ultrasound pallidotomy for Parkinson disease, Neurology 85 (6) (2015) 549–551, http://dx.doi.org/10.1212/WNL.0000000000001826.
[99] Schüpbach, J. Rau, J.-L. Houeto, P. Krack, A. Schnitzler, C. Schade-Brittinger, et al., Myths and facts about the EARLYSTIM study: myths and facts about the earlystim study, Mov. Disord. 29 (14) (2014) 1742–1750, http://dx.doi.org/10.1002/mds.26080.
[100] T.A. Mestre, A.J. Espay, C. Marras, M.H. Eckman, P. Pollak, A.E. Lang, Subthalamic nucleus-deep brain stimulation for early motor complications in Parkinson's disease-the EARLYSTIM trial: early is not always better: STN-DBS for early motor complications in PD, Mov. Disord. 29 (14) (2014) 1751–1756, http://dx.doi.org/10.1002/mds.26024.
[101] W.M.M. Schuepbach, J. Rau, K. Knudsen, J. Volkmann, P. Krack, L. Timmermann, et al., Neurostimulation for Parkinson's disease with early motor complications, N. Engl. J. Med. 368 (7) (2013) 610–622, http://dx.doi.org/10.1056/NEJMoa1205158.
[102] J.D. Rolston, D.J. Englot, P.A. Starr, P.S. Larson, An unexpectedly high rate of revisions and removals in deep brain stimulation surgery: analysis of multiple databases, Parkinsonism Relat. Disord. 33 (2016) 72–77, http://dx.doi.org/10.1016/j.parkreldis.2016.09.014.
[103] C. Canivet, N. Costa, F. Ory-Magne, C. Arcari, C. Mohara, L. Pourcel, et al., Clinical impact and cost-effectiveness of an education program for PD patients: a randomized controlled trial. Fasano A, editor, PLoS One 11 (9) (2016) e0162646, http://dx.doi.org/10.1371/journal.pone.0162646.
[104] D. Safarpour, D.P. Thibault, C.L. DeSanto, C.M. Boyd, E.R. Dorsey, B.A. Racette, et al., Nursing home and end-of-life care in Parkinson disease, Neurology 85 (5) (2015) 413–419, http://dx.doi.org/10.1212/WNL.0000000000001715.
[105] A.P. Vargas, A.P. Vargas, F.J. Carod-Artal, S.V. Nunes, M. Melo, Disability and use of healthcare resources in Brazilian patients with Parkinson's disease, Disabil. Rehabil. 30 (14) (2008) 1055–1062, http://dx.doi.org/10.1080/17483100701456079.