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Technology Assessment Program

Report No. 8

Stereotactic Pallidotomy for Treatment of Parkinson's Disease

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EXECUTIVE SUMMARY

Purpose

This MDRC Technology Assessment (TA) Program report was written in response to a request by VISN 9 for guidance from the Technology Recommendations Panel (TRP) on the effectiveness and appropriateness of stereotactic pallidotomy for the treatment of Parkinson's disease.

Consultants from TEMINEX\The HMO Group Site, HAYES, Inc. were commissioned to produce the report. Additions and edits to the report were made by the MDRC. The conclusions reflect the opinions of the MDRC, and not necessarily those of the consultants.

Background

Parkinson's disease (PD) is a progressive neurodegenerative disorder of unknown etiology that currently affects about one million Americans. Onset is usually age 50 or later with frequency increasing with age until it peaks at about age 70 years. PD is characterized by slow degeneration of the dopaminergic neurons of the nigrostriatal pathway and associated decrease in striatal concentration of the neurotransmitter dopamine. Clinically, PD is characterized by resting tremor, bradykinesia, rigidity, and impaired postural reflexes; the so-called "cardinal signs." Advanced stage PD brings dementia and death.

Pallidotomy is neurosurgical ablation of part or all of the globus pallidus. The theoretical rationale is that pallidotomy improves the function of motor inhibitory circuits in medically refractory PD patients by destroying overactive regions responsible for excessive inhibitory activity and restoring balance of neuronal activity in direct and indirect pathways. Pallidotomy was frequently performed in the 1940s and 1950s, but was largely abandoned with the introduction of levodopa in the 1960s and the advent of ventrolateral thalamotomy.

Pharmacologic management with dopamine replacement therapy continues to be the primary treatment for PD. A majority of levodopa sensitive PD patients manifest diminished response to therapy after 5 to 10 years. The emergence of a new "post-levodopa" subset of aging PD patients with advanced, refractory disease and severe levodopa-induced dyskinesia has renewed interest in posteroventral pallidotomy as treatment for this specific patient group.

Key Findings

Regulation

Pallidotomy is a surgical procedure and not subject to regulation by the Food and Drug Administration (FDA). The Health Care Financing Administration (HCFA) does not have a national coverage exclusion policy on pallidotomy.

Cost and reimbursement

No studies offering cost estimates or information on insurance coverage for the procedure were found.

Pallidotomy

Issues regarding techniques for electrophysiological localization of the precise target in the posteroventral globus pallidus and optimal patient selection remain unresolved. No studies in the published literature comparing outcomes after pallidotomy with and without mapping were identified. The neurosurgical community is divided on the benefits and risks of microelectrode mapping.

Prevailing data, derived exclusively from case series, suggest that pallidotomy ameliorates drug-induced dyskinesias and significantly improves PD symptoms without mortality or significant morbidity. However, all the studies have methodological limitations. No large scale randomized controlled trials have been conducted to substantiate the efficacy of pallidotomy. The reported benefits of pallidotomy are weakened by the overall limited nature of the available evidence.

High frequency stimulation
Alternative surgical treatments for PD are being developed. High-frequency stimulation of the globus pallidus is under current clinical investigation and may be an alternative to pallidotomy. The data are preliminary, and conflicting results have been reported. At this time, no conclusions can be reached as to the benefits, risks and potential of this technology.

Conclusions/Discussion
A systematic review of pallidotomy was published by the Health Care Technology Assessment (HCTA) Unit of the Alberta Heritage Foundation for Medical Research in Canada in January of 1997. This report concluded that while several trials reported relief of symptoms of PD and strong anecdotal evidence by patients of improved quality of life, the quality of the evidence was fair to poor with few data on long term outcomes. The HCTA Unit recommended that the procedure be performed in specialized centers that have both neurological and neurosurgical expertise. They also stressed the need for improved systematic data collection and comparative studies of pallidotomy versus alternative therapies.

The MDRC review includes more recent data from 1997. **The prevailing evidence is insufficient to conclude that the benefits of pallidotomy outweigh the risks for the patients represented in the literature.** This review confirms that the conclusions and recommendations from the Alberta review are durable.

A randomized, prospective cooperative trial in 15 VAMCs has been approved for planning by the Office of Research and Development, with the first of two planning meetings to take place in May of 1998. The trial will compare the efficacies, safety, and costs of pallidotomy with and without mapping versus high frequency pallidal stimulation in relieving symptoms of Parkinson's disease. The goal of the trial is to provide valid, objective information that will lead to more effective and efficient treatment for Parkinson's disease.

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I. INTRODUCTION

A. Purpose

This MDRC Technology Assessment (TA) Program report was written in response to a request by VISN 9 for guidance from the Technology Recommendations Panel (TRP) on the effectiveness and appropriateness of stereotactic pallidotomy for the treatment of Parkinson's disease.

Consultants from TEMINEX\The HMO Group Site, HAYES, Inc. were commissioned to produce the report. The consultants provided the body of the report; additions by the MDRC are noted. The conclusions are the opinions of the MDRC, and do not necessarily reflect those of the consultants.

B. Background

Pallidotomy, neurosurgical ablation of part or all of the globus pallidus, has long been used in the treatment of Parkinson's disease (PD). It was frequently performed in the late 1940s and 1950s by Leskell, Cooper, Spiegel, Wycis and other pioneer stereotactic surgeons (Baron, 1997; Favre, 1996). In 1952, Cooper reported improvement of contralateral Parkinsonian signs (resting tremor, bradykinesia and rigidity), after an accidental ligation of the anterior choroidal artery led to an ischemic infarct of the globus pallidus in a patient with PD. Thereafter, he began performing numerous ablative procedures targeting the basal ganglia to treat PD including anteromedial chemopallidotomy with injection of procaine and alcohol (Goetz, 1996).

Also in the early 1950s, Leksell reported on his investigation with radiofrequency electrocoagulation of the internal globus pallidus (GPi), noting that moving the target to the posterior portion of the GPi improved results (Baron, 1996). Long term follow-up of Leksell's ventroposterolateral (VPL) pallidotomies, reported in 1960 by Svennilson et al., confirmed sustained benefits. In 1954, when Hassler and Reichert reported superior relief of PD tremor after ventrolateral thalamotomy, pallidotomy was largely abandoned. With the advent of levodopa in the 1960s, dopamine replacement therapy became the standard of care for PD, and surgical treatment was sharply curtailed except in cases of intractable, asymmetrical, severe tremor.

Within the first two decades of the levodopa revolution for the treatment of PD, it became apparent that medical management was not a permanent solution. Clinical manifestations of PD were different when compared with those observed before the availability of long-term drug therapy. The efficacy of levodopa proved to diminish after 5 to 10 years. The majority of levodopa responsive patients manifested increasingly severe and frequent fluctuations in response to long term therapy. This adverse side effect has become known as "on-off syndrome." The syndrome consists of incapacitating episodes of sudden motor shifts in which "on" periods of medication induced relative mobility are abruptly interrupted by drug-induced dyskinesias (abnormal involuntary movements) or akinesia (loss of voluntary motion), with accompanying akinesia (loss of voluntary

motion) or bradykinesia (extreme slowness of motion) during "off" periods.

The spectrum of medically intractable PD patients has now shifted to include more elderly patients with more advanced disease who demonstrate loss of therapeutic response to levodopa with these associated symptoms. Emergence of this new subset of PD patients has renewed interest in pallidotomy as treatment for otherwise intractable PD symptoms (Baron, 1996; Favre, 1996; Goetz, 1996).

In 1985, Laitinen et al. continued the work of Leksell, Svennilson and others. They performed Leksell's posteroventral pallidotomy procedure on 38 patients with PD who had responded poorly to drug therapy. The study confirmed previous findings and reported on additional benefits such as amelioration of drug-induced dyskinesias (Laitinen, 1992). Leksell's approach, targeting the posterior and ventral aspect of the pallidum, replaced classical pallidotomy, which had targeted the anterior dorsal portion, and is the procedure currently in use today.

II. DIAGNOSIS

A. Description

Parkinson's disease is a slowly progressive neurodegenerative disorder of unknown etiology occurring about age 50 or later with frequency increasing with age. It is estimated that about one million Americans are affected and about 40,000 new patients are diagnosed yearly. Pathologically, PD is characterized by chronic degeneration of the dopaminergic neurons of the nigrostriatal pathway and accompanying decrease in the striatal concentration of the neurotransmitter dopamine. Eventually, lack of dopamine causes an overstimulation to other parts of the brain (Calne 1993; Goetz, 1996; Favre, 1996).

Postmortem neuropathologic examination of the brain is usually considered the gold standard for the diagnosis of PD. In the living, a diagnosis can only be reached based on a particular clinical picture. Diagnostic criteria for PD vary among geographically defined populations, but the cardinal signs are universally recognized (resting tremor, bradykinesia, rigidity and impaired postural reflexes). Common clinical features include duration of symptoms, asymmetry of cardinal signs and response to drug therapy. A diagnosis of PD typically requires a combination of at least two cardinal signs and a definite response to dopamine replacement therapy (Rijk, 1997).

B. Staging

Advanced stage PD leads to dementia and death. Degree of disability is generally divided into five stages formulated by Hoehn and Yahr (1967) as follows:

Stage I. Unilateral involvement only, usually with minimal or no functional impairment.

Stage II. Bilateral or midline involvement, without impairment of balance.

Stage III. First sign of impaired righting reflexes, evident by unsteadiness as patient turns or is demonstrated when patient is pushed from standing equilibrium with the feet together and eyes closed. Functionally, the patient is somewhat restricted but is capable of activities of daily living. Disability is mild to moderate.

Stage IV. Fully developed severe disabling disease. The patient is still able to walk and stand unassisted but is markedly incapacitated.

Stage V. Confinement to wheelchair unless aided.

Another scale commonly used to characterize the degree of PD severity is the United Parkinson's Disease Rating Scale (UPDRS Development Committee), which is divided into subsets as follows:

Subset I. Mental, behavior and mood. Maximum score=16.

Subset II. Activities of Daily Living (ADL) in "on" and "off" states. Maximum score=52.

Subset III. Motor in "on" and "off" states. Maximum score=108.

Subset IV. Part A. Dyskinesias. Maximum score=13. Part B. Clinical fluctuations. Maximum score=7.

For the "off" state, patients are evaluated between 8 and 9 hours following $\geq$12 hour withdrawal of drug therapy. They are examined subsequently in the "on" state when optimally medicated. Subsets II and III of the UPDRS scale are combined to produce the "overall" score. In all subsets, the higher the score, the greater the disease severity.

III. PROCEDURE

A. Theoretical Rationale

The globus pallidus is a part of the basal ganglia, subcortical structures involved with motor control through feedback loops with the cerebral cortex. The role of the different parts of the basal ganglia circuitry has been significantly studied and reappraised since the discovery that 1-methyl-4phenyl-1,2,3,6-tetrahydropyridine (MPTP), a spin-off of a designer street drug, provoked Parkinsonian syndrome in animals as well as humans. Studies of MPTP animal models showed that excessive neuronal activity in the internal globus pallidus (GPi) and the subthalamic nucleus (STN) is associated with development of Parkinsonian signs (Baron, 1996).

Based on these findings, it has been proposed that cortical input to the GPi is directed over two parallel pathways: a direct striatopallidal pathway that inhibits GPi neurons and the indirect pathway through the external globus pallidus (GPe) and the STN which stimulates GPi neurons. It is believed that decreased striatal dopamine leads to a decrease in activity through the direct pathway and an increase in activity through the indirect pathway, resulting in excessive inhibitory output from the basal ganglia causing Parkinsonian signs. Therefore, in PD patients there is no longer a mechanism to regulate the opposite effects of the basal ganglia's parallel processing system. Pallidotomy appears to improve function of motor inhibitory circuits in patients with PD by ablating cells in the overactive inhibitory areas and restoring balance of neuronal activity in direct and indirect pathways (Goetz, 1996; Young, 1997; Lang, 1997).

B. Surgical Procedure

Stereotactic pallidotomy is a neurosurgical, ablative procedure that uses a radiofrequency electrode to thermally induce lesions within the posteroventral portion of the internal globus pallidus. The procedure is performed under local anesthesia while patients are in the "off" state. The stereotactic frame is secured to the patient's skull, and the initial target is determined using magnetic resonance imaging (MRI) or computerized tomography (CT). Once anatomical target identification is accomplished, a burr hole is made, and an electrode is introduced into the brain. At this point, the procedure varies depending on whether or not microelectrode mapping is employed for electrophysiological localization of the precise target for placement of lesions.

A survey of pallidotomy practice in 28 North American centers (Favre, 1996) reports that 13 centers (46%) exclusively used MRI imaging to determine target coordinates, 6 centers (22%) used MRI and CT, 5 centers (18%) used MRI and ventriculography, and 4 centers (14%) exclusively used CT. Microelectrode mapping was performed in 14 (50%) centers. Pallidotomy can be performed unilaterally or bilaterally. Bilateral procedures can be either simultaneous or sequential (two unilateral surgeries separated by a brief time period).

When mapping is not used, as described by Kishore et al. (1997), stimulation trials commence as the electrode is advanced toward the target to the internal capsule and optic track. Particular movements of the patient's tongue will indicate that the probe is too close to the internal capsule. Patients will report a sensory response of flashing lights if the probe is too close to the optic tract. Trials continue 1 to 2 mm past the target in order to reach a position deep in the pallidum that did not evoke warning responses. Multiple lesions are made by electrocoagulation while the electrode is withdrawn 3 to 6 mm from the deepest lesion.

Pallidotomy with microelectrode mapping, as described by Baron et al. (1996), records single-cell activity by inserting a platinum-iridium microelectrode situated inside a stainless-steel guide tube superficially into the burr hole and advancing the microelectrode out of its guide tube towards the target with a hydraulic drive. Extracellular action potentials are displayed on an oscilloscope and played over an audio monitor. Boundaries of the encountered nuclei are identified based on distinctive neuronal discharge frequencies and patterns of striatal, GPe, GPi, and intralaminar border cells, which are like anatomical fingerprints. Within the GPi, neuronal responses to sensory or active movements of the patient's limbs, trunk, neck and face are also recorded. The optic track and the internal capsule are identified. Multiple passes of the microelectrode is made, until sufficient data are collected and mapped. After the proper target is identified, the microelectrode is replaced with a lesioning probe. Multiple lesions are made at about 1 to 2 mm intervals.

C. Cost and Reimbursement

The literature on pallidotomy does not offer cost estimates or information regarding insurance coverage for the procedure.

IV. INDICATIONS/CONTRAINDICATIONS

Precise indications for pallidotomy are still undefined. There is general agreement that levodopa replacement therapy is the standard of care for PD, and only those patients who can no longer be medically managed due to diminished response and disabling drug-induced dyskinesias should be considered as possible candidates for pallidotomy. However, the best candidate for pallidotomy remains to be identified. Patients with evidence of dementia, supranuclear palsy, striatonigral degeneration, mental illness, and life-threatening medical problems have generally been excluded from studies, although this is not consistent in the literature.

The majority of patients enrolled in published pallidotomy trials were less than 60 years old at the time of surgery. This presents potential bias and does not reflect the increasingly aging PD patient population. Only two studies stratified outcome by age. Baron et al. (1996) reported that patient age was inversely related to postoperative improvement in total UPDRS scores (f/u=3 months) but did not significantly correlate with postoperative Schwab and England level of independence scores. Uitti et al. (1997) reported similar outcomes after pallidotomy in patients greater than and less than 65 years of age. The issue of patient age highlights the fact that, while published studies generally include patients who are young, medically refractory, and severely impaired by levodopa-associated dykinesias, the studies do not infer that they are the optimal candidates for

surgery.

V. MORBIDITY AND MORTALITY

No perioperative mortalities related to pallidotomy are reported in the peer-reviewed scientific literature. Reported morbidity ranges from 0 to 35% and include worsening of balance, handwriting, and pre-existing depression, as well as dysarthria, dysphagia, cognitive impairment, facial weakness, hemiparesis, intracerebral hemorrhage, and visual field defects. It is presumed that hemiparesis and facial weakness are due to injury of the internal capsule. Visual field defect is believed to be caused by a heat lesion to the dorsolateral aspect of the optic tract. Adverse side effects of pallidotomy can be transient or persistent. Long-term neuropsychological sequelae of pallidotomy are unknown; only one published study presents follow-up data beyond three years (Fazzini, 1997).

VI. GOVERNMENTAL APPROVAL

Pallidotomy is a surgical procedure and not subject to regulation by the Food and Drug Administration (FDA). The Health Care Financing Administration (HCFA) does not have a national coverage exclusion policy on pallidotomy.

VII. TREATMENT ALTERNATIVES

Dopamine replacement therapy is the primary treatment for PD. Medical management is intended to reduce symptom severity and delay disease progression. Pallidotomy is not an alternative to drug therapy or considered a true alternative to other surgical treatments for PD with differing indications (i.e. severe tremor) such as thalamotomy and chronic thalamic stimulation (VIM).

High frequency stimulation of the globus pallidus is currently being investigated and may someday become an alternative to pallidotomy. In 1987, Benabid et al. found that high-frequency stimulation of the VIM alleviated tremor. Benabid's technique was later applied to the GPi and to the STN in MPTP-treated monkeys presenting with severe bradykinesia and rigidity by a team of French neurosurgeons (Gross, 1997). In both cases, PD symptoms decreased. These results encouraged investigators to try high-frequency stimulation of either the STN or ventroposterolateral portion of the GPi in humans to learn more about the functional organization of the basal ganglia and pathophysiology of PD, and to determine if this technology produces clinical outcomes comparable to pallidotomy.

The published literature reporting clinical outcomes on PD patients after high frequency pallidal stimulation is preliminary, limited to a few case reports and small case series of less than 8 patients. Reported outcomes are conflicting. Pahwa et al. (1997) reported on 5 cases, all resulting in significant improvement at 3 month follow-up in mentation, ADL and motor functions as measured by UPDRS, Hoehn and Yahr, and Schwab and England scales. Gross et al. (1997) presented data on 7 cases, all resulting in alleviation of akinesia, drug-induced dyskinesias and gait. Tronnier et al. (1997), reporting on 6 cases, found that pallidal stimulation improved drug-

induced dyskinesia but not PD symptoms. Too few clinical cases of high-frequency stimulation of the GPi are reported to permit conclusions as to the benefits, risks and potential of this technology.

VIII. METHODS FOR THE SYSTEMATIC REVIEW

A computerized search of the MEDLINE® and CURRENT CONTENTS® databases was conducted for the time period 1989 through November 10, 1997 using the text word term, "pallidotomy" and the subject headings, "therapeutic electrical stimulation" and "globus pallidus." Reference lists of identified articles were also searched for additional peer-reviewed published studies. Inclusion criteria for the review were English language studies that reported clinical outcomes for PD patients after treatment with pallidotomy.

The strength of the evidence is based on how well bias and confounding factors are controlled in the design and conduct of a study. Attributes that strengthen the validity of the findings include: presence of randomization, contemporaneous control subjects and blinding, a prospective design, sufficient power (larger size) and a multisite design. Common study designs containing these attributes are presented in Figure 1, from the most to the least rigorous design.[1]

Figure 1: Study Designs to Assess Effectiveness

Ranked according to decreasing strength of evidence provided

- Large randomized controlled trial, systematic reviews of RTCs
- Small randomized controlled trial
- Nonrandomized trial with contemporaneous controls
- Nonrandomized trial with historical controls
- Surveillance (database or register)
- Case series, multi-site
- Case series, single site
- Case report, anecdote

Sources: Adapted from Ibrahim 1985, and Goodman 1993.

IX. PUBLISHED FINDINGS

Only case series data on PD patients treated with pallidotomy have been published in the peer-reviewed scientific literature. No large scale randomized controlled trials were identified. Therefore, this assessment evaluated case series data as the only available data in the literature.

A case series is a relatively weak study design that does not provide strong evidence of effectiveness. Case series contain useful information about the clinical course and prognosis of patients, can *suggest* relationships between interventions and outcomes, and can help generate hypotheses for further research.[2]

Data from these studies are presented in the following tables. Table A lists published clinical studies of pallidotomy without mapping. Table B lists published clinical studies of pallidotomy with mapping.

[1] This paragraph and Figure 1 were added by the MDRC.

[2] This sentence was added by the MDRC.

Pallidotomy without mapping (See Table A). It is generally agreed that the literature on pallidotomy in the post-levodopa era begins with Laitinen and colleagues (1992) from Stockholm, Sweden. They tested Leksell's method of posteroventral pallidotomy on 38 PD patients between 1985 and 1990. An additional 8 patients were treated with pallidotomy in 1991, and a larger case series of 46 patients was published, also in 1992. The procedure reintroduced by Laitinen et al. identified the pallidal target by stereotactic CT imaging and electrical stimulation trials without single-cell neurophysical mapping prior to lesioning.

An additional five case series without mapping were reported in the literature: Iacono et al. 1995 (n=126); Sutton et al. 1995 (n=5); Johansson et al. 1997 (n=22); Kishore et al. 1997 (n=24); Soukup et al. 1997 (n=14). Favorable clinical outcome data, such as dyskinesia eliminated or significantly alleviated in 82-89% of patients, significant improvements in Parkinsonian signs and increased score of ADL, were reported. Design flaws included insufficient power, lack of objective outcome measures, poorly described patient selection criteria, insufficient duration of follow-up, variation in procedure type without separation of outcomes, and absence of uniform follow-up. All studies had methodological limitations which precluded drawing firm conclusions of the benefits and risks of pallidotomy without mapping from these data.[3]

Pallidotomy with mapping (See Table B). Seven case series were identified that evaluated the patient outcomes using pallidotomy with mapping: Baron et al. 1996 (n=15); Shima et al. 1996 (n=86); Fazzini et al. 1997 (n=11); Kopyov et al. 1997 (n=29); Lang et al. 1997 (n=40); Taha et al. 1997 (n=44); and Uitti et al. 1997 (n=20). As in the studies without mapping, there were significant study design limitations that precluded the determination of the safety and efficacy of pallidotomy with mapping. Variations in patient selection criteria, procedure and follow up interval, small sample size, and incomplete reporting of methodology and outcome measures in these studies weakened the evidence of reported benefit.[4]

No studies in the published literature comparing outcomes after pallidotomy performed without mapping versus with mapping were identified. It would seem logical to assume that mapping technology provides enhanced protection of optic track and internal capsule from heat lesion damage and improves precision of intraoperative target identification. However, mapping requires multiple explorative passes of the microelectrode to acquire sufficient data, and this potentially presents additional risk of intracerebral hemorrhage. Therefore, the best technique for navigating the GPi is unknown. Both targeting techniques are used, and each has its champions.

Another question yet unanswered by the literature is which lesion site produces the greatest improvement in symptoms while minimizing surgical complications. Conflicting results from Kopyov et al. (1997) and Lang et al. (1997) support the need for long-term follow-up to determine which lesion site within the GPi produces the greatest improvements in levodopa-induced dyskinesias and PD symptoms with the least adverse, persistent side effects.

[3] The conclusions in this paragraph are the opinions of the MDRC.

[4] This paragraph was added by the MDRC.

X. CONCLUSIONS/DISCUSSION[5]

A systematic review entitled "Posteroventral Pallidotomy in Parkinson's Disease" was published by the Health Care Technology Assessment Unit of the Alberta Heritage Foundation for Medical Research in Canada (Harstall, 1997). This report concluded that while several trials reported relief of symptoms of PD and anecdotal evidence by patients of improved quality of life, the quality of the evidence was fair to poor with few data on long term outcomes. They recommended the following:

1. Pallidotomy should be performed only in specialized centers with both neurological and neurosurgical expertise.
2. Systematic data collection including long-term follow-up is needed.
3. Comparative advantages of pallidotomy versus conventional management versus high-frequency pallidal stimulation should be reviewed.

The MDRC review includes more recent data from 1997. The evidence presented in the tables suggests that pallidotomy with and without mapping for indicated PD patients alleviates drug-induced dyskinesias, significantly improves Parkinsonian signs, and elevates level of ADL independence. Relief of tremor is inconsistent. However, all data are from uncontrolled case series which is considered the weakest level of evidence supporting an association between treatment intervention and patient outcome. The weakness of the prevailing evidence precludes the definitive assessment of the risks and benefits of pallidotomy with or without mapping; large-scale randomized clinical trials are needed to substantiate its efficacy. The MDRC review confirms that the conclusions from the Alberta review are durable.

A randomized, prospective cooperative trial in 15 VAMCs (estimated 300 patients) has been approved for planning by the Office of Research and Development, with the first of two planning meetings to take place in May of 1998. The trial will compare the efficacies, safety, and costs of pallidotomy with and without mapping versus high frequency pallidal stimulation in relieving symptoms of Parkinson's disease. The goal of the trial is to provide valid, objective information that will lead to more effective and efficient treatment for Parkinson's disease.

[5] This section reflects the opinions of the MDRC.

XI. Table A: Published Clinical Studies of Pallidotomy Without Mapping

Study/ Center	#Pts.	Methods	Results/comments
Laitinen, et al. 1992 Stockholm, Sweden	46	Patient Selection Criteria • Idiopathic PD, medically intractable, severe tremor, rigor, bradykinesia, gait difficulties and/or dyskinesia • Mean age=60 years (30-80) • Mean duration of PD=9 years (2-20) Procedure • Stereotactic, VPL pallidotomy without mapping • 41unilateral • 5 bilateral	Results • Mean f/u=30 months (2-78) • 40/46 patients report none to slight tremor • 42/46 patients report none to slight rigor and hypokinesia • No mortality and 15% morbidity reported Comments/Limitations • No objective methods used to evaluate outcome • 12 patients had combination pallidotomy and thalamotomy, outcomes not reported separately • Duration of f/u range very broad
Iacono et al. 1995 Loma Linda University, CA	126	Patient Selection Criteria • Idiopathic PD, all patients receiving optimally tolerated drug therapy Hoehn & Yahr= 3 to 5 "on" • Mean age =62 years(31-80) • Mean PD duration = 11 years (2-24) Procedure • Stereotactic posteroventral GPi pallidotomy without mapping • Unilateral=58 bilateral = 68 (19 sequential 49 simultaneous) • Multiple lesions made at 65 to 80 degrees C for 30 to 60 seconds depending on proximity to optic tract and internal capsule	Results • Mean f/u 4.5 months (1-12 months) • Hoehn & Yahr post-op average score "on" reduced to 2.0 from pre-op baseline of 3.4 ($p \leq 0.001$) • UPDRS motor subscores and dyskinesias reduced post-op ($p \leq 0.01$) • No mortality reported - 3.1% transient morbidity : macular hemianopsia-1 patient hemiparesis-3 patients - 3.2% permanent morbidity reported: macular hemianopsia-2 patients hemiparesis-2 patients Comments/Limitations • Patient selection and exclusion criteria not adequately described - do not know if consecutive patient series • Outcomes not separated by type of procedure • Patients not evaluated post-op at uniform intervals-results are combined together distorting temporal sequence of reported changes and potentially allowing inappropriate amount of immediate post-op data to skew results • Subjective outcomes also reported but methods of evaluation not described and results are not interpretable

Study/ Center	#Pts.	Methods	Results/comments
Sutton, et al. 1995 Los Angeles, CA	5	Patient Selection Criteria • Idiopathic, advanced PD, failure on medical therapy, severe motor fluctuations, levodopa-induced dyskinesia or dystonia • Mean age=67years (60-75) • Mean PD duration=11.6 years (4-20) • H&Y "off" range=2.5-5 • H&R "on" range=1.5-5 Procedure • Stereotactic, VPL pallidotomy without mapping • 3 unilateral • 2 bilateral • Multiple lesions done at 72-80 degrees C for 60 seconds after trial at 42 degrees C	Results • F/u=8 weeks no significant improvements found postoperatively using UPDRS, H&R, S&E and Hamilton depression inventory tools • One patient did demonstrate improvement in contralateral peak-dose dyskinesia Comments/Limitations • Pilot study too small to provide significant data • High morbidity reported • F/u period too brief to be conclusive • 2 patients underwent repeat surgery on same side when initial early improvements and subsequent relapse suggested lesions were too small
Kishore et al. 1997 Vancouver, Canada	24	Patient Selection Criteria • Idiopathic PD, medically intractable, history levodopa responsive, severe levodopa-induced dyskinesia • Exclusion criteria: dementia, supranuclear gaze palsy, cerebellar signs, severe dysautonomia • Mean age=61 years (37-74) • Mean duration PD=14.2 years (4-35) • Mean H&Y "off"=3.34 (2-5) • Mean H&Y "on"=2.48(2-4) Procedure • Stereotactic, unilateral, pallidotomy without microelectrode mapping • Multiple lesions made at 80 degrees C for 60 seconds after trials at 42 and 60 degrees; second made at 3mm and then 6mm intervals from deepest lesion and third lesions	Results • Mean UPDRS "off" motor score improvement stable at 12 months f/u (p=0.0001); mean ADL "off" score improvement sustained at 12 months f/u (p=0.0005) • "on" score for total dyskinesia improvement stable at 12 months (p=0.0003); improvement noted bilateral at 6 months f/u • Significant improvement at 6 months f/u contralaterally, ipsilateral improvement in tremor and bradykinesia noted but not sustained at 9 or 12 months • 1 case of permanent facial paresis reported Comments/Limitations • Blinded video assessments and un-blinded clinical assessment done pre-op, post-op and 3 months f/u-not possible to continue blinded f/u beyond 3 months because improvement of dyskinesia so dramatic • 11/24 patients lost to f/u at 9 months-excluded from analysis • Duration of f/u varies per outcome variable

Study/ Center	#Pts.	Methods	Results/comments
Soukup, et al. 1997 University of Texas, TX	14	Patient Selection Criteria • Idiopathic PD, currently on levodopa-average dose 851md/d(300-1520) • Exclusion criteria = Alzheimer-type dementia, supranuclear gaze palsy • Mean age=61.7 years (43-82) • Mean duration PD=7.4 years (5-15) Procedure Stereotactic, unilateral posteroventral pallidotomy without mapping	Results • Objective measurement of 24 cognitive variables showed no significant deterioration in cognitive status at 3 months post-op • Significant improvement found in motor coordination speed as measured by the Purdue Pegboard test (p=0.001) Comments/Limitations • Study designed to examine the cognitive consequences of surgery • Examiner unblinded • F/u period too brief to be conclusive
Johansson et al. 1997 University Hospital of Northern Sweden, Sweden	22	Patient Selection Criteria • Idiopathic PD, positive early response to levodopa, drug tx. now insufficient due to poor response or severe levodopa-induced dyskinesia. • Exclusion criteria: prior brain surgery (except for PD), degenerative or vascular brain diseases, advanced cortical atrophy and mental illness, secondary PD • Mean Hoehn & Yahr “on”=3.0 • Mean Schwab & England ADL “on” =72% • Mean age = 63.8 years (43-78) • Mean duration of PD=14.8 years (7-22) Procedure • Stereotactic posteroventral pallidotomy without mapping • Unilateral=20 bilateral=2 • Multiple lesions made at 75-83 degrees C for 30-60 seconds in 2mm increments	Results • F/u= 4 and 12 months motor fluctuation improved significantly post-op with proportion of dyskinesia periods significantly decreased and longer periods of normal mobility. No significant improvement in number of slow or absent mobility events • Limb dyskinesia completely resolved contralaterally and significantly improved ipsilaterally • No significant improvement shown in freezing, gait or posture • tremor improvement significant • 1 patient had permanent visual scotoma-no other m/m reported Comments/Limitations • Prospective consecutive patient series • 6 patients (27%) lost to f/u at 12 months and excluded from analysis • MRI f/u of position and size of lesion on 15 patients found no clear correlation between size of coagulated area and size of final lesion; estimated location of lesions coincided with the coagulated pallidal area in all patients • Motor fluctuations calculated as percentage of day based on observation q 30 minutes 8am-7pm • Levodopa doses uniform during study per protocol: 952mg baseline, 913mg 4 months and 931 mg 12 months

XII. Table B: Published Clinical Studies of Pallidotomy With Mapping

Study/ Center	#Pts.	Methods	Results/Comments
Baron et al. 1996 Emory University, GA	15	Patient Selection Criteria • Idiopathic PD, medically intractable, history levodopa responsive, Hoehn & Yahr score ≥ 3.0 "off" exclusion criteria = signs of mental illness • Mean age=57 years (38-71) • Mean PD duration=14 years (7-31) Procedure Stereotactic, unilateral, posterior GPi pallidotomy with microelectrode mapping	Results • Mean total UPDRS score improvement =30.1% (p=0.002), 24% (p=0.003) and 20%(p=0.006) at 3, 6 and 12 months respectively. Mean combined S&E ADL "off" and "on" scores improvement=33% (p=0.001), 30% (p=0.003), and 30% (p=0.007) at 3,6 and 12 months respectively • No evidence contralateral rest tremor in 7/8 patients at 1 year • Drug-induced dyskinesia ameliorated in 10/11 patients at 1 year • No significant post-op improvement at 1 year for "on" gait, postural stability, "on" and "off" freezing • No mortality reported, 1 patient developed persistent worsening of speech Comments/Limitations • Report on 15 of first 20 pallidotomy patients, not clear if consecutive series 11 patients completed 1 year f/u • 2 patients with dementia pre-op showed little benefit • Subjective analysis indicated quality of "on" time improved due to reduced anxiety about sudden shifts to "off" states • F/u protocol limited post-op medication adjustments to avoid possible effect on surgical outcome • Transient complications, facial weakness and confusion, reported mostly in elderly patients
Shima et al. 1996 Fukuoka, Japan	86	Patient Selection Criteria • Severe PD, receiving optimally tolerated drug tx, marked bradykinesia, freezing of gait, defects of postural balance with rigidity and tremor (bradykinesia type) or similar gait and postural symptoms with minimal signs of rigidity and tremor (pure akinesia type) • Mean age=63 years (41-79) • H&R "off" range=4-5 Procedure • Stereotactic posteroventral pallidotomy with microelectrode mapping • 58=unilateral • 18= simultaneous bilateral • 10=sequential bilateral	Results • Mean f/u=8 months (3-30) • Microelectrode mapping revealed that in bradykinesia type patients, background neural activity in the GPi was extremely overactive (80-200 Hz) while neurons in the GPe showed an irregular low discharge rate (40-60 Hz). In pure akinesia type patients, activity in both the GPi and GPe were significantly lower • Patients with pure akinesia showed significant early but transient improvement- all symptoms recurred 1-3 months post-op • 90% patients with bradykinesia showed improvement in tremor, rigidity, dyskinesia resolved • No mortality and 5.8% morbidity reported Comments/Limitations • Study designed to investigate neural activity and organization in basal ganglia and propose a neural mechanism in pallidotomy • Clinical outcome measures and means not described • Conclusion to exclude patients with pure akinesia from pallidotomy based on 4 patients with this type in 86 pt. series • Morbidity reported = worsening of speech and hyper-salivation in 3 patients.; hemiparesis in 1pt. and subcortical hemorrhage in 1 pt

Study/ Center	#Pts.	Methods	Results/Comments
Fazzini et al. 1997 New York University, NY	11	Patient Selection Criteria • Idiopathic PD, medically intractable, history levodopa responsive, bradykinesia and rigidity-predominant PD, marked "off-on" fluctuations, Hoehn & Yahr ≤ 3 "on" • Exclusion criteria: ataxia, dementia, supranuclear gaze palsy or blood pressure drop of greater than 30 mm Hg on standing • Mean age=61 years (56-79), • Mean PD duration=11.7 years (4-25) Procedure • Stereotactic, unilateral, ventral pallidotomy with microelectrode mapping • Multiple lesions made at 80 degrees C for 60 seconds, overlapped sequentially at 2-mm intervals to create cylinder shape	Results • UPDRS ADL mean scores improved from baseline of 15 to 6, 9 and 3 at 1,2 and 3 years respectively ($p<0.05$ for all years) • UPDRS mean motor scores improved from baseline of 32 to 11, 11 and 7 at 1,2 and 3 years respectively ($p<0.01$ for all years) • CAPIT "off" timed scores ipsilateral and contralateral improvement to 4 years ($p<0.5$) • Drug-induced dyskinesia did not return to any pt and post-op effectiveness of drug maintained at stable dosage • No morbidity or mortality reported Comments/Limitations • Initial study group of 18 patients in which 7 patients were excluded from f/u analysis: 4 patients underwent a second surgery (contralateral pallidotmy) and 3 patients were lost • Long term f/u varied among 11 patients: - 1 pt. f/u= 2years. (n=11) - 5 patients. f/u= 3 years (n=10) - 5 patients. f/u= 4 years.(n=5)
Kopyov et al. 1997 Los Angeles, CA	29	Patient Selection Criteria • Idiopathic PD (at least two cardinal signs), medically intractable, history levodopa responsiveness, 8-25 years disease duration • Exclusion criteria: dementia, neuro disorder, life-threatening medical problem, supranuclear palsy or unusual form of PD • H & Y "on"=1-3 • H & Y 'off"=3-4 Procedure • Stereotactic posteroventral medial pallidotomy with microelectrode mapping • Multiple lesions made at 80-85 degrees for 85 seconds	Results • F/u = 3 months • Hoehn & Yahr decreased "on" ($p=0.001$) and "off" ($p<0.001$) • UPDRS overall decreased "on" ($p<0.001$) and "off" ($p<0.01$) cardinal signs significantly improved dyskenisa improved ($p<0.001$) • 89.7% patients without tremor, • 6.9% patients with minimal tremor, • 3.4% patients with marked tremor • 0% mortality and morbidity Comments/Limitations • All pallidotomy procedures performed within 1 year to minimize potential confounding effects of changing techniques, patient population or technical advances • Tremor outcomes unusual as compared to those reported in other trials that found tremor improvement in just a fraction of patients after pallidotomy

Study/ Center	#Pts.	Methods	Results/Comments
Lang et al. 1997 Toronto, Canada	40	Patient Selection Criteria • Idiopathic PD, medically intractable, history significant response to levodopa, disabling levodopa-induced dyskinesia • Exclusion criteria: cognitive dysfunction, psychiatric symptoms, previous brain surgery, concurrent medical or neuro problems • Mean age=58.5 years (44-72) • Mean duration PD=12.9 years (4-25) • Mean H&Y"on"=2.5 (1.5-5) • Mean H&Y"off"=3.5(2-5) • Mean S&E"on"=78(35-100) • Mean S&E"off"=39(10-70) Procedure • Stereotactic, unilateral, posteroventral medial pallidotomy with microelectrode mapping • Multiple lesions made by sequential heating of probe 60,70, 80 and 90 degrees C for 60 seconds	Results • All "off" score measures-motor, ADL, gait, postural stability, tremor, rigidity, tapping and bradykinesia-significantly improved at 6 months f/u • "On" scores improved significantly at 6 months f/u only for ADL, tapping (ipsilateral and contralateral) • "On" scores for dyskinesias significantly improved contralateral and ipsilateral ($p<0.001$) at 6 months • Significant improvement in levodopa-induced contralateral dyskinesias sustained at 2 years - ipsilateral dyskinesia improvement sustained to 1 year and lost by second year • No mortality and 35% persistent adverse side effects reported Comments/Limitations • 39/40 completed 6 month f/u after which patients divided into 2 groups for longer f/u: 27/39 followed to 1 year and 11/27 followed to 2 years - group assignment process not described • 4 additional patients underwent surgery but lesions not made due to intraoperative complications: intracerebral hemorrhage in 1 patient, unsuccessful mapping in 2 patients and paranoia in 1 patient • Reported persistent side effects include, worsening of balance, handwriting, word-finding and dementia, changes in personality, dysarthria, dysphagia
Taha et al. 1997 University of Portland, Oregon	44	Patient Selection Criteria • Idiopathic PD, medically intractable, history of response to levodopa, severe levodopa-induced dyskinesia, bradykinesia, rigidity and tremor • Age range = 42-78 years • Exclusion criteria = PD plus symptoms, severe dementia Procedure • Stereotactic pallidotomy with mircroelectrode mapping • 25 unilateral • 19 simultaneous bilateral • 3 lesions spaced 2mm apart along same trajectory made at 84 degrees C for 60 seconds after initial trial at 10 seconds	Results • Mean f/u 6 months (3-9) • 31/44 patients preoperatively found to have moderate to severe tremor and 15/44 patients showed same post-op ($p<0.05$) • 67% of severe tremor patients report improvement of at least 50% • 4/44 patients (9%) report tremor abolition • f/u period not provided for these 4 patients • Tremor was better improved after pallidotomy if tremor-synchronous cells were recorded during surgery and included in lesion Comments/Limitations • Study designed to examine effect specifically on tremor and association between tremor-synchronous cells and post-op tremor relief • Surgical mapping included permitted identification of tremor-synchronous - all cells with burst discharges at 3-8 Hz in synchrony with tremor - for target inclusion • Outcome measure by subjective visual analog scale at variable intervals

Study/ Center	#Pts.	Methods	Results/Comments
Uitti et al. 1997 Jacksonville, FL	20	Patient Selection Criteria • PD with at least two of following: resting tremor, bradykinesia, rigidity, medically intractable, history of significant response to levodopa, advancing and disabling levodopa-induced motor fluctuations • Mean age: overall = 65.5 (49-78) 11 patients = 71.4(65-78) 9 patients = 56.3(49-62) • Mean duration of PD = 13.6 Procedure • Stereotactic unilateral, medial pallidotomy with microelectrode mapping • Multiple lesions made at 70 degrees for 60 seconds	Results • F/u = 3 months post-op • outcomes between younger (<65 years.) and older (≥65 years) patients compared • UPDRS mean motor scores improved 24% “on” and 20% “off”(p<0.001) subgroup comparisons between age grouped pre- and post-op scores did not vary significantly. • UPDRS mean ADL score significantly improved (p=0.01) • Based on patient diary data, overall mean daily “on” doubled post-op from pre-op score (p=0.015). Age was not found to be a significant factor in improvement • No mortality and permanent morbidity reported Comments/Limitations • Study designed to compare outcome in younger verses elderly patients • Study represents only analysis of outcome in patients 65 years or older • Neuropsychological f/u done on last 9 patients in series (2patients elderly)

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XIII. REFERENCES

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