Posteroventral pallidotomy in Parkinson’s Disease

Christa Harstall, David Hailey

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This Health Technology Assessment Report has been prepared on the basis of available information of which the Foundation is aware from public literature and expert opinion, and attempts to be current to the date of publication. It has been externally reviewed. Additional information and comments relative to the Report are welcome, and should be sent to:

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Summary

- Posteroventral pallidotomy (PVP) is a neurosurgical procedure which has been used to treat Parkinson’s Disease patients whose symptoms are no longer adequately controlled by medication. Perhaps 700 persons in Alberta would be potential candidates for the procedure.

- PVP is symptomatic treatment and does not halt progression of the disease or replace the need for medication.

- Technical aspects of the procedure continue to evolve, notably in relation to location of the target site and determination of the volume of tissue to be ablated. There is no consensus on whether microelectrode recording techniques should be used as part of the location process.

- Several trials have shown that PVP can be effective in relieving symptoms. The quality of the available evidence is fair to poor and there are few data on long-term outcomes.

- Alternative procedures, including radiosurgical pallidotomy and chronic high-frequency stimulation, have been used in small numbers of cases.

- There are strong anecdotal reports of individuals who have experienced a dramatic improvement to their quality of life following the procedure.

- PVP is associated with complications, though these should be regarded in the context of the severity of the disease in those who are candidates for the procedure.

- Economic data for the procedure in Alberta are not available. However, hospital stays for PVP are expected to be brief, and alternative medical treatments may be costly.

It is suggested that, for any future use of the procedure in Alberta:

- The procedure should be regarded as an evolving technology, with uncertain outcomes, until further data become available.

- PVP should be performed only in specialized centres which have combined neurological and neurosurgical expertise.

- Systematic collection of data on PVP cases in the province should be obtained, and include results of long-term follow-up.

- Close contact should be maintained with other centres undertaking PVP.
The comparative advantage of PVP should be kept under review, both in regard to conventional methods of management and to chronic high-frequency brain stimulation techniques, which may offer effective alternatives without ablation of brain tissue.
**Introduction**

This paper is intended as a short overview of the effectiveness and status of a neurosurgical procedure, posteroventral pallidotomy (PVP), which is used in the treatment of some people with Parkinson’s Disease. Details of the approach taken in searching for data on this technology are given in Appendix A.

Parkinson’s Disease is a chronic progressive neurological degenerative disorder. Motor dysfunction is the chief clinical manifestation, with cardinal features of resting tremor, muscle rigidity, hypokinesia, impairment of posture and loss of balance. The average age of onset is around 60 and the incidence increases with age. Over 1% of the population over the age of 60 has the disease (31). The crude prevalence rate in Alberta for 1984 to 1989 was 244.4 per 100,000 population (37). Assuming that this rate is still applicable, there are approximately 6,700 persons diagnosed with this condition in the province.

Treatment with dopaminergic therapy based on the use of levodopa is the standard approach to management of Parkinson’s Disease. As the disease progresses, the drug’s therapeutic effects decline. After three to five years of levodopa therapy, 50% or more of those with the disease show a diminishing drug response duration and between 28% and 84% have motor response complications (5, 38). The first fluctuation in motor response to become evident is a shortened duration of action following a single intake of levodopa – a “wearing off”, or “end-of-dose” deterioration. With further disease progression, there may be intermittent, unpredictable periods of immobility, unrelated to the timing of medication intake (the “on-off” effect).

Use of increasingly higher doses of levodopa as the disease progresses leads to more numerous and more serious side effects, sometimes culminating in the disease becoming refractory to treatment (8). The changes in response to levodopa manifest themselves in greater fluctuation in symptom control, increased dyskinesia (impairment of ability to initiate movement), peak dose dyskinesia, increased “on-off” periods with episodes of frozen movement, and increased fatigue. For severe cases which are refractory to medical treatment, PVP may provide some symptomatic benefit in appropriately selected patients.

PVP has now been undertaken on a number of persons with Parkinson’s Disease whose response to medication was no longer adequate. PVP is a symptomatic treatment and does not halt progression of the disease nor replace the need for medication. A major rationale for its use is to obtain a significant improvement in the patient's quality of life and for the patient to once again be effectively maintained on drug treatment.

If patterns of the disease and its treatment are similar in Alberta to those in the south and west of England (33), perhaps 10% of persons with Parkinson’s Disease, or about 700 in the province, would be potential candidates for PVP because they have become refractory to standard therapy.
History and nature of PVP

Stereotactic neurosurgery for Parkinson’s Disease was introduced in 1946 and classical pallidotomy was widely used in the 1950s. The procedure improved rigidity but had little impact on tremor and hypokinesia. Leksell modified the procedure in 1956 by lesioning the posteroventral part of the pallidum, and following the work of Laitinen et al. (22) this approach has been the basis for subsequent practice at a number of centres.

With the advent of levodopa therapy in the 1970s, use of neurosurgery in management of Parkinson’s Disease declined. The recent interest in PVP has developed as some of the longer term limitations of levodopa treatment have become more apparent and advances in stereotactic surgery and neuroimaging have been made. The theory behind neurosurgical intervention is that lesioning precisely targeted areas decreases or interrupts the hyperactive output of the globus pallidus, thereby reducing the motor symptoms. PVP has been reported by a number of groups to improve akinesia, drug-induced dyskinesia, tremor and rigidity (17, 21, 25).

According to Iacono et al. (16) current indications for PVP include akinesia partially responsive to medication, bradykinesia with freezing during repetition, asymmetric severe rigidity, frequent dystonia, frequent disabling dyskinesia or postural instability with falling. However, response of postural instability and falling to PVP has not been the experience of other groups (Lang, personal communication). Exclusion criteria include good control of symptomatology with medication, MRI evidence of brain atrophy or abnormalities and Parkinson’s Disease plus syndromes. Martin (personal communication) advises that many centres perform detailed neuropsychological testing prior to PVP and consider significant cognitive decline to be a contraindication to this procedure. A survey of practice at a number of centres in North America indicated that the procedure was considered most beneficial for controlling drug-induced dyskinesias and least beneficial for improving walking, tremor and gait disturbance (9).

PVP is performed under local anaesthesia. Following targeting by CT or MRI, a probe is inserted into the appropriate area of the brain via a burr hole. Careful target localization is essential as there is anatomical volume shrinkage of the brain due to the disease, and because the target area is close to the optic tract and the internal capsule. Also, the efficacy of the procedure depends on the precise identification of the target site and determination of the volume of tissue to be destroyed.

There is no consensus on the exact site and size of the lesion (2, 25, 28, 30). In practice, the effect of the intervention is assessed empirically during and after the procedure. Electrophysiological stimulation is used to enable accurate identification of lesion sites and improve safety. Electrical stimulation is used to detect the internal capsule and optic tract. The position of the lesion site is usually revised on the basis of electrophysiological mapping results from that initially determined by imaging studies (24).

Physiological confirmation of the target site may be achieved through macrostimulation used alone or in conjunction with microelectrode recording. The use of microelectrode
recording remains controversial. Advocates such as Lozano et al. (24) highly recommended the use of both techniques because instances have arisen when patients have recorded visual sensations with microelectrode recordings but not with macrostimulation. However, microelectrode recording is time consuming and involves risks associated with multiple needle passes through the brain (30). Furthermore, Olanow (30) notes that good results have been reported by Laitinen et al. (22, 23) using stereotactic pallidotomy with macrostimulation but not microrecording.

De Salles et al. (6) have drawn attention to the importance of ensuring that the lesion is correctly located, is large enough to make treatment feasible and that the patient has idiopathic Parkinson’s Disease. They comment that stimulation with 50Hz can increase outflow from the globus pallidus internum to the thalamus and increase in tone suggests proper placement of the electrode. A gradual increase in stimulation current provides a measure of the distance of the probe from structures to be avoided.

After the intended targets are carefully evaluated, lesions are made by radiofrequency-induced heating (8). The effects of PVP in alleviating symptoms are apparent in the short term. The length of hospital stay for this procedure is short; most patients are discharged within one to two days of surgery.

Most surgeons have used unilateral PVP to produce symptomatic benefit, primarily on the contralateral side. Although Parkinson’s Disease is a bilateral disease process, the use of bilateral PVP remains controversial because of potential complications. If bilateral PVP is warranted, a staged bilateral approach is recommended. However, Iacono et al. (16) and Laitinen (21) have reported successful bilateral PVP’s with no significant increase of adverse effects.

Another surgical procedure, stereotactic thalamotomy, is performed on some patients in whom tremor is the dominant disability. A report by ECRI (8) notes that several sites can be lesioned and that there is no consensus as to which is best. Outcomes from the two most targeted sites appear to be equivalent, giving 80-90% relief from tremor. Thalamotomy for relief of incapacitating unilateral tremor is well established (27).

The ECRI report notes that a few patients may be candidates for both procedures and in any case that surgery is performed only on those whose symptoms can no longer be controlled by pharmacological intervention. Thalamotomy is performed less often than PVP because severe tremor is less often a debilitating problem for those with Parkinson’s Disease.

Use of the procedure

The ECRI report noted that at least 28 centres in the US, Canada and Sweden offer the procedure, and that diffusion has been rapid, with about 80% of the programs being less than one year old in 1995. Results of a survey of current practice at 28 centres in North America were published by Favre et al. in late 1996 (9). Comments on that paper suggested that at least twice as many centres were active.
In the USA, the Current Procedure Terminology (CPT) code for PVP is 61720. The U.S. Health Care Financing Administration does not have a national reimbursement policy for PVP and coverage is at the discretion of local carriers. Some states consider it an acceptable procedure while others consider it experimental.

In Canada, a large number of PVPs have now been carried out at The Toronto Hospital, with some referrals from Alberta. The operation is also performed in Vancouver and London and is expected to be made available in Calgary and Edmonton in the near future.

Clinical outcomes

Data from published reports of the more detailed trials on PVP are summarised in Table 1. These studies provide evidence of benefit to persons with Parkinson’s Disease through use of PVP, but all have methodological limitations. In some areas comparison of the studies is difficult, because of differences in patient selection, patient assessment pre and post operatively / “on” or “off” medication, and reporting of outcomes. In the larger series, the technical aspects of the procedure varied over time, as would be expected with a developmental surgical procedure. The most recent studies by Laitinen et al. (21) and Iacono et al. (17) include some patients whose outcomes were reported in earlier papers.

The paper by Svennilson et al. (36) brings together the early experience of Leksell’s team. As these authors point out, this was not a homologous group of patients as the technique was evolving over a period of years. After constant treatment parameters had been established (for the final 19 cases), only 5% had unsatisfactory results or recurrence in regard to rigidity and tremor. For the entire series, including the developmental phase, 23.5% of cases had unsatisfactory outcomes.

The prospective study by Dogali et al. (7) had small numbers of subjects. Outcomes are reported in terms of scores for the whole group. Individual patient results are not available for most measures, though rigidity and bradykinesia decreased for all PVP cases immediately after surgery. However, outcomes in regard to medication are reported on an individual basis. One year after surgery, eight patients had increased and eight had decreased their dose of levodopa and in one there had been no change. In comparison, five of the control group had increased dosage, one had decreased and the other was unchanged. Amantadine use was discontinued in three of four subjects who received PVP, one patient stopped bromocriptine at 12 months follow-up, pergolide dosage remained the same in the 10 patients who used it, and dosage of selegiline dropped by 50% at 12 month follow-up in the 11 patients who used it.

The prospective study by Lozano et al. (25) also involved small numbers of subjects, who served as their own controls. Again, outcomes are given in terms of composite scores and individual patient results are not reported.

The reports of retrospective case series described by Iacono et al. (14, 16, 17) also give outcomes as overall composite scores. Mean follow-up time is short. Some individuals
early in the series have had much longer follow-up, though details of the procedure would have changed since they had surgery.

The retrospective case series reported by Laitinen (21), which is the largest group studied to date, reports individual outcomes, with 83% having good results and 14% fair results (substantial improvement). However, these were short-term findings and systematic follow-up was not undertaken.

Additional detail, including individual results, are given in the paper by Baron et al. (3) describing a prospective study on a small series which included appraisal of “on” and “off” states. PVP significantly improved tremor, rigidity, akinesia/bradykinesia, gait dysfunction and drug-induced dyskinesia. The mean total UPDRS scores improved by 30.1% at 3 months postoperatively, compared with pre-operative values. However, at the end of the first year, the UPDRS score was improved by only 19.7%. Also, mean combined “on-off” Schwab and England scale scores (measuring functional independence) increased from 48.8% to 73.0% postoperatively. The mean totals remained improved at one year postoperatively, though scores had declined from the 3-month values for a number of individuals.

Baron et al. (3) noted that when the post surgical Unified Parkinson’s Disease Rating Scale (UPDRS) “off” to “on” subscores were compared, the greatest improvements in parkinsonian symptoms were seen in the “off” state. Their study, along with the studies of Lozano et al. (25) and Dogali et al. (7) showed that post surgical benefit in the “on” state apart from drug related complications were neither significant nor sustained, contrary to the results reported by Iacono, et al (17) during the “on” state.

While these studies have shown that PVP can achieve benefits, the strength of evidence is limited. On the basis of a classification system that considers study design and conditions of scientific rigour (Appendix B), the strength of evidence would be regarded as fair to poor. There are still no well controlled, prospective studies of adequate power and follow-up.

Obeso et al. (29) have drawn attention to the possible problems of using current scoring scales to evaluate the impact of PVP, noting that in trials for new anti-Parkinson drugs the placebo effect has been estimated to be as high as 30%. They report conducting a detailed clinical and neurophysiological analysis of six patients to provide a more objective assessment of the effect of pallidotomy. They point out that in comparison with a total motor score improvement of 39%, separate analysis of movements at a number of sites revealed more drastic although localized changes. Goetz and Diederich (11) have pointed to the desirability of having a central registry of patients receiving PVP. Currently there is no mechanism in place for tracking safety, benefit or numbers of patients undergoing the procedure.

While the evidence of benefit is comparatively limited, there seems no doubt that many individuals have been helped by PVP. There are strong anecdotal reports (13, 34, Calne, personal communication) from patients who have experienced major relief of symptoms following PVP, with a dramatic improvement to their quality of life.
**Adverse effects**

Post-operative complications from PVP reported in the literature include hemianopsia, facial weakness, dysphasia, hemiparesis, intracranial abscess, subcortical hematoma, and intrapallidal hemorrhage (17, 23). Complication rates reported in recent studies range from 6 to 7% (17, 21). There are cognitive changes associated with pallidotomy and there is some evidence that patients who have some degree of underlying dementia do particularly poorly in terms of subsequent cognitive decline (Martin, personal communication). Brief details from the more detailed studies are given in Table 1.

Due to the relatively short follow-up period and incomplete data, the long-term effects and complications of PVP remain unclear. Adverse effects have to be considered in the context of the severity of the condition for those who are candidates for PVP and expected complications and morbidity associated with alternative management options.

**Economic considerations**

In the UK, the Development and Evaluation Committee report from the Wessex Institute of Public Health Medicine (33) includes estimates of the cost per QALY gained in the first year after surgery for moderately severe and severe cases of Parkinson’s Disease. The assumption is made that there is significant relief of symptoms.

Costs of PVP in the UK, based on tariffs of a major teaching hospital, are given as £4,309 for a neurosurgery inpatient. Annual cost of levodopa would be less than £100, and alternative medical treatment to pallidotomy, which includes apomorphine infusion, could cost in excess of £10,000 per year. Some centres have reported benefits from apomorphine given as a subcutaneous infusion in management of “on/off” fluctuations to levodopa.

Cost per QALY of PVP for moderately severe cases in the first 12 months might range from £25,000 to £65,000 depending on baseline assumptions relating to pre-operative status. If benefits from the procedure are realized for a longer period than 12 months than cost per QALY would be correspondingly reduced. Estimates of cost per QALY of PVP for severe cases in the first 12 months after treatment ranged from £15,600 to £27,000, again depending on the baseline assumptions made. These estimates did not include provision for potential savings which might result from pallidotomy substituting for apomorphine infusions.

Hospital charges in the USA for the procedure range from US $7,000 to $25,000 (8). In 1994, HCFA paid out 400 claims for pallidotomy under CPT code 61720, for a total of $722,000 with an average cost per procedure at $1,805 (Health Care Finance Administration, personal communication).

Economic data related to potential use in Alberta are not available. However, if a two day hospital stay were achieved in the province, charges for the procedure might be substantially less than those cited in US and UK publications.
Alternative approaches

PVP by stereotactic radiosurgery has been used in selected patients with idiopathic, advanced Parkinson’s Disease and related moving disorders. Rand et al. (32) reported preliminary results with use of the gamma knife for thalamotomy and PVP, with this technology providing relief in symptoms for some patients. In contrast, Friedman et al. (10) reported a negative experience in treating four patients with advanced Parkinson’s Disease with the gamma knife, with only one person’s symptoms changing significantly.

In their comments on the importance of electrophysiologic studies and neurologic examination during PVP surgery, De Salles et al. (6) suggest that the need for such procedures serves to advise patients to avoid radiosurgical pallidotomy because such monitoring is impossible with that technique. The implication is that location of the tissue to be destroyed will not be sufficiently precise.

Another treatment under investigation is chronic high-frequency stimulation of the pallidus and also of the sub-thalamic nucleus and the thalamus. Proponents emphasize reversibility, adaptability, and low morbidity of this approach. Long-term results are unknown, nor is the mechanism of action understood. Goetz & Diederich (11) point out that the stimulator can be turned off and on and even be removed if the procedure does not help the patient. Unlike pallidotomy, it is not a purposely destructive procedure.

In 1994 Siegfried & Lippitz (35) reported a preliminary study on use of bilateral chronic electrostimulation of the ventroposterolateral pallidum as an approach for alleviating Parkinson’s symptoms. Satisfactory results were obtained with three patients, with effects persisting up to 12 months in one case. Optimal parameters were a steady train of square-wave pulses 210ms in duration with a repetition frequency of 130Hz and an amplitude just less than that which elicited visual phenomena. Programmable pulse generators were implanted subcutaneously and connected to intracerebral electrodes implanted in the posteroverentralateral part of the pallidum.

They suggested that such stimulation presented an attractive alternative for patients with otherwise intractable Parkinsonian akinesia and other manifestations of the disease. They also commented that adverse effects might be less frequent than in destructive pallidotomy; that the safety, specificity and reversibility of the method make it accessible for older patients; and that a bilateral approach in one session is advantageous. Reported adverse events include transient facial dysesthesias (sensory impairment) and if the procedure is done bilaterally, slight speech disturbances (11).

Points made in comments on this work included the need to define the precise location of the electrodes in the pallidum and to clarify which symptoms of Parkinson’s Disease seem to respond to high-frequency stimulation. Also, the safety of the procedure would need to be demonstrated, with possible risks including dislodgment of the electrode or breaking of the wire. Infections after brain electrode implants have been reported in the order of 4-6% (1).
In a series of 62 patients, Iacono et al. (15) reported the elimination of akinetic features and other symptoms during intraoperative stimulation trials in areas anterior to the PVP target in 30 cases. For the other 32 patients stimulation at the PVP target site resulted in insignificant changes. The beneficial effects were achieved with as little as 0.25V at 100Hz. This was a consecutive series of patients who were undergoing PVP and being observed for effects of stimulation in various regions of the pallidum while refining probe location prior to lesioning. The effects in those that responded waned gradually over one to fifteen minutes following cessation of stimulation trials.

These authors suggest that while PVP has proven therapeutic significance in management of Parkinson’s Disease, the possibility of chronic pallidal stimulation is an attractive therapeutic option. This approach, as compared with PVP, could provide a better bilateral effect, the opportunity to target other brain regions to achieve benefits and a less invasive or physiologic alternative. Chronic stimulation would also avoid PVP associated risks of lesion induced permanent neurological damage. The Toronto Hospital is involved in a multicentre study with US and European groups to assess deep brain stimulation on regions other than the thalamus.

Results of a multi-centre trial of chronic electrostimulation of the thalamus, which included some patients with Parkinson’s Disease, have demonstrated an improvement through reduction in tremor, with 58% of the Parkinson’s cases having a marked reduction (18).

The more controversial neurosurgical treatment of striatal transplantation of fetal tissue is not considered here.

**Discussion**

As noted by Martin (26) there are many unanswered questions regarding PVP. There seems to be no consensus among surgeons on how the procedures are to be performed. Not all patients experience the same degree of benefit and further investigation of patient selection is required. The duration of benefit is currently unclear. Symptomatic response is primarily unilateral on the side opposite the pallidotomy. Most Parkinson’s patients have bilateral symptoms but the safety and efficacy of the bilateral procedure is unknown and requires further evaluation. Furthermore, it is difficult to assess post-operative improvement due to the variation in symptoms with which Parkinson’s Disease patients present and the speed with which the disease progresses (20).

Debate continues on which techniques are appropriate for localization of the target site for ablation (20). It has been estimated that half of the institutions that perform pallidotomy do not use microelectrode mapping for electrophysiological targeting (4, 9).

The review undertaken for the present report confirms other opinions that outcome data for the procedure are based on studies which provide relatively weak evidence. There are still few long-term follow-up data available. It is possible that placebo effects could be significant. Many patients are highly motivated individuals who want to get better (20).
Complications have been reported in a number of series, though these need to be put into the context of the seriousness of the condition.

The Wessex Institute of Public Health Medicine Development and Evaluation Committee concluded that the procedure was not proven, but that it held potential and that randomized controlled trials should be undertaken to evaluate the technique (33). The Emory University Hospital, Atlanta, is conducting a randomized clinical trial to measure the effectiveness and safety of PVP. The study will focus on the exact tissue area that should be destroyed and the longevity of the benefit obtained.

Laitinen (21) and Goetz and Diederich (11) consider that at this stage PVP is best suited to relatively young patients with intractable dyskinesia and “on/off” fluctuations. They suggest that, from the data available, patients with poor response to levodopa, prominent tremor or rigidity and without motor fluctuations are less likely to experience benefit and may be better suited for other treatments. Because of surgical and medical complexities it is important to perform this surgery in specialized centres where combined neurological, surgical and biostatistical expertise are available. Lang (personal communication) advises that specialized centres performing PVP should have expertise in both the neurological side of investigation, management and care of persons with Parkinson’s Disease, and in functional neurosurgery of movement disorders.

The use of chronic electrostimulation on one or both sides as an alternative to unilateral or bilateral PVP requires further study but potentially it could be a useful alternative to surgery in some patients.

PVP appears to be a promising technique for some patients with Parkinson’s Disease which is in need of further validation. While the current evidence on its efficacy is limited, there seems no doubt that at some centres many persons with Parkinson’s Disease have obtained substantial improvement to their quality of life following treatment with PVP. Surgical experience using stimulation trials and verification of target sites prior to surgery seems to result in the reduction of the adverse events since the margin of error reported by Kelly (20) is between two to three mm on either side of an ideal lesion. The technique will continue to be seen as an management option for cases where the disease has become refractory to medical treatment.

With regard to any future use of PVP in Alberta, or referral of patients elsewhere, it is suggested that:

- The procedure should be regarded as an evolving technology, with uncertain outcomes, until further data become available.
- PVP should be performed only at centres with appropriate specialized expertise.
- Systematic collection of data on PVP cases in the province should be obtained, to include long-term follow-up. Lang (personal communication) has commented that both “off” and “on” period assessments should be obtained in such data collection. This implies making transport and accommodation arrangements for some patients in the “off” periods.
• Contact should be maintained with other centres undertaking PVP.
• The comparative advantage of PVP should be kept under review, both in regard to more conventional methods of management and to chronic electrostimulation techniques, which may offer effective alternatives which do not involve destruction of tissue.
### Table 1: Clinical studies of PVP

<table>
<thead>
<tr>
<th>Author/Year</th>
<th>Study Details</th>
<th>Age Range (years)</th>
<th>Duration of Illness (years)</th>
<th>Patient Assessment</th>
<th>Procedure</th>
<th>Findings</th>
<th>Adverse Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Svennilson et al. 1960 (36)</td>
<td>• retrospective case series 1953 – 1957 • n=81</td>
<td>30-75 (65% over 50)</td>
<td>not available</td>
<td>disability no longer controlled by medication • disability graded by 2 indep. obs. as slight, moderate or severe • follow-up 1 to 5 yrs. by 2 independent observers</td>
<td>n=78 unilateral • n=3 bilateral • site of lesion was varied, technical adjustment continual in first 53 patients</td>
<td>77% (n=62) relief of rigidity &amp; tremor • 79% (n=64) relief of rigidity • 82% (n=67) relief of tremor</td>
<td>n=2 died at 3 mo. • n=3 transient hemiparesis • n=1 transitory hemiplegia &amp; epileptic fit • n=1 epileptic fit • total 9%</td>
</tr>
<tr>
<td>Laitinen et al. 1992 (22)</td>
<td>• retrospective case series 1985 – 1990 at 2 centres • n=38</td>
<td>30-80 mean 60</td>
<td>2-20 mean 9</td>
<td>motor performance assessed by writing, drawing and gait test 1 day before and 1 day after surgery • degree of dysfunction was graded as nil, slight, moderate and severe • follow-up at 2 to 71 mos. (mean 28)</td>
<td>localized target by CT • confirmation of site by electrical stimulation and impedance monitoring</td>
<td>89% (n=34) tremor, rigidity, and bradykinesia were completely or almost completely abolished contralaterally</td>
<td>n=6 homonymous scotoma and 1 of these patients had transitory facial weakness and dysphasia</td>
</tr>
<tr>
<td>Laitinen et al. 1992 (23) Note: This study includes patients from the earlier study.</td>
<td>• Retrospective case series 1985 – 1991 at 2 centres • n=46</td>
<td>30-80 mean 60</td>
<td>2-20 mean 9</td>
<td>the effect of conventional drug therapy was not satisfactory • motor performance assessed by writing, drawing and gait test 1 day before and 1 day after surgery • akinesia assessed with Purdue pegboard test • graded degree of dysfunction as nil, slight, moderate and severe</td>
<td>localized target by CT • confirmation of lesion site by impedance recordings and electrical stimulation</td>
<td>80% of the patients had complete or almost complete tremor relief • 91% of the patients had good relief of rigidity and hypokinesia</td>
<td>n=7 homonymous scotoma and 1 of these patients had transient dysphasia and facial weakness • n=1 transitory hemiparesis</td>
</tr>
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</table>
Table 1: Clinical studies of PVP (cont’d)

<table>
<thead>
<tr>
<th>Author/Year</th>
<th>Study Details</th>
<th>Age Range (years)</th>
<th>Duration of Illness (years)</th>
<th>Patient Assessment</th>
<th>Procedure</th>
<th>Findings</th>
<th>Adverse Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laitinen 1995 (21)</td>
<td>Retrospective case series 1985 – 1993 at 2 centres</td>
<td>30-87 mean 63</td>
<td>2-32 mean 12</td>
<td>not described in this publication</td>
<td>modified in 1992</td>
<td>results reported as good, fair or poor. Good means more or less complete relief of all symptoms contralaterally</td>
<td>n=11(4%) homonymous scotoma None of the last 100 patients treated in 1993 had this complication.</td>
</tr>
<tr>
<td></td>
<td>• n=259</td>
<td></td>
<td></td>
<td>no systematic follow-up, patients came from a number of countries</td>
<td>surgical target defined by CT and later by MRI</td>
<td>n=212 good results</td>
<td>n=2 foot apraxia</td>
</tr>
<tr>
<td></td>
<td>• modified in 1992</td>
<td></td>
<td></td>
<td>• electrical stimulation prior to lesioning without ventriculography</td>
<td>n=36 fair results (substantial improvement)</td>
<td>n=2 transitory facial weakness, 1 of which had dysphasia</td>
<td>n=2 transitory facial weakness, 1 of which had dysphasia.</td>
</tr>
<tr>
<td></td>
<td>• n=220 unilaterial</td>
<td></td>
<td></td>
<td>n=12 bilateral</td>
<td>n=11 poor results (minor or no improvement)</td>
<td>n=1 grand mal seizures</td>
<td>n=1 permanent neurological deficits</td>
</tr>
<tr>
<td></td>
<td>• n=18 one PVP and one thalamotomy</td>
<td></td>
<td></td>
<td>n=9 unilateral repeats</td>
<td>4% (n=11) did not improve 96% of patients had good to fair relief of all symptoms (tremor, rigor, bradykinesia and drug induced dyskinesia)</td>
<td>n=1 stroke</td>
<td>n=1 stroke</td>
</tr>
<tr>
<td></td>
<td>• n=9 unilateral repeats</td>
<td></td>
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</tr>
<tr>
<td>Iacono et al. 1994</td>
<td>retrospective case series 1990 - 1993 (PVP)</td>
<td>31-73 mean 58 (PVP)</td>
<td>2-24 mean 13 (PVP)</td>
<td></td>
<td>• localized target by MRI</td>
<td>total mean UPDRS scores for PVP decreased from 17.5 to 6.6 (62%) (p&lt;.05), all 16 items statistically significant except for the memory score</td>
<td>PVP (9%) n=1 transient hemiparesis N=3 intracranial hemorrhage secondary to platelet disorders and hypertension</td>
</tr>
<tr>
<td></td>
<td>(PVP) 1986 - 1989 fetal graft implementation (FGI)</td>
<td>39-68 mean 56 (FGI)</td>
<td>3-21 mean 11 (FGI)</td>
<td></td>
<td>• confirmation of site by ventriculography and electrical stimulation</td>
<td>total mean UPDRS scores for FGI decreased from 30.2 to 15.5 (49%) (p&lt;.05), only bradykinesia and postural instability of 16 items statistically significant</td>
<td>n=1 permanent neurological deficits</td>
</tr>
<tr>
<td></td>
<td>• n=55 PVP</td>
<td></td>
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<td></td>
<td>• not specified if all PVPs were unilateral</td>
<td></td>
<td>FGI n=1 died at 22 mos. of unrelated causes</td>
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<td></td>
<td>• modified in 1992</td>
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<td></td>
<td>• n=5</td>
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</table>
Table 1: Clinical studies of PVP (cont’d)

<table>
<thead>
<tr>
<th>Author/Year</th>
<th>Study Details</th>
<th>Age Range (years)</th>
<th>Duration of Illness (years)</th>
<th>Patient Assessment</th>
<th>Procedure</th>
<th>Findings</th>
<th>Adverse Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iacono et al. 1995 (15)</td>
<td>Note: This study includes patients from the earlier 1994 study.</td>
<td>31-80 mean 64</td>
<td>2-26 mean 13</td>
<td>Hoehn and Yahr grades of 3-5 when “on”</td>
<td>localized target by MRI</td>
<td>maximum reduction in tremor over a period of 1 to 6 mos.</td>
<td>n=4 intracranial haemorrhage related to hypertension and platelet disorders (1 suffered permanent neurological defect)</td>
</tr>
<tr>
<td></td>
<td>• retrospective case series at 1 centre 1990-1994</td>
<td></td>
<td></td>
<td>• all assessments conducted in “on” state</td>
<td>confirmation of site by ventriculographic &amp; electrical stimulation</td>
<td>average total Hoehn and Yahr score while “on” improved from 3.3 preop to 2.1 postop (p&lt;.05)</td>
<td>n=1 transient hemiparesis</td>
</tr>
<tr>
<td></td>
<td>• n=113 PVPs (not certain if this number refers directly to number of patients)</td>
<td></td>
<td></td>
<td>• pre and post surgery assessments included videotape, Hoehn and Yahr Staging 8UPDRS</td>
<td>number of unilateral and bilateral surgeries not clearly specified</td>
<td>average total UPDRS motor scores improved from 56.9 preop to 24.7 postop; dyskinetic scores significantly improved</td>
<td>n=2 permanent partial macular hemianopia</td>
</tr>
<tr>
<td></td>
<td>• 1 week preop. assessment conducted by an independent Parkinson’s Disease specialist</td>
<td></td>
<td></td>
<td>• follow-up at 1wk., 1mo. and sequentially up to 46 mos. (mean 12.1)</td>
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<td>“off” periods improved (p&lt;.05) and entirely eliminated in 51 patients</td>
<td>n=3 transient hemiparesis</td>
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<td></td>
<td>• Hoehn and Yahr grades of 3-5 when “on”</td>
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<td>axial symptoms: gait, posture and body bradykinesia resolved bilaterally</td>
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<td></td>
<td>• all assessments conducted in optimally medicated state</td>
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<tr>
<td></td>
<td>• videotape recordings and UPDRS, 1 wk. prior to surgery and 1 wk. post operatively</td>
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<td></td>
<td>• follow-up at 1 wk., 1 mo. and sequentially up to 12 mos. (mean 4.5)</td>
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<td></td>
<td>• localized target by MRI</td>
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<td></td>
<td>• confirmation of site by ventriculograms and electrical stimulation</td>
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<tr>
<td></td>
<td>• n=58 unilateral</td>
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<tr>
<td></td>
<td>• n=68 bilateral</td>
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<tr>
<td>Iacono et al. 1995 (17)</td>
<td>Note: This study includes patients from the earlier 1994 and 1995a studies.</td>
<td>31-80 mean 62</td>
<td>2-24 mean 11</td>
<td>Hoehn and Yahr grades of 3 to 5 when “on”</td>
<td>localized target by MRI</td>
<td>Hoehn and Yahr grades improved from preoperative average of 3.4 to 2.0 (p&lt;.05) in the “on” state</td>
<td>n=6 permanent partial macular hemianopia</td>
</tr>
<tr>
<td></td>
<td>• retrospective case series at 1 centre 1990-1994</td>
<td></td>
<td></td>
<td>• all assessments conducted in optimally medicated state</td>
<td>confirmation of the site by ventriculograms and electrical stimulation</td>
<td>all 10 UPDRS motor scores were improved and all were statistically significant</td>
<td>n=3 transient hemiparesis</td>
</tr>
<tr>
<td></td>
<td>• n=126</td>
<td></td>
<td></td>
<td>• videotape recordings and UPDRS, 1 wk. prior to surgery and 1 wk. post operatively</td>
<td>n=58 unilateral</td>
<td>70 to 85 % of patients showed improvement for the 10 UPDRS items at mean follow-up of 4.5 mos.</td>
<td>n=2 permanent hemiparesis</td>
</tr>
<tr>
<td></td>
<td>• Hoehn and Yahr grades of 3 to 5 when “on”</td>
<td></td>
<td></td>
<td>• follow-up at 1 wk., 1mo. and sequentially up to 12 mos. (mean 4.5)</td>
<td>n=68 bilateral</td>
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<tr>
<td></td>
<td>• all assessments conducted in optimally medicated state</td>
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<tr>
<td>Dogali et al. 1995 (7)</td>
<td>• controlled prospective study at 2 centres to determine effects of PVP on medically in-tractable Parkinson’s Disease patients • n=18 surgery (S) • n=7 no surgery (NS)</td>
<td>42-79 mean 60 (S) 43-77 mean 64 (NS)</td>
<td>4-25 mean 10 (S) 7-17 mean 12 (NS)</td>
<td>• selection by advisory board (2 neurologists, 1 neurosurgeon) • NS grp desired surgery but were awaiting surgical outcome • all assessment done at 12 hrs. off medication • Core Assessment Program for Intracerebral Transplantation (CAPIT) &amp; UPDRS • videotape recordings for assessment of timed motor scores, randomized and blindly rated by 2 investigators follow-up assessment at 1 wk, and every 3 mos for 1 yr.</td>
<td>CT or MRI defined anatomical target (first 10 patients had both CT &amp; MRI and thereafter only MRI was used) • electrical stimulation before lesioning • all unilateral</td>
<td>• S grp improved in total UPDRS (ADL &amp; motor) scores (p&lt;.05) by a mean of 65%; improved in CAPIT subtest scores (p&lt;.05) by a mean of 38.2% contralateral limb, 24.2% ipsilateral limb and improvement by 45% in walk score • NS grp no statistically significant improvement in UPDRS or CAPIT scores</td>
<td>• n=1 sexually inhibited for 24 hrs. • n=1 MCA stroke at 7 mos.</td>
</tr>
<tr>
<td>Lozano et al. 1995 (25)</td>
<td>• prospective controlled trial to determine the effects of PVP on motor function • n=14 with unilateral surgery the unoperated side serves as the control</td>
<td>44-71 mean 59</td>
<td>7-25 mean 14</td>
<td>• mean Hoehn and Yahr score of 3.9 (2.5-5) while “off”; mean “on” score 2.9 • CAPIT, UPDRS, evaluation of dyskinesia and timed manual task • scored after 12 hrs off medication (worst “off”) and 1 hr after morning medication (best “on”) • videotape recordings before and after surgery were randomized and scored by an independent “blinded” neurologist • follow-up assessments at 1 wk and at 3 mo. Intervals up to 6 mos.</td>
<td>localized target by MRI • confirmation of site by microelectrode and micro-stimulation recordings • all unilateral</td>
<td>results reported 6 mos. after surgery • UPDRS total motor score in the “off” state improved by 30% (p&lt;.05) and total akinesis score by 22% (p&lt;.05) • postural instability/gait disorder in “off” state improved by 23% (p&lt;.05) (assessed without blinding) • UPDRS total ADL score improved by 31% (p&lt;.05) (assessed without blinding) “off” period total rigidity score improved by 30% (p&lt;.05) greatest improvement contralateral side and no change ipsilateral (assessed without blinding)</td>
<td>• n=3 mild facial droop for 2-3 wks</td>
</tr>
</tbody>
</table>
### Table 1: Clinical studies of PVP (cont’d)

<table>
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<tr>
<th>Author/Year</th>
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<th>Duration of Illness (years)</th>
<th>Patient Assessment</th>
<th>Procedure</th>
<th>Findings</th>
<th>Adverse Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baron et al. 1996</td>
<td>prospective case series</td>
<td>37-71 mean 57</td>
<td>7-31 mean 14.3</td>
<td>screened by 2 neurologists, inclusion criteria: idiopathic PD; 2 of 4 cardinal signs; Hoehn and Yahr score 3.0 or higher while “off”</td>
<td>localized target by MRI or CT</td>
<td>mean total UPDRS score improved by 30.1% (p&lt;.05) at 3 mos. and remained improved at 6 mo. and 1 yr.</td>
<td>n=2 subclinical hemorrhages</td>
</tr>
<tr>
<td></td>
<td>n=15 Since Dec., 1992</td>
<td></td>
<td></td>
<td>CAPIT, UPDRS, evaluation of dyskinesia and timed arm movements and walking tasks. Single modified Schwab and England activities of daily living</td>
<td>optocap tract and internal capsule identified by microelectrode recording and microstimulation</td>
<td>87% (n=13) reduction in tremor was immediate and substantial (p&gt; .05)</td>
<td>n=1 worsening dysarthria</td>
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<td></td>
<td>scored after at least 12 hours “off” and best “on” following morning medication</td>
<td>all unilateral</td>
<td>93% (n=14) contralateral drug induced dyskinesia was absent, little improvement in ipsilateral dyskinesias</td>
<td>n=1 postsurgical superior quadrantopia</td>
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<td></td>
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<td>Preop monthly intervals beginning at 3 mos.</td>
<td></td>
<td>bradykinesia markedly improved (p&gt; .05)</td>
<td>transient postop confusion</td>
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<tr>
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<td></td>
<td>Follow-up evaluations at 3 mo., 6 mo., 1 yr.</td>
<td></td>
<td>3 mo. gait, falling, postural stability, freezing in “off” state improved (p&lt; .05). 1 yr. postural stability and freezing scores no longer significant</td>
<td>transient facial weakness</td>
</tr>
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<td></td>
<td></td>
<td>actual numbers not available for all adverse events</td>
</tr>
</tbody>
</table>
Appendix A: Identification of information


Terms used included: “pallidotomy”, “globus pallidus”, “parkinson disease”, “stereotaxic technique”. The search was limited to English language publications and human studies. All clinical trials using PVP were chosen. Additional articles were identified from relevant text books, the reference list of retrieved articles and health technology assessment reports.
## Appendix B: Levels of scientific evidence

<table>
<thead>
<tr>
<th>Level</th>
<th>Strength of evidence</th>
<th>Type of study design</th>
<th>Conditions of scientific rigour*</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Good</td>
<td>Meta-analysis of randomised controlled trials</td>
<td>Analysis of patient individual data Meta-regression Different techniques of analysis Absence of heterogeneity Quality of the studies</td>
</tr>
<tr>
<td>II</td>
<td>Large sample randomised controlled trials</td>
<td>Assessment of statistical power Multicentre Quality of the study</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>Small sample randomised controlled trials</td>
<td>Assessment of statistical power Quality of the study</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>Non-randomised controlled prospective trials</td>
<td>Concurrent controls Multicentre Quality of the study</td>
<td></td>
</tr>
<tr>
<td>V</td>
<td>Non-randomised controlled retrospective trials</td>
<td>Historical controls Quality of the study</td>
<td></td>
</tr>
<tr>
<td>VI</td>
<td>Cohort studies</td>
<td>Concurrent controls Multicentre Quality of the study</td>
<td></td>
</tr>
<tr>
<td>VII</td>
<td>Case-control studies</td>
<td>Multicentre studies Quality of the study</td>
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<tr>
<td>VIII</td>
<td>Non-controlled clinical series Descriptive studies: surveillance of disease, surveys, registers, data bases, prevalence studies Expert committees, consensus conferences</td>
<td>Multicentre</td>
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<tr>
<td>IX</td>
<td>Anecdotes or case reports</td>
<td>Quality of the study</td>
<td></td>
</tr>
</tbody>
</table>

* Quality of the study assessed by specific protocols and conditions of scientific rigour.

Source: Adapted from references 12 and 19.
References


