# Cell transplantation in Parkinson's disease

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## Findings by SBU Alert

**Technology and target group:** In Parkinsons disease, the brain cells that produce dopamine die. Approximately 15 000 patients in Sweden have Parkinsons disease. In its early stages, the disease can often be treated successfully by drugs. However, in most patients the disease progresses after a few years to a stage with complications where drugs no longer have a sufficient effect. In patients with Parkinsons disease, cell transplantation is intended to replace dead brain cells. A solution containing small fragments of brain tissue is injected into the patients brain. The results to date suggest that cell transplantation mainly benefits patients who still have a positive effect from medication but who have started to have complications. The size of this patient group in Sweden is estimated to be between 100 and 200 per year.

**Patient benefit:** A valuable level of symptom amelioration was achieved in three open studies of 15 patients who received cell transplantation. This outcome remained at 2-year followup. There are two randomized placebo-controlled trials including 74 patients with advanced disease. Patients were followed for one or two years post implantation. Small, but statistically confirmed, improvements were noted in the first trial in patients under 60 years of age and in the second study in patients with less advanced Parkinson´s disease. Survival of the transplanted dopamine neurons was, however, substantially below what had been reported in earlier studies. Stereotactic surgery, the method used in transplantation, carries a risk for cerebral hemorrhaging. Furthermore, there is a risk for immunological rejection. The results to date suggest, however, that these risks are small.

**Scientific evidence:** Cell transplantation in treating Parkinsons disease is currently an experimental method under development. There is poor* documentation on the effects of treatment. There is no* documentation on the cost-effectiveness of the method.

Until further evidence becomes available the method should be used only within the framework of scientific studies.

*This assessment by SBU Alert uses a 4-point scale to grade the quality and evidence of the scientific documentation. The grades indicate: (1) good, (2) moderate, (3) poor, or (4) no scientific evidence on the subject.

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## Technology

Cell transplantation in Parkinson's disease is a method intended to replace dead brain cells. When these brain cells malfunction and die, there is a sharp decline in dopamine levels in the parts of the brain that control movement initiation and coordination [1]. Animal studies have shown that immature dopamine cells from the midbrain of a fetus can be implanted and can develop to a point where the release of dopamine is restored to normal levels. Studies have shown that cell transplantation improves the mobility in animals with experimentally induced Parkinson's disease.

Current trials of cell transplantation in patients with Parkinson's disease involve the use of small fragments of brain tissue from aborted human fetuses six to eight weeks old. A solution containing dopamine-producing cells is prepared. To treat a patient, the cells from six to eight fetuses are needed to assure that a sufficient number of dopamine-producing cells survive transplantation. Treatment involves placing a stereotactic frame on the patient's head, and using CT or MRI to calculate the target points in the brain.The cell solution is injected under local or general anesthesia at three to ten sites, initially on one side of the brain and then, in a later surgical procedure, on the other. The patient is admitted to the hospital two days prior to each transplantation procedure and can be discharged after one week. Immunosuppressive therapy is provided for one year following transplantation to reduce the risk of rejection.

## Target group

In Sweden, approximately 15 000 patients have Parkinson's disease. Annually 1 000 to 2 000 people in Sweden get Parkinson's disease. The mean onset age is 55 years. Common symptoms include tremors, hypokinesia (slowness and poverty of movement) and rigidity (muscle stiffness). Pharmacological treatment using L-dopa is initially successful in most cases, but after several years the symptoms usually deteriorate and the patients enter a phase with complications. This is characterized by rapid changes between periods of good mobility and periods involving pronounced symptoms, so-called "on-off" fluctuations. Furthermore, patients often display dyskinesia (involuntary movements), dystonia (painful muscle cramps), and impaired balance.

Study results suggest that patients who have entered the complication phase, but still retain some effects from L-dopa, would receive the greatest benefit from transplantation of dopamine cells [6]. The size of this patient group in Sweden is estimated to be between 100 and 200 per year.

## Relation to other technology

Cell transplantation in Parkinson's disease, is currently an experimental method. If transplantation yields the desired effects, the method may have several advantages compared to other treatment [1]. The most attractive aspect is that it replaces the nerve cells that have been destroyed. This can restore the normal dopamine levels in patients. When successful, the method has led to substantial improvement, and patients have been able to discontinue L-dopa treatment. In contrast from patients' own dopamine producing cells, the transplants do not appear to be affected by the disease process. This suggests that the symptom-alleviating effects may remain for many years without needing to repeat the treatment. A major problem with the current method, and one which makes it impossible to apply in a large number of patients, is that cell survival has yet been unsatisfactorily low (5–20 percent). Achieving the minimum of 100 000 to 150 000 surviving dopamine cells, which are probably needed on each side to achieve an effective transplant, requires tissue from six to eight fetuses.

In addition to pharmacotherapy, several surgical procedures can help alleviate the symptoms of Parkinson's disease. Well-established treatment methods for reducing tremors include thalamus stimulation and thalamotomy. Pallidotomy, pallidum stimulation, and recently subthalamic stimulation are treatment alternatives for patients in the complication phase (see Alert Report "Pallidotomy in Parkinson's Disease"). There are no studies that directly compare cell transplantation and subthalamic stimulation, which appears to be the most effective of these surgical methods.

## Patient benefits

A review of three open studies from Lund (Sweden) and Tampa (United States) of 15 patients found, in the second year post implantation, a 30 percent to 40 percent reduction in Parkinson's symptoms (measured by the Unified Parkinson's Disease Rating Scale, UPDRS, motor score) [6]. There was about a 50 percent reduction in the duration of the "off" phase and a 16 percent to 45 percent reduction in L-dopa dose. The data from Lund, where 12 patients have received transplants since 1989, showed that in four cases it was possible to withdraw L-dopa medication for 0.5 to 6 years. Approximately two thirds of the patients transplanted have shown valuable improvement in symptoms such as improved mobility and reduced stiffness. Improvement in gait, balance, and speech were noted in several cases. Even a lower prevalence of involuntary abnormal movement was noted in several patients while others showed an increase. Measures of health-related quality of life clearly improved following transplantation [3].

There are results from two North American double-blind controlled trials that compared the effects of cell transplantation and placebo (sham) surgery. The transplantation method differs in several respects from the methods used by other clinical research groups. In one trial 40 patients with severe Parkinson´s disease were randomized to treatment or control intervention and were followed up one year after transplantation [2]. The results showed small, but statistically significant, improvement in patients younger than 60 years of age. There was no significant difference in improvement among patients older than 60 years of age. In two patients, who died from other causes at seven months and three years following surgery respectively, the number of surviving transplanted dopamine cells was substantially lower than what had been reported in earlier studies [4]. This would probably explain the limited improvement in symptoms. In the other trial 34 patients with advanced Parkinson´s disease were included. At two years followup no significant difference between groups were found [12]. For patients who, at the time for cell transplantation, had less severe disease a significant improvement was found. In these trials patients received no or only short term treatment with immunosuppressives. This has been suggested as a cause for the limited improvements found [12].

The survival level of transplanted cells can be studied by advanced methods (histopathological methods and positron emission tomography, PET) [4,5,7]. PET studies have shown that transplants can survive more than ten years without being affected by disease, while the patient's own dopamine cells continue to die [7]. PET studies also indicate that the transplants are functionally integrated in the nerve circuits of the patient's brain [8].

## Complications and side effects

The clinical experience of cell therapy in Parkinson's disease is limited, and techniques vary among various centers, rendering it more difficult to assess the risks. Published studies have reported few acute risks for patients. Stereotactic surgery can cause hemorrhaging in the brain. No cases of hemorrhaging have been noted in 18 patients who received transplantation in Lund, despite nearly 200 implantation sites. No cases of immunological rejection have been observed.

An increased level of dyskinesias (involuntary movements) during the "off" phase has been noted in a not negligible part of transplanted patients [2,9,12]. This has led to direct mobility problems in 7–15 percent of these patients. The underlying mechanisms are unknown. It has been suggested that this might depend on unbalanced increases in dopaminergic function [10], or that the grafts have been too small in the dyskinetic patients [9,12].

## Ethical aspects

Using brain tissue from aborted fetuses has substantial ethical implications. Hence, it is particularly important to develop a method that requires less tissue per transplanted patient than is currently the case. Legislation in Sweden that addressed transplantation regulates how fetal tissue can be used for various purposes. Directors of the gynecology departments where tissue is collected are required to seek approval from the National Board of Health and Welfare. Furthermore, ethics committees must approve these research projects. Tissue can only be used after informed consent is obtained from the woman who undergoes abortion.

## Costs and cost effectiveness

Cell transplantation in Parkinson's disease is currently an experimental method.

The developmental costs are covered largely by research grants. In Lund, the total cost for a bilateral transplantation is estimated to range from 150 000 to 200 000 SEK.

Although the costs for individual patients can be high, the total economic impact on health care in the near future will be minor.

## Structure and organization of health services

Cell transplantation in patients with Parkinson's disease requires a particular type of organization for the collection, preparation, and implantation of fetal cells. This requires close collaboration among specialists in gynecology, neurobiology, and neurosurgery. It also requires an organization to select and examine patients prior to surgery and later to manage followup. Specialists in neurology are required, as are advanced examination methods such as PET. Currently, the only hospital in Sweden organized for such treatment is the Lund University Hospital.

This method should be diffused slowly since it is still being developed, and there is considerable uncertainty about its effects, costs, and ethical implications.

## Diffusion in Sweden

In September 2003, a total of 18 patients with Parkinson's disease in Sweden had been treated with transplantation of fetal cells. All procedures were performed at the Lund University Hospital.

## Current evaluation research

Several key problems remain to be solved before cell transplantation for Parkinson's disease can be used as a treatment method. Continued research and assessment of the method focuses on the following questions:

**1. How can survival of transplanted cells be extended?**
There are several drugs which are shown to counteract acute cell death and yield a two- to three-fold increase in dopamine cell survival in animal trials. For a method to be clinically viable, cell survival must be five to ten times higher so that the tissue from a single donor is sufficient for transplantation in a single patient.

**2. Are there alternatives to using fetal cells from humans?**
There are two emerging alternatives to human fetal cells. One is to use animal transplants, mainly dopamine cells from pig fetuses. The second is to use stem cells. The advantage of stem cells is that they can increase in large number in cell culture. For application in patients with Parkinson's disease, stem cells must be developed to produce dopamine.

Researchers in the United States have shown that embryonic stem cells can be made to form dopamine neurons under the influence of growth factors and signaling molecules. At the Karolinska Institute, a procedure has been developed whereby immature stem cells are gene modified so that they can be developed to dopamine neurons. These trials have been conducted on mouse cells. It remains to be shown whether the cells can survive in sufficiently large numbers following transplantation and whether they can function in animals where Parkinson's disease has been induced. It also remains to be shown whether stem cells from humans can be made to differentiate and function in the same way.

**3. How should the therapeutic effects of transplantation be improved?**
This research aims at developing procedures so that transplantation can improve functions in larger areas of brain. Further attempts are being made to determine where the transplant should be placed in the patient's brain to alleviate certain symptoms.

## Expert

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