📾 Fetal dopaminergic transplantation trials and the future of neural grafting in Parkinson's disease

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Clinical use of allografts of fetal ventral mesencephalic tissue as a treatment to replace dopaminergic neurons in patients with Parkinson's disease was first done more than 20 years ago. Since then, many patients have received transplants, with variable results. During this time, our knowledge of Parkinson's disease has changed and the nature and extent of problems associated with the disorder have been better defined. Our understanding on how best to implement this cell-replacement strategy for patients has grown, but gaining this insight has entailed critical reappraisal of data from transplant trials that have already been undertaken.

Introduction

As we move towards an era of stem cell-based treatments for neurodegenerative disorders of the CNS, particularly Parkinson's disease, the rationale for use of dopaminergic cell-based approaches to treat this disorder needs to be considered. Allografting of fetal ventral mesencephalic tissue as a dopaminergic replacement therapy in Parkinson's disease was first undertaken more than 20 years ago and since then many patients have had this procedure. The results from these interventions have been variable and, thus, the merits of this approach have been both questioned and championed.

In this Review, we describe the rationale for use of fetal ventral mesencephalic allografts and discuss how, as our knowledge of Parkinson's disease has changed, our understanding has altered on how best to use this repair strategy for patients. This understanding is based on a better definition of the nature and extent of problems in Parkinson's disease but also has entailed a critical reappraisal of data from transplant trials that have already been undertaken. This reanalysis has led us to plan a clinical trial sponsored by the European Union (TRANSEURO), which will include careful selection of patients (age, stage of disease, type of Parkinson's disease), tissue preparation (number of cells grafted, dopaminergic vs serotonergic content of the graft), tissue placement (location, tract numbers), graft support (storage media, immunotherapy after grafting), and trial design (numbers of patients, follow-up time, endpoints). The discussions and analyses that have led up to this new trial form the basis for this Review.

Early clinical trials

Transplantation of cells and tissues to the brain has a long history, dating back to the late 19th century.¹ In the 1970s, conditions for good and consistent survival of neural tissues were elucidated more systematically. The idea to use cell transplants to substitute for loss of dopamine neurons in the brains of patients with Parkinson's disease evolved at a time when levodopa therapy had been in clinical use for about a decade. Although a great clinical success, the problems and limitations associated with long-term use of levodopa-

ie, the on-off fluctuations and the emergence of dyskinesias-had by then become apparent and suggested that there could be better ways to restore dopamine neurotransmission.

Experimental work undertaken in the early 1980s was based on the idea of restoring striatal dopamine release through reinnervation of the denervated striatum.^{2,3} The dopamine neurons used in these experiments were neuroblasts obtained from mid-trimester rat fetuses. Findings of these early studies showed that recovery of motor functions induced by the grafted dopamine neurons was well correlated with the extent of graft-derived reinnervation of the host caudateputamen and that the effect of the grafts on different aspects of motor behaviour depended on which part of the caudate-putamen was covered by the outgrowing axons.^{3–6} More complete behavioural recovery, therefore, was obtained only with transplants whose axonal terminal network covered a large part of the denervated striatal territory.

In March, 1986, the ethics delegation of the Swedish Society for Medicine issued provisional guidelines for the use of tissue from aborted fetuses for transplantation purposes (later included in Swedish law). This guidance paved the way for planning of clinical trials, the first of which was undertaken in Lund, Sweden, in 1987. Key to the clinical protocol was data from preclinical experiments showing that cell suspensions prepared from ventral mesencephalic tissue from fetuses aged 6.5-9 weeks survived well in the striatum of immunosuppressed rats with lesions induced by 6-hydroxydopamine, released dopamine, and were able to reverse the lesion-induced motor deficits in the grafted animals.7 Because these early trials had to be done in small groups of patients, in an open design, the assessments had to be as standardised and objective as possible, using a set of quantitative tests of motor function. This assessment protocol was developed by Olle Lindvall and became the core assessment programme for intracerebral transplantations (CAPIT protocol).8.9 Moreover, use of ¹⁸F-fluorodopa PET provided an additional objective measure that made it possible to monitor important aspects of these early trials-ie, survival and growth of the grafted dopamine neurons.

By 1991, six patients had undergone graft transplantation in Lund, four with advanced idiopathic Parkinson's disease¹⁰⁻¹² and two patients with parkinsonism induced after intravenous self-injection with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP).¹³ Moreover, similar programmes had been initiated in England,¹⁴ Spain,¹⁵ the USA,¹⁶ Mexico,¹⁷ Cuba,¹⁸ France,¹⁹ and Belgium.²⁰ In the USA, this development took place amid a debate about the ban on federal funding for fetal tissue research that had been introduced by the Reagan administration in 1988. The promising results reported in 1992 in three papers,13,21,22 just before the Clinton administration took over, most probably had a role in the new president's decision to lift this ban in January, 1993. This reversal opened the way for the National Institutes of Health (NIH) to provide funding for the two placebocontrolled studies that were to define the fate of fetal cell transplantation in the next decade.

Open-label studies

Despite the successful clinical outcome of ventral mesencephalic grafts in some patients, with correlative changes on 18F-fluorodopa PET and post-mortem data showing robust long-term cell survival, widespread adoption of this technique was still not realistic. Indeed, not all transplant recipients showed substantial clinical improvements, and although no adverse side-effects of the procedure were noted in these early studies, many patients showed no or only modest benefit (figure 1).^{11,27} This result could have been due to differences in the age of the donor tissue (6-11 weeks), the number of donors (1-7 donors per side), the target site for transplantation (either the putamen, the caudate nucleus, or both), the endpoints chosen for the trial, and the different immunotherapy regimens adopted. However, as shown in figure 1, even within the same centre, the variability in clinical outcome was striking, suggesting that heterogeneity of patients and the unique nature of ventral mesencephalic tissue transplants required further attention and that the transplant protocol still needed to be optimised.

The results of these open-label studies, while persuasive, were judged by some to be of insufficient quality to merit further investment until data from double-blind, placebo-controlled trials were available. Whether this area of research had evolved to the point that such studies were justified—since much of the methodology had still not been optimised—was a moot point. Nevertheless, the NIH decided to fund two trials in patients with Parkinson's disease.^{24,25}

Double-blind, placebo-controlled clinical trials

In the first NIH-funded study, undertaken by Freed and colleagues (referred to here as the Colorado/Columbia trial),²⁴ 40 patients with advanced Parkinson's disease were randomly allocated to either fetal nigral transplantation or sham surgery. Those assigned to the active treatment arm received culture-stored mesencephalic

tissue from four embryos, each between 7 and 8 weeks of age, that was implanted bilaterally into the putamen through four needle tracts (two on each side), using a frontal stereotaxic neurosurgical approach. Those in the sham surgery arm went through an identical procedure except that the dura was not penetrated and no needle was passed into the brain; these patients were offered transplantation 12 months after the initial surgery. No patients in either arm of the study received immunosuppressants. Patients were followed up for 1 year after surgery and the success of the trial was judged on the basis of a subjective self-report rating of clinical improvement or deterioration, scored by patients in their own homes and then sent to the investigator. Unified Parkinson's disease rating scale (UPDRS) performance, Schwab and England scores, and ¹⁸F-fluorodopa uptake by PET were also recorded.

Although graft survival and growth was confirmed by both ¹⁸F-fluorodopa uptake and subsequent postmortem data,²⁴ the Colorado/Columbia trial failed to meet its primary endpoint, with no difference between transplanted and non-transplanted patients in their perceived levels of improvement after surgery (mean global rating score for transplanted patients was 0.0 [SD 2.1] vs - 0.4 [1.7] for those who received sham surgery [negative score indicates worse disease]; p=0.62). Total UPDRS scores did not differ between



Figure 1: Change in UPDRS score for patients enrolled in ventral mesencephalic transplant trials

Data are taken from studies undertaken at five North American and European centres. Circles represent the % change from baseline in UPDRS score for every patient at every centre. UPDRS=unified Parkinson's disease rating scale. study arms. However, when each group was dichotomised according to age ($\leq 60 \nu s > 60$ years), scores on the UPDRS for the younger transplanted group improved significantly in terms of their undefined off scores after surgery (0.5 [2.1]) in the transplanted group vs -0.3 [1.7]in the sham surgery group; p=0.36). When the motor component of the UPDRS was analysed in isolation, the improvement was 34% in the younger group, greater than the standard 33% threshold used to judge the efficacy of levodopa responsiveness. In the older group, UPDRS scores did not differ between transplanted patients and those who received sham surgery. The interaction between the older and younger groups was not formally analysed. Additionally, improvement on the Schwab and England score was far greater in younger transplanted patients than in the older group. Five (15%) of 33 patients who ultimately received a transplant (including those from the sham surgery arm who elected to have the transplant after the study) went on to develop dyskinesias, typically within the first year after grafting. These persisted after a substantial reduction or elimination of dopaminergic medication, and although initially called runaway dyskinesias, they are now known as graft-induced dyskinesias. All these patients were younger than 60 years at the time of transplantation and had experienced severe on-off fluctuations and levodopainduced dyskinesias before surgery.

In a subsequent re-evaluation of the Colorado/Columbia study,28 Freed and colleagues discuss the problems and shortcomings related to the highly subjective endpoint used. Indeed, they comment that patients' perceived improvement (or lack of improvement) was very different when they were not simply asked how much better they felt but when they were shown a video of what they looked like preoperatively. In a second follow-up study, Ma and coworkers²⁹ reported the longterm outcome at 2 and 4 years' post surgery. This analysis, undertaken unblinded and without the original control group, showed significant improvements in UPDRS motor scores and 18F-fluorodopa PET, in line with the findings reported in the open-label studies that preceded this trial.^{27,30} Moreover, the post-transplant changes in ¹⁸F-fluorodopa uptake in the grafted putamen correlated significantly with the clinical outcome over the course of the study, whereas uptake in other nontransplanted areas (caudate and ventro-rostral striatum) showed a progressive decline.

In the second NIH-funded placebo-controlled trial, undertaken by Olanow and colleagues (referred to here as the Tampa study),²⁵ 34 patients were randomly assigned either to receive bilateral transplants of ventral mesencephalic tissue into the post-commissural putamen, using tissue obtained from either one or four donors per side (aged 6–9 weeks), or to undergo sham surgery (same procedure as that used in the Colorado/Columbia trial). Cells were transplanted as solid grafts via eight needle tracts

per side, and tissue was stored at 4°C for no more than 48 h before transplantation. All patients received 6 months of immunosuppression with ciclosporin after surgery. The primary endpoint for this study was a significant difference between treatment groups in the change in off state UPDRS score between baseline and the final visit (24 months after surgery). Secondary endpoints included the proportion of time spent in the on state without dyskinesias (measured by diary cards), change in putamenal ¹⁸F-fluorodopa uptake between baseline and final visit, and analysis of individual components of the UPDRS.

The primary endpoint of the Tampa study was not met for both active groups (one and four donors) despite evidence of good graft survival and reinnervation of the striatum. Although age did not play a part in the outcome of the trial, stratification by median baseline UPDRS score (\leq 49) indicated that patients with less severe disease who received transplants from four donors improved by a mean of 1.5 (SD 4.2) points on the UPDRS, compared with a deterioration of 7.3 (4.3) points in the group with one donor and 21.4 (4.3) points in the sham group. The difference between the four-donor group and the sham arm was borderline significant (p=0.06).

13 (57%) of 23 patients who received a transplant in both active groups (compared with none in the sham-operated group) developed graft-induced dyskinesias during the course of the Tampa study, typically 6–12 months' post surgery. In three patients the dyskinesias were disabling and needed further surgical intervention at the end of the trial. No correlation was reported between graft-induced dyskinesias and either on-medication dyskinesia scores, UPDRS score, levodopa dose equivalence, or striatal ¹⁸F-fluorodopa uptake.

The decision to stop immunotherapy after 6 months in the Tampa study was noteworthy because up to this point the grafted groups had improved at a rate similar to many of the successful open-label studies. However, patients deteriorated after immunotherapy was stopped and, thus, a delayed immune or inflammatory response might have compromised long-term survival, growth, or function of the grafted cells. Indeed, in four patients with post-mortem data, immunohistochemistry for activated microglia showed a prominent inflammatory reaction in and around the graft deposits.25 Others have argued that the patients were not as levodopa-responsive as in other trials and, therefore, many could have been too advanced to benefit from the dopamine cell-replacement approach. No long-term follow-up data are available for these patients and no further conclusions can be drawn. Of note, however, is the fact that sham-treated patients showed deterioration over time-ie, no evidence was noted of a placebo effect or any investigator bias.

Systematic review of ventral mesencephalic transplant trials

To further investigate the effect of patient selection on the outcome of these clinical trials, we have done a systematic

review based on data made available to us by five North American and European centres that have been actively involved in grafting of fetal ventral mesencephalic tissue in Parkinson's disease patients.^{11–13,19,23–27,30,31} This analysis included the Colorado/Columbia²⁴ and Tampa²⁵ studies in addition to the open-label studies from Lund, Sweden,¹³ Paris, France,^{19,26} and Halifax, Canada.²³

Patient characteristics are summarised in the table. For the Tampa study,²⁵ data could not be obtained on the age of patients or the duration of Parkinson's disease, and for the Halifax study,²³ the times of last follow-up were unavailable. Last follow-up times varied within trials, except for the Tampa study, in which the final follow-up time was 2 years post graft for 20 of 23 patients in the treated group and for 11 of 11 in the sham arm. Ages of donors were unavailable for all studies. Data on the type of immunosuppressant used were missing for the Paris study,^{19,26} and both the Paris and Tampa²⁵ studies were missing data on number of donors and transplantation site.

The % change in UPDRS score from baseline to last follow-up measurement is shown for every patient in every study as a scatterplot (figure 1), and the mean % change for every study is shown as a Forest plot (figure 2A). Change in UPDRS score after grafting varied between studies. A useful analysis would be identification of the characteristics that contributed to this noted change The effect of age at the time of transplantation is shown in a Forest plot (figure 2B). The effect is shown to be positive in most studies, indicating that UPDRS scores worsen by a greater amount in older patients after the grafting procedure. For two patients with an age difference of 10 years, the older patient would be expected to have a worsening in UPDRS score of 7.5 percentage points greater than that experienced by the younger patient.

The effects of other patients' characteristics-sex, duration of Parkinson's disease at grafting, Hoehn and Yahr stage off-medication, time of the last UPDRS observation, the number of donors, and transplantation site—on % change in UPDRS score were also assessed across studies. Results were inconclusive. When comparing women and men the estimated effect was -4.48 (95% CI -16.71 to 7.76). For every additional year of follow-up it was -0.16 (-0.45 to 0.12). With every unit increase in Hoehn and Yahr stage the estimated effect was 3.07 (-7.45 to 13.60). For every additional year of Parkinson's disease duration it was 0.04 (-1.27 to 1.35). With every additional donor the estimated effect was 2.98 (-7.11 to 13.08). The estimated effect of targeting transplantation to both the putamen and the caudate, versus targeting the putamen only, was -7.84 (-30.91 to 15.23). Use of immunosuppressants was not investigated because this variable did not vary within studies when data were available.

New trials and reanalysis of previous studies

The cell-therapy trials undertaken so far have produced highly variable results, which have divided clinicians in this area into those who feel this treatment can work if one just keeps going and those who feel it has had its day and been shown to fail. Here, we have sought through reappraisal to highlight common reasons why trials up to now have produced such variable results. By taking these factors into account, future trial designs could be improved.

Animal models

Models of Parkinson's disease are poor imitators of the clinical disorder. As such, the ability to translate experimental findings to patients in clinical trials is always a case of educated guesswork. The animal models used to support the cell-therapy approach only recapitulate the loss of the dopaminergic nigrostriatal pathway, typically through neurotoxin lesioning (using 6-hydroxydopamine or MPTP). Therefore, testing any cell therapy in these animals will only be informative about either the extent to which the implanted cells can restore dopaminergic neurotransmission or the integrity of the dopaminergic pathway, at anatomical and functional levels. Although neither outcome is the same as restoration of normal motor function in patients with Parkinson's disease, they are a useful starting point, since the central approach to treatment of people with this disorder is to restore dopaminergic connectivity and neurotransmission pharmacologically. Importantly, grafted human neuroblasts develop very slowly in their new location, and they could take many months to differentiate into fully functional dopamine neurons and establish sufficiently widespread axonal connections in the host striatum. Consideration of this factor might

	Halifax ²³ (n=10)	Lund ¹³ (n=14)	Colorado/ Columbia ²⁴ (n=33)	Tampa ²⁵ [treated] (n=23)	Tampa²⁵ [controls] (n=11)	Paris ^{19,26} (n=12)
Sex						
Male	7 (70%)	12 (86%)	15 (45%)	18 (78%)	6 (55%)	6 (50%)
Female	3 (30%)	2 (14%)	18 (55%)	5 (22%)	5 (45%)	6 (50%)
Age						
≤60 years	7 (70%)	13 (93%)	17 (53%)			9 (75%)
>60 years	3 (30%)	1 (7%)	15 (47%)			3 (25%)
Duration of Parkinson's	disease					
≤10 years	1 (10%)	5 (36%)	7 (22%)			4 (36%)
>10 years	9 (90%)	9 (64%)	25 (78%)			7 (64%)
Hoehn and Yahr stage						
≤3	4 (40%)	7 (50%)	18 (55%)	5 (31%)	2 (22%)	2 (17%)
>3	6 (60%)	7 (50%)	15 (45%)	11 (69%)	7 (78%)	10 (83%)
Last follow-up after graft						
≤40 months		6 (43%)	9 (27%)	23 (100%)	11 (100%)	7 (58%)
>40 months		8 (57%)	24 (73%)	0	0	5 (42%)

Data are number of patients (%). For the Tampa study,²⁵ treatment and control groups have been summarised separately. For the remaining studies, only data from treatment groups were available. Patients with missing values have been excluded from characteristic totals.

Table: Summary of patients' characteristics in ventral mesencephalic transplant trials





(A) Forest plot of the mean % change in UPDRS score. (B) Forest plot of the effect of age at the time of transplantation; estimates from univariate linear models. Overall estimate from random effects meta-analysis.^{32,33} UPDRS=unified Parkinson's disease rating scale.

require studies in MPTP-lesioned non-human primates, which allow for prolonged studies and for investigation of longer pathway reconstructions and more complex behavioural analysis.³⁴

Different cell-replacement strategies

Although all cell therapies used to date aim to replace the lost dopaminergic neurons of the substantia nigra, the ways in which they work are not the same. For example, the retinal pigment epithelial cells included in spheramine (Titan Pharmaceuticals, San Francisco, CA, USA) were proposed to work by releasing dopa, with the additional advantage that they might also release growth factors to promote endogenous repair.³⁵ However, data in support of this idea were scant, and the capacity of the cells to survive and release dopa to any significant extent was highly debatable.³⁶ Thus, findings of clinical trials with spheramine cells cannot predict what can be achieved with fetal ventral mesencephalic transplants. To discuss them all as being essentially similar is misleading and can lead to erroneous conclusions.

Placebo effects

In Parkinson's disease, the placebo effect is complicated because of the natural variability of the disorder, particularly in patients receiving drugs to manage symptoms,³⁷ and because the acute placebo effect could be mediated by endogenous dopamine.³⁸ Nevertheless, findings of open-label studies can provide clear signals

of efficacy when assessment is done in an unbiased way and follow-up is extended over several years, with a reviewer to assess all cases who is unaware of treatment allocation. Indeed, whether placebo effects really happen in the long term is debatable in view of data from the Tampa study.25 Similarly, in a state-of-the art, double-blind, sham surgery-controlled, gene-therapy trial,39 the overall change in UPDRS motor score in controls over the 6-month observation period was very small (12%). Although placebo effects are observed, this occurrence is not a feature of all surgical Parkinson's disease trials; it has been seen in some commercially sponsored trials40-42 but is unlikely to be sustained for years if follow-up is maintained.43 The size of clinical improvement that will have any long-term therapeutic importance, such as reductions in UPDRS scores of more than 50%, far exceeds that typically seen in placebo controls, even in trials entailing surgical intervention.44

Study duration and follow-up

The only way to take a new cell therapy to the clinic is by doing small open-label studies that enable safety and efficacy to be monitored. Optimisation of the treatment could take time and require several small open-label studies to be undertaken, because the whole process is an iterative one. Indeed, it is unlikely that the first trials will be correct in every respect, especially when tolerability of both surgery and the graft is paramount. Thus, all celltherapy approaches will evolve stepwise as information from carefully implemented exploratory trials becomes available. Only when all variables have been fully investigated can bigger and more definitive controlled trials be planned.

Furthermore, cells used for replacement approaches work by becoming integrated into the recipient's neural pathways. This process takes months to years and, thus, any trial that uses a short endpoint runs the risk of missing late effects, as seems to have been the case in the Colorado/Columbia study.^{24,29} Indeed, all cell-therapy trials should ideally have built into them long-term follow-up of all grafted patients, so late effects can be assessed properly—both positive and negative ones. Indeed, the two patients reported by Politis and colleagues⁴³ are still improving more than 15 years after receiving their ventral mesencephalic grafts.

Type and stage of Parkinson's disease

In early trials, Parkinson's disease was largely thought of in terms of a single disease state caused by loss of nigral dopaminergic cells. However, over the past 25 years, subtypes of the disorder have been defined,⁴⁵ only some of which might respond to dopaminergic cell treatments. Furthermore, as the disease progresses, a host of downstream events take place secondary to loss of dopaminergic neurons and the non-physiological treatment of this loss with oral dopaminergic therapy.^{66,47} Indeed, in some clinical trials, younger patients²⁴ or those with less advanced disease²⁵ have fared best. Moreover, evidence shows that patients with widespread dopaminergic loss outside the dorsal striatum have poorer outcomes.⁴⁸ Therefore, cell-based dopaminergic replacement approaches for Parkinson's disease might fail, not because of unsuccessful treatment per se, but because the patient had a non-responsive form of Parkinson's disease or the graft was given at the wrong stage of disease.

Side-effects

In the initial open-label studies of fetal ventral mesencephalic transplants, various clinical benefits and no clinically significant side-effects were reported. Subsequently, some patients developed graft-induced dyskinesias, the cause of which has been a matter of intense debate. These movement disorders were reported in only some individuals, all of whom had levodopainduced dyskinesias before grafting.

The relation of graft-induced dyskinesias to levodopainduced dyskinesias is unclear, but two theories have been advanced. The first idea posits that they arise as a result of non-homogeneous delivery of dopamine cells across the putamen, resulting in striatal dopaminergic hotspots.^{49,50} The second proposal is that serotonergic neurons in the transplant could be releasing dopamine in an unregulated manner, as a false transmitter.⁵¹

Pathological features

In 2008, grafts of fetal ventral mesencephalic tissue were reported to have a degree of Lewy body pathology within them, which has since been verified by evidence of neuronal dysfunction-ie, loss of tyrosine hydroxylase and the dopamine transporter.52-55 The reason why these grafts acquired these pathological features has been debated extensively, and two theories have been proposed that could explain this phenomenon. The first is that Lewy body pathology is a reaction to inflammation at the graft-host interface, possibly mediated by cellular stress induced by reactive microglia.56 In the second, pathological changes are suggested to represent the spread of α-synuclein to the graft from the host.^{57,58} Whatever the exact reason, these pathological changes are not likely to be a major limiting factor to the widespread adoption of cell-based replacement treatments because the number of cells with Lewy body-like pathology in the grafts is small compared with the number of healthy tyrosine hydroxylase-positive cells.^{55,59} Furthermore, patients can still be functionally stable, or even improving, more than a decade after the graft procedure, at a time when accumulation of α-synuclein has been described.43,60 Nevertheless, we cannot exclude the possibility that such pathological changes could ultimately lead to graft failure decades after implantation, but under such circumstances, the years of benefit outweigh the final fate of the transplanted cells.

Search strategy and selection criteria

Because only a few trials have been completed in this area, a formal systematic review of the scientific literature was not completed. Instead, since the published work is well known, articles were identified from the authors' own files, and original data were requested. Only papers published in English were reviewed. The final reference list was generated on the basis of relevance to the scope of this Review and accessibility to the raw dataset.

Commercial stem-cell treatments

The expansion of clinics offering unproven cell-based treatments for disorders of the nervous system, including Parkinson's disease, poses a serious threat to the whole research area.⁶¹ These therapies, which typically need to be paid for by patients or their families, include a whole range of different types of cells, and although most are given peripherally, delivery into the CNS is done at some centres, and in one case even led to tumours and death.⁶² Use of these unproven commercial agents is typically done without any clear regulation or experimental data to support their use, but the clamour to be seen to be effective could undermine the area of cell-based treatments and could derail the whole process.

Efficacy

Dopaminergic cell replacement will only ever work as well as the best dopaminergic agents, such as levodopa. As such, they will never be able to treat most of the nonmotor features of Parkinson's disease, many of which are non-dopaminergic in origin. Thus, cell treatments aimed at dopamine cell replacement will never be curative, in the same way that levodopa is not curative. But, if used early, they could substantially reduce the amount of medication needed by the patient and, therefore, strikingly alter the natural history of treated Parkinson's disease.

Conclusions and future directions

As we move into an era when dopaminergic cells are derived from stem-cell sources, the need to better understand how to develop cell-based experimental treatments, and how to implement them in clinical trials, becomes more pressing. Importantly, an increasing number of novel therapeutic approaches is now aimed at restoration of dopaminergic function in patients with Parkinson's disease, including gene therapy, growth factor infusions, and cell transplantation. All these approaches coexist against a background of improved symptomatic treatments, including dopaminergic agents, and novel neurosurgical interventions, such as deep brain stimulation. Insights gained from previous cell-therapy trials, judged in the context of our understanding of Parkinson's disease in the 21st century, will allow us to rationally and logically move forward to investigate the true potential of the dopamine cellreplacement approach for treatment of patients with this common and disabling disorder.

Contributors

RAB and AB wrote and edited the paper. JB did the meta-analysis. SLM collected data for the meta-analysis and wrote the paper.

Conflicts of interest

We declare that we have no conflicts of interest.

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