that transplanted fetal midbrain DA neurons survived without pathology after up to 14 years, suggesting the safety and feasibility of transplanted fetal brain cells for the treatment of PD [53], other two studies found that alpha-synuclein-positive lewy bodies eventually spread to the transplanted DA neurons in PD patients after 14 or 16 years of transplantation [54, 55]. These pathological changes suggest that PD can be an ongoing process.

The discrepancy may be the result of the difference between genetically and environmentally caused PD – a case of PD caused by genetic mutations would be an ongoing process, whereas a case of PD caused by environmental factors might be halted by the infusion of healthy cells. Therefore, it cannot be conclusively stated that DA neuron engraftment is a universally permanent treatment for PD; follow-up implantations may be required for optimal effectiveness. However, fetal midbrain cell transplantation did provide PD patients, on average, symptomatic improvements when compared to control groups, but it is not a recommendable therapy for PD unless significant improvements are made and issues regarding to consistency of improvements, recurrence of dyskinesia, and eventual spread of pathology are overcome. There is also, like all other allogeneic treatments, a risk of graft rejection – the fact that the midbrain tissue with which a patient is being treated has been sourced from a genetically distinct individual, causing immunogenic responses that must be repressed in the study [56, 57].

Moreover, the use of fetal primary tissue for PD treatment is not scalable, given the procurement difficulty and ethical concerns behind the use of NSCs from fetal brain tissues. Overall, the clinical trials with NSCs of fetal brains showed some improvements of symptoms and the survival of the transplanted cells in PD patients, but some results are controversial because of the limited cases or diversities of the PD patients [47]. Some of the clinical trials with fetal brain- derived NSCs or dopamine neurons are summarized in Table 1.

In order to further address the therapeutic effects of the transplanted NSCs for patients, a new multicenter and collaborative study of the European Union (TRANSEURO) was formed in 2010 to make new guidelines for clinical trials of fetal brain-derived cell therapy in PD. These include careful selection of patients: aged 30–68 at the time of inclusion, showing a good response to levodopa; early in the course of their disease (disease duration 2–10 years); systematic evaluation of cell preparation location of transplantation; clinical assessment standards; numbers of patients and; immunosuppression after transplantation and follow-up time. This study has completed the new clinical trial for more than 100 PD patients and results are in the analysis [58, 59]. A significant clinical outcome was recently reported in two PD patients who were transplanted with fetal ventral mesencephalic cells and were followed up to 15 and 18 years post-transplantation. The motor improvement was observed in the first year and continued to 18 years after transplantation with discontinued levo-dopa replacement therapy [60].

Human embryonic stem cells (hESCs)

Embryonic stem cells (ESCs) are pluripotent, self-renewing, and isolated from the inner cell mass of the pre-implantation blastocysts [61]. ESCs can therefore be differentiated into any kind of tissue cells, including

Table 1 Summary of the clinical trials using fetal brain cells for treatment of PD

No. of patients with cell transplantation	Follow-up Time	Symptom improvement	PET DA neuron survival	Side effect of Dyskinesia	Pathological lewy body	References And publication year
1	12 months	1/1	Yes	No	Not available	[43]
6	10–72 months	4/6	Yes	No	Not available	[77]
5	18–24 months	2/5	Yes	No	Not available	[36]
20/40	3 years	17/20	Yes	No	Not available	[45]
23/34	24 months	6/23	Yes	56 % dyskinesia	Not available	[48]
2	8 years	2/2	Yes	50 % dyskinesia	Not available	[7]
5	9–14 years	Not available	Yes	Not available	Not available	[42]
1	14 years	1/1	Yes	Dyskinesia	Lewy body	[55]
2	11–16 years	Not available	Yes	Not available	Lewy body	[54]
33	2–4 years	45 %	Yes	Not available	Not available	[8]
3	13–16 years	Yes	Yes	Not available	Not available	[8]
2	18 and 15 years	2/2	Yes	Not available	Not available	[24]

Note: 20/40 and 23/34 indicates that 20 of 40 patients and 23 of 34 patients are in the cell transplantation group and the other patients are in the control group