REVIEW

Pharmaceutical, cellular and genetic therapies for Huntington’s disease

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ABSTRACT

HD (Huntington’s disease) is a devastating neurodegenerative disorder caused by a polyglutamine expansion in the gene encoding the huntingtin protein. Presently, there is no known cure for HD and existing symptomatic treatments are limited. However, recent advances have identified multiple pathological mechanisms involved in HD, some of which have now become the focus of therapeutic intervention. In this review, we consider progress made towards developing safe and effective pharmaceutical-, cell- and genetic-based therapies, and discuss the extent to which some of these therapies have been successfully translated into clinical trials. These new prospects offer hope for delaying and possibly halting this debilitating disease.

INTRODUCTION

HD (Huntington’s disease) is an inherited neurodegenerative disorder, with the most common age of onset between 30–50 years of age, and with a mean disease duration of approx. 15–20 years from diagnosis to death. The incidence of HD in the Caucasian population is approx. 1 in 10 000 [1]. Onset is insidious and progressive, and is characterized by a triad of symptoms: movement disorder, behavioural manifestations and cognitive impairment.

Although the first motor signs, including clumsiness, problems with balance, involuntary movements or tremor [2], are generally taken as the formal onset of the disorder, cognitive signs may precede motor signs by up to 10 years and in retrospect it may be clear that psychiatric symptoms were already present [3]. Early stages may be dominated by either motor or cognitive or psychiatric symptoms, but by the middle stages most patients have symptoms and signs of all three. With disease progression, significant problems with planning and organization become increasingly evident, as well as selective memory deficits and impaired general cognitive status. The condition progresses relentlessly until, by the later stages, patients have marked restriction of mobility, often being wheel-chair or bed-bound, have significant cognitive loss (although this is difficult to assess formally due to the motor deficits) and are frequently mute. The precise cause of death is often unclear and may be multifactorial, but contributors are aspiration and starvation secondary to the dysphagia.

HD is an inherited disorder caused by an expanded CAG repeat length in exon 1 of the IT15 (interesting transcript 15) gene, now known as ‘huntingtin’, located on chromosome 4 [4]. This gene encodes the huntingtin protein, which appears to be involved in complex aspects of cellular metabolism and protein trafficking. Although the precise role of the huntingtin gene in normal development is still not fully understood, studies of knockout mice nullizygous for the HD gene homologue (Hdh) have revealed that it is vital for embryonic development [5–7]. Normal individuals have CAG repeat lengths of

Key words: clinical trial, gene therapy, Huntington’s disease, neurodegeneration, neurotransplantation, stem cell, treatment.

Abbreviations: BDNF, brain-derived neurotrophic factor; CAPIT, core assessment protocol for intracerebral transplantation; CNS, central nervous system; CNTF, ciliary neurotrophic factor; CoQ10, co-enzyme Q10; EG, embryonic germ; EHDN, EURO-HD Network; HD, Huntington’s disease; ES, embryonic stem; HDAC, histone deacetylase; HSG, Huntington Study Group; LGE, lateral ganglionic eminence; MGE, medial ganglionic eminence; NECTAR, Network of European CNS Transplantation and Restoration; NEST-HD, European Network for Striatal Transplantation in HD; NFG, nerve growth factor; NMDA, N-methyl-D-aspartate; 3-NP, 3-nitropropionic acid; NT, neurotrophin; SAHA, suberoylanilide hydrazine acid; SDH, subdural haemorrhage; Tgase, transglutaminase; VM, ventral mesencephalon; WGE, whole ganglionic eminence.

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The disease is invariably caused by a CAG repeat length of >40, and the very much longer repeat length (>70) is typically associated with juvenile-onset HD [8]. Within the intermediate range (36–39 CAG repeats), the development of HD appears to be increasingly likely but not certain [9], although the precise prognosis of patients whose CAG repeat length lies within this range is still a subject of debate and continued study.

### NEUROPATHOLOGY OF HD

In end-stage disease, at post-mortem, HD brains typically weigh approx. 10–20% less than age-matched controls [10], although of course in life most patients show less advanced degeneration, and of particular research value are the rarer brain samples collected from early stages in the disease [8]. From a macroscopic perspective, HD is characterized by a primary cellular pathology with associated atrophy in the caudate nucleus and putamen (together known as the ‘neostriatum’). Pathology in the caudate is usually more widespread and occurs earlier than for the putamen, and typically spreads in a dorsal-medial to ventral-lateral direction as the disease progresses [11]. As the neurones are lost, the tissue collapses, leading to a secondary characteristic enlargement of the lateral ventricles. As striatal degeneration progresses, degenerative changes occur to other brain regions connected to the striatum, in particular the neocortex but also including the thalamus, subthalamic nucleus, globus pallidus, substantia nigra pars reticulata and hypothalamus [10–12].

Within the striatum, the earliest affected and most vulnerable cells are the medium-spiny GABAergic projection neurons which constitute 90–95% of all neurones within these nuclei in rodents and approx. 80% in humans. Medium and large striatal interneurons are by comparison relatively spared [11,13]. Ideally, any therapy would, therefore, need to prevent the loss of these medium-spiny neurones and also preserve the corresponding connective circuitry.

It remains unknown whether the extrastriatal degeneration is a secondary anterograde and retrograde response to the primary striatal degeneration as opposed to independent sequelae of the disease process, although there have been strong arguments in favour of both positions. This is not just a theoretical issue: the nature of the association will critically determine whether neuroprotective or reparative treatments, such as cell transplantation targeted at the striatum, could conceptually halt the wider spread of the disease process, or whether such treatments can only be of transient benefit until more widespread degeneration within cortical-basal ganglia systems dominates the symptoms.

A neuropathological hallmark of HD is huntingtin aggregates, in which cleaved fragments of the mutant huntingtin protein aggregate to form large dense protein inclusions in particular in the nucleus of affected cells, but also occurring at smaller sizes within the cytoplasm of the cell soma, as well as in neurites and terminals. The precise role of the full-length mutant protein compared with the fragments containing the expanded polyglutamine in normal and pathological function of the protein and the role of the aggregates themselves in the cellular pathology remains unclear. One possibility is that aggregates are toxic, exerting a direct impact on normal cellular or nuclear processing. Conversely, aggregates may be neuroprotective by sequestering toxic fragments of mutant huntingtin into an insoluble form that prevents them from interacting with key cellular proteins [14,15].

At present, there is no known cure for this devastating disease and existing pharmacological therapies are targeted at managing, rather than preventing, symptoms. However, recent advances in neuroprotective approaches and reparative strategies are leading the way towards the development of an effective therapy for HD. The following sections review a number of therapeutic approaches for preventing, treating and possibly eventually curing HD (Table 1).

### PRESENT AND EMERGING PHARMACOLOGICAL APPROACHES TO SYMPTOMATIC THERAPY

Symptomatic therapies, aimed at assisting with the management of HD, fall into three categories: psychiatric agents, motor sedatives and cognitive enhancers. Currently, although a number of pharmaceutical therapies...
exist to alleviate motor and psychiatric symptoms, there are no pharmacological approaches to delay the rate of cognitive decline seen in HD.

Of the triad of symptoms associated with HD, psychiatric manifestations, including depression, irritability and apathy, are often reported to have the most distressing impact on the quality of life of the patient and their families [16]. Generally, the management of these symptoms is provided using standard antipsychotics and antidepressant drugs along with mood stabilizers (e.g. carbamazepine, risperidone, olanzapine, clozapine and quetiapine) [17,18]. Although alternatives, such as tricyclic antidepressants can help manage depression, patients with HD typically show better tolerability of SSRIs (selective serotonin reuptake inhibitors) [19].

There have been few systematic clinical trials to date on treatments for the psychiatric symptoms in patients with HD [20,21]. However, a small number of studies have detailed case reports on managing depression in HD [18,22,23]. Treatment of other psychiatric symptoms, such as apathy, irritability and aggression, remain open to investigation.

Chorea may be partially relieved by a number of pharmacological agents. The dopamine-depleting agent tetrabenazine, which has been reported to have a beneficial effect in treating a range of hyperkinetic movement disorders, including HD [24], is commonly used but may exacerbate parkinsonian symptoms and produce sedation and hypotension. Profound depression is also reported in a proportion of individuals on this medication [25]. Antipsychotic medications, such as sulpiride and haloperidol, are used, although again the antiparkinsonian and sedative side effects may be troublesome, and some authorities favour drugs such as amantadine and olanzapine (for a review, see [26]). Several medications have been administered to treat dystonia, including baclofen, benzodiazepines, such as clonazepam, and tetrabenazine, but success has been very limited. There are reports of moderate clinical improvement in patients with a predominantly parkinsonian-like presentation following administration of l-dopa or dopamine agonists [27,28], although it is less clear to what extent this response is sustained.

Although there are a number of pharmaceutical therapies available to assist with the management of HD, as yet none are neuroprotective or reparative. Over the past two decades there has been significant progress in developing strategies for prevention and repair. A number of these approaches are considered below.

**STRATEGIES TARGETED AT GENERAL PROCESSES OF CELL DEATH**

Early progress in developing novel treatment approaches is most likely in hereditary neurodegenerative disease where a genetic factor has been identified and thus provides a clear starting point for understanding the degenerative process. However, this does not necessarily follow gene identification, as shown through the example of HD in which knowledge of the genetic mutation has not yet revealed the precise nature of the relationship between the genetic cause and the cascade of cellular processes leading to neuronal dysfunction and cell death.

Over the past decade, a number of neuroprotective compounds targeted at relieving generic pathogenic stresses have been examined for their potential therapeutic benefit for HD and, although each compound is targeted at an individual mechanism, collectively these compounds may serve to interrupt critical stages of the pathogenic cycle. Determining whether a compound is selected for clinical trials is dependent on sufficient preclinical efficacy data. However, we must be conscious of publication bias towards positive results from preclinical studies and recognize that there may be other well-conducted unpublished trials of the same compound that have been unable to replicate positive results. Therefore, in order to increase the chance of identifying successful treatments, it has been suggested that neuroprotective compounds should be considered on the basis of preclinical efficacy data shown in two mouse models of HD from two independent research groups [29] (see Table 2 for summary and details of major clinical trials discussed below).

Apoptosis is a specific active process of cell death dependent upon protein synthesis under genetic control and mediated by a series of cysteine-aspartate proteases (caspases). Cell death involves a combination of interrelated processes, including glutamate release, changes in mitochondrial energy production and cellular metabolism, oxidative stress and calcium influx, that have together been described as a ‘cycle of neurotoxicity’.

Caspases have been identified as apoptotic initiators, apoptotic executors or inflammatory mediators [30], such that inhibition of specific caspases may offer neuroprotective benefit. In mouse models of HD, inhibition of caspases 1 and 3 have shown anti-apoptotic effects and delayed disease progression [31,32]. Minocycline-treated R6/2 mice exhibited a delayed impairment on the Rotarod test and extended survival by 14% compared with saline-treated mice [31]. Replication of these results, however, has been difficult [33].

Despite these inconsistent findings, the preliminary animal studies have led to a number of clinical trials [34–36]. The first clinical trial compared patients with HD receiving minocycline against a control group of patients with HD over a 6 month period. Slight improvements in both neuropsychological performance and motor function were reported for the experimental group. It is possible, however, that the results can be explained by a placebo effect. The HSG (Huntington Study Group) have now launched a double-blind placebo-controlled study.
<table>
<thead>
<tr>
<th>Pharmaceutical intervention</th>
<th>Target</th>
<th>n Design of trial</th>
<th>Outcome</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minocycline</td>
<td>Caspase inhibitor</td>
<td>Minocycline (100 mg/day) = 14; no treatment = 5</td>
<td>Open label study; 6 month trial</td>
<td>Safety and tolerability report. [34]</td>
</tr>
<tr>
<td>Minocycline</td>
<td>Caspase inhibitor</td>
<td>Minocycline (100 mg × 2/day) = 30</td>
<td>Open label study; 6 month trial</td>
<td>Safety and tolerability report. [34]</td>
</tr>
<tr>
<td>Minocycline</td>
<td>Caspase inhibitor</td>
<td>Minocycline (100 mg/day) = 18; minocycline (200 mg/day) = 19; placebo = 23</td>
<td>Double-blind placebo-controlled study; 8 week trial</td>
<td>Safety and tolerability report. [35]</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>Glutamine receptor blocker</td>
<td>Lamotrigine (334 ± 110 mg/day) = 28; placebo = 27</td>
<td>Randomized double-blind placebo-controlled study; 30 month trial</td>
<td>No clear influence of lamotrigine on delaying disease progression; patients receiving treatment reported symptomatic improvement. [38]</td>
</tr>
<tr>
<td>Creatine</td>
<td>Cellular energy production</td>
<td>Creatine (10 mg/day) = 13; age-matched controls = 4</td>
<td>Open label study; 12 month trial</td>
<td>Safety, tolerability and efficacy report; no change in functional capacity, motor score or neuropsychological testing. [55]</td>
</tr>
<tr>
<td>Remacemide</td>
<td>NMDA receptor antagonist</td>
<td>Remacemide (200 g/day) = 10; remacemide (600 g/day) = 11; placebo = 11</td>
<td>Double-blind placebo-controlled study; 5 week trial</td>
<td>Safety and tolerability report. [40]</td>
</tr>
<tr>
<td>CARE-HD (CoQ10 and remacemide)</td>
<td>Mitochondrial enhancer with antioxidant properties</td>
<td>Placebo = 87; CoQ (300 mg × 2/day) = 87; remacemide (200 mg × 3/day) = 86; combination = 87</td>
<td>Randomized double-blind, placebo-controlled study; 30 month trial</td>
<td>No significant slowing in functional decline in early HD; some side effects reported. [41]</td>
</tr>
<tr>
<td>Riluzole</td>
<td>Glutamate antagonist</td>
<td>Placebo = 22; riluzole (100 mg/day) = 18; riluzole (200 mg/day) = 23</td>
<td>Placebo-controlled; 8 week trial</td>
<td>No improvement in functional capacity; reversible liver transaminase abnormalities for riluzole (200 mg/day)</td>
</tr>
<tr>
<td>LAX-101</td>
<td>Phospholipases and caspases inhibitor. Possible mitochondrial-enhancing properties</td>
<td>135 HD patients</td>
<td>Double-blind randomized placebo-controlled study; 12 month trial</td>
<td>Selective benefit to motor score for lower CAG repeat numbers. [47]</td>
</tr>
</tbody>
</table>

* Small pilot studies have been omitted. For a more extensive listing, see [26].
of minocycline in a larger sample of patients with HD, with safety and tolerability of the drug during an 8 week preliminary trial published recently [35]. Efficacy will be reported at the end of the 18 month trial period.

Cell death in HD appears to involve an important excitotoxic component, associated with excessive release of the excitatory neurotransmitter glutamate, in particular at corticostriatal terminals. In turn, this gives rise to neurotoxic effects on the target striatal neurons and may underlie the striatal neurodegeneration seen in HD [37]. Hence a second potential therapeutic target is to focus on blocking the excessive release of glutamate or its action at the postsynaptic receptors.

Recent clinical trials have evaluated the effectiveness of glutamate receptor blockers in patients with HD. A clinical trial of lamotrigine, a glutamate antagonist, reported that there was no significant effect of this treatment on slowing disease progression despite the trend towards reduction of choreiform movements in HD patients receiving the drug [38]. Riluzole, another glutamate antagonist, has been evaluated in a multicentre trial [39]. Despite good tolerability and safety of riluzole over an 8 week period, there were no observed benefits to the functional progression of the disease. A more extensive evaluation of riluzole in Europe is taking place over a 36 month trial which is scheduled to report in 2005.

The effects of remacemide hydrochloride, a non-competitive inhibitor of the NMDA (N-methyl-D-aspartate) receptors, have been evaluated in a study of patients in the early stages of HD [40]. Although there was no significant difference in total function capacity between patient groups, a trend towards improvement in chorea was observed among the patients who received 200 mg/day of remacemide. Unfortunately, this short trial was unable to establish the long-term tolerability and efficacy effects of remacemide. Remacemide was also studied in the large CARE-HD (Co-enzyme Q10 and Remacemide: Evaluation in HD) study [41] mentioned below.

A third component in the cycle of neurotoxicity is reduced mitochondrial activity [42]. Normal huntingtin appears to have a role in regulating mitochondrial energy production, and it is possible that mutant huntingtin is actively disruptive to cellular respiration [43]. This disruption may lead to deficient energy metabolism, depleting levels of intracellular ATP, lowering the threshold for apoptosis, promoting free radical generation and increasing susceptibility to excitotoxicity [44]. Consequently, drugs that serve to enhance mitochondrial function may offer a third potential neuroprotective strategy for application in HD.

CoQ10 (co-enzyme Q10), which protects against excitotoxicity by raising neuronal energy levels, has good tolerability in patients with HD [45]. CoQ10 has been found to promote survival, attenuate striatal lesions and reduce weight loss and motor deficits in HD transgenic mice, both when administered alone and when given in combination with remacemide [46]. The CARE-HD study compared the effects of CoQ10 and remacemide on retarding disease progression in HD during a 30 month trial [41]. Despite a trend towards beneficial change in the CoQ10-treated groups in particular, changes in disease progression were not significant. Absence of a clear effect may have been due to insufficient power, the use of an inadequate dose, poor receptor selectivity or inappropriate stage of HD. The effect of CoQ10 on its own is therefore the subject of a second trial currently in progress with enhanced power over a longer evaluation period.

LAX-101 (Miraxion) is a novel compound that inhibits certain harmful enzymes, including phospholipases and caspas, and may also have mitochondrial-enhancing properties. A trial with 135 HD patients over a period of 12 months assessed the benefits of this potential treatment [47]. A favourable effect of LAX-101 compared with placebo was reported on TMS-4 (total motor score of UHDRS (Unified Huntington’s Disease Rating Scale)), and there was a correlation between clinical improvement and CAG repeat lengths. Exploratory analysis suggested a significant benefit of LAX-101 in patients with lower CAG repeat numbers, which is perplexing, and, to date, there is no clear explanation for this correlation. Moreover, there have been concerns that the significant positive outcome in this trial was dependent upon post-hoc selection of the subgroup. A Phase III trial, which takes this experience into account, is in preparation.

Cells affected by HD have abnormal gene expression thought to be a result of transcription dysregulation. One approach currently under investigation to counteract this effect is through the administration of HDAC (histone deacetylase) inhibitors to enhance the availability of the DNA in promoter regions of genes to transcription factors and thus increase transcription [48]. Evidence from a Drosophila model of HD has shown that HDAC inhibitors halted neuronal degeneration and extended survival [49]. A more recent study reported that administration of the HDAC inhibitor SAHA (suberoylanilide hydroxamic acid) to the R6/2 mouse model dramatically reduced motor phenotype [50]. These results await replication but, since HDAC inhibitors, including SAHA, have been approved by the FDA (Food and Drugs Administration), their use in clinical settings or Phase I trials should be considered seriously.

As discussed previously, the precise role of huntingtin aggregates in HD is unclear and it is possible that this neuropathological hallmark may be the trigger of a cascade of neurotoxic events leading to neurodegeneration. Tgase (transglutaminase) activity is up-regulated in HD and may serve as a catalyst to the formation of γ-glutamyl isopeptide bonds between substrate proteins, resulting in the insoluble protein complexes. Hence Tgase inhibitors that suppress aggregate formation are a potential therapy. Recent work examining the effects of...
cystamine in the R6/2 mouse model of HD reported significant improvement to motor phenotype, delayed weight loss, extended survival, reduced neuronal atrophy and loss of striatal neurons and attenuated development of huntingtin aggregates [51]. These findings, together with other preclinical studies, suggest that cystamine is a suitable candidate for treatment trials involving HD patients [52,53].

Creatine, a Tgase inhibitor, stimulates mitochondrial respiration and has antioxidant properties. Promising results from R6/2 mice receiving creatine supplements reported improved survival, reduced motor phenotype and slowed neuropathological progression [13,54]. A 12 month pilot study of patients with HD receiving 10 mg of creatine a day found that it was well-tolerated and safe [55]. A 2 year trial is currently underway, powered to identify any useful neuroprotective effect of creatine.

An alternative empirical strategy is high-throughput screening of licensed pharmaceuticals to identify and develop possible compounds that may be suitable for treatment of HD. Libraries of novel compounds are tested against a specific assay, for example anti-apoptosis or anti-aggregate formation in the case of HD. Libraries of up to several million compounds can be screened using yeast and mammalian cell-based models, and libraries of up to a thousand compounds can be screened using invertebrate models. Using this method, 25 benzothiazoles have been identified as blockers of huntingtin fibrillogenesis indicating their potential as polyglutamine aggregation inhibitors [56]. Although these findings are encouraging, high-throughput screening is recognized as a method that may be hindered by false positives and negatives, and thus requires a subsequent systematic validation of ‘hits’ [57].

REPARATIVE STRATEGIES

Transplantation repair with primary cells (striatal grafts)

Transplantation repair with primary cells aims to restore brain circuitry and function by surgical replacement of the cells lost as a consequence of acute injury, such as stroke, or to a progressive neurodegenerative disease, such as HD [58]. The clinically beneficial effect of transplantation with primary cells in HD is dependent on two main issues: firstly, whether the neural graft will survive and replace lost neurons in the place(s) where required, and secondly, whether the neural graft can integrate into the host neuronal circuitry and contribute to normal physiological processing within the host brain [58]. This approach can only be offered as a therapeutic tool for patients with HD once the safety and efficacy of the procedure has been confirmed in both animal models of HD and clinical trials of patients with HD [59].

Animal models of transplantation in HD

Physiological and anatomical evidence from animal models of HD has shown that cell-based therapies offer feasible methods of neural repair for the treatment of this neurodegenerative disease. Animal studies have shown that implants of fetal striatal tissue survive, develop afferent and efferent connections with the host brain, and alleviate both motor and cognitive deficits associated with striatal lesions [60–61]. The critical feature of all of the effective protocols is the identification of suitable donor tissues, taken from the developing ganglionic eminence, and at a precise stage in embryonic development (around E13 days of age in the rat embryo and 7–9 weeks of gestation for human embryos). The transplant tissue has to be prepared using protocols that maximize cell survival, and is typically implanted stereotactically using standard neurosurgical procedures. Considerable data are now available for optimizing these technical protocols [62].

Most animal studies have been based on lesion models of HD using either excitotoxins, such as quinolinic acid, or metabolic toxins, such as malonate or 3-NP (3-nitropropionic acid), to induce selective destruction of the medium-spiny projection neurons of the striatum. Although this reproduces well the striatal pathology of HD, it does not replicate the neuropathogenic processes giving rise to the progressive degeneration seen in patients with HD. Arguably, a more accurate animal model of HD can be obtained through the use of transgenic mice models of HD. However, in practice, there have been rather few studies of experimental striatal transplantation in transgenic mice [63,64] mainly because the early transgenic models featured more widespread inclusion pathology and less focal striatal cell death, proving to be relatively unsuitable for studies of striatal repair.

In summary, preclinical studies have successfully transplanted fetal tissue and shown that the grafts can anatomically reconstruct the damaged striatum and restore substrates involved in motor and cognitive function in animal models of HD [65]. On the basis of the animal studies, as well as the demonstration that similar embryonic tissue grafts could provide significant alleviation of many of the motor symptoms of Parkinson’s disease [66–68], groups in both North America and Europe have started working towards clinical studies of transplantation in HD.

Transplantation in HD

Human trials typically extrapolate parameters and procedures worked out in detail in experimental animals, and an important component of all clinical trials is to validate their clinical application. The following section considers the key issues in the context of past and ongoing clinical trials.
Ethics of human fetal tissue transplantation

The animal studies are clear; what works best is use of donor cells of the appropriate age and phenotype harvested from embryos of the same species. Although xenotransplantation across species can work, there are significant issues of tissue rejection that do not apply to allografts, and suitable procedures for reliable immunoprotection are not yet available for transplantation across the species barrier, even in a relatively privileged site like the brain. Similarly, although there is an active search for alternative sources of cells for transplantation such as stem cells (see below), which avoid the ethical, practical and quality control issues surrounding fetal tissue donation, it is not yet possible to control the differentiation of all such sources to yield reliable striatal phenotypes suitable for striatal repair. Consequently, any transplantation programme in HD is dependent on identifying a suitable ethical source of human fetal tissue for striatal tissue donation. Essentially, this requires collection of donor tissue from aborted fetuses during elective termination of pregnancy. Although the issue of abortion itself is ethically and socially controversial in many societies, professional and governmental ethical commissions from a growing number of countries tasked with considering the issue have concluded that the donation of human fetal tissue for research or therapy is ethical provided the subsequent use of the tissue does not influence the decision, timing and conduct of the abortion itself [69]. This is usually addressed by separating both the decision for termination of pregnancy from the request for tissue donation and the obstetrics and clinical neurotransplantation teams.

Donor tissue selection and preparation

During fetal development, the striatal neurons develop from the germinal cell layers of the LGE and MGE (lateral and medial ganglionic eminences respectively) in the floor of the anterior lateral ventricles. Optimal dissection remains unclear: the greatest density of DARPP-32-positive cells (where DARPP is dopamine and cAMP-regulated phosphoprotein), the most widely used marker for striatal tissue, is obtained in grafts derived from a restricted LGE dissection [70,71], whereas grafts based on a WGE (whole ganglionic eminence) dissection are more likely to contain the full complement of striatal neuronal types, but at the cost of containing more non-striatal neurons (primarily originating within the MGE [72]). Comparisons between WGE and LGE grafts in experimental animals have found either equivocal or better functional recovery for WGE grafts [71,73–75]. The functional and anatomical differences between WGE and LGE grafts will be more clearly defined upon collection of sufficient efficacy data.

Dissected tissue can be prepared either as a cell suspension by enzymatic and mechanical dissociation of the tissue or by mechanical dicing of the tissue into small pieces [76]. Determining which approach is superior will have to await the outcomes of the ongoing clinical trials (see below). An additional issue is that of tissue storage, which has major implications for the feasibility of neural transplantation approaches. Using current techniques, fetal brain cells appear to survive cryopreservation poorly and thus produce non-viable grafts. Fresh tissue survives the transplantation process much more readily, but needs to be transplanted within a short time frame (approx. 6–12 h following collection). This imposes severe constraints on the transplantation process; in particular, it may mean that the recipient has to be prepared for surgery, including attachment of a stereotaxic frame to the skull, before there is a clear indication that sufficient high-quality tissue has been collected for an operation to go ahead. Hibernation of the tissue using a cocktail of substances that slow down cellular metabolism have been used for transplantation of fetal ventral mesencephalic tissue in Parkinson’s disease [77]. This approach has been taken up and validated for striatal tissue [78,79] and has been used in the UK clinical trial [80].

For trials taking place within the EU, tissue that has been manipulated by dissociation or has been stored now falls under the EU tissue directive [81]. This requires that, following collection, any manipulation of the tissue takes place under stringent GMP (‘good manufacturing practice’) conditions, requiring highly specified conditions of laboratory practice and regulation.

Clinical trials

Clinical trials of neural transplantation in patients with HD began over a decade ago and are summarized in Table 3. The experimental nature of transplantation trials in HD has meant that the continued development of an optimal protocol is dependent on the safety and efficacy reports published for both clinical and preclinical trials.

The first report of cell therapy in HD was carried out over a decade ago by groups in Czechoslovakia and Cuba and reported by Sramka and co-workers [82]. Four patients with HD received bilateral embryonic mesencephalon implants using CT-guided stereotaxy into four or five loci in the caudate nucleus. The reasons for using mesencephalon were not made clear and it would not normally be considered an appropriate source of cells for the reasons outlined above. There were no significant side effects or complications pertaining to surgery, and there was the suggestion of partial functional recovery for hyperkinesias. However, there was little in the way of clear objective longitudinal assessment and so it remains difficult to draw any firm conclusions from this report. The second trial was carried out by a Mexican group in which patients with HD received unilateral embryonic WGE implants to the caudate nucleus [83]. There was no evidence that neurosurgery gave rise to any serious adverse events. Post-operative reports noted that progression of motor symptoms in patients was either slowed
Table 3  Published cell-based therapeutic trials in HD

<table>
<thead>
<tr>
<th>Location</th>
<th>Recipient (n)</th>
<th>Implants (n)</th>
<th>Age/source*</th>
<th>Dissection</th>
<th>Implant tracts</th>
<th>Immune treatment</th>
<th>Safety</th>
<th>Efficacy</th>
<th>Imaging</th>
<th>Anatomy</th>
<th>Reference</th>
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<tbody>
<tr>
<td>Cuba and Czechoslovakia</td>
<td>4</td>
<td>2–3</td>
<td>?</td>
<td>YM or WGE</td>
<td>2–3?</td>
<td>CyA</td>
<td>No pathological immunological response</td>
<td>Not yet possible to determine</td>
<td>MRI-guided stereotaxy; no reported follow-up</td>
<td>[82]</td>
<td></td>
</tr>
<tr>
<td>Mexico City</td>
<td>2</td>
<td>1</td>
<td>E12–13</td>
<td>WGE</td>
<td>CN cavity</td>
<td>CyA + Pred</td>
<td>No surgical incidents or subsequent SEs</td>
<td>Slow progression of disease</td>
<td>Not reported</td>
<td>[83]</td>
<td></td>
</tr>
<tr>
<td>Los Angeles</td>
<td>14</td>
<td>5–8</td>
<td>EB–10</td>
<td>LGE</td>
<td>One CN + four Pu [U]</td>
<td>Not reported</td>
<td>Safe; no serious SEs</td>
<td>Benefit motor, limited neuropsychological tests</td>
<td>MRI MRS and FDG PET</td>
<td>[84–86]</td>
<td></td>
</tr>
<tr>
<td>Boston</td>
<td>12</td>
<td>35–38</td>
<td>Porcine</td>
<td>TGE</td>
<td>Two CN + four Pu</td>
<td>CyA or anti-MHC</td>
<td>Safe; no serious SEs</td>
<td>No change over 12 months</td>
<td>Not reported</td>
<td>MRI and PET</td>
<td>[97]</td>
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<tr>
<td>Tampa</td>
<td>7</td>
<td>2–8</td>
<td>EB–9</td>
<td>LLGE</td>
<td>Two CN + four Pu [B]</td>
<td>CyA for 6 months</td>
<td>One death and three subdural haematomas</td>
<td>Modest (ns) changes in motor tests at 12 months</td>
<td>Two post-mor tem cases with good survival</td>
<td>[87,88,90]</td>
<td></td>
</tr>
<tr>
<td>Crétine</td>
<td>5</td>
<td>2–4</td>
<td>E7.5–9</td>
<td>WGE</td>
<td>Two CN + three Pu [B]</td>
<td>CyA for 1 year</td>
<td>Procedure safe</td>
<td>Motor and electrophysiological improvements continue over 4 years</td>
<td>MRI and FDG PET; graft survival in three functional cases</td>
<td>[91,92]</td>
<td></td>
</tr>
<tr>
<td>NEST-UK</td>
<td>4</td>
<td>2–3</td>
<td>EB–12</td>
<td>WGE</td>
<td>Two CN + four Pu [U]</td>
<td>Triple</td>
<td>Only SEs related to immunosuppression</td>
<td>Safety only, efficacy not reported</td>
<td>MRI; graft survival</td>
<td>[80]</td>
<td></td>
</tr>
</tbody>
</table>

* Source of the donor fetal tissue is human unless otherwise stated.
or remained stable. For both of these trials, fetal tissue was collected from spontaneous abortions, since voluntary abortions were not permitted in those two countries.

The first more extensive series of transplants in HD was undertaken by Oleg Kopyov and co-workers at the City of Hope Hospital in Los Angeles. Patients received bilateral implants from the embryonic LGE to the caudate nucleus and putamen. One year follow-up assessments of the first series of 14 patients reported good graft survival in the striatum with no adverse side effects [84]. There was no significant deterioration of motor function [85] and, in one case, there was improvement in specific cognitive functions [86]. However, these data need to be evaluated with care since transplant efficacy was measured using a limited assessment battery on only a subset of the original transplanted patients.

The other major centre for fetal striatal transplantation in HD in the U.S.A. is co-ordinated by Tom Freeman at the University of South Florida in Tampa [87,88]. Although still an open-label trial, this study has been undertaken more systematically with objective 12-month longitudinal assessment of patients according to an internationally agreed CAPIT (core assessment protocol for intracerebral transplantation; [89]). Of the seven patients who received bilateral implants (LGE), six showed moderate improvement in motor function, whereas one showed significant decline. Three patients developed SDHs (subdural haemorrhages) post-operatively, two of whom required further surgical intervention. SDH is a risk in all intracerebral surgeries, although extensive cortical atrophy appears to increase risk. Henceforth clinical trials should select patients with less advanced atrophy—a factor that has been integrated into the design of the UK and French clinical trials.

Absence of a clear positive result was possibly due to the selection of advanced HD patients reducing graft survival and therefore restricting functional improvement. Furthermore, the Tampa trial did not profile functional change beyond 12 months. Longitudinal assessments of transplantation studies should continue for at least 2–3 years to reduce the possibility of making a false-negative conclusion and to allow grafts to develop and integrate in the host (most likely more than a year).

Post-mortem histological analysis from one patient who died from causes unrelated to surgery 18 months after transplant indicated that all grafts survived well and were rich in neurons expressing a range of striatal-like phenotypes. There was no HD-related neurodegeneration within the grafts, and host neurons were able to project into the human striatal tissue grafts [90].

A UK network (NEST-UK; part of NEST-HD, the European Network for Striatal Transplantation in HD) published a safety report on the first four patients to have received unilateral transplantation of primary tissue cell suspensions [80]. The only adverse events reported were reversible and related to immunotherapy.

The best established evidence for safety and preliminary efficacy of neural transplantation in HD has been obtained through the French trial conducted by groups in Créteil and Orsay, co-ordinated by Marc Peschanski and Anne-Catherine Bachoud-Levi. The first five patients with HD to receive striatal grafts had no adverse neurosurgical events over a 1 year follow-up period, although there have been concerns about psychiatric stability and compliance with immunosuppression treatment [91]. Motor and cognitive profiles for the transplanted patients were recorded over 4 years prior to and following transplantation, with clinical benefits seen in three out of the five patients [92]. A subsequent publication by the same group [93] has provided evidence of activation in the frontal cortex in the patients from this group in whom there was evidence of a surviving graft and functional benefit. This, and the fact that the activation is seen only in these patients and not in those with a failed graft, suggests that the grafted cells are able to reconnect circuitry with appropriate brain regions (in this case, the frontal cortex).

Summary of clinical trials

To date, six clinical trials using human fetal neural implants in HD have been initiated. Although the safety and efficacy data to date offer preliminary evidence to support continuation of trials of implanted striatal tissue as a potential therapy for HD [80,84,92], proof of principle will have to await the outcome of the trials in progress. At the time of writing, two clinical trials are ongoing: the French group based in Créteil and the NEST-UK trial. Nonetheless, there are a number of outstanding issues surrounding the application of cell-based therapy to treat HD and, therefore, this remains an active area of scientific development.

Outstanding issues for primary fetal grafts

Although there is preliminary, but growing, evidence to suggest that primary cells may be used with beneficial clinical effect for the treatment of HD, it is essential that clinical trials continue to obtain convincing evidence that the procedure is safe and functionally beneficial. Firstly, the protocol for primary tissue grafts in HD continues to be modified according to analysis of data from the ongoing clinical trials. For instance, although immunosuppressive therapy has been included in clinical trials to promote the survival of the graft, it has the potential for adverse effects and the need for it is as yet not fully proven. This issue is difficult to address pre-clinically because, although the immune rejection process in rodent to rodent allografts can be studied, this may not be relevant to the response of the human brain to implanted human tissue. Secondly, despite the absence of HD pathology in the post-mortem analysis of grafted tissue (see above), it is conceivable that the graft tissue will
prove susceptible to this neuropathological processes if analysed over a longer period of time. Continued human trials are likely to resolve this issue. Thirdly, the pathology of HD is not restricted to the neostriatum and extends to regions of the brain, in particular the neocortex. Currently, it is not known whether this is due to a primary disease process in these other brain regions (in which case the usefulness of the graft will be in part determined by the pace of degeneration in these brain areas) or a secondary process due to neurons in these areas degenerating because they have lost their target neurons in the striatum. Fourthly, some previous research into Parkinson’s disease has advocated the implementation of placebo-controlled double-blind surgery, i.e. sham surgery, to the design of the study. There is strong consensus from European research groups that conducting blinded sham surgery in HD is unethical and that therapeutic trials of this nature should adopt open-label design [94]. This is primarily because the existing protocol for neural transplantation in HD is experimental and has the potential to harbour risks associated not only with the surgical procedure (anaesthesia, neurosurgery and immunosuppression), but also coping with the emotional stress [76,95]. There is also the further ethical issue of placing HD patients, who are desperate for hope, in an experimental situation where there is an equal possibility that they will receive sham surgery. Fifthly, variability in the outcome of results from striatal transplant trials may in part be due to differences in the trial protocol. Until 1996, there was no agreed protocol for conducting striatal grafting in patients with HD. CAPIT, developed by the NEST-HD [89], outlines inclusion and exclusion criteria, consent, schedule of evaluations and a comprehensive test battery to profile disease progression. This protocol has now been integrated to a number of research initiatives [80,88,91], and is currently in the process of being updated.

**Alternative sources of donor tissue**

Since the use of primary tissue derived from the fetus is limited by both ethical and practical issues, it is clear that this type of cell therapy is never going to be widely available to the HD population unless more readily renewable sources of donor cells can be identified. A number of alternative are under consideration, including stem cells and xenogeneic fetal cells which are considered below. For a more detailed review on this topic, see Kelly et al. [96].

**Xenografts.** Xenogeneic fetal cells from pigs provide a reasonable alternative tissue source because of their brain size, large litter counts and high reliability in localizing and dissecting the VM (ventral mesencephalon). To date, there has been one clinical trial of porcine LGE grafts in HD patients (n = 12; [97]). Follow-up results 12 months post-operatively reported that the procedure was safe, but without change to functional ability and without evidence of good graft survival. The major issue here is the immune rejection of the xenografted tissue; thus this approach, although promising in many respects, will have to await the development of new immune-modulation strategies.

**Stem cells.** Stem cells are derived from the early developmental stages of an embryo or adult tissue. Their potential advantage as a donor source is that, under the appropriate conditions, they are self-renewing in culture whilst retaining the capacity to differentiate into mature phenotypes, and they have been under consideration for as donor populations for neural transplantation for some years [58,98,99]. They also offer the possibility of standardization and quality control with respect to viability and purity, which is extremely difficult to achieve using primary fetal brain cells. However, the outstanding issue surrounds achieving directed differentiation towards specific neuronal phenotypes. Although there has been some success in directing ES (embryonic stem) cells towards a limited number of mature neuronal phenotypes, for example the dopaminergic projection neurons [100–102], there has been markedly less success in achieving viable grafts following the transplantation of such cells [103]. ES cells are derived from the inner cell mass of a blastocyst and readily proliferate given the appropriate conditions [104]. Human ES cells are now available for experimental purposes and, although there are differences in the proliferation conditions for mouse and human ES cells, successful protocols are now available for the maintenance of the human cells [105,106]. However, unresolved issues, such as the genetic instability of ES cells and the possibility of teratomas and unregulated cell growth, currently pose significant problems for the application of these cells into clinical trials [98,107].

EG (embryonic germ) cells are derived from human primordial germ cells in the gonadal ridge in the first trimester. Similarly to ES cells, EG cells are pluripotent [108]. However, their potential applicability for cell therapy is limited by problems with prolonged culture where spontaneous differentiation is difficult to control [109].

Somatic stem cells are undifferentiated stem cells specific to a tissue or organ. Somatic stem cells can be used to regenerate tissues in which they normally reside. The possibility of using neural stem cells to regenerate specific brain regions is currently under investigation.

Neural fetal stem cells are isolated from the embryonic CNS (central nervous system) and can be expanded in culture with the addition of mitogens such as FGF-2 (fibroblast growth factor-2) and EGF (epidermal growth factor) [110,111]. They retain the capacity to produce neural cells and have the advantage that they do not appear to produce differentiated cells of other lineages. However, their expansion capacity is more limited than that of ES and EG cells, and with continued expansion in culture the proportion of glial cells increases at the
expense of neuronal phenotypes [112,113]. Furthermore, default differentiation in culture is predominantly into GABAergic neurons with very few other specific phenotypes [114] and, under current conditions, their potential to form viable neuronal grafts following transplantation into rodent disease models declined with continued proliferation in vitro [115].

To summarize, although the potential of stem cells as donors for neural transplantation is considerable, there are substantial hurdles to be overcome before such cells are suitable for clinical delivery and, currently, it is not clear which starting source will prove to be the most appropriate for this purpose.

**STRATEGIES TARGETED AT GENES**

Since the identification of the genetic mutation responsible for HD, the possibility of protecting neural cells from the cascade of pathological events by the use of targeted genetic therapies has been considered. Although one goal would be to replace the DNA of the mutated gene with a normal version without the polyglutamine expansion [116], this is likely to present considerable technical difficulties. However, it is theoretically possible to down-regulate or even silence the expression of the defective gene without inducing new pathological consequences [5–7]. Surgical in utero manipulation during the stage of cell replication would require a delivery vector that specifically targeted the mutated IT15 allele whilst leaving the normal version of the gene intact. However, this is extremely demanding technically and at the present time has not yet been achieved.

There has been interest in exploring blocking of gene function by antisense or interfering RNAs [117] but, although these can be effective in vitro [118–121], they have proved technically challenging when applied in vivo HD models [116,119,122].

As an alternative strategy, a variety of growth factors may promote the survival and differentiation of specific neuronal populations. NGF (nerve growth factor), BDNF (brain-derived neurotrophic factor), CNTF (ciliary neurotrophic factor), NT (neurotrophin)-3 and NT-4/5 all increase survival of striatal neurons in culture [123–125] and in vivo [126,127]. Interestingly, NGF can also decrease the expression of huntingtin in primary striatal tissue [128]. There is also evidence that the endogenous levels of some trophic factors may be affected by having HD; in particular, BDNF has been found to be down-regulated by abnormal huntingtin in the cortex [129]. Below, we will concentrate on studies looking at the protective effects of CNTF, as this is the molecule that has received most attention in this context.

For growth factors to be effective in terms of neuronal and behavioural protection they must be delivered to the specific areas where they are needed within the CNS [130]. Unfortunately, the molecules are too large to be able to cross the blood–brain barrier and subcutaneous administration can result in significant undesirable side effects, such as cough, weakness and fever, without accompanying therapeutic effects [131]. Neurotrophins can also cause weight loss and pain when administered intrathecally [132]. The method of delivery therefore needs to be carefully explored to ensure safety and efficacy. We need the ability to deliver neurotrophins across the blood–brain barrier and also restrict delivery to precise cellular targets. Gene therapy is an obvious choice for this as highly localized and sustained delivery can be relatively easily achieved.

The genes must release physiological levels of trophic factor and maintain a stable long-term level of expression; therefore the delivery method is critical [133]. Vectors such as herpes simplex virus, adenovirus, adeno-associated virus and lentivirus have been explored with some success (Table 4; for a general review, see [134]; for a review on the use of lentiviral vectors, see [135]). Long-term expression of CNTF has been demonstrated in the striatum of transgenic mice a year after lentiviral-mediated transfection [136].

Most of the evidence for the potential efficacy of gene therapy comes from studies in animal models of HD in which viral-delivered CNTF has been found to be most effective in protecting against striatal lesion in both rodents [130,137,138] and primates [139]. There have been a number of promising studies conducted using viral-delivered neuroprotective CNTF therapy in these animal models [e.g. 136–138,140] that show protective and reparative effects on skilled motor and cognitive tasks in addition to preserving the functional neuroanatomy of the striatum [139,141]. However, there are some problems associated with in vitro viral delivery [142]. The expression of genes can be difficult to standardize and regulate, and maintaining long-term expression is a current challenge. Many viral vectors are highly toxic and viruses also differ in their ability to incorporate large genes for transfection.

Another approach is to genetically engineer cells in vitro so that expression and regulation can be fully characterized before they are transplanted. Suitable cells for ex vivo gene therapy must be easily obtainable, survive in vivo and divide at a sufficient rate to maintain expression [133]. These cells are then placed into bio-compatible polymer capsules before implantation in the brain. The capsule membrane contains pores that allow the release of the neurotrophin and the entry of nutrients and oxygen, but prevent the host immune system from penetrating and destroying the cells. An advantage of this method is that it can be used to contain cells that may otherwise be tumorigenic and xenogenic cells which may be easier to obtain and manipulate than human cells. The capsules can also be easily removed if necessary.

This trophin delivery method can protect against the neural damage and behavioural deficits normally seen...
Table 4 Summary of growth factor studies for HD

<table>
<thead>
<tr>
<th>Species</th>
<th>Vector</th>
<th>Delivery route</th>
<th>Therapeutic gene</th>
<th>Model</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rodent</td>
<td>CPT</td>
<td>Encapsulation</td>
<td>NGF</td>
<td>None</td>
<td>[146]</td>
</tr>
<tr>
<td></td>
<td>CPT</td>
<td>Encapsulation</td>
<td>CNTF</td>
<td>QA</td>
<td>[148]</td>
</tr>
<tr>
<td></td>
<td>RPP</td>
<td>Injection</td>
<td>CNTF, BDNF, NGF and NT-3</td>
<td>QA</td>
<td>[126]</td>
</tr>
<tr>
<td></td>
<td>–</td>
<td>Injection</td>
<td>GDNF</td>
<td>QA</td>
<td>[149]</td>
</tr>
<tr>
<td></td>
<td>RPP</td>
<td>Graft</td>
<td>BDNF, NT-3 and NT-4/5</td>
<td>QA</td>
<td>[127]</td>
</tr>
<tr>
<td></td>
<td>LV</td>
<td>Injection</td>
<td>CNTF</td>
<td>QA</td>
<td>[137]</td>
</tr>
<tr>
<td></td>
<td>AV</td>
<td>Injection</td>
<td>CNTF</td>
<td>3-NP</td>
<td>[138]</td>
</tr>
<tr>
<td></td>
<td>Tet-LV</td>
<td>Injection</td>
<td>CNTF</td>
<td>QA</td>
<td>[140]</td>
</tr>
<tr>
<td>Primate</td>
<td>RV</td>
<td>Injection</td>
<td>GDNF</td>
<td>3-NP</td>
<td>[150]</td>
</tr>
<tr>
<td>Human (Phase I clinical trial)</td>
<td>RV</td>
<td>Encapsulation</td>
<td>CNTF</td>
<td>QA</td>
<td>[141]</td>
</tr>
<tr>
<td></td>
<td>CPT</td>
<td>Encapsulation</td>
<td>CNTF</td>
<td>HD</td>
<td>[144]</td>
</tr>
</tbody>
</table>

after QA (quinolinic acid) lesion/3 NP insult [139,141]. In one study, monkeys had severe motor and cognitive deficits before capsule implantation, but the CNTF gradually improved task performance and the animals achieved significant restoration of function [139]. This suggests that this may be a viable treatment for HD if long-term sustained expression of CNTF can be achieved.

A Phase I clinical trial on the effects of CNTF in HD patients has recently been completed in Crêteil, France [143,144]. This trial focussed primarily on determining safety, efficacy and tolerability of the polymer-encapsulation method as well as clarification of any technical issues. Six patients received a unilateral ventricular implant of a semi-permeable polymer capsule surrounding CNTF-producing BHK cells. Patients were assessed using the CAPTT-HD assessment protocol [89] and an additional battery of neuropsychological and electrophysiological tests [145]. There were no adverse side effects such as have been reported with other trials, suggesting that it is safe to pursue this treatment method. Although no significant clinical benefit was uncovered, the placement of the capsule was not designed for maximum clinical effect [146], rather to minimize risk to the patient. However, a significant functional improvement of striatal circuitry was demonstrated in three patients, with the return of normal electrophysiological traces. A further trial is now planned once technical improvements have been made, including the long-term maintenance of CNTF at an appropriate physiological level.

There is still ongoing discussion and exploration of the most efficient way to deliver genes to the CNS [130,146], and the viability and benefit of this approach cannot be fully assessed at this stage.

**FUTURE DIRECTIONS OF CLINICAL TRIALS IN HD**

Until recently, controlled clinical trials in HD have been limited by insufficient statistical power and scientific merit [80,147]. With the advent of national and international collaborative groups (described below), it is now possible to conduct systematic research into the utility of possible therapies for HD.

**NECTAR (Network of European CNS Transplantation and Restoration)**

NECTAR, founded in 1990, centred on developing efficient, reliable, safe and ethically acceptable transplantation therapies for neurodegenerative diseases, in particular HD and Parkinson’s disease. With the support of NECTAR, NEST-HD has pioneered the first European safety and efficacy clinical trial of neural transplantation in HD in tandem with developing basic experimental, neurosurgical, assessment and follow-up procedures.

**EHDN (EURO-HD Network)**

Historically, European-based clinical trials have been difficult to implement, largely because of small population samples in the absence of a collaborative framework and the language barrier. Funded by The High Q Foundation, EHDN was initiated in 2003. EHDN has sought to overcome the language barrier by designing a sophisticated multilingual website to serve as a source of information, communication and data-entry (www.euro-hd.net).

**HSG**

The HSG (www.huntington-study-group.org), established in 1993, is a group of clinicians and other healthcare professionals...
advisors from medical institutions across the United States, Canada, Europe and Australia. To date, HSG has carried out multicentre trials to explore the symptomatic and neuroprotective effects of experimental interventions in HD.

**CONCLUSION**

At the time of writing, there is no known cure for HD and existing symptomatic therapies are only able to partially alleviate, rather than halt, some of the neuropsychiatric and motor symptoms. Some progress has been made in targeting non-specific HD pathogenic mechanisms, for instance, antiglutamatergic agents, antioxidants and mitochondrial enhancers possess potential therapeutic qualities, but treatments more directly targeted at the pathogenic mechanisms in HD await further scientific investigation. Meanwhile, gene therapy offers promising new directions for delaying and possibly preventing the course of the disease. Clinical trials into the safety and efficacy of fetal neural transplants have provided ‘proof-of-principle’. Despite this cell source being precluded by its practical and ethical limitations, the recent and rapid course of the disease. Clinical trials into the safety and efficacy of fetal neural transplants have provided ‘proof-of-principle’. Despite this cell source being precluded by its practical and ethical limitations, the recent and rapid development of alternative sources of cells, including stem cells, provides exciting new prospects for delaying or possibly halting this devastating disease.

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