Movement Disorders
Vol. 23, No. 11, 2008, pp. 1491–1504

CME

Reviews

The Current Clinical Management of Huntington's Disease

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Abstract: Huntington's disease is a neurodegenerative condition, characterized by movement disorders, cognitive decline, and psychiatric disturbance. We review the pharmacological management of the various movement disorders associated with the disease, the cognitive decline and the commonly encountered behavioral disturbances. We discuss the nonclassical features of the disease, important in the management of these patients. Nonpharmacological support including genetic counseling and therapy and the importance of palliative care are also addressed. Finally, experimental approaches that may soon impact upon clinical practice are discussed.

Key words: Huntington's disease; juvenile Huntington's disease; management; clinical features; UHDRS; biomarkers; multidisciplinary

Huntington's disease (HD) is an inherited neurodegenerative condition that classically constitutes a disorder of movement, cognition, and behavior. The genetic defect on the short arm of chromosome 4[1,2] leads to structural and functional alteration of a ubiquitous protein, huntingtin,[3] culminating in neuronal loss particularly in the caudate nucleus in early disease. The prevalence of the disease is around 1 in 10,000,[4] with onset usually in middle age, although the range of disease onset is wide, and disease duration is typically around 20 years.

Normally, the huntingtin gene has less than 36 cysteine-adenine-guanine (CAG) repeats, which encodes glutamine.[4–6] The mutant gene, which has greater than 39 CAG repeats, encodes for huntingtin with an elongated glutamine chain. Some people have "intermediate alleles" i.e. repeats longer than the normal 36 but less than 40, which display incomplete penetrance, and is more likely to result in clinical disease if it occurs in a person from an HD family than from the general population.[7] Interestingly, there are rare reports of pathologically proven HD occurring in patients with repeat lengths less than 30 (e.g. Kenney et al.[8]). The disease is fully penetrant if the patient inherits greater than 39 CAG repeats,[5] and because the elongated CAG repeat is unstable, it tends to expand as it is inherited, particularly down the paternal line, a process known as "genetic anticipation."[9,10] This accounts for the observation that juvenile-onset cases (that have long repeat lengths, typically greater than 55) are largely paternally inherited.[11] The number of CAG repeats correlates inversely with age at onset,[6,12] with elderly onset cases having a lower number of CAG repeats.[13] Overall, 50% to 69% of the variance of age at onset can be accounted for by CAG repeat length, with other currently unknown genetic factors and environmental influences also being important.[12,14–16]

The Unified Huntington's Disease Rating Scale (UHDRS) is typically used in the research setting to describe the severity of disease manifestations. The UHDRS was developed by the Huntington Study Group[17] to assess motor, cognitive, behavioral, and func-

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Potential conflict of interest: None reported.
Received 14 August 2007; Accepted 10 January 2008
Published online 25 June 2008 in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/mds.21971

tional domains. It is used both to assess individual patients and make judgments about speed of progression, and efficacy of treatment especially in therapeutic trials. Nevertheless, the UHDRS does have its limitations[18] and efforts to improve the reliability of the scale and to find more objective biomarkers are ongoing including the use of motor tasks,[19] eye movements,[20,21] metabonomics,[22] and structural and functional imaging.[23]

THE MOVEMENT DISORDER OF HD

Patients exhibit a variety of movement disorders: as Huntington himself said, the disease is "unstable and whimsical." The movement disorder typically associated with HD is chorea but often the patient is relatively untroubled by chorea; and typically bradykinesia, dystonia, and rigidity will in time come to predominate, and is generally more disabling. Juvenile HD patients often present with this latter phenotype, with minimal chorea. The comorbid dystonia may give the appearance of "hanging chorea."[24] At later stages of the disease, disability often relates primarily to motor impersistence. A complicated gait disorder, representing the sum of involuntary movements, motor impersistence, and postural instability, predisposes to falling. The patient often becomes wheelchair- or bed-bound.[25,26]

TREATMENT OF MOTOR DISABILITY IN HD

The hyperkinetic movement disorders of HD often respond to dopamine blockers such as neuroleptics, or dopamine depleters such as tetrabenazine (Table 1). Although typical antipsychotics have been used to treat HD for many years, their undesirable side effect profile and propensity to cause other movement disorders have discouraged their use. Newer "atypical" antipsychotics are widely used to treat chorea in HD. Clozapine, a non-neuroleptic dopamine receptor antagonist, has been shown to have antichoreic effects only in high doses, which engenders many adverse reactions,[29] and the necessity for full blood count monitoring also makes clozapine less attractive. Olanzapine may be a better choice: it reduces chorea, is a mood stabilizer, augments antidepressants, and also encourages weight gain. Olanzapine has probably a better evidence base than the other atypical antipsychotic drugs (with the exception of clozapine), including beneficial effects on the gait disorder of HD[30–32] and the psychiatric disturbance of HD.[30] There is evidence from case series or small clinical trials to support the use of risperidone,[33–36] and improvement of the motor subscore of the UHDRS has been described in case reports using quetiapine,[37,38] zotepine,[39] and ziprasidone.[40]

Tetrabenazine is thought to have good efficacy,[41,42] and a recent randomized controlled trial involving eighty-four patients showed that tetrabenazine significantly improved motor scores (5 points on the UHDRS, compared with 1.5 points in the placebo-treated group).[43] Use of this drug, however, must be balanced against the risk of developing or worsening depression, suicidality and sedation,[41,44] as well as parkinsonism, which is generally more disabling. Indeed, given that patients often do not complain of their chorea, and are sometimes unaware of it, antichoreic medication should be used judiciously. In contrast to antipsychotics, there are no reports of tardive dyskinesia following tetrabenazine use, but neuroleptic malignant syndrome has been reported.[45,46] Most patients determine their long-term response to tetrabenazine within 6 weeks of treatment,[47] and beneficial effects of the drug can decline with use.[48]

Some agents, primarily tested for their neuroprotective effects, have shown some symptomatic benefit for chorea: remacemide,[49] riluzole,[50] (-)-OSU6162,[51] and amantidine.[52] However, remacemide development was halted and the drug cost and need for monitoring of hepatic enzymes has limited the potential use of riluzole for chorea. Furthermore, the European Huntington's Disease Initiative Study Group have recently completed a randomized double blind controlled trial of riluzole (50 mg twice a day for 3 years) involving 537 patients.[53] Riluzole showed neither neuroprotective nor symptomatic benefits, and 158 patients dropped out of the study because antichoreic medication was required. Amantadine has been shown to have antichorea effects in one double-blind placebo controlled study,[52] but a similar study showed no benefit.[54]

Other drugs that have been used for chorea in HD, with limited or mixed evidence for efficacy, and studied in small series or case reports, include the following: choline, deanol, L-acetyl-carnitine, ketamine, dextromethorphan,[4] milacemide, muscimol, baclofen, clonazepam, diazepam, chlordiazepoxide, fluoxetine, cannabidiol, levetiracetam.[42,55]

Parkinsonism may be treated in the usual way, and there is some evidence for the beneficial use of levodopa,[56] pramipexole,[57] amantadine,[58] and cabergoline.[59] Most of the evidence, however, is limited to small studies and case reports, which tend to report on the effects of these drugs on the Westphal variant and not the "end-stage" rigidity of HD. We tend not to use ergot-derived dopamine agonists for obvious reasons relating to their side effect profile.

Bruxism has been reported to occur in HD, and is thought to be separate from a side effect of neuroleptics, and can be treated with botulinum toxin.[60]

TABLE 1. *Commonly used medications in the management of HD*

Drug	Mechanism of action	Indication	Side effects	Dosages
Tetrabenazine	Binds vesicular monamine transporters, inhibiting uptake of monoamines into synaptic vesicles; also blocks postsynaptic dopamine receptors	Hyperkinetic movement disorders	Drowsiness, Parkinsonism (around 30%), depression, insomnia, anxiety, acute dystonia, rarely confusion, orthostatic hypotension, hallucinations. NB No reports of tardive dyskinesia, but neuroleptic malignant syndrome has been reported.	12.5 mg bd, increased slowly to 12.5–25 mg tds (max 200 mg/day)
Risperidone	Serotonin-dopamine (D_2) antagonist	Hyperkinetic movement disorders; Mood swings; psychosis	Prolonged QT interval, postural hypotension, hyperglycaemia, tardive dyskinesia, Parkinsonism (milder than with sulpiride), fatigue, gastrointestinal	2 mg od, initially then usually 2–3 mg bd, max 16 mg/day. Liquid available
Olanzapine	Serotonin-dopamine (D_2) antagonist	Hyperkinetic movement disorders; Mood swings; psychosis; Depression; weight loss	Prolonged QT interval, postural hypotension, hyperglycaemia, tardive dyskinesia, Parkinsonism (milder than with sulpiride), marrow depression, hepatitis, fatigue. Caution with prostatic hypetrophy	10 mg od adjusted as required to 5–20 mg od. Max 20 mg/day
Citalopram	Selective serotonin reuptake inhibitor (SSRI)	Depression	Gastrointestinal, anorexia, hypersensitivity, drowsiness, syndrome of inappropriate antidiuresis (SIADH), postural hypotension, confusion	20 mg, increasing to 60 mg max
Fluoxetine	SSRI	Depression	Less sedating than citalopram, gastrointestinal, anorexia, hypersensitivity, SIADH, blood dyscrasia	20 mg, increasing to 60 mg max
Mirtazepine	Presynaptic α_2-antagonist, increases central noradrenaline and serotonin activity	Depression, weight loss	Drowsiness, tremor, myoclonus, reversible agranulocytosis	15 mg nocte, increasing to 45 mg (max) as required
Sodium valproate	Alters GABA, glutamatergic activity, and T-type calcium channel and potassium channel conductance	Mood swings	Hyperammonaemia, drowsiness, blood dyscrasia, hepatitis, dizziness, gastrointestinal, cognitive disturbance, endocrine	200 mg tds, increasing to 2.5g max if required
Carbamazepine	Inhibition of voltage-gated sodium channels. Action on monoamine, acetylcoline, and NMDA receptors	Mood swings, weight loss	Drowsiness, blood dyscrasia, hepatitis, hyponatraemia, dizziness, gastrointestinal	Usually 200–1,600 mg in 2–3 daily doses (max 2g)
Lamotrigine	Inhibition of voltage-gated sodium channels	Mood swings	Hypersensitivity, blood dyscrasia, dizziness, gastrointestinal, depression	25 mg/day increasing to 250 mg bd (max) if required

Dystonia may cause pain and significant functional impairment for patients but has not been the subject of a primary end-point in any trial of treatment in HD. However, olanzapine for example has been shown to improve the gait disorder of HD (of which dystonia often plays a part), and tetrabenzine is effective in the treatment of dystonia *per se*.[47]

COGNITIVE DECLINE

Patients may notice cognitive dysfunction at an early stage of their disease, even before the motor symptoms, but as the disease progresses, the patient will develop dementia. Often patients have impaired insight into their decline.[61]

Cognitive dysfunction is typically of a subcortical frontal dysexecutive type, with bradyphrenia, poor spatial and working memory, poor planning and organization, a lack of judgment, and poor mental flexibility.[25,26,62–64] The cortex is involved early in the disease process[65–68] and this may contribute to some of the deficits in early HD.

TREATMENT OF COGNITIVE CHANGES IN HD

Acetylcholinesterase inhibitors improve cognition in Alzheimer's and particularly Lewy Body Disease,[69] but their efficacy has not been adequately proven in HD. De Tommaso et al.[70] evaluated the effect of 2 years of treatment with 6 mg rivastigmine in a small open-labeled study and found that motor scores had improved; and a "trend"' toward improvement of cognitive function and functional disability was observed. It has been shown that donepezil has no effect on cognitive function in HD.[71] Clearly, to address whether cholinesterase inhibitors are effective in HD, larger randomized controlled trials with a reasonable follow up time should be undertaken; and clinically relevant benefit should also be demonstrated. In our practice, we do not routinely give cholinesterase inhibitors to HD patients with cognitive decline, given the paucity of data on this to date, the cost and the side effect profile of these agents.

PSYCHIATRIC DISTURBANCE

Psychiatric symptoms in HD include depression, anxiety, disinhibition, aggressive behavior, and a tendency to suicide.[72] Psychiatric symptoms are common and disabling but not necessarily progressive.[4] Suicide risk may wax and wane over the course of the disease. The greatest periods of risk for suicidal behavior include the time that symptoms first become apparent and then again when symptoms cause meaningful changes in life (e.g. loss of employment or driving privileges).[73]

Naarding et al.[74] have reviewed the literature pertaining to psychiatric manifestations of HD, since 2001. Most studies did not use DSM criteria, making standardization very difficult. Depression, in this literature review, was reported at around 40%, and suicide was around eight times more common than in the general population. Psychosis has been reported in around 30% of patients.[74]

TREATMENT OF PSYCHIATRIC DISTURBANCE

Behavioral strategies, such as behavior modification, may be helpful in the management of irritability and aggressive behavior, but most patients will require pharmacotherapy for mood and behavior. Trials of antidepressants are small and open-labeled, or limited to case reports e.g. mirtazapine,[75] fluoxetine,[76] monoamine oxidase inhibitors.[77] Electroconvulsive therapy has also been used with good effect in six HD patients with refractory depression.[78] Results of small, uncontrolled studies or case series suggest that antidepressants or antipsychotics may be helpful in the management of irritability or aggression.[79] Propranolol has been used in patients with aggression[80] but two of the three patients studied were also taking haloperidol. Sertraline,[81] lithium (in combination with haloperidol),[82] and buspirone[83–85] have also been used to manage aggressive behavior in HD. Obsessive compulsive symptoms in two patients have benefited from fluoxetine[86] and from sertraline in one.[87] The antipsychotic effect of risperidone has been reported,[34,88] and beneficial effects of olanzapine on behavior have also been observed.[30–32]

It may seem intuitive that apathy in HD would be as a result of depression but this is not necessarily the case.[89] Apathy is an important problem in HD as it contributes significantly to functional decline[90] but has not yet been subject to a treatment trial as an end point.

In our practice, we find that depression often responds to antidepressants such as selective serotonin reuptake inhibitors (SSRI) (Fig. 1, Table 1) and it is clearly important to recognize and treat depression, making the psychiatrist an invaluable part of the multidisciplinary team. Mood stabilizers such as carbamazepine, lamotrigine, and sodium valproate can be useful in the management of HD patients, and can be used to

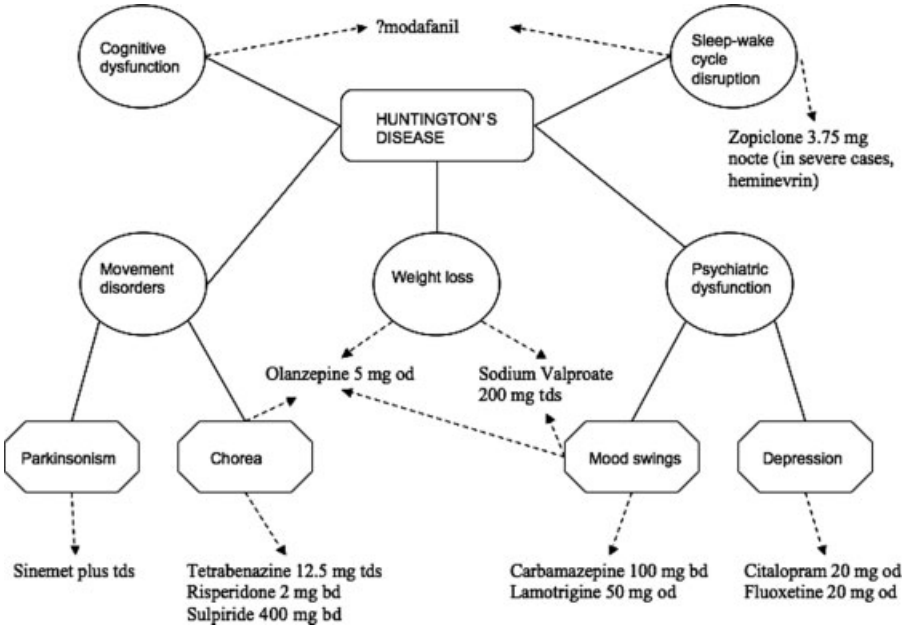

FIG. 1. Commonly used medications in the management of HD. The major manifestations of HD are shown in circles and the dashed arrows point to medication used to treat each symptom. Typical maintenance doses are shown, but medication can be increased to maximal doses.

augment the actions of antipsychotics and antidepressants.[32] Lamotrigine, however, does not slow functional decline in HD.[91]

"NONCLASSICAL" FEATURES OF HD

The disease is accompanied by a number of other physiological manifestations including sleep-wake cycle disruption[92] and weight loss (despite no loss of appetite).[93–95] As Huntington alluded to in an address to the New York Medical Society in 1909 "... two women, mother and daughter, both tall, thin, almost cadaverous, both bowing, twisting, grimacing." Such changes have long been recognized and thought to relate to the hyperkinetic movement disorder. However, there is increasing interest that it may be a part of the disease itself, with pathology possibly in the hypothalamus or in the peripheral tissues themselves.

In this respect, Hamilton et al.,[94] in collaboration with the Huntington Study Group, followed a large cohort of patients in several centers, for a mean of 3.4 years and found that weight loss and chorea were only weakly correlated, and suggested other factors may be at play. Pratley et al.[96] have shown that sedentary energy expenditure is higher in HD patients (although not total energy expenditure due to less engagement in voluntary activity when compared to controls). Robbins et al.[97] recently conducted a postal questionnaire of 78 patients and 63 controls and confirmed that HD patients are leaner than controls. They found that weight loss progresses with the disease and those patients fail to gain weight, initially before there is frank weight loss. The authors found that gastrointestinal and endocrine symptoms such as diabetes were not reported more commonly in HD patients compared to controls (although diabetes and high cortisol has been reported by some authors; reviewed by Petersen and Bjorkqvist[98]), and suggested a more subtle metabolic cause for the weight loss. Indeed, Underwood et al.,[22] conducted a metabonomic profiling study of serum from patients versus controls, and found a procatabolic metabolic signature in presymptomatic patients, paralleling a significantly similar profile in transgenic HD mice.

Weight loss may be due to hypothalamic pathology, as neurones, particularly somatostatin-containing cells, are lost in the nucleus tuberalis lateralis of the hypothalamus of HD patients[99]; as well as the orexin-containing cells in the lateral hypothalamic area.[100] Interestingly, given some reports of increased appetite and calorific intake in HD patients,[93] some studies have shown that HD patients have low levels of leptin (which promotes satiety) and high levels of ghrelin (which increases appetite).[101] Since lack of sleep increases ghrelin and reduces leptin,[102] it is interesting to speculate that this metabolic profile may be secondary to disrupted sleep in HD. Many patients with HD require dietary supplementation and percutaneous gastrostomy (PEG) feeding, which will be discussed later in the article.

Patients with HD report significant sleep disturbance, and this can be objectively measured using an activity monitor, worn like a wrist-watch[103] as well as electro-

physiologically.[92,104] Using a wrist-worn activity monitor, Morton et al.[105] have demonstrated that HD patients have a profound circadian rhythm disturbance, similar to that seen in transgenic mice. Interestingly, these mice also have reduced levels of circadian clock gene expression in the suprachiasmatic nucleus, thereby suggesting that the circadian rhythm disturbance is of central origin.

Hypnotics are particularly useful in the management of HD because insomnia is not only common and disabling, but "subclinical" sleep disturbance, with its deleterious consequences, is even more common.[105] Thus, we have a low threshold for prescribing hypnotics such as zopiclone or eszopiclone. In some cases it may be helpful to combine a hypnotic at night-time with a stimulant such as modafinil in the morning, to attempt to reinstate a more normal sleep-wake cycle in patients. However, the efficacy of this approach is still only at an anecdotal level.

Autonomic dysfunction has been noted in HD patients, with asymptomatic and early onset patients displaying sympathetic hyperactivity[106] and a lesser number of mid- and late-onset patients displaying autonomic hypofunction.[106–108] Peripheral nerve function is intact in HD patients,[107,108] and Kobal et al.[106] have postulated that the initial sympathetic hyperactivity may be secondary to diminished inhibition of brainstem autonomic centers due to cortical dysfunction, and late stage hypofunction is secondary to neurodegeneration of autonomic centers. The relevance of autonomic dysfunction in HD is unclear, but it may serve as a biomarker, and is sometimes symptomatically relevant. Urological symptoms have been described in HD patients,[109,110] although this may not be secondary to autonomic dysfunction.[109] Detrusor hyper-reflexia in HD has been treated with carbamazepine.[111]

JUVENILE HD

Juvenile onset patients present their own unique challenges, often displaying behavioral disturbances. Although chorea is the presenting feature in around a half of cases, the phenotype tends to be different to adult patients, with early dementia, dysarthria, epilepsy, myoclonus, dystonia, spasticity, and ataxia. Cognitive decline is early and severe and is often seen as a decline in school performance, typically in the context of poor behavior.[112,113]

The diagnosis of juvenile HD may be challenging and the major management difficulty is treatment of their behavioral problems, as well as the hypokinetic movement disorder. The genetic testing of children poses particular challenges. A diagnosis often needs to be established, but genetic testing is only undertaken if the child has clear evidence for a condition that could be juvenile HD clinically, and in whom knowing this information would influence management. In an HD family, it is generally accepted that it is the child's choice and a child should not be tested until he or she is of an age to appreciate the magnitude of such a decision. Of course this age may differ among individuals, and it is a difficult judgment to make.

Pharmacological management of the behavioral disturbance in juvenile HD is difficult, and there is no evidence base. Agents used to manage attention deficit hyperactivity disorder[114] might be of benefit in the behavioral problems of juvenile HD although there are no published reports of their use: methylphenidate, modafinil, clonidine, tricyclic antidepressants, selective noradrenaline reuptake inhibitors, and bupropion. Bupropion has been used to treat aggression in adult and juvenile HD.[83–85] Obsessive-compulsive behavior has been reported in HD and successfully treated in one adult patient with sertraline[87] and fluoxetine in two adults (one from a young age).[86] Five patients with juvenile HD displayed improved behavior after levodopa treatment (up to 6 weeks), although it is difficult to say whether this was a direct effect or secondary to improvement in hypokinesia and speech.[115] In this study, two children developed hyperkinetic movements and one a marked loss of appetite.

Since juvenile HD patients may present with Parkinsonism and rigidity, levodopa is often used to treat this hypokinesia.[115] A moderate improvement in limb (but not trunk) dystonia was noted in a 13-year-old patient with generalized dystonia and parkinsonism following bilateral pallidotomy, but the patient experienced worsening spasticity.[116] Myoclonus has been treated successfully with sodium valproate in a small series of seven patients, albeit in adults.[117] There are no published reports of treatment of spasticity in juvenile HD, but anecdotally this is often treated in the usual way with baclofen or tizanidine.

DIFFERENTIAL DIAGNOSIS AND PHENOCONVERSION

The differential diagnosis of HD with a negative genetic test is wide[118] and beyond the scope of this review. Clearly, in patients with a family history, and with the advent of genetic testing, the diagnosis of HD can be straightforward. The difficulty in this circumstance is to predict when the disease has commenced, rather than simply being a carrier of the gene. Such

phenoconversions may be subtle, can be cognitive ahead of motor, and clearly of significance especially in people employed in jobs of responsibility. Thus, careful attention has to be paid to this with thorough assessments including detailed neuropsychological testing.

The initial symptoms of HD tend to be rather subtle and are often psychiatric or cognitive in nature.[26] The cognitive decline in the early stages can on occasion be attributed to the psychiatric dysfunction, especially if the social circumstances involve severely affected HD family members. The development of motor features is a major diagnostic clue and in the early stage of disease minor motor abnormalities such as fidgeting and eye movement abnormalities may be seen. It may be necessary to 'bring out' the chorea, manifest sometimes as finger flicking when walking, or lower limb chorea while engaging the arms in a manual task.

MANAGEMENT

Genetic Counseling

Genetic counseling is a very important part of the care of HD. The diagnosis of HD affects everyone in the family, and because it is a late-onset disease, patients usually have started their families in advance of the diagnosis. Genetic counselors help family members understand their own disease risks and can identify and discuss reproductive options.

Presymptomatic identification of gene carriers can help with the planning of family and the future. Genetic counseling is an essential part of the process of testing for the gene in at-risk persons. Well developed pretest counseling protocols have been designed to address common ethical concerns such as genetic testing of unaffected minors, prenatal testing, persons at 25% risk by virtue of having an at-risk unaffected parent, and testing of potential adoptees. Follow-up in those who have undergone presymptomatic testing under the guidance of a counseling protocol suggests that catastrophic reactions to the testing process are very rare. Five years after predictive testing, distress scores are similar in gene carriers and noncarriers and are significantly decreased compared to the pretest levels.[119] Perhaps because of its untreatable nature and potential threats to insurability or employability, the uptake of presymptomatic testing is only about 5% to 20% of eligible at-risk population.

For some families, a diagnosis of HD may be new to the family. About 10% of HD patients have a negative family history.[120] In some cases, the proband has inherited a partially or completely penetrant allele and the parent carries a premutation or partially penetrant allele. However, in many cases, the family history is clouded by early death or disappearance of a gene-carrying parent or frank obfuscation by family members.[121] For such families, genetic counseling is essential to communicate reliable information on genetic risk. When patients are first seen in the clinic and a diagnosis of HD is being considered, it is of the utmost importance to ensure that the patient understands all the implications of a positive genetic test before any blood is taken. This is particularly true for patients without a family history who have no experience of the disorder and its implications, and much time and care should be spent with the patient to explain all the issues. This is especially pertinent when patients first present to neurologists outside of a joint or multidisciplinary medical genetic clinic.

The Multidisciplinary Team and Specialist Clinic

Because of its complex nature and evolution over time, HD patients require the care of many experienced professionals, with good coordination of services and support, and regular reassessments to meet changing needs. It has been recognized that many HD patients have needs that are not being met,[122,123] although the emergence of multidisciplinary clinics, worldwide networks, and patient information websites/literature (Table 2) are addressing this.

The multidisciplinary team may include:

- Neurologists specializing in movement disorders.
- Psychiatrists specializing in neuropsychiatry.
- Neuropsychologists.
- Genetic counselors.
- Specialist nurses: to provide a pivotal coordination role, enduring support for patients and families, as well as a readily accessible point of contact.
- Social workers: to provide help in the community with disability benefits, financial management, power of attorney, home caregivers, respite care, end of life issues including wills and advanced directives, etc. In the UK, the NHS and Community Care Act 1990 require assessment and assistance by social services, and this should be available to all patients.
- Palliative care consultants.
- Dieticians: to address weight loss, obsessions and eating habits, thickened food if dysphagia is an issue with small frequent meals to manage regurgitation if appropriate, along with advice on calorific dietary supplements and consideration of PEG feeding.
- Workers from lay organizations: to provide more specialist input including advice on appropriate places for respite care.

TABLE 2. *Sources of information for professionals, patients, and caregivers*

Organization	Web address
Primarily for patients and caregivers	
International Huntington Association	www.huntington-assoc.com
HD advocacy center	www.hdac.org
HD lighthouse	www.hdlighthouse.org
Hereditary disease foundation	www.hdfoundation.org
Huntington's disease association	www.hda.org.uk
Huntington's disease society of America	www.hdsa.org
Huntington's study group	www.huntington-study-group.org
Sue Ryder	www.suerydercare.org
Primarily for professionals	
European HD network	www.euro-hd.net
Worldwide education and awareness for movement disorders	www.wemove.org

- Physiotherapists: to improve mobility, aid in provision of walking aids and wheelchairs, improve motivation and through this provide a more stimulatory environment for the patient.
- Occupational therapist: to assess and address safety issues particularly in the home, and provide aids (e.g. special cutlery and bath/shower aids) for activities of daily living.
- Speech and language therapists: poor communication often compounds behavioral and psychiatric disorders, and speech therapists provide important assessments and advice on this, as well as advising on the safety of swallowing and need for PEG tube feeding.

A good relationship with the general practitioner is also very useful in the care of HD patients and their families, and dentists, chiropodists, aromatherapists, hydrotherapists, music therapists, and spiritual advisors may also provide important care. Good communication and coordination within the multidisciplinary team are essential and ideally at every clinic visit, each member of the team must assess the nature and severity of behavioral and motor symptoms and reassess the risk to benefit ratio of extant and proposed medication changes. Patients and their families feel that readily available access to information and support is important,[122] and this may be provided by the specialist nurse, lay workers, open access clinics, and websites/literature (Table 2).

Family members and caregivers often suffer from fatigue, loneliness, and stress-related illnesses,[122] and they should be included in the support offered by the multidisciplinary team.

Staging the Disease for Optimal Management

The disease may be divided into early, mid, and late stages (Fig. 2). It is important to recognize the problems inherent in each of these stages, to plan for expected difficulties and also to realize the potential interactions between different symptoms. For example, a decline in motor performance may be secondary to depression, and engagement in rehabilitation programs and therapies may be limited by depression or apathy.

Difficulties encountered in the early stages include adjustment to the diagnosis (for both patients and the family); cognitive and behavioral changes with their impact on employment, relationships, and driving; and monetary concerns (loss of employment, implications for insurance). Thus, the management at this stage involves discussions on the implications of the diagnosis for the future and how this will impact on employment, driving, etc. It is also useful to ensure the patient and family has contact with all the appropriate support agencies. Drug treatment at this stage is limited and may involve treatment for sleep and psychiatric problems more than for any movement disorder. It is essential at this stage of the disease that the patient and family feel well supported and are followed up in a multidisciplinary clinic with an interest in HD, and have access to possible new therapies.

In the mid-stage, movement disorders may become more apparent and the gait disorder more disabling. The complex gait disorder frequently leads to repeated falls. The personality of the patient may change, challenging behavior may emerge, and the family may need strong support. While drug therapies are more commonly required at this stage for treatment of the movement disorder and psychiatric problems, other valuable input needs to be sought from occupational therapists, physiotherapists, and speech/language therapists. Respite care may be appropriate and preparation for the late stage of the disease, including power of attorney, advanced directives, PEG feeding, and care placements, should be considered. In many ways, the

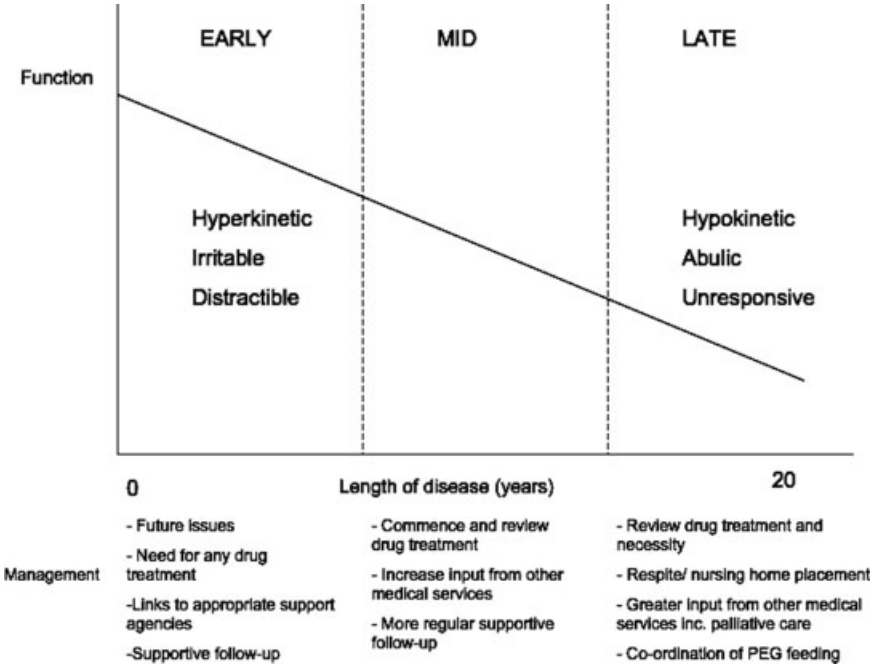

FIG. 2. Stages of HD. The phenotype of patients at early and late stages is described on the graph, and optimal management strategies in the text below.

earlier these topics are discussed openly, the easier the final decisions, as rushing such complex management issues often creates unnecessary tensions and stress. Thus, at this stage, management is dependent on support established earlier on in the disease course.

In the late stage of HD, the patient may be in a nursing home or hospice, and ideally the multidisciplinary team should still be involved, with an emphasis on good palliative care and support for the family. At this stage, it is often helpful to critically review the drug management of the patient to ensure that they are not taking medication that may be contributing adversely to their clinical state. For example, antichoreic medication may no longer be necessary as the chorea fades, but could be contributing to drowsiness and bradykinesia. Mood becomes difficult to assess and thus empirical courses of antidepressants are often given on a trial basis, but discontinued if no effect on behavioral symptoms are apparent. At this stage, sleep can be a major issue, and attention to good sleep hygiene and hypnotics is required. Dysphagia is common and PEG feeding may be appropriate. Typically patients are best managed in specialist units and in care homes with input from the multidisciplinary clinic, at least in terms of advice if not by visits. Management at this stage ultimately involves end of life issues and palliative care, and thus needs to be handled sensitively, with involvement of as many family members as are needed, and also palliative care teams.

Pharmacological Management

Bonelli and Wenning[42] have recently reviewed the pharmaceutical management of HD, and confirmed that there is a limited evidence base for the drugs used to treat HD patients. Kieburtz and Shoulson[4] have also recently reviewed therapeutic trials in HD. Multicenter randomized placebo-controlled trials are required, aided by widely accepted scales such as the UHDRS and organizational groups such as the Huntington's Study Group and EuroHD (Table 2), to improve the evidence base for pharmaceutical management. Of twenty level 1 trials identified by Bonelli and Wenning[42] since 1965, no specific treatment recommendation could be given. Bonelli again, in conjunction with Hofmann,[55] have also comprehensively reviewed treatment studies in HD since 1990 and again, concluded that there is little published evidence to support symptomatic (and neuroprotective) therapies in all aspects of HD. This is not to say, of course, that patients in HD clinics should not be given any symptomatic treatments; only that the currently accepted management of these patients has not been retrospectively confirmed in large randomized controlled trials. A "multihit" approach to prescribing is often helpful, e.g. olanzapine helps not only with chorea, but also abnormal behavior and weight loss.

Nonpharmacological Management

The importance of speech therapy, physiotherapy, and occupational therapy for the HD patient has been

described earlier. Relatively recently, interest has focused on environmental enrichment as a strategy to improve not only the patient's well being but possibly even as a neuroprotective strategy. Enrichment of the living conditions of laboratory animals, by providing toys and running equipment for example, enhances neurogenesis, improves cognition and substantially increases survival in both normal and transgenic mouse models of HD.[124–128] Many mechanisms are thought to be involved in this process including increases in vascular endothelial derived growth factor, insulin-like growth factor, brain derived neurotrophic factor (BDNF), angiogenesis, and synaptogenesis.[128] BDNF in particular is thought to mediate the improved phenotype of R6/2 transgenic HD mice in response to environmental enrichment.[126]

There are no experimental trials to provide evidence that physical therapy and rehabilitation works in HD patients, although many case reports and small series suggest that it is beneficial.[130,131] "Enrichment" of the HD patient (with, perhaps, physiotherapy, music therapy, day centers etc.) is not only intuitively beneficial, but has a plausible scientific basis, perhaps even with a disease modifying and life-prolonging effect. Thus, encouraging the patient and family to pursue such activities should be a priority in clinic.

Palliative Care and End of Life Issues

The patient with late stage HD is often managed in a nursing home, and continued involvement of the multidisciplinary team is very helpful. Nursing homes and hospices with a specialist interest in HD (or children's hospices for juvenile HD[132]), with frequent reviews by palliative care consultants, are invaluable. Some families however, prefer to care for relatives in the home[122] and every effort should be made to support families who choose to do this.

HD patients face similar issues to patients with other late stage dementias: sleep-wake cycle disruption, severe psychiatric and behavioral problems including delusions, screaming, and so on. Environmental enrichment such as a "multisensory environment"[27] is still important in these patients and every effort should be made to engage and support them, while also minimizing changes in the environment that may cause confusion or further disorientation. Patients may become anarthric and the help of the speech and language therapist should be enlisted, and very simple communication aids can be helpful. Dysphagia occurs particularly with HD patients but the instigation of PEG feeding is rarely appropriate in late stage demented patients.[28] Rather, planning for PEG feeding in mid stages of the disease is more desirable if the patient is beginning to experience signs of dysphagia with or without weight loss and aspiration pneumonia. Careful attention to mouth care is also important, at all stages, given that patients often have xerostomia (that can exacerbate dysphagia and dysarthria) and may neglect or be unable to attend to their own mouth care, particularly in the later stages of disease. Pain may arise from hyperkinetic movements and injury, or hypokinesis, dystonia and spasticity, and these abnormalities of movement and muscle tone, as well as good pain control should be addressed. Specialist knowledge of the peculiar problems faced by HD patients and families is important. For example, padding of bed-sides to prevent injury if the patient has severe choreiform movements, management of HD patients who smoke by providing them with nicotine replacements,[4] and sympathetic management of visiting families who may see a chilling glimpse of their own future.

EXPERIMENTAL AND EMERGING THERAPIES

Pharmacological management of HD patients is geared toward alleviating the symptoms of HD. While this is clearly important for patients, there is much interest in preventing the disease process from commencing, along with neuroprotection and cellular repair. Some such therapies have been subject to clinical trials, while others are as yet laboratory-based. Clearly a major discussion of this topic is beyond the scope of this review, but it is worth mentioning some possible new treatments that may impact on the clinic in the near future.

Perhaps the most convincing approach, at least in theory, is to halt the disease at the transcriptional level, using for example small interfering RNA.[133–135] The main problem with this approach, however, is drug delivery. Downstream, many agents have been developed to neutralize the mutant protein, including inhibitors of aggregation, activators of chaperones, alteration of huntingtin structure (such as promotion of phosphorylation using FK506) and promotion of degradation pathways. One example of this is promotion of autophagy to remove mutant huntingtin. Interestingly, mutant huntingtin aggregates sequester mammalian target of rapamycin (mTOR), which normally inhibits autophagy, thereby promoting its own degradation.[135] This observation has contributed to the debate as to whether aggregates are toxic or protective. Agents to promote autophagy such as rapamycin (this inactivates mTOR thus increasing clearance of both soluble and aggre-

gated mutant huntingtin) have shown promise in fly and mouse models of HD.[136,137] Other possible strategies include agents that reverse the deleterious consequences of mutant huntingtin (such as histone deacetlyase inhibitors, antiapoptotic agents, replacement of neurotrophic factors).[138] Creatine,[139] coenzyme-Q,[140] and LAX-101[141] are all compounds that enhance mitochondrial function and have been tested in clinical trials, although with disappointing results. Minocycline, an antiapoptotic and anti-inflammatory tetracycline, has also been tested clinically, but only in an open label study.[142] Other compounds tested in patients include remacemide, riluzole, α-tocopherol, and idebenone.[4]

Cellular repair has been attempted by implantation of fetal striatal tissue into the diseased striatum. This approach is, however, fraught with logistical and ethical problems, and it has been difficult to achieve a consistent improvement in transplanted patients, although some groups have reported encouraging results. Other cellular repair approaches include xenotransplantation, implantation of fetal stem cells, embryonic stem cells, and cells derived from them, as well as, more contentiously, adult non-neural tissue such as skin and bone marrow.[143] Another more experimental strategy is to attempt to stimulate the patient's own endogeneous neural stem cells[144]: either to repopulate the striatum,[145,146] or the hippocampus, in which neurogenesis is defective in mouse models of HD.[128,147–149] Such an approach could be combined with optimizing the microenvironment into which the newborn cells could emerge.[147,150]

SUMMARY AND CONCLUSIONS

Huntington described his eponymous disease "merely as a medical curiosity" and commented, "It seems at least to be one of the incurables."[4] HD is a relentlessly progressive and terrible condition, afflicting whole generations, and it is no surprise that "It is spoken of by those in whose veins the seeds of the disease are known to exist, with a kind of horror, and not at all alluded to except through dire necessity... (The disease develops) gradually but surely, increasing by degrees, and often occupying years in its development, until the hapless sufferer is but a quivering wreck of his former self."[4] Patients with HD now tend to be managed in a multidisciplinary fashion, with regular support and symptomatic therapies. The efficacy of such symptomatic therapies has not, however, been addressed comprehensively in clinical trials, and the situation for juvenile HD is even worse, particularly given such low numbers of patients. End of life issues remain complicated and largely under-investigated, but the discovery of the gene and intense research in recent years has provided a glimmer of hope for disease modifying therapies, including cellular repair.

Acknowledgments: We would like to thank Anna Goodman, Sarah Mason, and Sue Hill for their useful comments on this manuscript. Our own work in HD has been supported by the Medical Research Council, Huntington's Disease Foundation and the High Q Foundation. The helpful comments by three anonymous reviewers were much appreciated.

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