An Overview of Psychiatric Symptoms in Huntington's Disease

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Huntington's disease (HD) is an inherited autosomal dominant disorder characterized by neurologic, cognitive, and psychiatric symptomatology. Psychiatric symptoms in HD are often amenable to treatment, and relief of these symptoms may provide significant improvement in quality of life. This review will briefly describe neurologic, neuropsychologic and brain imaging data, and then review psychiatric syndromes seen in HD and their treatment.

Introduction

Huntington's disease (HD) is an autosomal dominant, neurodegenerative disease characterized by a triad of symptoms and signs, including a movement disorder, cognitive impairment, and psychiatric syndromes. These conditions may occur alone or in combination, and any one may predominate in an individual. Huntington' disease occurs worldwide, with a prevalence of 4 to 7 per 100,000 [1]. Up to half of all individuals present with purely psychiatric symptoms before onset of the movement disorder [2].

Etiology

Huntington's disease is caused by an abnormal expansion of trinucleotide (cytosine-adenine-guanine [CAG]) repeats coding for glutamine at the N-terminal of a protein called "huntingtin" (IT15 at 4p16.3) [3]. The function of normal huntingtin is unknown. Mutant huntingtin may cause HD via a toxic gain of function. An expanded IT15 CAG repeat of 37 or more is 100% specific, and 98.8% sensitive for HD [4]. Although in the US the mean age of onset is approximately 40, onset as early as age 2 and as late as 80 has been reported [5]. An inverse relationship between CAG repeat length and age of onset has been demonstrated, such that higher CAG repeat number is associated with earlier age of onset [6].

Neuropathology

The primary change is decline in the number of striatal medium spiny γ-aminobutyric acid (GABA) neurons, most markedly in the caudate, but also in the globus pallidus [7,8]. Receptor studies have demonstrated reduction in striatal D1- and D2-receptor binding in HD patients [9], which have been noted to be related to duration of illness [10].

Neurologic Abnormalities

Neurologic signs and symptoms in HD include both abnormal involuntary movements (chorea, dystonia, tremor), and rigidity and impairment of normal voluntary movements (gait disturbance, impairment of saccades and smooth pursuit, speech and swallowing difficulties). Impairment of eye movements may be one of the earliest signs. Table 1 provides a generalized description of the course of motor symptoms in HD. Patients with juvenile onset HD (age less than 20 years, approximately 6% of patients) have little chorea, and a clinical picture more consistent with parkinsonism. Seizures and myoclonus may occur in juvenile onset cases, and school failure is commonly reported.

In general, treatment of the movement disorder is not advised unless symptoms are disabling (*eg*, a patient can not sit due to lurching motions from severe chorea or suffers psychologic distress and social impairment). Symptomatic treatment of the movement disorder has included use of typical neuroleptics, dopamine depleting agents, and, more recently, atypical neuroleptics. Treatment with typical neuroleptics has been associated with minimal improvement of chorea at the expense of worsening gait and swallowing, and risk of causing tardive dyskinesia. Lamotrigene, baclofen, OPC-14117, and coenzyme Q and remacemide have all been examined in double blind, placebo-controlled trials [11–14]. To date there is no neuroprotective strategy that has proven efficacy in HD. Preliminary data suggest possible beneficial effects on motor and cognitive symptoms from intrastriatal transplant studies, but follow-up beyond 1 year is not yet available [15].

Cognitive Changes

Early HD is characterized by slowed thinking and impaired ability to manipulate information [16]. Memory impairment

Table 1. Generalized overview of motor symptom progression in Huntington's disease

	Early stages	Middle stages	Late stages	Comments
Chorea	+++	++	+	Usually begins in hands, feet, and face; patients are often unaware of movements and relatively unperturbed by them; for severe cases, weights on the legs may help the patient sit still; weighted silverware may help stabilize movements while eating; anxiety worsens chorea
Dystonia	+	++	+++	May be very disabling in the end stages of illness; can be exacerbated by neuroleptics
Rigidity	+/-	+/-	+	Seen most commonly in patients with juvenile onset Huntington's disease; usually seen in adult Huntington's disease patients at end stage illness
Speech and swallowing impairment	-	+/-	++	Speech/swallowing therapy may significantly improve quality of life; neuroleptics worsen symptoms; caregivers should be instructed on how to perform the Heimlich maneuver early in the course of the illness
Gait impairment	-	++	+++	Physical therapy may significantly improve quality of life
Eye movements: slowed smooth pursuit; irregular saccades	+	++	+++	Eye movement irregularities may contribute, along with slow reaction times, to difficulty driving; have been reported to be some of the earliest signs of Huntington's disease

is seen in HD. Recognition is generally intact, but recall is deficient [17,18]. Executive function has long been characterized as deficient in HD. These deficits can be seen on formal testing and in problems with performance of activities of daily living [19–21]. Rigid behavior and trouble planning may be a reflection of executive dysfunction. Finally, HD patients show deficits in skill and motor learning [22], which are probably mediated by frontal-striatal systems.

Testing

Direct testing for HD has been available since 1993. Linkage analysis, available since 1983, required several family members to give DNA samples, while direct testing can now be performed on one individual. Thus, family support and consensus is no longer needed for an individual to obtain genetic test results. Although there are approximately 150,000 people in the US currently at risk for HD, only about 3% of them have undergone presymptomatic testing [23], perhaps reflecting fear of genetic discrimination.

Huntington's Disease Society of America (HDSA) guidelines recommend that presymptomatic testing be done only at HDSA-certified testing program [24]. The guidelines suggest that minors should not be tested, except in extenuating circumstances. Individuals should be evaluated to determine whether they have considered the consequences of testing positive (*eg*, loss of family and other social supports, possible inability to find health insurance). They should also be urged to explore the impact of their genetic status on marriage, childbearing, and career. The consequences of testing negative (*eg*, survivor guilt, if other family members are affected) should also be addressed. Adverse outcomes, precipitating need for psychiatric treatment, have occurred after testing for HD [25], underscoring the need for involvement of psychiatrists in the evaluation process.

Brain Imaging Changes

Some MRI studies demonstrated basal ganglia atrophy in mildly affected HD patients [26], with early age of onset and longer CAG repeat length correlating with amount of atrophy in the caudate and total basal ganglia [27]. Generalized brain atrophy is seen early on MRI, and focal frontal lobe atrophy later [28].

Initial positron emission tomography (PET) studies with HD patients demonstrated caudate and putamenal decrease in glucose use [29,30], correlating highly with functional and motor abnormalities [31]. Antonini *et al.* [32] found decreased glucose metabolism and raclopride uptake (a measure of dopamine D2-receptor binding) in the caudate and putamen of patients and in presymptomatic gene-positive individuals several years prior to onset of symptoms. Functional imaging is being used to better estimate the time prior to symptoms when basal ganglia atrophy develops. Theoretically, this might be the best time to initiate neuroprotective strategies.

Only two imaging studies have addressed psychiatric symptoms in HD. Mayberg *et al.* [33] compared depressed and nondepressed early HD patients with control individ-

Table 2. Pharmacotherapy of psychiatric conditions in Huntington's disease

Condition	Recommended pharmacotherapy, in order of preference	Comments
Irritability, aggression	Atypical neuroleptic; standard neuroleptic if faster onset of action is needed	Consider augmentation with SSRI; standing doses of neuroleptics are helpful in preventing violence in patients with known irritability and aggression; Huntington's patients may be more susceptible to extra-pyramidal symptoms
Apathy	May try antidepressant with dopaminergic action, such as bupropion; pharmacotherapy probably provides little benefit	Very difficult to treat; education of families, environment with structured activities may help; ask "yes" or "no" and not open-ended questions
Depression	SSRIs, bupropion, nefazodone, TCAs	Equal efficacy of all SSRIs, nortriptyline is probably the most useful TCA, because it is the least anticholinergic; avoid MAOIs, because dietary restrictions are problematic when trying to maintain weight and have a high potential for lethal overdose; consider ECT if pharmacotherapy is ineffective (see text)
Mania	Divalproex, carbamazepine	Avoid lithium, if possible, because adequate hydration is difficult to achieve in Huntington's; augmentation with neuroleptics may be necessary for acute mania
Anxiety and obsessions/compulsions	SSRIs, nefazodone, buspirone	May need to use SSRIs in higher doses than those given for depression; may need to use clomipramine for treatment-refractory obsessions and compulsions
Psychosis	Atypical neuroleptic; standard neuroleptic as second line of therapy	Follow patients closely for orthostasis when on neuroleptics, especially if olanzapine or chlorpromazine is used; use standing doses of neuroleptics rather than only as needed treatment
Sleep disturbance	Small dose (0.5 mg) of long-acting benzodiazepine	Importance of daytime sleep hygiene, regular bedtime must be stressed to patients and families

ECT—electroconvulsive therapy; MAOI—monoamine oxidase inhibitors; SSRI—selective serotonin reuptake inhibitors; TCA—tricyclic antidepressants.

uals using PET. Basal ganglia and cingulate metabolism were lower in both groups of HD patients compared with the control group. Depressed HD patients had lower orbital frontal-inferior prefrontal cortex metabolism than nondepressed patients, suggesting that disruption of cortical-striatal connections may contribute to mood disorders in HD. A second study by Kuwert *et al.* [34] found decreases in anterior-posterior metabolic ratio in HD patients with psychosis, compared with control individuals, again suggesting a role for frontal dysfunction in the development of psychiatric symptoms in HD.

Psychiatric Disorders

Psychiatric symptoms may occur at any stage of HD, including prior to the onset of the movement disorder. No clear pattern of progression for behavioral symptoms has been shown [35]. Age of onset and presence of psychiatric symptoms have not been shown to correlate positively with CAG repeat length [36,37]. The wide range of psychiatric syndromes in HD is shown in Table 2. There have been only 2 double blind, placebo-controlled treatment studies for aggression in HD and one single blind study to date for treatment of psychosis. It is noteworthy that, to date, there have been no controlled clinical trials for depression or anxiety in HD (Tables 3, 4, and 5).

Irritability and Aggression

Irritability is commonly seen in HD, and is often accompanied by aggression. In a case review of 86 HD patients, Pflanz and colleagues [38] found a history of irritability at some stage in over 60% of patients, and aggression in over 40%. Nance and Sanders [39] found in a retrospective review of 97 HD nursing home residents that approximately one third were aggressive. A more recent study of 960 patients spanning a wide range of severity demonstrated that over 60% of HD patients or their caregivers reported aggressive behavior at their first visit to a Huntington's clinic [40••].

Behavioral management, such as adherence to a set schedule, may be helpful in prevention [21]. Ranen and colleagues [41] suggest careful evaluation for differentiation between restlessness, irritability and agitation, and consideration of motivating factors for the behavior (*eg,* hunger,

Table 3. Psychiatric treatment studies in Huntington's disease (aggression and irritability)

Condition	Agents tested	Study type and patients, *n*	Comments and outcome on target symptoms
Aggression, irritability	Olanzapine [80•]	Open trial, 11	Improvement in five patients on "overall behavior"; irritability improved, aggression unchanged; depression, anxiety, and obsessions also improved in some patients
	Olanzapine [81]	Case report, 1	Improvement in aggression and irritability (symptoms disappeared after 5 months of olanzapine treatment)
	Fluoxetine [82]	Case report, 1 with irritability and agression (second patient also treated with fluoxetine for movements only)	Improvement in irritability and aggression; authors suggest that this may be due to treatment of underlying obsessive-compulsive disorder
	Olanzapine and divalproex [83]	Case reports, 2	Improvement (psychotic symptoms with aggression)
	Buspirone [84]	Case report, 1	Improvement
	Sertraline [85]	Case reports, 2	Improvement
	Clozapine [78]	Retrospective case reviews, 2 with aggression, 2 with delusions (eight patients total, four tried clozapine for chorea only)	Improvement in aggression and delusions; considerable sedation in seven of eight patients
	Buspirone [86]	Case reports, 2	Improvement of aggression
	Buspirone [87]	Case report, 1 (juvenile onset)	Improvement of aggression; anxiety and checking behavior unchanged
	Pindolol [88]	Case report, 1	Worsened, underlying depression unmasked?
	Propranolol [89]	Case report, 1	Worsened, underlying depression unmasked (patient with a history of depression)?
	Propanolol [90]	Case reports, 3	Improved; one developed hypotension, two on haloperidol also
	Pindolol [91]	Double blind, placebo-controlled crossover, 1 with HD (10 other patients with organic brain syndromes also studied)	Improvement-refractory patient
	Haloperidol and lithium [92]	Double blind, placebo-controlled crossover, randomized, 6 (four treatment groups: lithium, haloperidol, lithium and haloperidol, and placebo)	Three patients improved with lithium and haloperidol combined

HD—Huntington's disease.

thirst, or pain). Undiagnosed psychiatric conditions such as depression, mania, or psychosis may be the underlying cause, and this may influence the course of treatment. Como *et al*. [42] found that nondepressed HD patients treated with fluoxetine showed a modest reduction in agitation and in the need for routine; they suggest this may be due to either mood stabilizing effects or treatment of underlying obsessions. Case reports and small studies of other agents are reviewed in Table 3.

Apathy

In a retrospective record study of all HD cases reported to a health board in one region, Pflanz and others [38] found that 57% of patients had loss of interest and concentration. Loss of interest tended to appear at approximately the same time as the movement disorder in the case records, which spanned various stages of the illness.

Apathy may be difficult to differentiate from depression, and family members may misinterpret it as such. Education of family members may be helpful to prevent them from putting unreasonable demands on the patient. With some patients, it is situational in that they will engage, at least partially, in more structured activities or participate if they are guided to do so, but will not initiate behaviors on their own [43]. Antidepressants, especially those with dopamine activity, such as bupropion, may be tried, but no case reports or studies have been conducted to validate this suggestion, and the authors have not seen significant improvement in apathy with any pharmacotherapy.

Table 4. Psychiatric treatment studies in Huntington's disease (apathy, affective disorder, and anxiety disorder)

Condition	Agents tested	Study type and patients, *n*	Comments and outcome on target symptoms
Apathy	studies	data	data
Affective disorder	Sertraline [44]	Case series, 7	Improvement (marked in five, moderate in two); one patient treated concomitantly with risperidone for psychotic depression; two patients treated with lorazepam for sleep
	Fluoxetine [42]	Open label trial, 8	Improvement in mood and function
	Fluoxetine and l-deprenyl [93]	Case report, 1 with paranoia and aggression	Improvement in all three psychiatric symptoms
	ECT [94]	Retrospective case reports, 6 (five unipolar depressed patients; one bipolar depressed patient)	Improvement in four of the unipolar patients and in the bipolar patient; patients with prominent delusions showed the most benefit; apathy showed the least improvement
	Clozapine [95]	Case report, 1 with psychotic depression	Improvement
	Sulpiride [96]	Case report, 1	Improvement
	Phenelzine and isocarboxazid [97]	Case series, 3	Improvement of mood; two of three patients showed improvement with concomitant psychosis
	Amoxapine [98]	Case report, 1	Improvement
	ECT [46]	Retrospective case reports, 2	Improvement
	TCA [43]	Open trial, 6	Five of six patients improved, but only on neurovegetative symptoms
	TCA [99]	Open trial, 10	Seven had some improvement of depression; sedation and anticholinergeric side effects seen in some, and some patients give neuroleptics
	Amytriptyline or chlorpromazine [100]	Open trial, 4 (three given amytriptyline, one given chlorpromazine)	Improvement with both treatments
	Haloperidol [100]	Open trial, 2 manic	Improvement
	Phenothiazines [67]	Case report, 1 manic	Improvement
	ECT [101]	Case report, 1	Improvement in patient with agitated depression
Anxiety disorder	Diazepam and amytriptyline [43]	Case report, 2	Improvement with both treatments

ECT—electroconvulsive therapy; TCA—tricyclic antidepressant.

Affective Disorders and Suicide

A recent review the literature on depression in HD by Slaughter *et al.* [44] found that, in the 16 English language studies in existence, the overall prevalence of depression was 30% in HD patients. They also noted that 5.6% of patients met *Diagnostic and Statistical Manual of Mental Disorders, Third Edition* (DSM-III) or DSM-III-Revised criteria for dysthymia in the 6 studies using those criteria. Levy *et al.* [45] found, in a sample of 34 HD outpatients, that depression was not significantly correlated with apathy. The authors concluded that, despite considerable overlap in the frontal and subcortical regions implicated in both conditions, the two conditions should be evaluated separately. Depression was significantly correlated with anxiety and with agitation (0.44 and 0.39, respectively).

As with other psychiatric symptoms, onset of depression may occur several years prior to that of neurologic abnormalities, which argues against a purely reactive depression. In fact, Folstein *et al.* [46] observed that depression might occur up to 5 years prior to onset of movement abnormalities. Shiwach [2] also found, in a sample of 110 patients with HD, that the lifetime prevalence of depression was almost 40%. One third of these patients displayed mood symptoms prior to onset of motor abnormalities. A case registry study by Jensen *et al.* [47] found that HD patients had significantly more psychiatric admissions and diagnoses than their unaffected relatives. The authors concluded that, at least with respect to severe psychopathology such as depression and psychosis, psychiatric symptoms follow onset of the motor abnormalities. In the authors' experience, this is not the case with substance abuse.

Several neurobiologic explanations have been suggested for the increased rates of depression in HD patients. Based on functional imaging studies in depressed HD patients described previously, Mayberg *et al.* [33] proposed that disruption of frontal-striatal circuitry cause depression.

Table 5. Psychiatric treatment studies in Huntington's disease (psychotic disorders)

Condition	Agents tested	Study type and patients, *n*	Comments and outcome on target symptoms
Psychotic disorders	Risperidone [77]	Case report, 1 with psychosis	Improvement
	Risperidone [102]	Case report, 1 psychotic	Improvement; possible EPS as side effect
	Clozapine and risperidone [103]	Case report, 1 with psychosis	Clozapine alone is effective for psychotic symptoms; risperidone for chorea
	Risperidone compared with haloperidol [104]	Single-blind, 3 with behavior problems and depression	Improvement in behavioral problems for all; two of three showed improvement in depression
	Various standard neuroleptics [43]	Case series, 6 (three schizophrenic, two atypical psychosis, and one paranoid)	Variable-clear improvement in both patients with atypical psychosis (medication not specified), and one patient with schizophrenia (on fluphenazine decanoate); little improvement shown in the other two with schizophrenia or one with paranoia (less agitated on haloperidol)
	ECT [105]	Case report, 1 with psychosis and depression	Improvement of both psychosis and depression
	Standard neuroleptics and TCAs [100]	Open trial, 2 with auditory hallucinations	Improvement
Sleep disturbance	No studies or case reports	No data	No data

ECT—electroconvulsive therapy; EPS—extrapyramidal symptom; TCA—tricyclic antidepressant.

Decreased caudate volume has also been seen in depressed individuals without HD compared with normal control individuals [48]. The striatum receives input from the limbic system, disruption of which could lead to changes in affect. Because the dorsomedial caudate, a primary target for limbic projection, was one of the earliest regions to show neuronal loss [49], this early pathology may explain why mood disorders are seen early on in some HD patients.

Levels of GABA and glutamic acid decarboxylase (GAD) cerebrospinal fluid (CSF) have been shown to be decreased in patients with major depression [50]. Deficits in the GABA system may contribute to development of affective disorders in HD. Reduced levels of GABA and GAD in HD brains have been reported by several groups [51–53], but no direct comparison has been made looking at GABA or GAD levels in depressed versus nondepressed HD patients. Serotonin levels in HD patients were elevated in the caudate and putamen, but normal in the substantia nigra and nucleus accumbens (*see* Peyser and Folstein [54] for a review), suggesting an effect of HD pathology on the serotonin system. Cerebrospinal fluid studies have shown no differences in 5-hydroxyindoleacetic acid levels in depressed versus nondepressed HD patients [55].

There have been no large scale studies of treatment for depression in HD. Small open trials and case reports suggest that standard medications, including selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants (TCAs), and also electroconvulsive therapy (ECT), for severe or refractory cases, are all useful (Table 4).

The prevalence of mania may be increased in HD relative to age-matched populations. Mendez [56] reviewed seven studies, and found the overall rate of mania in HD to be 4.8%; this estimate is somewhat problematic in that differing definitions of mania were used in the studies. Folstein [5] reported manic or hypomanic episodes in approximately 10% of HD patients. In the authors' experience, manic episodes in HD responded well to neuroleptics acutely, and to divalproex for long-term management. Weight gain often occurs with divalproex, but may be beneficial in HD, because individuals tend to lose weight as the disease progresses. Carbamazepine may also be used, but its usefulness is limited by its interactions with other medications. Lithium should be avoided, due to the difficulty of ensuring adequate hydration in a movement disorder.

Huntington's disease patients have a high rate of suicide when compared with that seen in the general population, perhaps due to their reported poor impulse control [57], or irritability, discussed previously. Reported suicide rates in HD vary from 3.0% to 7.3% of patients [58,59]. Farrer *et al.* [60] reported a 27.6% rate of attempted suicide in HD patients. This is significantly elevated from the 10 per 100,000 average rate of suicide in the general population. Lipe *et al.* [58] found that risk factors for suicide in HD were similar to those seen in the general population; suicide was more likely in patients who lived alone, were childless, unmarried, and depressed.

Anxiety Disorders

Huntington's disease patients experience a spectrum of anxiety ranging from appropriate concern over future disability to debilitating anxiety. Pflanz *et al.* [38], in their

study of 86 HD cases reported in a defined geographic region, found that, in the 34 men and 52 women, prevalence of general anxiety did not differ by gender (28% of men and 29% of women). They also found anxiety to be a relatively early symptom, with 23% of men and 13% of women reporting general anxiety as part of the presenting syndrome. As noted in the study by Levy *et al.* [45], anxiety and depression were significantly correlated in a sample of HD outpatients, suggesting that patients with anxiety should be evaluated for underlying depression. Many anxiolytic medications exert their effects through GABA receptors. Reductions in brain GABA and GAD, seen in HD, may contribute to development of anxiety [54].

To date, there is one case series in the literature describing the treatment of anxiety in HD [43]. In the authors' experience, patients respond to standard treatments for anxiety, although response may be incomplete. Selective serotonin reuptake inhibitors are often helpful for generalized anxiety in these patients, and obviously will treat concomitant depression. Small doses of benzodiazepines may also be useful in management of anxiety.

Huntington's disease patients may also have an increased frequency of obsessive and compulsive symptoms and obsessive-compulsive disorder (OCD). A recent review of 960 outpatients who were followed at 43 HD centers found that 22.3% had obsessions or compulsions at their first visit to a Huntington's Center [40••]. Several other neurologic disorders involve the striatum, and are known to produce obsessions or compulsions with high frequency, including Tourette's disease, Fahr's disease, Sydenham's chorea, carbon monoxide poisoning (which can cause globus pallidus damage), and nonspecific basal ganglia lesions [61–65].

There have been several case reports of OCD in HD [66–68]. De Marchi *et al.* [69] reported on a family with HD, and a strong association between OCD and pathologic gambling. The lifetime prevalence of OCD in the extended family was 34% for biologically related persons, the majority of whom had HD or were at 50% risk. A recent study of 27 HD patients indicated that, when a standard instrument, the Yale-Brown Obsessive Compulsive Scale (Y-BOCS), is used to probe for these behaviors, up to 50% of HD patients report obsessions or compulsions [70•]. This study also found significant performance deficits on neuropsychologic tests with more executive elements in HD patients with obsessions or compulsions compared with those without. Presence of obsessions or compulsions did not correlate with motor symptoms, duration of disease, or impairment in function.

It is the authors' experience that most HD patients with obsessions or compulsions do not meet DSM-IV [71] criteria for OCD, because they have little insight into the symptoms and are not troubled by them. Caregivers, however, often find these symptoms to be problematic. Thus, the authors generally recommend that treatment be initiated. There are no studies or case reports of treatment for obsessions or compulsions in HD. In the authors' own experience, obsessions and compulsions are usually responsive to treatment with SSRIs, the standard treatment for primary OCD.

Psychosis and Schizophrenia

Older reports indicated an increased prevalence of in schizophrenia in HD compared with age-matched populations, with some studies reporting from 4% to 12% of HD patients as having schizophrenia [72]. However, this has recently been challenged. Jensen *et al.* [47] indicated no patients with schizophrenia in a sample of 37 patients and 167 nonaffected relatives. Shiwach [2] found three patients with schizophrenia in a sample of 110 patients with HD, and only one of these patients had symptoms consistent with schizophrenia prior to onset of motor symptoms and dementia. However, Watt and Seller [73] found 12% prevalence in a sample of 65 HD patients. De Marchi and Mennella [74] suggest this lower prevalence found in newer work is due to more stringent definitions of schizophrenia in newest versions of the DSM-IV, especially because psychosis as part of a mood disorder is now less likely to be classified as schizophrenia. Also, some older samples of HD patients may have shown overrepresentation of those with schizophrenia, because the populations studied were in psychiatric hospitals. Folstein *et al.* [46] did not find an elevated prevalence of schizophrenia in their statewide sample of HD patients from Maryland. Marder *et al.* [40] found, in a study of 960 HD outpatients, that actual hallucinations were relatively uncommon, with 1.3% of patients reporting auditory hallucinations at their baseline visit. Patients with schizophrenia who have been treated with neuroleptics may have concomitant tardive dyskinesia, making diagnosis of HD problematic.

Psychotic symptoms, which do not meet criteria for schizophrenia, probably are more common in HD than in the general population. In a case registry study, Jensen *et al.* [47] reported no schizophrenia, but did find that other types of psychosis were more common in HD patients than in their relatives (11% vs 3%, respectively). Marder *et al.* [40••] found that 5.4% of outpatients reported fixed delusions at the baseline visit to a HD Center. A review by Mendez [56] of 11 studies of HD patients found psychosis to be present in 3% to 12% of patients, ranging from nonspecific paranoia to presentations similar to schizophrenia.

There is no one explanation for this increased prevalence of psychosis in HD patients. One possible contributing factor is the reduction of striatal dopamine receptors, discussed previously with brain imaging data. However, reduction of dopamine receptors can not fully explain psychosis in HD, because many patients with these changes do not have psychotic symptoms. Work by Tsuang *et al.* [75] comparing HD patients with and without psychosis found that HD patients who develop psychosis are significantly more likely to have a first-degree relative with psychosis ($P<0.02$), suggesting a familial predisposition toward development of psychosis.

There are limited data on treatment of psychotic symptoms in HD. Most reports are from treatment trials using neuroleptics for the movement disorder [43,76], and effect on psychotic symptoms is reported incidentally or based on chart review [77,78]. As is reviewed in Table 5, standard and atypical neuroleptics have all been used. In the authors' opinion, atypical neuroleptics are the first-line treatment for psychosis, due to the decreased risk of side effects.

Sleep Disturbance

Many Huntington's patients experience sleep disturbance due to their movements, particularly before falling asleep. Kirkwood *et al.* [79••], in a study of 1238 HD patients with a minimum 6-year history of symptoms, observed that change in sleep patterns were most commonly reported by family members of patients 2 to 5 years and 6 to 10 years after the onset of disease (17.4% and 17.1% of care givers reported these symptoms in their relatives in each of the two time frames, respectively). A small dose of clonazepam (0.5 mg) at bedtime may be helpful in stopping the movements until patients are able to fall asleep.

Conclusions

Despite the high prevalence of psychiatric symptoms in HD, there is a dearth of double blind placebo-controlled trials. The creation of the Huntington's Disease Study group in 1993 provides this opportunity, because relatively large numbers of HD patients are concentrated at Huntington's Disease Centers of Excellence, and can participate in multicenter trials. Knowledge gained in these trials with the HD population, who have a well-defined disease with known neuropathology, may contribute to better understanding of biologic basis of many psychiatric conditions.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

1. Harper PS: **The epidemiology of Huntington's disease.** *Hum Gen* 1992, **89:**365–376.
2. Shiwach R: **Psychopathology in Huntington's disease patients.** *Acta Psychiatr Scand* 1994, **90:**241–246.
3. Huntington's Disease Collaborative Research Group: **A novel gene containing a trinucleotide repeat that is expanded and unstable on Huntington's disease chromosomes.** *Cell,* 1993, **72:**971–983.
4. Kremer B, Goldberg P, Andrew S, *et al.*: **A worldwide study of the Huntington's disease mutation.** *N Engl J Med* 1994, **330:**1401–1406.
5. Folstein SE: *Huntington's Disease: A Disorder of Families,* edn 1. Baltimore: The Johns Hopkins University Press; 1989.
6. Andrew S, Goldberg P, Kremer B, *et al.*: **The relationship between trinucleotide (CAG) repeat length and clinical features of Huntington's disease.** *Nat Gen* 1993, **4:**398–403.
7. Hersch SM, Ferrante RJ: **Neuropathology and pathophysiology of Huntington's disease.** In *Movement Disorders: Neurologic Principles and Practice.* Edited by Watts RL, Koller WC. New York: McGraw-Hill; 1997.
8. Hedreen JC, Folstein SE: **Early loss of neostriatal striosome neurons in Huntington's disease.** *J Neuropathol Exp Neurol* 1995, **54:**105–120.
9. Turjanski N, Weeks R, Dolan R, *et al.*: **Striatal D1 and D2 receptor binding in patients with Huntington's disease and other choreas: a PET study.** *Brain* 1995, **118:**689–696.
10. Ginovart N, Lundin A, Farde L, *et al.*: **PET study of pre- and post-synaptic dopaminergic markers for the neurodegenerative process in Huntington's disease.** *Brain* 1997, **120:**503–514.
11. Kremer B, Clark CM, Almqvist EW, *et al.*: **Influence of lamotrigine on progression of early Huntington disease: a randomized clinical trial.** *Neurology* 1999, 53:1000–1011.
12. Shoulson I, Odoroff C, Oakes D, *et al.*: **A controlled clinical trial of baclofen as protective therapy in early Huntington's disease.** *Ann Neurol* 1989, **25:**252–259.
13. Huntington Study Group (HSG): **Safety and tolerability of the free-radical scavenger OPC-14117 in Huntington's disease.** *Neurology* 1998, **50:**1366–1373.
14. Huntington Study Group (HSG): **A randomized, placebo-controlled trial of coenzyme Q10 and ramacemide in Huntington's disease.** *Neurology* 2001, **57:**397–404.
15. Bachoud-Levi AC, Remy P, Nguyen JP, *et al.*: **Motor and cognitive improvements in patients with Huntington's disease after neural transplantation.** *Lancet* 2000, **356:**1975–1979.
16. Brandt J: **Cognitive impairments in Huntington's disease: insights into the neuropsychology of the striatum.** In *Handbook of Neuropsychology,* vol 5. Edited by Corkin S, Grafman J, Boller F. Amsterdam; Elsevier Publishers; 1991.
17. Weingartner H, Caine ED, Ebert MH: **Imagery, encoding, and retrieval of information from memory: some specific encoding--retrieval changes in Huntington's disease.** *J Abnorm Psychol* 1979, **88:**52–58.
18. Butters N: **The clinical aspects of memory disorders: contributions from experimental studies of amnesia and dementia.** *J Clin Neuropsychol* 1984, **6:**17–36.
19. Josiassen RC, Curry LM, Mancall EL: **Development of neuropsychological deficits in Huntington's disease.** *Arch Neurol* 1983, **40:**791–796.
20. Fisher JM, Kennedy JL, Caine ED, Shoulson I: **Dementia in Huntington disease: a cross-sectional analysis of intellectual decline.** In *The Dementias.* Edited by Mayeux R, Rosen RM. New York: Raven Press; 1983:229–238.
21. Moskowitz CB, Marder K: **Palliative care for people with late-stage Huntington's disease.** *Neurol Clin* 2001, **19:**1–17.
22. Knopman D, Nissen MJ: **Procedural learning is impaired in Huntington's disease: evidence from the Serial Reaction Time Task.** *Neuropsychologia* 1991, **29:**245–254.
23. Nance M, Myers R:**Trends in predictive and prenatal testing for Huntington's disease 1993-1999.** *Am J Hum Genet* 2000, **54:**A406.
24. Hersch S, Jones R, Koroshetz W, Quaid K: **The neurogenetics genie: testing for the Huntington's disease mutation.** *Neurology* 1994, **44:**1369–1373.
25. Almqvist EW, Bloch M, Brinkman R, *et al.*: **A worldwide assessment of the frequency of suicide, suicide attempts, or psychiatric hospitalization after predictive testing for Huntington disease.** *Am J Hum Genet* 1999, **64:**1293–1304.
26. Harris GJ, Pearlson GD, Peyser CE, *et al.*: **Putamen volume reduction on magnetic resonance imaging exceeds caudate changes in mild Huntington's disease.** *Ann Neurol* 1992, **31:**69–75.
27. Aylward EH, Li Q, Stine OC, *et al.*: **Longitudinal change in basal ganglia volume in patients with Huntington's disease.** *Neurology* 1997, **48:**394–399.
28. Aylward EH, Anderson NB, Bylsma F, *et al.*: **Frontal lobe volume in patients with Huntington's disease.** *Neurology* 1998, **50:**252–258.

29. Kuhl DE, Phelps ME, Markham CH, *et al.*: **Cerebral metabolism and atrophy in Huntington's disease determined by 18FDG and computed tomographic scan.** *Ann Neurol* 1982, **12:**425–434.
30. Berent S, Giordani B, Lehtinen S, *et al.:* **Positron emission tomographic scan of investigations of Huntington's disease: cerebral metabolic correlates of cognitive function.** *Ann Neurol* 1988, **23:**541–546.
31. Young AB, Penney JB, Starosta-Rubinstein S, *et al.*: **PET scan investigations of Huntington's disease: cerebral metabolic correlates of neurological features and functional decline.** *Ann Neurol* 1986, **20:**296–303.
32. Antonini A, Leenders KL, Spiegel R, *et al.:* **Striatal glucose metabolism and dopamine D2 receptor binding in asymptomatic gene carriers and patients with Huntington's disease.** *Brain* 1996, **119:**2085–2095.
33. Mayberg HS, Starkstein SE, Peyser CE, *et al.*: **Paralimbic frontal lobe hypometabolism in depression associated with Huntington's disease.** *Neurology* 1992, **42:**1791–1797.
34. Kuwert T, Lange HW, Langen KJ, *et al.*: **Cerebral glucose consumption measured by PET in patients with and without psychiatric symptoms of Huntington's Disease.** *Psychiatry Res* 1989, **29:**361–362.
35. Huntington Study Group (HSG): **Unified Huntington's Disease Rating Scale: reliability and consistency.** *Mov Disord* 1996, **11:**136–142.
36. Zappacosta B, Monza D, Meoni C, *et al.*: **Psychiatric symptoms do not correlate with cognitive decline, motor symptoms, or CAG repeat length in Huntington's disease.** *Arch Neurol* 1996, **53:**493–497.
37. Weigell-Weber M, Schmid W, **Spiegel R: Psychiatric symptoms and CAG expansion in Huntington's disease.** *Am J Med Genet* 1996, **67:**53–57.
38. Pflanz S, Besson JAO, Ebmeier KP, Simpson S: **The clinical manifestation of mental disorder in Huntington's disease: a retrospective case record study of disease progression.** *Acta Psychiatr Scand* 1991, **83:**53–60.
39. Nance MA, Sanders G: **Characteristics of individuals with Huntington's disease in long-term care.** *Mov Disord* 1996, **11:**542–548.
40.•• Marder KS, Zhao H, Myers RH, *et al.*: **Rate of functional decline in Huntington's disease: Huntington Study Group.** *Neurology* 2000, **54:**452–458.

In this study of 960 Huntington's patients, longer disease duration and better neuropsychologic performance at baseline were associated with less rapid decline of function. The percent of patients in this study reportidy psychiatric ronditions including depression / anxiety, suicidal thoughts, obsessive / compulsive symptoms, aggressive behavior, and delusions is examined.

41. Ranen NG, Peyser CE, Folstein SE: **A Physician's Guide to the Management of Huntington's Disease: Pharmacologic and Nonpharmacologic Interventions.** *New York:* Huntington's Disease Society of America: 1993.
42. Como PG, Rubin AJ, O'Brien CF, *et al.*: **A controlled trial of fluoxetine in nondepressed patients with Huntington's disease.** *Mov Disord* 1997, **12:**397–401.
43. Caine ED, Shoulson I: **Psychiatric syndromes in Huntington's disease.** *Am J Psychiatry* 1983, **140:**728–733.
44. Slaughter JR, Martens MP, Slaughter KA: **Depression and Huntington's disease: prevalence, clinical manifestations, etiology, and treatment.** *CNS Spectrums* 2001, **6:**306–326.
45. Levy ML, Cummings JL, Fairbanks LA, *et al.*: **Apathy is not depression.** *J Neuropsych Clin Neurosci* 1998, **10:**314–319.
46. Folstein SE, Abbott MH, Chase GA, *et al.*: **The association of affective disorder with Huntington's disease in a case series and in families.** *Psychol Med* 1983, **13:**537–542.
47. Jensen P, Sørensen SA, Fenger K, Bolwig TG: **A study of psychiatric morbidity in patients with Huntington's disease, their relatives, and controls: admissions to psychiatric hospitals in Denmark from 1969-1991.** *Br J Psychiatry* 1993, **163:**790–797.
48. Krishnan KRR, McDonald WM, Escalona PR, *et al.*: **Magnetic resonance imaging of the caudate nuclei in depression.** *Arch Gen Psychiatry* 1992, **49:**553–557.
49. Vonsattel JP, Meyers RH, Stevens TJ, *et al.*: **Neuropathological classification of Huntington's disease.** *J Neuropathol Exp Neurol* 1985, **44:**559–577.
50. Lloyd KG, Zivkovic B, Scatton B, *et al.*: **The GABAergic hypothesis of depression.** *Prog Neuropsychopharm Biol Psychiat* 1989, **13:**341–351.
51. Bird ED, Iversen LL: **Huntington's chorea: postmortem measurements of glutamic acid decarboxylase, choline acetyl-transferase, and dopamine in basal ganglia.** *Brain* 1974, **97:**457–472.
52. Bird ED: **Huntington's chorea.** In *Neurotransmitter Systems and Their Clinical Disorders.* Edited by Legg NJ. London: Academic Press; 1979:143–150.
53. Spokes EGS: **Neurochemical alterations in Huntington's chorea: a study of postmortem brain tissue.** *Brain* 1980, **103:**179–210.
54. Peyser CE, Folstein SE: **Huntington's disease as a model for mood disorders.** *Mol Chem Neuropathol* 1990, **12:**99–119.
55. Kurlan R, Caine E, Rubin A, *et al.*: **Cerebrospinal fluid correlates of depression in Huntington's disease.** *rch Neurol* 1988, **45:**881–883.
56. Mendez MF: **Huntington's disease: update and review of neuropsychiatric aspects.** *Intl J Psychiatry Med* 1994, **24:**189–208.
57. Cummings JL: **Behavioral and psychiatric symptoms associated with Huntington's disease.** In *In Behavioral Neurology of Movement Disorders,* vol 65. Edited by Weiner WJ, Lang AE. New York: Raven Press; 1995:179–186.
58. Lipe H, Schultz A, Bird TD: **Risk factors for suicide in Huntington's disease: a retrospective case controlled study.** *Am J Med Genet* 1993, **48:**231–233.
59. Di Maio L, Squitieri F, Napolitano G, *et al.*: **Suicide risk in Huntington's disease.** *J Med Genet* 1993, **30:**293–295.
60. Farrer LA: **Suicide and attempted suicide in Huntington disease: implications for preclinical testing of persons at risk.** *Am J Med Genet* 1986, **24:**305–311.
61. Leckman JF, Walker DE, Goodman WK, *et al.*: **Just right perceptions associated with compulsive behavior in Tourette's syndrome.** *Am J Psychiatry* 1994, **151:**675–680.
62. López-Villegas D, Kulisevsky J, Deus J, *et al.*: **Neuropsychological alterations in patients with computed tomography detected basal ganglia calcification.** *Arch Neurol* 1996, **53:**251–256.
63. Swedo SE, Rapoport JL, Cheslow DL, *et al.*: **High prevalence of obsessive-compulsive symptoms in patients with Sydenham's chorea.** *Am J Psychiatry* 1989, **146:**246–249.
64. Laplane D, Levasseur M, Pillon B, *et al.*: **Obsessive-compulsive and other behavioral changes with bilateral basal ganglia lesions: a neuropsychological, magnetic resonance imaging and positron tomography study.** *Brain* 1989, **112:**699–725.
65. Chacko RC, Corbin MA, Harper RG: **Acquired obsessive-compulsive disorder associated with basal ganglia lesions.** *J Neuropsychiatry Clin Neurosci* 2000, **12:**269–272.
66. Cummings JL, Cunningham K: **Obsessive-compulsive disorder in Huntington's Disease.** *Biol Psychiatry* 1992, **31:**263–270.
67. McHugh PR, Folstein MF: **Psychiatric syndromes of Huntington's chorea: a clinical and phenomenologic study.** In *Psychiatric Aspects of Neurologic Disease,* Edited by Benson DF, Blumer D. New York: Grune and Stratton; 1975:267–286.
68. Scicutella A: **Late life obsessive compulsive disorder and Huntington's disease.** *J Neuropsychiatry Clin Neurosci* 2000, **12:**288–289.
69. De Marchi N, Morris M, Mennella R, *et al.*: **Association of obsessive-compulsive disorder and pathological gambling with Huntington's disease in an Italian pedigree: possible association with Huntington's disease mutation.** *Acta Psychiatr Scand* 1998, **97:**62–65.

70.• Anderson KE, Louis ED, Stern Y, Marder KS: **Cognitive correlates of obsessive and compulsive symptoms in Huntington's disease.** *Am J Psychiatry* 2001, **158:**799–801.
This study of 27 Huntington's disease patients found obsessive and compulsive symptoms in over half of patients. Patients with obsessions and compulsions showed significantly greater impairment on neuropsychologic tests involving executive function than those without these symptoms.
71. American Psychiatric Association: *Diagnostic and Statistical Manual of Mental Disorders,* edn 4. Washington, DC: American Psychiatric Press; 1994.
72. Oliver JL: **Huntington's chorea in Northamptonshire.** *Br J Psychiatry* 1970, **116:**241–253.
73. Watt DC, Seller A: **A clinico-genetic study of psychiatric disorder in Huntington's chorea.** *Psychol Med Suppl* 1993, **23:**1–46.
74. De Marchi N, Mennella R: **Huntington's disease and its association with psychopathology.** *Harv Rev Psychiatry* 2000, **7:**278–289.
75. Tsuang D, Almqvist EW, Lipe H, *et al.*: **Familial aggregation of psychotic symptoms in Huntington's disease.** *Am J Psychiatry* 2000, **157:**1955–1959.
76. Bonuccelli U, Ceravolo R, Maremmani C, *et al.*: **Clozapine in Huntington's chorea.** *Neurology* 1994, **44:**821–823.
77. Dallocchio C, Buffa C, Tinelli C, *et al.*: **Effectiveness of risperidone in Huntington chorea patients.** *J Clin Psychopharm* 1999, **19:**101–103.
78. Colosimo C, Cassetta E, Bentivoglio AR, *et al.*: **Clozapine in Huntington's disease.** *Neurology* 1995, **45:**1023.
79.•• Kirkwood SC, Su JL, Conneally PM, Foroud T: **Progression of symptoms in the early and middle stages of Huntington disease.** *Arch Neurol* 2001, **58:**273–278.
A survey of 1238 individuals symptomatic for Huntington's disease that looked at involuntary movements, psychiatric symptoms, and other manifestations of the illness. Psychiatric symptoms were found to occur in early and middle stages of the illness. Sleep trouble was seen mainly in the middle stages.
80.• Squitieri F, Cannella M, Porcellini A, *et al.*: **Short-term effects of olanzapine in Huntington disease.** *Neuropsychiatry Neuropsychol Behav Neurol* 2001, **14:**69–72.
Eleven Huntington's disease patients were studied in an open-pilot design. Five patients showed significant improvement in behavioral measures after 6 months of treatment. Depression, anxiety, irritability, and obsessions showed significant improvement.
81. Bogelman G, Hirschmann S, Modai I: **Olanzapine and Huntington's disease.** *J Clin Psychopharmacol* 2001, **21:**245–246.
82. De Marchi N, Daniele F, Ragone MA: **Fluoxetine in the treatment of Huntington's disease.** *Psychopharmacology* 2001, **153:**264–266.
83. Grove VE, Quintanilla J, DeVaney GT: **Improvement of Huntington's disease with olanzapine and valproate.** *N Engl J Med* 2000, **343:**973–974.
84. Bhandary AN, Masand PS: **Buspirone in the management of disruptive behaviors due to Huntington's disease and other neurological disorders.** *Psychosomatics* 1997, **38:**389–391.
85. Ranen NG, Lipsey JR, Treisman G, Ross CA: **Sertraline in the treatment of severe aggressiveness in Huntington's disease.** *J Neuropsychiatry Clin Neurosci* 1996, **8:**338–340.
86. Byrne A, Martin W, Hnatko G: **Beneficial effects of buspirone therapy in Huntington's disease.** *Am J Psychiatry* 1994, **151:**1097.
87. Findling RL: **Treatment of aggression in juvenile-onset Huntington's disease with buspirone.** *Psychosomatics* 1993, **34:**460–461.
88. von Hafften AH, Jensen CF: **Paradoxical response to pindolol treatment for aggression in a patient with Huntington's disease.** *J Clin Psychiatry* 1989, **50:**230.
89. Stewart JT: **Paradoxical aggressive effect of propranolol in a patient with Huntington's disease.** *J Clin Psychiatry* 1987, **48:**385–386.
90. Stewart JT, Mounts ML, Clark RL: **Aggressive behavior in Huntington's disease: treatment with propranolol.** *J Clin Psychiatry* 1987, **48:**106–108.
91. Greendyke RM, Kanter DR: **Therapeutic effects of pindolol on behavioral disturbances associated with organic brain disease: a double blind study.** *J Clin Psychiatry* 1986, **47:**423–426.
92. Leonard DP, Kidson MA, Brown JGE, *et al.*: **A double-blind trial of lithium carbonate and haloperidol in Huntington's chorea.** *Aust N Z J Psychiatry* 1975, **9:**115–118.
93. Patel SV, Tariot PN, Asnis J: **L-Deprenyl augmentation of fluoxetine in a patient with Huntington's disease.** *Ann Clin Psychiatry* 1996, **8:**23–26.
94. Ranen NG, Peyser CE, Folstein SE: **ECT as a treatment for depression in Huntington's disease.** *J Neuropsychiatry Clin Neurosci* 1994, **6:**154–159.
95. Sajatovic M, Verbanac P, Ramirez LF, Meltzer H: **Clozapine treatment of psychiatric symptoms resistant to neuroleptic treatment in patients with Huntington's chorea.** *Neurology* 1991, **41:**156.
96. Knowling MR, Wrench W: **Treatment of Huntington's chorea with sulpiride.** *S Afr Med J* 1991, **79:**169.
97. Ford MF: **Treatment of depression in Huntington's disease with monoamine oxidase inhibitors.** *Br J Psychiatry* 1986, **149:**654–656.
98. Moldawsky RJ: **Effect of amoxapine on speech in a patient with Huntington's disease.** *Am J Psychiatry* 1984, **141:**150.
99. Shoulson I: **Huntington disease: functional capacities in patients treated with neuroleptic and antidepressant drugs.** *Neurology* 1981, **31:**1333–1335.
100. Folstein SE, Folstein MF, McHugh PR: **Psychiatric syndromes in Huntington's disease.** *Adv Neurol* 1979, **23:**281–289.
101. Heathfield KWG, Mackenzie ICK: **Huntington's chorea in Bedfordshire, England; Guys Hospital Report;** 1971: **120:**295–309.
102. Madhusoodanan S, Brenner R: **Use of risperidone in psychosis associated with Huntington's disease.** *Am J Geriatr Psychiatry* 1998, **6:**347–349.
103. Parsa MA, Szigethy E, Voci JM, Meltzer HY: **Risperidone in treatment of choreoathetosis of Huntington's disease.** *J Clin Psychopharmacol* 1997, **17:**134–135.
104. Meco G, Bonifati V, Alessandri A, Brusa L: **Risperidone in Huntington's disease.** *Hum Psychopharmacol* 1995, **10:**353–354.
105. Evans DL, Pedersen CA, Tancer ME: **ECT in treatment of organic psychosis in Huntington's disease.** *Convuls Ther* 1987, **3:**145–150.