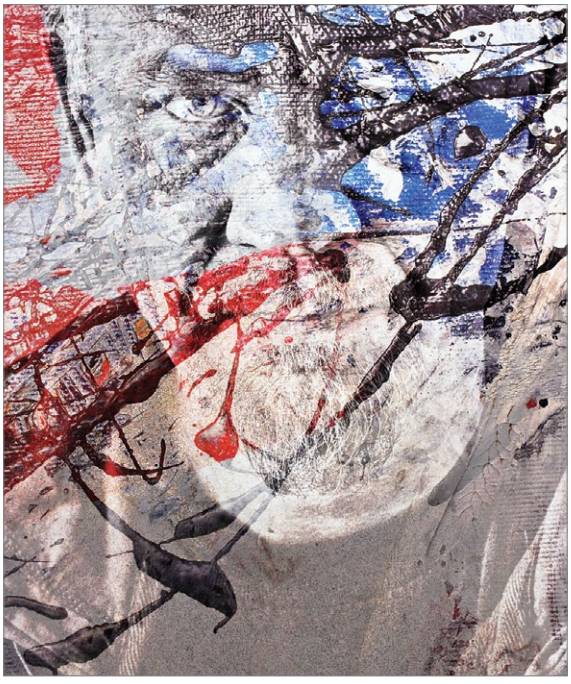
How to target psychiatric symptoms of Huntington's disease



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Clinical experience, limited evidence guide selection of symptom-focused treatments

Psychiatric symptoms are a common and debilitating manifestation of Huntington's disease (HD), a progressive, inherited neurodegenerative disorder also characterized by chorea (involuntary, nonrepetitive movements) and cognitive decline. The prevalence of HD is 4 to 8 patients per 100,000 persons in most populations of European descent, with lower prevalence among non-Europeans.[1] HD is caused by an abnormal expansion of a trinucleotide (CAG) repeat sequence on chromosome 4, and is inherited in an autosomal dominant fashion, meaning a HD patient's child has a 50% chance of inheriting the mutation. The expansion is located in the gene that encodes the "huntingtin" protein, the normal function of which is not well understood.

There's no cure for HD, and treatments primarily are directed at symptom control. Psychiatric symptoms include depression, apathy, anxiety, and psychosis (***Table***).[2-4] Treating patients with HD can be challenging because most psychiatrists will see only a handful of patients with this multifaceted illness during their careers. See this article at CurrentPsychiatry.com for a case study of a patient with HD.

Psychiatric sequelae

In general, psychiatric symptoms of HD become increasingly prevalent over time (***Box, page 37***).[3,5] In a 2001 study of 52 HD patients by Paulsen et al,[2] 51 patients had ≥1 psychiatric symptom, such as dysphoria (69.2%), agitation (67.3%), irritability (65.4%), apathy (55.8%), and anxiety (51.9%); delusions (11.5%) and hallucinations (1.9%) were less prevalent.[2] Similarly, Thompson et al[3] followed 111 HD

patients for ≥3 years and all experienced psychiatric symptoms.

Depressed mood and functional ability—not cognitive or motor symptoms[6]—are the 2 most critical factors linked to health-related quality of life in HD. Hamilton et al[7] found that apathy or executive dysfunction in HD patients is strongly related to decline in ability to complete activities of daily living, and may be severely debilitating.

Apathy. Often mistaken for a symptom of depression, apathy's presentation may resemble anhedonia or fatigue; however, research suggests that depression and apathy are distinct conditions. Naarding et al[5] noted that apathy is more common than depressive symptoms in HD patients and may be a hallmark symptom of HD.

Depression affects most HD patients, and often is most severe early in the disease course. Hubers et al[8] found that 20% of 100 HD patients had suicidal ideation. The strongest predictor was depressed mood.

Sleep disturbances and daytime somnolence are common among HD patients, and patients with comorbid depression report more disturbed sleep. Managing disturbed sleep and daytime somnolence in HD, with emphasis on comorbid depression, may improve the quality of life of patients and their caregivers.[9]

Anxiety was present in >50% of HD patients in a study by Paulsen et al[2] and 37% evaluated by Craufurd et al.[10] Craufurd et al[10] also reported that 61% of patients were "physically tense and unable to relax."

Among HD patients, 5% report obsessions and 10% report compulsive behaviors; these symptoms appear to become increasingly common as HD progresses.[4,10]

Impulsivity and disinhibition. Craufurd et al[10] found that 71% of HD patients experienced poor judgment and self-monitoring, 40% had poor temper control and verbal outbursts, 22% exhibited threatening behavior or violence, and 6% had disinhibited or inappropriate sexual behavior.[10]

Recent studies have shown higher rates of disinhibition in "presymptomatic" gene-positive subjects vs gene-negative controls, suggesting that these symptoms may arise early in HD.[11] Further, researchers demonstrated that patients lack symptom awareness and rate themselves as less impaired than their caregivers do.[11]

In our clinical experience, impulsivity frequently is encountered and creates significant conflict between patients and their caregivers. We speculate that when coupled with depressive symptoms of HD, impulsivity and disinhibition may play an important role in the high rates of suicidality seen in these patients.

Psychosis. Delusions and hallucinations are less common in HD than other psychiatric symptoms. Craufurd et al[10] reported 3% of HD patients had delusions, 3% had auditory hallucinations, 2% had tactile hallucinations, and no patients had visual hallucinations.

A few case reports and a small study by Tsuang et al[12] suggested that psychotic features in HD may be similar to those seen in paranoid schizophrenia. Tsuang et al[12] also noted that more severe HD-related psychosis tends to cluster in families, which suggests that susceptibility to HD psychosis may be heritable.

Table

Psychiatric symptoms of HD

Anxiety
Apathy
Delusions
Disinhibitions, impulsivity, aggressive behavior
Dysphoria
Euphoria
Hallucinations
Irritability
Obsessions and compulsions

HD: Huntington's disease

Source: References 2-4

Treating psychiatric symptoms

High-quality randomized controlled trials of pharmacotherapies for psychiatric symptoms in HD patients are lacking. Decisions regarding which agents to use often are

Clinical Point

Depressed mood and functional ability are the 2 most critical factors linked to health-related quality of life in HD

See this article at CurrentPsychiatry.com for a case study of a patient with Huntington's disease

Huntington's disease

Clinical Point

ECT may be a good choice for depressed HD patients who have failed several antidepressants, are suicidal, or have psychotic symptoms

based on case reports or clinical experience. The suggestions below are based on available evidence and our clinical experience.

Depression. Depressive symptoms in HD seem to respond to conventional pharmacologic treatments for major depressive disorder (MDD). A small trial of venlafaxine extended-release (XR) in 26 HD patients with MDD showed statistically significant improvements in depressive symptoms; however, this trial was not blinded and did not have a placebo group.[13] In addition, 1 in 5 patients developed significant side effects—nausea, irritability, or worsening chorea.[13]

Evidence for selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors, and tricyclic antidepressants (TCAs) is lacking. Antidepressant choice should be based on patient response, side effect profile, and the need for secondary therapeutic effects.[14]

We often prescribe sertraline, citalopram, or escitalopram for our HD patients because of the relative absence of drug-drug interactions and favorable safety profile in medically and surgically ill patients. However, it's important to tailor the treatment approach to your patient's needs—eg, patients prone to forgetting their medicine may benefit from a drug with a longer half-life, such as fluoxetine. We avoid TCAs because of their anticholinergic effects, which may worsen dementia symptoms. Because HD patients have high rates of suicidality, agents that are highly toxic when taken in overdose should be used with caution.

One small study of HD patients with MDD or bipolar disorder showed clinical improvement in depressive symptoms after electroconvulsive therapy (ECT).[15] Patients who suffered from comorbid delusions had the best improvements in mood.[15] ECT likely is a good choice for HD patients who have failed several antidepressants, are suicidal, or who have depression with psychotic features.[16]

Apathy. A 2011 review concluded that no evidence-based recommendations regarding pharmacologic treatment for apathy in HD can be made because of lack of research.[7] The Huntington's Disease Society of America's (HDSA) *A Physician's Guide to Managing Huntington's Disease* includes recommendations for treating apathy based on clinical experience.[16] It suggests a nonsedating SSRI, followed by a trial of methylphenidate, pemoline, or dextroamphetamine if SSRIs were unsuccessful.[16] The HDSA guide notes psychostimulants may worsen irritability in HD and have a high potential for abuse. ECT appears to have little effect on apathy.[15]

Anxiety. A small, open-label study of 11 patients found that olanzapine, 5 mg/d, significantly improved depression, anxiety, irritability, and obsessive behavior in HD patients.[17]

The HDSA guide suggests treating anxiety and obsessive-compulsive symptoms as you would in patients without HD. For anxiety, SSRIs and possibly a short-term trial of a low-dose benzodiazepine (ie, lorazepam, clonazepam) are suggested.[16] Benzodiazepines may increase the risk of falls and delirium in this population. Anecdotally, buspirone is helpful in some patients, with a starting dose of 5 mg 2 to 3 times per day and increased to 20 to 30 mg/d in divided doses.[16] For obsessive-compulsive symptoms, SSRIs are recommended; atypical antipsychotics are reserved for severe or refractory symptoms.[16]

Disinhibition and impulsivity. There's no research on treating disinhibition and impulsivity in HD. In our clinical experience, atypical antipsychotics are the most helpful. Factors regarding choosing an agent and dosing levels are similar to those for psychotic symptoms.

Psychotic symptoms. Most studies of typical and atypical antipsychotics for HD psychosis have shown beneficial effects.[14,16-21] Neurologists frequently use these agents for managing chorea. Both neurologic and psychiatric features of the patient's presentation must be considered when selecting a drug because treatment directed at 1 component of the disease may inadvertently exacerbate another. Specifically, higher potency antipsychotics

(eg, haloperidol) are effective for chorea but can dramatically worsen bradykinesia; lower potency agents (eg, quetiapine) are less helpful for chorea but do not significantly worsen rigidity symptoms.

Olanzapine has been shown to improve chorea, anxiety, irritability, depression, sleep dysfunction, and weight loss in addition to psychotic symptoms.[14,17] We find that olanzapine treats a constellation of symptoms common among HD patients, and we prescribe it frequently. Because olanzapine is considered a mid-potency agent, we find it's best suited for concurrent control of psychotic symptoms and mild to moderate chorea in patients with minimal bradykinesia. Start olanzapine at 2.5 mg/d and gradually increase to 5 to 10 mg/d as tolerated.[14]

Risperidone is effective for treating psychosis and chorea. It can be started at 0.5 to 1 mg/d, and gradually increased to 6 to 8 mg/d.[14] The depot formulation of risperidone has been shown to be effective in HD, which may help patients adhere to their medication.[18] Risperidone is a mid-high potency antipsychotic, and in our experience is best used to control psychotic symptoms in patients with moderate chorea and few or no symptoms of bradykinesia or rigidity.

Quetiapine reduces psychotic symptoms, agitation, irritability, and insomnia without worsening bradykinesia or rigidity,[19] but it is not beneficial for chorea. It can be started at 12.5 mg/d and gradually increased for effect as tolerated, up to 600 mg/d (depending on indication), in 2 or 3 divided doses.[14]

Haloperidol is a high-potency typical antipsychotic and may help psychotic patients with severe chorea; it should not be used in patients with bradykinesia. Start haloperidol at 0.5 to 1 mg/d and gradually increase to 6 to 8 mg/d as tolerated.[14] Because of higher likelihood of side effects with typical antipsychotics, we often reserve its use for patients whose psychosis does not respond to atypical agents.

Other antipsychotics. Aripiprazole in HD has been examined in only 2 single-patient case reports[20,21]; the drug appeared to reduce psychosis and possibly chorea. Clozapine's effectiveness for HD psychosis is not well known. It does not appear to be helpful for chorea and can cause agranulocytosis.[22]

Because one of the hallmarks of HD is dementia, it is worth noting that the FDA has issued a "black-box" warning on the use of antipsychotic drugs in patients with dementia because of concerns regarding increased mortality. However, drawing specific conclusions is difficult because the FDA warning is based on studies that looked primarily at Alzheimer's disease and vascular dementia, not HD.

Other pharmacotherapies

Tetrabenazine is the only FDA-approved drug for treating HD. However, it carries a "black-box" warning for increased risk of depression and suicidal ideation and is contraindicated in suicidal patients and those with untreated or inadequately treated depression.

Although several small trials have had conflicting results regarding its benefit, amantadine sometimes is used to treat chorea.[23-25] For more information about tetrabenazine and amantadine, see this article at CurrentPsychiatry.com.

continued

Box

Psychiatric symptoms of HD change over time

According to Thompson et al,[3] the presence and severity of apathy, irritability, and depression trend differently across the course of Huntington's disease (HD). Apathy worsens with disease progression, closely following cognitive and motor symptoms. Irritability increases significantly, but this effect seems confined to early stages of HD. Depressive symptoms appear to decline slightly as HD advances, although it is unclear if this is because of antidepressants' effects, increasing emotional blunting, and waning insight in later stages of HD, or another unknown factor.[3] This study did not examine psychotic symptoms over time because few patients were experiencing delusions or hallucinations.

Similar to Thompson et al, Naarding et al[5] found that apathy and depression in HD follow distinct time courses. Depression is a feature of early HD and apathy worsens with overall disease progression.

Clinical Point

Olanzapine has been shown to improve chorea, anxiety, irritability, depression, and sleep dysfunction in HD patients

See this article at CurrentPsychiatry.com for more information about tetrabenazine and amantadine for HD

Huntington's disease

Clinical Point

Tetrabenazine is FDA-approved for HD but can increase the risk of depression and suicidality

Related Resources

- Huntington's Disease Society of America. www.hdsa.org.
- Family Caregiver Alliance. Huntington's disease. www.caregiver.org/caregiver/jsp/content_node.jsp?nodeid=574.
- Huntington Study Group. www.huntington-study-group.org.
- Huntington's Disease Advocacy Center. www.hdac.org.

Drug Brand Names

Amantadine • Symmetrel
Aripiprazole • Abilify
Bupropion • Wellbutrin, Wellbutrin XL, others
Buspirone • BuSpar
Citalopram • Celexa
Clonazepam • Klonopin
Clozapine • Clozaril
Dextroamphetamine • Dexedrine
Escitalopram • Lexapro
Fluoxetine • Prozac
Haloperidol • Haldol
Lorazepam • Ativan
Methylphenidate • Concerta, Ritalin, others
Mirtazapine • Remeron
Olanzapine • Zyprexa
Pemoline • Cylert
Quetiapine • Seroquel
Risperidone • Risperdal
Sertraline • Zoloft
Tetrabenazine • Xenazine
Venlafaxine XR • Effexor XR

Disclosures

Dr. Scher is a consultant to the advisory board for Lundbeck.

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Bottom Line

Huntington's disease (HD) is a progressive, genetic, neurodegenerative disorder characterized by motor, cognitive, and psychiatric symptoms. Psychiatric manifestations of HD include depression, anxiety, impulsivity, and psychosis. Given the complex nature of HD, psychiatric symptoms are best addressed by a multidisciplinary team committed to holistic, collaborative patient care.

Box 1

Frustrated by declining function

Mr. M, age 50, was diagnosed with Huntington's disease (HD) 1 year ago. He returns to our psychiatric clinic for treatment of depressive symptoms and temper. Previously, he was prescribed citalopram, 40 mg/d; eventually low-dose olanzapine, 2.5 mg at night, was added. Mr. M reported better temper control, but his low mood, irritability, hopelessness, and amotivation were not significantly improved.

Mr. M left his job at a software company because he had difficulty completing tasks as the result of mood and cognitive changes. He wants to return to work, but feels that he would be unable to complete his job duties.

He begins a trial of bupropion, 150 mg/d, to improve the vegetative component of his mood symptoms to help him return to work. Mr. M now complains of worsening chorea, irritability, and insomnia, with continued difficulty completing tasks. He is intermittently tearful throughout the interview.

Mr. M continues to struggle with mood symptoms that likely are related to the stressful experience of declining function and the intrinsic evolution of HD. His chorea worsens on bupropion; this agent is discontinued and replaced with mirtazapine, 15 mg at night, for his depressive symptoms and insomnia. Citalopram and olanzapine are unchanged. Mr. M is advised to follow up with our HD psychiatry team in 1 month, and is referred for brief psychotherapy. We remind him—as we do for all of our HD patients—to call the HD clinic or 911 if he becomes suicidal. Ongoing treatment efforts likely will be complex, given the multifaceted and progressive nature of his disease.

Box 2

Tetrabenazine and amantadine for Huntington's disease

Tetrabenazine, the only FDA-approved drug for treating Huntington's disease (HD), is a dopamine-depleting agent given to control chorea. In a 12-week, randomized, double-blind, placebo-controlled clinical trial, tetrabenazine was shown to be effective in HD patients.[a] Treatment with tetrabenazine results in symptomatic improvement of chorea, but does not slow or alter the course of the disease. Tetrabenazine can provide relief from choreiform movements, but these benefits should be balanced with the risks of depression and suicidality.[a] Tetrabenazine is known to prolong QTc interval, and should be used with caution in combination with other drugs that have the potential to do the same (eg, antipsychotics).[a]

Several case reports have found an association between tetrabenazine and development of neuroleptic malignant syndrome (NMS).[b-d] Be aware of the clinical characteristics of NMS—mental status change, rigidity, fever, and dysautonomia—and use caution when starting patients taking tetrabenazine on antipsychotics or other agents known to cause NMS.

Amantadine also has been used to treat chorea in HD patients who are unable to tolerate tetrabenazine or antipsychotics. Our neurologists sometimes have found it to be beneficial in patients with juvenile-onset HD because these patients often have debilitating dystonia. Be aware that amantadine is known to precipitate or worsen psychosis.[e]

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