

New & Emerging Treatments for Huntington's Disease

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Learning Objectives:

Pharmacists:

After this completing this continuing education program, pharmacists will be able to:

1. Understand the etiology of the Huntington's disease and the affected population
2. Understand the symptoms of Huntington's disease
3. Understand current treatments for Huntington's disease, including a new medication specific for the disease
4. Describe ways in which pharmacists can help individuals and their caregivers manage the disease.

Pharmacy Technicians:

After completing this lesson, pharmacy technicians should be able to:

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2. Understand the symptoms of Huntington's disease
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4. Describe ways in which pharmacists can help individuals and their caregivers manage the disease.

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Introduction

Huntington's disease (HD) is an inherited neurological condition that affects 30,000 people in the United States and approximately 75,000 carry the defective gene that will eventually manifest into the disease. An individual who has a parent with the disease has a 50% chance of inheriting the defective gene and developing the disease. No cure exists for the disease but new treatments are emerging that offer new hope to individuals.

HD occurs because of a single abnormal gene on chromosome four. This gene codes for a defect called the "huntingtin" protein that has an unknown action. The huntingtin protein then forms clumps in the brain resulting in nerve cell death in the basal ganglia area responsible for movement coordination and the cortex area that controls thought, perception, and memory.

Symptoms of the disease usually manifest itself in mid-life. Early central nervous system (CNS) symptoms of HD often mirror those of other psychiatric disorders, Alzheimer's disease, or dementia. Symptoms include personality changes, decreased mental acuity, irritability, and memory loss. HD is a progressive condition. Symptoms generally develop slowly and death occurs between 10 to 30 years after diagnosis. Individuals diagnosed at a younger age often have a shorter lifespan. Most individuals become disabled and require long-term or nursing home care.

Treatment for HD typically focuses on managing the symptoms and not the underlying cause of the disease. Medications usually include psychotropic agents and agents used for Parkinson's disease to manage the movement disorders. In 2008, the Food and Drug Administration (FDA) approved Xenazine® (tetrabenazine, Prestwick Pharmaceuticals, Inc.) specifically for treatment of the chorea or movement disorder associated with HD. Other medications are in development for HD

and additional treatments may be available by the end of 2010 or 2011.

HD diagnosis

Individuals who have a parent with HD receive a blood test to determine whether they carry the gene. If a person carries the gene for HD, the disease will eventually manifest itself. Fetal testing using amniocentesis is an option for families who have a genetic history of the disease.

Symptoms of HD

Initially, symptoms of HD manifest as subtle involuntary movements and personality changes. These symptoms eventually, especially chorea, become worse over time and the individual eventually becomes incapacitated. Eventually, individuals develop dementia similar to Alzheimer's disease and become unable to walk, talk, or eat and eventually require full-time nursing home care. Death generally occurs because of aspiration pneumonia. A list of symptoms appears in Table 1.

Treatment of HD

Treatment for HD currently focuses on managing symptoms, not the underlying cause of the disease. Individuals receive dietary supplements, physical, occupational and speech therapy, medications, and psychosocial support. Treatment is primarily based on empirical findings based on patient response and is highly personalized.

Treatment of HD Chorea

Treatment for chorea focuses on improving functional capacity. Individuals with HD have high levels of dopamine that results in the movement disorders. Thus, treatment focuses on dopamine receptor blocking agents.

A dopamine receptor-blocking agent, Xenazine, was approved specifically for use in HD chorea. However, recent findings suggest that side effects limit its utilization for many HD patients. Side effects of Xenazine include severe depression, suicidal thoughts, and extrapyramidal symptoms (EPS). Clinical trials also showed that long-term use might result in mood, cognition, rigidity, and

functional capacity. FDA approved the agent under its Risk Evaluation and Mitigation Strategy (REMS) to ensure that the benefits versus the risk are properly evaluated prior to using the drug. The REMS program includes educational materials for pharmacists, physicians, patients, and caregivers about the risks associated with depression and suicidal thoughts. Pharmacists must provide a Medication Guide with each prescription for Xenazine dispensed.

Other medications used to treat chorea include older antipsychotic agents. Newer atypical antipsychotic agents have not been found to be effective in treating HD chorea. Tiapride is considered the medication of choice because of the favorable side effect profile. Other effective agents include pimozide, haloperidol, and phenothiazines. These agents must be used with caution because of EPS side effects and may further increase the risk of falls.

Medications used for Parkinson's disease are also used for chorea but generally, these medications are not as effective in HD. Levodopa, dopamine agonists, and anticholinergics are most effective in juvenile onset or the Westphal variant of HD. Like other agents, these medications must be carefully monitored because of a tendency to aggravate chorea and increase the likelihood of psychoses or other behavioral disturbances that are often present in individuals with HD.

Treatment of behavioral disturbances and psychoses

Behavioral disturbances are also treated with a variety of medications approved to treat other psychiatric conditions. Depression is common in individuals with HD but treatment with antidepressants must be carefully monitored because of the heightened likelihood of adverse effects in this population. Furthermore, research suggests that treatment of depression does not greatly improve functional capacity.

If depression is treated, tricyclic antidepressants (TCA) at the lowest dose possible should be the first-line therapy. Desipramine is often the medication of choice because it does not have the significant anticholinergic effects like others in the class. If TCAs are not effective, then monoamine oxidase inhibitors (MAOIs) or selective serotonin reuptake inhibitors (SSRIs) may be used.

Psychoses are often treated with classical antipsychotics that also reduce chorea but increase the potential for functional impairment. Atypical antipsychotics can be used in individuals who need to avoid further movement disorders.

Treatment of aggression includes medications such as lithium, buspirone, sertraline, benzodiazepines, beta-blockers, propranolol and pindolol, and the MAOI selegiline. Like other therapies, individual response is the primary indicator of successful treatment.

The future of HD treatment

Research and development for HD include determining the neurobiology and etiology of the disease. Research focuses on brain imaging to monitor the progression of HD and differences in the brain of individuals with HD. Genetic studies could lead to replacement therapy for the gene that causes HD or nerve cell replacement for individuals with the disease. Several clinical trials are ongoing for new medications to treat the cause of HD. A summary of the HD treatment pipeline follows, modified from the Huntington's Disease Society of America's website.

Nutritional supplements used to boost impaired energy metabolism in patients with HD include Phase III clinical trials with antioxidants CoQ10 and creatine. Another Phase III clinical trial with ethyl EPA, a purified version of eicosapentaenoic acid, an Omega 3 fatty acid found in fish oil found some benefit over six months but further research is necessary to determine effectiveness.

More dopamine stabilizers similar to Xenazine are also in the pipeline, including a Phase II clinical trial for a product called ACR-16 which will begin in the United States.

Anti-apoptosis agents are a class of drugs to inhibit programmed cell death. Medications under consideration in this class include:

- Minocycline, already approved as an antibiotic
- Tauroursodeoxycholic acid, an endogenous bile acid, is in Phase I clinical trials to inhibit mitochondrial apoptosis
- Methazolamide is an inhibitor of cytochrome c, an enzyme involved in apoptosis.

- Gene therapy is under consideration using a mutated form of the XIAP gene. XIAP stands for x-linked inhibitor of apoptosis protein.

Glutamate blockers or stabilizers are based on the excitotoxicity theory that overstimulation of glutamate can lead to cell death. Memantine is a glutamate stabilizer that is FDA approved to treat Alzheimer's dementia and now in Phase II clinical trials for HD.

Dimebon™ (dimebolin hydrochloride, Medivation, Inc. and Pfizer, Inc.) is an agent that has been approved in Russia for 25 years and is currently in clinical trials for HD and Alzheimer's disease in the United States for mitochondrial replacement to inhibit brain cell death. It would be one of the first medications to actually delay the progression of the disease with gene replacement therapy. Early clinical trials suggest that Dimebon improves cognitive function in HD patients measured by the Mini-Mental State Examination (MMSE) and the United HD Rating Scale. These patients also exhibited fewer falls than the placebo treatment group. The most common adverse events were headache, dry mouth, and depressed mood.

Brain derived neurotrophic factor (BDNF) protects brain cells and promotes neurogenesis, the growth of new ones. Levels of BDNF are known to be reduced in the brains of HD patients. SSRI (selective serotonic reuptake inhibitor) antidepressants are known to elevate BDNF and one such antidepressant, Celexa, is in Phase II clinical trials. Two agents that induce BDNF are under consideration; an ampakine in preclinical testing and Phase II trials of cysteamine is planned. Another agent, CEP-1347, an anti-apoptosis drug was found to improve the R6/2 mice by increasing BDNF levels.

In addition to BDNF, researchers are also looking at other neurotrophic factors and synthetic compounds that mimic their effects in HD. One agent, fibroblast growth factor 2 is in preclinical trials. This agent has been shown to promote neurogenesis and extended survival time in the R6/2 mice. A viral vector for delivering the neurotrophic factor neurturin into the brain is in Phase II clinical trials for Parkinson's disease and preclinical trials for HD.

The dysregulation of gene transcription has been shown to be a significant problem in HD. The HD protein interferes with the normal expression of genes. Histone deacetylase inhibitors (HDAC) may be able to reverse or partially reverse this dysfunction. Researchers at the University of California, Irvine successfully prevented death in a *Drosophila* fruit fly with the HD gene using an HDAC inhibitor currently in clinical trials for cancer. Another agent is in Phase I clinical trials

Anti-aging agents are under consideration to prevent premature cell death in the brain of HD patients. Researchers have isolated a group of genes called sirtuins - which appear to regulate aging - that has shown promise in HD-afflicted mice. Mice given sirtuins lived longer with less disability.

Another use for creatine and CoQ10 is to stop oxidative stress that causes cell aging and death in HD patients. The goal is to increase the number of antioxidants to allow free radicals of oxygen to bond thus avoiding the cell damage to proteins, lipids, and DNA caused by free radicals.

A process called autophagy helps to clear the damaged huntingtin protein in HD patients. Two drugs were found to be effective in *Drosophila* fruit flies and will next be tested in mice.

Both excess copper and excess iron have been shown to contribute to HD pathology. Preclinical testing is experimenting with copper chelators in mice with HD.

Research shows that there is an aberrant amplification of the adenosine 2A receptor signaling in striatal cells in people with HD. One receptor antagonist called KW-6002 (istradefyllin) is in clinical testing for Parkinson's disease.

Inhibition of an enzyme called caspase 6 may help to cleave the defective HD protein and stop accumulation in cell nuclei. Using a mouse model, researchers have shown that resistance to caspase 6 may stop the development of HD.

Research is also focusing on a method to interfere with RNA replication of the HD protein and thus stop the expression. If this occurs, it could be a cure for HD. Another approach, called antisense is somewhat different in that it is possible for a drug to do this on a periodic basis; the goal is to find an optimal time in which the cell can recover from the HD protein without being harmed by the absence of the normal protein.

Research with the HD mice suggests that stopping the HD gene from expressing itself would result in improvement even well into the progression of the disease. However, restorative treatments to replace damaged brain cells will likely be necessary for full recovery of later stage patients. Preclinical work is being conducted on a line of stem cells that has shown efficacy in a cell model of HD.

Summary and Role of the Pharmacist in HD

Today, treatment for HD primarily focuses on managing the symptoms associated with chorea, psychoses, aggression, and depression associated with the disease. Each individual receives very personalized treatment based primarily on response to treatment. Response to treatment is generally measured by functional improvement. Pharmacists can work with physicians and caregivers to ensure that medication therapy is appropriate for each

individual patient. All the medications given to HD patients have potentially dangerous side effects that can often exacerbate existing HD symptoms and therefore these products must be selected wisely.

The future of HD treatment looks promising. As more knowledge is obtained about the pathology of the disease, researchers are seeking ways to stop the progression or prevent the disease at the cellular level. FDA may approve new treatments in 2010 or 2011.

Pharmacists should educate themselves on new therapies and be prepared to communicate information to patients or caregivers. A number of resources exist for patients with HD, including the Huntington’s Disease Society of America, and other groups that sponsor research and development as well as provide information to families. Families could benefit from these resources as both a support network as well as ways to find helpful therapies.

References are available on request.

**Table 1
Huntington’s Disease Symptoms**

Motor disturbances
Chorea (seen in approximately 90% of patients)
Impaired voluntary movements (akinesia, bradykinesia, hypokinesia)
Dysarthria
Dysphagia (may cause death by choking, aspiration or asphyxia)
Abnormal gait
Ideomotor apraxia
Eye movement dysfunction
Rigidity [either primary (as in juvenile-onset disease or the Westphal variant) or secondary to, or associated with, chorea]
Bradykinesia
Seizures/convulsions
Cognitive impairment
Dementia
Lowering of IQ
Recent and remote memory impairment
Reduced ability to perform motor tasks
Reduced problem solving ability
Impaired concentration
Psychiatric disorders
Personality alterations (e.g. irritability, apathy, emotional lability, impulsiveness, aggression)
Mood disturbances (e.g. depression and increased suicide risk)
Psychoses (e.g. schizophrenia)
General manifestations
Severe bodyweight loss