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HUNTINGTON DISEASE: A FATAL GENETIC DISORDER THAT CAUSES THE PROGRESSIVE BREAKDOWN OF NERVE CELLS IN THE BRAIN

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ABSTRACT

Huntington's disease is a progressive brain disorder caused by a single defective gene on chromosome 4 - one of the 23 human chromosomes that carry a person's entire genetic code. This defect is "dominant," meaning that anyone who inherits it from a parent with Huntington's will eventually develops the disease. The disorder is named for George Huntington, the physician who first described it in the late 1800s. The defective gene codes the blueprint for a protein called huntingtin. This protein's normal function isn't yet known, but it's called "huntingtin" because scientists identified its defective form as the cause of Huntington's disease. Defective huntingtin protein leads to brain changes that cause abnormal involuntary movements, a severe decline in thinking and reasoning skills, and irritability, depression and other mood changes.

INTRODUCTION

Huntington disease:

HD is a progressive neurodegenerative disorder with an established genetic origin and symptoms that are referred to specific regions of brain disease. Cellular and molecular techniques are rapidly elucidating the pathogenesis of the disorder and are leading to approaches designed to develop rational treatments. Thus HD serves as a model for the future study of those psychiatric disorders in which abnormal brain function is thought to arise from predominantly genetic factors.

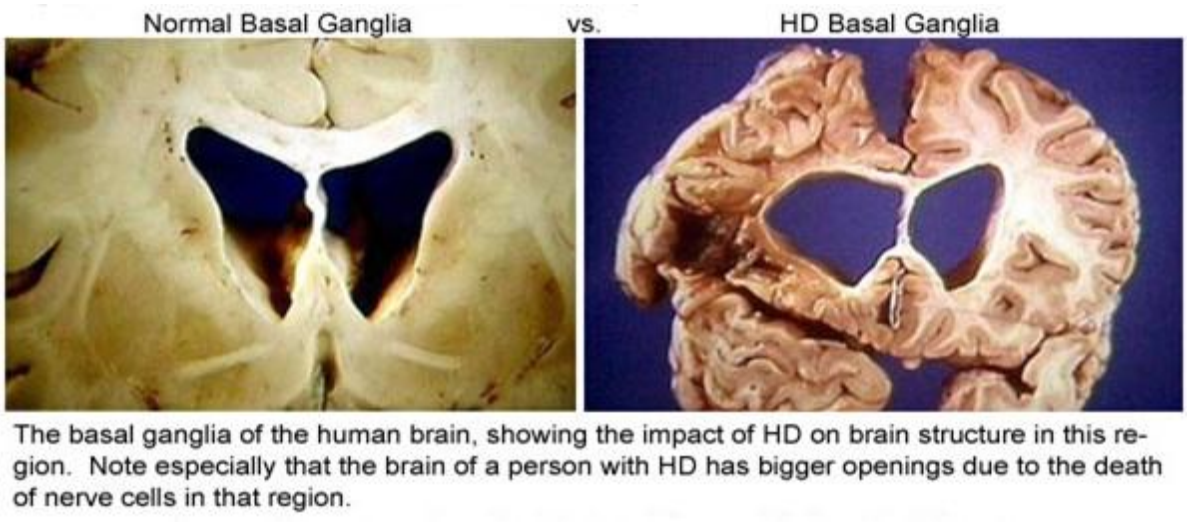

Fig. 1 Difference between Normal Basal Ganglia and Huntington's Disease Basal Ganglia

Clinical Features

HD can be described as a triad of motor, cognitive, and emotional disturbances. Symptoms usually begin between the ages of 35 and 50 years, although the onset may occur at any time from childhood to old age. Death occurs an average of 15 to 20 years after symptoms first appear, with some patients dying earlier from falls or suicide and others surviving for 30 to 40 years.

The Genetics of HD

HD is a hereditary neurodegenerative disorder caused by an expansion of a repeating CAG triplet series in the Huntington gene on chromosome 4, which results in a protein with an abnormally long polyglutamine sequence. HD is one of a larger family of polyglutamine repeat disorders all of which are neurodegenerative. HD is an autosomal dominant disease, which means it affects males and females with equal likelihood. Each child of an affected person has the same 50%

chance of inheriting the abnormal gene, and therefore developing the disease one day. Inheriting a normal Huntington gene from the unaffected parent does not prevent or counteract the disease-causing effects of the abnormal gene.

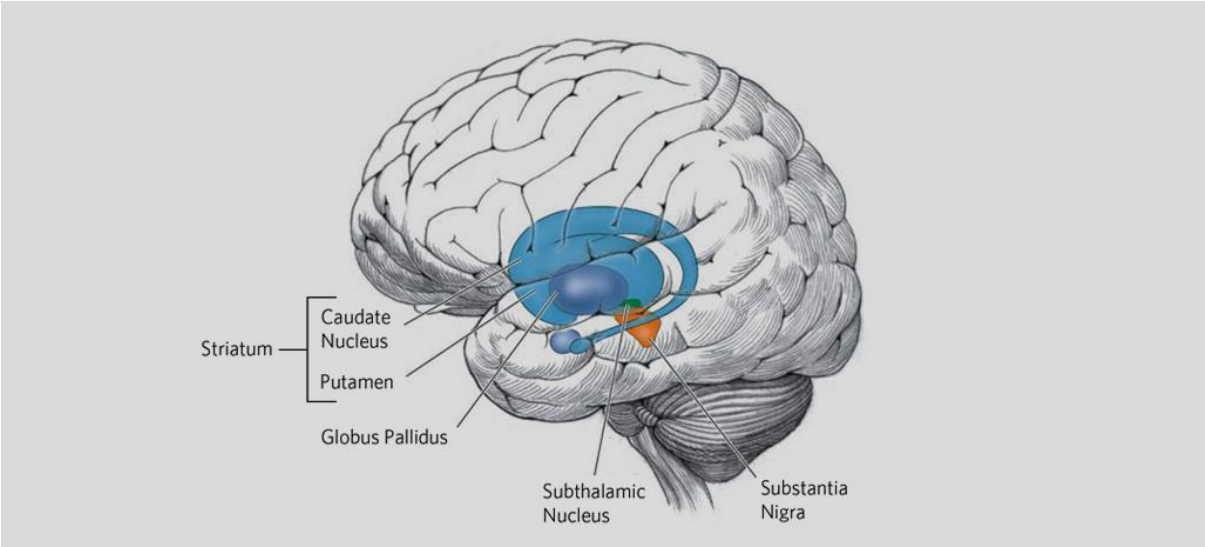

Figure 2: Genetics of Brain

In those rare cases where a person carries two abnormal copies of the gene, the person will develop HD, and each child has a 100% chance of inheriting an abnormal gene. The normal function of Huntington is not known, but the expanded poly glutamine sequence in the Huntington protein is in some way toxic to brain cells. Certain neurons appear to be especially vulnerable. Atrophy is most marked in the corpus striatum of the basal ganglia, including the caudate and put amen. In later phases of the disease other regions of the brain are also affected.

Movement of Disorders

The movement disorder of HD consists of two components: involuntary movements and abnormal voluntary movements. Chorea, or choreoa the tosis is the movement abnormality most frequently associated with HD. It consists of continuous and irregular jerky or writhing motions. Disturbances of voluntary movement however, are more highly correlated with functional disability and disease severity, as measured by the degree of brain disease. The disordered voluntary movements observed in HD include the following abnormal eye movements such as slow hypo metric saccades and uncoordinated arrhythmic and slow fine motor movements dysphasia and dysarthria, dysdiadochokines is rigidity and gait disturbances.

The nature of the motor symptoms changes over time. The onset is usually insidious. Early complaints include clumsiness, difficulty with balance, and jerky movements or tremor. In addition to limb and truncal movements, patients may have motor or chorea involving respiratory, laryngeal, pharyngeal, oral, or nasal musculature. Chorea often plateaus and even wanes in the later stages of the disease, but disturbances in voluntary movement continue to progress. In late-stage HD patients typically become akinetic and largely nonverbal with severe rigidity and joint contractures. At this point, they may have few involuntary movements except for occasional movements of the entire body, resembling myoclonic jerks, when disturbed. Difficulties with swallowing commonly lead to death in HD, either directly from suffocation or aspiration or indirectly from starvation. When HD begins in childhood or adolescence (juvenile onset HD) the presentation is often somewhat different with prominent bradykinesia rigidity and dystonia and minimal chorea. Involuntary movements may take the form of tremors and patients may develop seizures and myoclonus.

Cognitive Disorders

Cognitive difficulties usually begin about the same time and proceed at the same rate as the abnormal movement although some patients may have considerable motor impairment with very little dementia or the reverse. Early in the course of HD aphasia and agnosia are usually much less obvious the cortical dementia such as Alzheimer disease whereas deficits in cognitive speed and flexibility are more common. In contrastto Alzheimer disease patients with HD seem to have trouble with retrieval rather than storage of memories. They are more apt than patients with Alzheimer disease to recognize words from a previously memorized list or to respond to other cues to help them recall information. This distinction has led to the classification of HD as a sub cortical dementia. Cognitive losses accumulate progressively. Deficulties in memory visuospatial abilities and judgment develop and patients with late stage. Cognitive Disorders Cognitive difficulties

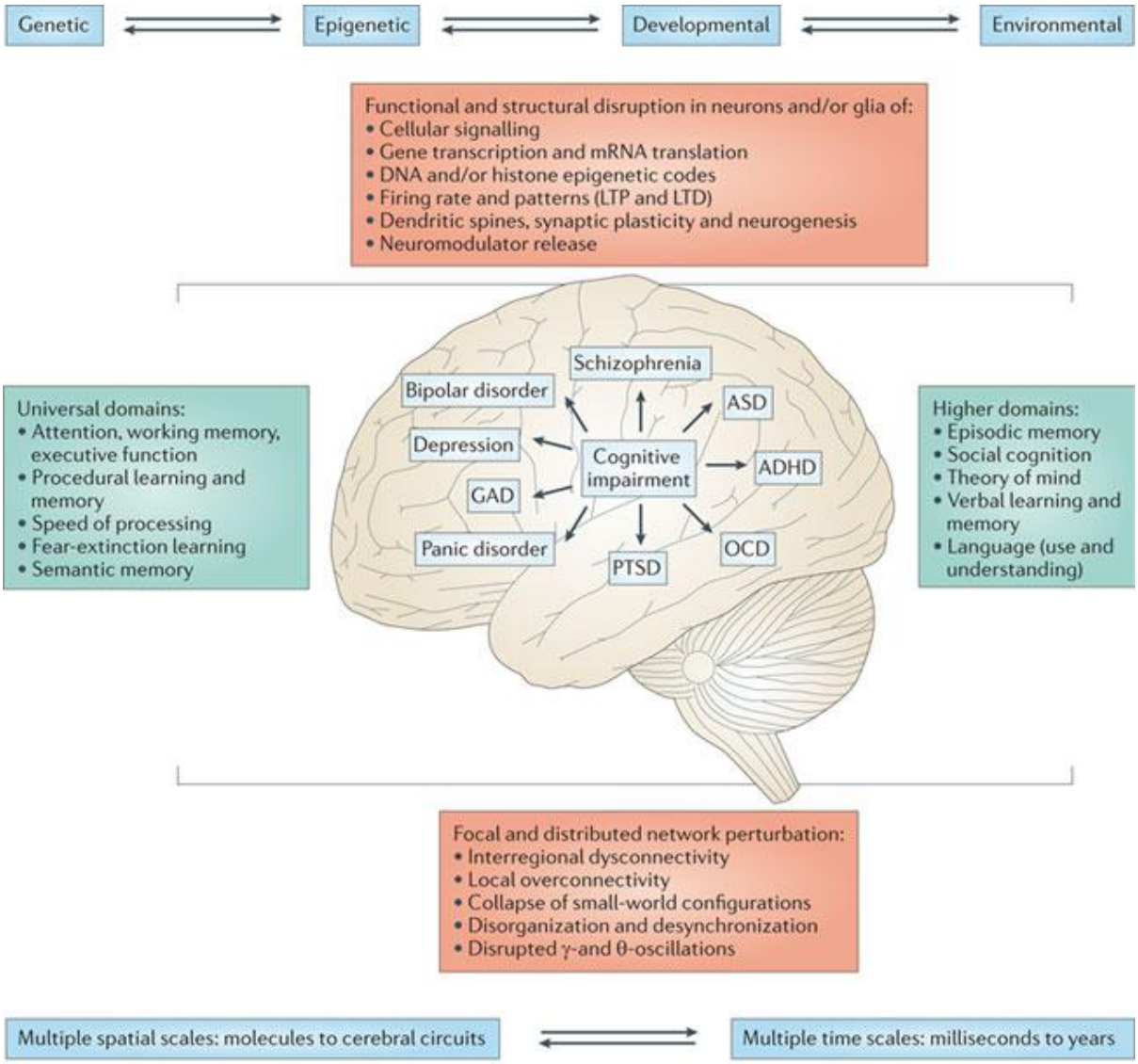

Figure 3: Cognitive Dysfunction

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Psychiatric Disorders

Patients with HD frequently develop psychiatric symptoms, most commonly depression irritability and apathy. The behavioural expression of these symptoms varies considerably and it may include aggressive out bursts impulsiveness social withdrawal and suicide. This aspect of HD can be devastating to both the patient and his or her family. The suicide rate alone estimated at up to 12.7%, and indicates the magnitude of the problem. Yet of all the complications of HD the psychiatric manifestations are the most amenable to treatment. Affective (mood) disorder is extremely common Epidemiologic and phenomenological evidence indicates the effective disorder in HD is a function of the brain disease itself rather than a reaction to changes in life circumstance. HD related major depression resemble the idiopathic form of major depression. Prominent symptoms include feelings of worthlessness or guilt, self-blame, changes in sleep and appetite, anxiety an hedonic loss of energy, hopelessness, and diurnal variation of mood with more severe symptoms in the morning. Delusions and hallucinations when present tend to be mood congruent delusions of poverty illness or guilt auditory hallucinations of derogatory or threatening voices. The diagnosis of major depression may be more difficult in patients with advanced disease, but the condition is often signal by a departure from baseline levels of activity or functional capacity. Severe irritability is another common symptom, present in one-third of patients in the Maryland HD survey. Irritability and aggression may occur in patients without a prior history of a short temper, but these symptoms are more common in patients that have had these traits all their lives. Apathy may become evident at any time in the course of the disease. Once present it tends to persist or worsen. Irritability can coexist with apathy. Either apathy or irritability may exist independently or as part of an affective syndrome. Patients with HD occasionally develop classic obsessive compulsive disorder with typical symptoms such as fear of contamination or excessive hand washing. More commonly however, patients may display an obsessive preoccupation with particular ideas or plans (e.g obtaining cigarettes getting a refill of coffee) and may become irritable when these requests are not honoured. Rarely patients develop schizophrenia like syndrome with prominent delusions, hallucinations or thought disorder in the absence of an abnormal mood. HD is a progressive disease.

Medications

The symptoms evolve over time and medications which were effective in the early stages may be unnecessary or problematic in later stages, and vice versa. For example, medications that are started in the early to middle stages to control chorea may exacerbate the rigidity and bradykinesis of the later stages, and result in delirium or over-sedation. The medication list and the rationale for each medication should be re-evaluated at regular intervals. Sometimes the most helpful intervention a physician can perform is to discontinue an unnecessary drug. People with HD, like others with diseases and injuries of the brain, are highly vulnerable to side effects, particularly cognitive side effects, of medications. The physician should begin with low doses and advance medicines slowly. Poly pharmacy should be avoided where possible. Many of the drugs used in treating symptoms of HD such as antidepressants, neuroleptics and tetrabenazine will not have immediate efficacy; people with HD need to be told that they may feel worse before they feel better, because they will experience the side effects before the beneficial effects have appeared. Pharmacologic interventions should not be launched in isolation but in a setting of education, social support, and environmental management. Symptomatic treatment of HD needs to be approached like any other medical problem. The clinician should elicit the details of the symptom, its character, onset and duration, and its context including precipitating, exacerbating and ameliorating factors. A differential diagnosis should be generated, non-pharmacologic interventions should be considered, and the clinician should have a way of determining whether the goals of treatment are being met and should formulate a contingency plan if treatment is not working. Sharing some of this reasoning process with the person with HD and their family can be reassuring.

SYMPTOMATIC TREATMENT

There are no currently accepted specific treatments to slow the rate of clinical progression of emotional disturbances is treatment options was prepared by Rosenblatt and colleagues.

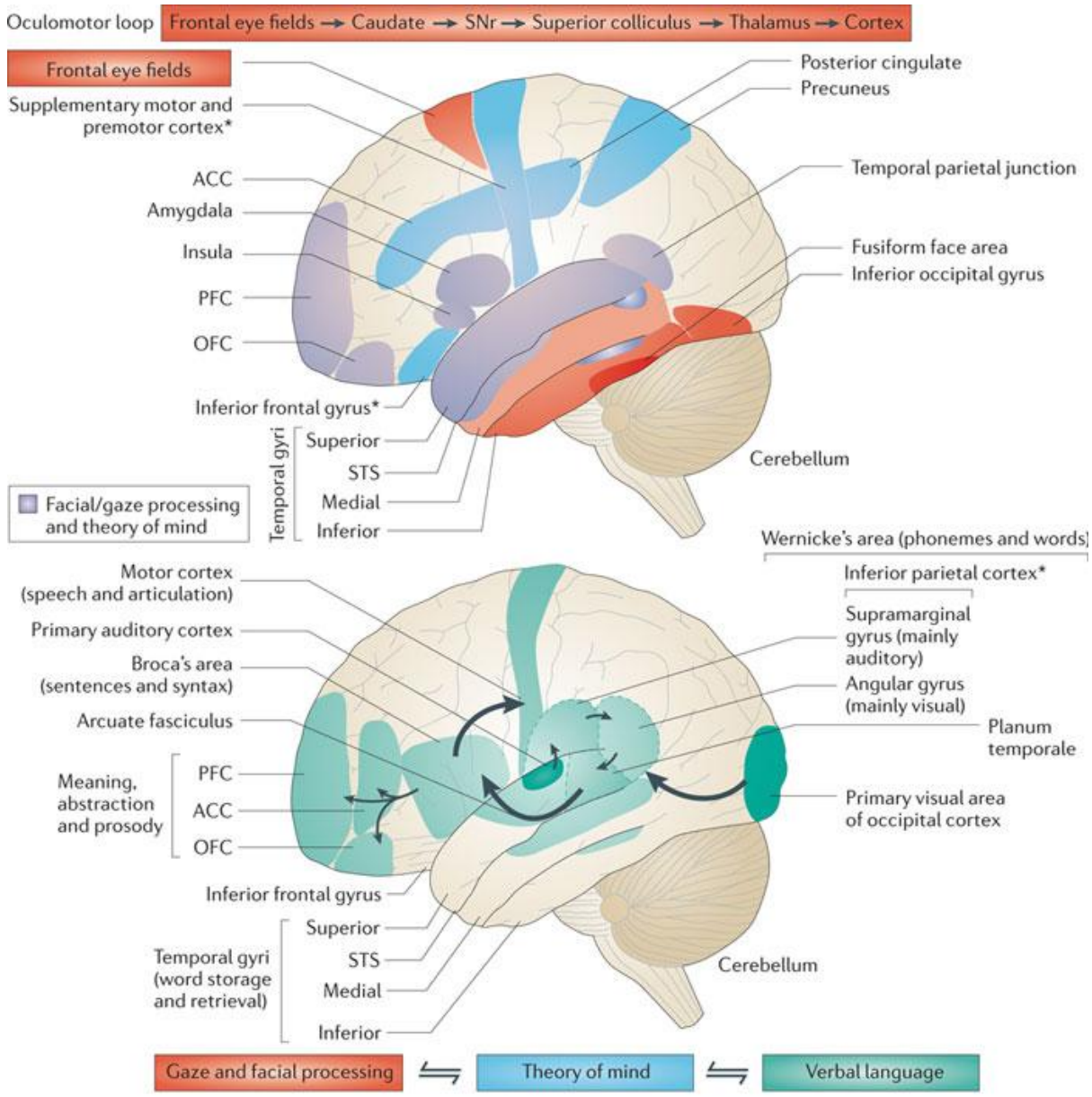

Figure 4: Cognitive dysfunction in psychiatric disorders

Treatment of Movement Abnormalities

Chorea may be a disabling symptom, leading to bruises, fractures, or falls and impairing the ability of patients to feed themselves. Other patients find the chorea of major cosmetic concern. Treatment with high-potency neuroleptics such as **haloperidol** and **fluphenazine** may be indicated in such cases, but with important caveats. These medicines may exacerbate the disturbance of voluntary movement, which, as noted earlier, correlates best with functional

disability. Furthermore neuroleptics increase morbidity by making patients more rigid, sedated, and apathetic. If pharmacologic treatment for chorea is initiated, starting doses of neuroleptics should be low for example, 0.5 to 1 mg of **haloperidol** or **fluphenazine** per day. Doses higher than 10 mg per day of haloperidol yield little or no benefit over lower doses. If patients experience unacceptable rigidity, akathisia or dystonia creactionsto high potency neuroleptics lower potency agents such as **thioridazine** may be better tolerated. However, use of lower potency neuroleptics increases the risk of sedation anticholinergic side effects and postural hypotension. Dopamine depleting agents such state of patient should be monitored carefully. The benzodiazepine clonazepam may also be useful in the treatment of chorea, and it may be of benefit in the later stage so the disease when neuroleptic medication often has little effect.

Treatment of Cognitive Abnormalities

There is no known effective pharmacologic treatment for the dementia of HD. Cholinergic agents have not been systematically assessed in HD but the rationale for us concentrate on one at a time. Complex cognitive tasks should be minimized, and, as the disease progresses, questions should be framed in a choice format with the provision of frequent cues to assist recall.

Treatment of Psychiatric Disorders

Major depression in HD responds to the same treatments used in idiopathic depression. In general, depression in HD is under diagnosed and undertreated perhaps because of the propensity of clinicians to see it as an understandable reaction to having the disease. Although no controlled studies exist, our experience is that both tricyclic antidepressants and selective serotonin reuptake inhibitors are effective. As with any neuropsychiatric disorder, patients should be started on low doses that are slowly increased while the patient is closely monitored for adverse effects, particularly delirium. It is important to remain with a medication for a full therapeutic trial at adequate doses and blood levels.

Depressed patients should always be questioned about thoughts of suicide. When suicide is a concern, the patient should receive as few pills as possible, especially if they are to be kept in the patient's care. The addition of antipsychotic medication is indicated as an adjunct to antidepressant treatment in depressed patients with hallucinations or delusions. Clozapine and other atypical neuroleptics may have the advantage over traditional neuroleptics medications such as haloperidol of causing fewer extra pyramidal side effects and therefore not worsening aspects of the voluntary movement disturbance. Electroconvulsive therapy is indicated for

depressed patients who are refractory to treatment with medication, for patients with delusions, for those who are not eating or drinking because of their depression, or for those who are at high risk of suicide. For patients with bipolar disorder carbamazepine divalproex sodium ,or lithium may the initial treatment of choice again it is prudent to start with low doses that are gradually increased until symptoms respond, side effects make further dose increases counterproductive, or therapeutic blood levels have been reached. In treating irritability, it is important to attempt to identify and to minimize precipitants such as hunger pain, inability to communicate frustration with failing capabilities boredom difficult interpersonal relationships, and minor unexpected changes in routine. Pharmacologic treatment can be very effective. We have had success using selective serotonin reuptake inhibitors and divalproic. Sexual disorders in HD particularly aggressive hyper sexuality can be treated with anti androgenic medications.

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