Huntington's disease: a review and therapeutic proposal

Sean Michel Newbill

The University of Toledo
Huntington’s Disease: A Review and Therapeutic Proposal

Sean Michel Newbill
The University of Toledo
2009
Dedication

I would like to dedicate this to my lovely wife and daughter for their support during this journey. I would also like dedicate this to my parents and family for unending support. I would also like to dedicate this to the 2008 PA class of UT-HSC.
Acknowledgements

I would like to thank Professor Karen Graham for her infinite patience and understanding. I would also like to acknowledge the library staff at UT-HSC for their patience during my endless requests for articles. I would also like to acknowledge all of the scientists and physicians who are spearheading the fight against this terrible disease.
<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Introduction and Background</td>
<td>1</td>
</tr>
<tr>
<td>Pathophysiology</td>
<td>2</td>
</tr>
<tr>
<td>Presentation</td>
<td>4</td>
</tr>
<tr>
<td>Depression and Cognitive Decline</td>
<td>7</td>
</tr>
<tr>
<td>Pharmacological Treatment Options</td>
<td>14</td>
</tr>
<tr>
<td>Non-Pharmacological Treatment Options</td>
<td>21</td>
</tr>
<tr>
<td>Other Considerations</td>
<td>24</td>
</tr>
<tr>
<td>Conclusion</td>
<td>27</td>
</tr>
<tr>
<td>References</td>
<td>29</td>
</tr>
<tr>
<td>Figures</td>
<td>35</td>
</tr>
<tr>
<td>Abstract</td>
<td>37</td>
</tr>
</tbody>
</table>
Introduction

Huntington’s disease (HD) is a late onset (in roughly 85 to 95% of cases) complex progressive inherited neurodegenerative disease that manifests as a triad of movement, psychiatric, and cognitive disorders. HD is relatively rare, and interesting work has been done to trace over 1,000 cases of the disease in the United States back to its origin in Europe. Historically, but not uncommon for the times, HD (like almost all psychiatric disorders) was feared. In fact, one of the most notorious “witches,” The Groton Witch, was found to be a descendant of two brothers who emigrated from the region of England where the first cases of HD were reported. This region, Suffolk England, was less than 50 miles from George Huntington’s ancestral home (Conneally, 1984). George Huntington was the first person to publish a full description of the disease’s presentation and the first scientific document to address chorea. This paper was his first and only published scientific work entitled “On Chorea.”

Because it is generally a late onset disease, it is often passed to the progeny of the carriers unknowingly. Even with the recent explosion in science and medicine, the true pathophysiology and optimal HD management are poorly understood. In fact, until 2006 there were no evidence-based reviews of treatment studies available despite the numerous published reports on pharmacological interventions (Bonelli & Wenning, 2006). The purpose of this research was to review current available literature concerning pharmacological and non-pharmacological management of HD and propose a treatment plan based on the findings.
Pathophysiology

Huntington’s disease is an autosomal dominant neurodegenerative disease, and the crux of its pathogenesis is attributed to the accumulation of the protein huntingtin. If a disease like HD is propagated in an autosomal dominant pattern, it is passed down through generations of families with a 50% chance that it will be passed along if only one parent is a carrier of that mutation. The mutation in HD that results in the protein accumulation is located on the IT15 gene on chromosome 4; the influence of this accumulation is not yet fully understood. The mutation results in an expanded glutamine tract that encodes for the amino acid glutamine (Ramaswamy, Shannon, & Korhower, 2007). HD is the most prevalent of a group of neurodegenerative diseases caused by trinucleotide (CAG) repeats. This list includes spinobulbar muscular atrophy and some spinobellar ataxias among others (Dellen & Hannon, 2004). People with fewer than 35 of the CAG repeats will not develop HD. Those with 36 to 39 repeats are at a significantly increased risk for developing the disease, and those with 40 or more repeats will always develop the disease in a lifetime. Again, the role of the accumulation is still debated. Some believe the accumulation to be toxic. Some believe that the accumulation is a natural byproduct of the pathogenic process, while others believe that the accumulation may even be neuroprotective (Bates, 2003). Recent evidence suggests that the expanded glutamine code confers a toxic gain of function. In other words, the accumulation induces a hyperactive state that become harmful, and the protein progressively disrupts function of vulnerable neurons (Dellen & Hannon, 2004).

One aspect of the accumulation is certain; there is a definite inversely proportional relationship between the length of the repeated portion and the age of onset. Also, the number of repeats has not yet been demonstrated to make a difference in the rate of progression (Ward et
al., 2006) as progression of the disease is roughly 15 to 20 years from the onset of symptoms until the patient dies no matter how many repeats are present (Metzger et al., 2006). One study, however, demonstrated that the rate and scope of brain atrophy is influenced by the length of CAG repeats (Ruocco, Boniha, Li, Lopes-Cendes, & Cendes, 2007).

At first it was believed that neurodegeneration was primarily responsible for the symptoms in HD. Although cell death and brain atrophy are no doubt involved in the disease process, cell death actually occurs very late in the disease suggesting that early manifestations including behavioral changes are the result of cell dysfunction rather than cell death (Dellen & Hannon, 2004). A study presented by Sugars and Rubinstien (2007) showed that the aggregates form protein inclusion bodies which induce dysfunction through abnormal protein-protein interaction. More specifically, proteosome components and transcription factors have been found to bind to the expanded polyglutamine portion of the mutation. Thus protein production and intracellular management are directly affected by the disease process.

Damage is most pronounced in the neurons of the cerebral cortex and medium spiny neurons of the striatum; why the disease shows an affinity to these regions is also not fully understood. It has also been determined that the mutation induces selective dysfunction of the neurotransmitter receptors and synaptic signal transduction pathways including gamma-amniobutyric acid (GABA) receptors in the cortex and striatum. Striatal dopamine and adenosine receptor binding are also decreased. These changes occur long before the onset of visible symptoms in HD (Dellen & Hannon, 2004). The results of this finding have launched a proposal that is referred to as excitotoxin theory, which suggests that the neurodegeneration seen in HD is actually the result of an excess of neurotransmitters including, GABA.
Presentation

Most commonly the HD patient will initially present with motor symptoms in their fourth or fifth decade of life. They will report a sense of clumsiness, uncontrolled jerky movements, or imbalance; the most common of these are the trademark choreiform movements. The movement abnormalities typically begin with facial grimaces or piano-like finger movements which progressively work up the limbs toward and eventually including the trunk. In more advanced cases, the involuntary muscle involvement may also include the respiratory, laryngeal, pharyngeal, and nasal musculature (Margolis & Ross, 2003) which presents a particularly challenging set of problems for the patient and the provider. HD also affects voluntary movements which can be observed by the presentation of poor visual tracking, slow, poorly coordinated, arrhythmic fine motor movements, dysarthria, dysphagia, rigidity, and ataxia (Margolis & Ross, 2003).

There has been recent evidence however that challenges the viability of this “typical” motor presentation of HD. A study presented Becker, Munhoz, Raskin, Werneck, & Tieve, (2007) demonstrated that even among a relatively small group of HD patients (n=44) of which seven were evaluated at the onset of their motor symptoms, there were a variety of presentations that could be easily confused with other disorders. Of that group of seven, four presented with parkinsonism, two with dystonia, and one with motor tics. The authors state that because of the broad range of possible HD presentations, direct diagnosis via genetic testing is necessary for an absolute diagnosis.

Although chorea will generally be the presenting symptom for an HD patient, the cognitive and social decline will most likely begin at the same time or even precede the motor
involvement. Behavioral changes like irritability and hostility will present a difficult challenge for the provider and may hide the true nature of the problem.

Of all the possible cognitive changes that may occur, cognitive speed and efficiency will be the most noticeable at first (Margolis & Ross, 2003). It is important to note that though these early symptoms may be detectable if one is looking for them, they will often go unnoticed until later in the process. As more and more neurons are involved in the disease process, a more global type of dementia will become evident. A four year study of cognitive function in HD patients presented by Ward et al. (2006) showed some interesting results, including definitive decline in cognitive function over time. One of the variables in this study that seemed to influence disease progression was that those with higher levels of education showed a slower decline than their less educated cohorts. Additionally, women showed a slower decline in overall function than men. One aspect of cognition that did not change over time was word knowledge, but performance of word reading, comprehension, and color naming did decline.

Any patient with a medical condition has a higher risk of depression. The presence of depression comorbid with any other medical condition makes each condition respectively more difficult to manage; thus the presence of depression in HD cannot be overlooked. For patients with HD, the rates of depression are two times higher than that reported by the general population. Moreover, only half of the cases of reported depression in HD patients sought medical intervention for their condition, and 10% reported at least one suicide attempt. Depression might even be the presenting symptom, preceding clinical diagnosis by 20 years (Paulsen et al., 2005). Other reported psychiatric symptoms comorbid with HD include obsessive-compulsive disorder, mania, and suicidal tendencies (Kingma, Duijn, Timman, Mast, & Roos, 2008). Generally speaking, most patients suffering from depression will not be
forthright about their condition so the provider must find a way to make the patient feel comfortable discussing their depression and work from subtle cues provided by the patient.

There is currently no cure for HD (Ramaswamy et al., 2007). The patients will progress from a relatively functional individual to a patient that cannot function independently at all and will require total care in all activities and functions. Invariably, the HD patient will die 15-20 years after diagnosis of the disease (Margolis & Ross, 2003). Although the movement disorder can lead to death, the most common cause of death in HD patients is cardiovascular disease and pneumonia (Conneally, 1984). Other common causes of death are aspiration, falls, and suicide.
Depression and Cognitive Decline in HD

The Huntington’s disease patient is more prone to exhibit behavioral disturbances than a non-carrier. The prevalence of comorbid psychiatric conditions has been estimated at over 90% (Paradiso et al., 2008). This presents a unique set of challenges for the provider in that the pathophysiological nature of the disease is hyperkinetic in nature, and most of the medications used to treat psychiatric illnesses (i.e. antidepressants) may actually worsen the movement disorders that are associated with HD.

A study presented by Berrios et al. (2002) attempted to determine if there is a truly detectable difference between asymptomatic HD patients and non-carriers of the HD gene. A determination of this sort would aid in the assessment of a patient at risk for developing HD and might facilitate an earlier intervention. The authors discovered that among their participants, there was a significant difference in the psychiatric profile between the asymptomatic HD carriers and the non-carriers. They also found that in the HD carriers with no detectable psychosocial impairments there were subtle impairments in memory. They determined that HD carriers have an increased prevalence of irritability over the non-carriers, implying that irritability can be detected very early in the disease process. It should be mentioned that in this study there was no statistically significant difference in depression between the two groups.

There may be periods when the HD patient is more vulnerable to the effects of depression or other mental illnesses. Paulsen, Hoth, Nehl, & Stierman (2005) performed a study involving 4714 HD patients to determine if and when HD patients were most at risk for suicidal ideation. The authors confirmed that HD patients are at a significantly higher risk for suicidal ideation than the general population. This study was the largest scale study of its kind. Interestingly, they also found that HD patients had two periods during the course of their illness at which they
were at increased risk for suicide. The risk doubled from the time when the patient was
asymptomatic to when the patient began to display symptoms. They also found that when a
patient is in the second stage of the disease, they are at a slightly higher risk for suicide and
suicidal ideation. Huntington’s disease patients for these studies are divided into groups based
on their score on the Unified Huntington’s Disease Rating Scale (UHDRS). This scale is a
standardized rating scale that is designed to assess cognitive, motor, behavioral, and functional
capacity and the score on this test determines which stage of the disease the patient is in. It is
during the second stage that HD patients begin to noticeably become less autonomous and
become increasingly dependant on others for their daily activities. These times of higher risk
require very thorough and comprehensive patient, caregiver, and provider awareness and
education. If these findings are accurate, those closest to the HD patient must be informed so
that they may pick up on warning signs and perhaps avoid tragic event. Most important was the
authors’ conclusion that making a diagnosis of HD does not increase the likelihood of suicide or
place the patient at higher risk for suicidal ideation. On the contrary, this study found that when
the patients actually receive confirmation of a HD diagnosis, their risk for suicide reduces
dramatically (see Figure 1). This supports very timely and early diagnostic measures if HD is
suspected or if a person is at an increased risk for developing the disease. It appears that if HD is
suspected or someone is at risk, it is in the patient’s best interest to know as soon as possible.

One study (Codori, Slavney, Young, Miglioretti, & Brandt, 1997) made an attempt to
delineate specific risk factors for those testing for HD surrounding the time of diagnosis. More
specifically, they tested the ability of the individual to adjust to the genetic testing and the
consequent diagnosis received. The authors defined adjustment as “emotional distress” which
included hopelessness, pessimism, and depressive symptoms. They determined that baseline
hopelessness, marital status, parenting status, and a few other predictors did play a significant role in the patients’ ability to cope with the testing and diagnosis of HD. They found that if patients were married, without children, and were closer to the onset of symptoms at the time of diagnosis, their ability to cope with the test and diagnosis was actually lowered. This might seem counterintuitive. One might presume that having a strong social support network would increase the patient’s ability to deal with this situation, but this study showed results to the contrary. The authors did not have an explanation for this finding, but perhaps it is the concern of the individual potentially with HD of how their impending diagnosis will affect those around them that compounds their inability to cope with the news. This is, of course, only speculation.

Padariso et al. (2008) made the first attempt to place a physiological face to the dysphoria that is often associated with the HD patient. The authors defined dysphoria as a “state of altered emotions characterized by fear, sadness, anger, and mental discomfort” (pg. 82). A small group of HD patients was compared to a group of healthy individuals using magnetic resonance imaging (MRI) and positron emission tomography (PET) imaging in an attempt to discover a difference in neural activity and differing responses to stimuli between the two groups. They found that HD patients experience more dysphoria and show lower neural activity in various portions of the brain, specifically in the prefrontal lobe, right thalamus, and cerebellum. This study is unique and more studies like it need to be performed to determine the practicality and utility of this type of screening.

Lemeire, Decruyenaere, Evers-Kiebooms, Vandenbussche, & Dom (2002) conducted a longitudinal study of HD patients to determine if their method of cognitive testing was able to detect a difference in cognitive function in the asymptomatic HD patient when compared to the symptomatic HD patient. The authors state that there is a great deal of evidence that supports the
idea that brain function deficits and behavioral manifestations of HD are clinically detectable long before the movement disorder becomes evident. The authors determined that their method of testing was sensitive enough to detect both subtle and overt differences in cognitive function between the two groups. They also confirmed that there was a significant difference in cognitive function between the symptomatic, asymptomatic, and the gene carriers (those with the mutation that have not received diagnosis). Their methods of testing may lead to further and more broad application of this type of evaluation which may help providers begin intervention through early detection when treating HD patients or those who are potentially at risk for developing HD.

Another study published in 2007 (Whalin, Lundin, & Dear) supported the idea of detectable cognitive decline prior to the onset of motor symptoms in HD patients. They tested 24 asymptomatic HD carriers against 31 non-carriers and were able to demonstrate that there were statistically significant differences between the two groups. The authors found that HD carriers performed poorer than the non-carriers on multiple areas of cognitive function including memory and executive function. They also divided the HD carriers into sub-groups separated by predicted time of onset of symptoms and discovered an interesting fact. They proved that brain damage in the HD patient was acquired over time through the disease process and is not present at birth. Their findings also support the idea that there is indeed a prodrome period in the disease process that manifests as cognitive and psychosocial decline.

A similar study was conducted by Verny et al. (2007) to determine if there was detectable cognitive decline in asymptomatic HD carriers. They tested 44 patients that were carriers of the HD mutation against 39 non-carriers and found that the HD patients did in fact show lower cognitive performance on all the tasks they tested them on when compared to the non-carrier group. The tasks included intellectual activity, cognitive speed, memory, executive function, and
attention capabilities. The authors concluded that there are noticeable cognitive functional
deficiencies that precede the onset of motor symptoms for HD patients. They hope that these
findings will initiate a change in the way that HD is perceived. It is generally considered a
disease of movement and is diagnosed as such. If those at risk are well monitored, the diagnosis
could be made by the decline in cognitive and behavior long before the onset of kinetic
symptoms appear, enabling the possibility of initiating earlier intervention for these issues.

Another study had outcomes different than the others mentioned with respect to cognitive
decline in HD. Kirkwood et al. (2002) found no statistically significant difference between those
with manifest HD and those who were pre-symptomatic. The authors stated that perhaps if their
tests were more focused at specific behavioral and psychosocial deficits, the idea of a prodrome
in HD might have been supported. The only detectable difference in psychosocial decline was
between the manifest group and the non-manifest group. There was no difference between the
non-manifest group and the non-carriers in their study.

Considering all of the possible early signs of HD and the evidence that HD does not in
fact present as a motor dysfunction but rather as cognitive or psychosocial dysfunction, it is
plausible that primary care providers will be the front line for these patients who may present to
the clinic with depressive-like or cognitive symptoms long before they present with dyskinesia.
Treatment of depression is key in the overall health of the patient, particularly one that has the
risk of developing HD. An otherwise healthy person with depression places themselves at a
higher risk for cardiac disease from depression alone (Nemeroff, Musselman, & Evans, 1998).
Some authors suggest that given the associated risk factors, depression alone could be considered
an independent risk factor for heart disease. This is a complication that needs not to be added to
the laundry list of issues inherent with HD. They state that patients with depression show
dysfunction in their sympathoadrenal system which in turn places inappropriate amounts of catecholamines in the system. This catecholamine response adversely affects the heart, blood vessels, and platelets (Nemeroff, et al. 1998). Fortunately, depression is a very treatable disease (Compton & Nemeroff, 2000). It is imperative that the clinician elicit a full patient psychiatric history. If depression is diagnosed, pharmacological and non-pharmacological methods are available to help the HD patient cope with depression. However, while diagnosing depression, a medical cause needs also to be considered (Compton & Nemeroff, 2000). For HD patients or those at risk for developing HD, that illness should of course be at the top of the differential for possible medical causes of depression.

Selective serotonin re-uptake inhibitors (SSRIs) are currently among the most widely utilized drugs for the treatment of depression. Some examples include fluoxetine, paroxetine, citalopram, and buproprion. They work by increasing the availability of neurotransmitters at the synapses in the neural networks of the brain. They are relatively safe in that they require a relatively low dose to be effective, have a relatively small list of adverse reactions, and are not lethal at high concentrations (Compton & Nemeroff, 2000).

Although antidepressant medications are generally efficacious in the otherwise healthy patient, they are nearly always at the top of the list of drugs that will react negatively with medications that are utilized to treat the choreiform movements that present in HD. Additionally, there is very little information available regarding their efficacy in HD patients. HD is associated with hyper-kinetic activity most of the time. If one of the leading theories of the pathophysiology of HD is correct, excessive or above normal amounts of available neurotransmitters may worsen the choreiform symptoms. Thus providers must be exquisitely careful when prescribing these kinds of drugs for the HD patient. They must start at the lowest
possible dose of the drug that they are most comfortable dealing with and tailor the dose to each individual’s needs. Hopefully through a combination of a multi-focal attack on the depression or behavioral issues, the patient may eventually go into full remission of the depression, enabling providers to focus their efforts on the other issues associated with HD.
Pharmacological Treatment Options

This review of pharmacological management of HD will comprise some of the most commonly utilized medicines for this condition. Currently, there are no HD specific drugs in use in the form of a uniform type of approach. Antipsychotic drugs are often used to treat HD, but, as with all antipsychotics, there are adverse affects to consider that can limit their use. Currently there are no evidence based therapeutic guidelines designed to manage the full range of symptoms related to HD.

Haloperidol is an antipsychotic medication that has multiple indications. For HD, it is utilized for its anti-hyperkinetic properties. It is the first of the butyrophenone series of major antipsychotic drugs. Although its exact mechanism of action has not yet been clearly established, it is believed to be useful for psychosis by producing dopaminergic receptor blockade in the mesocortex and limbic system of the brain, thereby reducing positive psychotic symptoms like hallucinations and delusions. It also blocks dopamine in the nigrostriatal pathway as a side effect. It is this extrapyramidal motoric side effect that is utilized in the treatment of hyperkinetic activity related to HD. Other adverse effects include tardive dyskinesia, dry mouth, sedation, akathia, muscle stiffness and cramping, restlessness, and depression; even suicide has been reported in patients who participate in long term haloperidol treatment plans. Recently, tachycardia, hypotension, hypertension, QT prolongation, and/or ventricular arrhythmias have been added to the possible adverse reactions to this drug. Most of these adverse reactions only occur in high doses taken over long periods of time, and the treatment of HD with this drug is usually at low doses. The most significant adverse reaction to this drug is neuroleptic malignant syndrome (NMS), a life-threatening condition almost exclusively induced by medications that block dopamine ("RxList: The Internet Drug Index: Haloperidol"). NMS has never been
reported in a HD patient as the result of haloperidol treatment (Bonelli & Wenning, 2006).

Another reaction that needs to be monitored closely is depression since HD patients are at a significantly higher risk for developing depression over the course of the disease (Paulsen et al., 2005).

Another consideration that has to be made before prescribing this drug is the exceedingly long list of drug interactions that it carries. Haloperidol induces inhibition of CYP3A4 and CYP2D6 and their substrates which interact with and effect drugs like amphetamines, beta-blockers, risperidone, ritonivir, tricyclic antidepressants, anticholinergics, antihypertensives, statins, carbamazepine, verapamil, levadopa, lithium, selective serotonin reuptake inhibitors (SSRIs), and many more ("RxList: The Internet Drug Index: Haloperidol").

According to a review conducted by Bonelli and Wenning (2006), in two single blinded crossover studies, haloperidol was shown to have positive effects on chorea when compared to tetrabenazine (a drug that will be discussed later). Conversely, Haloperidol was shown to have no difference in effect on chorea when compared to lithium in a double blind crossover study. Unfortunately, haloperidol lacks any recent large scale studies to prove or disprove its efficacy in its use for treating HD. All reports on the use of haloperidol are smaller studies and case reports.

One study conducted by Barr, Fischer, Koller, Spunt, & Singhal (1987), which focused on serum haloperidol concentration and choreiform movements, demonstrated a significant improvement in abnormal movements with a greater than 30% improvement from baseline at serum concentrations between 2 and 5 ng/ml (which is correlated to a dosing of 1.5-10 mg/day). This study also demonstrated no advantages to dosing higher than these doses. Another similar study conducted by Girotti et al. (1984) also showed improvement in hyperkinetic activity when patients were treated with haloperidol.
Although almost all of the studies involving haloperidol were relatively small and lacked double-blinded placebo controls, nearly all of the articles reviewed reported positive effects on hyperkinesias in HD patients when haloperidol was prescribed (Adams & Jankovic, 2008; Bonelli & Hoffman, 2007; Bonelli et al., 2004; Ramaswamy et al., 2007; Wright et al., 2002). Moreover, there was little report of serious adverse effects when patients were taking this drug, making it an overall good choice of treatment of HD.

On December 6, 2007 tetrabenazine (TBZ) was the first drug approved by the FDA in the US specifically for hyperkinesia in HD. It has been utilized for decades for chorea outside the US and is considered the drug of choice by many for HD. It works similarly to other antipsychotics by reducing available dopamine levels at synapses in the brain, but it works differently in that it binds to post-synaptic dopamine receptors. Also, this blockade is limited to the central nervous system, thereby sparing the peripheral nerves of this blockade. It is this dual action that is thought to make it so effective in treating chorea ("Tetrbenazine: How does it work? "). Like its antipsychotic counterparts, it carries with it side effects that are usually the rate limiting factor for patients taking this medication. Some of the side effects include drowsiness, GI disturbances, hypotension, insomnia, parkinsonism, febrile states, decreased levels of consciousness, and depression, which is the most significant side effect of this drug ("Tetrbenazine: How does it work? "). A single blind study conducted by Gimenez and Mateo in 1989 focused on treatment of HD with TBZ. In this study, three of eleven patients displayed severe depression, including one suicide attempt. TBZ also has some of the same drug interactions as haloperidol, although not nearly as many. SSRIs, monamine oxidase inhibitors (MAOIs), ethyl alcohol (ETOH), and levadopa (L-Dopa) top the list of absolute drug
contraindications. Also, if the patient has a pre-existing depression disorder this drug should not be used.

Despite the risk of depression and other adverse affects associated with TBZ, it continues to be tested since its recent approval by the FDA in the US, although most trials are still small and limited. A randomized single blind study (n=84) supporting the use of TBZ by Kenny and Jankoviuc (2006) demonstrated that patient adjusted doses with a maximum of 100mg/day showed a 68-90% reduction in choreiform movements. Moreover, the study showed that if the doses are closely monitored and adjusted to each individual patient, the patients tolerate the drug very well. Another more recent study (Kenney, Hunter, Davidson, & Jankovic, 2007) supported this finding when 10 patients were given between 37.5 and 175mg/day in an attempt to discover the “best dose” and determine short term effects of TBZ in HD patients. They found that TBZ has a definite positive effect on choreiform movement in HD patients over a short period of time. Four of ten patients did not return to baseline, which was the reference point for determining the efficacy of this drug. This short-term study did not report any of the adverse effects of TBZ (Kenney et al., 2007). Later that year another report was published (Kenney, Hunter, & Jankovic, 2007) which focused on the long term effects of TBZ. In a trial lasting over seven years, they found that of 448 patients, 25% displayed drowsiness, 15.4% displayed parkinsonism, 7.6% showed depression, and 7.6% displayed akathisia. Another study showed similar beneficial effects of TBZ and fewer adverse effects than other studies (Ondo, Tintner, Thomas, & Jankovic, 2002). The evidence suggests that when TBZ is closely monitored and the dosing is tailored to the individual, it is efficacious and is tolerated fairly well. TBZ should definitely be considered for treating HD patients.
Olanzapine, an atypical antipsychotic, has recently been added to the list of possibilities for treating HD, and the results have been promising. Like many neuroleptic medications, its exact mechanism of action is unknown. It has been shown to have high affinity for multiple receptors including D1, D2, D4, 5-HT2A, 5-HT2C, 5-HT3, α-adrenergic, and muscarinic receptors (Kenney et al., 2007). It shows a higher affinity for 5-HT receptors than it does for D2 receptors. It is also unique in its affinity for D4 receptors. It may be this unique D2/D4 ratio that makes it so effective for treating HD. Additionally, its efficacy may be attributed to its affinity to so many different receptors (Dipple, 1999). Presumably, it is its affinity to dopamine receptors that is utilized for treatment of dyskinesia in HD patients, although its primary indications are for treating schizophrenia and acute manic episodes in bipolar patients.

Olanzapine also has multiple adverse effects to consider which include the some of the same as TBZ and haloperidol i.e. drowsiness, GI disturbances, hypotension, insomnia, parkinsonism, febrile states, with weight gain and increased appetite added to the list. This unique property is probably due to its serotonin reduction properties (Bonelli & Hoffman, 2007).

Despite the risks of adverse effects, olanzapine has shown great promise as a treatment for HD. In a study presented in 2002 (Bonelli, Manhurt, & Niederwieser) (n=11), olanzapine was shown to improve (with no adverse effects) oculomotor function, orolingual function, fine motor tasks, chorea, and gait in six of the patients after only two weeks of treatment. Also, six of the patients who participated in this trial had no reduction in functional capacity after two years of taking this drug (Bonelli et al., 2002). Another study supporting the use of olanzapine in HD was published in 2008 (Adams & Jankovic) which showed improvement in psychiatric conditions associated with HD including depression, anxiety, irritability and obsessive disorders.
Riluzole is in a class of drugs that act as glutamate antagonists and is currently used for treating patients who suffer from amyotrophic lateral sclerosis (ALS). It does this by a direct inhibition of glutamate release, inactivation of dependant sodium channels, and interference of intracellular events that follow transmitter binding at excitatory amino acids ("RxList: The Internet Drug Index: Rilutek (riluzole)"). It is the glutamameric blockade that is useful for HD patients. This blockade inhibits convulsive activity. Unfortunately, riluzole’s inhibitory properties are only available at doses two times what is recommended for human consumption.

This drug’s adverse effect include asthenia, nausea, dizziness, diarrhea, decreased lung function, pneumonia, and many more. In an evaluatoion of riluzole’s efficacy verses its adverse effects for 982 ALS patients, 14% of the patients discontinued treatment due to adverse effects (Bonelli, Niederwieser, Diez, & Koltringer, 2002). Currently, no studies have examined its interaction with other drugs. Since it is metabolized by the liver, riluzole is potentially hepatotoxic, and any drug that has CYP-1A2 interactions must be monitored when prescribing riluzole.

Riluzole has had mixed reviews as a treatment option for HD patients. Effects are transient in nature if it is effective at all. An open label study (Seppi et al., 2001) showed that it had marked efficacy in the short term in ameliorating choreiform movement in HD patients. At twelve months into the treatment it was no longer effective. It did, however, show sustained effects in behavior and psychomotor speed (Seppi et al., 2001). This study only included nine patients and also allowed other drugs to be used while the test subjects were participating in the trial, so its results require scrutiny. Another study (Rosas et al., 1999) with a similar number of patients showed similar results. This study was also short (8 weeks) and had many confounding variables as well so its conclusions must also questioned.
Another proposed approach is to increase or enhance available concentrations of GABA for neurotransmission. GABA is the most prolific inhibitory neurotransmitter in the human brain. Isoniazid is a GABAergic drug that has had several trials to test its efficacy in treating HD and has unfortunately been proven ineffective (Bonelli and Wenning, 2006). In fact, Bonelli and Wenning (2006) found no GABAergic drugs that were proven effective to date with the possible exception of benzodiazepines. Benzodiazepines (benzos) are a class of sedative hypnotic drugs that also act by modulating GABAa receptors. Benzos change receptor conformation so that they have a much higher affinity for GABA thus prolonging/enhancing its inhibitory effects. Benzos have a wide variety of uses including anti-convulsant, anxiolytic, insomnia, sedation, alcohol dependance, and mania as therapeutic uses. They also have a wide variety of side effects including sedation, drowsiness, nausea, headache, confusion and many more including possible withdrawal symptoms.

Unfortunately there is very little documented research available regarding the use of benzos in HD. Benzos are also depressants by design. So again, if the HD patient has already displayed evidence of depression, this drug should not be considered. More research is needed to determine if these drugs can be useful for treating HD.
Non-Pharmacological Treatment Options

Unfortunately, little information is available regarding the availability and efficacy of non-pharmacological alternatives (i.e. directed activity) for treating or improving motor function for a symptomatic HD patient. A search undertaken by Busse and Rosser (2007) only uncovered 10 studies addressing this; these were case reports and not scientifically designed studies. Therefore, the results of these studies have to be considered anecdotal at best. This is unfortunate considering that the disease’s most debilitating manifestations are motor in nature. Bilney, Morris, and Perry (2003) did however uncover some weak evidence that exercise may be beneficial for patients who are in the early stages of the disease and that speech therapy may decrease the likelihood of aspiration. Clearly the more that the motor symptoms affect the patient, the less autonomy the patients will be able to practice making them more and more dependant on others to function on a daily basis. Even if there is only a slight chance that physical, occupational, or speech therapy will help, they should be implemented as a part of the care plan for the HD patient.

There is evidence that supports the notion of physical activity benefiting the depressive symptom associated with HD. Phillips, Kiernan, and King (2003) reviewed literature and concluded that there is great support for the idea that “physical intervention of as little as four weeks can significantly and beneficially affect depression” (p 147). They went on to surmise that not only was aerobic activity helpful but anaerobic activity (which may be more practical for the moderately to severely affected HD patients), flexibility, and yoga training were also beneficial. Phillips et al., (2003) suggested that this is of great interest not just for HD patients or depressed patients, but it represents a very easily accessible low cost alternative or adjunct to medicine for everyone.
A very early study presented by McCann and Holmes (1984) tested this theory. Their results clearly support the idea that aerobic exercise can reduce depression. Recommending exercise for patients with HD is predicated on the presumption that both HD and depression have been identified very early in the disease process. Exercise becomes far more complicated as the chorea becomes more severe and debilitating, but should not be abandoned until it becomes physically impossible for the patient to participate.

Another possibility is cognitive-behavioral therapy (CBT). This should always be considered as an adjunct to pharmacological therapies when dealing with mood disorders. Silver (2003) published a case report of her experience with a 44 year old woman who had recently been diagnosed with HD. The patient developed anxiety that was severe enough to make her believe that choreiform movements had begun. However, it was her anxiety that was responsible for her physical signs. The patient admitted that she was having difficulty dealing with her situation that was compounded by pre-existing poor self-esteem, poor self-image, and a history of sexual and psychological abuse. The patient was diagnosed with anxiety, hopelessness, and depression at the onset of her CBT. Specific goals were set that included exercise, a religious affiliation, a strategy to identify and deal with her emotions constructively, and a sleep regulation regimen. The patient reported that as therapy progressed she was becoming more adept at facing her thoughts (which she had previously avoided through alcohol abuse) by not allowing them to mandate her reality. The patient was very actively involved in her own therapy which empowered her and gave her a sense of control over her disease. Ultimately, the patient no longer had diagnosable anxiety and felt better equipped to deal with every stage of her disease. Larger studies similar to this are needed to support this idea so that CBT can be part of the HD treatment formulary.
An interesting study presented by Coulsen, Buchanan, and Aubeeluck (2007) emphasized support when considering care plans for the HD patient. They examined the effects of an online support group specifically for HD patients. The authors analyzed 1313 anonymous internet postings by 793 individuals and used the social support behavioral code to measure the emotional efficacy of this style of help. This is a novel concept in that this medium (the internet) carries with it a sense of anonymity which may be preferred over the classic face to face support group settings. With this sense of anonymity, the individual may be more open or feel more inclined to share some of their more intimate details that they may otherwise keep closer to themselves. Given the relatively rare nature of HD, the internet allows the HD patient access not limited by geography or time, allows them to present their ideas with more clarity and precision, and allows for an infinitely wider variety and number of individuals to participate. They found that information postings (i.e. advise, referrals, education) were accessed the most followed by networking, emotional support, and tangible evidence (Coulson et al., 2007).

The different categories of help in this study seemed to be tailored to the different stages of the disease process. The information segment was more beneficial for those who were in and around the time of testing for HD. The authors also stated that the emotional support segment was beneficial for both the reader and the poster in that it helped validate the HD experience for both parties. Ultimately, the authors concluded that the exchange of information via internet support groups represented a “key function” for the patients and others simply looking to become informed. It is also beneficial for those who care for and/or are close to the HD patients because it can help all of those involved form a clearer and more intimate understanding of what the HD patient is experiencing in such a way that may not otherwise be obtained (Coulson et al., 2007).
Other Considerations

There are other aspects of the disease that are not as overt as some of the more commonly discussed issues that affect both the patient and the provider. These include the sexuality of the HD patient, the affect that the HD diagnosis and progression has on the caregivers of the HD patient, the burden that those who care for HD patients carry, and how to deal with the disease as it reaches the end of the process.

A paper presented by Mayers and Heller (2003) addressed the sexuality of the HD patient. The authors interviewed nine patients of whom five were male and four were female. This study was an attempt to determine the needs and thoughts related to sexuality for HD patients in the latter stages of the disease. They discovered through these interviews that three of the participants had no sexual interests at all. Two of these three were men who were physically incapable of having an erection. Of the remaining six, two participants only stated that they had no sexual partner and did not wish to further discuss the topic. The remaining four (three female and one male) described their lack of sexuality as a significant loss. Theses patients vocalized a nearly uniform (except for the difference between male and female preferences respectively) remaining interest in their sexuality and felt a loss in its absence. The authors suggested that the caregivers cannot overlook this aspect of the HD patient if it is present. The authors presented no conclusions on how this may benefit the patient, but it is arguable that providing a patient with care that fulfills any need could only be beneficial, even if that need is socially disagreeable at times.

When considering the complexity and the wide variety of complications associated with HD, there is an immeasurable burden placed on the family and everyday caregivers for the HD patient (Aubeeluck & Moskowitz, 2008). There is little research directed at the burden that the
caregivers must carry (Pickett, Altmaier, & Paulsen, 2007). Generally, the HD patient is in their fourth or fifth decade of life when the disease really begins to take hold thus caregivers are presumably around that same age. These caregivers may have children as well over the up to 30 year course of the disease. The authors found that health care providers may not be willing or able to manage the HD patient because of the behavioral manifestations that are often present in the disease i.e. irritability and hostility. The authors of this research wished to examine this burden on the caregivers in some depth and found that how well the caregiver copes with this awesome responsibility was contingent on the inherent strengths of the caregiver. They found a correlation between the problem solving skills of the provider and the level or existence of depression in the caregiver. Additionally, they discovered a negative correlation between the physical capabilities of the patient and the burden of the caregiver. Ultimately, the authors presented three factors that made the biggest difference as a predictor for the well being of the caregiver: caregiver subjective appraisal of the burden, caregiver personal control, and patient depression. They suggest that the caregivers need attention as well and should be aided in every possible way during their effort to care for the HD patient (Pickett et al., 2007).

A study in support of this notion was presented by Aubeeluck and Moskowitz (2008). They found in their review that the life of the caregiver or family member is extremely compromised. In this study the authors demonstrated how the disease affects those who are impacted by it and state that the caregivers of the HD patient are all too often the forgotten person in the network of those dealing with the disease. They also state that few spouses, health care providers, social workers, and so on are equipped and ready to handle the level of care that a HD patient requires and that few are aware of the impact that HD has on family life (Aubeeluck
& Moskowitz, 2008). The authors suggested that based on their findings very close attention needs given to the providers for the HD patient.

As HD progresses, the patient becomes unable to communicate their needs, they become entirely dependant on their providers, and they will eventually be unable to comprehend what is being said to them. This is a description of the end stage situation that is invariably reached in the HD patient. Currently, there is not an established guideline available for management of this portion of the disease. Simpson (2007) presented a few ideas based on experience with HD patients in this stage of the disease. The author stated that some of the patients made an attempt to familiarize their caregivers with themselves as they were before the disease took control in an attempt to remind the caregiver that there is still a person beneath the mask of HD. The author also noted that the patients would make notes to themselves and to their providers. The author also emphasized the importance of advanced directives and plans for the end stage care while the HD patient retains the capacity to do so. Mostly, the author emphasized the need to treat the HD patient as any other patient or person would expect to be treated. They would expect to be treated with as much autonomy, respect, care, and grace as any other person or patient deserves.

There have been some recent advancements for possible future treatments of HD and not just the management of its symptoms. There is some promising potential for gene therapy. This could not only aid in the prevention of the disease but also help patients who are in the more advanced stages of the disease (Mochizuki, Yasuda, & Mouradian, 2008).
Conclusion

In conclusion, everyone involved with the HD patient needs to commit to a level of care and understanding that is higher than most other patients will need. They will be required to have access to multiple sources of aid and will need to be proficient at implementing the advice that they receive. It has been emphasized over and over throughout the literature reviewed for this paper that there is a terrible lack of any structured tested guidelines for a provider to reference if they are faced with caring for a HD patient. In light of the apparent lack of literature or evidence based information, providers must take matters into their own hands, do some research, and decide for themselves what they feel is best to do in these situations. Medicine is still considered an art, and this is an opportunity for the provider to be an artist. There will most likely be no typical presentation or course when dealing with a HD patient, and the treatment needs to reflect the individuality of the patient and the presentation.

There is a definite base of literature that supports the early identification of the disease. Confirmation of the disease reduces mortality from suicide and/or suicidal ideation (Paulsen et al., 2005). There are of course a myriad of ethical issues surrounding genetic testing and that are beyond the scope of this paper. Now that there are tests sensitive enough to detect the subtle changes that are occurring before the movement disorder presents, it could be beneficial for the patients to know rather than wonder why they are having these unique experiences.

There is also little to no evidence based medicine with regard to how to treat chorea (Bonelli & Wenning, 2006). However, based on the medicines reviewed for this article, olanzapine is the drug with the most promise. Not only did it show significant improvement in treating chorea with few adverse reactions, it also addressed with some success the behavioral changes that can be associated with HD (Adams & Jankovic, 2008). If there is a possibility to
address both manifestations of the disease with one drug than this one needs to be considered first line for treating HD. Adult dosing for the currently approved uses for olanzapine ranges from 5mg to 20mg/day. It is often good to start at the lowest dose and work upward until the desired outcome is achieved. An acceptable starting point is 2.5mg twice a day with a titrating dose as needed to achieve clinical improvement of the disease.

There is even less literature available on how to treat depression or any behavioral dysfunction that presents in HD. There is evidence that supports a very broad approach to treating this aspect of the disease which varies little from how one would treat a patient that does not have HD. Exercise in whatever form possible has been proven to be an effective mediator of depression in HD (Phillips et al., 2003). This in combination with speech therapy which lowers the risk of aspiration (Bilney et al., 2003), CBT which will empower and provide the patient with HD the necessary tools to cope with the various stages of the disease (Sliver, 2003), a vast network of social support with unlimited access, and caregivers who are up to the challenge is what will be required when treating the HD patient. This is a very comprehensive approach that needs implemented to provide the quality of care that the HD patient requires and deserves (See Figure 2). Autonomy is of course crucial when considering how to treat the HD patient (or any patient). It is ultimately up to the patient how the treatment will unfold. It is the preservation of autonomy that is paramount for the patient with Huntington’s disease.
References


Figure 1 Risk of suicide in HD patients (Paulsen, Hoth, Nehl, & Stierman, 2005)
Figure 2 Cycle of care for HD patients
Abstract

**Objective.** Huntington’s disease (HD) is a progressive neurodegenerative disease for which there is no treatment consensus. The objective of this paper is to review literature for pharmacological and non-pharmacological approaches for treating HD and to propose a treatment plan. **Methods.** Pubmed, MEDLINE, Google, and CINAHL search engines using key words Huntington’s disease, therapy, pharmacological management, non-pharmacological management and depression in Huntington’s disease were utilized for current (1980-2008) literature. **Results.** There is a lack of literature for the treatment of HD and one FDA approved drug for the treatment of chorea. There are few studies available discussing how to manage the psychological and sociological issues with HD. **Conclusion.** There is little evidence for treatment of HD. Olanzapine at 2.5mg twice/day has the most promise for treating HD associated chorea and depression. Non-pharmacological aids such as exercise, social support, speech and physical therapy, are important in treating the varying manifestations of HD.