Managing the symptoms of Huntington’s disease

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Unfortunately, there is currently no cure for Huntington’s disease and management is therefore focused on alleviating symptoms. This article discusses the treatment options available for managing the motor and psychiatric symptoms associated with Huntington’s disease.

Huntington’s disease (HD) is a relatively rare condition; however, it can be a complex and devastating disease for both patients and carers. HD is a progressive, genetic, neurodegenerative condition that is autosomal dominant. The huntingtin gene (HTT) encodes for the huntingtin protein. The normal version, known as the ‘wild-type’ protein, plays a role in normal neuronal functioning, although its specific role remains unclear. It is thought to be involved in vesicle transportation and gene transcription.

One area of the HTT gene contains a CAG trinucleotide repeat. This is normally repeated between 9 and 35 times. A mutation in the gene leads to expanded CAG trinucleotide repeats, which gives rise to the pathology seen. Typically, CAG expansions greater than 35 will increase the risk of a person developing HD, with expansions greater than 40 resulting in patients definitively developing the condition. An ‘intermediate’ group of patients, with CAG repeats between 27 and 35, may show HD phenotypes and are at risk of passing extended alleles to offspring through the process of gene anticipation. Patients with 36–40 CAG repeats may be considered of ‘reduced penetrance’ and are at higher risk of developing HD but the age of onset of symptoms may be later. Interestingly, one study highlighted that approximately 1 in 400 people in the general population have extended CAG repeats of between 36–38, and suggested that often such patients are not diagnosed with HD due to low penetrance.

The abnormal CAG repeats result in neuronal cell death, particularly within the striatum including the corticostriatal pathway. The average duration of illness until death is approximately 20 years and is most often due to aspiration pneumonia, with the second most common reason being suicide. The prevalence of HD in European populations is estimated at between 10–15 per 100,000 and this appears to be rising, perhaps due to more accurate diagnoses and improved life expectancies. HD affects males and females equally. The
average age of onset is around 40 years but, depending on the severity of CAG repeats, it can affect patients from infancy to old age.

**Symptoms**
Initial symptoms often precede diagnosis and can be subtle motor, cognitive or psychiatric complaints. Without a known positive family history of HD, initial non-motor symptoms may be misdiagnosed as primary psychiatric disorders, leading to a delay in diagnosis. A positive family history should make the clinician at least consider HD when presented with motor, cognitive or psychiatric complaints, and discuss this accordingly with the patient. At this point, if the patient agrees, a referral to the local genetic service can be organised. Patients may demonstrate irritability, mood disturbance, personality change and may struggle with multi-tasking. As the condition progresses, motor symptoms usually become more apparent with classical choreiform movements developing.¹

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**Figure 1.** Suggested treatment algorithm for patients presenting with specific Huntington’s disease (HD) symptoms

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Chorea involves involuntary, brief movements that affect the trunk, limbs and orofacial region, including abnormal eye movements, especially slow saccadic movements. This can be problematic on a functional level, affecting one’s ability to work or manage activities of daily living independently at home. On a social level it can cause embarrassment, social withdrawal and low self-esteem, contributing to anxiety and depressive symptoms. Studies have reported that rates of depression in people with HD are greater than twice that of the general population, one study also citing that at least 10% of patients with the diagnosis having attempted suicide at least once.

Pharmacological management

There is no cure for HD. Management is focused on symptom control. Specialist HD clinics may be available, which are usually run by specialist doctors or nurses with experience in HD. It is worth noting that evidence-based guidelines for HD are limited and that treatment recommendations are often based on a small number of trials and expert opinion. A Cochrane review highlighted limited evidence for the treatment of many psychiatric symptoms of HD, and suggested exploring placebo-controlled studies relating to specific areas of management.

Many GPs may be unfamiliar with prescribing antipsychotics or movement disorder medications without specialist input. In such circumstances, particularly if there are concerns about suicidality or prominent movement disorder that may be exacerbated by such drugs, a referral to specialist Huntington’s services or mental health team may be appropriate prior to commencing treatment. Acutely urgent mental health issues should be directed to appropriate mental health services.

A suggested treatment flowchart for patients presenting with symptoms of HD is shown in Figure 1.

Movement disorder

The main motor problems encountered by patients with HD are choreoathetoid movements and loss of co-ordination. The former is not related to illness duration or stage while the latter correlates with duration of illness. Initial, often subtle, symptoms of the condition can include dropping items and poor balance, leading to stumbling. Loss of motor control relates more to loss of co-ordination rather than involuntary movements. Movement disorder does not require routine treatment and should not be offered if the patient does not identify it as an issue. Patients often have reduced awareness of the involuntary movement disorder, so if treatment is requested it is useful to clarify the reason. Always ensure the patient is aware of the limitations of treatment. Movement disorder treatments suppress the involuntary movements but do not improve co-ordination; in other words, treatments are associated with a visual reduction in voluntary movements but no associated improvement in functioning.

Several treatments targeting particular neurotransmitters (especially dopamine, glutamate and GABA) have been studied but few have produced positive results. Treatment often focuses on dopamine depletion, usually with atypical antipsychotics, or by using tetrabenazine, a monoamine depletor. Doses depend on individual patient response, but typically the lower end of recommended doses in the BNF are suggested and titrated up as necessary.

Antipsychotics have shown mixed results. The literature suggests olanzapine, aripiprazole, risperidone, sulpiride and haloperidol as options. One Cochrane review suggested that neuroleptics showed no clear effectiveness in controlling chorea. Placebo-controlled trials have demonstrated little benefit of typical antipsychotics; however, one trial showed a 30% reduction in chorea compared to baseline with the use of haloperidol. A 2017 paper recommended haloperidol, risperidone, olanzapine and fluphenazine as potential options for the treat-

### Table 1. Suggested treatments for movement disorder in Huntington’s disease

<table>
<thead>
<tr>
<th>Class</th>
<th>Medication</th>
<th>Dosage</th>
<th>Side-effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monoamine depletor</td>
<td>Tetrabenazine</td>
<td>25mg three-times daily to max. 200mg daily</td>
<td>Depression/ anxiety, Confusion, drowsiness, GI symptoms, Insomnia, Parkinsonism</td>
</tr>
<tr>
<td>Antipsychotic</td>
<td>Olanzapine</td>
<td>2.5–5mg daily to max. 20mg daily</td>
<td>General side-effects for antipsychotics: Agitation, Arrhythmia, Sedation/drowsiness, Urinary retention and constipation (typical antipsychotics) Metabolic syndrome, Seizures, Dyskinesia/movement disorders</td>
</tr>
<tr>
<td></td>
<td>Quetiapine</td>
<td>25–50mg daily to max. 750mg daily</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Risperdone</td>
<td>0.5–1mg daily to max. 4–6mg daily</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Aripiprazole</td>
<td>5–10mg daily to max. 30mg daily</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Haloperidol</td>
<td>0.5mg–1mg daily to max. 10mg daily</td>
<td></td>
</tr>
<tr>
<td>NMDA antagonist</td>
<td>Amantadine</td>
<td>100mg daily for one week then increased weekly to max. 400mg daily</td>
<td>Anxiety, Confusion/dizziness, Headache, GI symptoms</td>
</tr>
</tbody>
</table>

For full details, refer to BNF. At present only haloperidol and tetrabenazine are licensed to treat chorea in Huntington’s disease. We would recommend informing patients of the off-licence prescribing of other medications.
ment of chorea. It did not recommend quetiapine or clozapine, and highlighted the significant side-effect burden that can come with clozapine.11 It should be borne in mind that antipsychotics may cause akathisia, extrapyramidal side-effects and apathy, which could worsen pre-existing movement problems or amotivation caused directly by HD.

Tetrabenazine depletes the monoamines dopamine, serotonin and norepinephrine. It is indicated for the treatment of movement disorders due to HD. The suggested starting dose for adults is 25mg three times daily and the maximum dose is 200mg daily. The main side-effects include sedation, anxiety, confusion and, likely due to monoamine depletion, depression. There is evidence that tetrabenazine improves chorea.8 The TETRA-HD study examined the safety and effectiveness of tetrabenazine plus an antidepressant in patients with HD. It showed no increased incidence of depression if patients were taking an antidepressant alongside tetrabenazine and noted an improvement in chorea symptoms; however, there was no impact on the rate of decline. It is worth noting that tetrabenazine is metabolised by CYP2D6, the liver enzyme that is induced by fluoxetine and paroxetine, so alternative antidepressants may need to be considered when co-prescribing. Tetrabenazine should be avoided in patients with uncontrolled depression (eg not on antidepressants) or with a history of suicidality.8

Amantadine is an NMDA-receptor antagonist, which is licensed for use in Parkinson’s disease. Some studies have shown it to be beneficial in reducing choreiform movements in HD patients; however, other studies have shown no significant clinical benefit.12,13

Dosages and side-effects of suggested medications for movement disorders in Huntington’s disease are shown in Table 1.

**Mood and anxiety disorders**

Depression is common in HD with an estimated prevalence between 33% and 76%.14 There is a lack of evidence for the treatment of depression specifically in HD but it is suggested that the condition responds to standard treatments for depression and anxiety, namely SSRIs in the first instance. However, care should be taken due to the increased suicidality in HD; for example, by having a higher threshold for prescribing tricyclic antidepressants (TCA), which tend to be more fatal in overdose. There have also been some case reports of dyskinesias in patients receiving TCAs, perhaps due to their anticholinergic and dopamine-ergic properties.15 However, one study did suggest using amitriptyline and mirtazapine for depression.16 TCAs (eg amitriptyline) should only be considered in significant depressive disorders where first-line treatments (eg SSRIs) have proved ineffective. Their use should also be discussed with the psychiatric team or Huntington’s service as opposed to being managed by primary care clinicians in isolation. Clonazepam can be a helpful short-term solution for insomnia (off-licence use). It can be useful if there is an additional anxiety component.

For refractory depression, antipsychotics can be considered, with olanzapine, risperidone, aripiprazole and clozapine showing some benefit in small studies. Apathy may be associated with HD or depression, but there have been no convincing studies highlighting specific treatments. Consideration should be given to a reduction in tetrabenazine or antipsychotics if permissible. Evidence for treatment of obsessive-compulsive symptoms in HD is, again, limited; one paper highlighted “expert agreement” for using SSRIs first line with clomipramine monotherapy recommended by a smaller number of experts experienced in its use.17

Dosages and side-effects of medications used for depression and anxiety in Huntington’s disease are shown in Table 2.

**Irritability and psychosis**

SSRIs may be of benefit but behavioural strategies to prevent outbursts of irritability or aggression in HD may prove more successful. For impulsivity or aggression, mood stabilisers (such as valproic acid, carbamazepine or lamotrigine) or antipsychotics can be considered should SSRIs or behavioural strategies prove ineffective. Psychosis and delusions are less common (3–11%) in HD, but if significantly distressing then treatment using an atypical antipsychotic may be indicated. Behavioural problems and mood instability may respond to mood stabilisers such as carbamazepine or valproic acid.8 In line with guidance from the Medicines and Healthcare products Regulatory Agency (MHRA), valproate medicines should not be used in women and girls of childbearing potential unless conditions of the Pregnancy Prevention Programme are met. This is due to the significant risk of neurodevelopmental disorders and congenital malformations.

<table>
<thead>
<tr>
<th>Class</th>
<th>Medication</th>
<th>Dosage</th>
<th>Side-effects</th>
</tr>
</thead>
</table>
| SSRI   | Sertraline | 50–100mg daily to max. 200mg daily | • Anxiety  
• GI symptoms  
• Appetite change  
• Arrhythmia  
• Sexual dysfunction |
|        | Citalopram | 10–20mg daily to max. 40mg daily (max. 20mg daily in the elderly) | |
|        | Fluoxetine | 20mg daily to max. 60mg daily | |
| NaSSA  | Mirtazapine | 15mg daily to max. 45mg daily | • Sedation  
• Helpful if insomnia |
|        | Clonazepam | 0.5mg daily to max. 1–2mg daily | • Sedation  
• Can cause ataxia |

For full details, refer to BNF. Clonazepam use is off-licence and should be short-term only.

Table 2. Suggested medications for depression and anxiety in Huntington’s disease

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Table 3. Suggested mood-stabilising medication for use in Huntington’s disease

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dosage</th>
<th>Side-effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Valproic acid</td>
<td>750mg daily divided into 2 to 3 doses</td>
<td>• Agitation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Weight gain</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Alopecia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Anaemia, thrombocytopenia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Drowsiness</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>100–200mg daily to max. 1.6g daily</td>
<td>• Agitation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Drowsiness</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Risk of blood dyscrasias</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Skin reactions</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>25mg daily increased slowly to max. 400mg daily</td>
<td>• Agitation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• GI symptoms</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Rash</td>
</tr>
</tbody>
</table>

*For full details, refer to BNF

Dosages and side-effects of suggested mood-stabilisers for Huntington’s disease are shown in Table 3.

Non-pharmacological management

In addition to medications, non-pharmacological therapies may prove beneficial in targeting specific needs in patients with HD. Guidelines exist for physiotherapy, speech and language therapy, occupational therapy, nutritional support and oral healthcare in HD. Physiotherapy can range from improving gait and balance to optimising respiratory function, and occupational therapy may focus on problem solving, driving and personal care. A 2003 review highlighted a lack of strong evidence for such non-pharmacological interventions. However, it did highlight the benefit of speech therapy in reducing the risk of aspiration and noted the benefits of exercise for addressing specific impairments in patients with minimal Huntington’s symptoms.

Future treatments

Worldwide clinical trials are currently underway targeting the mutant HD protein. Antisense oligonucleotides (ASOs) are being developed as ‘huntingtin reducing’ therapies, designed to reduce the production of the abnormal huntingtin protein and thereby slow the progression and, depending when administered, delay the onset of HD. ASOs are administered via the intrathecal route. There are two ASO research trials for HD in different stages of drug development. Wave Life Sciences are currently in the early stages (phase 1b/2a) assessing pharmacokinetics, pharmacodynamics and tolerability while Roche have commenced a phase 3 trial. Results of these trials are eagerly awaited.

References


Declaration of interests

None to declare.

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