What evidence there is for the drug treatment of Huntington’s disease

Elizabeth Bevan and Carol Paton searched Medline, EMBASE and the Cochrane Library for evidence up to September 2006 and, in this article, they review the literature on the pharmacological management of chorea and the psychiatric co-morbidity in patients with Huntington’s disease.

Huntington’s disease (HD) is a hereditary disease that involves slow progressive degeneration of the neurones in the basal ganglia and cerebral cortex. It is an autosomal dominant disease caused by a mutation of a gene on chromosome 4; there is an expansion of a trinucleotide repeat within the part of this gene that encodes the Huntington protein. Neurones are damaged when the mutated protein aggregates and interferes with normal metabolism and functioning but the mechanism is poorly understood, making it difficult to develop drugs that slow or stop progression. In western Europe the prevalence of HD is between three and seven per 100,000.

Symptom onset is usually between the ages of 35 and 50 years, but can occur in early childhood or old age. The greater the number of trinucleotide repeats, the earlier the age of onset. HD usually has a course of 15 to 20 years, although juvenile onset cases often progress more rapidly. The clinical presentation is characterised by increasingly severe involuntary movements (chorea) and cognitive decline. Choreiform movements and dementia are core symptoms of HD and both psychosis and depression are common. The cause of death is usually respiratory infection secondary to failure of the gag reflex and respiratory muscles. 

Evidence supporting the pharmacological management of chorea and the psychiatric manifestations of HD is summarised below. Adjunct psychotherapy, physiotherapy and speech therapy should be applied to provide optimal management. The use of these strategies is outside the scope of this review.

Chorea
Choreiform movements occur in approximately 90 per cent of patients. Chorea is most prominent in the early stages of the disease while other movement disorders, such as dystonia, bradykinesia and rigidity, become more prominent as the disease progresses. The first intervention in mild chorea should always be to discontinue drugs that have the potential to exacerbate symptoms. Examples include piracetam and dopamine agonists, such as levodopa, amantadine and cabergoline. There are no published data pertaining to psychotropic drugs that can increase dopaminergic neurotransmission, such as aripiprazole and venlafaxine. These drugs should be considered as potential causes of exacerbations in dyskinetic movements and their use is probably best avoided, at least as first-line treatments. Adverse effects, including sedation, insomnia, pseudoparkinsonism, depression, anxiety and akathisia. Serious side effects, such as neuroleptic malignant syndrome and dysphagia leading to death from aspiration pneumonia, have also been reported. The decision to treat chorea with tetrabenazine must be balanced against the added risk of developing parkinsonism and depression, both of which are already common in HD.

Levetiracetam also showed some benefit in a patient’s best interest. If choreiform movements are more rapid, it is unclear if higher doses of atypical antipsychotics may be required to achieve an optimal response in chorea, but these should be considered if lower doses produce a suboptimal response. Several case reports suggest that moderate doses of risperidone (6mg) are needed to have a significant effect on motor disability. However, other case reports support lower doses (1mg twice daily) of risperidone in the treatment of chorea. Tetrabenazine, a dopamine-depleting drug, is effective in treating moderate to severe choreiform movements. Efficacy is supported by double-blind placebo-controlled crossover trials. However, up to 80 per cent of patients experience adverse effects, including sedation, insomnia, pseudoparkinsonism, depression, anxiety and akathisia. Serious side effects, such as neuroleptic malignant syndrome and dysphagia leading to death from aspiration pneumonia, have also been reported. The decision to treat chorea with tetrabenazine must be balanced against the added risk of developing parkinsonism and depression, both of which are already common in HD.

For personal use only. Not to be reproduced without permission of the editor (permissions@pharmj.org.uk)
to those used in Parkinson’s disease, although patients with HD usually respond less well.

Anticholinergics, levodopa and dopamine agonists are used but these drugs all have the potential to worsen chorea and precipitate psychosis. Dosage adjustment is often required to obtain the best balance between efficacy and side effects. Muscle relaxants, such as diazepam can also be effective in treating rigidity and are usually well tolerated, although aspiration secondary to sedation is a potential risk.

Psychosis, depression and dementia

It is estimated that between 23 and 73 per cent of patients with HD develop depression, psychosis or dementia during the course of their illness.12 Such patients are likely to be referred to a psychiatrist for advice and management but few psychiatrists see enough cases to build up expertise in this area of practice.

Psychosis

Approximately 23 per cent of patients with HD will develop psychotic symptoms.13 These tend to present early in the course of the illness and ameliorate as cognitive function deteriorates. Early neuropsychological changes include atrophy of the medial caudate. Neurotransmitter changes are complex but include a reduction in gamma-aminobutyric acid and acetylcholine and an increase in glutamatergic activity. The net result appears to be a hyperdopaminergic state.14 It follows that antipsychotic drugs are likely to be effective. Case reports and case series show the benefit of individual agents but no randomised controlled trials have been conducted.

The use of antipsychotic drugs in HD psychosis is complicated by the risk of exacerbating the underlying movement disorder. Some evidence supports the efficacy of typical antipsychotics, particularly haloperidol, when the HD is mild to moderate.15 As the disease progresses, typical antipsychotics tend to be poorly tolerated, due to dystonia and parkinsonism.16 Atypical antipsychotics tend to be used at this point although the evidence to support their efficacy and tolerability is also limited to case reports and series. Members et al.17 compared risperidone with haloperidol in three patients with HD and found that risperidone was comparable to haloperidol in two patients (and superior to haloperidol in the other patient) in reducing both dyskinesia and psychotic symptoms. Additional case reports support the efficacy of risperidone,18 quetiapine19 and amisulpride,20 although extrapyramidal side effects can be problematic with all of these drugs.

Depression

Depression is common in HD. Estimates of the point prevalence range from 9 to 63 per cent but the true rate is probably between 40 and 50 per cent.21 The suicide rate is four to six times higher than in people without HD.22 Suicide among patients diagnosed with HD tends to occur early in the course of illness. It has been suggested that this reflects the occurrence of suicide before motor skills decline to the point where the person is no longer physically able to take his or her own life.23

There are no randomised controlled trials to guide treatment choice. Case reports of successful treatment with tricyclic antidepressants (TCA’s), monoamine oxidase inhibitors (MAO I), mirtazapine,23 and selective serotonin reuptake inhibitors (SSRI) have been published. Patients with HD seem to be particularly prone to the side effects that are commonly associated with the TCAs, namely sedation, falls and anticholinergic-induced cognitive impairment. MAOIs are also potentially problematic because they can worsen choreiform movements, possibly through their effects on dopamine neurotransmission. There has been almost no new primary literature in this area over the past 20 years. The use of SSRIs is tended to be favoured because these drugs may also reduce the irritability and apathy that are commonly seen in HD.24 The choice of SSRIs is not affected by the patient having HD.25 Electroconvulsive therapy seems to be relatively well tolerated in HD patients.26 Reviews state that lithium is best avoided; clinical experience suggests that response is likely to be poor and that toxic effects can be particularly problematic. There is no primary literature.

Dementia

Almost all patients with HD develop subcortical dementia. Patients in the later stages of the disease tend to have profound dementia.27 No robust data could be found on the use of cholinesterase inhibitors to treat dementia in HD. There are, however, some data to suggest that galantamine can be used to regulate mood and behaviour, thus improving some of the psychotic features associated with HD. It is thought that this occurs through allosteric modulation of nicotinic acetylcholine receptors.28 There is no reason to suspect that the efficacy and tolerability of cholinesterase inhibitors would be any different in HD patients than in those with Alzheimer’s disease.

Summary

With the exception of tetrabenazine which is used to treat choreiform movements, no placebo controlled or randomised controlled trials were identified. The literature consists entirely of case reports and case series. Most are old and treatment is largely empirical. There is, therefore, poor evidence on which to base decisions for the management of psychiatric symptoms in patients with HD.

Systematic studies are required before any definite conclusions can be drawn as to the efficacy of various approaches. However, this is unlikely to happen owing to the small number of patients diagnosed with HD. Clinicians who treat patients with HD should be encouraged to publish reports of both positive and negative outcomes to increase the primary literature base in this neglected area of care.

References

13. Mateo D, Munzo-Blanco J, Gimenez-Roldan S. Neuropsychiatric features associated with HD. It is thought that this occurs through allosteric modulation of nicotinic acetylcholine receptors. There is no reason to suspect that the efficacy and tolerability of cholinesterase inhibitors would be any different in HD patients than in those with Alzheimer’s disease.

Summary

With the exception of tetrabenazine which is used to treat choreiform movements, no placebo controlled or randomised controlled trials were identified. The literature consists entirely of case reports and case series. Most are old and treatment is largely empirical. There is, therefore, poor evidence on which to base decisions for the management of psychiatric symptoms in patients with HD.

Systematic studies are required before any definite conclusions can be drawn as to the efficacy of various approaches. However, this is unlikely to happen owing to the small number of patients diagnosed with HD. Clinicians who treat patients with HD should be encouraged to publish reports of both positive and negative outcomes to increase the primary literature base in this neglected area of care.

References

13. Mateo D, Munzo-Blanco J, Gimenez-Roldan S. Neuropsychiatric features associated with HD. It is thought that this occurs through allosteric modulation of nicotinic acetylcholine receptors. There is no reason to suspect that the efficacy and tolerability of cholinesterase inhibitors would be any different in HD patients than in those with Alzheimer’s disease.