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REVIEW ARTICLE

Evidence-Based Review on Symptomatic Management of Huntington's Disease

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ABSTRACT

Huntington's disease (HD) is a neurodegenerative disorder characterized by motor, behavioral, and cognitive impairments and significant impacts on patient quality of life. This evidence-based review, conducted by the Korean Huntington Disease Society task force, systematically examines current pharmacological and nonpharmacological interventions for symptomatic management of HD. Following PRISMA guidelines, databases were searched for studies up to August 2022 that focused on 23 symptoms across four domains: motor, neuropsychological, cognition, and others. This review provides a comprehensive and systematic approach to the management of HD, highlighting the need for more high-quality clinical trials to develop robust evidence-based guidelines.

Keywords Huntington's disease; Review; Pharmacological; Non-pharmacological.

INTRODUCTION

Huntington's disease (HD) is a neurodegenerative disorder caused by an autosomal dominant trinucleotide repeat expansion in the huntingtin gene, which is located on chromosome 4p16.3. The prevalence rate is estimated to be approximately 2.7 per 100,000 worldwide; however, it has been consistently reported to be lower (0.4 cases per 100,000) in the Asian population.[1] A recent report suggested that the 10-year prevalence in South Korea is estimated at approximately 2.2 per 100,000 people on the basis of national health insurance system registration data.[2]

The signs and symptoms of HD are known to manifest in a triad of motor disturbances, behavioral/psychiatric symptoms and cognitive impairment.[3] The mean age of onset is approximately 35–45 years, which is inversely correlated with the number of CAG repeats in the HD gene. Compared with other genetic disorders, HD has relatively greater penetrance.[4] Progressive neurological abnormalities tend to manifest at a younger age with successive generations, a phenomenon known as anticipation. The overall survival duration for HD patients is estimated to range from 15 to 25 years following the onset of motor symptoms, including in a study from South Korea.[5,6] Given that onset usually occurs in early middle age, the disease inevitably leads to a significant reduction in quality of life for patients and their families.[7]

Despite more than a century of research since its initial description, HD remains an untimately fatal disease with no cure.

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Moreover, comprehensive documentation of symptomatic treatments targeted for troublesome motor, behavioral and cognitive symptoms is lacking. Importantly, the available treatment options are not equally accessible in different regions around the globe. This dearth of evidence may contribute to variations in care, which is predominantly reliant on clinical experience rather than scientific evidence. In a recent survey conducted by the Korean Huntington Disease Society (KHDS) task force, many physicians (36.7%) stated that the lack of treatment guidelines and evidence-based review of the available treatment options in South Korea is one of the huddles in managing HD patients (Supplementary Figure 1 in the online-only Data Supplement).

In recent years, there has been a surge in clinical trials and studies evaluating both pharmacological and nonpharmacological interventions for various clinical problems associated with HD. On the basis of this need, the KHDS task force for the treatment of HD was established, and this study was a systematic review of up-to-date evidence on the symptomatic management of HD, incorporating both pharmacological and nonpharmacological treatments.

MATERIALS & METHODS

The KHDS task force for the systematic review was organized in August 2022. The members of the task force were appointed by the executive committee of the KHDS. This systematic review follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[8]

Search strategy

We searched PubMed, Web of Science, Embase, KoreaMed, Scopus and the Cochrane Review for papers that had been published before August 2022. We selected 22 symptoms that were classified into 4 major HD-related symptom domains: motor, neuropsychological, cognition, and others. The detailed list of 22 symptoms are Motor (Chorea, Dystonia, Swallowing difficulty, Gait and balance, Rigidity, Myoclonus and Bruxism), Behavior (Apathy, Depression, Obsession, Irritability, Akathisia, Anxiety, Suicidal idea or attempt and Sexual disorders), Cognition (Dementia, Hallucination and psychosis), and Others (Sleep, Pain, Weight loss, Hypersalivation and Respiratory dysfunction). The search terms were chosen on the basis of a list of symptoms and were customized depending on the symptoms (For example, suicidal idea, ALL = [huntington] OR ALL = [huntington's] OR ALL = [huntington's disease]) AND (ALL = [suicide] OR ALL = [suicidal] OR ALL = [suicidal ideation]). We included clinical trials, observational studies, case series and case reports for 22 symptoms that were published from 1994 to 2022. However, for chorea, we excluded single case reports. After the identification phase, we removed duplications, and the list of articles entered the screening phase. The titles and abstracts of the

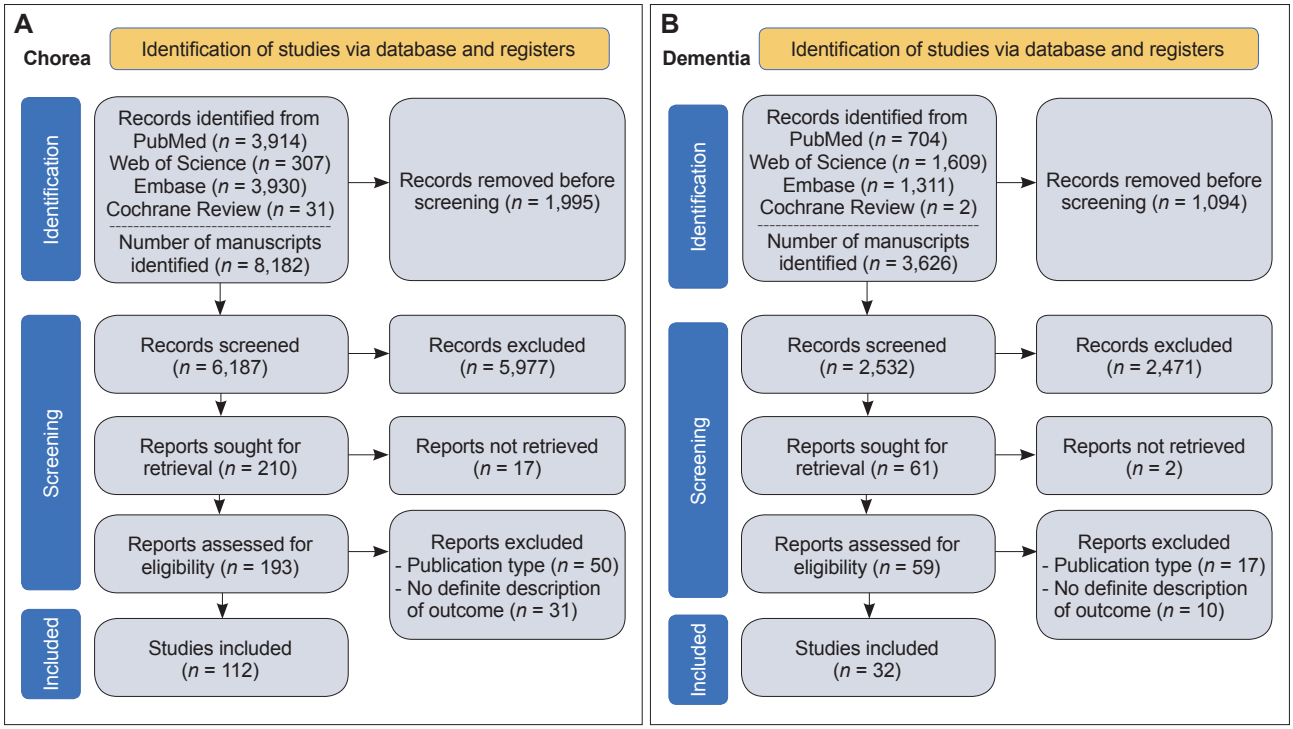

Figure 1. PRISMA flow diagram of studies identified for chorea (A) and dementia (B) in Huntington's disease. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

articles were manually reviewed for exclusion. The exclusion criteria included animal studies, nonmedical articles, and non-English articles. All the articles were subsequently sought for retrieval, and the reports that were unable to be retrieved online were excluded. Finally, reports were assessed for eligibility. In this phase, review articles and studies without reported outcomes were excluded. The flowcharts of each symptom were drawn with the PRISMA flowchart and are shown in Figure 1 and Supplementary Figures 2-23 (in the online-only Data Supplement). The availability of the treatment options in South Korea as of July 2024 is noted in Supplementary Figures 2-23 (in the online-only Data Supplement). Owing to the limited space for references, some of the references for Class U studies are provided in the Supplementary Material (in the online-only Data Supplement).

Efficacy evaluation

As we reviewed studies, including case series and case reports, we used the AAN classification of evidence.[9] From the criteria, we labeled every article with Classes I, II, III and IV as defined in the criteria. We then marked the level of evidence for each treatment option as levels A, B, C and U.

Method for reaching a consensus

The initial manuscript by the task committee was constructed and sent to the clinical experts of HD, who were chosen by the executive committee of the KHDS. Recommendations and expert opinions were obtained in two rounds and were met with consensus by the entire task force.

RESULTS

Motor symptoms

Chorea

Chorea, characterized by involuntary, irregular, random, and unsustained movements, is the most apparent and cardinal motor feature of HD, and the current consensus guidelines recommend that pharmacological interventions should be considered when the patient experiences functional discomfort or suffering from chorea.[10-12]

Selective vesicular monoamine transporter 2 inhibitors

Tetrabenazine was assessed in a 12-week Class I randomized clinical trial as antichoreic therapy in 84 study patients.[13] This TETRA-HD study demonstrated that tetrabenazine effectively ameliorates chorea and is well tolerated.[14] Fifty HD patients treated with tetrabenazine had a significant reduction in the mean difference (±standard deviation) in the total maximal chorea score on the Unified Huntington's Disease Rating Scale (UHDRS) compared with 34 placebo-treated patients (-5.0 ± 0.5 vs. -1.5 ± 0.7), with a treatment difference of -3.5 (95% confidence interval [CI] -5.2 to -1.9; $p < 0.0001$).[14] In addition, a Class II randomized clinical study evaluating chorea after tetrabenazine withdrawal reported that the discontinuation of tetrabenazine was significantly related to reemergent chorea.[15] Clinicians might offer tetrabenazine to reduce chorea in HD patients (Level B), but there are safety concerns about the use of tetrabenazine, which can cause depression, parkinsonism, neuroleptic malignant syndrome and prolonged QT intervals.[13-17] When patients have poorly controlled depression or suicidality, tetrabenazine is contraindicated.[13-19] Recently, two Class I randomized controlled studies examined deutetrabenazine and valbenazine for chorea.[20,21] In a 12-week randomized controlled trial (RCT) involving 90 patients with HD, deutetrabenazine treatment resulted in a reduction of 4.4 units from the baseline in the UHDRS, the total maximal chorea score, compared with a reduction of 1.9 units on placebo treatment (treatment difference -2.5, 95% CI -3.7 to -1.3; $p < 0.001$).[20] A 12-week, 128-subject KINECT-HD study revealed that UHDRS total maximal chorea scores significantly decreased by -4.6 in 64 patients receiving valbenazine vs. -1.4 for placebo (treatment difference -3.2, 95% CI -4.4 to -2.0; $p < 0.0001$).[21] Both new-generation vesicular monoamine transporter 2 (VMAT2) inhibitors have demonstrated effectiveness on chorea and can be used as first-line antichoreic therapies in HD (Level B), particularly when patients are intolerant to tetrabenazine.[19-22] However, new-generation VMAT2 inhibitors are not available in South Korea as of January 2024.

Antipsychotic drugs

Antipsychotics are currently used as first-line monotherapy or second-line off-label alternatives to suppress HD chorea by a considerable number of respondents in several opinion surveys of HD experts.[18,23-25] Clozapine has shown little benefit in reducing HD chorea in Class II clinical trials[26] and single-arm observation studies[26] (Level U). In a small class III crossover trial, aripiprazole had a beneficial effect on China that was comparable to that of tetrabenazine.[27] Other atypical antipsychotic drugs (APDs), including olanzapine and risperidone, have been studied only in small uncontrolled clinical trials (Level U).[28-30] However, longitudinal, observational data from an Enroll-HD multicenter study with 1,612 patients revealed that olanzapine and risperidone appeared to have antichoreic efficacy comparable to that of tetrabenazine.[29,31] Overall, although limited in evidence, several studies support the effect of APDs on choreic manifestations in patients with HD.

Other pharmacological agents

Amantadine is a weak, noncompetitive N-methyl-D-aspartate (NMDA) antagonist. For Huntington's chorea, one Class II trial involving acute intravenous (IV) amantadine challenge followed by chronic oral amantadine for 1 year and another 2-week Class II crossover clinical trial involving oral amantadine showed that amantadine had a modest effect on reducing the incidence of chorea.[32,33] However, the other 2-week Class I crossover trial using oral amantadine showed contrasting results, with insignificant effects on objective measures, although some patients reported subjective improvement in China.[34] Taken together, the data are inconclusive in terms of supporting or refuting the regular use of oral amantadine for controlling chorea in HD patients[32-36] (conflicting Class I and II studies, Level U).

Apomorphine is a nonselective dopamine receptor agonist that has been used to attenuate motor complications in Parkinson's disease (PD) patients.[37] One small class III clinical trial of acute administration of subcutaneous apomorphine revealed a favorable antichoreic effect.[38] Apomorphine resulted in a significant decrease in the chorea at rest (-50.00%, $p < 0.01$) and the chorea during voluntary movement score (-30.18%, $p < 0.05$) of the quantified neurological examination from the baseline, whereas no significant change was found after placebo.[38] Another 5-day Class II crossover controlled study involving continuous subcutaneous apomorphine injection (CSAI) also revealed a significant and sustained reduction in chorea in HD patients.[39] The abnormal involuntary movement scale score was significantly lower in patients receiving apomorphine injection (-34.4% ± 14.6%, $p < 0.0001$) than in those receiving placebo (-0.20% ± 3.7%).[39] These data suggest that apomorphine may be effective for the short-term management of chorea in HD patients (Level C); however, the long-term antichoreic efficacy of apomorphine, including CSAI, is unknown.[39,40]

Multiple RCTs of ethyl-eicosapentaenoic acid (ethyl-EPA)[41-44] and latrepirdine[45,46] have failed to show benefits in chorea patients with HD (Level A). Coenzymes Q10,[47,48] creatine,[49-54] pepinemab[55] and PBT2[56] were also not effective for chorea in HD (Level B). (-)-OSU6162,[57] AFQ-056 (mavoglurant),[58] atomoxetine,[59] bupropion,[60] cannabidiol oral spray,[61] citalopram,[62] donepezil,[63,64] fluoxetine,[65] lamotrigine,[66] OPC-14117,[67] SBT-020,[68] selisistat,[69] and nabilone[70,71] did not show antichoreic efficacy and are possibly ineffective for reducing chorea in HD (Level C). There are insufficient or conflicting data to draw recommendations on HD chorea about riluzole, cysteamine IONIS-HTTRx (tominersen), rivastigmine, minocycline, memantine, valproic acid, levetiracetam, ketamine, idebenone, nilotinib, proglumide, rilmenidine, triheptanoin, remacemide, pridopidine and cysteamine (Level U, Supplementary Material in the online-only Data Supplement). Data are also inadequate to support or refute cell-based therapy, including fetal cell transplantation and gene therapy using ciliary neurotrophic factor on chorea in HD (Level U, Supplementary Material in the online-only Data Supplement).

Physical therapy and dietary interventions

Physical therapies are possibly effective for reducing HD-associated chorea in two Class II clinical trials[72-74] (Level C). Additional Class III clinical trials and case reports further indicate that physical therapy and rehabilitation can improve chorea in HD patients.[75-81] However, while two longitudinal observational studies[82,83] have explored dietary interventions in HD patients, there is insufficient evidence to support dietary interventions for chorea (Level U).

Brain modulation therapy

Case-based studies in multisensory stimulation, transcranial magnetic stimulation (TMS), pallidal deep brain stimulation (DBS) and pallidothalamic tractomy have shown improvements in chorea in HD patients (Level U, Supplementary Material in the online-only Data Supplement). However, additional well-designed clinical trials are needed to confirm their effects.

Summary

VMAT2 inhibitors (tetrabenazine, deutetrabenazine and valbenazine) are effective pharmacological options for treating chorea in HD. The use of apomorphine, amantadine and atypical antipsychotics requires careful consideration due to limited evidence. Nonpharmacological approaches, including exercise programs and physical therapy, may show potential benefits. The treatment evidence for chorea in HD patients is summarized in Table 1.

Korean HD expert comment

Although VMAT2 inhibitors are the most reliable treatment option, tetrabenazine is the only available drug in South Korea. However, fewer than 10% of HD patients in South Korea are prescribed this drug, possibly due to poor accessibility and high cost.[2] New-generation VMAT2 inhibitors (deutetrabenaine and valbenaine) have not yet been introduced in South Korea. Notably, deutetrabenazine is reported to be relatively safe in terms of QT prolongation (see related comment in Depression section).[84] VMAT2 inhibitors should be cautiously prescribed for patients with severe depression or suicidal tendencies, as they may worsen these conditions. Atypical antipsychotics may be considered as a second-line off-label alternative treatment. The importance of exercise and physical therapies in HD patients has been overlooked, which warrants a well-designed clinical trial in South Korea.

Table 1. Summary of the treatment evidence targeting chorea in Huntington's disease

Effective					No benefit					Conflicting				
Class	I	II	III	IV	Class	I	II	III	IV	Class	I	II	III	IV
					Level A					Level U				
					Ethyl-EPA	3	1			Riluzole	1	1		1
					Latrepirdine	2				Cysteamine	1			2
Level B					Level B					Rivastigmine		1	1	
Tetrabenazine	1	1		3	Pepinemab	1				Amantadine		4		1
Valbenazine	1				Coenzyme Q10	1	1			Minocycline		2		3
Deutetrabenazine	1			1	Creatinine	1	2	1	2	Clozapine		1		1
					PBT2	1				Remacemide		2		
										Pridopidine	3	1	1	3
Level C					Level C									
Apomorphine		1	1		Bupripion		1							
Physical therapy		4	3	3	Cannabidiol oral spray		1							
					Citalopram		1							
					Donepezil		1		1					
					Fluoxetine		1							
					Lamotrigine		1							
					OPC-14117		1							
					SBT-020		1							
					Nabilone		1							
					(-)-OSU6162		1							
					AFQ-056		1							
					Atomoxetine		1							

Therapies with undetermined evidence (U) for effective or no benefit domain were excluded from this table.
EPA, eicosapentaenoic acid.

Dystonia

Whereas chorea is the most widely recognized involuntary movement in HD, dystonia is also frequently reported. The majority of HD patients experience dystonia to some degree, whereas the dystonia of HD patients manifests as a variety of movements and postures that are not typical of what is most common in idiopathic child-onset torsion dystonia (e.g., foot inversion) or adult-onset focal dystonia (e.g., blepharospasm, torticollis, writer's cramp), and patients are rarely aware of their dystonic movements or postures.

One Class II RCT demonstrated that deutetrabenazine is possibly effective in improving dystonia in patients with HD (Level C),[20] whereas other pharmaceutical management methods, including riluzole,[85] fluoxetine,[65] minocycline,[86] and ethyl-EPA,[42] are possibly ineffective (Level C). There is insufficient evidence to assess the efficacy of pridopidine and IV administration of amantadine and cannabinoids on dystonia in HD patients (Level U, Supplementary Material in the online-only Data Supplement). Data are inadequate for assessing the efficacy of surgical interventions, including pallidal DBS, internal globus pallidotomy, and fetal neural transplants (Level U, Supplementary Material in the online-only Data Supplement). There is also insufficient evidence to assess the efficacy of noninvasive brain stimulation, namely, direct current stimulation (Level U, Supplementary Material in the online-only Data Supplement).

Summary

Deutetrabenazine may be effective for dystonia in HD patients, but there is limited evidence supporting the use of other medications (Table 2).

Korean HD expert comment

Tetrabenazine may be considered, despite limited evidence, depending on its availability. In cases of troublesome dystonia, typical antidystonia medications (anticholinergics, clonazepam, baclofen, etc.) can be used in HD patients, although there is a lack of evidence. For severe dystonic spasms in young-onset patients with advanced stages of HD, gabapentin or pregabalin—alpha-2 delta ligands—may relieve symptoms despite the lack of sufficient evidence in HD. Notably, higher doses than those typically used for pain relief may be needed.

Gait and balance

Gait impairment in HD patients can be influenced by con-

Table 2. Summary of the treatment evidence targeting dystonia and gait in Huntington's disease

Effective					No benefit					Conflicting				
Class	I	II	III	IV	Class	I	II	III	IV	Class	I	II	III	IV
Dystonia														
Level C					Level C					Level U				
Deutetrabenazine		1			Riluzole		1		1	Pridopidine		2		
					Fluxetine		1							
					Minocycline		1							
					Ethyl-EPA		1							
Gait														
Level B										Level U				
Pridopidine	1									Gpi DBS				4
Level C														
Physical therapy		1	1	12										

Therapies with undetermined evidence (U) for effective or no benefit domain were excluded from this table.
EPA, eicosapentaenoic acid; Gpi, globus pallidus interna; DBS, deep brain stimulation.

comitant chorea or impaired balance. As a result, HD patients may experience frequent falls and become physically dependent. Physical therapy or exercise has been studied in the context of gait impairment in HD patients, with home-based exercise showing some improvement in an RCT and a single-blind controlled trial (Level C).[73,87] Gait improvement after physical therapy or exercise was also observed in 11 out of 12 case series.[75,88-97] One study did not show improvement in gait after exercise, but this study only included short-duration exercise (20 minutes on a treadmill), which might have been insufficient.[79]

In terms of pharmacological treatment, RCTs have been conducted using pridopidine, a dopaminergic stabilizer. While there was no significant change in the total motor score, subitem scores of gait and balance showed improved (Level B).[98] Conventional neuroleptics generally improve chorea, but they do not have a beneficial effect on gait (Level U, Supplementary Material in the online-only Data Supplement). Gait and balance improvements were observed in some patients treated with tetrabenazine and olanzapine (Level U, Supplementary Material in the online-only Data Supplement). Two case reports revealed improved parkinsonism, including gait and balance, when levodopa and amantadine (Level U, Supplementary Material in the online-only Data Supplement) were used. Other case reports revealed improved gait or balance after the use of zotepine, bromocriptine, and caryolanemagnolol (Level U, Supplementary Material in the online-only Data Supplement).

There is insufficient evidence to assess the efficacy of DBS in improving gait in HD patients (Level U). In one study, improvements in gait and balance, along with chorea, were observed following DBS,[99] whereas in three studies, there was no gait improvement after DBS.[100-102] After DBS, some patients experience worsened gait and bradykinesia as side effects.[102]

Summary

Home-based exercise and pridopidine may be effective in reducing gait and balance impairment in HD patients. There is insufficient evidence to recommend the use of any medication to improve gait impairment in HD patients (Table 2).

Korean HD expert comment

In patients with severe chorea, particularly in the legs, antichoreic medications can help improve gait. In some patients with predominant parkinsonian symptoms, small-dose levodopa (mostly 450 mg/day or less) can help improve bradykinesia and short-step shuffling gait.

Parkinsonism

Parkinsonism can manifest in the later stages of adult-onset HD as the predominant akinetic rigidity or as the Westphal variant in juvenile cases.[103] Parkinsonism may also occur as drug-induced parkinsonism caused by medications such as tetrabenazine,[104,105] neuroleptics[106] and levetiracetam.[107] Additionally, there have been reports of concomitant PD and HD.[108]

There are only case-based reports that have assessed the efficacy of treatment in improving parkinsonism in HD patients. In adult cases, studies have reported that levodopa (200 mg/day to 600 mg/day),[109] amantadine, a combination of levodopa/amantadine and rasagiline improved parkinsonism in HD patients (Level U, Supplementary Material in the online-only Data Supplement). A case series showed that nabilone improved parkinsonism induced by tetrabenazine in HD patients.[110] In juvenile patients, five childhood HD patients with rigidity and bradykinesia, rigidity and hypokinesia improved when levodopa was used at doses ranging from 75 mg/day to 600 mg/day (Level U, Supplementary Material in the online-only Data Supplement). Additionally, a patient who did not respond to levodopa

150 mg/day showed improvements in rigidity and gait when treated with pramipexole ranging from 0.27 mg/day to 1.08 mg/day (Level U, Supplementary Material in the online-only Data Supplement). Pyridostigmine did not effectively improve rigidity (Level U, Supplementary Material in the online-only Data Supplement).

Summary

Antiparkinsonian medications, including levodopa, dopamine agonists, amantadine and/or rasagiline, may be beneficial for parkinsonism in HD patients.

Korean HD expert comment

In advanced cases with concomitant rigidity and dystonia, antidystonic medications can be first attempted, followed by small-dose levodopa. Other antiparkinsonian medications, including dopamine agonists, may be attempted in patients with parkinsonism.

Myoclonus

Myoclonus is a relatively uncommon feature of late-onset HD but can present with tremors. In the juvenile form of HD, nonepileptic myoclonus may present as a dominant symptom that may impair the functional capacity and activity of daily living. There are case series and reports showing benefits from valproate, clonazepam, or their combination (Level U, Supplementary Material in the online-only Data Supplement). Piracetam and haloperidol/valproate combinations have been reported in case reports showing some improvement in myoclonus (Level U, Supplementary Material in the online-only Data Supplement). These symptomatic medications improve the clinical outcome when they are used appropriately to balance risk and benefit, especially for elderly individuals, who are monitoring for potential somnolence and falls.

Summary

Valproate and clonazepam might be beneficial in relieving myoclonus in HD patients.

Korean HD expert comment

Because myoclonus is relatively rare in adult-onset HD, there is a lack of research on pharmacological treatments targeting myoclonus in HD. However, fast chorea can sometimes be mistaken for myoclonus. Recurrent sudden vomiting can be caused by myocloniform diaphragmatic hyperkinesia. Although evidence is limited, levetiracetam, valproic acid and clonazepam may be used to manage myoclonus symptoms.

Akathisia

Akathisia is defined as the inability to remain still and is a neuropsychiatric syndrome that is associated with psychomotor restlessness. Akathisia may be a side effect of antichoreic medications, including the VMAT2 inhibitor tetrabenazine[13,14,111,112] or deutetrabenazine.[20,22,113] Most cases are mild, with a prevalence ranging from 6%–14%. Cessation of responsible medications may result in symptom remission. There are reports of akathisia with a cariprazine trial[114] for mood and cognition and M6 nabilone[110] for the treatment of resistant motor symptoms in HD patients.

Summary

Akathisia may present as a side effect of antichoreic medications in HD. Cessation of responsible medications can lead to remission of akathisia.

Korean HD expert comment

Medication-induced akathisia can be closely monitored and controlled.

Behavioral symptoms

Apathy

Apathy is characterized by a quantifiable reduction in goal-directed behavior,[115] which becomes prevalent in the advanced stages of HD. One RCT and 6 therapeutic intervention studies were included to evaluate the evidence of available therapies for apathy in HD patients.[60,114,116-120] One Class II RCT demonstrated that bupropion is possibly ineffective in improving apathy in patients with HD[60] (Level C), whereas other pharmaceutical management methods, including rasagiline, cariprazine, cannabinoids, and risperidone, also have insufficient evidence for managing apathy (Level U, Supplementary Material in the online-only Data Supplement). Data are inadequate for assessing the efficacy of contemporary dance practices (Level U) or time-restricted ketogenic diets (Level U, Supplementary Material in the online-only Data Supplement).

Summary

There is no available evidence-based therapy for managing apathy (Table 3).

Korean HD expert comment

There are no treatments specifically effective for apathy in HD. In patients with unique cognitive features associated with apathy, cognitive enhancers such as choline esterase inhibitors may be used, as in other degenerative diseases. In some patients with concomitant depression, antidepressants may be beneficial. Clini-

Table 3. Summary of the treatment evidence targeting behavioral symptoms in Huntington's disease

Effective					No benefit				
Class	I	II	III	IV	Class	I	II	III	IV
Apathy									
					Level C				
					Bupropione		1		
Depression									
Level B									
Citalopram	1								
Suicidal ideation									
					Level C				
					SRX246		1		
					Laquinimod		1		
Irritability									
Level C									
Aripiprazole		1		2					
Anxiety									
					Level C				
					Pridopidine		1		

Therapies with undetermined evidence (U) for effective or no benefit domain were excluded from this table. There were no treatments classified as having conflicting evidence in this category.

cians may consider reducing the dosage of sedative medications in patients with HD with apathy.[10]

Depression

Depression is a common psychiatric symptom in HD patients and may appear in any stage of the disease, even in the premanifest stage, and affects their ability to perform activities of daily living. One RCT reported a positive effect of citalopram (Level B).[62] Fluoxetine was used to treat nondepressed HD patients and failed to improve functional capacity (Level U).[65] Several case reports have applied venlafaxine, cariprazine and lamotrigine, which are effective in relieving symptoms of depression (Level U, Supplementary Material in the online-only Data Supplement). There are case series regarding electroconvulsive therapy (ECT) and TMS as a treatment for depression, which also have positive effects (Level U, Supplementary Material in the online-only Data Supplement). Finally, some studies have shown the benefit of physical therapy/rehabilitation as a treatment option for depression in HD patients (Level U, Supplementary Material in the online-only Data Supplement).

Summary

Citalopram is likely efficacious for relieving depression in HD patients, whereas there is limited evidence for the effectiveness of other medications, TMS, or physical therapy (Table 3).

Korean HD expert comment

Selective serotonin reuptake inhibitors (SSRIs) can be tried first for moderate to severe depression in HD. Combining SSRIs and antipsychotics requires caution, as it can lead to QT prolongation. Deutetrabenazine can be considered a viable option because of its relative safety regarding QT prolongation.[84] Nonpharmacological therapies such as TMS or transcrinial direct current stimulation (tDCS) are worth studying for depressive symptoms in HD patients.

Suicidal idea or attempt

The incidence of suicidal ideation is estimated to be as high as 19%, and the complete suicide rate in HD patients is reported to be as high as 13%.[121,122] Depression, anxiety, bipolar disorder, antidepressant or anxiolytic use, and a prior suicide attempt at baseline are associated with increased suicidality in HD patients.[123] There were randomized phase 2 clinical trials that showed insignificant results for suicidality with SRX246 (a vasopressin 1a receptor antagonist)[124] and liquinimod (Level C). There are several case report-based pharmacological interventions showing some benefit in terms of suicidality in HD patients treated with mirtazapine, lithium, and olanzapine (Level U, Supplementary Material in the online-only Data Supplement). Several case reports have shown improvements in suicidal ideation with ECT and psychotherapy (Level U, Supplementary Material in the online-only Data Supplement).

Summary

SRX246 and laquinimod did not reduce suicidal ideation. ECT and psychotherapy may reduce suicidal ideation or attempts (Table 3).

Korean HD expert comment

In HD, suicidal ideation can occur from the early stages of the disease and is associated with a higher mortality rate, necessitating close monitoring throughout the disease course.

Obsession

The treatment strategy for obsession in HD patients is similar to that for obsessive–compulsive disorder (OCD) patients.[125] All of the studies targeting HD and obsession have been case reports. Cognitive behavioral therapy (CBT) improved OCD symptoms in one patient,[126] and the use of SSRIs or tricyclic antidepressants such as fluoxetine, clomipramine, and sertraline also led to improvements in OCD symptoms (Level U, Supplementary Material in the online-only Data Supplement). Antipsychotics such as paliperidone reduced aggression, and the use of quetiapine and olanzapine improved OCD symptoms (Level U, Supplementary Material in the online-only Data Supplement).

Summary

There is insufficient evidence for the management of obsession in HD patients, with some case reports of improvement after the use of SSRIs, antipsychotics and CBTs.

Korean HD expert comment

Psychiatric symptoms, including obsession, are rarely observed in isolated symptoms but are commonly accompanied by some cognitive or motor impairment in HD patients, for which physicians have difficulty assessing severity.

Irritability

Irritability is a common and major nonmotor symptom that affects 38%–73% of HD patients. The irritable and aggressive behavior of medical staff, other patients and caregivers results in ineffective treatment for HD. Aripiprazole has been reported to improve irritability (Level C).[127-129] A small double-blind RCT revealed that the combination of lithium and haloperidol was effective but not effective when these drugs were administered separately[130] (Level U). On the basis of case reports and series, buspirone, cannabinoids, olanzapine, risperidone, valproate, sertraline,[131] quetiapine, and lamotrigine have shown positive effects. Conflicting results have been reported with propranolol (Level U, Supplementary Material in the online-only Data Supplement). No definite effect was found with SRX246,[132] donepezil[63] or ECT.[133]

Summary

Aripiprazole and a combination of haloperidol and lithium may be effective for treating irritability in HD patients (Table 3).

Korean HD expert comment

Aripiprazole may be used to manage irritable behavior.

Anxiety

Anxiety is one of the commonly observed nonmotor symptoms in HD patients, although it has been underrecognized in clinical practice. In addition to available therapeutic options for anxiety in the general population (i.e., SSRIs, serotonin-norepinephrine reuptake inhibitors, or anxiolytics), one RCT and 5 therapeutic intervention studies were reviewed to evaluate the evidence of available therapies for anxiety in HD patients.[81,116,134-137] One Class II RCT revealed that pridopidine tended to improve anxiety symptoms, but the changes were insignificant compared with those associated with placebo[136] (Level C). There is insufficient evidence for olanzapine (Level U, Supplementary Material in the online-only Data Supplement). Multidisciplinary rehabilitation intervention and CBT also require further studies to establish sufficient evidence for managing anxiety in patients with HD (Level U, Supplementary Material in the online-only Data Supplement).

Summary

There is insufficient evidence for the management of anxiety in HD patients. Pridopidine and neuroleptics, multidisciplinary rehabilitation and CBT have provided limited evidence for their ability to improve anxiety (Table 3).

Korean HD expert comment

As with other psychiatric symptoms, anxiety is often accompanied by other psychiatric and neurologic symptoms in HD patients. Furthermore, psychiatric symptoms are also linked to neurodegeneration in HD patients, which can progress over time, and nonpharmacological interventions are worth further investigation.

Sexual disorders

The behavioral symptoms of HD often result in a prevalence of sexual disorders of up to 85%.[138] Most sexual disorders are hypoactive disorders that are not frequently managed. In the case of hypersexuality in HD, behaviors should be controlled. There is limited evidence with case reports for the use of haloperidol, leuprolide acetate, cyproterone and medroxyprogesterone (Level U, Supplementary Material in the online-only Data Supplement).

Summary

There is insufficient evidence to recommend any medication to manage hypersexuality in HD patients.

Korean HD expert comment

Sexual disorders in HD patients are often overlooked in neurologic clinics, but they need to be regularly monitored.

Cognition

Dementia

Cognitive impairment is one of the major nonmotor symptoms of HD, with behavioral and motor symptoms. The earliest change is characterized as psychomotor slowing, which may be reveled at the premanifest stage[139] and progresses over time. Executive and attention dysfunction is characteristic of HD, which may contribute to difficulty in multitasking.[140] Emotional processing and memory are also significantly impaired in HD patients.

However, the majority of clinical trials have failed to show a benefit in cognitive function in HD patients. Several RCTs with pridopidine have targeted the cognitive features of HD but have

shown no effect[98,141,142] (Level A). A single RCT with donepezil[64] did not significantly improve cognition in HD patients (Level B). RCTs with citalopram,[62] atomoxetine,[59] fetal striatal grafting and cannabinoids (sativex)[61] failed to show any benefit (Level C). Studies with latrepirdine[45,46] and rivastigmine[143,144] have shown conflicting results (Level U). Several case series have shown that multidisciplinary rehabilitation/physical therapies[145,146] improve cognition or stabilize cognitive progression (Level U). Globus pallidus interna (GPi) DBS[147-149] showed nonsignificant or conflicting results for cognition in HD patients (Level U). One small randomized sham-controlled trial using tDCS revealed immediate improvement in working memory function in HD patients without confirmation of long-term benefit[150] (Level U). There was insufficient evidence for the use of cariprazine, memantine, a ketogenic diet and TMS (Level U, Supplementary Material in the online-only Data Supplement).

Summary

Pridopidine, latrepirdine, donepezil, rivastigmine and GPi DBS showed nonsignificant or conflicting results for managing dementia in HD patients (Table 4).

Korean HD expert comment

Cognitive changes in HD patients may not be effectively measured with routine neuropsychological tests. While more studies are needed to elucidate the causes of cognitive impairment in HD patients, nonpharmacological interventions such as noninvasive stimulation, cognitive training or rehabilitation may be worth investigating.

Psychosis and hallucination

Psychotic symptoms, which impair the quality of life of patients and caregivers, are reported to occur in 3%–20% of HD patients.[151] In the juvenile form of HD, psychosis is reported in more than one-third of individuals, with visual hallucination being the most common symptom, followed by auditory hallucinations.[152] Thus, juvenile HD may be misdiagnosed as schizophrenia.[153]

Antipsychotics, including risperidone, olanzapine, aripiprazole and quetiapine, have been reported to be effective on a case-report basis (Level U, Supplementary Material in the online-only Data Supplement). One case report revealed benefits with the addition of reboxetine to antipsychotics. Several studies have reported positive outcomes with clozapine, especially in patients refractory to other antipsychotics (Level U, Supplementary Material in the online-only Data Supplement). Clozapine treatment necessitates regular complete blood count monitoring due to the risk of agranulocytosis. In case reports and series, ECT could improve psychosis in HD patients, including those who are resistant to medication and those in urgent clinical settings (Level U, Supplementary Material in the online-only Data Supplement).

Table 4. Summary of the treatment evidence targeting cognitive and other nonmotor symptoms in Huntington's disease

Effective					No benefit					Conflicting				
Class	I	II	III	IV	Class	I	II	III	IV	Class	I	II	III	IV
Dementia														
					Level A					Level U				
					Pridopidine	3				Latrepirdine	2			
					Level B					Rivastigmine	1	1		
					Donepezil	1				Gpi DBS		1	3	4
					Level C									
					Citalopram		1							
					Atomoxetine		1							
					Fetal striatal grafting		1	1						
					Cannabinoid (sativex)		1							
Sleep														
					Level C									
					Pridopidine		1							
Respiratory function														
Level C														
Home-based respiratory muscle training program		1												

Therapies with undetermined evidence (U) for effective or no benefit domain were excluded from this table.
Gpi, globus pallidus interna; DBS, deep brain stimulation.

Summary

Antipsychotics and ECTs may reduce hallucinations and psychosis in HD patients.

Korean HD expert comment

First-line management of psychosis may involve the administration of antipsychotics. However, antipsychotic use is linked to increased mortality in the neurodegenerative population; thus, cautious prescriptions and close monitoring of adverse events are needed.

Other nonmotor symptoms

Sleep disturbance

Approximately two-thirds of patients with HD suffer from sleep disturbances with various causes and diverse clinical manifestations.[10] In addition to available therapeutic options (i.e., lifestyle modification and hypnotics) in the general population, one RCT and 2 therapeutic intervention studies were included to evaluate the evidence of therapies for sleep disturbance in HD patients.[136,137,154] One Class II RCT failed to show the efficacy of pridopidine for improving sleep disturbance in HD patients[136] (Level C). Quetiapine also has insufficient evidence for treating insomnia in patients with HD (Level U, Supplementary Material in the online-only Data Supplement). Multidisciplinary rehabilitation intervention also requires further studies to establish sufficient evidence for managing sleep disturbance in HD (Level U, Supplementary Material in the online-only Data Supplement). Although the relationship between sleep-disordered breathing and HD is not yet clear, one case report revealed a reduction in apnea and respiratory arousal after continuous positive airway pressure was used (Level U, Supplementary Material in the online-only Data Supplement).

Summary

There is insufficient evidence to recommend therapeutic interventions for sleep disturbance in HD patients (Table 4).

Korean HD expert comment

Disruptions in sleep structures and insomnia need to be systematically studied in HD patients, and more therapeutic trials are needed in the future.

Bruxism

Bruxism, which is characterized by grinding and clenching of the teeth, is a relatively uncommon presentation in HD. After the initial report by Tan et al.[155] in 2000, subsequent cases were reported.[156] The underlying phenomenology is understood as the form of oromandibular dystonia. Bruxism may not respond or worsen despite successful treatment of chorea. The symptoms may accompany dysphagia and worsen with neuroleptics. The only treatment option that is reported to relieve bruxism is botulinum toxin injection[155,157] (Level U). The main injection site was the bilateral masseter muscles, with a total of 60–100 units.

Summary

Botulinum toxin injections have been found to be helpful in improving bruxism.

Korean HD expert comment

Neuroleptics used for chorea can exacerbate bruxism, so if bruxism is severe, adjusting the causative medication may be necessary. Additionally, the use of botulinum toxin injections could be beneficial for treating bruxism.

Hypersalivation

Treatment for hypersalivation includes the use of topical scopolamine, oral glycopyrrolate, and botulinum toxin injections,[158] but there have been no studies specifically targeting patients with HD. There were two cases in which cannabinoids improved hypersalivation, leading to the discontinuation of previously used botulinum toxin A injections (Level U).[118]

Summary

There is insufficient evidence to recommend any therapeutic options for the management of hypersalivation in HD patients.

Korean HD expert comment

This symptom is not common. Pathophysiology studies are needed for severe cases with hypersalivation.

Respiratory muscle function

In an RCT in which home-based respiratory muscle training was conducted for four months, the training group presented increased vital capacity and inspiratory and expiratory pressure (Level C).[159] In a 12-week gym and home walking exercise program, an improvement in the respiratory exchange ratio was observed (Level U).[160]

Summary

Respiratory muscle training and/or exercise may be beneficial for respiratory function in HD patients (Table 4).

Korean HD expert comment

Further studies with respiratory muscle training and rehabilitation exercise are worth being conducted in HD.

Pain

Pain has not been well recognized in HD, with only a few reports described to date.[161] In a large global cohort study, the prevalence of pain was estimated to be 38% in the early stages, which increased as the disease progressed. Furthermore, 26%–29% of HD mutation carriers reported pain interference.[162] Pain in HD may originate from degenerative changes in the central nervous system (including the cortex, subcortex, and spinal cord), degeneration of the peripheral nervous system, and/or associated musculoskeletal problems.[161] However, because cognitive and emotional disturbances can affect the communication ability of HD patients, patients cannot describe their pain symptoms and are therefore often underestimated or neglected.[10] This systematic review did not find any studies reporting effective pain management strategies in HD patients.

Summary

There is no evidence to recommend any therapeutic options for the management of pain in HD patients.

Korean HD expert comment

Physicians need to be alert to pain in HD patients. It has also been suggested that sensitivity to pain and temperature is altered in HD. Even if there is no complaint of pain, physicians need to monitor whether there is any organic damage. Further studies on HD pain are needed.

Weight loss

Weight loss is common in patients with HD at all stages, even in patients who maintain a normal diet.[163] Studies have shown that body mass index (BMI) is significantly lower in individuals with HD than in healthy controls, which is observed from the early stages of the disease.[164] Progressive weight loss is correlated with the number of CAG repeats.[165] Severe weight loss adversely affects daily activities, leading to difficulties in walking, speaking, and swallowing.[166] Several mechanisms have been proposed for weight loss in HD, including an increased metabolic rate due to hypothalamic dysfunction, mitochondrial dysfunction, malnutrition resulting from swallowing difficulties, and increased energy expenditure due to hyperkinetic movements.[167-170]

However, evidence from prospective studies on the symptomatic management of weight loss in HD patients is limited. A single-arm observational study indicated that nutritional support in HD patients did not alter BMI, although it did stabilize some anthropometric variables[82] (Level U). The use of mesoridazine did not result in weight gain; however, the use of antipsychotics, including risperidone, was associated with relatively high BMI among HD patients in a cross-sectional study (Level U, Supplementary Material in the online-only Data Supplement). Case series focusing on in-hospital rehabilitation for HD patients with low BMI have shown improvements in BMI and overall functional recovery (Level U, Supplementary Material in the online-only Data Supplement).

Summary

There is insufficient evidence for the management of weight loss in HD patients. Rehabilitation and nutritional support may help improve weight loss in HD patients.

Korean HD expert comment

Providing dietary support, including a high-protein, high-calorie diet, can help maintain the nutritional status and functional outcomes of HD patients. Timely decisions regarding the use of feeding tubes, such as L-tubes or PEG (percutaneous endoscopic gastrostomy), may be crucial in managing weight loss and preventing fatal malnutrition in HD patients.

Dysphagia or difficulty swallowing

Most patients with HD eventually suffer from dysphagia, and aspiration pneumonia is the leading cause of death.[171] One pilot RCT and 4 therapeutic intervention studies were reviewed to evaluate the evidence of available therapies for swallowing difficulty in HD patients.[134,159,172-174] The impact of pharmacological treatment (i.e., olanzapine) has rarely been studied (Level U). There is also insufficient evidence to assess the impact of rehabilitative strategies, including home-based respiratory muscle training programs, compensatory techniques, and speech therapy, as well as nursing interventions (Level U, Supplementary Material in the online-only Data Supplement).

Summary

There are no proven therapeutic strategies to improve dysphagia in HD patients.

Korean HD expert comment

Dysphagia should be assessed from the early stage of the disease to reduce the medical complications of HD. HD patients may develop parkinsonian features in the advanced stages of the disease. At this stage, patients easily develop dysphagia with continuing antipsychotic (such as haloperidol) treatment for their chorea, for whom discontinuation of the offending drug may improve dysphagia.

DISCUSSION

In this review, we systematically compiled clinical evidence pertaining to various motor and nonmotor symptoms of HD.

Undoubtedly, HD manifests as an enormous spectrum of motor and nonmotor symptoms that significantly impact the quality of life of both patients and caregivers. While curative treatment for HD remains elusive, numerous studies have explored diverse approaches to provide care and comfort for HD patients.

The pharmacological management of motor symptoms, particularly chorea, has garnered support from well-designed RCTs employing VMAT2 inhibitors, which have demonstrated significant improvements in symptoms and overall quality of life. However, the majority of other motor and nonmotor symptoms lack Level A evidence supporting their clinical benefits. The uniqueness of the current systematic review is that we included open-label trials and case series that may show potential therapeutic benefits in HD patients, which have not been systematically examined in prior reviews. By adopting this approach, we revealed that nonpharmacological interventions such as physical therapy have shown some promise by highlighting potential benefits. From this standpoint, we emphasized studies with multidisciplinary approaches that integrate both pharmacological and nonpharmacological strategies in HD.

However, we found that there is a relative scarcity of well-designed double-blind RCTs, with the exceptions of studies on chorea, depression and dementia. The management of symptoms may have to rely on open-label studies, case series, or case reports. Consequently, management strategies for most symptoms lack robust clinical and statistical power. Alternatively, we included comments from Korean HD experts on each segment of this review, contributing practical insights to this systematic review.

Nonetheless, there is no doubt that well-designed RCTs will contribute to clarifying uncertainties and establishing robust evidence-based guidelines. The relative scarcity of well-designed clinical trials stems largely from the rarity of HD, hindering the feasibility of conducting double-blind placebo-controlled trials on large samples.[10] Therefore, establishing and sustaining HD cohorts on a regional basis, not in a single country, is crucial. Unfortunately, the creation of a multicenter international cohort in Asia has been challenging.

Recently, a novel class of drugs has been developed, including antisense oligonucleotides, small interfering RNAs, splicing modulators, and enzyme replacements, with some currently undergoing clinical trials.[175] Although no novel classes of drugs, including antisense oligonucleotides, have yet proven their clinical effectiveness, these new drugs target disease-modifying effects, in contrast with current therapeutics for symptomatic management of HD. Thus, these new drugs hold promise for the future treatment of HD and should be reviewed in a separate article in the future.

In summary, this systematic review by the task force of the KHDS addressed the currently available options for the symptomatic management of HD. We found that many of the neurologic symptoms of HD patients lack robust evidence for effective management, and there is limited accessibility to various treatment options in South Korea. Unfortunately, this review does not address potential curative or disease-modifying therapies that are currently under investigation. Ongoing and forthcoming clinical trials focused on symptomatic management and disease-modifying therapies should be incorporated into future evidence-based reviews. Finally, more clinical trials are needed in this region to establish comprehensive, evidence-based guidelines for the management of HD.

Supplementary Materials

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Conflicts of Interest

The authors have no financial conflicts of interest.

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