

Pridopidine in the pharmacological treatment of Huntington's disease

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The available treatment options for Huntington's disease (HD) are only symptomatic, partly with a limited symptom control and often accompanied by serious side effects. This review summarizes the current management of HD and elucidates why pridopidine might represent a turning point in the treatment of the condition. Pharmacology, clinical evidence, safety and tolerability of the drug will also be addressed. As pridopidine is a member of a new class of compounds, it opens up the field for new treatment strategies that might be more efficient in controlling motor symptoms, with fewer side effects than the treatment options currently available. In a Phase II and III study, pridopidine significantly improved motor functions in Huntington patients with an adverse-event profile comparable to that of a placebo.

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Worldwide there are approximately 100,000 patients suffering from Huntington's disease (HD; more than 30,000 in Europe as well as in the USA/Canada) [101]. Prevalence in the Western Hemisphere is thought to be 6–7 per 100,000. However, an article recently published in *The Lancet* revealed that the prevalence in England and Wales, which is assumed to be comparable to the rest of Europe, must be at least 12.4 per 100,000 of the population [1].

HD is a neurodegenerative, autosomal, dominantly inherited disease, meaning that if a parent is affected, all offspring have a 50% chance of carrying the mutation. With a possible manifestation from infancy to senescence, HD exhibits a mean age of onset of 40, with a progression of 15–20 years [2]. The mutation within the Huntingtin gene on chromosome 4p, leads to a CAG triplet repeat expansion that encodes an expanded polyglutamine stretch. Longer CAG repeats predict earlier onset, accounting for up to 50–70% of variance in age of onset, with the remainder likely to be due to modifying genes and the environment [3].

Clinical features include a triad of cognitive decline, psychiatric disturbances and progressive motor dysfunction such as chorea, dystonia, bradykinesia or incoordination. Though not equally prominent, many patients have substantial cognitive or behavioral disturbances before the onset of diagnostic motor deficits [4]. Individuals might become irritable or disinhibited and unreliable at work; multitasking becomes difficult and forgetfulness and anxiety mount. Eventually, this prediagnostic phase merges with the diagnostic phase, during which time affected individuals show the characteristic motor signs [4].

HD results in profound disablement, complicated by catabolic weight loss, dysphagia and aspiration. The most common causes of death in people with HD are bronchopneumonia and heart disease, with choking, nutritional deficiencies and chronic skin ulcers also associated with mortality [5].

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Current disease management

Currently there is no treatment that is capable of influencing the course of HD. The treatment options are only symptomatic, often with limited symptom control and accompanied by serious side effects, respectively improving one symptom while worsening another. Therefore, non-drug-based measures, such as physiotherapy, speech therapy and psychological treatments are important factors in disease management and should not be trivialized.

Chorea is rarely a disabling symptom in the early stages of the disease; therefore, and due to the possibility of considerable side effects, it should not be treated as long as it does not have any serious impact on quality of life. In any case, physicians and patients must consider individually whether chorea requires treatment. Table 1 gives a synopsis of the results of a review that was published in 2012 and serves as a possible guideline in treating HD chorea [6].

If HD chorea becomes unbearable, clinicians should prescribe tetrabenazine, the only US FDA-approved drug for treating HD chorea, amantadine or riluzole (Level B). If adverse events (AEs) occur, they should be monitored and discussed, particularly depression/suicidality and parkinsonism with tetrabenazine and elevated liver enzymes with riluzole. Clinicians may also prescribe nabilone for modest decreases in chorea (Level C) [6].

Cognitive improvement through pharmacologic interventions remains a considerable treatment challenge for patients and caregivers. Substances that have been investigated for HD-associated cognitive impairment are typically repurposed from Alzheimer's disease and Parkinson's disease and include the cholinesterase inhibitors, rivastigmine and donepezil [7].

In management of behavioral disturbances, benzodiazepine anxiolytics, typical/atypical antipsychotics, selective serotonin reuptake inhibitors, serotonin–norepinephrine reuptake inhibitors and sedatives are all potentially useful [7]. Clinical trials in HD have been conducted with fluoxetine, atomoxetine, venlafaxine and citalopram. While not showing substantial clinical benefits in motor or cognitive function after 4-month fluoxetine treatment (20 mg/day), a slight improvement in other psychiatric symptoms such as agitation was found. Similarly, the norepinephrine reuptake inhibitor atomoxetine had no significant benefit on cognitive, psychiatric or motor functions in 20 patients with mild HD in a 10-week, double-blind, crossover study. In a study of 26 HD patients with major depression, venlafaxine-XR was highly effective, but with frequent adverse effects such as nausea and irritability [8]. Results of a recently completed study investigating effects of citalopram on psychiatric, motor, and executive function among HD patients are awaited.

Disease-modifying strategies aim to slow or stop the course of HD progression. Riluzole, for example, was found to increase HD serum concentrations of brain-derived neurotrophic factor, a protein necessary for the survival of striatal neurons known to be markedly lower in HD patients [7].

Introduction to the compound

Pridopidine, also known as ACR16, was discovered in 1998 and belongs to a group of agents called dopaminergic stabilizers. Carlsson Research (Gothenburg, Sweden), and later the Scandinavian company NeuroSearch (Ballerup, Denmark), had developed pridopidine, until Teva (Petah Tikva, Israel) acquired it in October 2012 and added it to their research pipeline [101].

Pridopidine has been tested in various studies, including the MermaiHD and HART study, which showed significant improvement on motor function, proving

Table 1. Published recommendations for treatment of Huntington's disease chorea.

Treatment (dose)	Effect
Tetrabenazine (up to 100 mg/day)	Very important antichoreic effects
Riluzole (200 mg/day) [†]	Moderate benefits are likely [‡]
Amantadine (300–400 mg/day)	Unknown degree of benefit
Nabilone	For modest decrease [§]
Other substances	
Ethyl-EPA	Likely ineffective Moderate benefit cannot be excluded
Creatine	Likely ineffective Moderate benefit cannot be excluded
Minocycline	Likely ineffective Moderate benefit cannot be excluded
Coenzyme Q10	Likely ineffective Modest benefit cannot be excluded
Donepezil [¶]	Insufficient evidence to make recommendations
Clozapine	Insufficient evidence to make recommendations

[†]100 mg/day not recommended for moderate (2- to <3-point UHDRS chorea change) short-term benefits or for any long-term (3-year) HD antichoreic goals.

[‡]2- to <3-point changes on the UHDRS chorea score.

[§]1- to <2-point changes on the UHDRS chorea score.

[¶]One class I RCT had insufficient precision to support or refute donepezil efficacy for HD chorea.

Ethyl-EPA: Ethyl-eicosapentaenoic acid; HD: Huntington's disease; UHDRS: Unified Huntington's Disease Rating Scale; RCT: Randomized, controlled trial.

Data taken from [6].

positive effects on voluntary and partly on involuntary motor actions.

■ Pharmacology

Mechanism of action

The HD brain exhibits a defective regulation of certain neurotransmitters that are indispensably required to orchestrate movements and execute thoughts.

Although many neuronal systems are affected in HD, dysfunction and subsequent neurodegeneration in the basal ganglia and cortex are the most apparent pathologies [9]. There is massive striatal neuronal cell death in the HD brain, with up to 95% loss of GABAergic medium spiny neurons (MSNs), whereas large interneurons are selectively spared. Furthermore, atrophy affects the cerebral cortex, subcortical white matter and other brain regions, leading to a miscommunication between different parts of the brain [3].

Motor symptoms of HD are associated with abnormalities in dopamine and glutamate transmission within the corticostriatal pathways [10]. In the healthy brain, striato-thalamic output pathways act in balance: while the direct pathway is to ensure performance of voluntary motor functions (dopamine type 1 [D_1] receptor-mediated), the indirect pathway prevents involuntary movements (dopamine type 2 [D_2] receptor mediated) [9].

In manifest HD, progressive degeneration of striatal MSNs weakens output to the direct and indirect pathways, resulting in aberrant functioning of the corticostriatal network. Reduced activity in the direct pathway is hypothesized to lead to impaired ability to perform voluntary motor functions. Conversely, decreased output from MSNs in the indirect pathway is hypothesized to result in reduced inhibition of unwanted movements [102].

Pridopidine belongs to a new pharmacological class of CNS ligands called dopaminergic stabilizers that normalize psychomotor activity in animal models where dopamine and glutamate neurotransmission have been perturbed [102]. By inhibiting the indirect pathway via D_2 receptor antagonization, pridopidine attenuates involuntary movements. This hypothesis is in line with findings from the MermaiHD study that showed that pridopidine reduced dystonia. On the other hand, alleviation of impairments in voluntary motor function is ascribed to the strengthening of glutamate transmission in the frontal cortex via increased synaptic activation of NMDA receptors, which ultimately enhances D_1 receptor stimulation in the striatum. This is also in line with clinical outcomes from the MermaiHD and HART studies that suggested that pridopidine improved gait and hand movements in HD patients [102].

In summary, the psychomotor-stabilizing profile of pridopidine is associated with a shift in dopamine balance from D_2 to D_1 receptor signaling, in combination

with increased activity in corticostriatal NMDA receptor-mediated communication.

What additionally makes pridopidine unique in its mechanism of action is the way it acts on the D_2 receptor.

Pridopidine has been shown to bind to striatal dopamine D_2 receptors *in vivo* and, similar to dopamine D_2 receptor antagonists, lacks intrinsic activity at dopamine D_2 receptors. This factor argues against partial agonism as the underlying mechanism for dopaminergic stabilization [9,11].

By working as a D_2 receptor antagonist, pridopidine prevents dopamine from binding to the receptor for as long as it is bound; but due to its rapid receptor-dissociation kinetics, it only transiently antagonizes dopamine, giving the same occasional opportunities to bind. This accounts for the much lower propensity for extrapyramidal side effects and a lack of sustained prolactin elevation [11].

Box 1 gives an overview of characteristics that differentiate pridopidine from other D_2 antagonists [11–14].

■ Pharmacokinetics

After an oral absorption close to complete, pridopidine is eliminated partly by urinary excretion and partly by hepatic metabolism, primarily via the CYP2D6 pathway. Pridopidine is metabolized in extensive metabolizers (EM) by CYP2D6 to one main inactive metabolite (ACR30), while the contribution from other enzymatic pathways does not seem to be significant. Poor metabolizers on the other hand depend on renal excretion as their main elimination pathway. Renal clearance of pridopidine at steady state ranges from 90 to 116 ml/min, which corresponds well to the glomerular filtration rate [15].

It has been shown that during multiple dose administration, pridopidine can inhibit its own CYP2D6-driven metabolism, meaning that upon repeated dosing, renal elimination becomes a more important elimination pathway than the polymorphic CYP2D6 metabolism. At steady state, poor metabolizers and EMs exhibit comparable exposure due to a reduction in pridopidine elimination in EMs over time. Therefore, there is no need for

Box 1. Pharmacological characteristics of pridopidine.

- No detectable intrinsic activity
- Lower affinity for D_2 receptors
- Preferential binding to activated D_2 receptors (dopamine-bound D_2 receptors)
- Rapid dissociation from D_2 receptors
- D_2 receptor antagonism that is surmountable by dopamine
- Rapid recovery of D_2 receptor-mediated responses after washout

D_2 : Dopamine receptor 2.

Data taken from [11–14].

dose adjustment or genotyping for CYP2D6 metabolizer status when considering long-term treatment [16].

Nevertheless, as a CYP2D6 inhibitor, drug–drug interactions of pridopidine with coadministered CYP2D6 substrates could be expected, and drugs metabolized by CYP2D6 might have to be dosed accordingly [15].

The first study (ACR16C007) that evaluated the efficacy and safety of pridopidine was conducted in 2004 by Carlsson Research. Four years later, the Phase III MermaiHD and Phase IIb HART studies followed, both being continued in an open-label extension (OLE). Subsequently, a meta-analysis of the two studies was performed, enabling data from a large pool of patients to be analyzed and data from the two studies compared.

■ Phase I studies

As part of the Phase I program, NeuroSearch conducted a multiple-ascending dose study on 36 healthy male and female subjects [17]. Considering the benign safety and tolerability seen with pridopidine in large HD studies with 45 mg twice daily (b.i.d.), this study was aimed at exploring the tolerability of even higher doses. A dose of 90 mg b.i.d. was found to be the maximum tolerated dose in healthy volunteers. However, it never attained a planned dose of 112.5 mg b.i.d. due to tolerability issues observed at 90 mg b.i.d. and was stopped at this dose. The AE-profile is described in the ‘Safety and tolerability’ section.

■ Phase II studies

In 2004, Carlsson Research conducted the first randomized, double-blind, placebo-controlled study (ACR16C007) of pridopidine in 58 patients with HD [18]. Pridopidine hydrochloride (50 mg; $n = 28$) or matched placebo ($n = 30$) was administered once daily (q.d.) for 4 weeks. The primary objective of the study was to assess the effects of pridopidine on cognitive function. The secondary objective was to assess motor symptoms, affective symptoms, sleep quality, safety and tolerability of the treatment.

The change from baseline in weighted cognitive score compared with placebo was not significant. However, the weighted cognitive score showed significant improvement from baseline in patients receiving pridopidine. In patients treated with pridopidine, the mean modified motor score (mMS; measuring voluntary motor function) changed significantly from baseline, by -2.0 after 2 weeks and -2.3 after 4 weeks ($p < 0.01$ for both). In patients displaying a baseline mMS > 10 , the change from baseline in the pridopidine group after 4 weeks of treatment was statistically significant compared with placebo [16]. In summary, the most notable effect of pridopidine was improvement in voluntary motor performance;

the substance was well tolerated and no safety concerns were identified in this small study population.

In the Phase IIb HART study, NeuroSearch and the Huntington Study Group teamed up to study pridopidine further. With the intention of evaluating its efficacy and safety as well as establishing an optimal dose, 28 centers across the USA and Canada took part in this randomized, double-blinded, placebo-controlled study. HART enrolled 227 patients, who were randomized to treatment with three different doses of pridopidine (10, 22.5 or 45 mg, all b.i.d.) or placebo. The primary end point of the HART study was the change from baseline at 12 weeks on the modified Motor Score (mMS), a subscale of the Unified Huntington’s Disease Rating Scale (UHDRS) Total Motor Score (TMS). For the pridopidine 45-mg b.i.d. dose group, the effect versus placebo on the mMS did not reach significance, although it did show a strong trend, with $p = 0.078$. On the secondary outcome measure, the TMS, a significant change from baseline at week 12 was reached: total motor function improved by 2.8 points ($p = 0.039$). For both the TMS and mMS, a statistically significant improvement in the change from baseline was seen with increasing doses of pridopidine, thus demonstrating an important dose–response relationship. Pridopidine 45 mg b.i.d. also showed significant effects on the patients’ gait and balance as well as hand movements. For the TMS motor domains for dystonia, chorea and eye movements, positive trends were observed [104].

The OLE of HART was initiated in March 2011 and concluded enrollment in December 2011 with 118 patients (55%) [105]. Results are not yet available. HART backed up the findings of the MermaiHD study by showing consistent effect sizes for both the mMS and the TMS [104].

Phase III studies

From 2008 to 2009, NeuroSearch undertook a randomized, double-blind, placebo-controlled trial to assess the efficacy of pridopidine in treating motor deficits in patients with HD: the MermaiHD Phase III study [19]. A total of 437 patients from 32 clinics in eight European countries were randomly assigned to one of three groups: 45-mg q.d., 45-mg b.i.d. or placebo.

The primary outcome measure was change in the mMS from baseline to week 26. Secondary outcome measures were the clinical global impression improvements assessment, the UHDRS cognitive and behavioral assessments, and the hospital anxiety and depression scale. Amongst others, tertiary outcome measures included changes in motor function, as measured by the UHDRS-TMS, and individual items within the mMS (gait and dysarthria).

Of all 437 patients, 403 (92%) completed the study. The primary reasons for discontinuation were AEs and withdrawal of consent.

The improvement after treatment with 45-mg pridopidine b.i.d. compared with placebo was -0.99 (97.5% CI: -2.08–0.10; $p = 0.042$). Due to a prespecified Bonferroni correction for multiplicity, the alpha level was set to 0.025, hence the effect of treatment with 45 mg b.i.d. was not statistically significant compared with placebo and the study failed to meet its primary hypothesis. In the per-protocol analysis however, the improvement after treatment with 45 mg b.i.d. compared with placebo was statistically significant with -1.29 (97.5% CI: -2.47 to -0.12; $p = 0.014$) [106]. For the secondary outcomes, by week 26, none of the changes from baseline were statistically significant.

The TMS, being the motor part of the UHDRS and a tertiary end point in this study, displayed very significant results: patients taking 45 mg of pridopidine b.i.d. had a 3.0 point improvement, at a statistical significance level of $p = 0.004$, which was driven by improvements in dystonia and eye movements and to a lesser extent by hand movements, gait and balance. No significant improvements in non-motor secondary and tertiary outcome measures, which assessed deficits in cognition and functional capacity, were recognised.

Pridopidine was very well tolerated with an AE profile similar to placebo [19]. Further analysis of results from MermaiHD demonstrates that pridopidine not only has symptomatic effect, but also appears to slow the disease progression depending on the patients' disease-genotype [107]. Data from the placebo-treated patient group in the MermaiHD study confirm a strong correlation between the rate of symptoms progression and the number of CAG repeats to the HD gene [19]. The more CAG repeats there are in the gene, the faster is the progression of clinical symptoms. In patients treated with pridopidine, the CAG-dependent rate of motor symptoms progression, as observed in the placebo group, was not apparent, lending support to the drug's ability to potentially modify the underlying disease progression [107].

After the MermaiHD trial, patients were given the opportunity to continue participating in a 6-month OLE in order to assess the long-term safety and tolerability of pridopidine. The OLE enrolled a total of 353 (81%) patients who had completed the first 26 weeks of randomized treatment with pridopidine 45 mg q.d. or b.i.d. or placebo. In the study extension, all the patients were treated with pridopidine 45 mg b.i.d., and 305 patients completed the entire 12-month treatment.

Pridopidine displayed a favorable safety and tolerability profile in patients with HD over the 12-month treatment period [108]. For exact results see 'Safety and tolerability'.

Subsequently, the results of the MermaiHD and HART study were integrated in a meta-analysis. On the UHDRS-TMS, the meta-analysis showed a significant improvement compared with placebo from treatment with pridopidine (45 mg b.i.d.) of -2.1 points ($p < 0.01$) at week 12 (combined data) and of -3.3 points ($p < 0.001$) at week 26, as well as in the items 'hand movements', 'balance and gait' and 'dystonia' [109]. On the mMS, the meta-analysis showed a placebo-corrected change of -0.6 ($p = 0.12$) at week 12 and a significant improvement of -1.2 points ($p < 0.01$) at week 26 [110]. Table 2 shows the comparison between the motor scale results of the Phase II and III studies.

■ Safety & tolerability

Throughout the clinical trials, pridopidine showed good safety and tolerability, with an AE profile similar to placebo.

The most common AEs included nausea – as the only AE explicitly mentioned in all four studies – falls, diarrhea, sleep disturbances, headache and dizziness (Table 3).

The most common AE reported during the 12-month MermaiHD trial were falls (14% of patients), Huntington's chorea, originally reported as a worsening of pre-existing chorea (13%), depression (8%), irritability, nasopharyngitis, fatigue, dizziness (each reported for 7% of patients), insomnia, nausea and diarrhea (each

Table 2. Motor scale results of Phase II and III studies of pridopidine.

Study/author (year)	Dosage	Patients (n)	mMS	TMS	Ref.
Phase II					
ACR16C007/Lundin <i>et al.</i> (2004)	50 mg q.d.	58	-2.3 [†] ($p < 0.01$) [‡]	Not specified	[18]
HART/Kieburts <i>et al.</i> (2008)	45 mg b.i.d.	227	-1.2 ($p = 0.08$) [§]	-2.8 [†] ($p = 0.04$) [‡]	[104]
Phase III					
MermaiHD/De Yebenes <i>et al.</i> (2008)	45 mg b.i.d.	437	-1 ($p = 0.042$) [§]	-2.96 [†] ($p = 0.004$) [‡]	[19]

[†]Statistically significant.
[‡]Secondary outcome measure.
[§]Primary outcome measure.
[†]Tertiary outcome measures.
 b.i.d.: Twice daily; mMS: Modified Motor Score; q.d.: Once daily; TMS: Total Motor Score.

Table 3. Adverse events in MermaiHD and HART.

Adverse event	MermaiHD (n; %)		HART (n; %)	
	Placebo (n = 144)	Pridopidine (n = 145) [†]	Placebo (n = 58)	Pridopidine (n = 58) [†]
Fall	9 (6)	13 (9)	7 (12.1)	8 (13.8)
Chorea	9 (6)	10 (7)	2 (3.4)	3 (5.2)
Diarrhea	5 (3)	9 (6)	3 (5)	2 (3.4)
Fatigue	8 (6)	4 (3)	5 (5.8)	2 (3.4)
Nausea	9 (6)	5 (3)	4 (6.9)	5 (8.6)
Nasopharyngitis	5 (3)	9 (6)	1 (1.7)	3 (5.2)
Depression	8 (6)	6 (4)	4 (6.9)	2 (3.4)
Dizziness	6 (4)	7 (5)	0	4 (6.9)
Insomnia	5 (3)	8 (6)	2 (3.4)	1 (1.7)
Headache	4 (2.8)	5 (3.5)	3 (5.2)	3 (5.2)
Excoriation	0	2 (1.4)	4 (6.9)	1 (1.7)

[†]90 mg per day.
Data taken from [19,111].

reported for 6% of the patients) [108]. When comparing patients treated with pridopidine in both the randomized study and the open-label extension to those treated with placebo in the 6-month randomized phase, the AE profile appears similar during the OLE, except for chorea. Huntington's chorea, that is, a worsening of chorea, was reported with a higher incidence for patients on drug for 12 months (12.5%) than for those on drug for 6 months (6.2%). However, no similar pattern was observed on the chorea subscale of the UHDRS, indicating no general aggravation of chorea at study end for the patients treated for 12 months compared with patients treated for 6 months [108].

Concomitant treatment with neuroleptics, concerning approximately 40% of the patients included in the study, did not show any influence on the positive treatment effects of pridopidine [19].

In the HART study, the AE findings were consistent with the observations in the MermaiHD study. Treatment was discontinued due to AEs for 7% of patients, and nine serious AEs were reported in six patients (recurrent breast cancer, suicidal ideation, depression, bipolar disorder, adjustment disorder, testicular torsion and three episodes of convulsions) [104]. Since no clinically meaningful changes in vital signs and ECG were observed during earlier trials, it came as a surprise that results of the multiple ascending dose indicated a QT interval prolongation in healthy volunteers, for both the 67.5 and the 90 mg b.i.d. groups [17]. The 90-mg q.d. dose was well tolerated, even though QT prolongation at this dose level was higher than seen in the foregone clinical studies. Additionally, when compared with previous studies, higher incidences of headache, vomiting and nausea were observed among all groups. As the

placebo group displayed an equal rise in AEs, pridopidine did not seem to be related to the latter. However, the frequency of dizziness was indeed higher in the pridopidine 67.5- and 90-mg b.i.d. arms compared with placebo [17].

Dosing & administration

It is noteworthy that pridopidine has merely been granted Orphan Drug status in Europe and the USA, and that no evidence-based recommendations with regard to dosage and administration of the drug have been made [103].

Given the outcome of the studies, that is, the statistically significant improvement on the TMS, the positive effects observed on both voluntary and involuntary motor symptoms and the overall good safety and tolerability, an oral dosage of 45 mg b.i.d. (morning and afternoon) seems appropriate. Regular ECGs should be performed and a possible cardiac aggravation due to other QT-prolonging medication, for example attention should be paid to the commonly used antidepressant selective serotonin reuptake inhibitors in HD.

Future perspective

Based on the results of MermaiHD and HART, NeuroSearch lobbied the FDA and European Medicines Agency to accept pridopidine as a treatment for HD. Both authorities required additional evidence to confirm the previously observed effect on TMS and to further support the clinical relevance of this finding [103]. NeuroSearch had worked on designing a confirmatory Phase III program for pridopidine for the treatment of HD until Teva acquired it in October 2012. The latter have not yet announced any development plans for the compound.

Future perspective

HD is a fatal disease with no available drug to influence its course. Especially when taking into account the innumerable compounds that failed to meet physicians' and patients' expectations in the past, one has to be very careful expressing hope for new treatment options.

The dopaminergic stabilizer pridopidine seems to be a promising compound, not least from a pharmacological point of view. It is the first of its class to have demonstrated a significant effects on motor symptoms in HD patients in a Phase II and III study. Though individually, neither MermaiHD nor HART lived up to the original standards the researchers had set out to meet.

However, statistical significance was reached when the results of the two studies were combined, and when the UHDRS-TMS was used to evaluate patients.

Dopaminergic stabilizers might become a treatment option for a range of neurological and psychiatric disorders associated with an aberrant dopamine- and glutamate transmission, that is, schizophrenia or Parkinson's disease [10]. What might make pridopidine superior to other drugs is the fact that it seems to improve voluntary and involuntary movements as well as behavioral symptoms without any worsening of psychiatric or motor function.

Making proper disease management in HD even more difficult is the lack of drug combinability. More

than 40% of patients in the Phase III MermaiHD study were on neuroleptic medication while taking pridopidine. However, treatment effects and AEs did not differ from patients who did not take any additional drugs.

Since the D₂ receptor is a major target of pridopidine, it is notable that throughout the last two decades studies have proven the existence of different polymorphisms in the dopamine D₂ receptor gene as well as a considerable variability of D₂ receptor density in healthy subjects [20–23]. Genetic variants of this receptor were hypothesized to influence the response of neuroleptics in schizophrenia patients [24,25]. Unfortunately, there has not yet been a similar investigation of D₂ receptor polymorphisms and their impact on HD treatment, which makes it impossible to say whether the ability of pridopidine to act on the receptor would be altered in any way.

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Executive summary

Characteristics of Huntington's disease

- Huntington's disease (HD) is a neurodegenerative and autosomal dominantly inherited disease.
- The mutation within the Huntingtin gene on chromosome 4p leads to a CAG triplet repeat expansion.
- Clinical features include a triad of cognitive decline, psychiatric disturbances and progressive motor dysfunction such as chorea and dystonia.
- The treatment options are only symptomatic and incapable of influencing the course of the disease.

Pharmacology

- Pridopidine belongs to a new class of CNS ligands called dopaminergic stabilizers.
- Its dual mechanism of action consists of antagonizing striatal Dopamine receptor 2 receptors and strengthening of the cortical glutamate transmission, which ultimately enhances striatal Dopamine receptor 1 receptor stimulation.
- Pridopidine is metabolized in the liver by CYP2D6 while renal elimination becomes more important upon repeated dosing.

Phase I & II studies

- So far, the maximum tested dose was well tolerated (90 mg twice daily [b.i.d.] in healthy volunteers).
- Both Phase II studies were randomized, double blind and placebo controlled.
- Patients receiving pridopidine in the ACR16C007 trial showed a significant change from baseline on the modified motor score.
- HART displayed a significant change from baseline on the Total Motor Score (TMS) and 45 mg b.i.d. led to significant effects on the patients' gait and balance as well as hand movements.

Phase III studies

- In the randomized, double-blind and placebo-controlled MermaiHD study, only the TMS, one of its tertiary end points, displayed significant results.
- A meta-analysis integrating HART and MermaiHD showed a significant improvement compared with placebo, on the TMS as well as on the modified motor score, for a dosing of 45 mg b.i.d.

Safety & tolerability

- Throughout the clinical trials, pridopidine showed good safety and tolerability, with an adverse-event profile similar to placebo.
- Most common adverse events included nausea, falls, chorea and fatigue.
- Concomitant intake of neuroleptics did not show any influence on the positive treatment effects of pridopidine.

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