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Recent advances in the therapeutic development for Huntington disease

Tiago A. Mestre*

Parkinson's Disease and Movement Disorders Center, Division of Neurology, Department of Medicine, The Ottawa Hospital Research Institute, The University of Ottawa Brain and Mind Institute, Canada

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ABSTRACT

Introduction: Huntington disease (HD) is a rare genetic neurodegenerative condition. The availability of a genetic diagnosis makes HD an attractive model for the development of therapies that can delay or, at best, halt the progression of neurodegenerative conditions. Tetrabenazine and deutetrabenazine are the only treatment options with a formal indication (chorea) for this patient population.

Methods: Literature review on HD and clinical trials using the medical databases Pubmed, Web of Science, and clinical trial registries. Recent clinical trials conducted with the goal of disease-modification or new symptomatic treatment indications were included. Non-pharmacological interventions were excluded.

Results: Therapeutic approaches aiming at disease-modification include huntingtin-lowering strategies, the modulation of huntingtin homeostasis and neuroinflammation. Huntingtin-lowering strategies are of particular interest by targeting the mRNA of the huntingtin (HTT) gene at the core of HD biology. Antisense oligonucleotides (ASO) are the only huntingtin-lowering strategies in clinical development. The initial results suggest that the first non-allele specific ASO was safe and associated with a reduction in the levels of mutated huntingtin protein (mHTT). Other clinical trials for disease-modification in HD have generated negative results or are ongoing. Assays to measure CSF mHTT and brain nuclear imaging specific to HD can support the rational development of these therapies. Novel symptomatic treatment indications explored in clinical trials include motor disability, irritability and apathy.

Conclusions: The years ahead are promising for novel and revolutionary therapies aimed at core disease mechanisms in HD. Clinical research platforms such as Enroll-HD are expected to potentiate the conduction of clinical trials in HD.

1. Introduction

Huntington disease (HD) is a genetic autosomal dominant neurodegenerative condition caused by a CAG trinucleotide expansion in exon 1 of the huntingtin gene (*HTT*) [1]. The clinical disease typically presents in a variable combination of 1) a complex movement disorder, 2) cognitive problems predominantly of the dysexecutive type and 3) behavioural problems ranging from apathy, irritability to depression. There is no cure for HD, and the disease progresses relentlessly with an expected survival of 15–20 years after the initial symptom presentation [2]. Variations in the clinical presentation of HD include Juvenile HD with onset before age 21 and a distinct clinical phenotype [3], and late-onset HD after age 60 [4].

2. Overview of current treatment options in HD

Chorea is the only approved treatment indication in HD. Tetrabenazine, an inhibitor of the vesicular monoamine 2 transporter, was the first treatment approved for this indication. More recently, a deuterated version of tetrabenazine (SD-809) was approved by the US Food and Drug Administration (FDA), following a 12-week randomized, double-blind, placebo-controlled trial suggesting equivalent efficacy and potentially a better tolerability profile relative to tetrabenazine [5]. The claim of better tolerability has important limitations since it is based on a historical comparison with the TETRA-HD study [6]. Preliminary data from the ongoing ARC-HD study (ClinicalTrials.gov, NCT01897896) assessing the overnight switch of tetrabenazine three times daily to deutetrabenazine twice daily show that 54% of the participants experienced at least one adverse event, but there were low rates of neuropsychiatric adverse events, a main concern in the clinical

* Parkinson's Disease and Movement Disorders Centre, Division of Neurology, Department of Medicine, Civic Campus of the Ottawa Hospital, The Ottawa Hospital Research Institute, University of Ottawa, 1053 Carling Avenue, Rm 2174, Ottawa, Ontario, K1Y4E9, Canada.
E-mail address: tmestre@toh.ca.

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use of tetrabenazine [7]. Most of the symptoms and signs of HD do not have management options supported by data generated in controlled trials. The few clinical trials where non-motor symptoms were studied failed to show the efficacy of the tested intervention [8]. The current management of HD is based on clinical experience and the application of the best evidence available from other conditions. There is no treatment available that prevents phenoconversion in premanifest/prodromal individuals or delays the progression of symptoms and signs in manifest HD subjects.

3. Emerging experimental therapies for disease modification

The current landscape of therapeutic development in HD holds great promise, namely, for interventions being studied for a disease-modifying effect. The field of HD is shifting away from therapies which rational was based on non-disease specific concepts of neurodegeneration to interventions targeting core upstream disease-specific processes. The most emblematic example of this paradigm shift is the ongoing effort to lower levels of the mutated huntingtin protein (mHTT). Conceptually, the strategies in consideration aim at reducing the amount (or pathological effect) of mHTT and include gene therapy, inhibition of synthesis of mHTT, and modulation of HTT homeostasis. Another novel putative strategy for a disease-modification therapeutic goal is immunomodulation (Table 1, for a summary of recent or ongoing clinical trials of interventions tested for disease modification). The current review does not include surgical interventions such as the transplantation of human mesenchymal stem cells (ClinicalTrials.gov, NCT02728115) or neurostimulation (ClinicalTrials.gov, NCT02535884).

3.1. Huntingtin-lowering therapies

The strategies to reduce the synthesis of mHTT have been primarily focused on inhibiting the process of mRNA synthesis either by blocking transcription (Zinc finger motif proteins), preventing post-transcriptional processes and promoting early mRNA degradation (antisense oligonucleotides, ASO) or inhibiting its translation (short interfering RNA, siRNA). Two types of ASOs are presently in clinical development in HD: the non-allele specific ASO, IONIS HTTRx (ClinicalTrials.gov, NCT02519036), and the allele-specific ASOs, WVE-120101 (ClinicalTrials.gov, NCT03225833) and WVE-120102 (ClinicalTrials.gov, NCT03225846).

The IONIS HTTRx compound, formerly labelled ISIS 443139, is a non-allele specific human huntingtin ASO and thus targets both *wild-type* HTT and mHTT. ASOs are engineered single-stranded DNA molecules complementary to a target mRNA. The formation of an ASO/RNA complex is signalled for degradation by the endogenous enzyme RNase H [9]. The first-in-human clinical trial (IONIS HTTRx study) was conducted to assess the safety, tolerability, pharmacokinetics and pharmacodynamics of multiple ascending doses of lumbar intrathecal administration of IONIS 443139 in a maximum of 48 subjects with early manifest HD. The pharmacokinetic and pharmacodynamics were characterized using predominantly CSF (but also plasma) samples dosing HTT. Neurofilament light chain was also quantified to indirectly determine the neuronal original of CSF HTT. This clinical trial is now completed with preliminary data suggesting that IONIS 443139 is safe, well-tolerated and associated with a dose-dependent mean reduction of 40% in CSF HTT concentration [10]. Although levels of mHTT in cortex have been estimated based in CSF levels of mHTT, it is important to determine how the results of this trial match the preclinical data in non-human primates documenting a reduction of mHTT by IONIS 443139 to be less in caudate nucleus (˜15–20%) compared with the cortex (˜50%) [11], since each target is associated with a particular phenotypical expression [12]. Currently, an open-label extension is ongoing (ClinicalTrials.gov, NCT03342053) and the planning for a multinational, multicenter phase III trial is underway.

Table 1
Recent clinical development of therapies for disease-modification in HD.

Class of compounds	Compound	Mechanism of action	Study Name; Phase (Status)	Registration ID	Main Results
Huntingtin-lowering therapies	IONIS HTTRx	Non-allele specific antisense oligonucleotide	First in human study (completed, not published)	NCT02519036	Safe and well tolerated *(press release)*
	WVE-120101	Allele specific antisense oligonucleotide	PRECISION-HD 1 and 2; Phase II (ongoing)	NCT03225833	–
	WVE-120102			NCT03225846	
Modulation of huntingtin homeostasis	PBT2	Metal-protein attenuating compound	Reach2HD; Phase II (completed, published)	NCT01590888	Positive (cognition)
	Selisistat	Sirtuin-1 inhibition	Two phase II studies (completed, one published)	–	Negative[a]
Immunotherapy	VX15/2503	Humanized monoclonal antibody of semaphorin 4D	SIGNAL; Phase II (ongoing)	NCT02481674	
	Laquinimod	Nf-kb inhibition	LEGATO-HD; Phase II (completed, not published)	NCT02215616	Negative[a] *(press release)*
Other	Cysteamine	Various (see main body)	CYST-HD; Phase II/III (completed, published)	NCT02101957	Negative[a]
	BN82451	Various (see main body)	Phase IIa (terminated)	NCT02231580	Poor recruitment
	Resveratrol	Dietary Supplement	REVHD; Phase II (ongoing)	NCT02336633	–
	Fenofibrate	Lipid lowering medication	Phase IIa (ongoing)	NCT03515213	–
	Triheptanoin	Anaplerotic therapy	TRIHEP3; Phase II (ongoing)	NCT02453061	–
	SBT-20	Mitochondrial function	CHALLENGE-HD; Phase Ia/II (ongoing)	EUCTR2016-003730-25-NL	–

[a] Negative for efficacy outcome measures.

The PRECISION-HD1 (WVE-120101) and PRECISION-HD2 (WVE-120102) studies are twin randomized, double-blind, placebo-controlled trials assessing the safety, tolerability, pharmacokinetics and pharmacodynamics of single and multiple ascending doses of WVE-120101 and WVE-120102, respectively. Forty-eight subjects with early manifest HD are planned to be recruited for each trial, and the primary outcomes are safety and tolerability. An approach based on allele-specificity has the conceptual appeal of only targeting the mHTT and avoiding the unknowns of targeting the *wild-type* HTT. This feature comes with challenges: allele-specificity is based on the ability to target a specific nucleotide sequence (or SNP) that is not present in all patients with HD. Consequently, only a select group of HD patients is eligible for each compound, and regulatory agencies will require an independent development and approval for each allele-specific ASO, which is time and resource consuming. Finally, some HD patients may never be eligible for allele-specific ASOs in the future.

The IONIS HTTRx study and the PRECISION-HD1/2 studies will inform about the safety of targeting both *wild-type* HTT and mHTT *vs.* exclusively mHTT in human subjects and thus provide guidance on the significance of allele specificity for huntingtin-lowering therapies.

As part of modern and rational drug development, robust data on target engagement and proof-of-principle in humans has been collected for huntingtin-lowering therapies. Several studies of validation of pharmacodynamic biomarkers are under development or have been completed recently and include: 1) the measurement of mHTT in the CSF [13], and 2) brain imaging of mHTT using the PET ligand CHDI-00485180 [9]. The development of the PET ligand CHDI-00485180 is in clinical development, and results are not available [9]. Regarding the measurement of mHTT in the CSF, a novel ultrasensitive single-molecule counting mHTT immunoassay has been reported that targets the expanded polyglutamine of the mHTT with a femtomolar detection threshold and a very good specificity and sensitivity [13]. In the same study, the mHTT was not detected in control subjects, and CSF concentration of mHTT was three-fold higher in manifest HD compared with premanifest HD [13]. Significant associations were reported of CSF mHTT levels with the 5-year probability for phenoconversion as well as motor and cognitive measures [13], but these results have limitations due to the cross-sectional study design and the small sample size of the study. In addition, this study also showed that there are premanifest subjects for which mHTT was not detected and a marked variability of CSF mHTT levels exists for subjects within the same HD stage as well as an overlap between HD clinical stages [13]. More recently, the assay was clinically validated following established Food and Drug Administration and European Medicine Agency guidelines [14]. A more comprehensive understanding of the dynamics of the HTT presently quantified in CSF, and the correlation with clinical outcomes of interest in HD are necessary [9]. An observational study (HDClarity) is underway with the goal of obtaining CSF samples in HD populations in a multi-national multi-center effort that can contribute for therapeutic development in HD, namely, for development of pharmacodynamics markers, including mHTT. HDClarity is expected to find answers to some of the current gaps of knowledge described above. These efforts are instrumental to steer drug development programs in a more rational manner.

Currently, various efforts in the field of huntingtin-lowering therapies are at a preclinical stage. These include multiple non-allele specific iRNA compounds using an Adeno-associated virus as vector administered by a single intracerebral stereotactic injection, and an allele-specific zinc finger compound carried by an AAV vector. Other options in development for allele-specific therapies are the use of intrabodies (intracellular antibody portions interfering with the aggregation of the mHTT gene) [15]. To reduce the invasiveness of the modes of administration of huntingtin-lowering therapies, technology is being developed to allow the crossing of the blood-brain barrier of novel small-molecule therapeutics or systemic Adeno-associated virus delivery systems [16].

3.2. Homeostasis of mHTT protein

3.2.1. Inhibition of HTT aggregation

PBT2 is a second-generation 8-hydroxyquinoline analogue labelled as a metal-protein attenuating compound (MPAC). MPACs have been tested clinically in Alzheimer's disease (AD) [17]. PBT2 acts as a synthetic chaperone designed to disrupt interactions between biological metals such as copper and zinc and target proteins in the brain [18]. In HD, PBT2 is thought to reduce copper-induced aggregation of mHTT and in preclinical studies showed an associated prolonged survival in the R6/2 mice model of HD [19].

PBT2 has been assessed in the Reach2HD study [18], a 26-week phase II randomized, double-blind, placebo-controlled study in 109 patients with early to mid-stage HD to assess safety and tolerability primarily using doses of 100 mg or 250 mg/d. The change in time of cognitive function, motor disability and functional level were also included as outcome measures. Results have been presented: five serious adverse events occurred in PBT2 groups while one occurred in the placebo group. All but one of these events was deemed unrelated to study drug. Although the change in the main composite cognitive score was not different in the PBT2 groups and placebo, the change in the Trail Making Test Part B score was better in the PBT2 250 mg group (17.65 s, 96% CI: 0.65, 34.65; $p = 0.04$) but not in the 100 mg group (0.79 s improvement, 95% CI: -15.75, 17.32; $p = 0.92$). An isolated statistically significant result for a single cognitive test and not on the main cognitive outcome is of questionable clinical relevance. Moreover, the FDA issued a Partial Clinical Hold in 2015 (still in effect) due to safety concerns raised by non-clinical data concerning the 250 mg dose. For the hold to be lifted, additional pharmacological and toxicological data for the clinically relevant dose of 250 mg/day needs to be conducted [20]. A Phase III clinical trial has not been announced.

3.2.2. Promotion of HTT clearance

Selisistat is a first-in-class SirT1 (silent information regulator T1) inhibitor thought to increase the rate of clearance of mHTT: down-regulation of the orthologue gene of human SirT1 or inhibition of its corresponding protein was associated with the decrease in the intracellular levels of mHTT in a Drosophila model of HD [21]. Selisistat 10, 50, 100 and 200 mg/day have been tested in two double-blind, placebo-controlled clinical trials mainly focused in safety and tolerability assessing a short-term (14 days) [22] and longer-term treatment duration (12 weeks) [23]. Selisistat was associated with reversible increases in liver function test [23], and there were no significant differences between selisistat and placebo groups in terms of efficacy outcomes measures, that included motor disability, cognition and functional capacity [22,23]. There are no phase III trials planned, and the clinical development is apparently halted.

3.3. Neuroinflammation

3.3.1. Inhibition of nuclear factor kappa B

Laquinimod is an orally administered carboxamide derivative studied as a disease-modifying treatment for relapse-remitting multiple sclerosis (MS) and progressive MS [24]. In HD, laquinimod was suggested to have therapeutic potential by the observation that mHTT can be associated with a hyperactivation status of monocytes and microglia [25]. Nevertheless, the precise mechanism of action is still unknown: inhibition of astrocyte activation, restoration of BDNF levels, modulation of the MAPK signalling pathway have been proposed [25] or activation of caspase-6 [26]. Although the role of laquinimod may go beyond a strict action in neuroinflammation, the true significance in the pathophysiology in HD remains to be fully documented.

In HD, laquinimod was recently assessed in the LEGATO-HD study, a phase II, 12-month multicenter randomized, placebo-controlled, double-blind trial using the doses of 0.5 and 1.0 mg/day. An initially planned dose of 1.5 mg/day was discontinued due to safety concerns

Table 2
Recent clinical development of therapies for symptomatic treatment in HD.

Symptom indication	Compound	Mechanism of action	Study(ies) Name(s); Phase (Status)	Registration ID	Results
Motor impairment	OMS643762	Inhibition of Phosphodiesterase 10A	Phase II (suspended)	NCT02074410	–
	PF-02545920	Inhibition of Phosphodiesterase 10A	APACHE; Phase II (completed, published)	NCT01806896	–
	PF-02545920	Inhibition of Phosphodiesterase 10A	Amaryllis; Phase II (completed, not published)	NCT02197130	Negative *(press release)*
	Pridopidine	Dopamine reverse agonist	PRIDE-HD; Phase III (completed, not published)	NCT02006472	Negative *(press release)*
Chorea	SOM3355 (*alias* Bevantolol)	Vesicular monoamine transporter 2 inhibitors	Phase II (ongoing)	NCT03575676	–
Irritability	SRX246	Vasopressin 1a receptor antagonist	STAIR; Phase II (ongoing)	NCT02507284	–
Cognitive impairment	(2)-epigallocatechin-3-gallate	Polyphenol	ETON-Study; Phase II (completed, not published)	NCT01357681	–
Apathy	Bupropion	Norepinephrine-dopamine reuptake inhibitor	Action-HD; Phase II (completed, published)	NCT01914965	Negative
Functional ability (cognition/behaviour)	Varenicline	Nicotinic agonist	VCAS-HD; Phase II (ongoing)	ACTRN12616001611415	–

*negative for efficacy outcome measures.

reported for MS in a dose of laquinimod of 1.2 mg/day. The LEGATO-HD study primarily assessed the change in the Total Motor Score (TMS) of the Unified Huntington Disease Rating Scale (UHDRS) and used for the first time the recently developed Huntington Disease Cognitive Assessment Battery (HD-CAB) [27]. Other outcomes were the UHDRS-TFC, the CIBIC-Plus global score, caudate volume (MRI) as well as the Q-Motor scale [28] using a quantitative motor assessment device. The preliminary results of LEGATO-HD have been released: the primary endpoint of change was not met, but the MRI outcome of the caudate volume was met [29]. More data is required to understand the significance of a positive imaging outcome with a negative clinical outcome but likely represents another negative study.

3.3.2. Immunotherapy (VX15/2503)

Immunotherapy is a novel (not validated) strategy currently in consideration as a therapeutic target in HD. Contrary to AD in which immunotherapy targeted beta amyloid, in HD the target currently being assessed is not HTT but semaphorin 4D (SEM4D). SEM4D is a transmembrane signalling molecule that can exist in a soluble dimer form and plays a role in cellular trafficking. In the central nervous system, SEM4D is mainly expressed in infiltrating immune cells and processes of neuroinflammation. Blockage of SEM4D in the preclinical YAC128 mouse model of HD was associated with improvement in striatal and cortical atrophy and behavioural measures [30]. VX15/2503 is a humanized monoclonal antibody targeting SEM4D currently being assessed in HD in the SIGNAL study (ClinicalTrials.gov, NCT02481674). VX15/2503 is also being evaluated in MS (ClinicalTrials.gov, NCT01764737). The SIGNAL study is a phase II, multi-center, randomized, double-blind, placebo-controlled study up to a maximum of 18 months of treatment using monthly intra-venous administrations of VX15/2503 (200 mg per dose) in subjects with late prodromal and early manifest HD. The SIGNAL study evaluates primarily safety and tolerability and, ultimately, attempts to assess if VX15/2503 delays the onset of clinical HD or the progression of clinical symptoms and signs in early HD. Secondary outcomes include the HD-CAB [27], the Q-Motor [28] scale, volumetric MRI, FDG-PET, and 11C-PBR28 (TSPO) PET to assess inflammatory cell activation in a sub-group of study participants. Clinical outcomes assessing behaviour, functional ability and global function will also be collected. Interestingly, individuals labelled as being in the prodromal stage were included in this clinical trial and were defined as CAG-age product score of greater than 200 and a UHDRS Diagnostic Confidence Level of 2 or 3. The estimated date for final data collection of the primary outcome measure is May 2020 (ClinicalTrials.gov, NCT02481674). The initial 36 participants have completed six months of study intervention, but detailed results have not been released.

3.4. Multiple targets

3.4.1. Cysteamine

The putative disease-modifying effect of cysteamine in HD is based on preclinical data that highlights its role in three putative cellular processes: control of reduced oxidative species by increasing levels of glutathione, promotion of protein catabolism through inhibition of transglutaminase and induction of a heat shock protein response and increased levels of BDNF [31]. Among these potential mechanisms, the inhibition of transglutaminase initially suggested as the primary mode of action has been put into question by recent observations in R6/2 and zQ175 mouse models of HD knocked-out for the transglutaminase gene [32]. The CYST-HD study was a phase II/III 18-month randomized, double-blinded, placebo-controlled clinical trial assessing the delayed-release formulation of cysteamine (RP103) in 96 HD patients. Cysteamine was not associated with an overall treatment effect, namely for the primary endpoint, the UHDRS Total Motor Score, although a *post-hoc* analysis described an effect for the most disabled study participants. Thirty-eight patients (86%) from the placebo group and 48 patients

(92%) from the RP103 group experienced at least one adverse event (AE); being most commonly gastrointestinal in nature [33].

4. Compounds assessed for symptomatic treatment in HD

In this section, a selection of clinical trials is presented in detail for their representation of new treatment indications that are presently gaps in the management of HD. A comprehensive list of recent or ongoing clinical trials conducted for symptomatic treatments in HD is provided in Table 2.

4.1. Inhibition of phosphodiesterase 10A (OMS643762 and PF-02545920)

Preclinical data documents that phosphodiesterase 10A (PDE10A) enzyme is expressed almost exclusively in the basal ganglia and suggests that PDE10A enzyme levels decline with the progression of neurodegeneration in HD [34,35]. As with huntingtin-lowering therapies, there have been efforts to provide a more robust rationale for inhibition of PDE10A as a therapeutic target in HD. PET imaging data using the ligand [(18)F]MNI-659 that targets PDE10A was obtained in various cross-sectional studies and one longitudinal study in HD [36–39]. For the validation of its use to monitor disease progression, the single longitudinal study available is of greatest relevance [37]. This study corresponds to a relatively small cohort of both premanifest and early manifest HD subjects (Stage I and II) with predominantly motor or behavioural clinical onset [37]. At baseline, the binding potential of [(18)F]MNI-659 was significantly reduced by 50% in the HD cohort compared with healthy controls and results presented a wide variability. After a mean of 14.7 months, the binding potential of [(18)F]MNI-659 declined in all subjects in the HD cohort with a greater mean annualized rate in the caudate (16.6 ± 0.12%) compared with the globus pallidus (6.9 ± 0.04%) and the putamen (5.8 ± 0.07%). Six out of the eight HD subjects declined in terms of functional capacity and corresponding HD stage, but there were no statistically significant changes in clinical measures perhaps owing to the small sample size [37]. PEARL-HD (NCT02061722) is a cross-sectional study assessing the binding potential for PDE10A and the D2 receptor (D2R) using the ligands [18F]MNI-659 and [11C]raclopride, respectively. PEARL-HD aimed at recruiting pre-manifest and manifest HD subjects, and healthy controls in a total of 45 subjects and showed that striatal PDE10A binding potential is more severely reduced than striatal D2R in the earliest stages of HD and this reduction does not reflect partial volume loss [36,39].

The cumulative data concerning PDE10A activity suggest inhibition of PDE10A as a potential therapeutic tool in HD. Nevertheless, it remains to be established in human HD whether declining enzymatic levels of PDE10A are a downstream or upstream event of the core neurodegenerative process in HD, and how such effect will translate into greater potential for a symptomatic *vs.* disease-modifying effect. So far, two PDE10A inhibitors have been assessed in humans: the OMS643762 and the PF-02545920, both aimed at symptomatic treatment. Both compounds were tested previously in schizophrenia. The drug development program for OMS643762 halted in 2014 after a phase II randomized, double-blind, placebo-controlled study to evaluate safety and efficacy of OMS643762 in subjects with HD (ClinicalTrials.gov, NCT02074410) was stopped due to safety concerns in preclinical models. A decision by FDA is awaited. PF-02545920 is a PDE10A inhibitor that has been assessed in two pivot clinical trials: the APACHE and Amaryllis trials. The APACHE (or ICM) trial (ClinicalTrials.gov, NCT01806896) was a phase II, double-blind, randomized, placebo-controlled study of PF-02545920 (10 and 40 mg/d) for 28 days in subjects with early HD to evaluate the safety, tolerability and brain cortical-striatal function. The latter was assessed by various fMRI paradigms with the goal of eliciting ventral striatal activity and assess monetary motivation (*vs.* emotional motivation) using a grip strength task. In this study [40], a relatively frequent adverse event in the PF-02545920 group was worsening of chorea. There were no cases of neutropenia, which was a special concern given the experience in schizophrenia trials. The results suggest that there was an effect of higher doses of PF-02545920 in grip strength for situations of monetary motivation *vs.* emotional motivation [40].

The Amaryllis trial was a recent phase II, 26-week, randomized, parallel group, placebo-controlled, double-blind trial of PF-02545920 (10 and 40 mg/d) for the treatment of motor impairment in HD measured primarily by the change from baseline in the UHDRS-TMS after 26 weeks of treatment. The Amaryllis trial recruited 272 manifest subjects in an earlier HD stages (UHDRS-Total Functional Capacity > 6) (ClinicalTrials.gov, NCT02197130) and a preliminary release by the pharmaceutical company reports negative results for the primary endpoint as well as other secondary outcomes such as functional ability [41]. A 12-month open-label extension initially planned at a dose of PF-02545920 40 mg/d to assess long-term safety and tolerability (ClinicalTrials.gov, NCT02342548) was discontinued in February 2017 [41].

4.2. SRX246

The SRX246 compound is a first-in-class vasopressin 1a receptor antagonist that crosses the blood-brain barrier following oral administration [42]. SRX246 is currently being assessed for irritability and other behavioural problems in HD in a 12-week randomized, double-blind, placebo-controlled, dose-escalation study in primarily irritable subjects with early symptomatic HD (ClinicalTrials.gov, NCT02507284). The estimated primary completion date is October 2018 (ClinicalTrials.gov, NCT02507284).

4.3. Pridopidine

Pridopidine is considered a modulator of the dopamine 2 receptor for its state-dependent antagonism although other mechanisms are being explored such as activation of the sigma-1 receptor [43]. Pridopidine was previously studied in two large phase III trials (MermaiHD [44] and HART [45]) that showed consistent negative results for the primary efficacy outcome, the modified motor score of the UHDRS. Both documented significant results of efficacy for the change in the UHDRS-TMS, which prompted the conduction of the study Pride-HD, a phase II, dose-finding, randomized, double-blind, placebo-controlled study aimed at evaluating the safety and efficacy of pridopidine 45 mg, 67.5 mg, 90 mg, and 112.5 mg twice daily. The primary endpoint was motor impairment after 26 weeks of treatment using the UHDRS-TMS. The study also included functional outcomes such as the Physical Performance Test. The results of the study were presented in a preliminary report, and the primary endpoint was not met. A statistically significant difference was found in the change in time of the UHDRS-TFC favouring pridopidine at 12 months, after a decision to lengthen the study duration [46]. These results deserve further scrutiny and the access to the full report is warranted for a critical appraisal. Nevertheless, the recent decision by the pharmaceutical company to halt the development of Pridopidine is suggestive of a non-compelling efficacy signal.

5. Conclusions

In the present review, the reader is guided through a landscape of emerging experimental therapies either with recent or ongoing clinical development in the field of HD. The years to come hold promise for novel, revolutionary therapies aimed at core disease mechanisms, a long-awaited promise for HD patients and families. In addition, the more recent negative results of clinical trials presented in this review are deemed to unlock gates for further therapeutic development as well as for a better study design and drug development in HD. The new genetic-based therapies hold great promise. In addition, multiple efforts are looking at establishing the rational use of imaging to trace the

neurodegeneration in HD either by the use of disease-specific markers or through the use of multimodal imaging [47]. Clinical research platforms based on worldwide registries such as Enroll-HD are expected to potentiate the conduction of clinical trials in HD [48], and a greater participation of the patient population for all HD patients including people with JHD that rarely take part in clinical trials. The faster disease progression found in patients with JHD may permit the identification of a more robust efficacy signal in a shorter trial duration and thus contribute decisively to the development of disease-modifying therapies. Finally, the new genome editing tools adapted from the microbial CRISPR-Cas system [49] are a powerful new therapeutic weapon that surely has a reserved place in drug development in HD, although with important ethical questions that need to be addressed.

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