The risks of converting post-hoc findings into primary outcomes in subsequent trials

Filipe B. Rodrigues, Joaquim J. Ferreira

HD is a promising disease model to study neurodegeneration, due to several characteristics, including: a precise pathogenic agent (4), a natural history that comprises a long presymptomatic phase (10,11) followed by an extended diseased survival (12), a broad symptomatic spectrum including most of the clinical features present on neurodegenerative diseases (motor, behavioural and cognitive) (1), well-validated assessment tools (13-16), pioneering imaging and biofluid biomarkers (10,17), and well-organized research and patient networks (18). These factors have encouraged drug developers to invest in HD as shown by the proportionately high number of clinical trials conducted in this rare disease population. Unfortunately, the success rate of the development pipeline underperforms when comparing with other disorders (5).

Genetic interventions are only now coming to age due to recent breakthroughs in DNA and RNA manipulation techniques, and optimization of drug stability, immunogenicity and delivery. There is optimism that these new tools may help change the fate of diseases like Huntington's. The ideal drug development program needs to happen with minimal human and financial burden and maximal efficiency. This includes informative preclinical data and early phase trial results, but also early “go/no go” decision timings and criteria.

Pridopidine is an interesting molecule from the pharmacological perspective (Figure 1). Acting on the...
dopaminergic system—which is primarily involved in the genesis of the disease phenotype—it is classified as a modulator as it can have both an agonistic and antagonistic effects through a state-dependent effect on dopamine receptors. When there is overactivity it acts as an antagonist, under underactivity conditions as an agonist, and has little to no influence under physiological circumstances. In addition, it also seems to interact with N-Methyl-D-aspartate (NMDA) and sigma-1 receptors.

Thus far pridopidine has been tested in four successive randomized controlled trials (RCTs) in HD, enrolling a grand total of over 1,000 participants (Table 1) (19,20,22,24). Unfortunately, in all of them the primary outcome was not met.

At first, a small RCT tested 50 mg of pridopidine a day against placebo in 58 people with manifest HD, recruited from 6 centres in Sweden and Norway. The trial followed participants for 4 weeks and was not able to show an effect on its primary outcome, a composite cognitive score. Nevertheless, secondary and exploratory analyses revealed a nominal improvement in the modified motor score (mMS), especially in a subgroup of more severely affected participants. This subscore of the Unified Huntington’s Disease Rating Scale (UHDRS) total motor score (TMS) comprises items related with voluntary motor control (i.e., items 4–10 and 13–15) (19).

Building up on these results, two follow-up randomized controlled studies ensued: the MermaiHD study in 32 European centres and the HART study in 27 North American centres. Based on the assumption that pridopidine could have an effect on voluntary movement control, both were designed and powered to show a difference in the mMS and recruited people with manifest HD and a mMS of 10 or more.

The MermaiHD study recruited 437 participants to investigate 45 and 90 mg of pridopidine daily compared with placebo over 26 weeks. Alas, this trial did not show an effect for its primary and secondary outcomes. Nonetheless, the analyses were statistically significant for the comparison 90 mg versus placebo in the per-protocol sample (i.e., 70% or greater compliance with treatment and completed the study) for the mMS and in the intention-to-treat sample for the UHDRS TMS (20).

The HART study had a similar design and tested 3 dosages of pridopidine (20, 45 or 90 mg daily) against placebo in 227 participants. The primary outcome evaluated at 12 weeks depicted no differences between the different dosages and the placebo arm, however secondary analyses showed a significant difference for UHDRS TMS for the comparison 90 mg versus placebo (22).

Lastly, the PRIDE-HD study recruited 408 participants with manifest HD, at least 25 points on the UHDRS TMS and 90% or less in the UHDRS independence score (IS), from 53 sites across 12 countries in Europe, North America and Australia. Follow-up was 53 weeks, and four doses of pridopidine (45, 67.5, 90 and 112.5 mg daily) were tested against placebo. The primary outcome was changed in the UHDRS TMS at 26 weeks and failed to be achieved. Exploratory analyses for all tested dosages showed similar results at 52 weeks. Exploratory analyses revealed an effect on the UHDRS total functional capacity (TFC) in the 45 mg arm. Subgroup post-hoc tests found this effect to be more evident in participants in earlier disease stages (24).

To summarise, the clinical development pipeline of pridopidine began with a negative, relatively small and short-lasting trial aimed at cognition but with interesting findings on a voluntary movements’ secondary outcome. It was followed by two well-powered but also negative trials designed to investigate the effects on voluntary movements. Both showed differences in a semi-structured neurological exam scale at the highest tested dosage (90 mg daily). A forth well-powered trial was deployed to investigate the effects on motor signs across a range of dosages. The trial was also negative, and none of the dosages shaped compelling differences after 6 months and 1 year on motor signs, but exploratory investigations disclosed an effect on functional capacity with low-dose pridopidine in early disease.

The cumulative evidence from these four trials seems to support that pridopidine is relatively safe and well-tolerated. The a priori hypothesis that it has an effect on the cognitive features of HD has been proven false. The findings on motor effects learnt from the earliest trials were not replicated in a large built-for-purpose trial. Were the first ones spurious positive results stemming from exploratory analyses, or were the results of the latter trials just unfortunate? The investigators blame an unexpectedly high response by the placebo group in the primary

Figure 1 Pridopidine molecule.
<table>
<thead>
<tr>
<th>Name</th>
<th>NCT</th>
<th>N</th>
<th>Design</th>
<th>Population</th>
<th>Duration (weeks)</th>
<th>Active arm(s)</th>
<th>Comparator</th>
<th>Primary outcome</th>
<th>Secondary/ exploratory outcomes</th>
<th>Sponsor</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lundin et al. 2010 (19)</td>
<td>N/A</td>
<td>58</td>
<td>RCT</td>
<td>Manifest HD</td>
<td>4</td>
<td>Pridopidine 50 mg/d (n=28)</td>
<td>Placebo (n=30)</td>
<td>Weighted cognitive score at 4 weeks*</td>
<td>Motor, behavioural, sleep, Sweden AB cognition, safety and tolerability</td>
<td>NeuroSearch AB</td>
<td>NS Δ in primary outcome, and Δ on mMS (baseline mMS ≥10)</td>
</tr>
<tr>
<td>MermaiHD NCT00665223 (20)</td>
<td>437</td>
<td>26</td>
<td>RCT</td>
<td>Manifest HD</td>
<td>26</td>
<td>Pridopidine 45 (n=148) and 90 mg/d (n=145)</td>
<td>Placebo (n=144)</td>
<td>mMS at 26 weeks</td>
<td>Motor, behavioural, cognition, safety and tolerability</td>
<td>NeuroSearch A/S</td>
<td>NS Δ in primary outcome, and Δ on UHDRS TMS (90 mg/d) and mMS (90 mg/d, per-protocol)</td>
</tr>
<tr>
<td>Squitieri et al. 2013 (21)</td>
<td>N/A</td>
<td>353</td>
<td>OLE</td>
<td>Completion of MermaiHD</td>
<td>26</td>
<td>Pridopidine 90 mg/d (n=353)</td>
<td>N/A</td>
<td>Safety and tolerability at 52 weeks**</td>
<td>Adherence</td>
<td>NeuroSearch A/S</td>
<td>Pridopidine is safe and well-tolerated</td>
</tr>
<tr>
<td>HART (22) NCT00724048</td>
<td>227</td>
<td>12</td>
<td>RCT</td>
<td>Manifest HD</td>
<td>12</td>
<td>Pridopidine 20 (n=56), 45 (n=55) and 90 mg/d (n=58)</td>
<td>Placebo (n=58)</td>
<td>mMS at 12 weeks</td>
<td>Motor, function, behavioural, cognition, safety and tolerability</td>
<td>NeuroSearch A/S, NeuroSearch Sweden AB</td>
<td>NS Δ in primary outcome, and Δ on UHDRS TMS (90 mg/d)</td>
</tr>
<tr>
<td>Open-HART NCT01306929 (23)</td>
<td>118</td>
<td>156</td>
<td>OLE</td>
<td>Completion of HART</td>
<td>156</td>
<td>Pridopidine 90 mg/d (n=118)</td>
<td>N/A</td>
<td>Safety and tolerability at 156 weeks</td>
<td>Motor and function</td>
<td>Teva Pharmaceutical Industries</td>
<td>Pridopidine is safe and well-tolerated</td>
</tr>
<tr>
<td>PRIDE-HD NCT02006472 (24)</td>
<td>408</td>
<td>52</td>
<td>RCT</td>
<td>Manifest HD</td>
<td>52</td>
<td>Pridopidine 45 (n=81), 67.5 (n=82), 90 (n=81), and 112.5 mg/d (n=82)</td>
<td>Placebo (n=82)</td>
<td>TMS at 26 weeks</td>
<td>Motor, function, behavioural, cognition, quality of life, safety and tolerability</td>
<td>Teva Pharmaceutical Industries</td>
<td>NS Δ in primary outcome, Δ on UHDRS TMS (45 mg/d)</td>
</tr>
<tr>
<td>Open PRIDE-HD NCT02494778 (24)</td>
<td>248</td>
<td>364</td>
<td>OLE</td>
<td>Completion of PRIDE-HD</td>
<td>364</td>
<td>Pridopidine 90 mg/d (ongoing)</td>
<td>N/A</td>
<td>Safety and tolerability at 364 weeks</td>
<td>N/A</td>
<td>Prilenia</td>
<td>Study terminated but yet not reported</td>
</tr>
</tbody>
</table>

*, based on Symbol Digit Modalities Test, Verbal Fluency Categorical, Stroop Color Naming, Stroop Word Reading and Stroop Interference Test; **, double blinded phase plus OLE; Δ, change. N/A, not applicable or available; RCT, randomized controlled trial; HD, Huntington’s disease; NS, non-significant; mMS, modified motor score (UHDRS TMS items 4–10 and 13–15); UHDRS TMS, Unified Huntington’s Disease Rating Scale total motor score; OLE, open-label extension.
outcome. Indeed by the end of the study period, this was
the arm with the largest effect size. The sponsor, Teva
Pharmaceutical Industries Ltd., focused their attention on
exploratory and post-hoc subgroup analyses concluding that
“pridopidine demonstrates slowing of progression of Huntington
disease in PRIDE-HD study as measured by Total Functional
Capacity”. After sparked criticism from the clinical and
scientific community, aware of the potential damages caused
by such interpretations, the European Huntington’s Disease
Network toned down the sponsor’s statement explaining
that “this should not be misunderstood as a demonstration of
disease modification or of neuroprotection”.

While there are multiple possible justifications for these
results, one should always consider the possibility that
pridopidine, as any other compound in development, may not
induce the hypothesised clinical effect. The central nervous
system therapeutic area has a low success rate from first-in-
man to registration of around 7–8% comparing with the
grand mean of 11%, and other therapeutic areas such as
cardiovascular where the success rate is around 20% (25).
In neurology, the drug development pipeline performs
appreciably poorly in the phase III and registration phases (25).
In HD only 2 molecules survived these phases, and overall
the success rate is even lower than that of other therapeutic
areas (5). Many reasons have been hypothesized to explain
such phenomenon: incomplete understanding of the disease
physiopathology; weak association between the therapeutic
target, and the disease pathogenesis and natural history;
limited animal models; incomplete evaluation of preclinical
effects; suboptimal pharmacokinetic and pharmacodynamic
characteristics; limitations of current study designs
(no biomarkers, short study durations); unenthusiastic
commercial interests, among others.

Pridopidine is an example where several of these factors
came into play, halving the already low chances of first-in-
man to registration success. It is well established that only
a small proportion of science generates positive results,
including rigorous and well-report clinical trials (26).
While the scientific milieu should reward progress, industry
and researchers are often motivated by other factors. As
tempting as it may sound to regard these after-the-event
announcements relevant, history has taught us that
hypotheses and new trials generated by post-hoc positive
results are legitimate but may be wrong.

Understandably and in the absence of better approaches,
this strategy is frequently used across medicine. Pridopidine
seems unlikely to be clinically helpful for people with HD
but we hope this story will teach us about the design of drug
development programmes and what to avoid in the future
in order to deliver efficacious medicines and optimise drug
development.

Acknowledgments

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest
to declare.

Ethical Statement: The authors are accountable for all
aspects of the work in ensuring that questions related
to the accuracy or integrity of any part of the work are
appropriately investigated and resolved.

References

1. McColgan P, Tabrizi SJ. Huntington’s disease: a clinical
review. Eur J Neurol 2018;25:24-34.
2. Rodrigues FB, Abreu D, Damásio J, et al. Survival,
mortality, causes and places of death in a European
Huntington’s disease prospective cohort. Mov Disord Clin
Pract 2017;4:737-42.
polymorphic DNA marker genetically linked to
4. A novel gene containing a trinucleotide repeat that
is expanded and unstable on Huntington’s disease
chromosomes. The Huntington’s Disease Collaborative
years of clinical trials in Huntington’s disease: a very low
clinical drug development success rate. J Huntingtons Dis
6. Rodrigues FB, Ferreira JJ, Wild EJ. Huntington’s disease
clinical trials corner: June 2019. J Huntingtons Dis
2019;8:363-71.
International guidelines for the treatment of Huntington’s
versus deutetrebamazine for Huntington’s disease: twins or
metrics matter: letter regarding article “indirect tolerability


