Title page

Fifteen years of clinical trials in Huntington's disease: a very low clinical drug development success rate

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Running title: Clinical trials in Huntington's disease

Abstract and Keywords

BACKGROUND: Drug development in Huntington's disease (HD) is particularly challenging, and only two compounds are approved by the FDA. It is therefore essential to appraise drug development programs in order to understand the reasons for their failure during the early stages of development.
OBJECTIVES: To describe the landscape of HD therapeutic development and critically explore the causes of compound attrition in the different stages of drug development, from phase 1 to phase 4.
METHODS: All HD clinical trials registered in the WHO International Clinical Trials Search Portal, from inception to May 2017, were analyzed. Two independent authors selected and extracted data. Success rate in a trial phase was calculated as the number of compounds that progressed to the next trial phase divided by the number of compounds in that phase. The overall success rate was calculated as the ratio between the number of compounds that receive regulatory approval and the total number of compounds.
RESULTS: Ninety-nine trials assessing 41 compounds and eleven non-pharmacological interventions (devices and cell therapies) were identified. Twenty-four (24.2%) were phase 1 trials, 46 (46.5%) phase 2, 20 (20.2%) phase 3, and two (2.0%) phase 4. Sixty trials (60.6%) received industry sponsorship. The most frequently studied compounds were creatine, latrepirdine and pridopidine. The mean number of participants enrolled was 92.0 and the length of treatment was 262.9 days, and both increased from phase 1 to phase 3 trials. The success rate was 25.0% from phase 1 to phase 2, 19.4% from phase 2 to phase 3, and 14.3% from phase 3 to approval. The overall success rate was 3.5%.
CONCLUSIONS: Although HD is a rare condition, 99 HD trials were identified in a comprehensive clinical trial registry. We found a low success rate at earlier phases of drug-development and a very low trial success rate at later phases. There is a significant gap between drug discovery and development success rates that warrants careful appraisal and improvement.

Keywords: Huntington disease, clinical development, clinical trials, medicines

Introduction

Huntington's disease (HD) is a progressive disease with an autosomal dominant genetic inheritance. It is associated with functional impairment in motor, cognitive, and behavioral domains, secondary to chorea, parkinsonism, postural instability, depression, apathy, irritability, and progressive cognitive impairment [1,2]. It is the most common hereditary neurodegenerative disorder and is fatal [2,3]. For the Caucasian population, its estimated incidence ranges from 0.11 to 0.8 per 100,000 per year and its prevalence is estimated at 5.70 per 100,000 [4]. It is also estimated that approximately 6,000 people in the United Kingdom (UK) and 30,000 in the United States (US) are affected, and at least 150,000 other Americans have a 50% risk of developing HD [5].

The first drug that was approved by the US Food and Drug Administration (FDA) for HD was the dopamine-depleting agent tetrabenazine (TBZ), used to treat chorea [6]. It has a similar indication in some European countries (the license predates the existence of EMA). More recently, in 2017, the US FDA approved deutetrabenazine, also for the treatment of chorea associated with HD [7]. No other drugs are licensed for the treatment of other symptoms or the delay of HD progression [8,9].

Drug development in HD has faced significant obstacles: several therapies have failed to demonstrate efficacy or were associated with significant toxicity [10]. It is thus urgent to identify interventions that improve the various symptoms and signs of HD, or that have a significant impact on disease progression by delaying symptomatic onset or slowing symptoms/disability.

The World Health Organization (WHO) International Clinical Trials Search Portal (ICTRP) is a central database that contains the trial registration datasets provided by 17 clinical trial registries [11]. Clinicaltrials.gov was made available to the public in 2000 [10], and it is the largest clinical trials registry, with 42,772 studies as of May 18, 2017, representing about 75% of all available trials in WHO ICTRP. The Australian New Zealand Clinical Trials Registry (ANZCTR), the European Union Clinical Trials Register (EU-CTR) and the International Clinical Trials Registry Platform (ICTRP) are some of the other databases indexed in WHO ICTRP [11]. Since 2005, the International Committee of Medical Journal Editors (ICMJE) requires trial registration as a condition for publication [12]. In 2006, the WHO stated that all clinical trials should be registered [13]. Currently, it is anticipated that the great majority of ongoing clinical trials are, or will be, captured and recorded by clinical trials databases [14].

We examined WHO ICTRP to determine the characteristics of clinical trials in HD registered in the last 17 years, including currently ongoing trials. The goals of our study were to assess the history of clinical development in HD therapeutics, characterize trends in drug development phases and assess the characteristics of HD candidate therapies. Ultimately, we want to provide an overall snapshot of HD therapy development and identify possible causes for frequent failures in drug development.

Materials and Methods

Interventional trial records were searched using the term “Huntington” on the ICTRP website from inception (1999) to May 2017. The abstracted data were combined with the data available in the original records of the clinical trials registries. Data were abstracted into an electronic database that included trial title and phase, intervention type (drug, device or procedure, or cell transplantation), sponsor, funder (industry, National Institutes of Health [NIH], others or combinations of these), registration and last updated dates, trial identification number, status (completed or active), study start and study estimated end dates, number of patients, study duration, location (US, non-US or both US and non-US), primary and secondary outcomes, inclusion and exclusion criteria, allocation (randomized or not), end-point classification (safety, efficacy, other), intervention model (single group, parallel group, cross-over), and masking (double-blind, open label). Trials were also classified into those assessing a potential disease modifying effect or those assessing a symptomatic effect, according to the analysis of primary endpoints and following the classification of previous authors [15,16].

Two independent authors (AMT, FBR) performed the selection of trials and extracted data. Disagreements were solved by consensus or by a third author (JJF). Trials on behavior interventions were excluded. We did not exclude trials due to incomplete data reporting.

Statistical analyses were conducted using the Statistical Package of Social Sciences version 20.0.0 (SPSS Inc., Chicago, IL, USA). Descriptive statistics were calculated, unpaired Student's t test was used for comparisons between two groups, and one-way analysis of variance (ANOVA) with Tukey's post hoc test applied for comparisons of continuous variables of more than two groups. All tests were two-sided, and a p-value of 0.05 was deemed statistically significant.

Success and attrition rates for each trial phase were calculated. The success rate in a trial phase was calculated as the number of compounds that progressed to the next trial phase divided by the number of compounds in that phase. The attrition rate was the inverse of this. The overall attrition rate was also calculated as the ratio between the number of compounds that did not receive regulatory approval and the total number of compounds.

Results

A total of 99 clinical trials were identified from 1999 to May 2017. The majority of the clinical trials (n=90, 9%) were available from the ClinicalTrials.gov database.

Drug development phase

The included trials were distributed according to the phase of drug development: 24.2% (n=24) phase 1 trials, 46.5% (n=46) phase 2 trials, 20.2% (n=20) phase 3 trials, 2.0% (n=2) phase 4 trials, and 7.1% (n=7) were not specified (Table 1). The number of registered trials was highest in 2009 (18% [n=18]), followed by 2015, 2011 and 2014 (10.1% each [n=10]). Only 7 trials were registered prior to 2004.

Geographic location of the clinical trials

Thirty-four trials (34.3%) were conducted exclusively in the US, 48 trials (48.5%) were conducted exclusively outside the US, and 17 trials (17.2%) were conducted both in and outside the US.

Funding of trials

Most trials were funded by the pharmaceutical industry: 41 (41.4%) trials exclusively by the industry, 19 (19.2%) both by the industry and other entities, and 10 (10.1%) were funded by the NIH. Furthermore, 29 (29.3%) trials were funded exclusively by other organizations, including governmental agencies, universities, and hospitals.

Interventions

The interventions assessed included pharmacological interventions, devices or radiation therapy, and cell transplantation. Not all compounds were tested in consecutive phases (e.g., riluzole, resveratrol and pridopidine). The vast majority of registered trials (87 [89.9%]) evaluated pharmacological interventions, in a total of 41 different compounds. Eight trials (8.1%) evaluated devices or radiation

therapy, and four (4.0%) evaluated cell transplantation; it corresponds to eleven different non-pharmacological interventions. There were no phase 3 or 4 trials evaluating devices, radiation or cell transplantation. The most frequently evaluated compound was latrepirdine (Figure 1). The temporal and sponsor aggregation of the trials evaluating this drug suggest that, although they are considered separately in ICTRP Search Portal, some of them must correspond to components of the same trial. Interventions with the goal of changing disease progression were evaluated in 43 (43.4%) trials, and interventions for symptomatic treatment were evaluated in 56 (56.6%) trials.

Development process for interventions

Seven drugs (58.3%), three devices or procedures (25.0%) and two cell transplantation therapies (16.7%) were evaluated in registered phase 1 trials from 1999 to 2017. Thirty-three drugs (91.7%), two biological compounds (5.6%) and one device (2.8%) were tested in registered phase 2 trials. Since phase 1 trials are safety studies usually performed in healthy volunteers, and some of the interventions tested in HD had been previously tested in other conditions, we only included 3 interventions tested both in phase 1 and phase 2 trials, representing a success rate of 25.0%. Furthermore, 14 compounds were tested in phase 3 clinical trials, of which seven were also tested in phase 2 trials, corresponding to a success rate of 19.4%. During the period covered by our study, only two agents tested in a phase 3 trial obtained FDA approval, i.e., TBZ and deutetrabenazine, which represents a success rate of 14.3%. Only TBZ was assessed in phase 4 trials. Overall, 57 interventions were tested in one or more clinical trials, but only two received FDA approval. This represents a success rate of 3.5% (Figure 2).

Study characteristics

The mean length of treatment was 262.9 days (standard deviation [SD] = 364.4). Data were not available for 9 (9.1%) trials. The mean length of treatment was 103.4 days (SD=183.0) for phase 1 trials, 279.2 days (SD=357.7) for phase 2 trials, 456.0 days (SD=489.3) for phase 3 trials and 28.5 days (SD=38.9) for phase 4 trials. A significant difference in the length of treatment was found between phases (p=0.018).

The mean number of participants enrolled in each trial was 92.0 (SD= 121,3). Two (2.1%) trials did not report this information. The mean number of participants was 25.2 (SD= 19,1) for phase 1 trials, 83.4 (SD=100.6) for phase 2 trials, 227.7 (SD= 175.8) for phase 3 trials and 15 (SD= 7.1) for phase 4 trials. There was a significant difference in the number of participants between phases ($p<0.0001$).

Status of clinical trials

Sixty-seven trials (67.7%) were classified as completed, five (5.1%) as of unknown status and 27 (27.3%) as ongoing. Among ongoing trials, three (11.1%) were phase 1 trials, 10 (37.0%) were phase 2 trials, five (18.5%) were phase 3 trials and two (7.4%) were phase 4 trials (Table 2). Three drugs evaluated in these trials are being tested in more than one trial: pridopidine in 3 clinical trials, and OSU 6162 and TBZ in 2 clinical trials. Six of the eight trials evaluating devices are ongoing, and the majority is related to procedures of transcranial stimulation.

Discussion

Through an analysis of clinical trials registered in the ICTRP, the present study was undertaken to characterize the clinical development of therapeutic interventions in HD and understand their evolution over time. The majority of the 99 trials identified in this study were registered in ClinicalTrials.gov, as required by the FDA since 2007, and were conducted (exclusively or not) in the US. The number of registered trials per year increased throughout this time, which we interpret as being due not only to a greater number of trials being conducted, but also to an increase in the number of trials being registered in public databases [17]. The majority of registered trials were phase 2 trials. Since there is no obligation to register phase 1 trials, these may be underrepresented [13].

The majority of trials evaluated drugs, followed by devices and radiation therapy. Of note, dietary supplements and other compounds such as traditional medicines could be underrepresented in the current dataset. The same is true for non-pharmacological interventions such as exercise programs or other rehabilitation therapies. Although these need to be included in a registry to satisfy ICMJE requirements, they are not covered by the FDA legislation of 2007 [14]. Six of the eight trials evaluating devices are ongoing. In fact, the rate of approval for medical devices by the FDA has increased in the last decade [18] and several National Institute of Building Sciences (NIBS) studies document the great interest in the use of technology for neurologic diseases, such as Parkinson's disease and Alzheimer's disease [19,20], which may explain the increase in the number of devices recently tested in HD. There are few stem cell transplantation studies, with only some early phase trials reported.

There is a limited footprint of non-industry funding sources in HD, with 60 trials (60.6%) being funded by the industry, exclusively or not. However, this is low when compared with other diseases. For example, 78% of clinical trials in Alzheimer's disease are funded exclusively by industry [21]. We hypothesize that the orphan disease status of HD may explain the lower interest of industry.

The attrition rate of interventions was 75.0% from phase 1 to phase 2, and 80.6% from phase 2 to phase 3, and the overall success rate was 3.5%. If these rates were to apply to the 27 compounds being currently evaluated, 0.75 of the compounds in phase 1 and 1.9 of the compounds in phase 2 would advance to the next phase and only 0.9 therapies would receive approval. Thus, with the current development efforts the likelihood of success for a single compound is very low. The overall

success rate of cancer therapy development is about 19% [22] and this value encourages the pharmaceutical industry to invest time, effort, and funds in evaluating cancer therapies. Moreover, when comparing the HD field with neurology in general and other therapeutic areas, HD success rates are higher from phase 1 to phase 2 but lower from phase 2 to phase 3 and from phase 3 to regulatory approval [23-25]. Indeed, the likelihood of approval for neurological diseases in general is about 9%, the success phase from phase 2 to phase 3 is 30%, and the success phase from phase 3 to approval is 61% [23]. Analyzing some common neurological conditions, the likelihood of approval from phase 1 is about 10.7% for pain and 7.2% for psychiatric disorders [23]. Another example are the orphan drugs, in which the success phase from phase 1 to phase 2 is 86.8%, the success phase from phase 2 to phase 3 is 70.0%, and the success rate from phase 3 to approval is 66.9% [23]. Importantly, therapy progression is not sequential. Thus, not all compounds tested at a certain phase were necessarily evaluated in previous phases, and some of the trials may not be registered. A therapeutic agent can be tested in a phase 3 trial, without necessarily having been evaluated in other phases [26]. For example, riluzole was evaluated in a phase 3 trial but was not tested in phase 1 or phase 2 trials, or these studies were not registered. This drug is approved by the FDA for amyotrophic lateral sclerosis and it was evaluated in previous phases for this indication, so the security and tolerability of riluzole for each dosage were already evaluated in other disease [27]. Furthermore, an agent may be tested simultaneously in phase 1 and phase 3 trials as part of an adequate assessment of the drug's interactions and effectiveness.

Of the currently active trials, only three trials are phase 1. Additionally, a small number of trials were registered in the years 2016 and 2017. Although repositioned drugs for HD may enter the process at later phases, these data suggest that relatively few new agents are entering the drug-development process [28]. The possibility that some trials may not be yet registered in trials databases must also be considered.

This study has several limitations. First, the data presented here only focus on registered trials. Similarly, as previously observed, phase 1 trials and trials evaluating complementary medicines and related therapies may be underrepresented. Second, there is a significant amount of missing or unsubmitted data for certain data fields, which limits the completeness of the analyses and thus the interpretability of the results presented [29,30]. Third, our results may not contemplate all ongoing

trials. A recent study showed that 67% of published trials are registered retrospectively and that 3% are not registered at all [31].

An urgent need exists to increase the number of compounds being assessed in trials and progressing successfully towards new therapies for patients with HD. Future studies should access the current use and future directions of trial designs in therapy development, learning from prior successes and failures in the use of these designs. Furthermore, reasons for lack of efficacy in well-conducted trials must be accessed to improve the success rate for drug development. This is applicable to HD as it is for any other disease. We propose that some of these reasons are the strength and quality of target validation, the absence of demonstrated efficacy of compounds, their tolerability and security related to the administered doses, the inadequate selection of treatment endpoints, the inadequate choice (or the absence) of good scales to evaluate the effects of the compounds, and the accuracy and the rational of the selection of patients. The escalating clinical trial costs along phases may also explain a suboptimal design of more advanced.

In conclusion, the analysis of the trajectory of clinical trials provides significant resources concerning improvement of therapy development. We show that the trends in HD therapy development could be assessed and monitored over time. A large attrition rate at earlier phases and a very high trial failure rate in trials at later phases of drug-development were observed. The overall therapy development success rate was 3.5% corresponding to one drug being currently approved for this condition. Still, 27 trials for HD are being conducted, testing 25 different interventions. It is urgent to develop strategies to improve the success rate of HD drug development.

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Conflict of interest

Tiago A Mestre and Joaquim J Ferreira were investigators in a clinical trial assessing the efficacy of ethyl eicosapentaenoic acid for the treatment of Huntington's disease.

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Tables

Table 1. Distribution of HD trials by clinical phase and year of registration.

Year of registration	Phase 1	Phase 2	Phase 3	Phase 4	Unknown phase	Total
1999-2004	1	6	0	0	0	7
2005-2009	13	17	13	1	0	44
2010-2017	10	23	6	2	7	48
Total	24	46	19	3	7	99

Table 2. Ongoing clinical trials (May 22, 2017).

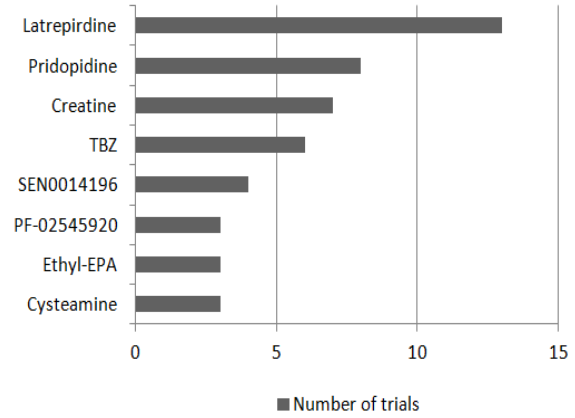
	Phase 1	Phase 2	Phase 3	Phase 4	Unknown	Total
Drugs	1	9	5	2	3	20
Devices and radiation therapy	1	1	0	0	4	6
Cell transplantation	1	0	0	0	0	1
Total	3	10	5	2	7	27

Figure Legends

Figure 1. Ranking of most frequently evaluated interventions. TBZ, tetrabenazine; Ethyl-EPA, ethyl eicosapentaenoic acid.

Figure 2. Number of compounds by phase and overall success rate.

Figures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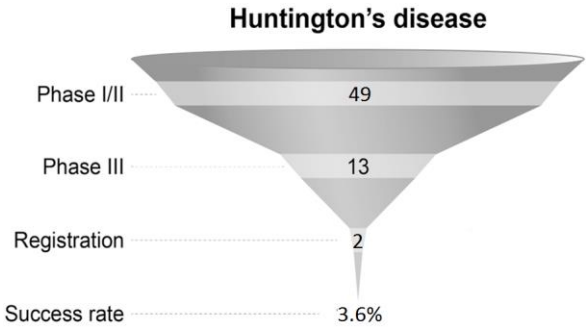
Number of trials


Huntington's disease
Phase I/II
49
Phase III
13
Registration
2
Success rate
3.6%