Neurobiology of Disease 130 (2019) 104530

Contents lists available at ScienceDirect

Neurobiology of Disease

journal homepage: www.elsevier.com/locate/ynbdi

Review

Cysteamine as a novel disease-modifying compound for Parkinson's disease: Over a decade of research supporting a clinical trial

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A B S T R A C T

To date, medical and surgical interventions offered to patients with Parkinson's disease (PD) serve only to manage clinical symptoms; they have not shown the capacity to halt nor reverse degenerative processes. There is therefore an urgent need to identify and/or develop therapeutic strategies that will demonstrate 'disease modifying' capacities. The molecule cystamine, and its reduced form cysteamine, act via a number of pathways determined to be critical to the pathogenesis of PD. In particular, cystamine is capable of crossing the blood-brain barrier, and both agents (cystamine and cysteamine) can promote the secretion of neurotrophic factors, inhibit oxidative stress, reduce inflammatory responses and importantly, have already been trialed in humans for a number of other clinical indications. In the last decade, our laboratory has accumulated compelling evidence that both cystamine and cysteamine can halt, and even reverse, ongoing neurodegenerative processes in a number of different models of PD, and as such, should now be taken forward to clinical trials in PD.

It has been estimated that there are as many as 10 million individuals currently living with Parkinson's disease (PD) worldwide, with a prevalence > 1900 people per 100,000 amongst the elderly (Association European Parkinson's Disease, 2018; Parkinson's Disease Statistics, 2018; Feigin et al., 2017; Pringsheim et al., 2014). The world's population continues to age at an unprecedented rate and as of today, 8.5% of people on the planet are 65 years of age or older, and this percentage is projected to increase to nearly 17% by 2050 (He et al., 2016). Given that aging is the single biggest risk factor for developing PD, the need to find a well-tolerated disease-modifying therapy is imperative. In this review, we make the case that one such agent that offers great promise is **cysteamine** and that the time is right to trial it in PD.

1. The pressing need for new treatments

PD is a chronic neurodegenerative disorder that is characterized by motor features (bradykinesia, resting tremors, muscular rigidity and gait problems) (Obeso et al., 2017; Magrinelli et al., 2016; Mazzoni et al., 2012) as well as a range of non-motor problems (anosmia, sleep disruption, mood disorder, constipation, etc.) (Tibar et al., 2018; Biundo et al., 2017). The pathological basis for this includes: 1) the loss of specific neuronal populations within the central and enteric nervous systems, the most notable of which is the dopaminergic nigrostriatal pathway (McGregor and Nelson, 2019) and 2) the presence of Lewy bodies/neurites largely composed of misfolded α-synuclein (α-Syn) protein (Braak et al., 1999; Spillantini et al., 1997). Pharmacotherapeutic tools, targeting dopamine replacement, remain the cornerstone of medical care but their long-term use are limited by adverse motor complications and suboptimal responses (Ahlskog, 2007; Olanow, 2004), including a number of neuropsychiatric problems. These drugs, while helping some of the motor features of PD, do not slow down disease progression. Indeed, there are no disease-modifying interventions for PD and this represents a major unmet clinical need. The question therefore arises as to what might such a disease-modifying drug correspond to? One possibility is to develop an agent that targets some key node in the pathway and which, if corrected, would stop all the downstream pathogenic events - e.g. switching off abnormal α-Syn production. An alternative, and not mutually exclusive approach, is to use a drug, or drugs, that target multiple pathways linked to pathogenesis with the hope that this will summate to stop, or dramatically slow down, the disease process.

2. Cystamine/Cysteamine: potential candidates with disease-modifying properties

Cystamine is an organic disulfide that is formed by the dimerization of cysteamine molecules linked by disulphide bonds. Endogenous cysteamine, as well as its oxidized form cystamine, are by-products of the metabolism of coenzyme A in tissues (Pitari et al., 1992). Cystamine and cysteamine are natural scavengers of hydroxyl radicals, which confers, in part, their radioprotective action on DNA irradiation

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https://doi.org/10.1016/j.nbd.2019.104530
Received 10 June 2019; Received in revised form 4 July 2019; Accepted 9 July 2019
Available online 10 July 2019

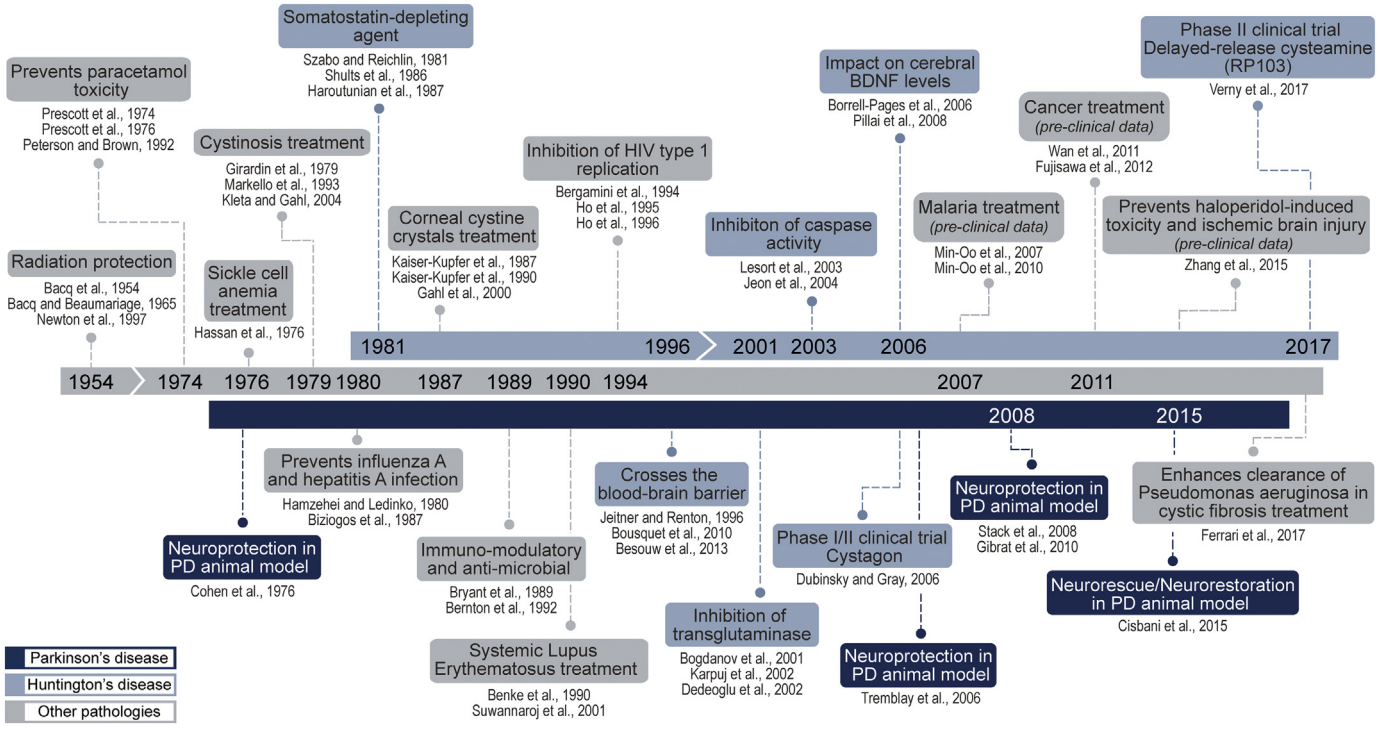

Fig. 1. The repertoire of properties of cystamine/cystemaine - timeline of related discoveries and uses. Abbreviations: BDNF, brain-derived neurotrophic factor; HD, Huntington's disease; HIV, human immunodeficiency virus; PD, Parkinson's disease.

(Newton et al., 1997; Bacq and Beaumariage, 1965; Bacq, 1954). This antioxidative capacity could be linked, in some measure, to their ability to increase glutathione levels. Cystamine can also augment concentrations of cysteine, another well-known antioxidant, as observed in cell culture (Fox et al., 2004; Ishii et al., 1981a, 1981b) and animal models (Pinto et al., 2005). High doses of cystamine delivered through the drinking water have also been shown to attenuate oxidative stress and, consequently, the deleterious effects of the toxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) in mitochondrial function (Stack et al., 2008). Aside from their prominent anti-oxidant role, cystamine and cysteamine have also been demonstrated to be hepatoprotective against acetaminophen poisoning, by enhancing levels of the anti-oxidant glutathione (Peterson and Brown, 1992; Prescott et al., 1976; Prescott et al., 1974). More recently, these molecules have been recognized as antiviral agents effective against influenza A and hepatitis A (Biziagos et al., 1987; Hamzehei and Ledinko, 1980), and more remarkably against the human immunodeficiency virus (HIV)-1 ((Ho et al., 1996, Ho et al., 1995; Bergamini et al., 1994; also see Toohey, 2009 for review) (Fig. 1) (Ferrari et al., 2017; Zhang et al., 2015; Besouw et al., 2013; Wan et al., 2011; Min-Oo et al., 2010; Pillai et al., 2008; Min-Oo et al., 2007; Tremblay et al., 2006; Jeon et al., 2004; Kleta and Gahl, 2004; Lesort et al., 2003; Dedeoglu et al., 2002; Karpuj et al., 2002; Bogdanov et al., 2001; Suwannaroj et al., 2001; Gahl et al., 2000; Jeitner and Renton, 1996; Markello et al., 1993; Bernton et al., 1992; Benke et al., 1990; Kaiser-Kupfer et al., 1990; Bryant et al., 1989; Haroutunian et al., 1987; Kaiser-Kupfer et al., 1987; Shults et al., 1986; Szabo and Reichlin, 1981; Girardin et al., 1979; Cohen et al., 1976; Hassan et al., 1976). Indeed, cysteamine, in various different preparations, holds 7 rare drug designations, including treating cystic fibrosis (De Stefano and Maiuri, 2015) and pancreatic cancer (Food and Drug Administration, 2018; Fujisawa et al., 2012) as well as being approved by the Food and Drug administration (FDA) and the European Medicines Agency (EMA) for cystinosis since 1994. Consequently, the safety and efficacy of various formulations of cysteamine have already been extensively tested in clinical trials, including for neurodegenerative disorders such as Huntington's disease (Verny et al., 2017; Prundean et al., 2015; Dubinsky and Gray, 2006).

Based on this, it is logical to speculate that this drug may also be beneficial in the context of PD. Over the last 10–15 years, we have sought to answer this question using a wide range of preclinical approaches. In particular, we have demonstrated that 1) cystamine is neuroprotective in toxin-induced animal models of PD (Cisbani et al., 2015; Gibrat and Cicchetti, 2011; Gibrat et al., 2010; Bousquet et al., 2010), 2) that it can cross the blood-brain-barrier (Bousquet et al., 2010), a feature which carries enormous clinical implications given the rarity of drugs that displays this property, 3) it prevents cell death in part by increasing levels of brain-derived neurotrophic factor (BDNF) (Gibrat et al., 2010) and more importantly 4) cystamine, and its reduced derivative cysteamine, can halt and reverse ongoing neurodegenerative processes in chronic lesion models of PD and therefore serve as a disease-modifying strategy in this disorder (Cisbani et al., 2015). To increase the applicability of our findings to the clinic, we also used induced pluripotent stem cells (iPSC) derived from patients with a synuclein alpha gene (SNCA) triplication. Cells exposed to the toxin 6-hydroxydopamine (6-OHDA) and subsequently treated with cysteamine depicted a morphology and neurite arborization that was very similar to normal conditions (unpublished data). Our most recent work suggests that cysteamine can slow down the onset of behavioral deficits in pre-symptomatic Thy1-α-Syn transgenic mice that over-express human α-Syn as well as improve behavioral deficits in symptomatic mice. Post-mortem analyses further revealed diminished levels of the phosphorylated form of the α-Syn protein within the brain regions targeted by the disease in symptomatic mice (unpublished data) (Fig. 2). This relates, in part, to the ability of cystamine/cysteamine to be a competitive inhibitor of transglutaminase, which is implicated in the formation of protein aggregates (Hsu et al., 2008), as has been shown in animal models of Huntington's disease (Borrell-Pages et al., 2006).

In addition to these findings highlighting the multiple pathways by which cysteamine can generate benefits, we tested the possibility that it could improve other aspects of PD, including cognitive impairments. Changes in cognitive abilities are now recognized as a common non-motor symptom of PD. In fact, mild cognitive decline is reported in

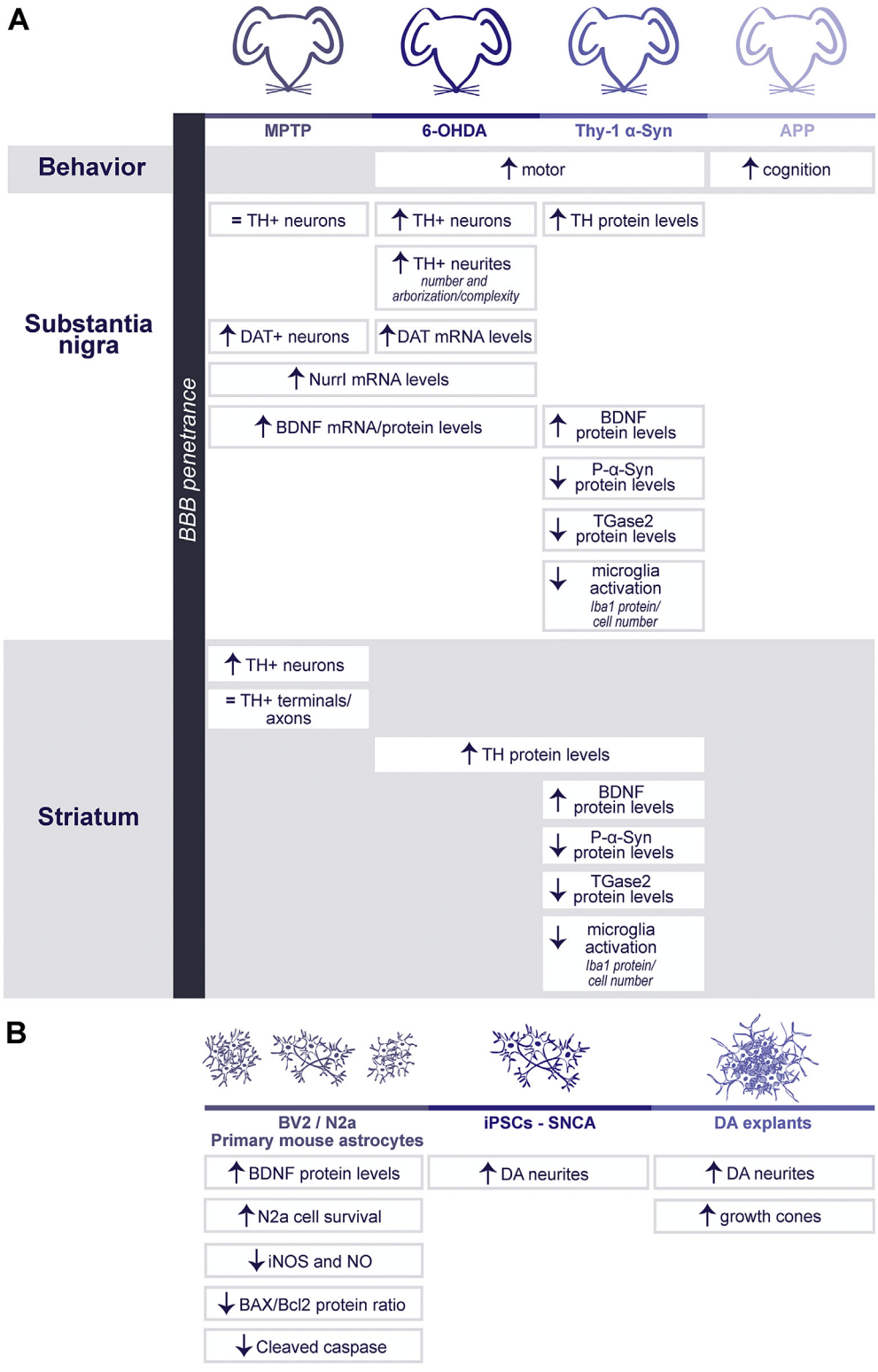

Fig. 2. The effects and mechanisms of action of cystamine - pre-clinical data.
A. Summary of behavioral and post-mortem data collected in various mouse models including the MPTP, 6-OHDA, Thy1-α-Syn and APP mice. **B**. Summary of data collected in various in vitro paradigms using BV2 microglial cells, N2A neuroblastoma or primary cultures of mouse astrocytes, DA neurons derived from iPSC with a SNCA mutation or DA explants. Abbreviations: APP, amyloid-β precursor protein; BAX, Bcl-2-associated X protein; Bcl2, B-cell lymphoma 2; BDNF, brain-derived neurotrophic factor; BV2, immortalized murine microglial cell line; DA, dopamine; TH, tyrosine hydroxylase; DAT, dopamine transporter; Iba1, Ionized calcium binding adaptor molecule 1; iNOS, nitric oxide synthase; iPSCs, induced pluripotent stem cells; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; mRNA, Ribonucleic acid messenger; NO, nitric oxide; Nurr1, nuclear receptor related protein 1; N2a, mouse neural crest-derived cell line; P-α-Syn, phosphorylated alpha-synuclein; SNCA, synuclein alpha gene; TGase2, transglutaminase 2; TH, Tyrosine hydroxylase; Thy-1, Thymocyte antigen 1; 6-OHDA, 6-hydroxydoapmine.

20–50% of patients, with longitudinal studies revealing that > 40% of patients have demented by 10 years (Williams-Gray et al., 2013) and up to 80% of patients with disease duration exceeding 20 years (Goldman et al., 2018). However, a very limited number of currently available animal models of PD depict frank cognitive impairments (Magen and Chesselet, 2011). We therefore opted to work in a related neurodegenerative disorder, Alzheimer's disease, using a genetic mouse line APP-Psen1 (B6-Tg (Thy1-APPswe; Thy1-PS1 L166P) expressing human transgenes for the amyloid precursor protein (APP) bearing the Swedish mutation and presenilin-1 (PSEN1) containing an L166P mutation, both under the control of the Thy-1 promoter (Radde et al., 2006). Chronic cysteamine treatment (daily injections for a period of 4 months) led to significant improvements in the habituation and spatial learning deficits (Fig. 3). These findings, although very preliminary, indicate that the benefits of cysteamine are varied and are likely to go beyond the motor deficits associated to PD which is highly relevant given the increasing recognition that PD, such as other proteinopathies of the aging central nervous system, have a mixed pathology including vascular

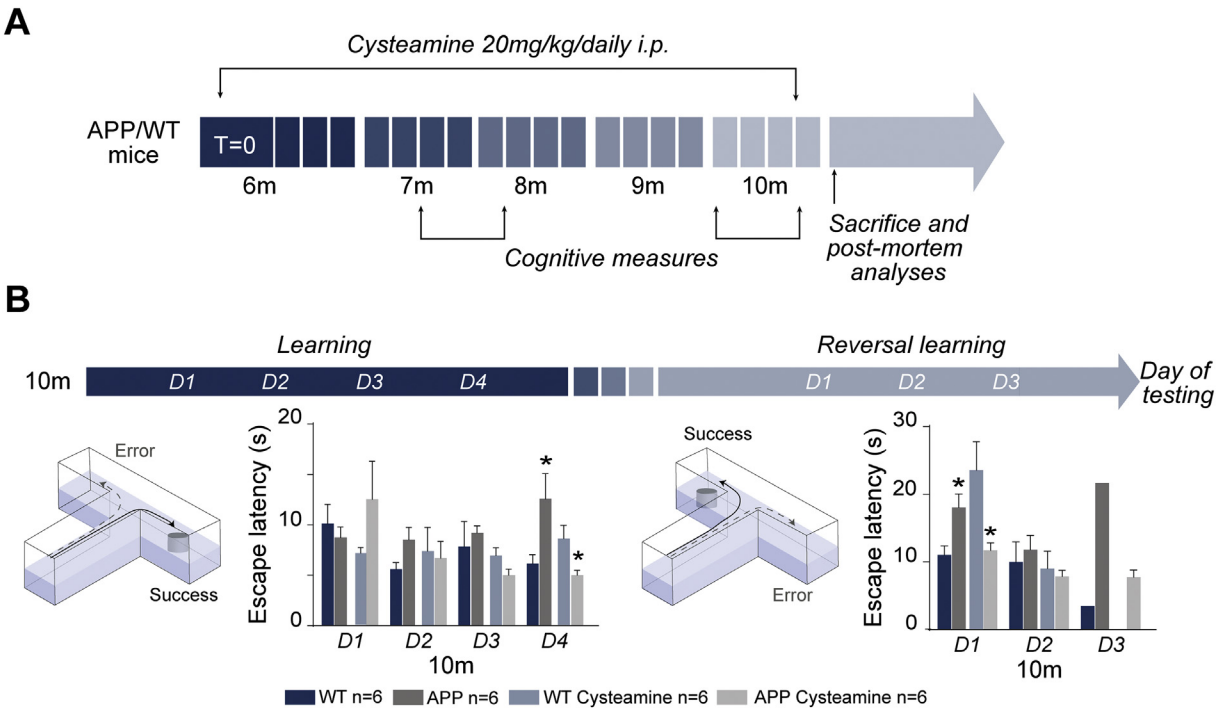

Fig. 3. Evidence for the benefits of cysteamine on cognitive impairments - preliminary observations.
A. Timeline of experimentations. **B**. Effects of cysteamine on learning and reversal learning in APP mice using a T-water maze. Statistical analyses were performed using a Two-way ANOVA followed by a Bonferroni post-test. $N = 6$ per group. Abbreviations: APP; amyloid-β precursor protein; D, day; i.p., intraperitoneal injection; m, month; s, second; WT, wild type.

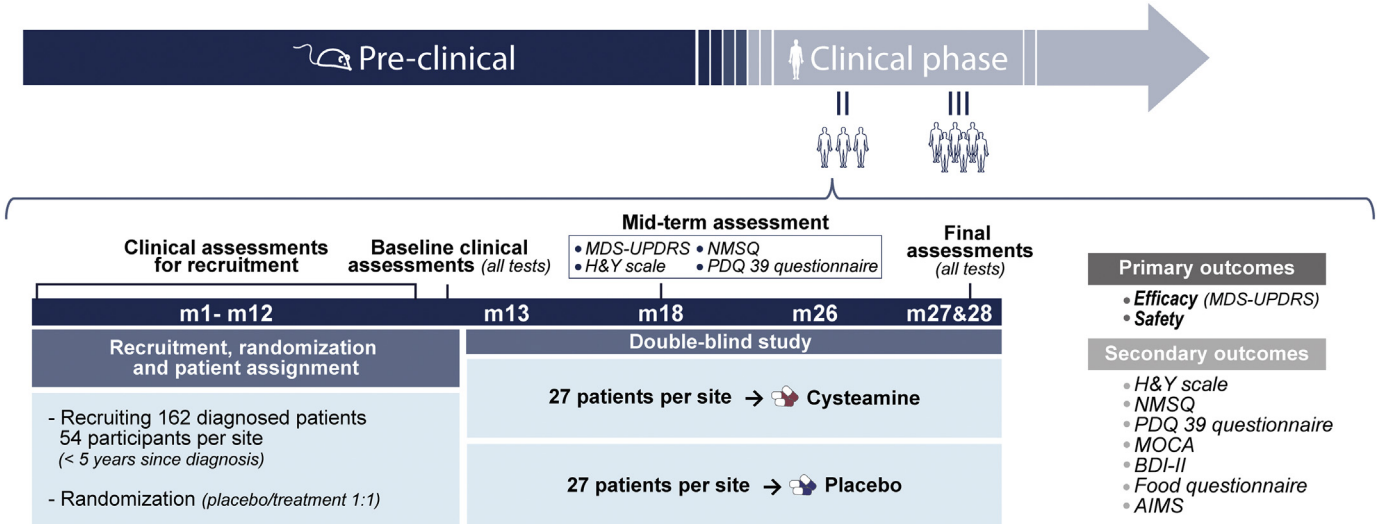

Fig. 4. Putative clinical trial design for testing the disease-modifying potential of cysteamine in PD patients. Abbreviations: AIMS, abnormal involuntary movement scale; BDI-II, Beck Depression Inventory-II; H&Y scale, Hoehn and Yahr scale; m, month; MDS-UPDRS, movement disorder society - unified Parkinson's disease rating scale; MOCA, Montreal cognitive assessment; NMSQ, non-motor symptoms questionnaire; PDQ, Parkinson's disease questionnaire.

problems, amyloid, tau and α-Syn aggregation (Robinson et al., 2018; Rahimi and Kovacs, 2014).

Taken together, there is very strong evidence to test cysteamine in PD patients. In our opinion, the best approach would be a double-blind, placebo-controlled, multicentre study distributed over at least 3 clinical sites to facilitate recruitment. For this trial, we would focus on patients with early diagnosis (< 5 years). Primary outcome measures would include safety and efficacy, while secondary outcomes would target improvements of various other clinical aspects, including cognitive-related symptoms. Patients would be randomized (1:1) and cysteamine, or the matched placebo, would be administered for a period of 14 months. At month 7 of the double-blind study, i.e. mid-trial, a mini-battery of selected clinical measures (new MDS-UPDRS, Hoehn and Yahr scale, Non-motor symptom assessment for PD (NMSQ) and PDQ 39 questionnaire) would be performed to evaluate tolerability and any signs of clinical efficacy. At the end of the trial, a final and complete assessment would be performed (see Fig. 4). We have evaluated that recruiting approximately 160 patients would achieve 80% power to detect a 4-unit improvement of MDS-UPDRS Score. Following a successful phase II trial, cysteamine would progress to a phase III trial where the drug would be tested in a larger group of individuals to confirm efficacy, monitor side-effects and compare it to commonly used

treatments.

In conclusion, there is a strong corpus of work showing how cysteamine could help in PD with extensive preclinical evidence indicating that it does slow down or arrest disease progression. As such, we believe that cysteamine is ready for translation into a clinical trial in early stage PD patients to determine its potential as a disease-modifying agent.

Conflict of Interests statement

F.C., L.S.D., A.S. and H.L.D. declare no conflicts of interest.

Funding sources

Research Chair from the Fonds de Recherche du Québec en santé (FRQS).

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