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Journal

Journal of Neurology, 261(8)

ISSN

0340-5354

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Publication Date

2014

DOI

10.1007/s00415-013-7172-z

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J Neurol (2014) 261:1461–1468
DOI 10.1007/s00415-013-7172-z

REVIEW

Pharmacological therapies in post stroke recovery: recommendations for future clinical trials

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Received: 16 September 2013 / Revised: 20 October 2013 / Accepted: 21 October 2013 / Published online: 13 November 2013
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Abstract Stroke is a leading cause of serious long-term disability in adults and is the second leading cause of death worldwide. Early reperfusion and neuroprotection techniques have been the focus of much effort with the aim of very acute treatment of the stroke. Targeting different mechanisms, pharmacological therapies have the potential to reduce disability in a large fraction of patients who survive the acute stroke. The brain's capacity to reorganize after stroke through plasticity mechanisms can be modulated by pharmacological agents. A number of therapeutic interventions are under study, including small molecules, growth factors, and monoclonal antibodies. Recently it has been shown that the SSRI fluoxetine improved motor deficit in patients with ischaemic stroke and hemiplegia which appeared to be independent of the presence of depression. In this context, it is of major importance to support innovative research in order to promote the emergence of new pharmacological treatments targeting neurological recovery after stroke, as opposed to acute de-occlusion and neuroprotection. This paper is the work of a group of 14 scientists with aim of (1) addressing key areas of the basic and clinical aspects of human brain plasticity after stroke and potential pharmacological targets for recovery, (2) asking questions about the most appropriate characteristics of clinical trials testing drugs in post stroke recovery and (3) proposing recommendations for future clinical trials.

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Keywords Stroke recovery · Brain plasticity · Pharmacology · Clinical trials · Clinical scales · Outcome scales · Statistical analysis

Introduction

Stroke is a leading cause of serious long-term disability in the United States in adults and is the second leading cause of death worldwide [1]. Considerable advances have been achieved in the past 25 years in terms of stroke primary and secondary prevention, mainly with the control of vascular risk factors and with the treatment of the cause.

Early reperfusion and neuroprotection techniques also have been the focus of much effort with the aim of very acute treatment of the stroke [2]. During the twentieth century, preclinical studies identified at least 75 agents as potentially active that were tested in 178 clinical trials. Only three of them were positive and only one drug (rtPA) was registered by the health authorities. Finally the main gain came from stroke care organizations and stroke units which were shown to improve stroke mortality and morbidity [3].

Pharmacological therapies have the potential to reduce disability in a large fraction of patients who survive the acute stroke [4]. The brain's capacity to reorganize after stroke through plasticity mechanisms can be modulated by pharmacological agents. A number of therapeutic interventions are under study, including small molecules, growth factors, other large molecules such as monoclonal antibodies, or stem cells. Recently the FLAME (fluoxetine for motor recovery after ischaemic stroke) study showed that the selective serotonin reuptake inhibitor (SSRI) fluoxetine improved motor deficit in patients with ischaemic stroke and hemiplegia which appeared to be independent of the presence of depression [5].

In this context, it is of major importance to support innovative research in order to promote the emergence of new pharmacological treatments targeting neurological recovery after stroke, as opposed to acute de-occlusion and neuroprotection, and at the same time to avoid the mistakes and pitfalls of past studies [3, 6]. The treatment should be optimally "patient, physician and healthcare system friendly". It should be suitable for administration to a large number of patients, compatible with other treatments like acute thrombolysis, usable without major technical facilities and acceptable in terms of cost.

This paper is the work of a group of 14 scientists who participated in a 2012 workshop with aim of (1) addressing key areas of the basic and clinical aspects of human brain plasticity after stroke and potential pharmacological targets for recovery, (2) asking questions about the most appropriate characteristics of clinical trials testing drugs in post stroke recovery and (3) proposing recommendations for future clinical trials.

Pathophysiology, treatment targets: a rational basis for future clinical trials

Treatment target differs at the very acute stage of the stroke and at later phases. Different cellular (metabolic, genetic, and inflammatory) processes, which are dependent on the time that has elapsed after stroke onset, play a role in the final outcome. Early reperfusion techniques aim at limiting damage and reversing cellular dysfunction. Reperfusion damage affects the neurovascular unit and includes the formation of free radicals, vasogenic oedema, blood brain barrier leakage, leukocyte infiltration and enhanced activation of microglia. While early reperfusion saves (part or all of) the penumbra, late reperfusion may be detrimental. Neuroprotective agents have been investigated in the hope that they could influence the various complicated pathways at the level of cell metabolism. None of them have been shown to be beneficial in randomized clinical trials.

With respect to outcome, we do not know the impact of the different cellular processes that occur during the first days after stroke onset. However, they have been described in basic research and animal experiments. Cellular dysfunction, including selective neuronal death, metabolic depression, inflammation, blood brain barrier leakage and axonal growth inhibition, starts almost immediately after stroke and can affect the salvaged penumbra. Subsequently, processes such as secondary expansion of infarction, programmed apoptosis, neovascularization/angiogenesis, release of growth factors and neurotoxic chemokines, neurogenesis and neural stem cell migration, circuit remodelling, and reorganisation of large-scale neural networks occur. Laboratory studies suggest that it might be possible to promote brain plasticity and neurological recovery by pharmacological or cell-based treatments [7–9].

Two intertwined mechanisms of brain adaptive or sometimes maladaptive plasticity are classically

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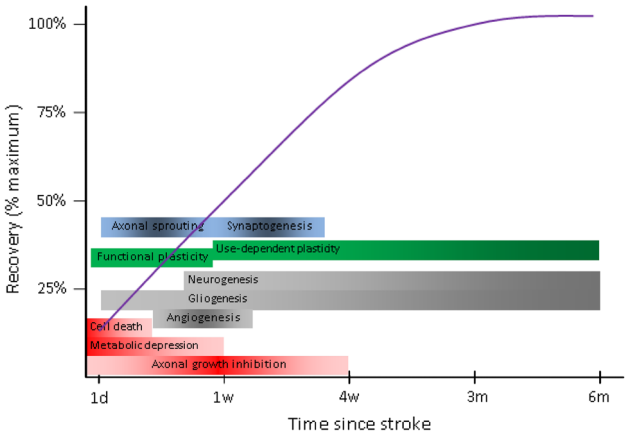

Fig. 1 Time course of post stroke recovery (adapted from Wieloch and Nikolich [10])

differentiated. The first is functional plasticity, in the form of altered neuronal connections, excitability and synaptic efficacy, which develops spontaneously after the stroke. This begins within hours of symptom onset and gives way to heightened use-dependent functional plasticity and relearning. In animals, these processes are maximally active around 1 week after stroke, and seem to reach a plateau by 3–4 weeks, although they can be modulated in the chronic stage using appropriate intervention. The second mechanism is morphological plasticity, which is underpinned by dendritic spine remodelling, axonal sprouting and synaptogenesis in the initial stage. Finally, although still unproven, cell genesis may also support recovery of function in surviving tissues, and is the target of treatments aimed at neural repair mechanisms (Fig. 1) [10].

Functional recovery after stroke usually evolves over months and, in some cases, years. Two different behavioural processes are involved in functional recovery after stroke: (1) restoration of the lost functions and (2) acquisition of new behavioural strategies to circumvent rather than to restore lost functions. Neuroplasticity is defined as the ability to adapt neuronal functions and connections at the molecular, cellular or functional level [11]. Modern neuroimaging techniques have shown that it can take place in the perilesional areas and also in remote areas (ipsi- or contralesional hemisphere or cerebellum). Recovery is a dynamic process and different regions at different time-points may support recovery of function. The neuronal activation in these areas is probably the key factor in the process of "use-dependent" brain plasticity (Fig. 1) [12].

It is probable that the intensity of rehabilitation plays an important role in the process of brain plasticity and it has been shown that rehabilitation techniques affect brain reorganization [13]. Rehabilitation after stroke should aim at reducing impairment and restoring function, and should also work on adaptive and compensatory strategies. Rehabilitation should probably start as early as possible, preferably in the stroke unit and should be guided by a well-trained multidisciplinary team. Rehabilitation procedures are difficult to quantify and there is no real consensus on how the techniques should be standardized. Moreover, the qualitative aspect of rehabilitation remains in

Table 1 Main clinical trials testing SSRI in stroke recovering patients

	Drug	Dose, regimen, treatment duration	Number of patients	Trial design	Time of inclusion	Clinical outcome criteria	Other outcome criteria	Rehab program	Main results	Depression
Dam et al. [20]	Fluoxetine Maprotiline	20 mg o.d. 90 days	48	Parallel groups (3 groups)	1–6 months	HSS	None	Yes	Positive	No
Chollet et al. [17]	Fluoxetine	20 mg (single dose)	8	Cross over	15–30 days	Finger tapping and grip	fMRI	Yes	Positive	No
Zittel et al. [19]	Citalopram	40 mg (single dose)	8	Cross over	More than 6 months	Nine hole peg test	None	Yes	Positive	No
Chollet et al. [17]	Citalopram	10 mg o.d. 30 days	20	Parallel groups (2 groups)	Not reported	NIHSS	TMS	Yes	Positive	No
Chollet et al. [5]	Fluoxetine	20 mg o.d. 90 days	118	Parallel groups (2 groups)	<10 days	Fugl Meyer score	None	Yes	Positive	No
Mikami et al. [21]	Fluoxetine Nortriptiline	20 mg o.d. 90 days	83	Parallel groups (3 groups)	Within 6 months	Rankin	None	Yes	Positive	Both

question as no consensus exists for standardized programmes [14].

Although supported by animal model experiments, modulating the tone of a specific brain neurotransmitter in humans is an approach that remains insufficiently studied. Some studies have used drugs that target multiple brain monoaminergic receptors (e.g., dopaminergic drugs, amphetamines). The results of clinical studies are mixed [15–18].

Studies of serotonergic agents after stroke have shown improved functional outcomes [19, 20] (Table 1). In the double-blind, placebo-controlled trial "fluoxetine for motor recovery after acute ischemic stroke" (FLAME) [5], non-depressed patients who had an ischemic stroke and had hemiplegia or hemiparesis were randomized to fluoxetine (20 mg o.d.) or placebo for 3 months starting 5–10 days after the onset of stroke. Fugl Meyer Motor Scale (FMMS) improvement at day 90 was significantly greater and the number of patients who became independent was higher in the fluoxetine group. The benefit appears to be independent of the direct antidepressant action. To date, the FLAME trial is the most important well designed pharmacological study to show a positive effect on stroke motor recovery. Other studies suggest a long lasting effect of the drug [21].

Other therapeutic avenues are currently under investigation [4, 11] with growth factors, other large molecules or stem cells [22] aiming at repairing the damaged brain. Some data are already available but until now no positive effect has been shown.

Stroke is a complex disease and a heterogeneous condition [23]. It is necessary for a clinician to match the right patients with the right therapy. Cerebrovascular disease appears to be the end product of many different diseases and risk factors. Stroke injury, stroke clinical expression and stroke outcome vary greatly from one patient to the next. Sometimes these differences are trivial in practice but, in most cases, they are associated with real differences in the behavioural sequelae. They influence the approaches to optimizing the effects of restorative therapies. Bath et al. [24] recently noted that "In stroke trials, the impact of covariates such as age and severity on outcome is typically much larger than the treatment effect that is being measured".

The pharmaco-economics of a new therapy are non-medical and non-scientific issues that are not often considered by researchers but they are a major question in industrialized countries and probably more so in developing countries. Studies on cost effectiveness are hampered by the fact that the published costs of stroke vary considerably with time and place and do not take post-stroke disorders into account when assessing cost effectiveness [6]. Low cost care management and low cost treatment are a major challenge [6, 25].

Questions regarding clinical trials for pharmacological therapies in stroke recovery

Clinical trials for pharmacological therapies in post-stroke patients should be hypothesis-driven, and if possible, buttressed by data from basic research. Those data should include not only cellular and molecular mechanisms but also integrative basic research using animal models. This is an important aspect to understand, at least partially, the mechanism of the drug on brain network dysfunction. Conversely, while such scientific data are essential for the understanding of the mechanisms of actions, clinical research often is ahead of the basic science understandings of specific therapies. The need for clear scientific explanations for the efficacy of a therapy should not hamper the testing of therapies that have shown promise in patients [26].

What is the appropriate timing for post-stroke recovery clinical trials?

The key period for recovery is probably within the first 3 months after stroke onset and may well be within the first 2–3 weeks (Fig. 1). It is probably during this period that, first, the magnitude of potential recovery is at his highest and, second, treatments are potentially efficient as they can interact with the spontaneous process of recovery [27, 28].

In order to maximise its effects, pharmacological treatment should therefore be started as soon as possible after the stroke, probably within one or 2 weeks as supported by preclinical data. The treatment duration should be 6–12 weeks so as to cover the period of maximal spontaneous recovery. It is likely that the treatment duration could be shorter in patients with mild to moderate deficit in order to avoid any ceiling effect [29].

Baseline measures should be made at a standardized time within a limited time window for inclusion, due to spontaneous, fast evolution of the patient's condition. A second measurement should be made at the end of treatment. An intermediate measurement can be useful to detect whether a treatment effect is present if a parameter is suspected to influence the speed of recovery. A follow-up measure at 6 or 12 months after stroke is important for investigating the potential long-term benefits. However, long-term measurements can be difficult to interpret as many confounding factors may have occurred in such a long period of time such as recurrent stroke or other serious comorbid diseases.

Clinical studies show that recovery may still occur after 3 months but with lower speed and smaller magnitude. Drug treatments and clinical trials should consider the fact that the expected effect of the intervention will probably be smaller. Recovery, however, may be longer in some brain systems, such as those related to cognitive functions [29].

What is the target population and sample size?

There are two main advantages to having an identified target population. First, the variance and, consequently, the sample size is reduced and the power of the study is strengthened. Second, the effect of a therapy may be maximal if the presence of the biological target can be confirmed. For many of the approaches to restorative therapy, the intervention is unlikely to help if the main brain elements targeted by therapy have been destroyed by the stroke. Similarly, if the brain regions important to recovery of the behavioural endpoints are severely injured, such as the corticospinal tract in a study focusing on upper limb function or gait velocity, effects of a restorative therapy may be limited. The counterpart is that recruitment may be slow.

The main idea is to maximize the likelihood that a patient's features match those present in the animal models that demonstrated preclinical therapeutic efficacy. This issue was raised in an analysis of data from the Phase III "Everest Trial" of epidural motor cortex stimulation [30]. The rodent and primate studies that demonstrated preclinical efficacy all required preserved motor evoked potentials, but the human study did not. While the overall trial did not find a difference, a post hoc analysis did find that preserved motor evoked potentials were associated with a significantly higher rate of clinical benefit.

Non-clinical biomarkers can help to target the population or to stratify within the selected population. Serum or other body fluids/tissues could be used to derive a measure of relevant biomarkers, such as of inflammatory mediators or neurotrophin levels [34]. Increasing evidence suggests that genetic variation in systems related to neural repair is associated with differences in brain plasticity and stroke recovery [31]. A number of anatomical methods, such as structural multimodal MRI, may be useful to define patient subpopulations: volume infarct, extent of injury to a key grey matter region, hand motor area identification [32], white matter tracts, such as the corticospinal tract defined using diffusion tensor tractography [33], voxel based morphometry, cortical thickness. Other methods such as isotope-based methods near-infrared spectroscopy, magnetoencephalography and electroencephalography, transcranial magnetic stimulation or transcranial current simulation also provide information on intracortical and interhemispheric function, as well as the functional integrity of descending motor pathways [29].

The choice of method should be guided by the message of available preclinical and clinical data. Centres should be selected appropriately.

What are the appropriate criteria to assess recovery in clinical trials?

Several clinical scales have been used to measure recovery. Some are very analytical scales that focus on a single function, e.g. grip strength or finger tapping test, which measure variation in motor capacities. Other scales are designed to evaluate neurological deficits (National Institute of Health Stroke Scale/NIHSS, FMMS). Additional scales are global functional scales designed to estimate handicap (modified Rankin Scale—mRS). No scale is perfect nor does a single scale assess all the features of a complex disease such as stroke; still, all are useful in some way to assess recovery. A global scale like mRS, used once at a certain time point after stroke, measures the patient's outcome, i.e. the consequences of recovery on the patient's life while more neurological scales used at baseline and later time points, like FMMS or NIHSS, measure the clinical phenomenon of recovery over time. However, the main judgement criteria for any intervention in the field of post-stroke recovery will consider a global scale designed to evaluate changes in the daily life of the patients.

The modified Rankin Scale has good intra- and inter-observer variability but has also some limitations. Only six categories are used to assess quality of life (0–1), independence (2), dependence, walking capacity and daily activities (3–5). The distance between the six points is not similar and there is an interaction with other parameters not strictly measured with mRS (mood, cognition, environment, etc.). Finally, dependence and independence can vary with age, activities, cultural background, cognition and context [36]. On the other hand, this sort of functional scale also incorporates any detrimental effects of the drug on extra-neurological functions.

The choice of the primary outcome criteria should vary according to the type of clinical trial. Early trials aimed at proving a concept or a mechanism (phase IIa) might find that a scale that focuses on a specific neurological deficit to be appropriate. In that case, global scales can be considered as secondary criteria. On the other hand, in later trials, a global scale is necessary to measure the impact of the intervention on patients' lives. Other scales (NIHSS, FMMS, cognitive scales, depression scale, etc.) will be of interest in confirming the suspected mechanism of action [26, 35]. Finally, surrogate markers of biological effects, such as fMRI or TMS, are useful to implement as a substudy in order to underpin the mechanisms of action and correlation with clinical outcome of the pharmacological agent tested.

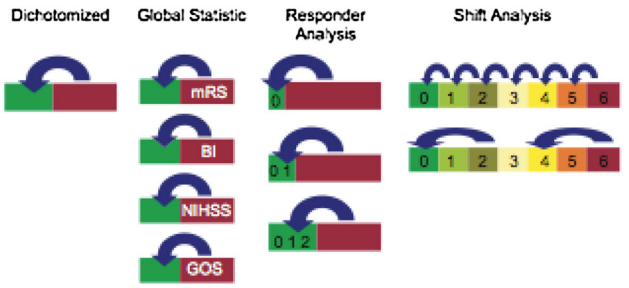

Fig. 2 Statistical analysis of clinical trials. (From Saver et al. [38], *Stroke*)

What is the appropriate method to analyze outcome criteria?

Examples exist in the literature showing that different results would have been found in the same clinical trial when other statistical methods had been used to analyse the data [37].

If we consider mRS, dichotomized end point analysis has been widely used until now [39]. The principle is to compare the proportion of patients with mRS 0–2 (for example) at the end of the treatment between the two groups. So an ordinal score is changed into a binary system with a need to determine a cut-off. This can be done with other scales (Barthel index/BI, NIHSS) with the advantage of great clinical significance, ease of comprehension and the capacity to calculate the NNT (number needed to treat). On the other hand, the choice of the cut-off is something of a gamble and it is difficult to consider that patients scoring 0–2 or scoring 3–5 on the mRS are in the same category [39]. Moreover, intermediate data are not included in such an approach.

The global statistical analysis is a method grouping together several parameters of post-stroke recovery. The idea is that no one scale is capable of accounting for all aspects of a patient's condition. For example, the quality of post-stroke recovery could be the result of neurological deficit, daily living dependence, cognitive status, and quality of life. The association of several scales allows the study power to be increased. On the other hand, clinical significance can be difficult to assess with this technique and it gives no information on the specificities of the drug's action.

The responder analysis (adjusted dichotomous) method, also called baseline severity analysis, is based on the concept of response to treatment and has the advantage of adjusting judgement to the initial severity of the patient's condition [26, 35–40]. The question is: has the patient improved when compared to the initial condition? The advantage is a more accurate analysis of the treatment effect, independently of the expected outcome which is dictated by the topography and extent of the permanent tissue damage; the difficulty lies in defining what a responder is (e.g., 50 %).

The shift analysis method is aimed at assessing differences among treatment groups at each point of the scale considered. The question is: does the treatment induce a change of at least one point on the scale? This identifies improvement and worsening with no necessity to define an objective for treatment response in advance. The main difficulty of the method is that the data are difficult to understand and to interpret. However, the re-analysis of a number of clinical trials has shown that the shift analysis may be more effective than a dichotomized analysis (Fig. 2) [38].

All these methods are potentially appropriate and it is difficult to choose one of them exclusively. If dichotomized analysis appears to be the best to show the clinical benefit of the treatment, we think that it may be used in combination to other methods.

Conclusion: recommendations for future pharmacological clinical trials in post-stroke recovery

On the basis of all aspects of stroke recovery, it is possible to propose some guidelines for future clinical trials of drugs in order to maximize the ability to detect treatment effects, if present.

1. Clinical trials should be hypothesis-driven and should include some understanding of the drug's mechanism. They need to be associated with conventional rehabilitation procedures.
2. Both the choice and the timing of administration of a drug intended to improve recovery after stroke should, as far as possible, be based on evidence from preclinical studies. Preclinical research policy is strongly needed in order to build rational hypotheses and to identify mechanisms of action.
3. Standardization of rehabilitation procedures does not currently exist and will be difficult to achieve. Indirect measurements, like the daily intensity of treatment and the duration of rehabilitation in weeks, should be implemented in any clinical trial testing therapies that target recovery after stroke.
4. Selection of the population is a key point as precise selection can reduce statistical variance and increase the study's power. It should be based on clinical arguments. Biomarkers can also be recorded and used for pre hoc stratification or in post hoc analysis but they cannot be considered as primary efficacy criteria. Patients with confounding factors should be excluded. The relevant biomarker may be specific for assessing the responses to the drug that is being tested.

5. It is useful to differentiate trials investigating recovery and trials investigating outcome.
    - Trials investigating recovery should be used at an early stage in drug development with the aim of validating the concept. They should use neurological scales (FMMS, NIHSS…) as primary criteria. They could test a precise hypothesis in a strictly selected population of patients. Global scales should be used as secondary criteria.
    - Larger trials investigating outcomes should be used as the ultimate step in drug development. They should use a global scale as primary criterion and will need a bigger sample of patients as the sensitivity of the scale is lower. Currently, the mRS appears to be the most appropriate global scale. Other scales (NIHSS, FMMS, cognitive scales, depression scales, etc.) will be used as secondary measures of responses. They can focus on the quantification of the modality-specific effects of the intervention.
6. Clinical trials should enroll subjects as soon as possible after stroke, preferably within the first 2 weeks when the preclinical data support this approach. The treatment duration should cover the first 3 months after stroke. It should last at least 6 weeks and up to 3 months. Trials investigating recovery should include measurement of outcome measures at baseline that are repeated at the end of treatment. Intermediate measures should be included. Trials investigating outcome need a clear primary endpoint at a specified time after stroke. Long-term follow up (at 6 or 12 months) is potentially useful.
7. In order to augment sensitivity to drug treatment effects, dichotomized endpoint analysis should be used alone and in combination with other methods considering the patient's initial condition.

Acknowledgments We deeply thank the "Institut de Recherche Pierre Fabre", particularly Dr. L Mansuy, Dr. E André, Mr. P Sokoloff and Mr. JP Caubère to have accepted to sponsor the workshop. Sponsoring of the 2012 workshop by "Institut de Recherche Pierre Fabre".

Conflicts of interest FC received honoraria from Servier and has consultancy for IRPFabre. SC is PI for a NIH grant, received speaker horaria from Sanofi, Pierre Fabre, Genentech, Asubic, has consultancy for GlaxoSmithKline and Pfizer. CS is PI for a Health Research Council and Neurological Foundation grant and received honoraria for examination fees. JK received payment for speakers' bureau Bayer and Boeheringer and has consultancy for Boehringer. JCB: no disclosure. CW is PI for Deutsch Foundation G, worked as expert witness, has consultancy for Pierre Fabre. MH received payment for speakers' bureau appointment. PA is PI for a French Ministry of Heath grant, worked as expert withness in legal assessments and received honoraria from IRPF. US: no disclosure. TM: no disclosure. JT received honoraria and has consultancy for IRPF. MV: no disclosure. SM: received honoraria from Astra Zeneca, Lundbeck, Pfizer, Servier, Pierre Fabre and has consultancy for Richter, Sanofi, Takeda. HAis PI for NINDS, Merck and Medtronic grant, received honoraria from IRPFabre.

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