Available online at
ScienceDirect
www.sciencedirect.com

Elsevier Masson France
EM|consulte
www.em-consulte.com

Movement disorders

Guidelines for clinical pharmacological practices in Huntington's disease

G. Désaméricq [a,b,c,d], K. Youssov [a,b,c,d], P. Charles [e], N. Saleh [a,b,c,d,1], A. Olivier [f], C. Sherer-Gagou [f], C. Verny [f,g], the multidisciplinary working group [2], A.-C. Bachoud-Lévi [a,b,c,d,*]

[a] Faculté de médecine, université Paris Est, 94010 Créteil, France
[b] Inserm, U955, équipe 01, neuropsychologie interventionnelle, 94010 Créteil, France
[c] École normale supérieure, département d'études cognitives, 75005 Paris, France
[d] Neurologie cognitive, centre de référence maladie de Huntington, hôpital H.-Mondor-A.-Chenevier, AP–HP, 94010 Créteil, France
[e] Département de génétique, centre de référence maladie de Huntington, groupe hospitalier Pitié-Salpêtrière, AP–HP, 75013 Paris, France
[f] Service de neurologie, Centre national de référence des maladies neurogénétiques, CHU d'Angers, 49933 Angers, France
[g] UMR Inserm 1083/CNRS 6214, université d'Angers, 49933 Angers, France

INFO ARTICLE

Article history:
Received 12 April 2016
Received in revised form
2 July 2016
Accepted 25 July 2016
Available online 22 August 2016

Keywords:
Huntington's disease
Symptomatic treatment
Guidelines
Evidence-based practice
Drug trials

ABSTRACT

Objective. – Evidence-based medicine is a difficult goal to achieve in rare diseases where randomized controlled trials are lacking. This report provides guidelines that capitalize on both the literature and expertise of the French National Huntington Disease Reference Centre to optimalize pharmacological therapeutic interventions for Huntington's disease (HD).

Material and methods. – HD experts conducted a systematic analysis of the literature from 1965 to 2013, using a scoring procedure established by the French National Authority for Health. These experts offered their views when evidence was missing to set up provisional guidelines for care in HD. These guidelines were then scored and amended through two subsequent online questionnaires (using SurveyMonkey® scoring), and one face-to-face meeting with an external multidisciplinary working group as a step towards validation.

Results. – Except for the beneficial effects of tetrabenazine in chorea, none of the published recommendations were grounded on established scientific evidence. Second-generation

* *Corresponding author*. Service de neurologie, centre de référence maladie de Huntington, hôpital Henri-Mondor, 51, avenue du Général-de-Lattre-de-Tassigny, 94010 Créteil, France.
E-mail address: bachoud@gmail.com (A.-C. Bachoud-Lévi).
[1] Present address: Department of Public Health, Epidemiology and Biostatistics, Lebanese University, Fanar, Lebanon.
[2] Neurologists: Pr Christine Tranchant (Strasbourg); Pr Jean-Philippe Azulay (Marseille); Dr Marie Mercedes Testard (Berk); Dr Philippe Chemouilli (CMR-HD Créteil); Physiotherapist: Dr Brigitte Soudrie (Hendaye); Geneticists: Pr Patrick Calvas (Toulouse); Pr Cyril Goizet (Bordeaux); Psychiatrist: Dr Valérie Ducoulombier-Herent (Bordeaux); neuropsychologist: Mme Kathy Dujardin (Lille); Nurse: Mme Graça Morgado (Créteil); General practitioners: Dr Alain Ibagnez (Chatenay-Malabry); Dr Philippe Placais (Chemellier); Patients' associations: Mme Emilie Hermant (DingDingDong, Paris); Mme Françoise Chorain (Huntington Avenir, Charvieu-Chavagneux).

http://dx.doi.org/10.1016/j.neurol.2016.07.012

antipsychotics are nevertheless the first choice for patients with psychiatric manifestations (low level of evidence). All other guidelines are based on low-level evidence and little professional agreement.

Conclusion. – Patients' care has greatly improved over the last few years despite the lack of high-level evidence standards. Guidelines are based on the expertise of trained specialists from the French National Plan for Rare Diseases. This strategy should now be extended internationally to promote future studies and to harmonize worldwide care of HD.

1. Introduction

Huntington's disease (HD) is a rare neurodegenerative disorder of the central nervous system, with a genetic autosomal-dominant inheritance, that first involves basal ganglia (caudate nucleus and putamen) and results from unstable expansion of a CAG trinucleotide repeat in the HTT (huntingtin) gene: alleles with 40 or more repeats are fully penetrant. The disease is characterized by motor, cognitive and psychiatric disorders. Progressive worsening leads to a bedridden state with cognitive deterioration. Death occurs about 20 years after the onset of symptoms.

Despite a major effort in research for neuroprotective and curative agents, most of the progress made in the last few years has come from multidisciplinary care and better knowledge of the natural evolution of the disease. Recent reviews of available drug trials and case reports [1–3] conclude that the management of HD is poorly documented. Accordingly, therapeutic decision-making is often guided by clinical experience [4], with patterns of care varying widely across countries [5,6].

In 2004, a decree from the Ministry of Health established a list of reference centers for rare diseases to improve patients' care through centralization of such patients to dedicated centers. Thus, the increasing numbers of patients referred to these centers has provided invaluable expertise in the field. In return, the acquired knowledge has been translated into guidelines, compiled through literature reviews, to be disseminated to health professionals and patients following recommendation by the Ministry of Health.

The present report proposes guidelines, issued from the National Centre of Reference for Huntington's disease, for clinical pharmacological practices in HD, based on evidence from the available literature and compiled by expert consensus. These guidelines have also been validated by an external multidisciplinary group comprising health practitioners and patients' associations.

2. Materials and methods

Three neurologists, one pharmacologist, experts in HD from the National Huntington Disease Reference Centre (Créteil and Salpétrière) and two neurologists from the reference center for neurogenetic diseases in Angers constituted the guidelines committee for the pharmacological treatment and management of HD. They used a consensus method provided by the French National Authority for Health (HAS) adapted for rare diseases. This formal method ensures the quality and reliability of the protocol (Fig. 1).

2.1. *Literature search methods for data selection*

All pharmacological interventions for HD published between 1 January 1965 and 31 January 2013 in French and English were selected. The allowed data came from clinical trials, observational studies, meta-analyses, systematic reviews, case studies, previous recommendations and summaries of congresses. Studies including patients with HD clinical features and a confirmatory genetic diagnosis or, for studies published before discovery of the gene in 1993, a compatible family history were identified. The list of symptoms to be analyzed was determined through discussions by the guidelines committee and the European Huntington's Disease Network (EHDN; comprising neuroprotective, rehabilitative and cognitive working groups).

Trials were identified using the terms 'Huntington disease', 'drug therapy' and some named symptoms (for example, 'sexual disorder', 'psychotic symptoms' and 'dysphagia') to find additional data in electronic databases, including Cochrane, Embase, MEDLINE, PASCAL, BMJ Clinical Evidence, Current Contents, Infobanque AMC, National Guidelines Clearinghouse, PEDro and BDSP (Public Health Database).

The literature for unpublished trials was also consulted, including ClinicalTrials.gov, OpenSIGLE (System for Information on Grey Literature in Europe) and hand-searched abstracts from international congresses of the Movement Disorder Society. Drug manufacturers and authors were also contacted to obtain additional information on unpublished trials or trials identified in other sources. The reference lists of identified studies and relevant reviews were also searched.

2.2. *Data extraction and analysis*

The exclusion of non-relevant studies was performed, by two additional committee members, separately by title and by abstract analyses before extracting the full studies. Also, a pair of neurologists from the guidelines committee independently analyzed each study through a formal grid that assessed methods (quality of the study) and results (contents of the study), and assigned a level to the scientific evidence according to the HAS classification (Table 1). For each study, the following items were summarized: authors and date; intervention and daily dose (active drug and placebo); genetic diagnosis; study design; number of participants; duration of