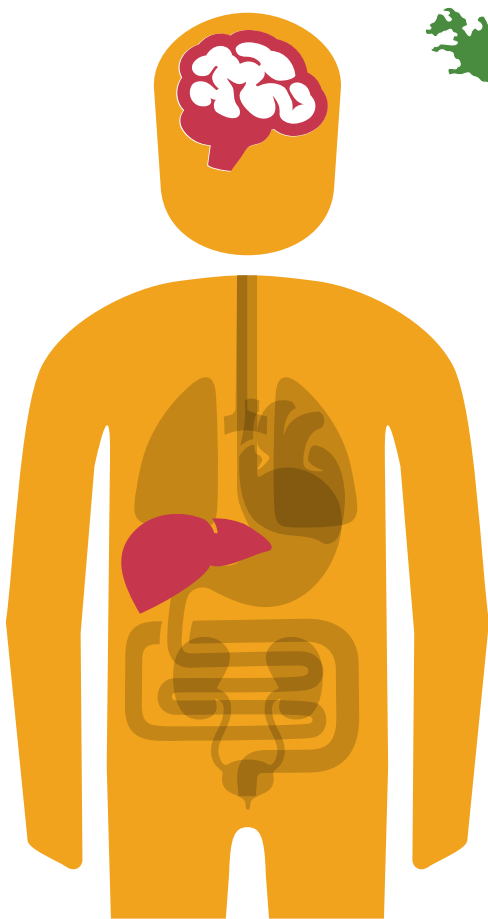


The burden of liver disease in Europe

The case of Hepatic Encephalopathy



Executive summary

Within the context of the global liver disease crisis, hepatic encephalopathy (HE) has emerged as an area where a number of acute challenges face patients, carers and health systems. HE is characterised by a loss of brain function, resulting in mild to severe incapacity, and is sometimes subtle and difficult to notice. HE occurs when the liver doesn't remove sufficient toxins from the blood and is estimated to affect up to 200,000 people in Europe. This policy white paper covers key HE issues with a focus on underdiagnosis, undertreatment, data gaps and access to diagnosis and treatment. For each key challenge identified, the collaborative parties of this white paper have endorsed clear, actionable policy solutions for implementation at EU and national level. With the 2019 European elections approaching, Members of the European Parliament and other EU stakeholders will have the opportunity to pursue the improvement of health management through the policy solutions proposed in this paper in order to drive change at the EU and national level.

Introduction

The world is facing a veritable liver disease crisis with patient numbers on the rise and liver diseases constituting a major cause of mortality and morbidity across the world.¹ Recent global estimations show that more than 844 million people worldwide suffer from chronic liver disease (CLD).² With a mortality rate of two million deaths per year the scale is comparable to that of other major public health epidemics, such as diabetes and cardiovascular diseases.² About half of these deaths are due to advanced chronic liver disease, classified as cirrhosis, a condition which results from long-term damage to the liver.³ Every year, CLD induces cirrhosis in 633,000 patients, and has a prevalence of 4.5% to 9% worldwide.² Despite liver disease being defined as a WHO priority disease area, this worrying trend continues.⁴

Europe has a large burden of liver disease, and worldwide it is a problem that is expected to grow across many countries.⁵ It is estimated that 500,000 EU citizens are living with advanced chronic liver disease.⁶ However, the epidemiology of liver disease varies, with some countries facing an even more severe challenge than others.⁵ In the UK, for instance, liver disease has been ranked as the fifth most common cause of death.⁷

Liver disease²



844 million worldwide

2 million deaths

Pulmonary diseases²



650 million worldwide

6.17 million deaths

Diabetes²



422 million worldwide

1.6 million deaths

HE is a serious complication of advanced chronic liver disease and affects up to 200,000 people in Europe

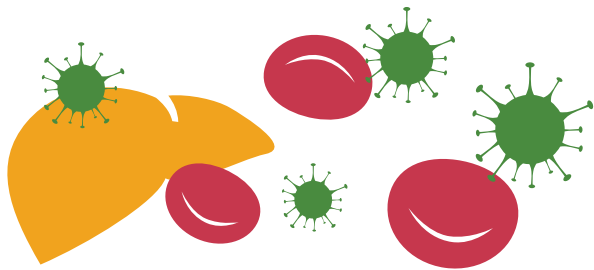


This policy white paper seeks to identify challenges and concrete solutions. It also calls on policymakers to take action – for the benefit of Europe’s patients, their carers and families, and its societies.

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Hepatic encephalopathy (HE) is a serious complication of advanced chronic liver disease characterised by a loss of brain function, which occurs when the liver fails to remove sufficient toxins from the blood.



The condition affects a large portion of people suffering from advanced chronic liver disease – with up to 30-40% of people with cirrhosis developing symptoms of HE during their clinical course.⁸

HE is associated with increases in hospitalisation, healthcare costs and mortality.⁹



In Europe, HE affects up to 200,000 people although the exact incidence of the condition remains unknown.⁹ Despite the severity of the condition, HE remains largely underdiagnosed and undertreated, resulting in poor quality of life for patients and their carers.⁸

These issues were captured in the *Time To DeLiver: Getting a grip on HE* report.¹⁰ Some progress has been made since the publication of this report three years ago. Notably, HE has been included under the next International Classification of Disease (ICD) code, ICD-11 – a milestone which, subject to timely implementation, could help improve diagnosis and treatment of the disease by improving data on prevalence, cost and disease burden. However, a number of specific challenges around HE still remain.

HE from the patient's perspective

Every person suffering from HE is affected by it in different ways. Given that HE can be persistent or episodic in nature, the goals of treatments also vary. Many people with HE experience a combination of mental and physical symptoms, including:¹⁰

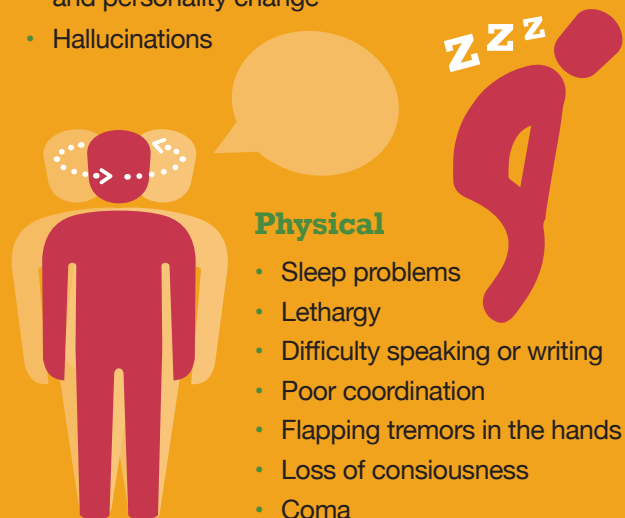
Mental

- Forgetfulness
- Reduced ability to concentrate
- Poor judgement
- Apathy and irritability
- Disorientation and confusion
- Inappropriate behaviour and personality change
- Hallucinations



Physical

- Sleep problems
- Lethargy
- Difficulty speaking or writing
- Poor coordination
- Flapping tremors in the hands
- Loss of consciousness
- Coma



HE is sometimes difficult for medical professionals to identify if they are not specialists, so it is often the responsibility of the patient or the caregivers to inform medical professionals of HE symptoms in order for the condition to be diagnosed. In addition, symptoms can quickly change or worsen, creating a situation where the disease needs to be consistently monitored by patients, their carers and medical professionals.



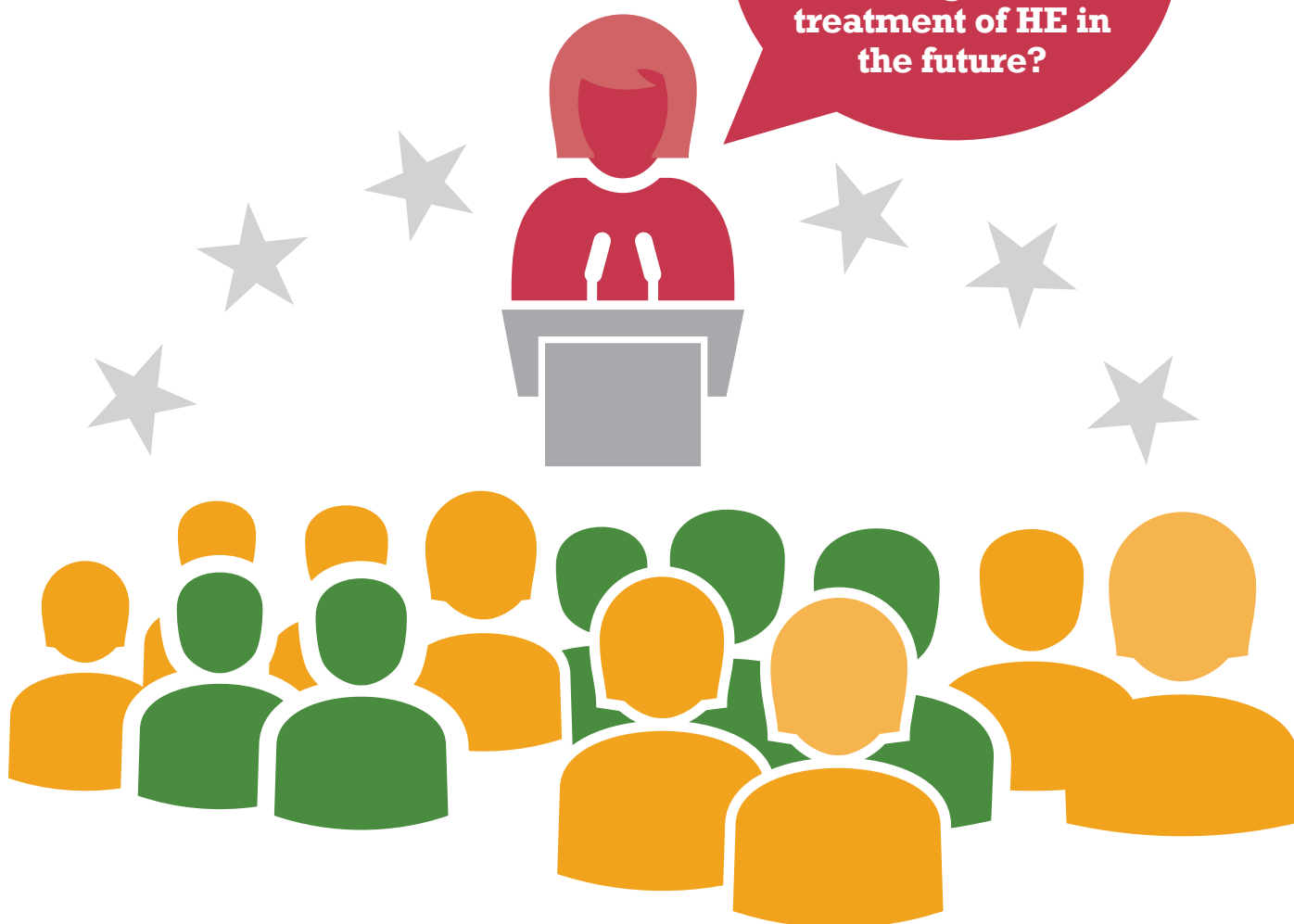
Multi-stakeholder engagement in HE

In the first half of 2018, ELPA, as the voice of HE patients, engaged with high-level Brussels stakeholders on the need for policy change in HE. Meetings were held with senior stakeholders from the European Parliament, the European Commission, patient groups and umbrella organisations with an interest in HE and liver diseases more broadly.

The engagement roundtable was successful in raising awareness of HE at EU level, as demonstrated by the 28 September 2018 [parliamentary question to the European Commission](#) on HE posed by Nessa Childers MEP and co-tabled by other leading MEPs in liver health such as Cristian-Silviu Buşoi MEP.¹¹ The [answer](#) to this question from the European Commission reflects a growing recognition of HE as an area where further research and action is needed.¹²

Despite the rise of HE on the health policy agenda, **concrete policy action is required** to address the challenges facing people with HE and their families and carers.

What can the EU and its member states do to ensure better diagnosis and treatment of HE in the future?



Key areas for action in HE

Informed by the engagement round, input from the ELPA Steering Group and previous *Time To DeLiver* materials, the following key themes have been identified for further action in HE:

Diagnosis of HE

Despite the severity of HE, it remains underdiagnosed and undertreated, resulting in poor quality of life for patients and their carers. The symptoms of HE are often subtle and easily missed, resulting in underdiagnosis of the condition. Importantly, effective diagnosis and treatment of HE can improve outcomes by maintaining remission and reducing the risk of hospitalisation. In addition, HE, and liver disorders more broadly, carry a heavy stigma which stops patients seeking the help that they need.



Data on HE

Closely linked to the issues surrounding the diagnosis of HE, limited data on the epidemiology, triggers, burden and treatment of HE continues to stunt the European community in measuring, benchmarking and improving outcomes for patients. Following the inclusion of coding for HE in ICD-11, it will be important to ensure timely implementation of the new coding system to enable better diagnosis, management and treatment of HE. Beyond ICD-11, further data collection, data sharing and research on HE should be encouraged. This will also help show the scale of the problem that patients and societies are facing.

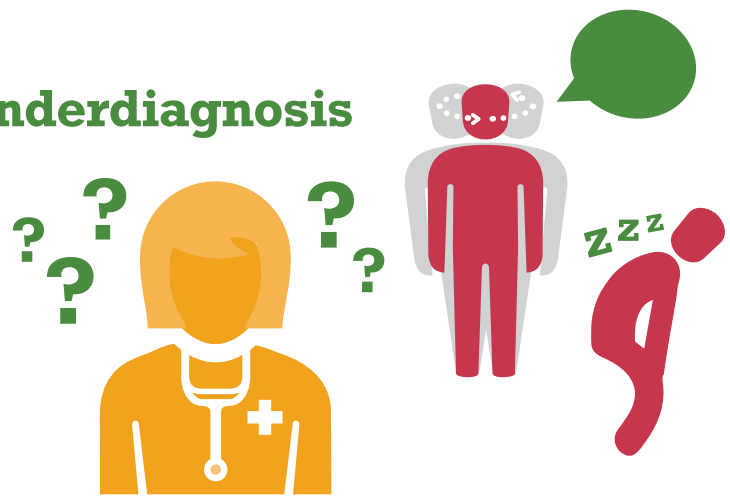


Access to treatment for HE

Although HE may be recurrent, the most important aspect of HE management is prompt recognition of the episode and immediate initiation of treatment, as progression of the HE is often rapid. Many symptoms can be successfully managed if such measures are taken. Unfortunately, not all treatments are available and/or reimbursed in all European countries, meaning that patients often do not benefit from access to the right treatment at the right time. Furthermore, there is often a lack of (human, technical and financial) resources which impedes access to care and support for patients and their carers.



Tackling the challenge of underdiagnosis and undertreatment of HE



► The underdiagnosis of HE

A key challenge is that HE is still a commonly underdiagnosed condition – for a number of reasons:

Firstly, HE is marked by non-specific signs and symptoms which are subtle and easily missed, for instance, a change in personality or trouble sleeping.¹⁰ Among complications of cirrhosis, none are more complex than HE. As a result, medical professionals who do not deal with patients with HE on a frequent basis may fail to identify HE as a likely cause of these symptoms.¹³

This situation is complicated further by the fact that, until recently, HE did not have a specific International Classification of Diseases (ICD) code. This hampered the gathering of information about common symptoms described by patients, which are needed in order to diagnose the condition more easily.¹⁰

In the meantime, the lack of an agreed standard diagnostic test or clinical procedure poses additional barriers to the diagnosis of HE. In addition, this contributes to a fragmented clinical understanding of the condition.¹⁴ This poses difficulties in terms of developing a better clinical consensus over guidelines and pathways for people with HE.

Considering that HE is heterogeneous, its better stratification and classification would favour better diagnosis, thus helping patients and caregivers.

► The undertreatment of HE

As a result of being underdiagnosed, HE is a commonly undertreated condition. Treatment pathways should follow a refined diagnosis procedure composed of the following three steps: excluding all other potential causes of HE, identifying and managing precipitating causes and performing a quick empirical treatment, and monitoring the patient by expert staff for at least 24-48 hours. Support services to inform and treat HE patients and their caregivers are suboptimal and HE caregivers are usually not part of a multi-disciplinary care team.¹⁵ This leads to a lack of coordination of care and support services and therefore to a fragmented care experience.¹⁵

Indeed, one issue affecting patients with HE is that the EASL guidelines on HE, a valuable resource for medical professionals across Europe, are not being implemented systematically.⁸ Medical professionals tend to focus on treating the trigger of HE rather than managing the condition in the long-term – to the detriment of patients and their carers. We should take into account that this approach is related to the fact that patients initially in their acute episodes are attended to in the emergency room before being hospitalised. Patients are then often treated by the non-specialised medical professionals and, after being discharged during the long term follow up, they will receive care from different professionals. Such an approach to managing HE is not cost-effective.

Finally, as some European health systems underprioritise HE, undue restrictions on prescribing appropriate treatments on the basis of cost or duration may occur.¹⁰ This challenge will be discussed in the section below entitled *Ensuring better and equal access to treatment for HE*.



► Stigmatisation and HE

A significant number of patients with HE feel stigmatised as a result of having a disease which is often associated with the false assumption of alcohol misuse.¹⁰ According to a recent survey, 89% of patients with HE expressed the feeling of being stigmatised in at least one aspect of their lives due to public misunderstanding about HE.¹⁶

Patients recording high levels of perceived stigma also face high rates of depression and are usually less prone to seeking medical care. These patients also report a worse quality of life.¹⁶ Moreover, HE has a significant impact on patients' social interactions as well as their sense of well-being. HE is characterized by unpredictable changes in cognitive function and progressive disability.

Stigmatisation is also an issue in the carer community, with carers facing discrimination as they take on the care burden. Caregivers feel their ability to work is impaired and report a sense of entrapment coupled with a degradation of their own personal physical and mental health.¹⁷

These examples show the impact stigmatisation has on underdiagnosis as well as undertreatment, through making patients less likely to seek medical care across the care pathway and carers less likely to discuss the issues that they and their patients are facing.



According to a recent survey, 89% of patients with HE expressed the feeling of being stigmatised in at least one aspect of their lives due to public misunderstanding about HE

The low awareness of HE

Problem

- HE is underdiagnosed, undertreated and stigmatised across Europe partly due to a lack of awareness amongst key stakeholders and the general public about what HE is and how it affects patients

Solutions

- MEPs and patient organisations to support national HE awareness and education campaigns in order to raise awareness and dispel myths on HE among patients, policymakers, carers and medical professionals
- MEPs and patient organisations to support patient and carer access to an informed point of contact on HE who can provide advice and organise interventions at an early stage and throughout the illness process

The poor implementation of clinical guidelines on HE

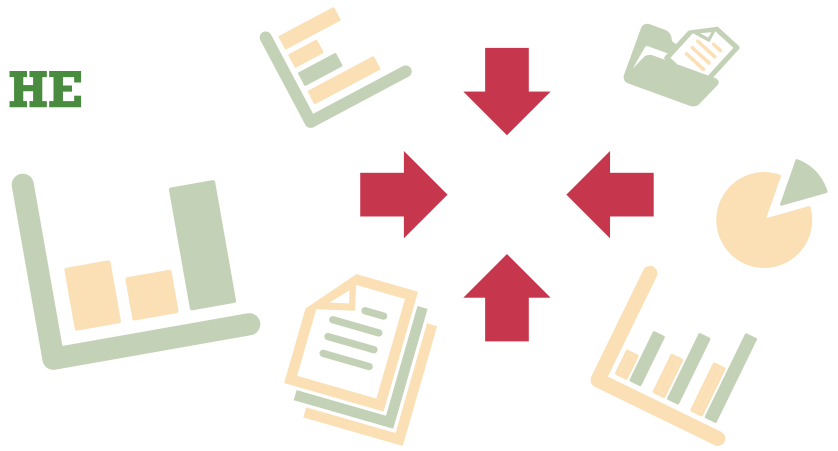
Problem

- The EASL guidelines on HE, a valuable resource for medical professionals, are not being implemented systematically across Europe. This is possibly due to lack of funding and the difficulties inherent to basic HE treatment which should increase bowel movements (via the administration of laxatives and enemas)

Solutions

- MEPs, patient organisations and medical societies to call for the systematic implementation of existing EASL guidelines in Europe
- MEPs and patient organisations to support an EU level benchmarking exercise on the variations in clinical adherence to the guidelines and clinical approaches to HE
- The development of a shorter and simplified version of the EASL guidelines to allow easier application in clinical practice

Closing the data gaps in HE



► Limited data on HE

Closely linked to the issues surrounding the underdiagnosis and undertreatment of HE is the limited data on the epidemiology, burden and treatment of HE. On a systematic level, this lack of data continues to stunt the European community in measuring and benchmarking.

For instance, European data for hospitalisations due to HE are currently unknown, however, are likely to be consistent with USA figures where approximately 110,000 hospitalisations each year are due to HE.⁸ Data of this nature must be collected to ensure that we can paint an accurate picture of the impact of HE in Europe.

► The impact of limited data

The lack of European data reporting on the epidemiology of HE or resulting hospital admissions poses a barrier to fully understanding the condition as well as its scale and burden across Europe, including health inequalities between countries.

Until recently, an important barrier to the collection of relevant information was the lack of a specific ICD code for HE. The recent inclusion of HE in ICD-11 is expected to improve the level of data related to HE. However, the implementation of ICD-11 will only start in 2022 and data collection is a lengthy process.¹⁸ Therefore, while ICD-10 remains the main reference for health data comparison purposes, it is important to conduct further research into HE and generate comparative data through other channels.

Data gaps in HE

Problem

- The lack of data on HE limits the understanding of its burden, of health inequalities in HE and of the value of treatments for HE

Solutions

- MEPs, patient organisations and medical societies to support the timely implementation of ICD-11
- MEPs, patient organisations and medical societies to collaborate in the generation and sharing of robust data on HE, including on patient reported outcomes (perceived quality of life), the burden of HE on patients, society and healthcare systems and employment and work issues



The lack of data on HE is stopping us from understanding its burden and scale across Europe

Ensuring better and equal access to treatment for HE



► The value of treatment for HE

As is the case with other complications of liver cirrhosis, available treatments for HE are effective, improve patient outcomes and reduce the burden of the disease. Many patients can be successfully managed if such measures are taken. The goals of patients who have overt HE are to:

1. Confirm the diagnosis of HE
2. Identify and treat possible precipitating factors (infection, hemorrhage, psychodrugs)
3. Reduce the duration of hospitalisation and
4. Consider evaluation for liver transplantation

The management of HE has undergone relatively few changes in the last years, and implementation of clinical guidelines is urgently needed. The most important aspect of HE management is prompt recognition and immediate initiation of treatment as progression of the condition is often rapid until HE stage IV - coma status. In addition, treatment can mitigate the substantial direct costs attributable to hospitalisations for HE as well as indirect costs such as opportunity costs for informal carers and patients themselves.^{8,19}

► Barriers to access

Unfortunately, not all treatments are reimbursed in all European countries, meaning that patients often do not benefit from access to the right treatment at the right time. Even where the reimbursement of treatments is taking place, this may not be for the optimal treatment duration.

These issues are typically due to a lack of funding for HE treatments and because some treatments are not deemed to be cost-effective by national and regional payers.¹⁰

In light of this, there is a pressing need to reconsider the value of treatment for HE given its impact on patients, carers and healthcare systems. Notably, HE causes direct costs through frequent hospital admissions, as well as indirect costs, such as the opportunity cost when patients and caregivers must miss work owing to their condition. Such costs are more prevalent if patients do not have access to treatment and cannot manage the disease properly.²⁰

The lack of data on the impact of treatments for HE is a barrier to informed value assessment. For instance, real world data on HE patients has shown a correlation between increased access to the right treatment and decreased numbers of emergency visits and hospitalisations.

Unequal access to treatment for HE

Problem

- Currently, some patients with HE are unable to access the right treatment at the right time in order to manage HE in the long-term

Solutions

- MEPs and patient organisations to support the reform of value assessment methods and pricing and reimbursement systems to recognise the expected savings from HE treatments that can counteract the costs of care and hospitalisation across the care pathway
- MEPs and patient organisations to advocate for sufficient national and regional budgets to support the reimbursement of approved therapies for an optimal treatment duration for patients, treatment follow-up (including post diagnostic and post hospitalisation clinics), support, information and funding of carers for people with HE

Getting a grip on HE: calls to action for better care for patients

Please see below the consolidated policy recommendations to address the key challenges raised in this document:

The low awareness of HE

Problem

- HE is underdiagnosed, undertreated and stigmatised across Europe partly due to a lack of awareness amongst key stakeholders and the general public about what HE is and how it affects patients

Solutions

- MEPs and patient organisations to support national HE awareness and education campaigns in order to raise awareness and dispel myths on HE among patients, policymakers, carers and HCPs
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Data gaps in HE

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- MEPs, patient organisations and medical societies to collaborate in the generation and sharing of robust data on HE, including on patient reported outcomes (perceived quality of life), the burden of HE on patients, society and healthcare systems and employment and work issues

The poor implementation of clinical guidelines on HE

Problem

- The EASL guidelines on HE, a valuable resource for medical professionals, are not being implemented systematically across Europe. This is possibly due to a lack of funding and the difficulties inherent to basic HE treatment which increases bowel movements (via the administration of laxatives and enemas)

Solutions

- MEPs, patient organisations and medical societies to call for the systematic implementation of existing EASL guidelines in Europe
- MEPs and patient organisations to support an EU level benchmarking exercise on the variations in clinical adherence to the guidelines and clinical approaches to HE
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Advocacy opportunities to make policy change a reality

As we approach the 2019 EU elections and 2019-2024 mandate, the white paper and its policy recommendations provide a valuable resource to inform the health policy agenda and policy action at EU and national level. In parallel, engagement with national stakeholders, in the context of the EU elections or focused around national political events, is a further key opportunity to drive change at national level.

Conclusions and next steps



This white paper has highlighted the key challenges facing patients with HE, their families and carers in the areas of diagnosis, data and access to treatment. It identifies policy solutions and calls on policymakers to take concrete action for the benefit of Europe's patients, their carers and families and its societies.

The paper is a starting point for advocacy and policy action to improve treatment and care for people with HE. It is crucial that this begins with the EU elections and continues into the 2019-2024 mandate. Only through consistent action can we bring about the changes required to ensure a fair and equitable future for people with HE in Europe.

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