



**EARLY INTERVENTION: BRIDGING THE EARLY DIAGNOSIS AND TREATMENT GAP**



**POLICY WHITE PAPER  
TOWARDS OPTIMIZING  
RESEARCH AND CARE  
FOR BRAIN DISORDERS**

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EBC RESEARCH PROJECT - THE **VALUE OF TREATMENT** FOR BRAIN DISORDERS

**The European Brain Council (EBC)** is a non-profit organisation gathering patient associations, major brain-related societies as well as industries. Established in March 2002, its mission is to improve the lives of those living with brain disorders by advancing the understanding of the healthy and diseased brain through bringing together science and society.

## EBC Final Conference, 22 June 2017, held under the auspices of the Maltese EU Presidency

### MULTIPLE GOALS

- Target **unmet needs** to achieve **high value for patients**
- Conduct **cost-effectiveness analysis in health care** (comparing costs and values of defined interventions) and assess the **benefits of seamless, coordinated care** in the prevention and treatment of brain disorders
  - Propose **solutions with a societal impact** and reflect on **new research developments**
  - Release **evidence-based policy recommendations**

### A BOTTOM-UP METHOD WITH CASE STUDIES DATA ANALYSIS AND CONVERGENCE OF EVIDENCE TO POLICY

## TABLE OF CONTENTS

AUTHORS PART1	7
ACKNOWLEDGEMENTS	8
FOREWORD	14
EXECUTIVE SUMMARY	16
<b>PART 1: VALUE OF TREATMENT RESEARCH PROJECT OVERALL OBJECTIVES AND POLICY RECOMMENDATIONS</b>	22
BACKGROUND - WHAT ARE BRAIN DISORDERS?	22
ABOUT THE VALUE OF TREATMENT PROJECT	23
1. CONTEXT	24
1.1. Epidemiology and impact of diseases	24
1.2. Unmet needs and treatment gaps	26
1.3. Why early intervention is key for brain disorders	28
1.3.1. Early detection and intervention – Potential risk reduction capacity in mental health care	28
1.3.2. Early detection and intervention – Essential in neurological disorders	29
1.3.3. Addressing stigma	31
1.4. State of play of research initiatives and public health policies at European level	31
1.4.1. Medical research and frameworks of action	31
1.4.2. Public health policies and frameworks of action	35
2. RATIONALE: VOT RESEARCH METHODOLOGY	36

3. KEY FINDINGS ACROSS CASE STUDIES	42
3.1. Case studies findings	42
3.2. Challenges to bridge the treatment gap	54
3.2.1. Health services challenges	54
3.2.2. Other challenges: non-adherence to treatment and unaffordable access to care	56
4. CONCLUSIONS AND POLICY RECOMMENDATIONS	59
REFERENCES	68
<b>PART2: SUMMARIES OF THE CASE STUDIES</b>	73
AUTHORS PART2	74
Schizophrenia	75
Restless Legs Syndrome	80
Parkinson's disease (PD)	84
Multiple Sclerosis (MS)	89
Stroke	94
Normal Pressure Hydrocephalus (NPH)	97
Headache	100
Epilepsy	105
Alzheimer's disease (AD)	110
REFERENCES	113
SPONSORSHIP	116



## AUTHORS PART 1:

**EBC team:** Quidbach V<sup>1</sup>, Esposito G<sup>1</sup>, Destrebecq F<sup>1</sup>, Kramer S<sup>1</sup>

**EBC academic partners:** Tinelli M<sup>2</sup>, Knapp M<sup>2</sup>, Guldemond N<sup>3</sup>

**Working group leaders:** Dodel R<sup>4</sup>, Gaebel W<sup>5</sup>, Kälviäinen R<sup>6</sup>, Kehler U<sup>7</sup>, Mitsikostas D<sup>8</sup>,  
Sørensen PS<sup>6</sup>, Trenkwalder C<sup>9</sup>, Vanhooren G<sup>10</sup>, Visser PJ<sup>11</sup>

**EBC executive board:** Nutt D<sup>1</sup>, Boyer P<sup>1,5</sup>, Di luca M<sup>1,12</sup>, Oertel W<sup>1,4</sup>

1. European Brain Council (EBC)
2. London School of Economics (LSE)
3. The Institute of Health Policy & Management (iBMG), Erasmus University
4. Philipps-Universität Marburg
5. European Psychiatric Association (EPA)
6. European Academy of Neurology
7. Dept. of Neurosurgery, Asklepios Klinik Altona, Hamburg, Germany
8. European Headache Federation (EHF)
9. Paracelsus Elena Klinik and University of Goettingen
10. European Stroke Organization (ESO)
11. VU University Medical Center Amsterdam
12. Federation of European Neuroscience Societies (FENS)

## ACKNOWLEDGEMENTS

### Schizophrenia Working Group

Wolfgang Gaebel	European Psychiatric Association (EPA)
Silvana Galderisi	European Psychiatric Association (EPA)
Danuta Wasserman	European Psychiatric Association (EPA)
Cyril Höschl	National Institute of Mental Health, Klecany, Czech Republic; 3rd Faculty of Medicine, Charles University, Prague, Czech Republic
Pavel Mohr	European Psychiatric Association (EPA); National Institute of Mental Health, Klecany, Czech Republic; 3rd Faculty of Medicine, Charles University, Prague, Czech Republic
Petr Winkler	National Institute of Mental Health, Klecany, Czech Republic; Health Service and Population Research Department, IoPPN, King's College London
Patrice Boyer	European Brain Council (EBC) and European Psychiatric Association (EPA)
Aagje Ieven	The European Federation of Families of People with Mental Illness (EUFAMI)
Hilkka Kärkkäinen	Global Alliance of Mental Illness Advocacy Networks (GAMIAN) - Europe
Paul Arteel	Global Alliance of Mental Illness Advocacy Networks (GAMIAN) - Europe
Amir Inamdar	Takeda Development Centre, Europe, Ltd.
Meni Styliadou	Takeda Development Centre, Europe, Ltd.
Christoph Van der Goltz	H. Lundbeck A/S
Veronica Zilli	Janssen EMEA
Cristiana Maria	Janssen EMEA
Bart Malfait	Janssen-Cilag, Beerse, Belgium
Kristel van Impe	Janssen EMEA
Karin Becker	Boehringer Ingelheim GmbH



**Dementia Working Group**

Pieter Jelle Visser	VU University Medical Center; Amsterdam Neuroscience;
Sietske Sikkes	Alzheimer center, Department of Neurology, VU University Medical Center; Amsterdam Neuroscience; Department of Epidemiology & Biostatistics, VU University Medical Center, Amsterdam, the Netherlands
Ron Handels	Department of Psychiatry and Neuropsychology and Alzheimer Centre Limburg, School for Mental Health and Neurosciences, Maastricht University, Maastricht, The Netherlands; Department of Neurobiology, Care Sciences and Society, Center for Alzheimer Research, Division of Neurogeriatrics, Karolinska Institutet, Sweden
Lisa Vermunt	Alzheimer center, Department of Neurology, VU University Medical center; Amsterdam Neuroscience, Amsterdam, the Netherlands
Philip Scheltens	VU University Medical Center; Amsterdam Neuroscience;
Joel Bobula	Pfizer Inc
Charles Faid	Pfizer Inc
Amir Inamdar	Takeda Development Centre, Europe, Ltd.
Meni Styliadou	Takeda Development Centre, Europe, Ltd.
Michele Potashman	Biogen
Tresja Bolt	Biogen
Francois Chazelle	Merck Scharp & Dohme Europe Inc. (MSD)
Boris Azais	Merck Scharp & Dohme Europe Inc. (MSD)
Veronica Zilli	Janssen EMEA
Jan Sermon	Janssen EMEA
Cristiana Maria	Janssen EMEA

**Headache Working Group**

Dimos Mitsikostas	European Headache Federation
Matilde Leonardi	European Brain Council (EBC) WHO Liaison; Neurology, Public Health, Disability Unit- Foundation IRCCS Neurological Institute Carlo Besta, Milan, Italy
Koen Paemeleire	European Headache Federation
Timothy Steiner	Lifting the Burden
Elena Ruiz de la Torre	European Federation of Neurological Associations (EFNA)
Annik K Laflamme	Novartis Pharma AG, Basel, Switzerland
	Teva Pharmaceuticals

**Epilepsy Working Group**

Reetta Kalviainen	Epilepsy Center/Neurocenter, Kuopio University Hospital and University of Eastern Finland, Kuopio, Finland
Chantal Depondt	ILAE; Department of Neurology, Erasme Hospital, Université Libre de Bruxelles, Brussels, Belgium
Tony Marson	ILAE; Department of Molecular and Clinical Pharmacology, University of Liverpool
Angela Boland	Liverpool Reviews and Implementation Group (LRiG); University of Liverpool
Rumona Dickson	Liverpool Reviews and Implementation Group (LRiG); University of Liverpool
James Mahon	Liverpool Reviews and Implementation Group (LRiG); University of Liverpool
Paul Boon	European Academy of Neurology (EAN)
Philippe Ryvlin	European Academy of Neurology (EAN); Epilepsy Alliance Europe; Department of Clinical Neurosciences, CHUV, Lausanne, Switzerland
Janne Martikainen	School of Pharmacy, University of Eastern Finland, Kuopio, Finland
Ann Little	European Federation of Neurological Associations (EFNA); International Bureau for Epilepsy
Peter Dedeken	UCB Biopharma, Brussels, Belgium

**Normal Pressure Hydrocephalus (NPH) Working Group**

Uwe Kehler	Dept. of Neurosurgery, Asklepios Klinik Altona, Hamburg, Germany; International Hydrocephalus Society – ISHCSF
------------	---

### Multiple Sclerosis Working Group

Per Soelberg Sorensen	European Academy of Neurology (EAN); Danish Multiple Sclerosis Center, Dpt. Neurology, University of Copenhagen Rigshospitalet, Copenhagen, Denmark
Kerstin Hellwig	Department of Neurology, St.Josef Hospital, Bochum Germany
Maura Pugliatti	European Academy of Neurology (EAN); Dept. of Biomedical and Surgical Sciences, University of Ferrara, Italy
Andreea Antonovici	European Multiple Sclerosis Platform (EMSP)
Monica Moroni	School of Medicine, University of Ferrara, Italy
Bettina Hausmann	European Multiple Sclerosis Platform (EMSP)
Rob Hyde	Biogen
Emanuele Degortes	Biogen
Annik Laflamme	Novartis AG
	Teva Pharmaceuticals
	Roche

### Parkinson's Disease Working Group

Richard Dodel	European Academy of Neurology (EAN)
Günther Deuschl	European Academy of Neurology (EAN); Prof. Dr. med, Department of Neurology, UKSH Kiel, CAU Kiel, Germany
Wolfgang Oertel	European Academy of Neurology (EAN); Hertie Senior Professorship; Dept. Neurology, Philipps University Marburg, Germany
Lizzie Graham	European Parkinson's Disease Association (EPDA)
Eleanor Flanagan	Grayling Belgium; European Parkinson's Disease Association (EPDA)
Frank Michler	Jung & Parkinson, Germany
Jutta Ahmerkamp-Böhme	Jung & Parkinson, Germany
Gudula Petersen	Grünenthal GmbH
Daniela Myers	Pfizer Inc
Charles Faid	Pfizer Inc
Marja Kolis	Grünenthal GmbH
Silke Walleser Autiero	Medtronic

## Restless Legs Syndrome (RLS) Working Group

Claudia Trenkwalder	Paracelsus-Elena-Klinik, Center of movement disorders, Kassel, Germany/ University of Goettingen, Goettingen, Germany
Joke Jaarsma	European Alliance for Restless Legs Syndrome (EARLS)
Roselyne Rijsman	Center for Sleep and Wake Disorders, Haaglanden Medical Center, The Hague, The Netherlands
Giorgios Sakkas	Department of Health, Plymouth Marjon University, Plymouth, UK & University of Thessaly, Trikala, Greece
Raffaele Ferri	Department of Neurology IC, Oasi Research Institute (IRCCS), Troina, Italy
Yves Dauvilliers	Sleep Disorders Center, Department of Neurology, Gui-de-Chauliac Hospital, Inserm, U1061, Montpellier, France
Wolfgang Oertel	European Academy of Neurology (EAN); Hertie Senior Professorship; Dept. Neurology, Philipps University Marburg, Germany
Anna Mezzacasa	Vifor Pharma UCB Biopharma, Brussels, Belgium

## Stroke Working Group

Geert Vanhooren	European Stroke Organization (ESO) Department of Neurology, AZ Sint-Jan Brugge-Oostende, Brugge, Belgium
Vincent Thijs	Belgian Stroke Council; Florey Institute of Neuroscience and Mental Health, Melbourne University, Melbourne, Australia
Eivind Berge	Norwegian Stroke Organization, Dept. of Internal Medicine, Oslo University Hospital, and Institute of Clinical Medicine, University of Tromsø, Norway
Alastair Webb	European Stroke Organisation (ESO); Department of Clinical Neuroscience, University of Oxford, UK
Ana Catarina Fonseca	Universidade de Lisboa, Faculdade de Medicina, Institute of Molecular Medicine, Portugal
Bo Norrving	European Stroke Organization (ESO); Dept. of Clinical Sciences Lund, Neurology, Lund University, Sweden
Valeria Caso	European Stroke Organization (ESO)
Franz Fazekas	European Academy of Neurology (EAN)
Jon Barrick	Stroke Alliance for Europe (SAFE)
Gary Randall	Stroke Alliance for Europe (SAFE)
Stephanie Roso	Pfizer Inc.
Charles Faid	Pfizer Inc.

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### Current EBC Team Members :

Frédéric DESTREBECQ, Giovanni ESPOSITO, Stephanie KRAMER, Tadeusz HAWROT, Vinciane QUOIDBACH, Cécile GREBET, Vania PUTATTI and Marijn SCHOLTE

### Past Members :

Ester BONADONNA, Alison TURNER, Lara INGRAM and Monika KALKUSOVA

## FOREWORD

**Unprecedented innovation in technology and medical processes** is rapidly revolutionizing human life. Current health systems, however, have **not been able to adapt quickly enough to maximize the value to patients**. This is **particularly true for brain disorders, and is particularly challenging for policy makers**.

**Value-based healthcare** is currently gaining traction in Europe **as the desired solution or path forward in improving health systems**. This **holistic approach** towards seamless care models critically intertwines **wider patient and societal outcomes with efficient spending of resources**. Doing this should **lead to both a more sustainable framework for payers and improved care for patients**.

On 22 June 2017, the European Brain Council (EBC) will release the Value of Treatment (VoT) 2015-2017 Research Project Policy White Paper with case studies findings and policy recommendations, at a final conference organized under the auspices of the Maltese EU Presidency. The Research Project is building on the EBC Report "The Economic Costs of Brain Disorders in Europe" published in 2005 (Balak and Elmaci 2007) and updated in 2010 (Gustavsson et al. 2011) that **provided robust estimates of the costs of brain disorders in Europe and enlightened necessary public health policy implications for more patient-oriented and sustainable care models as well as the need for more research**. This policy paper focuses on **"Prevention and Early Intervention, Bridging the Early Diagnosis and Treatment Gap"**.

Starting from **case studies data analysis** covering a wide range of brain disorders **and ending in evidence-based policy recommendations**, the project **assesses the treatment gap and the cost of non- or inadequate treatment**. Our findings recommend early intervention and the promotion of a holistic healthcare approach (as opposed to fragmentation in separate medical "silos"), **address combined research and public health policy gaps and opportunities at the EU level, and translate the findings into policy recommendations**.

With this new study, EBC is not only looking **at the socio-economic impact and value of healthcare interventions, but is also emphasizing how timely care pathways are likely to need greater integration** and how **better collaboration** can be achieved in the future for the benefit of those living with or at risk of a brain disorder.

We address **patients' biopsychosocial needs and concerns**, and pinpoint cognitive, educational and vocational aspects as **common denominators linking studies of brain disorders**. We highlight the **value of early intervention** as a **solution** to improve patient quality of life and to sustain health and social systems. Research **links early intervention to measurable health gains such as improved survival rates, reduced complications and disability**,

**better quality of life and lower treatment costs.** However, as recently pointed out by the OECD and the European Commission, **effective implementation of early diagnosis and treatment varies widely across health systems and many European countries are still lagging a long way behind, with wide clinical practice variations even within countries (health inequalities).** There is a **considerable gap in terms of diagnosis and treatment. This is particularly blatant for mental illness in Europe** (ranging from alcohol use and dependence, with the widest treatment gap, to schizophrenia) **but also for neurological disorders such as** Alzheimer's disease, Epilepsy, Headaches, Normal Pressure Hydrocephalus, Parkinson's disease, Multiple Sclerosis, Restless Legs Syndrome and Stroke. VoT is addressing **these obstacles** while providing **innovative solutions.**

In joint initiatives promoted by the European Commission such as in the areas of **brain research and health** (e.g. Horizon 2020), it has proved essential **to put scientific evidence into care standards, and to use case studies to make available evidence-based diagnostics and treatment guidelines as well as quality assurance norms covering all stages and aspects of care.** This leads us to the **seamless, coordinated care approach** with an expectation that it might support the achievement of the so-called **"Triple Aim" in the respect of patient's needs:** a simultaneous focus on **improving health outcomes, enhancing the quality of care and increasing efficiency in the use of resources.** To realize this aim, the European Commission and the WHO are calling on policy makers to **initiate a process of reorganisation of care delivery, with the following priorities:** access to care, sustainability of healthcare systems and cost-effectiveness of interventions (workforce, technologies including the potential of digital health, ...).

We are at a pivotal time of change; our new study couldn't be more opportune in exploring the beginnings of **a European paradigm shift towards value-based healthcare interventions for brain disorders.**

This EBC VoT Study is a starting point. We don't have all the solutions in once, but these are promising and the research will be pursued based on a common approach. Through building up evidence, EBC is providing **the necessary policy recommendations to address the treatment gap and its consequences.** I would like to take the opportunity to thank all EBC members and partners for being part of this challenging "journey".

David Nutt  
President of EBC

## EXECUTIVE SUMMARY

The vision is clear: **mental and neurological disorders**, or “**disorders of the brain**” are **complex and interlinked with hundreds of specific diagnosis, codified in diagnostic classifications systems** (currently under revision WHO International Classification of Diseases, ICD-11 and American Psychiatric Association Diagnostic and Statistical Manual of Mental Disorders, DSM-V)<sup>1-2-3</sup>. **Until recently, brain disorders** were associated with **disciplinary fragmentation in research and practice**, using different concepts and approaches. **There is today greater awareness on their common denominators, burden and challenges to manage them in a more integrated approach**, and even **to prevent** some of them<sup>4</sup>.

**Brain disorders** are becoming more prevalent over time and are threatening not only the quality of life of millions of European citizens but are also creating major challenges for the EU’s capacity to achieve the goals of its Europe 2020 strategy on economic growth and job recovery.

**Budgetary restrictions across the EU** are threatening the sustainability of the European social welfare model as a whole, and make it even more important to achieve cost-effectiveness in the use of resources in health systems and its deliverables. In fact, the sizeable share of public money that is devoted to health and the ever-increasing cost pressures and demands to cut public expenditure, put **health systems at the heart of many policy debates**. In particular, **challenges** are multiple because of the medical, social and economic impacts of **chronic disabling conditions**. Together, these emphasize the need for an ambitious **patient-empowering research policy and a cross-cutting, multidisciplinary approach to brain disorders**.

Covering a range of mental and neurological disorders, **the EBC Value of Treatment study** examined health gains and socio-economic impacts resulting from **best health interventions (pharmacological and psychosocial) in comparison with current care, or – in some cases – comparison with no treatment at all**. **Care pathways** were mapped for each specific disorder along the whole care process from prevention, prodromal, early diagnosis to disease management in order **to identify the major unmet needs and causes for treatment gaps** (both those needing research and better evidence to inform treatment decisions and those needing better organization of services).

**The following research questions** were addressed **to examine the best options for optimizing research and care for brain disorders**:

- *What is the scale of **current unmet needs** in health care in Europe? What is the size of so-called “**treatment gaps**”, not only within the provision of medicines and medical devices, but also within health care systems and services? Considering **obstacles** such as misdiagnosis, delayed treatment, inadequate treatment, limited access to care due to country healthcare infrastructure or unaffordable access to care and pricing including innovative*



therapies, reimbursement and social safety net cutbacks<sup>5</sup>... and non-adherence. What are the **socio-economic benefits** of targeting these gaps (e.g. avoidable costs...)? What have we learned from the **"Patient Journey" or the patient care pathway analysis**? What about the **potential benefits of seamless, coordinated care** combining **effective team care and patient-centred care planning**?

- What is the added value of the Value of Treatment study? *What are the new research developments in early intervention to improve [primary and secondary] prevention and treatment, knowing that, as of today, there is no cure?*
- How can we ensure that evidence built from robust research can have an impact on policy? *What are the priorities for policy making in the current context of health systems reforms (articulating their impact investment social return) while continuing in investing in health ("health is wealth") and legislation implementation?*

There is still **no cure for most brain disorders**; hence, it is necessary to **focus on risk reduction, preclinical and early detection and diagnosis, and timely intervention**. **Primary and secondary prevention strategies** remain essential (available diagnostic tools for neurological disorders and routine mental health screening). **More research is needed to understand the causes but also the progression of brain disorders and to develop new treatments that do not only symptomatically improve the condition but may modify, i.e. slow down, or even stop their course.**

**Early detection and intervention with the necessary psychosocial support** is also crucial to **reduce stigmatization and fear of disclosure**.

The solutions proposed by VoT experts are clearly identified. **Results from the case studies** provide important new insights into recent progress in the areas of pharmacology and biopsychosocial approach, as well as in relation to healthcare services delivery, continuous care and care networks.



For the case studies findings, see section 3 (Part 1) and case studies summary (Part 2)

The case studies results highlight the need for implementation of evidence-based guidelines that emphasize **cost-effective, coordinated healthcare interventions** in order to develop better prevention and timely treatment **"Brain: time matters"**, such as:

- **Schizophrenia** is one of the most severe and disabling mental illnesses. The treatment success rate can be high if **early identification of patients at risk, early detection of psychotic symptoms, and early intervention at the prodromal phase** are enabled. Depending on the stage of the disorder, antipsychotic medication or psychosocial interventions or both are needed.

- The availability of **biological markers (biomarkers)** for **early disease screening and diagnosis** will impact the management of **Alzheimer's disease** in several dimensions. It will help to identify patients at risk for Alzheimer's disease, including patients with subjective cognitive decline (SCD) or mild cognitive impairment (MCI), stages at which prevention efforts might be expected to have their greatest impact; and it will provide a measure of disease progression that can be evaluated objectively.
- **Stroke** together with dementias are among the leading causes of severe adult disability. There is **solid evidence on the benefits of stroke unit care and integrated, multidisciplinary care teams to improve stroke outcome**. Early use of intravenous thrombolysis with alteplase, and more recently, mechanical endovascular thrombectomy in acute ischemic stroke due to occlusion of a large artery supplying the brain, have proved very successful in reducing disability and mortality from ischemic stroke.
- **Multiple sclerosis (MS)** is the first cause of non-traumatic disability in working young adults, with clinical onset in the prime of life. **Quality of life is poor in relation to 'invisible' symptoms such as fatigue and cognitive impairment**. In MS, the **key paradigm is early diagnosis and early use of disease-modifying treatments (DMTs)** through a personalised medical approach, and optimised target treatment. Disease-modifying treatments (DMTs) at the early stage of **relapsing-remitting multiple sclerosis (RRMS)**, including **clinically isolated syndrome (CIS)** with visible abnormalities on MRI scans, are available to slow down the progression rate and disability accumulation. Unhealthy lifestyle (e.g. cigarette smoking) or low vitamin D serum levels can worsen the disease or contribute to its increase in the general population. Early intervention and lifestyle choices can reduce the societal burden of MS.
- In **Parkinson's disease (PD)**, the diagnosis is difficult but critical to maintain quality of life. Despite recent success, more research is needed to identify prodromal stages of PD with certainty. This research will help to measure preclinical progression and to identify biomarkers and endpoints for future neuroprotective trials. Neuroprotective agents are on the horizon but still need to be developed. At present for patients with manifest PD treatment remains symptomatic, but if skilfully delivered these medical (as well as nonpharmacological) **treatment options can be highly effective from early to late stage PD**. Personalised care planning is key for success.
- **Normal Pressure Hydrocephalus (NPH)** is a very common disease in the elderly, but the awareness of NPH in the population and in medical professionals is low. **NPH is a treatable neurological disorder, and is one of the few causes of reversible dementia, but it is substantially underdiagnosed**. Treatment by diversion of cerebrospinal fluid (CSF) to the peritoneal cavity (Ventriculo-peritoneal-shunt) is successful in reversing symptoms of dementia, incontinence and gait disturbance in more than 80% of the patients.

- **Restless Legs Syndrome (RLS)** is a chronic progressive sleep-motor-pain disorder of still unknown cause. Despite its high prevalence, awareness for RLS in the population is low. Patients often wait for years before a diagnosis is made and thus receive inadequate therapy. Effective symptomatic therapy for RLS is available, but its long-term use carries the risk to even augment the symptoms. Thus, **education about RLS is urgently needed** to increase the expertise of health care professionals on how to diagnose and manage RLS. **The search for the cause(s) of RLS and for new treatment strategies has to be intensified in order to reduce the suffering of people with RLS and the high societal costs.**
- **Headaches**, particularly tension-type headache, migraine, and medication-overuse headache affect half of the European population. Headaches are treatable but are still significantly under-diagnosed and wrongly treated in the population. **Education of primary care practitioners and pharmacists can play a key role in increasing diagnosis, proper treatment and appropriate referral to tertiary level of care for the most complex cases. Implementation of structured headache services** (usually a three-tier model, but always based in primary care) is a good way to achieve higher population coverage. Such intervention needs **support by educational initiatives** aimed at both patients and healthcare providers to achieve better adherence.
- Up to 70% of people with **epilepsy** could become seizure free with timely and appropriate anti-epileptic drug (AED) treatment. For 30% of people with epilepsy, seizures cannot be controlled with drugs and require other interventions, including surgery. There is a **marked treatment gap with respect to delayed diagnosis and access to specialist services and appropriate treatment**. Timely intervention and access to expertise is essential for optimal management. Healthcare services need to be well **coordinated, networked and accessible** allowing management from first seizure through to complex epilepsy surgery, whilst also taking into account co-morbidities.

**As noted by the WHO<sup>6</sup>, the people-centred and coordinated care approach** promises to raise care quality, improve outcomes and enable better resource allocation, but most health systems are yet to fully embrace it. **Health spending is rising again in the EU** but not for more efficiency, rather the contrary. The **OECD Health Ministers forum**, early this year (January 2017), advocated for **waste reduction** in healthcare<sup>7</sup>.

**EBC Value of Treatment Policy White Paper on value of treatment is very timely.** This is the right time for policy recommendations to reach policy makers.

### Box: Summary of policy recommendations for brain disorders

#### Key findings:

- Low understanding of the diseases aetiology, risk and preventive factors
- Lack of disease awareness in the general public and lack of training for health care providers
- Lack of primary and secondary prevention programs
- Lack of timely and adequate diagnosis and treatment
- Fragmentation of health care services and lack of coordination between health and social services

#### Conclusions & recommendations in alignment with economic analysis:

- Invest in more basic and clinical & translational neuroscientific research
- Increase brain disease awareness, patient empowerment and training for health care providers at all levels of care
- Address prevention and timely intervention as a priority based on needs
- Address health care services delivery and support clear patient pathways
- Foster seamless care through validated models of care & tools implementation, legislation and incentives

**In alignment with findings and study conclusions – and these could be the basis to pursue further the Value of Treatment research project – policy recommendations are the following:**

- **At the healthcare level**, improving **the patient flow** in the whole process of care (care pathway<sup>8</sup>) for better outcomes (adopting tools to overcome treatment gaps and implementing best practices) and assessing the impact of brain disorders on the manifestation and outcome of other medical and surgical diseases (the challenge of co-morbidity);
- **At research level**, addressing **1) the research gap** (causes of most brain disorders are uncertain and more basic and clinical&translational research is needed) such as prevention and the use of biomarkers for risk assessment - when available (e.g. Alzheimer's disease) to identify patients with a brain disorder as early as possible in the disease stage; **2) policy implementation research at the healthcare level** – conduct health systems evaluation, when an intervention has demonstrated impact, to replicate in similar settings (e.g. return on investment initiatives and short-term indicators);

- **At macro health system governance level**, based on existing plans of action (EU Horizon 2020, EC Health Programme 2014-2020, and other plans from WHO,...), it is essential:

- 1) to converge action towards developing an EU-wide research and public health combined Brain Plan to address brain health in a comprehensive (biopsychosocial and seamless care approach), transversal (across diseases) and collaborative way<sup>9</sup>;
- 2) to promote the set up of Knowledge Hubs (common research platforms to share data and results of conducted or current research e.g. EU BrainBank, BrainNet like Orphanet, Clinical Trial Network for brain disorders);
- 3) to foster collaboration with European Reference Networks for Rare Diseases (for better integration between primary, secondary and tertiary care);
- 4) to promote the development of Joint Actions, and other EU initiatives such as the Cancer Control "CanCon" Joint Action (initiative set up to build upon the cooperation and results of the European Partnership for Action Against Cancer, EPAAC), the EC Integrated Care for Breast Cancer Initiative, ... as illustrations of excellent collaboration with Member States and tangible achievements – which could be replicated for Brain Disorders.

In the following sections, we elaborate on the **epidemiology and impact of brain disorders** as well as the **scale of unmet needs**, examining the **cost-effectiveness of early intervention**. Based on key findings and rapid appraisal of challenges faced, we also **highlight future perspectives and policy recommendations to optimize research, diagnosis, therapy and care at the European level**.

## PART 1: VALUE OF TREATMENT RESEARCH PROJECT OVERALL OBJECTIVES AND POLICY RECOMMENDATIONS

### BACKGROUND - WHAT ARE BRAIN DISORDERS?

#### Brain disorders in a word

- A reality: the brain, source of intellectual capacities, emotions and behaviour, is essential for people's personal and professional lives, as well as their participation in society. When the brain is damaged, it can affect different functions of the human body and can lead to disorders impacting both the individuals as well as society at large<sup>11</sup>.
- Heterogeneity: brain disorders encompass all the conditions and disabilities affecting the brain, caused by illness, genetics, traumatic events or injuries. It refers to a wide variety of diseases, varying greatly in their symptoms and level of severity. Brain disorders are classified into different categories, including neurogenetic diseases, neurodevelopmental disorders, neuroinflammatory diseases, **neurodegenerative diseases, cerebro-vascular diseases, metabolic diseases, traumatic brain injury, brain tumours**, addiction to drugs and alcohol, **and the large category of psychological/mental disorders**.
- **Neurological disorders include a large variety of diagnosis:** examples of symptoms include paralysis, muscle weakness, poor coordination, loss of sensation, seizures, confusion, pain, and altered levels of consciousness<sup>12</sup>.
- **Mental disorders** comprise a broad range of problems, with different symptoms. However, they are generally characterized by some combination of abnormal thoughts, emotions, behaviour and relationships with others. Examples are schizophrenia, depression, intellectual disabilities and disorders due to drug abuse. Most of these disorders can be successfully treated<sup>13</sup>.
- Brain disorders are difficult to diagnose: variety of forms and symptoms can overlap
- For the same brain disorder: different patient profiles, many care pathways

## ABOUT THE VALUE OF TREATMENT PROJECT

The **global framework of the project** “how better healthcare practice can improve the lives of European citizens and have a positive socio-economic impact”, was **designed by the EBC Board**.

**EBC 2015-2017 Value of Treatment research project end goals are threefold:**

- 1) To develop case studies demonstrating (i) health gains and (ii) socio-economic impacts resulting from best health interventions. Benefits of best clinical interventions are compared with the current standard of care or, where appropriate non-treatment;
- 2) To perform a robust analysis to support the research framework with empirics;
- 3) To make policy recommendations grounded in relevant and solid scientific knowledge. The main findings of the analysis will be reported at 22 June 2017 EBC final conference to a wide audience including representatives of Ministries of Health and Social Affairs, the European Commission, WHO, OECD and other key international institutions, as well as international experts to support evidence-based policy making in the context of the current EU research and health policy

Both **Academic Partners** (the London School of Economics and Political Science for the “economic evaluation” and the Institute of Health Policy and Management, Erasmus University Rotterdam for the “patient care pathway analysis”) **developed the VoT research methodology in consultation with the EBC Value of Treatment Project Management Team**.

**The EBC Value of Treatment Project Management Team** has been leading the research project to ensure 1) methodology consistency and rigorousness, 2) direct follow-up with the case studies Working Groups with regards to analysis, interpretation of data and reporting, and 3) harmonization of the findings based on a standardized approach.

**Case studies Working Groups** were formed with **experts** within the network of EBC member organizations (e.g. European Academy of Neurology, European Psychiatric Association, European Federation of Neurological Associations, GAMIAN-Europe) as well as other industry and patient associations representatives.



For the complete list of the participants to the Working Groups, [see Annex](#).

The groups were established to ensure **a high level of expertise** (participation of clinicians, health economists, epidemiologists, patient group representatives, ...) and **an innovative “bottom-up” approach with case studies data analysis (see fig. 1: case studies covering a range of brain disorders and objectives)**.

**Figure 1:** Case studies covering a range of brain disorders and objectives

<b>CASE STUDIES (9)</b>	<b>Mental Health:</b> Schizophrenia
	<b>Neurology (*):</b> Alzheimer's disease, Epilepsy, Headaches, Parkinson's disease, Multiple Sclerosis, Restless Legs Syndrome, Stroke
	<b>Neurosurgery/Neurology (*):</b> Normal Pressure Hydrocephalus
<b>OBJECTIVES</b>	<ul style="list-style-type: none"> <li>- <b>Identify treatment gaps and causing factors along the care pathway, and propose solutions to address them</b></li> <li>- <b>Evaluate the socio-economic impact of these solutions</b></li> </ul>

(\*) Neurology and neurosurgery are listed in the WHO 11<sup>th</sup> International Classifications of Diseases (ICD-11) under “nervous system diseases”.

## 1. CONTEXT

### 1.1. Epidemiology and impact of diseases

**Brain disorders** refer to the multiple mental including substance use and neurological disorders. **These include amongst others** Alzheimer's disease and other dementias, schizophrenia, depression, stroke, migraine and other headache disorders, epilepsies, Parkinson's disease, multiple sclerosis, sleep disorders, anxiety, chronic pain, autism, brain tumours, addiction to drugs and/or alcohol.

Together they will affect **more than one in three European citizens during their lifetime - currently 165 million people in Europe** (an estimated **38.2%** of the EU population annually)<sup>14</sup>.

**The prevalence of brain disorders is growing** due to the so-called epidemiological transition from acute to chronic diseases and the increase in life expectancy but also because of a number of socio-economic, environmental and behavioural health determinants, some of which are still not entirely understood.

**The causes of brain disorders are heterogeneous** ranging from degeneration or dysregulation of the immune process to developmental and functional abnormalities, **and frequently implicate a complex interplay between genetic and environmental factors**. A better understanding of these causes is a necessity to improve treatment and primary or secondary prevention.

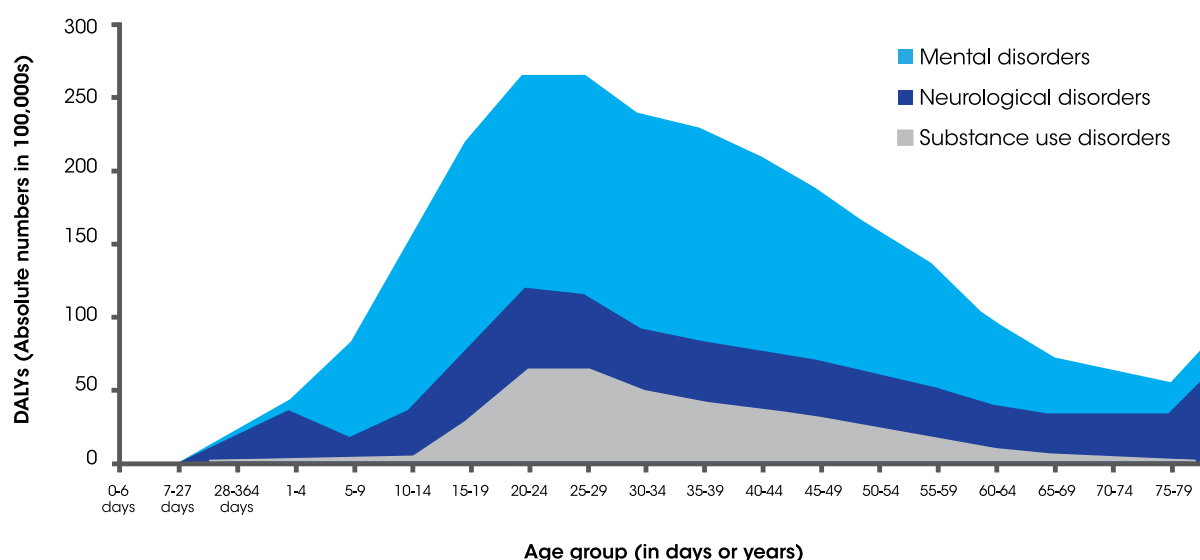




For more epidemiological data on specific disorder, see [Part 2](#) with case studies analysis.

**Major depression together with stroke, dementias and alcohol use** are among the top four causes in the **burden of disability** (in terms of “Disease-Adjusted Life Year”, DALY<sup>15</sup>) in the European region<sup>16</sup> and globally, migraine is the third cause of disability under 50s in the Global Burden of Disease (2015), and the most common neurological disorder<sup>17</sup>. Recent analysis (2015) from the Global Burden of Disease Study 2010 indicates that DALYs occur **across lifespan**; however, there is **a peak in early adulthood (between 20 and 30 years) for mental and substance use disorders compared with neurological disorders, where DALYs are more constant across age groups**<sup>18</sup> (see *fig. 2: Absolute DALYs Attributable to Mental, Neurological, and Substance Used Disorders, by Age, 2010*).

**Figure 2:** Absolute DALYs Attributable to Mental, Neurological, and Substance Used Disorders, by Age, 2010



**Main characteristics** are:

- On the one hand, older people represent **the largest portion of recipients of health and long-term care**: as a result, the burden of brain disorders is increasing together with a rising trend of the impact as the population ages (e.g. different dementias)<sup>19</sup>.
- On the other hand, many brain disorders have **an early-onset in life and, due to their chronic course, have an enormous health and socio-economic impact** (e.g. schizophrenia, bipolar disorder or anxiety)<sup>20</sup>.
- Last but not least, brain disorders occur **at younger working age** and at the **beginning of a professional life** (for instance, multiple sclerosis, epilepsy, headaches, restless legs

syndrome)<sup>21,22,23,24</sup> or before retirement and even earlier in some cases (Parkinson's disease, stroke)<sup>25,26</sup>.

The **consequences** extend well beyond the healthcare system: **high cost of technological progress, loss of healthy life years and quality of life, burdens on health and social welfare systems, implications for labour markets** with prolonged impairment, great dependency and significant reduced productivity.

Direct healthcare and non-medical **costs of brain disorders** make up for **60%<sup>27</sup> of the total costs** which EBC estimated at **800 bln€/year in Europe<sup>28</sup>**. For the remaining indirect costs, almost 40% is attributable to lost productivity (whether it is absenteeism or presenteeism). At European level, this health budget far exceeds that of cardiovascular diseases, cancer and diabetes together<sup>29</sup>. **All types [direct, indirect] of costs** including the impact on family or informal carers **increase** with the **increasing severity and chronification** of the disease<sup>30</sup>.

## 1.2. Unmet needs and treatment gaps

**Numerous needs of individuals at risk and patients are unmet.** An estimated 3 to 8 out of 10 people living with a brain disorder remain untreated or inadequately treated although effective treatments exist<sup>31</sup>. **Despite the escalating costs of brain disorders, this public health issue has not been properly addressed.**

Being the seat of many **chronic disabling** diseases<sup>32</sup>, **brain disorders** are particularly **challenging**, as they most often correspond to the **management of long-term conditions under their different aspects: co-morbidities (physical health, psychiatric), loss of independence, occurrence of acute, relapsing episodes and rehabilitation phases (motor, cognitive, social).**

**The long-term and transversal nature of care and treatment** for mental and neurological disorders have all served to confound hospital traditional, fragmented and top-down led responses. The **chronically ill patients and subjects to co-morbidities, are in special need of continuous care<sup>33</sup>**. These require a more **longitudinal or multidisciplinary network approach linking health and social care (paradigm shift) and payment systems** that can cope with care provided **in more than one setting<sup>34</sup>**.

More than **50% of people with chronic illness** have multiple conditions with complex health needs, the so-called "high needs, high costs", a **multiplier effect on the burden of disease<sup>35</sup>**. Prevalence of co-morbidity increases with age but is not just an issue for older adults<sup>36</sup>. The actual number of people with **multimorbidity** is **higher at younger age and is more common among those living in deprived areas<sup>37</sup>**. People within lower socio-economic groups are at particular risk of poorer outcomes (health inequalities).

## ILLUSTRATION 1

**People with severe mental health problems such as schizophrenia and bipolar disorder face increased risk of physical health problems, including diabetes, hypertension, coronary heart disease and cardiovascular disease.**

Weight gain, metabolic change and smoking mean that most patients with severe mental illness by the time they reach 40 are already on a path that which includes CVD, diabetes and premature death<sup>38</sup>. The high prevalence of mental and physical health conditions highlights the need to ensure that healthcare systems deliver care that takes physical and mental comorbidity into account. Further, the higher prevalence of multimorbidity among persons with low educational attainment emphasizes the importance of having a health care system providing care that is beneficial to all regardless of socioeconomic status<sup>39</sup>.

**Co-morbid mental illness generates significant additional costs in and beyond the health-care system: co-morbid mental health problems raise total health care costs by at least 45% for each person with a long-term condition and co-morbid mental health problem<sup>40</sup>. There is a strong economic case to be made for investment in interventions that promote/preserve the physical health of people with mental illness: screening for physical health problems and early intervention are essential** with a key role identified in primary care.

## ILLUSTRATION 2

**To address the issue of fragmentation and overcome treatment gaps from a health services delivery perspective, it is necessary to “optimize care and rationalize costs”.**

There is a need for a **healthcare system transformation** based on shared-vision and a practical roadmap to implementation of a coordinated system at national, regional level (care network).

In such a system, health promotion, disease prevention, detection and early diagnosis, treatment and rehabilitation are seen as **one seamless process of actions across different healthcare professionals and complementary disciplines** (e.g. hospitals, psychiatric hospitals, specialists care, primary care, community care, homecare, institutional care or nursing home, pharmacies), that should work together according to a team-based approach **in order to deliver patient care and improve health outcomes<sup>41</sup>**. The potential benefits for care **integration** are being explored through the case studies analysis and the conclusions are highlighting them. Solid evidence is built to assess and support the best option **for further policy development**.

### 1.3. Why early intervention is key for Brain Disorders?

To ensure the **continuity of care** from the very beginning, early intervention is key **for optimal management of the disease and for achieving better clinical outcomes**. A large body of research links **early intervention** to **measurable health gains** such as improved survival rates, reduced complications and disability, better quality of life **and lower treatment costs**.

However, **effective implementation of early diagnosis and treatment** varies widely across health systems and many European countries are still lagging a long way behind, with wide clinical practice variations even within countries.

**In the absence of cure** for most brain disorders, there is an **increasing focus on early (including prodromal) detection and intervention from an organizational and research perspective: "time matters"**.



#### 1.3.1. Early detection and intervention - Potential risk-reduction capacity in mental health care

**Early detection and intervention** are **recognized for their potential risk-reduction capacity**. Early intervention aims to identify people who might be at risk, to prevent a particular health problem (risk factors). **Most community health organizations** have found that the most effective prevention programs work on both reducing risks and enhancing protective factors. But of course, early detection means also to recognize the first symptoms of a disease even at the prodromal phase.

For instance, **schizophrenia and acute psychosis** can have devastating consequences. It is usually associated with a prodromal period brief of 1-3 years, and in very high risk patients, and in 20-40% of very high risk subjects, the "transition" to schizophrenia appears within a year<sup>42</sup>. During the prodromal period, brief intermittent psychotic symptoms may develop. Psychosis and/or schizophrenia are commonly associated with anxiety, depression, post-traumatic stress disorder (PTSD), personality disorder and substance misuse. Although

many people with acute psychosis respond to drugs, 80% relapse within 5 years due to poor adherence to treatment. Approximately 50% have a moderately good long-term outcome. In the last decade, there has been much more emphasis on early detection and intervention, with a more positive approach to long-term recovery<sup>43</sup>.

Unless clear-cut psychotic symptoms are already present, there is no indication for treatment with antipsychotic drugs. The prodromal phase is likely to include negative symptoms and/or anxiety and/or some decline in cognitive and/or psychosocial functioning only; all these aspects, unless they are considered as secondary to psychosis (in the case psychotic symptoms can be recognized), do not benefit from available antipsychotic treatment.

This area deserves more research. If best practices are indicated to be implemented, then psychosocial interventions and close monitoring should be in place<sup>44</sup>.

### Box 1: Routine mental health screening

Routine mental health screening “short diagnostic interviews” in primary care can detect possible symptoms of depression and other mental illness, much like a blood pressure test can identify AVC risk factors.

The MMSE (Mini Mental State Examination) is a validated cognitive screening tool to identify adults with cognitive impairment.

- > Recent studies demonstrate that **making mental health checkups routine** is key to early identification and critical to prognosis for those who suffer from mental illness<sup>45</sup>.
- > **MMSE** is used by healthcare professionals to quickly assess cognitive functioning (e.g. for patients presenting dementia-like symptoms of mild cognitive impairment or patients with cognitive impairment associated with a cerebrovascular accident or traumatic brain injury)<sup>46</sup>.

#### 1.3.2. Early detection and intervention - Essential in neurological disorders

For most of the disorders, early detection and diagnosis - primary and secondary prevention remain essential. Some brain disorders can be asymptomatic until it (the first attack or episode) occurs. In the case of **ischemic stroke**: ~10% is preceded by a transient ischemic attack (TIA). Screening and treatment of vascular risk factors hypertension, diabetes mellitus, atrial fibrillation (with recommended oral anticoagulants) including changes of lifestyle can occur in the primary care setting<sup>47-48,49</sup>. **Multiple sclerosis** is the most common non-traumatic cause

of disability in young adults and can be diagnosed at the time of the first symptom using MRI, blood and CSF biomarkers<sup>50</sup>. **Parkinson's disease** is the second most common neuro-degenerative diseases. As there are **no PD-related biomarkers** yet, the diagnosis often is delayed. PD can begin with non-motor symptoms such as loss of smell (hyposmia) and rapid eye movement sleep (REM-sleep) behaviour disorder. These are followed by motor symptoms that can be so subtle in the early stages that they go unnoticed before they gradually advance over time into the typical clinical picture<sup>52</sup>. **For epilepsy**, early and appropriate intervention should improve early remission rates, maximize education and employment opportunities and minimize increased risk of death related to epilepsy. However, **no biomarkers exist** to allow early identification of patients destined to be refractory and who would benefit from epilepsy surgery or neuro-modulation<sup>53</sup>.

In **Normal Pressure Hydrocephalus (NPH)** it is also proven that early treatment shows better results<sup>53,54</sup>. Bedridden patients with severe dementia still benefit from intervention, however, they usually do not become independent again, whereas early treated patients remain autonomous for many years autonomously. Raising the awareness of NPH and the development of more sensible tests to detect NPH earlier<sup>55</sup> are some measures on the way.

As a result, **biomarkers are increasingly being researched** to contribute to the early detection process or to confirm the diagnosis.

## Box 2: Diagnostic tools available

Diagnostic tests and procedures are vital tools that help physicians confirm or rule out the presence of a neurological disorder, other medical condition or injury. There are **accurate tools to diagnose disease and to test how well a particular therapy may be working.**

### > Laboratory screening tests (biological and genetic biomarkers)

Several different biological indicators (biomarkers) in body fluids such as **the brain and spinal fluid (cerebrospinal fluid; CSF)**, in the **blood** and **urine** as well as in **skin biopsy** are proposed for use in the diagnostic workup of neurological disorders. In addition to biological biomarkers, recent research into **genetic biomarkers** for early PD for instance has also shown promising results<sup>56</sup>.

### > Neuroimaging techniques

Several neuroimaging approaches (various techniques to either directly or indirectly image the structure, function/pharmacology of the nervous system) are used as an additional tool in the examination of the brain in order to make a diagnosis of brain diseases<sup>57</sup>.

For instance, **Computed Tomography (CT scan) and Magnetic Resonance Imaging (MRI) are** used to detect blood clots or bleeding in patients with stroke. **MRI** is used to diagnose neurological disorders such as multiple sclerosis and aetiology of epilepsy. **Positron Emission Tomography (PET) Scan** and **Single Photon Emission Computed Tomography (SPECT) Scan** are both types of radioactive scans used in patients to diagnose Alzheimer's disease and Parkinson's disease, as well as epilepsy to help pinpoint the area of the brain involved in producing seizures<sup>58</sup>. **Electroencephalography (EEG)** is an essential component in the evaluation of epilepsy. The EEG provides important information about background EEG and epileptiform discharges and is required for the diagnosis of specific electroclinical syndromes.

Early intervention **at onset of the disease is essential to modify the course, i.e. slow down disease progression rate** e.g. MS disease-modifying treatments "new treatment paradigm, treat early and effectively"<sup>59</sup>. There have been huge advances in treatment in the last few years, particularly in **relapsing-remitting Multiple Sclerosis** with the development of disease-modifying therapies (DMTs) since early 2000 and, recently effective treatment of **progressive Multiple Sclerosis** is available<sup>60\_61\_62</sup>.

In **epilepsy**, newer drugs have provided more and better tolerated treatment options. However, they have not reduced the prevalence of drug resistant epilepsy. Also, current treatment has no impact on the natural history of epilepsy and do not prevent the development of epilepsy in patients at high risk, such as those with a traumatic brain injury<sup>63</sup>. However, **timely intervention is important**, ensuring that seizure remission is achieved as soon as possible, minimizing disruption to education, employment, relationships and other opportunities. This requires the provision of coordinated, networked and accessible healthcare services that allow management from first seizure through to complex epilepsy surgery, as well as the management of important co-morbidities. Prolonged seizures (status epilepticus) are a neurological emergency where treatment needs to be started immediately within 5 minutes in the case of convulsive status epilepticus (SE)<sup>64</sup>.

**For those suffering chronically from migraine**, an early care path and prevention can provide relief and positively benefit to the burden of illness of the patient's life, reducing impact on disability and physical functioning and everyday activities. Specific interventions under the **stepped-care paradigm** focusing on primary care as a first step, aim to avoid "chronification" as well as medication overuse and to implement appropriate, effective and cost-effective treatments in a biopsychosocial approach<sup>65,66</sup>.

**Persons with the diagnosis of Normal Pressure Hydrocephalus and limited comorbidity** can be treated with a ventrilo-peritoneal-shunt<sup>67</sup>.

**Research is actively looking at potential disease-modifying treatments (e.g. anti-amyloid drugs), which were previously tested only in patients with AD dementia** with a view to stopping or slowing the course of the disease: these are now being tested in selected asymptomatic populations who are at high risk of AD because of an established biomarker burden as measured by PET imaging or a specific genetic profile<sup>68,69</sup>. A similar approach is now favoured in the future therapy of **Parkinson's disease**<sup>70</sup>.

**More research** is needed to understand the progression of brain disorders and to develop new treatments that may modify their course, progression.



### 1.3.3. Addressing stigma

**Early detection and intervention is paramount** to reduce stigmatization, discrimination and marginalization. A diagnosis can have significant clinical, social and emotional consequences, and **psychosocial support is essential**<sup>71</sup>.

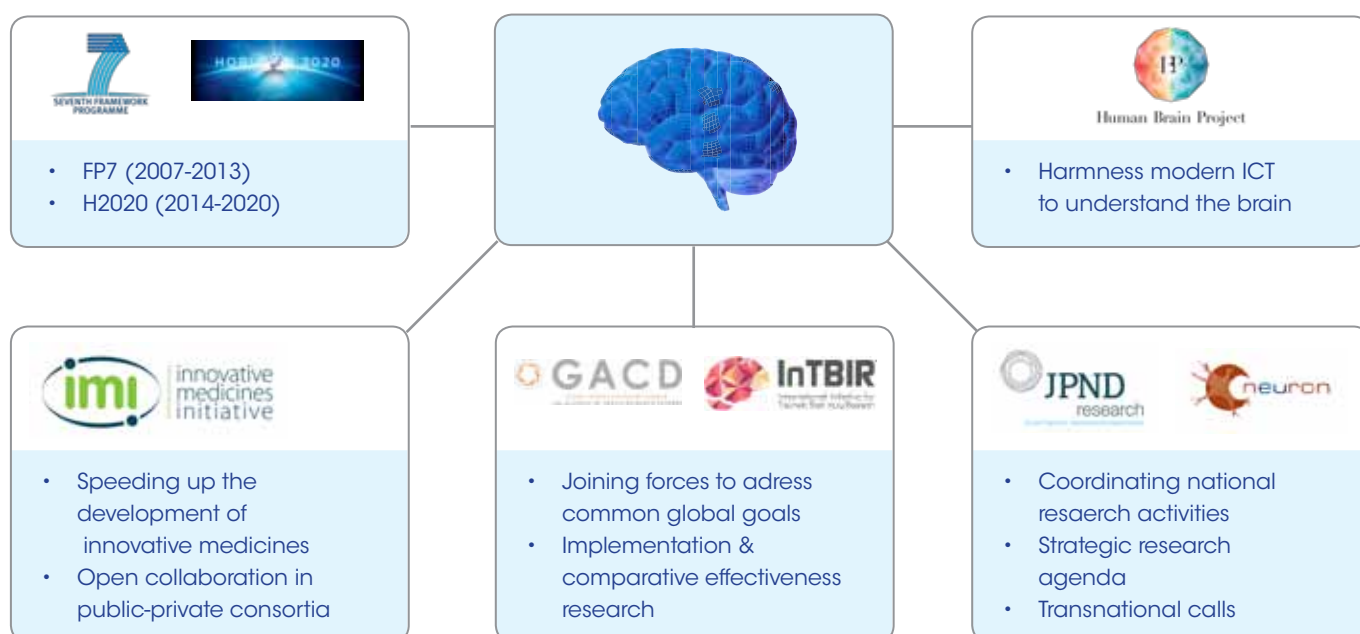
## 1.4. State of play of research initiatives and public health policies at European level

**The purpose of this section** is to provide an overview of current frameworks of action in the research and health domains, and to identify priority areas. The VoT project aims also to **address combined research and public health policies gaps and opportunities at EU level and translate study findings into policy recommendations**. This is the added-value of the project, **bridges** need to be built based on both frameworks of actions outcomes and VoT findings, and **collaboration** should be encouraged.

### 1.4.1. Medical research and frameworks of action

The European Commission fosters **medical research cooperation** across countries and facilitates coordination **through funded frameworks of action such as the EU Framework Programme for Research and Innovation “FP7” and “Horizon 2020”** (see *fig. 3: Status of EU Brain Research, addressing the continuum from knowledge to care delivery*).

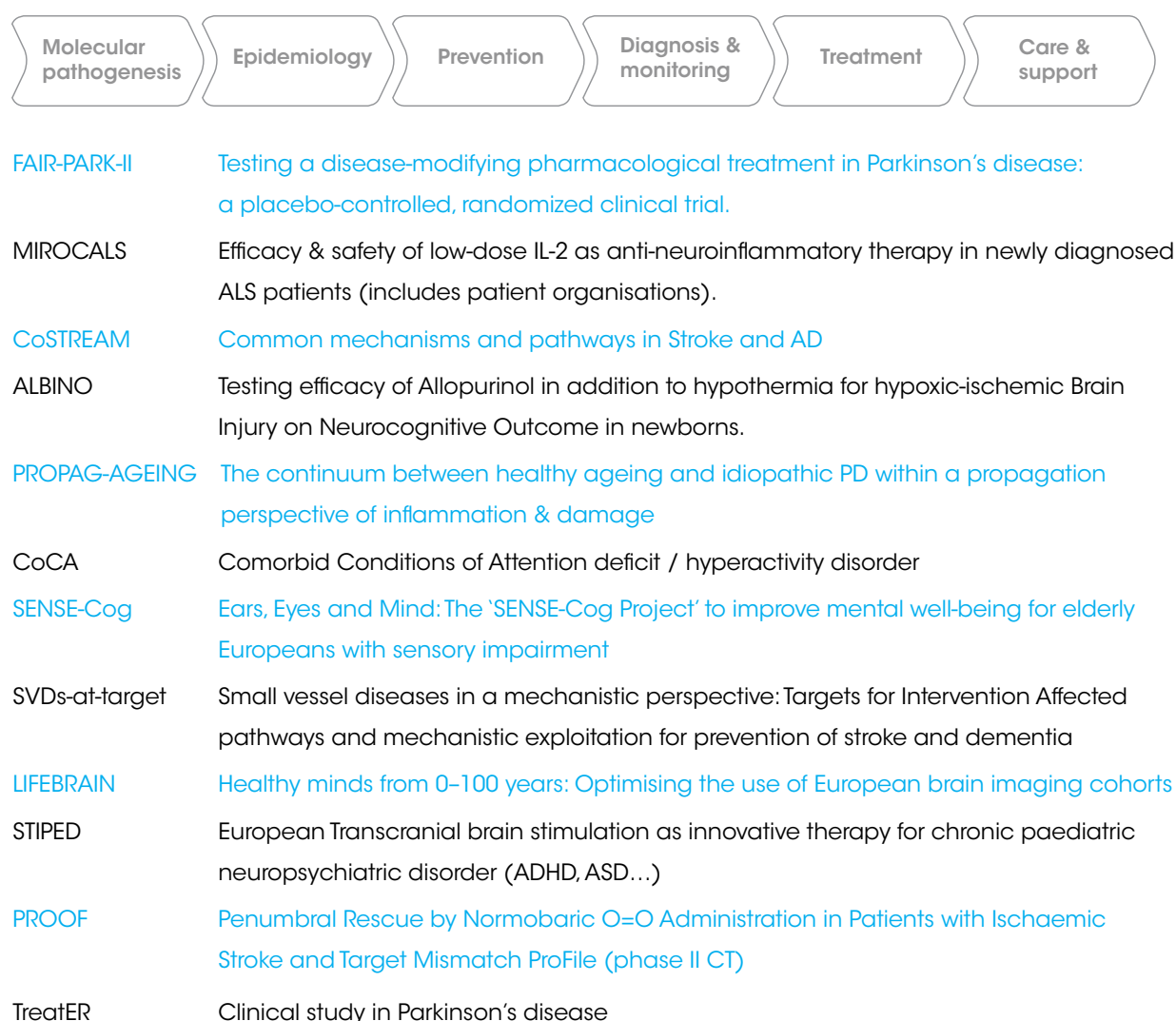
**Figure 3:** Overview EU Brain Research, 2017<sup>72</sup>



A **network of collaborative projects in major neurosciences areas** have been set up through **FP7** (e.g. brain functions and processes, neurodegenerative disorders, neurological disorders, neuropsychiatric disorders, rare brain disorders, public health) and pursued under **Horizon 2020 “Societal Challenges”**. Research aims to translate science to benefit citizens, departing from disease-oriented approach to better depict biological variations<sup>73</sup> (*see fig. 4: EU Horizon 2020 Neurosciences projects*).

**Figure 4:** EU Horizon 2020 Neurosciences projects to date

## EU Horizon 2020 - Neurosciences



**Opportunities for more brain research contributing to public health** is also provided under the Network of European Funding for Neuroscience Research (**NEURON II in neurosciences, neurology, psychiatry**) and the Joint Programme on Neurodegenerative Diseases (**JPND**), the Innovative Medicines Initiative (**IMI**), the International Initiative for Traumatic Brain Injury Research (**InTBIR**), and the Human Brain Project. **These projects activities** although very relevant and achieving key results would require to be more optimally coordinated as projects are existing rather isolated alongside each other. A long-term strategy with priority setting would be essential in the European research framework, for example addressing the challenge

to identify brain disorders in the prodromal stage and to develop preventive therapies, does not exist in the European research frame work yet.

#### 1.4.2. Public health policies and frameworks of action

Also, **EU health strategies** complement national policies and brings added value in improving health outcomes **through frameworks of action such as the third multi-annual 2014-2020 Health Programme which contributes for instance to innovative, efficient and sustainable health systems (e.g. European Reference Networks for rare diseases, Registries and Surveillance Information for rare diseases,...).**

**Public health policies at international level** aren't binding instruments (except the WHO Framework Convention on Tobacco Control being the first global public health treaty, the legislation on medical products and medical devices, the directive on cross-border health care, and the directive in the field of tissues and cells, blood, organs,...) but they provide a frame to countries for priority action areas and interventions. The WHO and the EU support mental health and neurological disorders policies and action plans (*see fig. 5: WHO and EU health policies overview*). These are major initiatives, but similarly to the European brain research projects, they should be more impactful at country level. With health becoming such a central issue on economy and politics in the world, leadership directions are needed, many issues are transnational and should be addressed at the international level. Policies cannot be effective without actionable measures. Project outcomes such as produced validated indicators and methods – should be the pillars for implementation and impact evaluation at country level.

**Figure 5:** WHO and EU health action plans overview

<b>WHO</b>	WHO Global Action Plan for the <b>prevention and control of NCDs 2013-2020</b>
	WHO Global Action Plan on <b>mental health 2013-2020</b>
	WHO Regional Office for Europe Action Plan on <b>mental health 2013-2020</b>
	WHO Regional Office for Europe for <b>the prevention and control of NCDs for 2016-2025</b> <i>Note:</i> this is the first time that mental illness is mentioned - It goes beyond the traditional 4 majors NCDs CVDs, cancer, diabetes BCPO - as well as it highlights the need for implementing more coordinated patient-centred care models
	WHO adopted resolution on <b>Epilepsy, May 2015</b>
	WHO adopted global action plan on <b>Dementia, May 2017</b>
	WHO adopted resolution on the global strategy and action plan on ageing and health <b>2016-2020</b>
<b>EU</b>	<b>EU Joint Action on Mental Health and Well Being 2013-2016</b>
	<b>EU-Compass for Action on Mental Health and Well-being 2015-2018</b>
	<b>EU Joint Action on Chronic Diseases and Healthy Ageing CHRODIS 2013-2016</b> as well as the recently adopted CHRODIS Plus
	<i>Note:</i> Mental and neurological disorders have been included in CHRODIS Plus.

## 2. RATIONALE: VOT RESEARCH METHODOLOGY

### Starting with the definition, what do we mean by “treatment gap” and “value”?

Analyzing the “**treatment gap**” has been central in the study: **unmet needs** are not only within the provision of medicines and medical devices, but also within health care systems and services. A definition of the treatment gap is “the number of people with an illness, disease or disorder who need treatment but who do not get it or receive inadequate treatment”<sup>74,75</sup> or “anytime the care offered to the patient does not correspond to his or her needs and or to the stage of the disease or the lack thereof”<sup>76</sup>. It is used **as an outcome measure in health care**.

**The VoT study addresses the obstacles to optimal treatment** which are defined as “missed diagnosis”, “delayed” or “inadequate treatment”, “non-adherence”, “no access to care”, “unaffordability”, “over-use or under-use”, ... (see **fig. 6: multiple factors to treatment gap**<sup>77</sup> which refers to **fig. 8 in the conclusions with proposed solutions p.62**).

**Figure 6:** Possible causes of the treatment gap

NATURAL HISTORY OF THE DISEASE
<ul style="list-style-type: none"> <li>- Asymptomatic phase of illnesses</li> <li>- Illnesses usually with no symptoms</li> <li>- Low understanding of the disease aetiology, symptoms, risk and preventive factors</li> </ul>
DEFICIENCIES IN HEALTH SERVICE ALONG THE CARE PROCESS (PREVENTION, SCREENING, DIAGNOSIS, TREATMENT, FOLLOW-UP AND REHABILITATION)
<ul style="list-style-type: none"> <li>- Not available services, systems or policies</li> <li>- No health insurance</li> <li>- Limited access to care (primary and secondary care)</li> <li>- Fragmented, poorly organised or or uncoordinated care</li> <li>- Lack of primary and secondary prevention programs</li> <li>- Delay in detection and diagnosis leading to late treatment</li> <li>- Drugs not available for whatever reason</li> <li>- Physician misses detection, diagnosis</li> <li>- Inadequate treatment</li> <li>- Low disease awareness in general public and lack of training, expertise from healthcare providers</li> <li>- No patient empowerment to facilitate adherence, compliance – non-adherence to treatment being intentional or unintentional</li> <li>- Absence of support for caregivers</li> </ul>

**ECONOMIC FACTORS**

- Costs of treatment
- Limited access to drugs and devices

**SOCIAL FACTORS**

- Fear of disclosure
- Stigma discourages seeking treatment (e.g. epilepsy, mental illnesses)
- Isolation and vulnerability

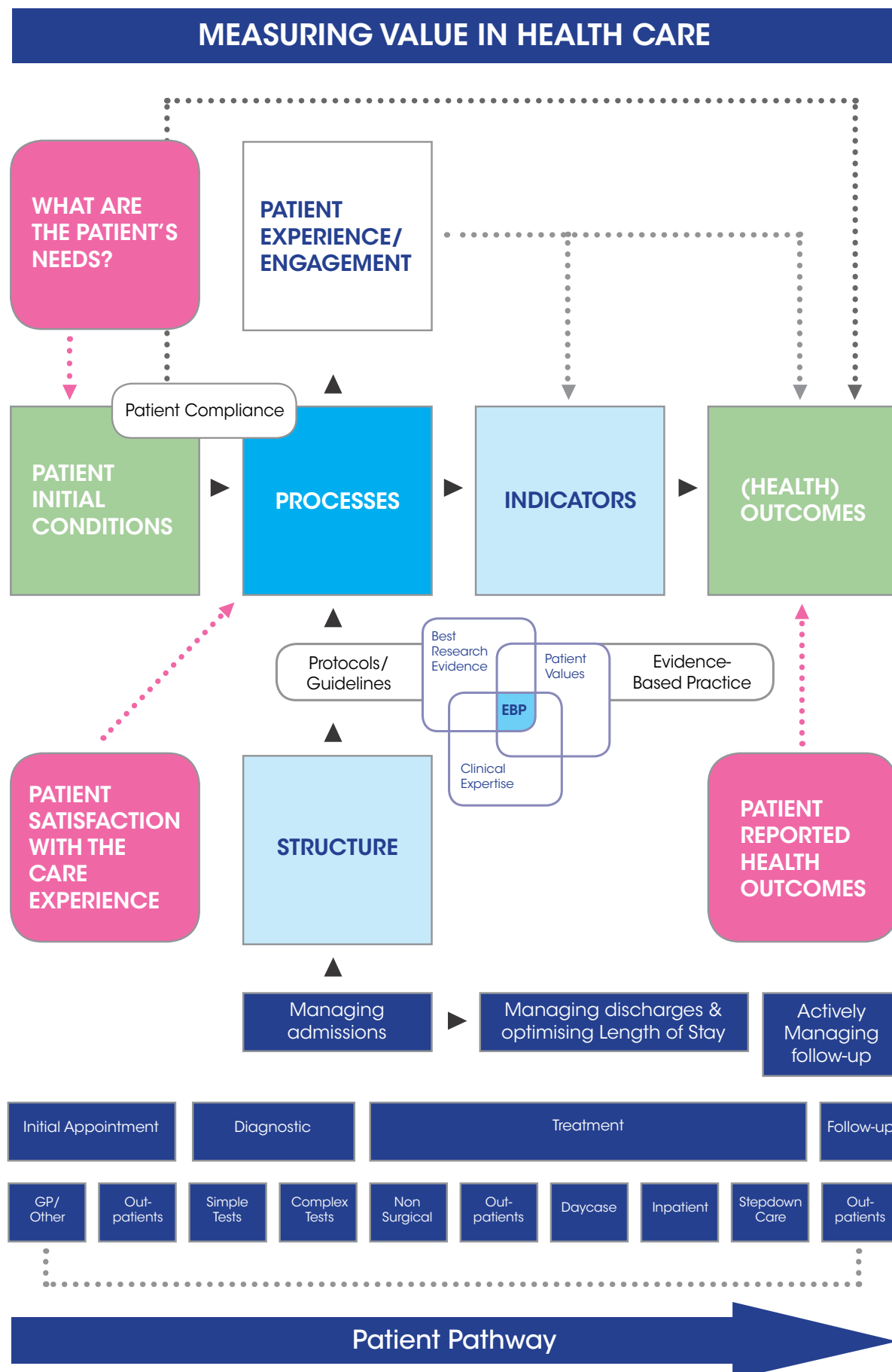
**OTHER FACTORS (unknown because of lack of research)**

Source: Adapted from R. Kale. The treatment gap. *BMJ. Epilepsia* 435(suppl 6) :31-33, 2002.

**Optimizing healthcare processes with an outcomes-based approach:** achieving high value for patients is the overarching goal of health care delivery, **with value defined as the health outcomes achieved per money spent**<sup>78</sup>. **Treatment is based on the needs of the patient ("demand") instead of on the offer/supply of treatment structures.** Each age group according to disease stage has specific needs to be addressed along the care process (biological, psychological, health care services, social needs)<sup>79</sup>. **Care for people with brain disorders usually involves multiple specialties and numerous interventions, with final outcomes** determined by interventions **across the full cycle of care.**

Measuring, reporting, and comparing outcomes are crucial **to improve outcomes and make informed choices about how to optimize healthcare and rationalize costs** (see *fig. 7a: patient-centred, measuring value in health care and the patient pathway*)<sup>80</sup>.

**Figure 7a:** Measuring Value in Health Care by achieved outcomes, starting with defining the patient's needs (in-patient care pathway)



This is **the objective of VoT with the case studies analysis: “delivering health care value by improving outcomes”** (see **Fig. 7b**), refining data and indicators, an overarching outline<sup>81</sup>.

**Figure 7b:** Delivering health care value for brain disorders by improving outcomes

Outcomes	Rational of measures and data sources
From Deaths	<ul style="list-style-type: none"> <li>- Mortality and life expectancy               <ul style="list-style-type: none"> <li>• Public health perspective</li> </ul> </li> </ul>
To Disorders/Diseases	<ul style="list-style-type: none"> <li>- Prevalence and incidence of disorders/diseases</li> <li>- Outcome measures to capture the reduction in morbidity and for specific disorder or disease, Quality-Adjusted Life Year (QALY) gained, Healthy Life Years (HLYs) gained.               <ul style="list-style-type: none"> <li>• Medical/clinical perspective</li> </ul> </li> <li>- Linking to cost/value               <ul style="list-style-type: none"> <li>• At system level: burden of disease studies</li> <li>• For specific service and interventions: cost-effectiveness studies</li> </ul> </li> </ul>
To Disability	<ul style="list-style-type: none"> <li>- Outcomes to address the way a health system deals with disabilities               <ul style="list-style-type: none"> <li>• At system level: Disease-Adjusted Life Year (DALY)</li> <li>• At health services: e.g. Resident Assessment Instruments (RAI)</li> </ul> </li> </ul>
To Discomfort and Dissatisfaction	<ul style="list-style-type: none"> <li>- Outcomes experienced by patients               <ul style="list-style-type: none"> <li>• PROMs (patient reported outcomes measurement) including EQ5D</li> <li>• PREMs (patient reported experience measurement)</li> </ul> </li> </ul>

**The case studies research combined methodology** encompasses **1) patient care pathway analysis** (qualitative research) followed by **2) economic evaluation of specific clinical interventions across different brain disorders, assessing their impact on costs and outcomes** (quantitative research).

## Research methodology framework 1

### Guidelines – A patient care pathway analysis from both patient and clinician perspectives [qualitative approach]

The aim was to map the **patient experience and treatment gaps**, describing patient needs and issues along the whole care process from prevention, prodromal, early detection to disease management. The results of the analysis were built based on epidemiology analysis, available

evidence-based diagnosis and treatment guidelines, quality standards and other information such as expert and patient opinions. **Gap(s) was assessed along a set of indicators defined** (see figure 7a and 7b, such as access, adherence, satisfaction, QoL, EQ5D e.g. pain and fatigue) **and recommendations were proposed on how these can be improved.**

### Challenges and limitations

Although we introduced a general methodological approach with instructions to perform the treatment gap analysis and possible solutions inventory, each working group had their own application of the patient journey/care pathway analysis presented principles. Differences were found in the composition of the stakeholders involved, the number of meetings, semi-structured interviews conveyed with patients and iterations to identify issues and discuss solutions as well as the geographical and cultural aspects, which were all taken into consideration. Accordingly, there are some difference across working groups in the approach to identify the treatment gaps and the formulation of recommendations.

## Research methodology framework 2

### Guidelines - Economic evaluation framework and case study analysis from both a societal and healthcare perspective [quantitative approach]

The aim of the proposed economic case study summaries was to make more and better economic evidence on the value of treatment in brain disorders available to policy decision making. The analyses were built on previously published research in the field, particularly where it has generated evidence on effectiveness, and used methods successfully employed in published studies to explore the economic case for closing treatment gaps in brain disorders.

The quantitative case study analysis aimed at producing a compendium of the economic evidence of treatment gaps in brain disorders. **It examined the economic case for a diverse range of brain disorder interventions and the treatment gaps previously identified via the patient journey analysis.**

Mathematical modelling, such as a simple decision tree, was populated with data from the literature, previous randomised or quasi-experimental studies, observational studies or routine management information systems (secondary data). Models are simulations of what might happen in reality, tracing pathways through care for individuals with particular characteristics/ treatment gaps, estimating the associated outcomes and costs, and then comparing them in order to better understand whether one is more effective, cheaper or more cost-effective than the other.



Where there was a completed economic evaluation in European settings we extrapolated the findings, and commented on relevance to the VoT project. We updated the costs to current price levels. We updated the costs to current price levels and supplemented the economic evidence if and when there was a possibility (e.g. to span a wider range of systems or sectors than in the original study, or for more years through modelling).

### Challenges and limitations

Where there was an older economic evaluation in Europe or an evaluation from outside Europe (but one that was still relevant), with the support of the experts we adapted the findings so that they reflected what could be expected in Europe today, at today's prices.

Where there was only effectiveness evidence and no previous economic evaluation we explored with the experts whether an economic case could be examined by using reported findings in the literature (eg patterns of (some) service use or impacts on patient employment, and it was possible to convert these into costs or savings). The input from the experts was vital to fill in any gap generally, and build modelling ex novo when no economic data were published in the literature.

Where evidence of effectiveness was limited we agreed with the experts on specific patient stories (or case studies) to be used as key examples of the treatment gaps. We gathered their personal opinion on the use of resources in the different scenarios and provided source of unit cost from their local country public tariff and their personal practice data.

For each model two alternatives were compared, including for example baseline scenarios (e.g. delayed diagnosis, current care, etc) vs. their respective target treatment. Timeframe varied according to the individual model (short 1-2 years, medium 3-5 years, and long term (more than 5 years). Interventions were examined from each of a range of perspectives – societal, the social care and health care system, or the whole public sector. In many cases, however, we did not expect to have a complete economic picture, and in those cases we looked only at those economic impacts that could be estimated from the data available. Outcomes measures (when included in the modelling) varied across application and data availability for the specific case study; they included a series of indicators, such as quality adjusted life years (QALYs) gained, healthy life years (HLYs) gained, life saved (see figure 7b). A discount rate of 3.5% was applied as appropriate.

### 3. KEY FINDINGS ACROSS CASE STUDIES (see Part 2: for figures and graphs) AND CHALLENGES

#### 3.1. Case studies findings

The case studies findings highlight that an adequate implementation of evidence-based guidelines<sup>82</sup>, cost-effective healthcare interventions and more research evidence to develop **better prevention and treatment options** definitely appear to be necessary.

#### Overview of the main findings:

- **Schizophrenia** is one of the most severe and disabling mental illnesses. The treatment success rate can be high if **early identification of patients at risk, early detection of psychotic symptoms, and early intervention at the prodromal phase** are enabled. Depending on the stage of the disorder, antipsychotic medication or psychosocial interventions or both are needed<sup>83,84</sup>.
- The availability of **biological markers (biomarkers) for early disease screening and diagnosis** will impact the management of **Alzheimer's disease** in several dimensions. It will help to identify patients at risk for Alzheimer's disease, including patients with subjective cognitive decline (SCD) or mild cognitive impairment (MCI), stages where prevention efforts might be expected to have their greatest impact; and it will provide a measure of disease progression that can be evaluated objectively<sup>85,86</sup>.
- **Stroke** together with dementias are among the leading causes of severe adult disability. **There is solid evidence on the benefits of stroke unit care and integrated, multidisciplinary care teams to improve stroke outcome.** Early use of intravenous thrombolysis with alteplase, and more recently, mechanical endovascular thrombectomy in acute ischemic stroke due to occlusion of a large artery supplying the brain have proved very successful in reducing disability and mortality from ischemic stroke<sup>87,88,89</sup>.
- **Multiple sclerosis (MS)** is the first cause of non-traumatic disability in working young adults, with clinical onset in the prime of life. **Quality of life is poor in relation to 'invisible' symptoms such as fatigue and cognitive impairment.** In MS, the **key paradigm is early diagnosis and early use of disease-modifying treatments (DMTs)** through a personalised medical approach, and optimised target treatment. Disease-modifying treatments (DMTs) at the early stage of **relapsing-remitting multiple sclerosis (RRMS)**, including **clinically isolated syndrome (CIS)** with visible abnormalities on MRI scans, are available to slow down the progression rate and disability accumulation. Unhealthy lifestyle (e.g. cigarette smoking habit) or low vitamin D serum levels can worsen the disease or contribute to its increase in the general population. Early intervention and lifestyle choices can reduce the societal burden of MS<sup>90,91,92,93</sup>.

- In **Parkinson's disease (PD)**, the diagnosis is difficult but critical to maintain quality of life. Despite recent success, more research is needed to identify prodromal stages of PD with certainty. This research will help to measure preclinical progression and to identify biomarkers and endpoints for future neuroprotective trials. Neuroprotective agents are at the horizon but still need to be developed. At present for patients with manifest PD treatment remains symptomatic, but if skilfully delivered these medical (as well as nonpharmacological) **treatment options can be highly effective from early to late stage PD**. Personalised care planning is key for success<sup>94-95</sup>.
- **Normal Pressure Hydrocephalus (NPH)** is a very common neurodegenerative disease with gait disturbance, incontinence and cognitive decline/dementia. NPH is one of the few causes of reversible dementia. Despite the very high prevalence in elderly (around 5%) the awareness in the population and also between health professionals is low. NPH is always a progressive disease and ends untreated with patients bedridden with severe dementia, the mortality rate is- if untreated - 90% in 5 years<sup>96</sup>. Patients get often only after many years a diagnosis and treatment. **Treatment by diversion of cerebrospinal fluid (CSF) to the peritoneal cavity (Ventriculo-peritoneal-shunt) is highly successful in reversing symptoms of dementia, incontinence and gait disturbance in more than 80% of the patients**; the results are better the earlier treated. Earlier diagnosis and therapeutic interventions reduce suffering of patients and their families and caregiver burdens as well<sup>97-98</sup>.
- **Restless Legs Syndrome (RLS)** is a chronic progressive sleep-motor-pain disorder of still unknown cause. Despite its high prevalence, awareness of RLS in the population is low. Patients often wait for years before a diagnosis is made and thus receive inadequate therapy. Effective symptomatic therapy for RLS is available, but its long-term use carries the risk to even augment the symptoms. Thus, **education about RLS is urgently needed to increase expertise of health care professionals on how to diagnose and manage RLS. The search for the cause(s) of RLS and for new treatment strategies has to be intensified in order to reduce the suffering of people with RLS and the high societal costs**<sup>99-100</sup>.
- **Headaches**, particularly tension-type headache, migraine, and medication-overuse headache affect half of the European population. Headaches are treatable but are still significantly under-diagnosed and wrongly treated in the population. Education **of primary care practitioners and pharmacists can play a key role in increasing diagnosis, proper treatment and appropriate referral to tertiary level of care for the most complex cases. Implementation of structured headache services** (usually a three-tier model, but always based in primary care) is a good way to achieve higher population coverage. Such intervention needs **support by educational initiatives** aimed at both patients and healthcare providers to achieve better adherence<sup>101-102</sup>.

- Up to 70% of people with **epilepsy** could become seizure free with timely and appropriate anti-epileptic drug (AED) treatment. For 30% of people with epilepsy, seizures cannot be controlled with drugs and require other interventions, including surgery. There is a marked treatment gap with respect to delayed diagnosis and access to specialist services and appropriate treatment. Timely intervention and access to expertise is essential for optimal management. Healthcare services need to be well coordinated, networked and accessible allowing for management from first seizure through to complex epilepsy surgery, whilst also taking into account co-morbidities<sup>103,104</sup>.

**2** For the overall presentation of EBC case studies findings, see the summaries with the patient journey analysis and the economic evaluation per case study in [Part 2](#).

## **Overview findings per case studies: averting long-term societal and healthcare costs of diseases by prevention and early intervention**

# Mental health **Schizophrenia**

## Key findings

### Studied healthcare setting: specialists care

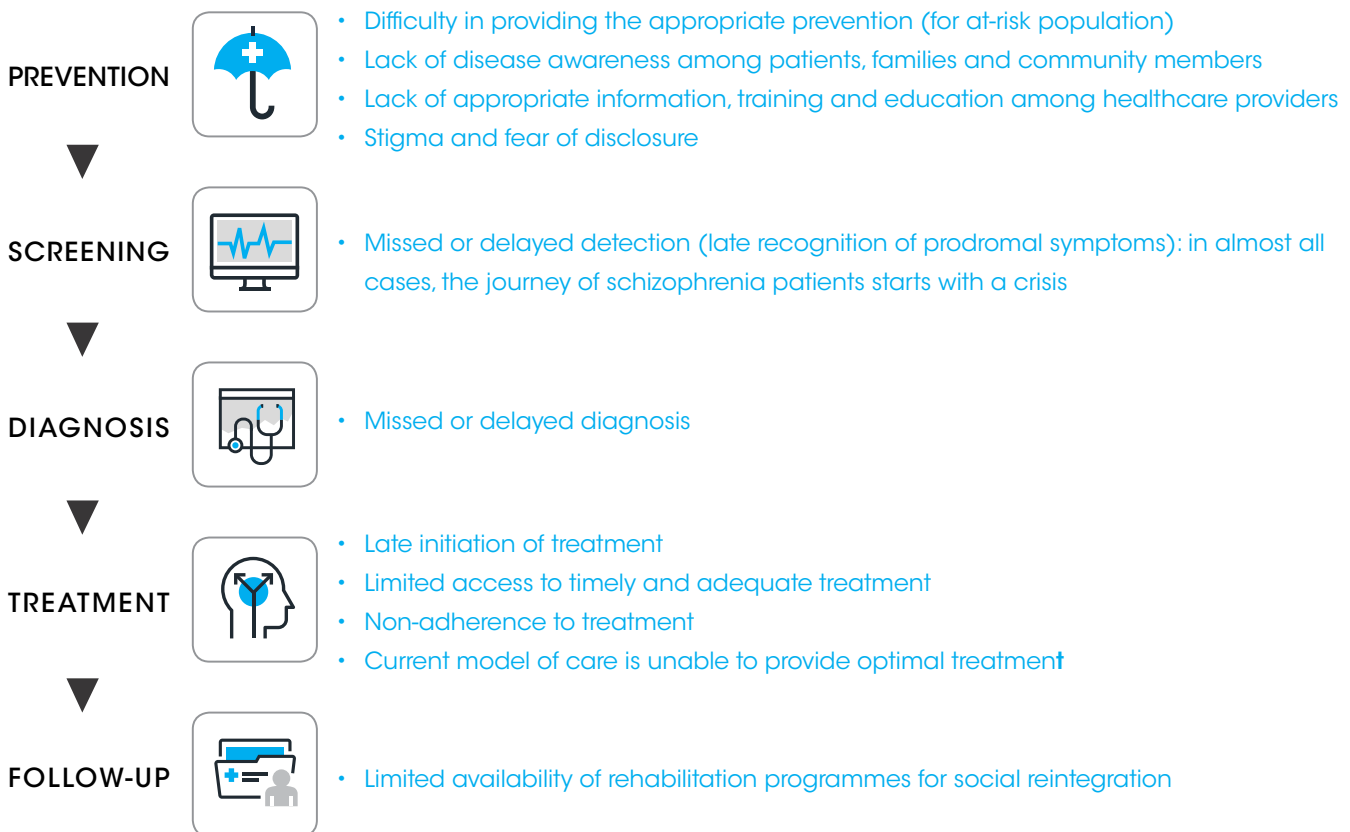
**Study objective:** to provide evidence-based information on what is available and needed to overcome treatment gaps in schizophrenia in a cost-effective manner (intervention strategies in the early illness course of schizophrenia).

> **Schizophrenia care pathway analysis:** the analysis focuses on 1) early detection (when there are prodromal signs of an attenuated psychotic syndrome), 2) reduction of the duration of untreated psychosis (DUP) by early intervention, 3) relapse prevention and integrated pharmacological and psycho-social treatment (recovery approach)

> **Economic evaluation:** assessment of the socio-economic impact of early detection (ED) and early intervention (EI) programmes in two separate healthcare systems in Europe: UK (where ED and EI are already available) and Czech Republic (where ED/ EI are not yet available, but they could be developed within the current mental health care reform).

**Setting data used :** NHS UK and Czech Republic

### Key care pathway analysis results: obstacles to optimal treatment



### Conclusions :

Prevention and early intervention services for people with prodromal symptoms and first episode of psychosis is paramount and cost-effective compared to usual care.

## Neurology Alzheimer's Disease (AD)

### Key findings

#### Studied healthcare setting: specialists care

**Study objective:** to develop a simulation model and estimate the impact of a hypothetical disease-modifying treatment (DMT) for AD in terms of wellbeing and resource use costs in a population of people at risk of AD from a societal perspective.

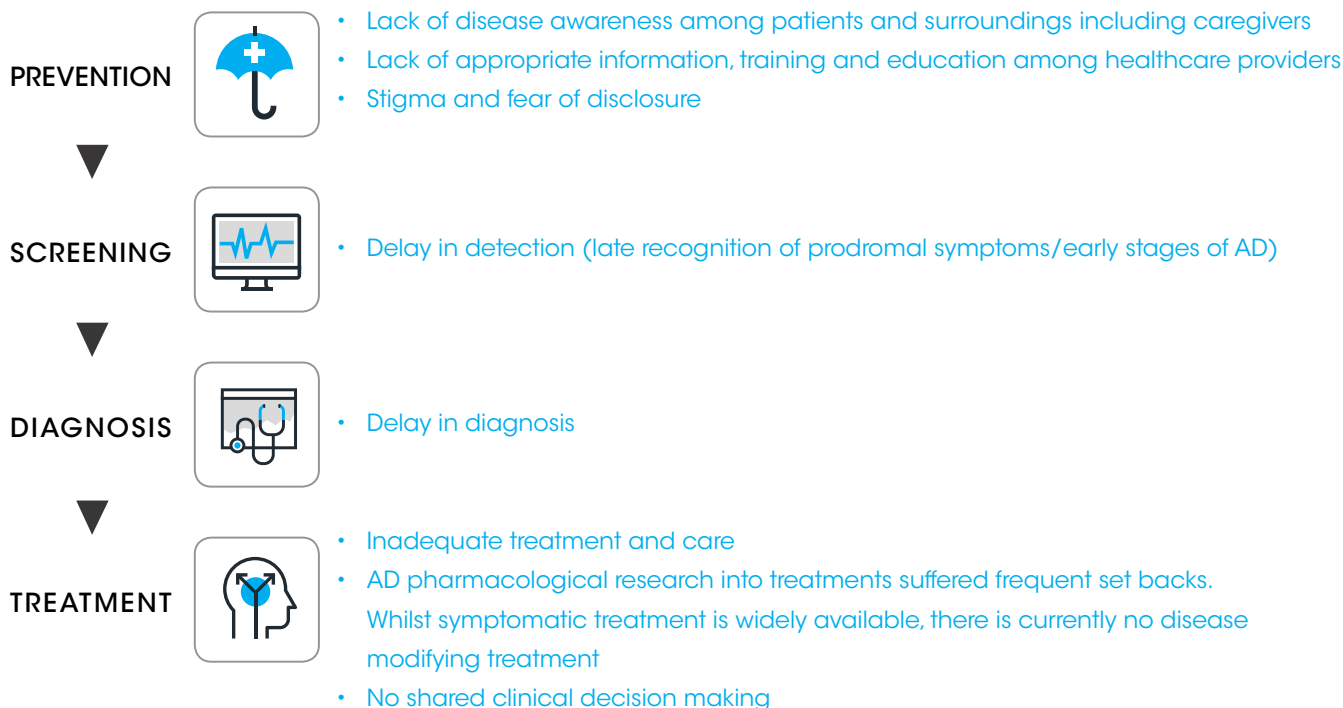
**> AD care pathway analysis:** identification of patients and caregiver needs and the potential effect of a hypothetical early intervention in patients with subjective cognitive decline (SCD) or mild cognitive impairment (MCI)

**> Health Economic model:** assessment of the potential value of such hypothetical treatment for people with amyloid pathology who have not yet developed AD dementia.

**Settings :** memory clinics and various care provider settings during the progression of AD (home setting, day care, hospital care and institutionalization).

**Setting data used :** multiple European countries were involved in the health economic analysis.

#### Key care pathway analysis results: obstacles to optimal treatment



#### Conclusions :

If screening can accurately identify pre-dementia patients at risk of progression, earlier treatment with DMTs has the potential benefit to patients of prolonging time in milder disease, reducing time spent with more severe disease, increasing time in the community, and reducing time in long-term care.

## Neurology Headaches

### Key findings

#### Studied healthcare setting: specialists care

**Study objective:** to develop an interventional model for the management of headaches (migraine, tension type and medication overuse headaches) and to value the socioeconomic impact and health gains of best practice in early detection (early intervention) compared with current care (no/ poor treatment) in the adult population.

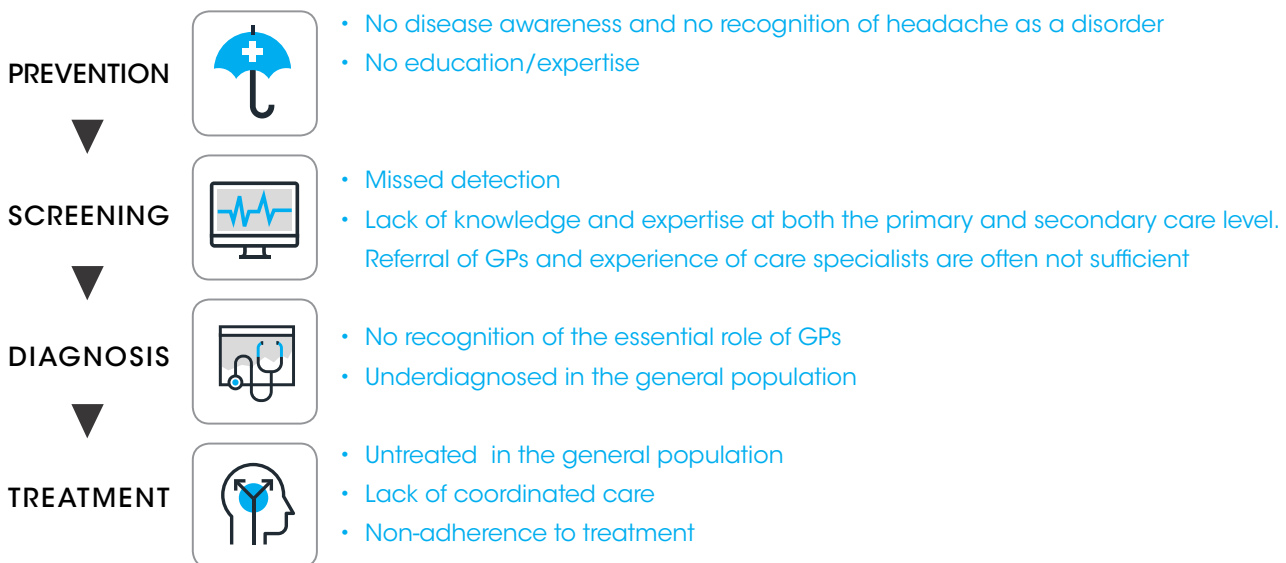
**> Headaches care pathway analysis:** an assessment was carried out to identify the major unmet needs and causes for treatment gaps and describe early diagnosis and treatment gaps looking at proposed solution of education of primary care professionals and pharmacists to provide sufficient reach. Structured headache services at second or third level of care should provide adequate diagnosis and treatment to the more complex situations (to avoid chronification) and should provide tailored multidisciplinary care when needed.

**> Economic evaluation:** cost-effectiveness was modelled of structured headache services delivering treatments with known efficacy for each of the selected headache type.

**Settings :** primary care, specialists care, pharmacists

**Setting data used :** Russia, Luxembourg and Spain

#### Key care pathway analysis results: obstacles to optimal treatment



#### Conclusions :

Treatment is available and often not properly provided. The analysis suggested that full implementation of education could increase proper diagnosis, treatment and appropriate referral to tertiary structured headache services. Cost-effectiveness of the proposed intervention overall and across headache types is demonstrated from the healthcare perspective.

## Neurology Stroke

### Key findings

#### Studied healthcare setting: specialists care

**Study objective:** to perform a systematic analysis of cost-effectiveness of the core acute and secondary treatment modalities in acute ischemic stroke: focus on Stroke Unit and capture LT benefits of secondary prevention.

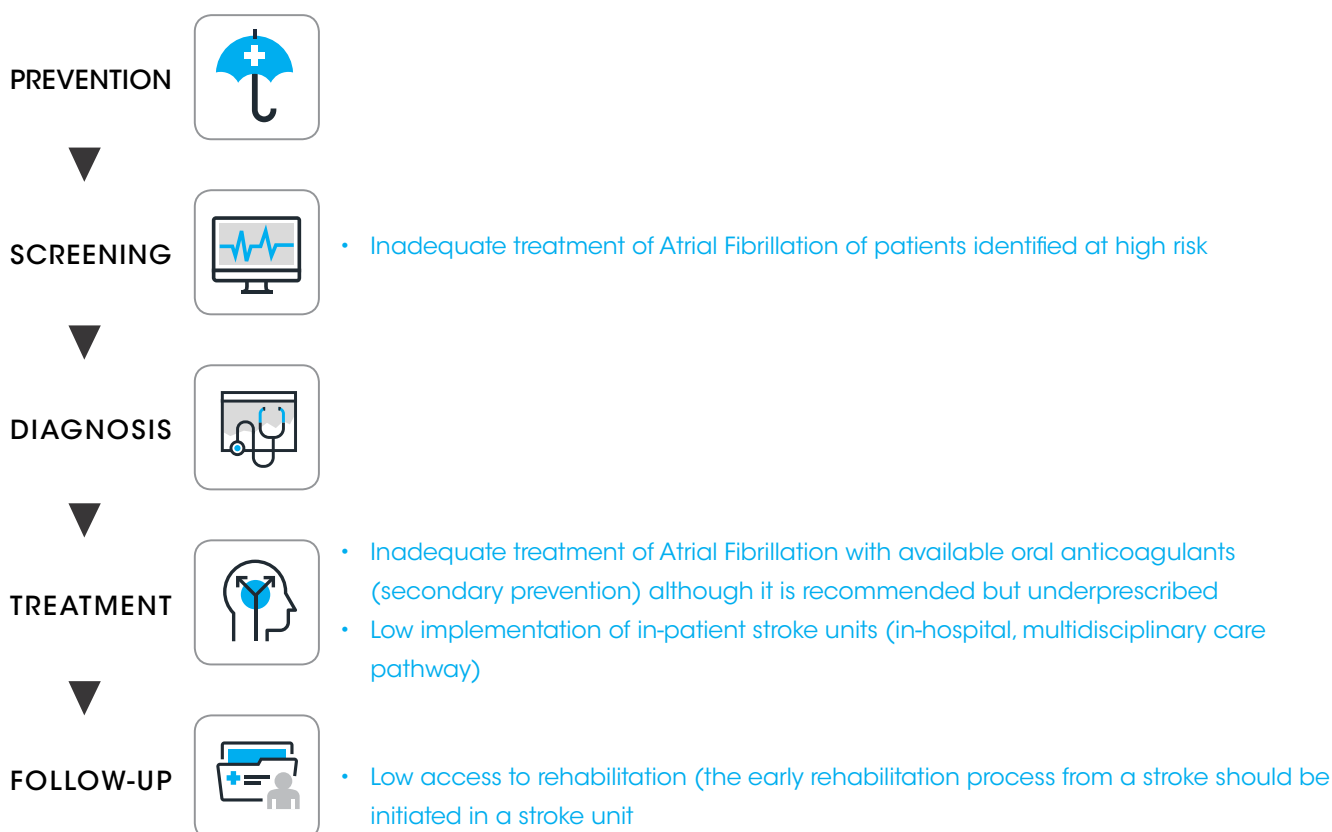
> **Stroke care pathway analysis** describes how to improve Stroke care in the future through the delivery of evidence-based interventions within the stroke unit.

> **Economic evaluation:** analysis of a full implementation of acute stroke unit care.

**Settings :** memory clinics and various care provider settings during the progression of AD (home setting, day care, hospital care and institutionalization).

**Setting data used :** UK

#### Key care pathway analysis results: obstacles to optimal treatment



### Conclusions :

The analysis suggested that full implementation of acute ischemic stroke services would be cost effective in the UK healthcare setting.



## Neurology Parkinson's Disease

### Key findings

#### Studied healthcare setting: specialists care

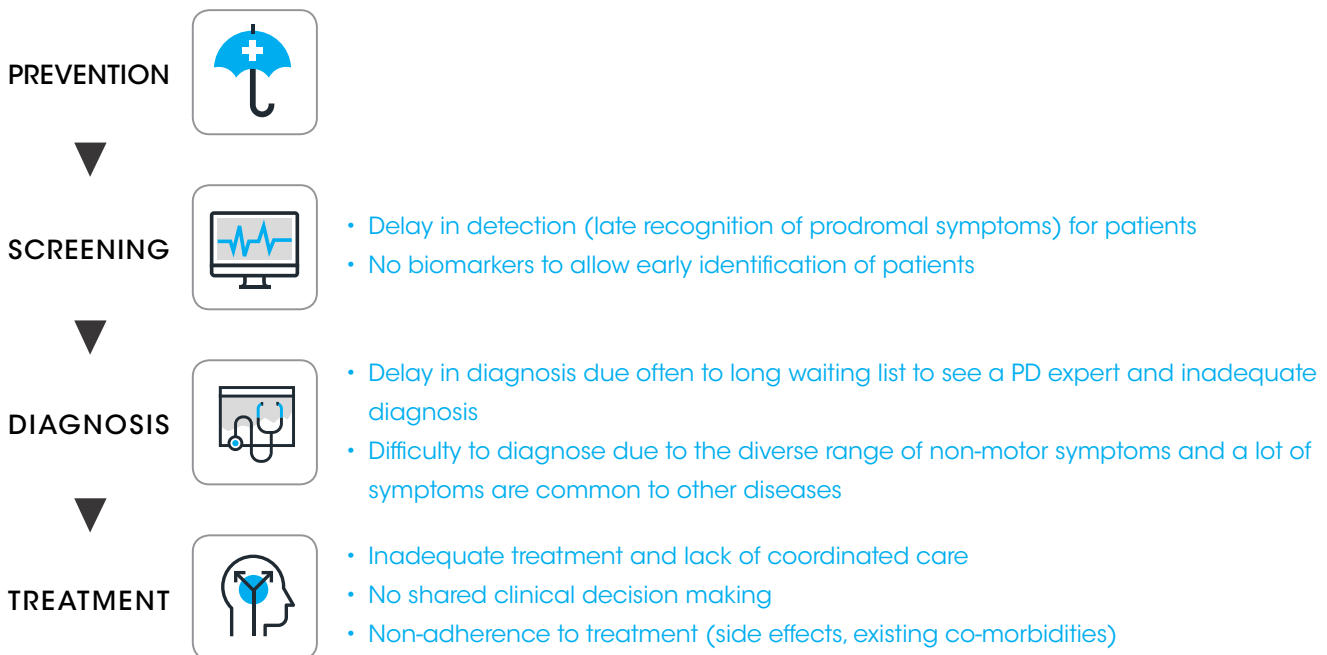
**Study objective:** to identify issues and gaps in the treatment of Parkinson's Disease (PD) in Europe, from initial diagnosis until the diverse complications of the late stage of the disease. The prodromal phase of a subgroup of PD (REM sleep behaviour disorder, RBD) is identifiable. Skin biopsy for phospho-alpha-synuclein aggregates potential biomarker for prodromal PD. Early detection of patients at high risk for developing PD is possible (RBD, gene carrier), supported by skin biopsy and imaging.

> **PD care pathway analysis** describes the issues and unmet needs

> **Economic evaluation** showcased their impact on the healthcare providers and society in 2 different healthcare systems

**Setting data used :** Germany and UK

#### Key care pathway analysis results: obstacles to optimal treatment



### Conclusions :

Patients with PD should be actively involved in treatment decisions and receive sufficient attention to their quality of life concerns and specific needs. This will help identify adequate treatment of the individual symptoms and reduce potential side effects of PD medication. Better information and empowerment of patients will lead to increased treatment adherence, especially when the carers are involved as well. New techniques might support the patient to identify the best individual treatment.

## Neurology Epilepsy

### Key findings

#### Studied healthcare setting: specialists care

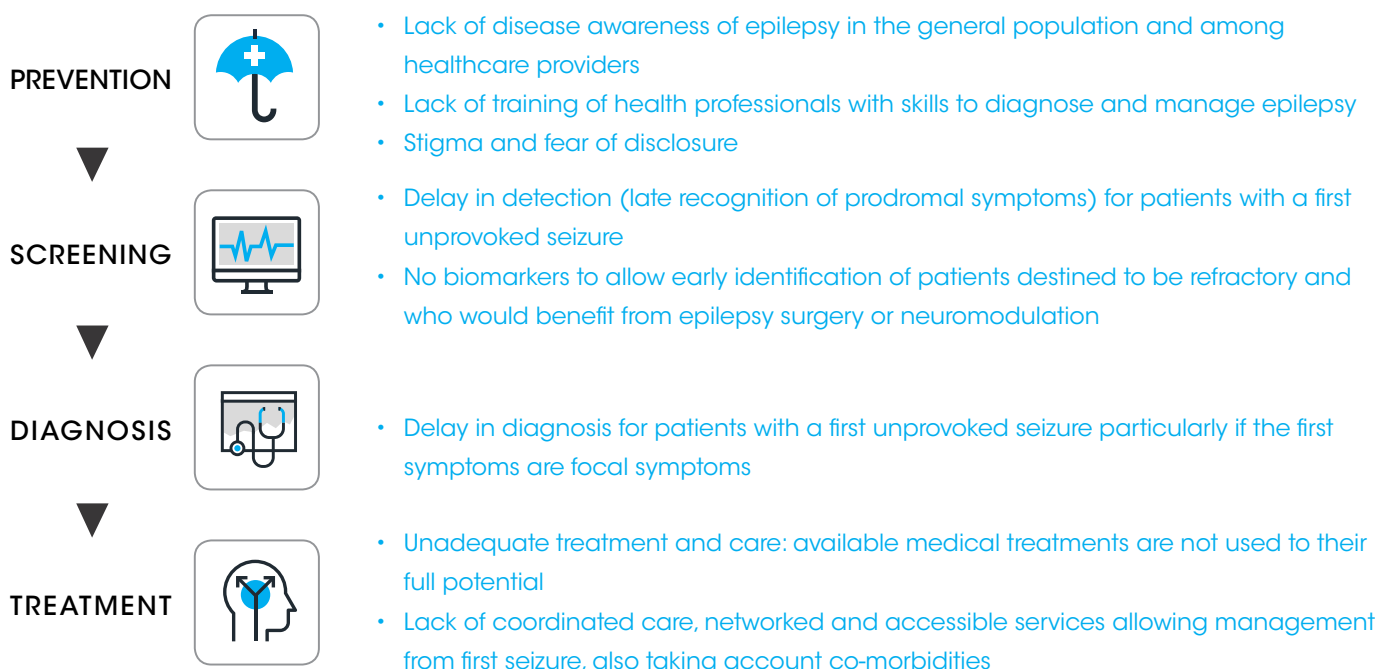
**Study objective:** « new » antiepileptic drugs have had little impact on the proportion with refractory epilepsy and only a minority is suitable for surgery. The best option to improve QoL and efficiency is to guarantee services are resourced and configured to meet patients needs, and to ensure that available medical treatments are accessible and used to their full potential. Three care scenarios were considered : 1) investigation and management following an initial unprovoked seizure ; 2) treatment of patients who have had two (or more) unprovoked seizures and 3 ) treatment of patients with epilepsy that is refractory to medical treatments.

> **Epilepsy care pathway** was assessed to identify the major unmet needs and causes for treatment gaps

> The **study** aims to 1) assess the health and economic outcomes of ideal versus existing services and 2) propose a care model starting with diagnosed epilepsy

**Setting data used** : Liverpool, UK

#### Key care pathway analysis results: obstacles to optimal treatment



#### Conclusions :

Up to 70% of people with epilepsy could become seizure free with best management currently available anti-epileptic drugs (AEDs) treatment. But there is a marked treatment gap with respect to delayed diagnosis and access to specialist services & appropriate treatment.

## Neurology Multiple Sclerosis (MS)

### Key findings

#### Studied healthcare setting: specialists care

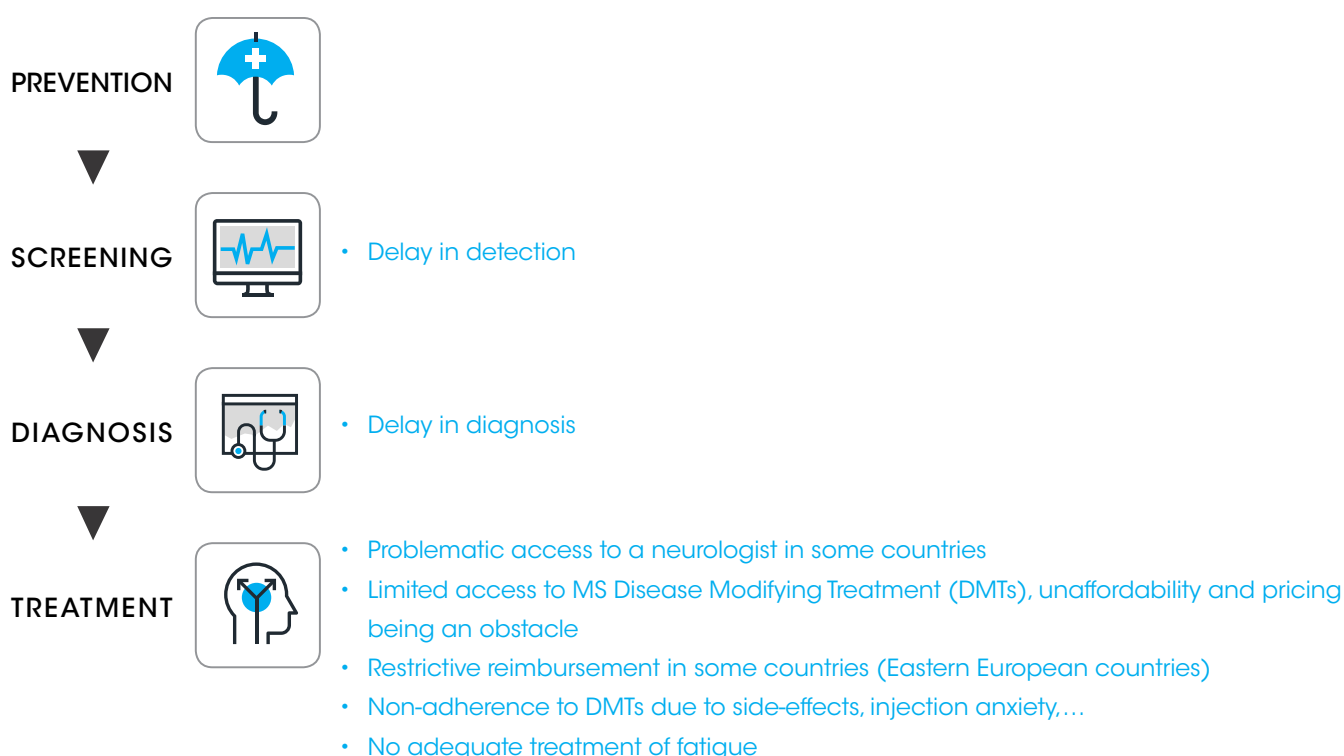
**Study objective:** to value the socio-economic impact and health gains of early treatment on Clinically Isolated Syndrome (CIS) and secondary prevention with regard to lifestyle risk factors, ie., cigarette smoking habit, low vitamin D serum levels, on conversion to multiple sclerosis (MS) and disease worsening, respectively.

> **MS care pathway analysis** emphasizes early intervention as key for optimal management of the disease and for achieving better clinical outcomes

> **Economic evaluation** estimated 1) the socioeconomic impact of early treatment reducing the onset of MS in at risk population and 2) the socioeconomic impact of reducing MS risk factors such as smoking and vitamin D insufficiency.

**Setting data used :** Italy, Sweden and Spain

#### Key care pathway analysis results: obstacles to optimal treatment



### Conclusions :

Early treatment is key in MS to slow disease activity and progression. In addition, reduced exposure to lifestyle factors such as cigarette smoking, and low vitamin D serum levels have also been reported to decrease disease progression. Economic evidence is provided to base appropriate public health interventions to reduce the MS burden.

## Neurology Restless Legs Syndrome (RLS)

### Key findings

#### Studied healthcare setting: specialists care

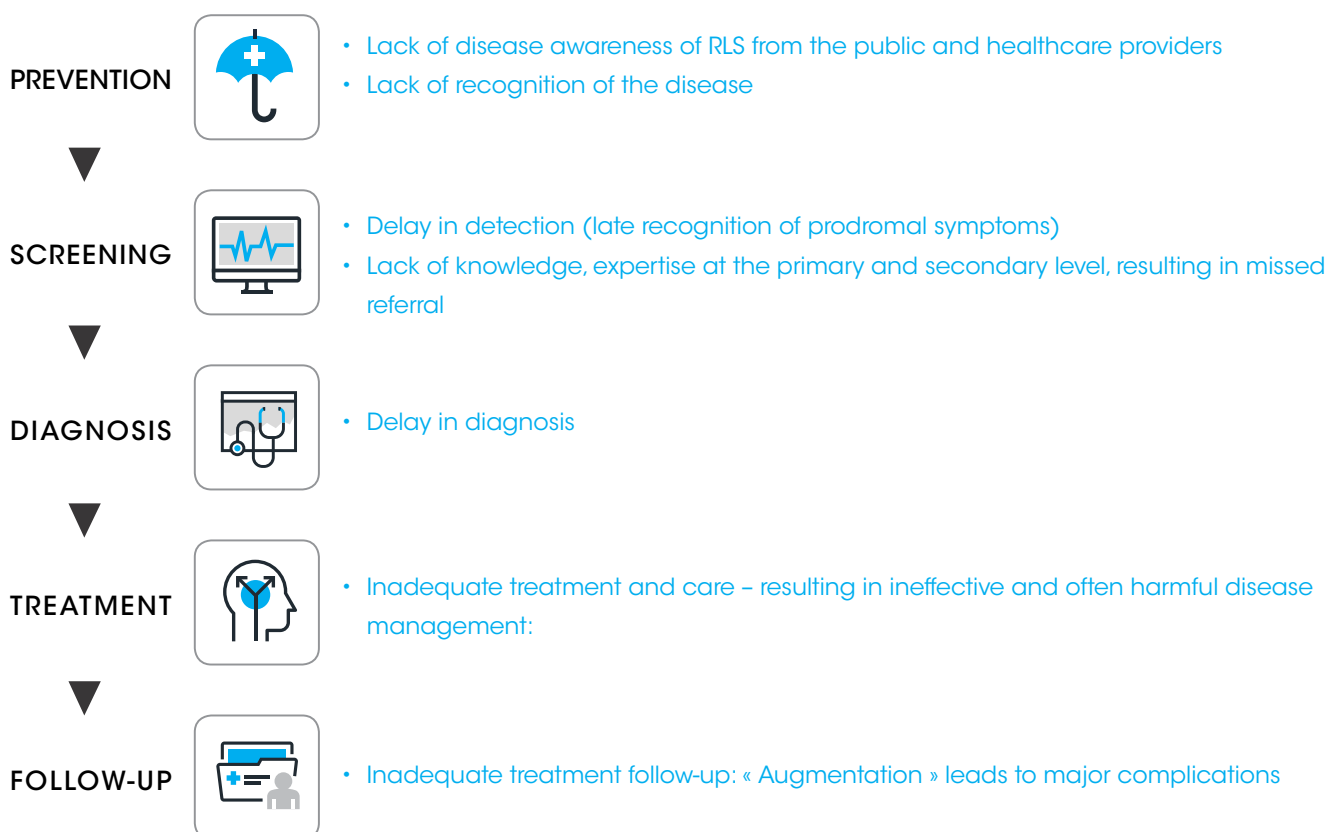
**Study objective:** to assess the current burden of RLS to healthcare and society in Europe and address specific patient care pathway gaps (early intervention, etc...).

> **RLS care pathway analysis** identifies the major unmet needs and the underlying causing factors

> **Economic analysis** was performed to calculate the socio-economic impact of inadequate treatment and to illustrate the potential benefit of delivering optimal RLS treatment.

**Setting data used :** France, Germany, Italy

#### Key care pathway analysis results: obstacles to optimal treatment



### Conclusions :

It is important to share new costs of illness data for RLS disease awareness. Recognizing the disease is crucial and providing secondary prevention (proper case history) may lead to improvement of this situation (increased knowledge and expertise from primary, secondary and tertiary care health professionals on how to manage the disease. Research on the cause of RLS and for the development of new therapy is urgently needed considering the high societal costs.

## Neurosurgery/Neurology Normal Pressure Hydrocephalus (NPH)

### Key findings

#### Studied healthcare setting: specialists care

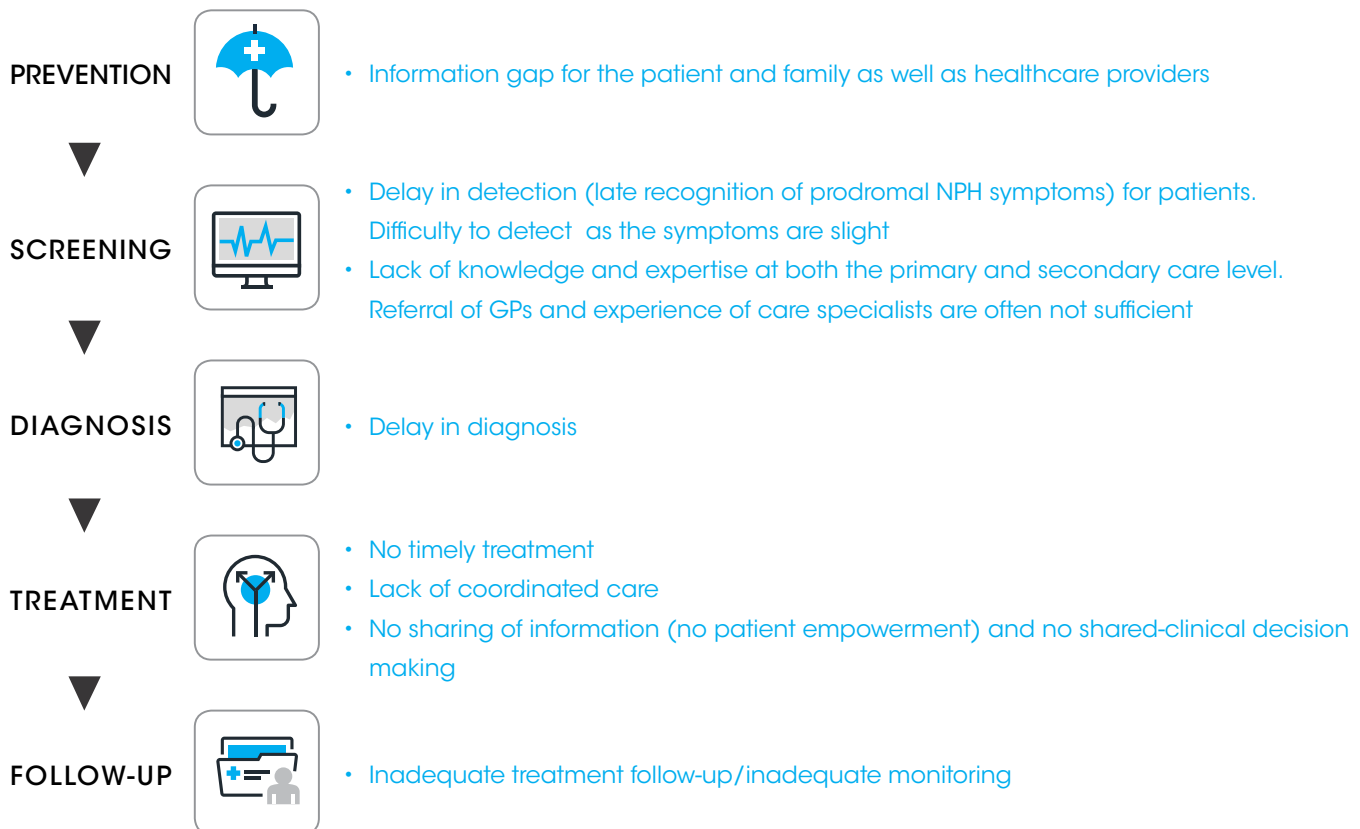
**Study objective:** to assess the cost effectiveness of NPH treatment and to assess the socio-economic impact of NPH non-treatment (burden) and address unmet needs in order to: 1) increase awareness; 2) improve the possibilities for diagnosis and treatment of NPH.

> **NPH care pathway analysis** describes the issues throughout the course of the disease which prevent NPH patients to receive adequate and timely treatment.

> **Economic evaluation:** the socio-economic impact of delivering timely and adequate NPH treatment (shunt surgery) was assessed.

**Setting data used :** Germany

#### Key care pathway analysis results: obstacles to optimal treatment



### Conclusions :

The socio-economic impact of delivering timely and adequate NPH treatment was assessed in the economic evaluation. Cost of non-treatment is an important aspect: early treatment (surgery) expected outcomes are improved quality of life and independence. Findings indicate that the shunt operation can reduce the caregiver burden.

### 3.2. Challenges to bridge the treatment gap

**Primary care** is increasingly taking on a greater role in both the assessment and the long-term care of people. **Integration of mental health services as well as neurological services** into the primary care system needs to be a **significant policy objective in countries**.

#### A clear referral

To address the needs of persons with mental and neurological disorders for health care and social support (e.g. help with living, employment arrangements), a clear referral and linkage system needs to be in place.

#### 3.2.1. Health services challenges

Every European country is challenged with the organization of its mental health services and neurological health services **to address the treatment gaps**.

#### Box 3: Mental health services: overcome barriers and model shift

Across Europe, much effort has been made over recent decades to overcome treatment gaps and to ensure high-quality longer-term care.

These efforts started with new pharmacological treatments for psychoses which radically changed the prognosis of severe mental disorders, and the emergence of new psychosocial interventions and new concepts of mental health care organization in several European countries. For instance, sector psychiatry in France, social psychiatry and mental health in primary care in the UK, psychiatric reform and deinstitutionalization in Italy<sup>105</sup> as well in Belgium ("Psy107")<sup>106</sup> became significant landmarks.

These initiatives were followed by a multitude of developments **to advance mental health care in many European countries**: improvements in the living conditions in psychiatric hospitals, development of community services, integration of mental health care within primary care, development of psychosocial care (housing, vocational training), protection of the human rights of people with mental disorders and increasing participation of patients and families in the improvement of policies and services<sup>107</sup>. Research into many of these developments has provided an increasing evidence base to guide investment into appropriate mental health care systems.

Nowadays there is a **broad consensus on the need to shift from the model of care based on the traditional large psychiatric institutions to modern comprehensive community-based models of care, including acute patient units at general hospitals**<sup>108</sup>.

Accessibility to mental health care for people with longer-term mental disorders is much better with community-based services than with the traditional psychiatric hospitals: greater user satisfaction and increased met needs, better continuity of care, more flexibility, making it possible to identify and treat more often early relapses, and to increase adherence to treatment.

These services better protect human rights of people with mental disorders and prevent stigmatization.

#### Studies:

- show significantly better outcomes on adherence to treatment, clinical symptoms, quality of life, housing stability, and vocational rehabilitation.
- suggest that care in the community for acute psychoses is generally more cost effective than care in a hospital, although these results cannot be generalized to all patients requiring admission to psychiatric beds.
- also show that, for patients who require prolonged stays in the hospital, hostel wards provide a cost-effective alternative preferred by the patients themselves. Other studies show that, when deinstitutionalization is correctly developed, the majority of patients who moved from hospital to the community have less negative symptoms, better social life and more satisfaction.

However, institutions such as the WHO<sup>109,110,111</sup> indicate that much more has to be done to provide accessible, effective and high quality longer-term mental health care to all people with severe mental disorders in Europe.

### Box 4: Neurological health services

Insufficient diagnostic services remain a major barrier to the provision of appropriate care for patients with neurological disorders. Timely and correct diagnosis is a prerequisite for access to support services.

The organization of services for delivery of neurological care has an important bearing on their effectiveness. Countries have various forms of service organization and delivery strategies. The differing availability of financial and human resources also affects the organization of services. Depending on the health system in the country, there is a variable mix of private and public provision of neurological care.

### Primary, secondary, tertiary care

The three traditional levels of service delivery are primary, secondary and tertiary care. Primary care includes treatment and preventive and promotional interventions conducted by primary care professionals (GP, nurses, other healthcare staff and nonmedical staff). Primary care represents the point of entry for most people seeking care and is the logical setting where neurological disorders should begin to be addressed. Users of primary care are more likely to seek early help because of the wide availability of facilities, easy accessibility, cultural acceptability and reduced cost, thus leading to early detection of neurological disorders and correct diagnosis and to better clinical outcomes.

Integration of neurological services into the primary care system needs to be a significant policy objective in countries<sup>112</sup>. Providing neurological care through primary care requires significant investment in training primary care professionals to detect and treat neurological disorders. Ongoing training should meet the needs of primary care professionals such as doctors, nurses and community health workers.

Primary care centres are limited in their ability to adequately diagnose and treat certain neurological disorders. For the management of severe cases and patients requiring access to diagnostic and technological expertise, a secondary level of care is necessary.

Tertiary care is the most specialized form of neurological diagnosis, treatment and rehabilitation, and is often delivered in teaching hospitals. They also serve as facilities for clinical research, collection of epidemiological data, and the creation and distribution of health educational materials.

Neurological specialist services require a large complement of trained specialist staff. Very few countries have an optimal mix of primary, secondary and tertiary care. Even within countries, significant geographical disparities usually exist between regions. In some countries, neurological conditions are at the forefront of national initiatives to improve health services for particular patient groups or conditions<sup>113</sup>.

Integrated and coordinated systems of service delivery need to be developed where services based in primary, secondary and tertiary care complement each other.

#### 3.2.2. Other challenges: non-adherence to treatment and unaffordable access to care

Any therapeutic strategy must take into consideration factors impacting treatment adherence - such as polypharmacy, depression, deficits in the management of cognitive processes, poor quality of life and symptoms control, lack of social support/partner, cost of medications<sup>114</sup>.



### Box 5: Poor treatment adherence is also a significant challenge to optimizing health outcomes

Medication non-adherence is prevalent in brain diseases and associated with an increase in costs of inpatient care (>20% of hospitalizations in elderly patients are attributable to non-adherence)<sup>115</sup>. Non-adherence among patients suffering from chronic conditions represents 50% on average<sup>116</sup> and is, for instance, particularly high for patients with Parkinson's disease, resulting in substantial motor dysfunction. Estimates of non-adherence prevalence in PD range widely, from 15-20% by self-report, to 67% and higher in studies using pharmacy refill data and pill counts<sup>117</sup>.

Non-adherence to antiepileptic drugs range from 40% to 60% of patients with epilepsy. Mortality rates are more than threefold higher in nonadherent compared to adherent individuals with epilepsy<sup>118</sup>.

Non-adherent individuals are more likely to report being untreated, rather than recognizing that their sub optimally controlled symptoms may be caused by their non-adherence to treatment. Similarly, the healthcare provider may react by changing the medicine regimens or questioning the diagnosis, leading to additional diagnostic testing, patient stress, and further non-adherence<sup>119</sup>.

Efforts to empower patients to be engaged in responding to their health needs may improve adherence to treatment and help them to make informed decisions related to their health<sup>120</sup>.

There is a direct correlation between out-of-pocket medication costs and use of medication and health care services and stopping treatment<sup>121</sup>. Ensuring that patients have access to essential and affordable medicines is one of the core objectives of the EU<sup>122</sup> and the WHO<sup>123</sup>.

The increasingly high cost of medicines and shrinking public health budgets jeopardize access to essential medicines.

### Box 6: Access to treatment

For instance, there are considerable variations in access to treatment for MS patients: the proportion of all MS patients including patients with Relapsing-remitting MS (RRMS) receiving Disease-Modifying Treatments (DMTs) vary from Poland (13%), UK (21%) and other Eastern Europe countries as poor performers, to Germany (69%)<sup>124</sup>.

Insufficient access to essential medical products poses a serious threat to the well-being of a large section of the population in Europe. Difference in access can be explained by a series of factors including healthcare infrastructure

Access to a neurologist can be problematic in some member states. The role of GPs and nurses has been highlighted in assisting in the management of the diseases and the use of treatments, restrictive reimbursement (being amongst Eastern European countries with the lowest access to MS DMDs resulting in a high number of untreated patients) and affordability (it remains a barrier in some Eastern European countries).

New results from an observational study in EU countries have recently been released (2017), which looked beyond the access statistics, seeking to better characterize what barriers prevent people with MS access to good clinical care. The study highlighted how MS affects the workforce participation and that there is a need for health care services at all disease levels, resulting in one of the major cost components in MS in all countries<sup>125</sup>.

Proper access means that medicines, even those for rare illnesses, should be made readily available and affordable in addition to being safe, effective, and of high quality. Various factors influence their availability: selection of medicines on the market, the focus areas of pharmaceutical research, the supply systems, financing mechanisms, pricing, reimbursement and cost-containment policies of individual countries, as well as rigid patenting rules. The high prices of new treatments for diseases such as Hepatitis C for instance recently prompted member states to call for EU-wide measures to enable patients to access affordable and innovative therapies<sup>126</sup>.

Many initiatives at EU level were taken in that direction. PRiority Medicines (PRIME) is a scheme that was launched in March 2016 by the European Medicines Agency (EMA) to enhance support for the development of medicines that target an **unmet medical need**<sup>127</sup>. This voluntary scheme is based on enhanced interaction and early dialogue with developers of promising medicines, to optimize development plans and speed up evaluation so these medicines can reach patients earlier. Through PRIME, the Agency offers early and proactive support to pharmaceutical industries to optimize the generation of robust data on a medicine's benefits and risks and enable accelerated assessment of medicines applications. This will help patients benefit as early as possible from therapies significantly improving their quality of life. The Council of the European Union has also adopted in June 2016 conclusions on strengthening the balance in the pharmaceutical systems in the EU and its Member States<sup>128</sup>.

## 4. CONCLUSIONS AND POLICY RECOMMENDATIONS

**Brain disorders** as referred to mental and neurological disorders, are a **heterogeneous range of disorders that owe their origin to a complex array of genetic, biological, psychosocial, and social factors. Brain disorders** are grouped together, and this is particularly important in the VoT Study because **they share several important characteristics, notably:** all owe their symptoms and impairments to some degree of brain dysfunction; social determinants play an important part in the aetiology and symptom expression, they frequently co-occur in the same individual; their effect on families and wider society is profound; they are strongly associated with stigma and discrimination; they often take a chronic or relapsing course; and they all share an inadequate response from health-care systems in all European countries.

**A range of interventions, spanning medicines, psychological treatments and social interventions,** are available to address **the human and economic burden of brain disorders.**

### Main conclusions of the VoT study:

1. There is still no cure for most brain disorders; hence, it is necessary to focus on risk reduction, preclinical and early detection and diagnosis, and timely intervention. To develop and implement primary and secondary prevention strategies is essential.
  2. To address biopsychosocial needs and cognitive, educational and vocational aspects as common denominators linking studies of brain disorders. To develop and implement strategies to reduce stigma and discrimination, also for vulnerable populations with complex needs.
  3. To address seamless, coordinated care from a social and cost-effective perspective.
  4. To address patients, families and informal carers information needs as first line partners through health education “empowerment” and “shared clinical decision making”.
  5. To address organizational [health services delivery/healthcare systems related] and research [scientific knowledge] barriers to optimal treatment.
- > Health services challenges to bridge the treatment gap:
- Insufficient diagnostic services remain a major barrier to the provision of appropriate care for patients with neurological disorders. Timely and correct diagnosis is a prerequisite for access to support services
  - Primary care is increasingly taking on a greater role in both the assessment and the long-term care of people – in order to ensure an efficient collaboration between primary care physicians and specialists care, incentives should be created and expertise should be built

- Integration of primary, secondary and tertiary care and training for healthcare providers
- A clear referral and linkage system needs to be put in place
- Problematic access to psychiatry/neurology services – can be explained by a series of factors including healthcare infrastructure

> Other challenges:

- Poor treatment adherence/compliance is also a significant challenge to optimizing health outcome
- Insufficient access to essential medical products
- Seamless care tools implementation for better processes and outcomes

> Basic and clinical research

- More investment in targeted research to understand the causes but also the progression of brain disorders, and to develop new treatments that do not only symptomatically improve the condition but may modify, i.e. slow down, or even stop their course.
- Be part of collaborative initiatives

## **Building elements:**

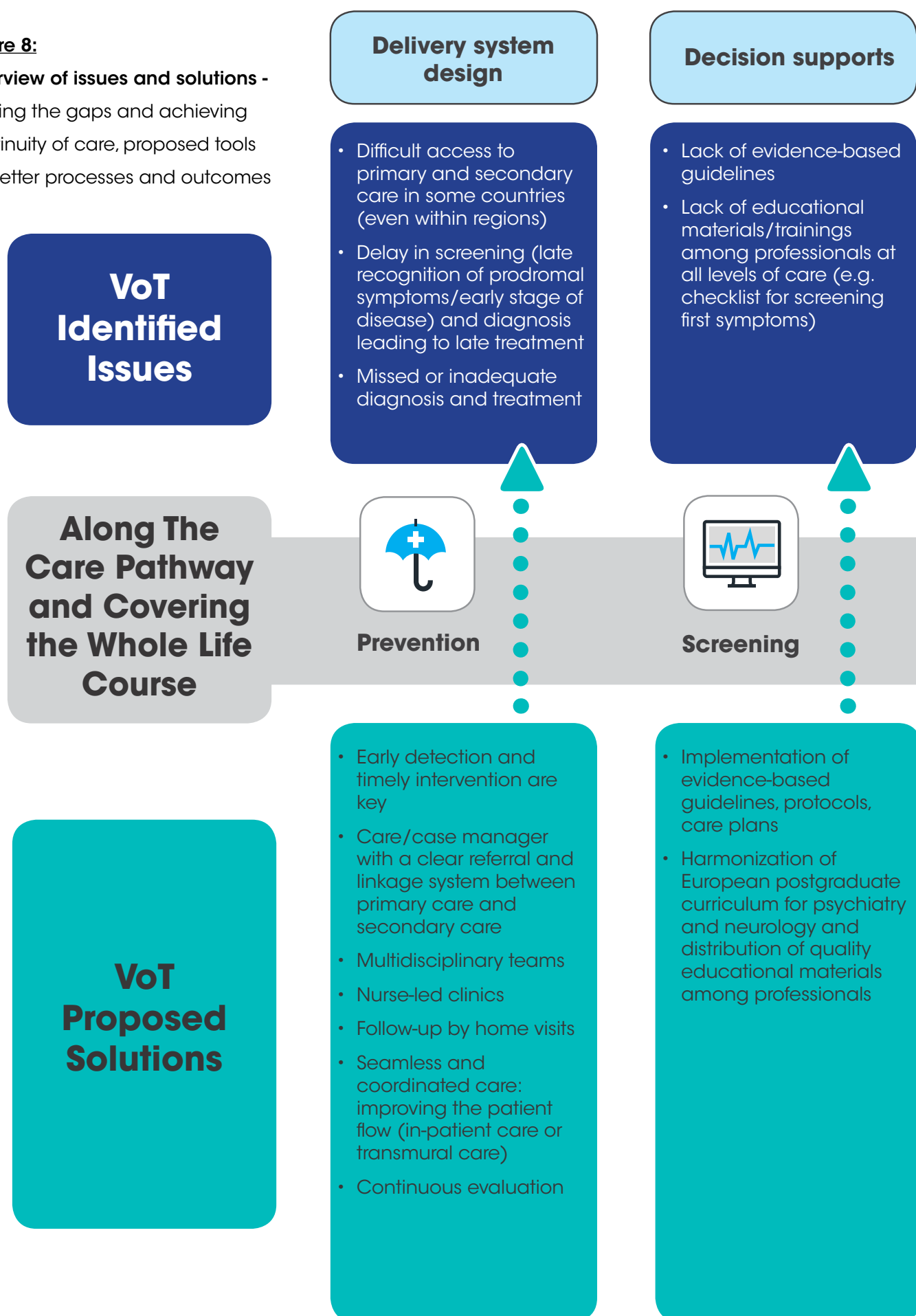
1. The “**treatment gap**”, defined as the proportion of people with a brain disorder who require screening and treatment but do not receive these or receive inadequate treatment, has been proposed as a useful parameter to compare access to and quality of care for patients across populations.
2. In this study we assessed **the care pathway** to identify the major unmet needs and causes for treatment gaps (both those needing research and better evidence to inform treatment decisions and those needing better organization of services). We also performed an analysis to identify the economic and health benefits “Current” disease management vs evidence-based “Best” disease management strategies.
3. **People with a fully controlled brain disorder** need lifelong treatment, but can live their own life if they receive timely and proper treatment. Optimal management requires a paradigm shift in the focus of the (disorder) treatment, from symptom control, achieving and maintaining remission, to the emphasis of recovery/rehabilitation.
4. Changing the organisation of care paradigm means **challenging adaptations of health and social care, moving away from fragmentation to a seamless care model**.
5. **Mental and neurological disorders** are **complex and interlinked with hundreds of specific diagnosis, codified in diagnostic classifications systems** (currently under revision WHO International Classification of Diseases, ICD-11 and American Psychiatric Association Diagnostic and Statistical Manual of Mental Disorders, DSM-V)<sup>129,130,131</sup>. **Until recently, brain disorders** were associated with **disciplinary fragmentation in research and practice** using different concepts and approaches. **There is today a greater understanding of their common denominators, impact and challenges to manage them in a more integrated approach**, and even **to prevent** some of them<sup>132</sup>.

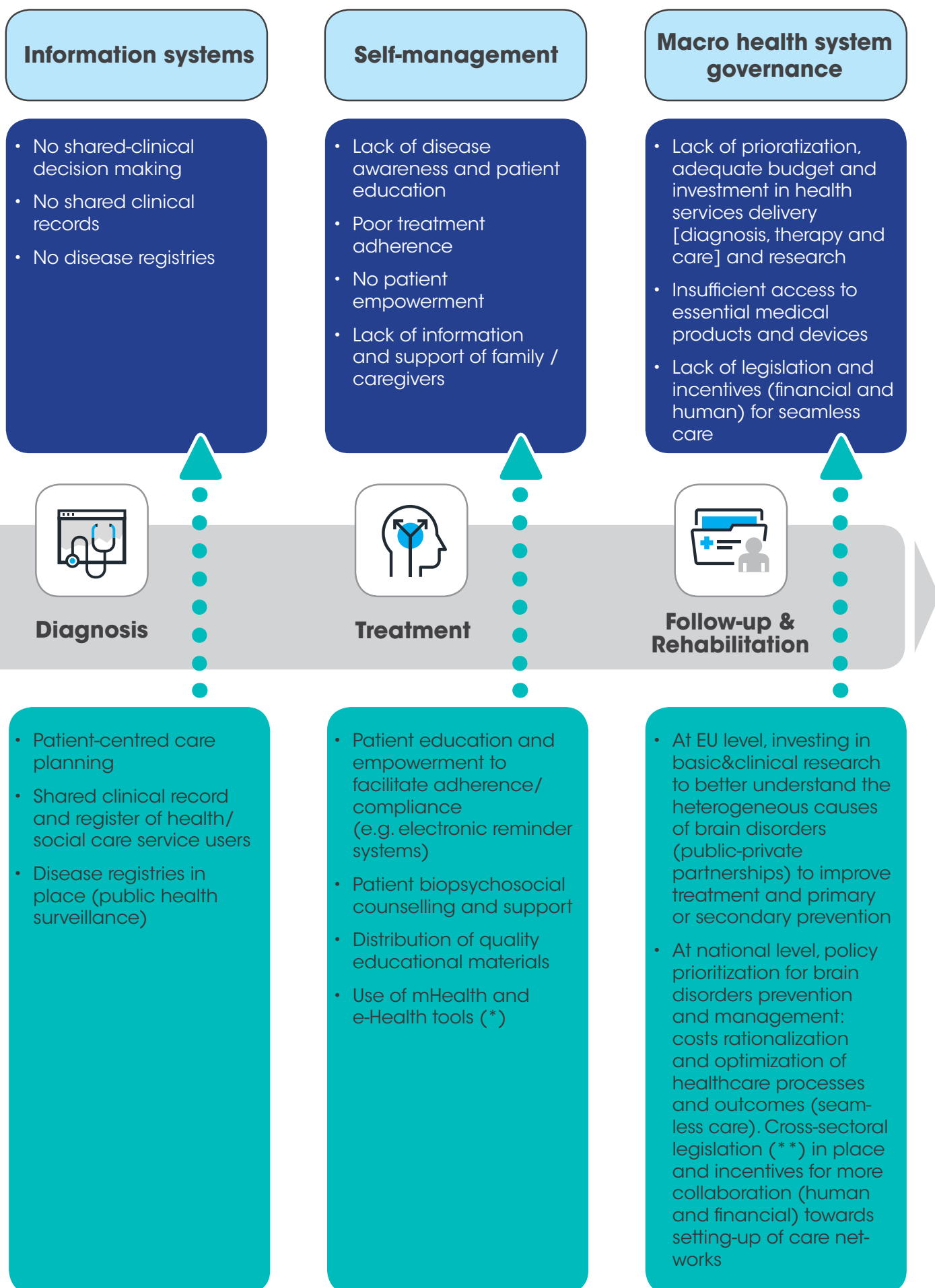
## **Proposed solutions**

**Optimizing healthcare services and removing treatment gaps** are essential by implementing initiatives around patient-centred and seamless care (*see fig. 8: Overview issues and solutions, which refers also to fig. 6: Possible causes of the treatment gap*).

**Figure 8:****Overview of issues and solutions -**

Closing the gaps and achieving continuity of care, proposed tools for better processes and outcomes





(\*) e-health tools are considered transversally in this table, not only for self-management.

(\*\*) cross-sectoral legislation: education, employment, social and health.

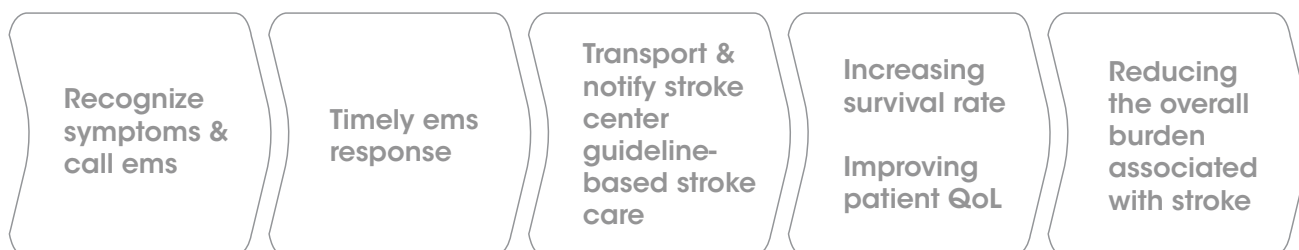
Source: Adapted from Nolte & McKee 2008, citing Zware et al. 2006

**Various forms of effective provider networks and interventions** have been set up at country level across Europe. The aim is for instance **to close the gap between primary and hospital services combining information and communication technology (eHealth) as facilitator** (in-hospital patient journeys, intra-extra mural care pathways, multidisciplinary care models based on the bio-psychosocial approach...) with **promising health outcomes and indications of worthwhile investment**: evidence on cost-effectiveness and sustainability is increasingly researched.

There are effective interventions to be shared, like **a comprehensive stroke unit, case management and the Resident Assessment Instruments ("RAI") for mental health ("RAI MH"), and "RAI for home care"**.

### ILLUSTRATION 3

Acute stroke care and optimizing healthcare in the chain of survival - **The extreme importance of time and comprehensive stroke unit**. Every step of the patient trajectory from symptoms onset to start of treatment should be optimized in order to decrease loss of time.



See VOT case study on stroke: identifying the treatment gaps and improving care for ischemic stroke patients:

- Intravenous thrombolysis (IVT) with recombinant tissue plasminogen activator (rt-PA) is one of very few effective treatments for acute ischemic stroke. In most centers, however, only a small proportion (2%–7%) of patients with ischemic stroke receive this treatment<sup>133</sup>.
- The most important factor limiting IVT administration is time: it has to be administered within 4.5 hours of symptom onset. Even within that window, reducing 'time-to-needle' (the time between symptom onset and IVT administration) can improve functionality and reduce complications for the patient.
- The clinical benefit from IVT declines rapidly however. Brain: time matters, and every minute counts.

Put simply, a shorter delay from symptom to IVT (the so-called symptom-to-needle time) can make the difference between being independent and being dependent.



**Policy implications:**

- Reducing the symptom-to-needle time is vital. Most time is lost in the prehospital period (patients waiting before they seek medical attention). Unfortunately, awareness campaigns have been found to have limited impact in addressing this.
- Inside the hospital, the focus should be on decreasing the time from arrival to IVT administration – the so-called door-to-needle time (DNT)<sup>134</sup>. In most countries, national guidelines recommend that the DNT should not exceed 60 minutes. However, 15 years after IVT was proven to be clinically effective, in most institutions, the DNT is still more than 60 minutes for the majority of patients.
- Reducing DNT will also increase the proportion of patients eligible for IVT, because more patients can be treated within the 4.5-hour time window.

**ILLUSTRATION 4**

**Case management for highly complex or high risk patients by a healthcare provider being responsible for the assessment of needs and implementation of care plans** can be an additional support to coordinate medical care, paramedical care and well-being and therefore can help **to avoid unplanned hospital admissions (due to increased frailty, falls, adverse drug events...)** and **to monitor polypharmacy (medicines optimization)**. It is usually required for individuals who have a serious and persistent mental illness<sup>135</sup> or severe neurodegenerative disease and need ongoing health as well as social care support (e.g. patients with a major psychotic disorder or with a severe neurological condition, such as advanced Parkinson's disease or dementia).

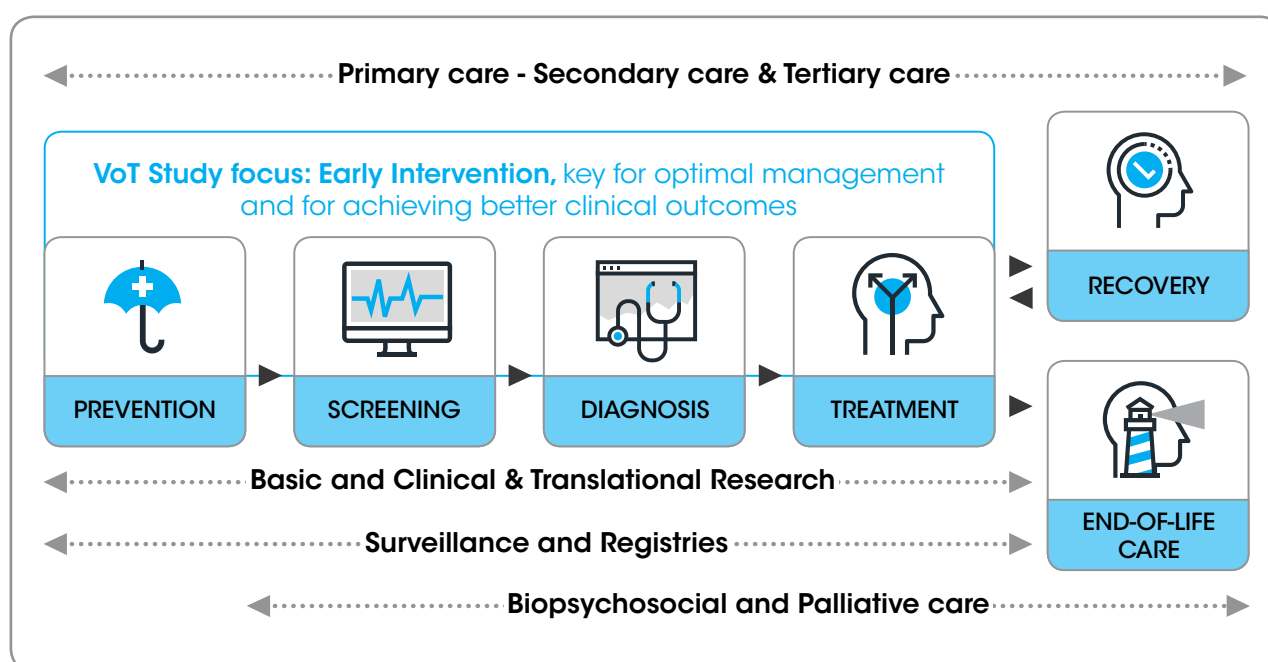
**ILLUSTRATION 5****Resident Assessment Instruments**

- **RAI MH is a comprehensive, multidisciplinary mental health assessment system for use with adults in facilities providing acute, long-stay, forensic, and geriatric services.** The Resident Assessment Instrument-Mental Health (RAI-MH) comprehensively assesses psychiatric, social, environmental, and medical issues at intake, emphasizing patient functioning. Data from the RAI-MH are intended to support care planning, quality improvement, outcome measurement, and case mix-based payment systems.
- **RAI for home care** is the same instrument but used particularly for patients ranging from medically complex patients needing close attention to relatively well older adults who receive and require less formal support.

**Policy recommendations:**

Proposed policy recommendations and future directions are **very much aligned to VoT conclusions and the needs emphasized throughout the VoT research**, see fig. 9. *Care pathway – addressing research and organisational needs for brain disorders*).

**Figure 9:** Care pathway – addressing research and organisational needs for brain disorders

**Key findings:**

- Low understanding of the diseases aetiology, risk and preventive factors
- Lack of disease awareness in the general public and lack of training for healthcare providers
- Lack of primary and secondary prevention programs
- Lack of timely and adequate diagnosis & treatment
- Fragmentation of the healthcare services and lack of coordination between health and social services

**Conclusions & recommendations in alignment with economic analysis:**

- Invest in more basic and clinical & translational neuroscientific research
- Increase brain disease awareness, patient empowerment and training for health care providers
- Address prevention and timely intervention as a priority, based on needs
- Address health care services delivery and support clear patient pathways
- Foster seamless care through validated models of care and tools implementation, legislation and incentives

In alignment with findings and study conclusions – and these could be the basis to pursue further the Value of Treatment research project – policy recommendations are the following:

- **At the healthcare level**, improving the **patient flow** in the whole process of care (care pathway)<sup>136</sup> for better outcomes (adopting tools to overcome treatment gaps and implementing best practices) and assessing the impact of brain disorders on the manifestation and outcome of other medical and surgical diseases (the challenge of co-morbidity);
- **At research level**, addressing 1) **the research (scientific) gap** (causes of most brain disorders are uncertain and, more basic and clinical&translational research is needed) such as prevention and the use of biomarkers for risk assessment - when available (e.g. Alzheimer's disease) to identify patients with a brain disorder as early as possible in the disease stage; 2) **policy implementation research at the healthcare level** – conduct health systems evaluation, when an intervention has demonstrated impact, to replicate in similar settings (e.g. return on investment initiatives and short-term indicators);
- **At macro health system governance level**, based on existing plans of action (EU Horizon 2020, EC Health Programme 2014-2020, and other plans from WHO,...), it is essential:
  - 1) to converge action towards developing an **EU-wide research and public health combined Brain Plan to address brain health in a comprehensive (biopsychosocial and seamless care approach), transversal (across diseases) and collaborative way**<sup>137</sup>;
  - 2) to promote the set up of **Knowledge Hubs** (common research platforms to share data and results of conducted or current research e.g. EU BrainBank, BrainNet like Orphanet, Clinical Trial Network for brain disorders);
  - 3) to foster collaboration with **European Reference Networks for Rare Diseases** (for better integration between primary, secondary and tertiary care);
  - 4) to promote the development of **Joint Actions**, and **other EU initiatives** such as the Cancer Control "CanCon" Joint Action (set to build upon the cooperation and results of the European Partnership for Action Against Cancer, EPAAC), the EC Integrated Care for Breast Cancer Initiative, ... as illustrations of excellent collaboration with Member States and tangible achievements – **which could be replicated for Brain Disorders**.

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EBC RESEARCH PROJECT  
THE **VALUE OF TREATMENT** FOR BRAIN DISORDERS

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## POLICY WHITE PAPER - PART 2

# SUMMARIES OF THE — CASE STUDIES —

## AUTHORS PART 2

**EBC team:** Esposito G<sup>1</sup>, Quoidbach V<sup>1</sup>, Kramer S<sup>1</sup>

**EBC academic partners:** Tinelli M<sup>2</sup>, Knapp M<sup>2</sup>, Guldemond N<sup>3</sup>

**Workin group leaders:** Dodel R<sup>4,6</sup>, Gaebel W<sup>5,13</sup>, Kälviäinen R<sup>6,14</sup>, Kehler U<sup>7</sup>, Mitsikostas D<sup>8,15</sup>,  
Sørensen PS<sup>6,16</sup>, Trenkwalder C<sup>9</sup>, Vanhooren G<sup>10,17</sup>, Visser PJ<sup>11</sup>

**EBC executive board:** Nutt D<sup>1,18</sup>, Boyer P<sup>1,5,19</sup>, Di luca M<sup>1,12,20</sup>, Oertel W<sup>1,4,6</sup>

1. European Brain Council (EBC);
2. London School of Economics (LSE);
3. The Institute of Health Policy & Management (iBMG), Erasmus University;
4. Philipps-Universität Marburg;
5. European Psychiatric Association (EPA);
6. European Academy of Neurology;
7. Asklepios Klinik Altona, Hamburg, Germany;
8. European Headache Federation (EHF);
9. Paracelsus Elena Klinik and University of Goettingen;
10. European Stroke Organization (ESO);
11. VU University Medical Center Amsterdam;
12. Federation of European Neuroscience Societies (FENS);
13. Heinrich-Heine-University, Medical Faculty, Duesseldorf, Germany;
14. University of Eastern Finland, Kuopio, Finland;
15. Kapodistrian University of Athens, Athens, Greece;
16. University of Copenhagen Rigshospitalet, Copenhagen, Denmark;
17. Department of Neurology, AZ Sint-Jan Brugge-Oostende, Brugge, Belgium;
18. Imperial College, London, UK;
19. Universite Paris-Diderot, France;
20. University of Milan, Italy.

In this chapter, we present a summary of each case study, briefly setting out the context, the treatment gaps identified and the proposed recommendations to tackle them, while highlighting the potential socio economic impact of their implementation. The results of the case studies have been, or will be, submitted to peer review journals. All the documents related to the project and to the individual case studies - including posters, reports and publications - are available online: <http://www.braincouncil.eu/activities/projects/the-value-of-treatment>.

## SCHIZOPHRENIA

### The value of early intervention, integrated treatment and care

Mohr P<sup>1</sup>, Ieven A<sup>2</sup>, Arteel P<sup>3</sup>, Winkler P<sup>4</sup>, La Park A<sup>5</sup>, Boyer P<sup>1</sup>, Galderisi S<sup>1</sup>, Karkkainen H<sup>2</sup>, Wasserman D<sup>1</sup>, Gaebel W<sup>1</sup>

<sup>1</sup>European Psychiatric Association (EPA); <sup>2</sup>EUFAMI; <sup>3</sup>GAMIAN Europe; <sup>4</sup>National Institute of Mental Health, Klecany, Czech Republic; <sup>5</sup>London School of Economics (LSE)

### CONTEXT

Schizophrenia is a severe mental disorder, which affects 0.8-1.5% of the population over 18 years of age. Approximately 7 or 8 individuals out of 1,000 will be diagnosed with schizophrenia over their lifetime<sup>1</sup>. Schizophrenia is a clinically heterogeneous illness, characterised by several symptom dimensions: positive symptoms including hallucinations, delusions, disorganised thoughts and speech, behavioural disturbances and psychomotor symptoms, negative symptoms (such as asociality, anhedonia, avolition, diminished speech), affective symptoms (depression, anxiety) and cognitive symptoms (memory impairment, impaired concentration, difficulties with planning of daily tasks). Moreover, people with schizophrenia have a higher mortality rate and a higher lifetime risk of suicide than the general population; these increased rates may lead to a premature mortality of up to 30 years<sup>2</sup>. The course of illness is highly variable, typically episodic, with frequent relapses that contribute to neurobiological impairment, functional and social decline, and poor treatment response. In addition, chronic disease comorbidities are common among patients and further exacerbate the course of illness and clinical outcomes.

Schizophrenia may have a substantial impact on patients, their families and society as a whole. It is one of the top 25 leading causes of disability worldwide<sup>3</sup>, which negatively affects all the aspects of a person's life. The economic cost of psychotic disorders remains high for both individuals and society (totalling €93.9 million PPP, 2010)<sup>4</sup>.

Although a cure for schizophrenia is still not available, this disease can, in most cases, be effectively managed, and full recovery and social reintegration through adequate treatment and care (including early interventions) is possible. However, the treatment gap in this area is currently huge, as the majority of people with schizophrenia are yet to receive timely and adequate treatment, or do not receive any treatment at all. The WHO estimates that more than 50% of people with schizophrenia do not receive appropriate treatment<sup>5</sup>.

In this study, we analysed the care pathway of schizophrenia patients to identify the major barriers preventing patients with schizophrenia from receiving timely and adequate treatment, and proposed recommendations on how to overcome them<sup>6</sup>. In particular, we found that the provision of early intervention (EI) programmes is of great importance for an effective management of the illness. Moreover, we performed an economic evaluation to assesses the socio-economic impact of EI programmes in two separate healthcare systems in Europe: the UK, where EI are already available, and Czech Republic, where EI is not yet available, but could be developed within the current mental health care reform (Box 1)<sup>6</sup>.

## CARE PATHWAY ANALYSIS RESULTS: BARRIERS TO OPTIMAL TREATMENT

**HEALTHCARE SERVICES: MISSED (OR DELAYED) DETECTION/DIAGNOSIS.** As reported by the consumers groups, in almost all cases, the journey of schizophrenia patients and family members start with a crisis, which is clear evidence that delays in the detection of the disease were too long. Unfortunately, the current health care systems have limited funding and difficulties in providing the appropriate indicated prevention (for subjects at risk) and early intervention services before and after the onset of psychosis. Lack of disease awareness among patients, families and community members, as well as lack of appropriate information, training and education on psychosis and schizophrenia among primary care providers often limit the access to a psychiatric expert and/or unit and the possibility of a correct and timely diagnosis. Stigmatizing attitudes and beliefs about schizophrenia are also widespread and may interfere with people's willingness to discuss their problems and seek treatment. Studies showed that more than 20% of patients that experienced barriers to contact a doctor to treat physical problems reported stigma and fear of disclosing their mental health problem to their general practitioner<sup>7</sup>.

**LIMITED ACCESS TO TIMELY AND ADEQUATE TREATMENT.** Patients and family members that do recognise the disease and seek help often face limited access to adequate treatment. People with schizophrenia need lifelong treatment, but can live their own life if they receive timely and adequate treatment. Timely detection and intervention is paramount, leading to better treatment response, control of symptoms and overall functional outcome. Schizophrenia is often a multi-episodic disorder; every relapse worsens the course and outcome of the disease. Thus, relapse prevention is an important goal of disease management to maintain remission, and achieve functional recovery. Optimal treatment requires a coordinated team approach involving psychiatrists and a range of health and social care professionals, the adequate utilisation of pharmacological and psychosocial interventions, and proper patient monitoring to ensure treatment success and social functioning. The current model of care is unable to provide optimal treatment for schizophrenia patients mainly due to poor collaboration among

health and social care professionals, lack of continuity of the antipsychotic treatment, and scarce availability of psychosocial programs targeting cognitive impairment, social skills and work/school (re)-integration. Furthermore, there is a lack of cooperation between care providers, patients and their families to ensure that recommendations on treatment goals and strategies are met.

**NON-ADHERENCE TO TREATMENT.** Non-adherence to medication is a recognised problem with many severe negative consequences for treatment success and patient outcomes in the broadest sense. A major factor causing non-adherence, in addition to illness-related factors such as lack of insight, is that patients are often not well informed on the medications' side effects and/or how to manage them.

**LIMITED AVAILABILITY OF REHABILITATION PROGRAMMES.** Rehabilitation emphasizes social and vocational training to help people with schizophrenia participate fully in their communities. Since the onset of schizophrenia is typically during the critical career-development years (ages 18 to 35)<sup>1</sup>, patients' professional and social life trajectories are compromised; they need to develop new skills to reintegrate. Rehabilitation programs include employment services, money management counselling, cognitive remediation, and social skills training. These non-pharmacological interventions play an important role in the long-term schizophrenia management, helping to improve overall functioning and social reintegration.

**LOW IMPLEMENTATION OF COMMUNITY CARE.** This is particularly relevant for the countries of Central and Eastern Europe (CEE), but not only. In the region of CEE, mental health care systems are predominantly hospital-based and community services are unavailable to most of those who need them<sup>8</sup>. This leads to people with schizophrenia being hospitalized for excessively long periods of time, sometimes for their whole life<sup>9</sup>. Deinstitutionalization should be pursued as it has been demonstrated to be beneficial to the patients while not leading to severe adverse consequences<sup>9,10</sup>. The objective in terms of deinstitutionalization should not only be to bring the people back to their own environments out of the hospital setting, but to keep the patients there permanently by preventing relapse.

## CONCLUSIONS & RECOMMENDATIONS

People with schizophrenia need lifelong treatment, but can live their own life if they receive timely and proper treatment. Optimal management requires a paradigm shift in the focus of schizophrenia treatment, from symptom control, achieving and maintaining remission, to the emphasis on recovery. Changing the paradigm requires challenging adaptations of health and social care moving away from fragmentation to a seamless care model. For this purpose, effective mental health policies are needed.

## Main Recommendations

- **Raise awareness** of the public and medical professionals and fight stigma.
- **Promote indicated prevention and early intervention programmes**, which have beneficial socio economic impact (Box1)<sup>6</sup>.
- **Support patients and caregiver groups** with information, expertise, shared experiences, and advocacy.
- **Build partnerships and cooperation** with other stakeholders, e.g. the media organisations (local, regional, national, European and academic institutions), trade unions, pharmaceutical industry, governments, regulatory bodies and insurers.
- **Invest in research** to continue developing new treatments that can improve quality of life, functioning in the community and reduce associated direct and indirect costs.

## Complementary Recommendations

- **Support advocacy and peer group** community and empower them in the discussions to voice their needs with healthcare professionals and within the treatment alliance
- **Train healthcare professionals** and look into incentives systems to promote a timely diagnosis and referral, as well as treatment and care.

### Box 1. ECONOMIC EVALUATION:

#### The socio economic impact of early intervention (EI) programmes

Decision modelling was performed to assess the economic impact of adopting and/or scaling up EI services in two countries representing old and new EU member states, compared to care as usual.

**In the United Kingdom**, we assessed the economic value of providing EI for individuals in the prodromal phase and after the onset of psychosis. The costs were calculated on the basis of services used following referral and the impact on employment, criminal justice and housing at national level (Euros; 2016 values). In the short-term (1-2 years), EI was more costly than usual care due to an additional cost incurred in health care services (more than 39 million Euros extra cost). However, in the medium (2-5 yrs) to the long-term (>5 yrs), EI may generate cost-savings due to reduced inpatient care costs, improved employment and crime costs, 20 - 32 million Euros savings respectively. EI was less costly and more effective than usual care and resulted in cost savings of 11645 euros in the short-term due to improved employment, reduced crime costs and housing costs.

**In Czech Republic,** the economic model estimated the incremental value of adopting indicated prevention for individuals at high risk of psychosis and EI services after the onset of psychosis. These services are currently not available in the country, but they could be developed within the current mental health care reform. It has been estimated that costs of care as usual could be reduced by 25 % if only indicated prevention services were adopted, 33 % if only EI services were adopted and 40 % if both, indicated prevention and EI services, were adopted in the country. This means a potential overall annual cost savings of about 11.3, 15.2 or 18.3 million Euros respectively.

Our results suggest that adopting indicated prevention and EI services in both United Kingdom and the Czech Republic has the potential to be cost saving. The incremental benefits have been found more pronounced in the Czech Republic, likely due to the fact that the Czech mental health care system relies largely on psychiatric hospitals, where people are commonly admitted and treated as in-patients for excessively long periods of time.



## RESTLESS LEGS SYNDROME

**Increase disease awareness to alleviate patient suffering and to reduce societal costs**

Jaarsma J<sup>1</sup>, Dauvilliers Y<sup>2</sup>, Ferri R<sup>3</sup>, Rijsman, R.<sup>4</sup>, Sakkas GK<sup>5</sup>, Trenkwalder C<sup>6</sup> and Oertel W<sup>7</sup>

<sup>1</sup>European Alliance for Restless Legs Syndrome (EARLS); <sup>2</sup>Gui-de-Chauliac Hospital; <sup>3</sup>Oasi Research Institute (IRCCS); <sup>4</sup>Center for Sleep and Wake disorders, Haaglanden MC; <sup>5</sup>Plymouth Marjon University; <sup>6</sup>Paracelsus Elena Klinik and University of Goettingen; <sup>7</sup>European Academy of Neurology (EAN)

### CONTEXT AND COST OF ILLNESS ANALYSIS RESULTS

Restless Legs Syndrome (RLS) or Willis/Ekbom Diseases (WED) is a common neurological disease, the severe form of which affects approximately 20 million European citizens. This study is based on moderate to severely affected RLS patients with symptoms at least twice a week and a prevalence of 2.7%<sup>11</sup>.

RLS is characterized by an uncontrollable urge to move (legs and sometimes other body parts) combined with unpleasant pain-like sensations, mainly at night and during sleep, leading to chronic sleep disturbance and deprivation which often causes depression and leads to reduced work capacity. Due to the severity and nature of the symptoms, RLS significantly affects patients' lives, disrupting both family and social participation. According to the current definition, the diagnosis of RLS is done based on five major clinical criteria, but only those patients suffering from moderate to severe RLS, according to the International RLS Rating Scale, should be pharmacologically treated<sup>12</sup>.

The economic burden of RLS was estimated for the first time using the framework adopted by the European Brain Council (EBC) in "The economic cost of brain disorders in Europe 2010"<sup>4</sup> in three separate healthcare systems, France, Germany and Italy, as examples of European Union (EU) nations with different healthcare systems. When considering the overall burden of the brain disorders subsample given by the three countries, RLS is ranked the fifth largest economic disease burden in the EU (with mood disorders at first place, followed by Dementia, Psychotic and Anxiety disorders). This estimate includes additional health care costs as well as indirect costs to society, such as lost productivity due to the reduced ability to work or to work at full capacity<sup>13</sup>.

RLS still remains without a cure, and current treatment concentrates entirely on symptom suppression, which can effectively be managed if timely and adequate treatment is delivered. However, RLS is often unrecognized or misdiagnosed. Consequently, RLS patients often do not receive timely and adequate treatment, which leads to worsening of the disease symptoms,



unnecessary suffering and unnecessary medical expenses for both the national health systems and the patients.

In this study, we analysed the RLS care pathway to identify the major unmet needs and the underlying cause factors<sup>13</sup>. We also performed an economic analysis to calculate the socio-economic impact of inadequate treatment and to illustrate the potential benefit of delivering optimal RLS treatment (Box 2)<sup>13</sup>.

## CARE PATHWAY ANALYSIS RESULTS: BARRIERS TO OPTIMAL TREATMENT

This section summarises the major areas of unmet needs of RLS patients in need of pharmacological treatment along the care pathway.

**MISSED OR DELAYED DIAGNOSIS.** Currently, it is very likely that RLS patients would never receive a diagnosis or would have to wait a number of years before getting a knowledgeable health care provider to make a correct diagnosis. This may depend on the country or region where the patients live, but in general, there is a lack of knowledge among GPs and neurologists across Europe. Out of a group of 4,200 patients, 69% waited three years or more for diagnosis after their symptoms had begun (Patient Study, European Alliance for Restless Legs Syndrome, unpublished data). RLS patients often only visit a physician after many years of suffering; patients, including those that have the familial form of the disease and have seen this in their families, often still firmly believe that nothing can be done about their complaints. There is a lack of knowledge and expertise at both the primary and secondary care levels— the referral of GP's and the experience of medical specialists is often insufficient, resulting in delayed diagnosis and/or misdiagnosis. The problem could be characterised as a wrong routing of the patient, resulting in ineffective and often harmful disease management. As a consequence, many patients do not have access to appropriate RLS care.

**NO TIMELY AND ADEQUATE TREATMENT** .Due to wrong or delayed diagnosis, RLS patients often do not receive timely and adequate treatment, resulting in the worsening of disease symptoms and/or insufficient response to medication. This failure of the medication to reduce symptoms leads only to further worsening, as patients become desperate and depressed from not finding relief or cure. Overtreatment with first-choice medication (dopaminergic drugs) is also very common, leading to dramatic consequences for RLS patients. Administration of high dosages of dopaminergic RLS medication results in reduced efficacy or – paradoxically – in augmentation: the medication causes the symptoms to get worse, to occur earlier and spread all over the body, for more hours of the day.

**INADEQUATE TREATMENT FOLLOW UP.** Augmentation leads to major complications in the treatment of RLS. There is still very limited knowledge of how to handle severe augmentation,

as no European or national guidelines for management of augmentation are available due to the lack of evidence from clinical trials. The number of RLS-specialized neurologists – or even so-called centres of excellence for research, diagnosis and therapy in RLS – is very low in all European countries. One reason consists of the lack of medical knowledge handling these complications of treatment, with no randomized controlled trial to compare different approaches to augmentation available. Generally, augmentation is treated by abrupt cessation of the medication, leading to severe withdrawal reactions and leaving the patient with a “cold turkey” sensation and extreme stress levels.

## CONCLUSIONS & RECOMMENDATIONS

RLS is a serious neurological and chronic disease affecting millions of European citizens. Due to the lack of knowledge of the disease and its treatment, patients often go through long periods of suffering until the correct diagnosis is made and proper treatment started. This leads to an unnecessary burden on health care budgets. Extensive education of both patients and medical professionals is needed to improve this situation. Since the existing available treatments are far from optimal, more research into the pathophysiology of RLS and the disease mechanisms is needed to provide specific symptomatic and future curative treatments. Furthermore, the lack of disease recognition and awareness, especially among health care professionals and general practitioners, is the major underlying cause of the inadequate care of RLS patients. Policies aiming to increase disease recognition among doctors would allow RLS patients to receive adequate treatment and alleviate their suffering. Thus:

- **Include RLS and sleep medicine in the general and specialist medical education across all of Europe.** In order to address the lack of awareness and knowledge of RLS symptoms, diagnosis and treatment options, education of relevant healthcare professionals such as general practitioners, neurologists, psychiatrists and sleep medicine specialists, as well as gynaecologists and surgeons, is needed. This should be done through continuing medical education, and through attention to RLS in medical and paramedical curricula, with the aims of reaching sustainable improvement of knowledge. Most importantly, knowledge about RLS and sleep medicine should, in general, be included in the curricula and exams of medical students.
- **Improve access to information and dissemination.** Better access to information through different communication channels from professional groups and responsible authorities should be provided. Communication for professionals should include information on the clinical aspects of RLS, the different symptoms and events, diagnostic steps, disadvantages of non-treatment, complications and augmentation. This should be complemented with dissemination of RLS guidelines and adherence to the respective treatments. RLS guidelines will further stimulate uniformity of the necessary procedures.

## Box 2. Socio economic impact of inadequate RLS treatment across different healthcare systems

RLS patients often receive no or a wrong diagnosis and this prevents them from timely and adequate access to treatment, resulting in poor clinical outcome and increased healthcare and societal costs. In this economic analysis, we calculated the cost difference between adequate and inadequate treatment in three typical RLS cases, depicting the story of hypothetical patients. France, Germany and Italy were identified as alternative healthcare systems with regard to financing and coverage.

**Delayed diagnosis:** Catherine is a 67-year-old RLS patient who has had RLS her whole life. She received the correct diagnosis only after enduring years of suffering. Subsequently, medication was given at too high a dosage, and, as a consequence, her symptoms worsened and augmentation eventually occurred. Due to her poor health condition, she had to go on long-term sick leave and eventually quit her job. The model assumes that by receiving a correct diagnosis and timely/adequate treatment, Catherine would have had less use of health care resources, a better health outcome and she would have been able to keep her job and continue to be an active member of society. When calculating the difference in direct costs for the healthcare provider adequate treatment provides a cost saving of 1,600-33,300 euros over a period of 54 years across the three healthcare systems. When health care and productivity costs incurred by the whole society are considered, adequate treatment provides the cost saving is increased to 35,000-50,500 euros (France).

**Insufficient response:** Camilla is a 51-year-old woman who complained of insomnia since her youth and later started presenting RLS symptoms. It took three years to receive a correct diagnosis. Her symptoms responded poorly to the medication and started to relapse with increased severity. After a few years, she was admitted to a sleep centre as an inpatient because of insufficient sleep quality. She presented a mild memory decline causing some difficulties in the activities of daily life. The model provides a conservative estimate of the impact of adequate treatment on direct costs; throughout a 11-year time horizon, there is a cost saving of 3,600-7,800 euro per patient.

**Augmentation:** Peter is a 67-year-old male who presents very severe RLS symptoms. He has consulted several neurologists, who treated him as inpatient. As a consequence of his poor response to the treatment, the dose of his medications was steadily increased for several years, with the high dosage of medication eventually leading to Peter's hospitalisation with severe RLS symptoms and the diagnosis augmentation was made. When calculating the difference in indirect costs for the healthcare provider, adequate treatment would provide a cost saving of 8,900-36,000 euro per patient in 4-year time horizon.

These results confirm the economic benefit of adequate treatment once in place. When translating RLS costs caused by misdiagnosis and therapeutic mismanagement of these three cases to that of the entire European general population, a substantial economic impact well beyond the current estimate may be the case. Epidemiological studies define RLS only according to three questions used in epidemiological surveys, but not along the need of pharmacological treatment. Therefore, the current numbers may only be a rough estimate.

## PARKINSON'S DISEASE (PD)

### Improving outcomes of a neurodegenerative disorder without a cure

Ahmerkamp-Böhme J<sup>1</sup>, Petersen G<sup>2</sup>, Deuschl G<sup>3</sup>, Michler F<sup>1</sup>, Flanagan E<sup>4</sup>, Graham L<sup>5</sup>, Oertel W<sup>3</sup>, Dodel R<sup>3</sup>

<sup>1</sup>Jung & Parkinson; <sup>2</sup>Grünenthal; <sup>3</sup>European Academy of Neurology (EAN); <sup>4</sup>Grayling; <sup>5</sup>European Parkinson's Disease Association (EPDA)

### CONTEXT

Parkinson's Disease (PD) is a chronic progressive disorder of the central nervous system. With approximately 1.25 million, or 0.2%, people, affected in Europe<sup>4</sup>, it is the second most common neurodegenerative disorder next to Alzheimer's disease. Due to the ageing of the European population, the number of patients is expected to double within the next 20 years<sup>14</sup>. Although it is a disease more common in older age groups, one should keep in mind that about 10% of patients are affected at an age below 50 years.

The diagnosis is based on the clinical evidence of the following cardinal symptoms: bradykinesia, tremor, rigidity and impaired postural reflexes. In addition, a considerable number of non-motor symptoms may also occur during the course of the disease, such as gastro-intestinal and autonomic disturbances, as well as behavioral and psychological symptoms (e.g. depression, cognitive impairment).

The diagnosis is still a clinical one and is based on the identification of at least one or several main symptoms. Typically, if first symptoms occur, a loss of over 70% of the neuronal cells in the substantia nigra has already become obvious.

Since Parkinson's is a progressive disease, the financial burden for both the individual and society increases over the course of the disease. About € 13.9 billion of healthcare costs and about € 5.5 billion of direct-non medical costs are currently spent per year (€PPP figures from the year 2010)<sup>4</sup>. This is more than 12% of the total European budget allocated to neurological diseases.

In this study, we describe some of the key issues and unmet needs along the patient's journey – from the challenges associated with the initial diagnosis until the diverse complications of the late stages of the disease. We identified three key treatment gaps and described potential solutions and best practices to give recommendations on how to improve care in the future. In an economic evaluation, we also assessed the impact of closing these gaps in reducing the burden of the disease on healthcare providers and society in two different EU healthcare systems (Box 3)<sup>15</sup>.

## CARE PATHWAY ANALYSIS RESULTS: BARRIERS TO OPTIMAL TREATMENT

**DELAYED OR INADEQUATE DIAGNOSIS AND MISDIAGNOSIS.** Barriers to optimal treatment are numerous. Nearly one third of all patients who notice first symptoms wait twelve months or more before seeking medical help<sup>16</sup>. Furthermore, long waiting times to see a PD expert also contribute to the delay of the diagnosis. Although PD's symptoms are well known, the issue of a missed or misdiagnosis is relevant as well<sup>16</sup> for several reasons, including delay of improvement for the patient. There is evidence showing that nearly half of the diagnoses (47%) are incorrect when performed in the primary care setting<sup>16</sup>. This high percentage might be because the range of non-motor symptoms is extremely diverse and that many symptoms are common to other diseases too. Furthermore, the absence of well-established biomarkers also increases this risk. As the deterioration of the quality of life is already significant in the early phase of the disease, the diagnosis should be given as early as possible.

**TREATMENT GAPS.** The treatment of each patient needs to be adopted individually and carefully to his needs and depending on the disease stage. In the beginning, the medication helps to control the symptoms (this initial phase is the so-called 'honeymoon'), but these positive effects wane from year to year. No disease-modifying therapies are currently available. The impact of the disease increases over time and, in the advanced stage, PD may lead to a considerable loss of quality of life, disability and care dependency. Recommended therapies in more advanced disease stages – but only for selected patients – include deep brain stimulation and pump therapies. The access, however, to these therapies is quite limited in some European countries.

Treatment of non-motor symptoms like depression, pain and others should be in focus of PD care as well, as they have a major impact on the patient's quality of life<sup>17</sup>. Their perception of symptoms often differs from clinician's view, which may have an impact on their effective management of PD.

Most patients depend on the help of their partners, families and/or on the support of health-care professionals (PD is often called a 'family's disease') and the burden to them is extremely high compared to other non-neurological chronic disorders<sup>18</sup>.

Patients in Central and Eastern Europe especially often have the feeling of being left alone with their problems – from the time of diagnosis to the later stages of the disease, when carers seem to be ignored or excluded from the decision making process.

**NON-ADHERENCE TO DRUG TREATMENT.** PD patients in general seem to have poor adherence to prescribed therapies, which is not only critical for their wellbeing, but also costly for the health system. Reasons for this non-adherence might be the fear of secondary effects, existing comorbidities and the complexity of dosing schedules, especially in patients with cognitive deficits<sup>16</sup>.

## CONCLUSIONS & RECOMMENDATIONS

Although the majority of patients with PD are of older age, they should be actively involved in treatment decisions and receive sufficient attention to their quality of life concerns and specific needs. This will help identify adequate treatment of the individual symptoms and reduce potential side effects of PD medication. Better information and empowerment of patients will lead to increased treatment adherence, especially when the carers are involved as well. New techniques might support the patient to identify the best individual treatment.

**Empower patients and involve families/caregivers.** Good coordination and communication among the various healthcare providers is another important aspect, which leads to high patient and carer satisfaction. Studies from several European countries reveal considerable differences between the existing healthcare systems, and identify that the creation of multi-disciplinary care systems is still a long way ahead. However, the Netherlands and Israel have already established integrated, multi-disciplinary care models which focus on the patient's needs, and could serve as examples for other countries<sup>19,20</sup>.

**Promote a multi-disciplinary approach involving all concerned parties.** PD patients in the advanced stages of the disease may benefit from a team effort including neurologists, GPs, occupational therapists, physiotherapists, etc. who may assist whenever a problem occurs. Communication and information transfer generally need to be improved; more efficiency is not only desirable for the patient-doctor relationship, but also for the cooperation between the different European countries. It has already been demonstrated that this approach will even lead to significant savings of healthcare costs, which could, in turn, be invested in better education and training of providers.

**Individualized treatment as well as access to new and advanced therapies is vital.** The public needs to be much better informed about PD, the typical symptoms and the special needs patients have. Patients should not need to worry about stigmatization, they have more than enough to cope with the disease itself. Increasing public awareness of PD and the needs of PD patients (including employers) will help not only the individual patient but also society as a whole to identify solutions for the increasing impact that PD has on the health and economic systems in Europe.

**Raise disease awareness and promote research.** Parkinson's disease occurs with many different faces, which require a joint effort of all stakeholders. Decision and policy makers need to realize that they have to act now in order to adequately face the high tide of upcoming high occurrence of brain disorders as not to be drowned by it. More funding to research is needed at different levels, including basic science, disease-oriented research and healthcare research. Allocation to brain disorders is not adequate and funding is considerably lower compared to other non-neurological disorders such as cancer<sup>21,22</sup>. The US Institute of Medicine panel, as well as European governmental institutions, proposed the concept that the amount of disease-specific research funding should be systematically and consistently allocated depending on the impact of the disease on the population and the economy of the respective society<sup>23</sup>. These aims have not been reached at present time.

### Box 3. ECONOMIC EVALUATION: the socio economic impact of timely, adequate, and adherent approaches to PD treatment

The purpose of the economic analysis was to measure the economic impact of closing the current treatment gaps in Parkinson's disease with particular attention to providing timely and optimal care to PD patients. In particular, we have focused on three major topics:

**Lack of early/timely treatment.** The first economic analysis looked at the short-term cost-effectiveness gains attached to treatment starting at different stages in the patient journey (graded according to Hoehn and Yahr stages (H&Y) compared with no treatment). Our model suggests that at one year the hypothetical PD treatment intervention is cost-effective regardless of the initial health state of the patient receiving the treatment (Germany cost savings between -1,000 and -5,400 Euros with 0.10 QALY gain per patient; UK cost saving of -1,800 and -7,600 with 0.10 QALY gains per patient); when the treatment enables the patient to improve to a less severe H&Y stage (e.g. transitions from H&Y stage 2 to 1, from stage 3 to 2 or from H&Y stages 4/5 to 3), it was found to be not only a more effective but also less costly option (compared to no treatment). The cost savings increased with the severity of the disease (e.g. the transition from H&Y stage 4/5 to 3) were more cost saving than from H&Y stage 3 to 2; e.g. -5,400 Euros vs. -1,030 Euros as economic impact of 0.10 QALY gain in Germany; -7,600 Euros vs. -6,000 Euros as economic impact of 0.10 QALY gain in UK). If we extrapolate the study findings to a long period (5 years or more) we can anticipate that timely/early intervention practices would enable the reduction of disease symptoms and related societal and healthcare costs across healthcare systems.

**Lack of access to adequate treatment for advanced PD.** A second set of analyses evaluated the cost effectiveness of best treatment in advanced PD (deep brain stimulation (DBS) and best medical treatment (BMT)) compared with current care. The model looked at direct costs and QALYs, comparing a current scenario where only a small proportion of eligible patients received best treatment (2% on DBS+BMT vs 88% on BMT vs 10% no treatment), with a target scenario of a larger number of patients receiving best treatment (15% on DBS+BMT vs 85% on BMT only). Published economic evidence representing clinical progression and capturing treatment effect (QALY) and costs were used to provide long term (5 years) cost and QALY evidence for two different healthcare settings (Germany and UK). Results showed that making available the adequate treatment to more patients is cost effective (ICER Euros 15,000 to 32,600 across country settings), where an increase in direct costs is accompanied by a gain in QALYs (compared with current care).

**Lack of treatment adherence to drug treatment.** A third set of analyses evaluated the economic impact of improved adherence rates compared with current care. More specifically, we looked at the change in average patient healthcare costs according to the level of adherence and of a shift towards increased adherence to treatment in the PD patient

community. Outcomes for the economic evaluation were healthcare costs (drug costs, A&E, hospitalizations, GP visits, day care and care home stays). The perspective adopted was for the public health insurance (Germany) and National Health Service (UK). Results showed that over a timeframe of 1.5 years, low levels of adherence would correspond to an increase in annual patient costs (an increase of 20-40% in Germany and 80-300% in the UK, depending on the definition of adherence used). Intensified use of hospital and residential/nursing care home services were the main drivers of such increases. Meeting the target adherence to treatment rates (defined by the experts) would generate a cost saving of 239,000-576,000 Euros (Germany) and 917,000-2,980,000 Euros (UK) every 1,000 patients treated adequately.



## MULTIPLE SCLEROSIS (MS)

### Averting Multiple Sclerosis long-term societal and healthcare costs: early intervention and lifestyle choices as key to success

Pugliatti M<sup>1,5</sup>, Moroni M<sup>1</sup>, Antonovici A<sup>2</sup>, Hausmann B<sup>2</sup>, Hellwig K<sup>3</sup>, Sorensen PS<sup>4,5</sup>

<sup>1</sup>University of Ferrara, Italy; <sup>2</sup>European Multiple Sclerosis Platform (EMSP); <sup>3</sup>St.Josef Hospital, Germany; <sup>4</sup>University of Copenhagen, Denmark; <sup>5</sup>European Academy of Neurology (EAN)

#### CONTEXT

Multiple sclerosis (MS) is a chronic, inflammatory demyelinating and degenerative disease of the central nervous system that typically presents in the third or fourth decade of life. MS is the first cause of non-traumatic disability in young adults.

MS occurs when the immune system attacks the protection coat of a person's nerve fibers (axons) in the brain and spinal cord which get damaged. No two people with MS will experience the same set of symptoms, and many of the symptoms are invisible. To date, there is no cure for MS, yet MS has become a treatable disease.

It is estimated that more than 2 million people have MS worldwide. An estimated number of 700,000 people live with MS in Europe. Prevalence and incidence vary considerably between regions and populations. Europe is considered a high prevalence region for MS (prevalence  $\geq 1/1000$ ), containing more than half of the global population of people diagnosed with MS<sup>24</sup>. MS incidence is increasing, particularly among women: MS is at least twice as common in women.

Social impact and economic consequences are considerable: MS imposes a high burden on society and the disease societal costs increase significantly with disability. In the cost societal perspective, the annual direct costs for treatment and care range from €23,000 per annum for mild MS to €77,000 per annum for severe MS<sup>25</sup>. Also, MS involves important indirect costs: productivity losses for sick leave, incapacity to work and early retirement up to 18 year earlier than the general population. In addition, there are considerable informal care costs largely falling outside of the health and social care systems, and borne by people with MS and their families. A person's disease course implies different stages, depending on the duration of the disease, such as onset, eg. from a clinically isolated syndrome (CIS) which may or may not convert to MS, to the later stages of life which may feature severe cognitive decline and high physical disability. There is a similar drop in the quality of life of patients with increased disability<sup>25</sup>. The most common onset of the disease is relapsing MS (RRMS) affecting 85% of people with MS. In the beginning, patients recover from their MS attacks, called relapses. The relapses gradually leave more damage. More than half will develop secondary progressive MS.

The causes remain unknown. MS is an acquired immune-mediated inflammatory disease. It is believed that environmental factors need to come together in person with genetic predisposition to cause MS. More than 100 genes are known to contribute to the risk of MS. Lifestyle factors, such as cigarette smoking and vitamin D insufficiency have been consistently associated with increased risk of MS onset in the general population or disease worsening <sup>26</sup>. A better understanding of these causes is a necessity to improve treatment and primary or secondary prevention. The benefit of early intervention with a disease modifying drug (DMT) is well supported by scientific evidence, along as the promotion of a 'brain-healthy' lifestyle as part of a comprehensive approach to treatment. Effective DMT and lifestyle interventions should be started at the time of MS diagnosis to protect neurological reserve. However, the actual access to DMTs is very heterogeneous across populations in Europe<sup>27</sup>, it is often delayed and/or subject to restrictions in licensing, and prescription and reimbursement policies.

In this study, we analysed the MS care pathway describing the major challenges and needs accompanying the patient's disease course from onset to later stages. The care pathway description emphasizes early intervention as key for optimal management of the disease and for reducing accumulation of permanent disability and conversion to progressive MS. Early treatment is reducing the onset of multiple sclerosis in patients with clinical isolated syndrome (CIS). Furthermore, for the first time to our knowledge, we estimated the socio economic impact of reducing MS risk factors such as smoking and vitamin D insufficiency (Box 4) <sup>28</sup>.

## CARE PATHWAY ANALYSIS RESULTS: BARRIERS TO OPTIMAL TREATMENT

**Three significant challenges or main treatment gaps** are highlighted in the care pathway analysis:

**LIMITED ACCESS TO INNOVATIVE TREATMENTS.** There are varieties of factors influencing access to innovative treatments for MS patients that vary across Europe. These certainly include diagnosis and clinical management of MS, differences in the reimbursement process and patient eligibility for treatment and affordability of MS drugs<sup>29</sup>. Access to neurologists and other healthcare professionals that can assist in providing access to MS treatment is seen particularly problematic especially in some member states. Moreover, although in most countries all first line products are reimbursed, there are restrictions imposed on the use of the medicines, which limits or delays patient access. Second or third line treatment is needed for more active courses of MS. In many countries, access to some of these treatments is limited. Finally, affordability due to the high price of MS drugs, continue to act as a barrier to access.

**SPECIFIC NON-ADHERENCE TO DISEASE MODIFYING TREATMENTS (DMTS).** The adherence problem to MS treatment may be different from adherence to treatment for other diseases. This is because current disease-modifying treatments are more preventative than symptomatic and all cause adverse events of varying degrees of severity. Thus, main factors affecting adherence to treatment include forgetfulness, injection anxiety (as four of the eight currently available medications involve self-injection), perceived lack of efficacy and coping with adverse events. Continuous education and consistent reinforcement of the value of treatment are essential strategies in the maintenance of treatment adherence along with management of treatment expectations and minimization of adverse events.

**NO ADEQUATE TREATMENT OF FATIGUE.** Fatigue is a common symptom of multiple sclerosis, with an important impact on cognition, quality of life and ability to work. The pathophysiology of fatigue is not well established and a prerequisite of an effective treatment is a mechanistic understanding of fatigue. Levels reported in research vary greatly, from a little more than half of all people with MS up to almost everyone (96%) suffer from fatigue<sup>30</sup>. While some of the symptomatic treatments are quite efficacious, research in the pathophysiology and treatment of fatigue is urgently needed.

## CONCLUSIONS & RECOMMENDATIONS

Treating MS nowadays should aim to preserve brain and cognitive reserve through the early use of adequate treatment along as adopting a 'brain-healthy' lifestyle. This implies a more holistic approach to treatment and care, which comprises the shared decision between the patients and the MS neurologist about the most effective treatment to initiate, patients' values and preferences.

### Our specific recommendations are:

**Early diagnosis and treatment is key:** we call on the EU to fight disparities in access to diagnose and treatment across Europe. Very recently, common guidelines for the use of disease modifying therapy were issued jointly byECTRIMS (European Committee for Treatment and Research In Multiple Sclerosis) and EAN (European Academy of Neurology). These should be applied to secure optimal therapeutic intervention.

**Need for a more holistic approach to care.** Promote a shared decision-making process between patients and doctors for optimal treatment strategies to decrease disability disease progression while fostering treatment adherence and side effects management. We also need a more consistent multi-disciplinary approach to care across Europe, including access to a network of specialised MS nurses, access to rehabilitation, and in some cases also palliative care. A holistic approach to addressing MS also implies increased awareness of the fluctuating nature of the disease and its symptoms – many of them invisible –, which have an impact

on people's ability to work. If these were better understood and addressed, people with MS could continue to live independent lives, which would considerably lower the costs of disease. The EU can play an important role in raising awareness and helping people stay in work.

**People can influence their own health through their lifestyle choices:** Life style choices can help to either prevent the onset of the condition or delay disability. For the first time, we have quantified the impact of smoking and low Vitamin D levels on MS, and what would be the impact if people with MS or at risk for it change behaviour. Healthy eating, stress-management and consistent sports, even at moderate levels, are also considered to help patients manage the disease.

**Promote and foster research** to identify predictors as well as genetics and environmental risk factors of disease. Particularly important is also research aiming to develop new disease modifying treatments, both for early intervention and for treatment of progressive MS, the latter involving neuroprotective or remyelination treatments. In addition, symptomatic treatments such as for fatigue and cognitive symptoms are urgently needed.

#### Box 4. The impact of risk factors reduction and early treatment of Multiple sclerosis.

Early treatment is key in MS to slow disease activity and progression. In addition, reduced exposure to lifestyle factors such as cigarette smoking and low vitamin D serum levels has also been reported to decrease disease progression. Based on MS cost and epidemiological data, we aimed to value the impact of such factors to avert MS societal costs compared with current care. Efficacy data on early treatment reducing conversion to MS from CIS, as well as data on increased risk of MS secondary progression or disability from exposure to cigarette smoking and low vitamin D levels were taken from meta-analyses or systematic reviews<sup>26,31,32</sup>. The estimates were compared between the 10 country settings (Czech Republic, Sweden, France, Germany, Spain, UK, Italy, The Netherlands, Poland) with a societal perspective on annual costs<sup>33</sup> inflated to 2017 figures (EUR), and effectiveness in terms of Quality Adjusted Life Years (QALYs). Sensitivity analyses were applied to test the robustness of the models according a range of effectiveness levels<sup>4,34,35</sup>. Cost-effectiveness was reported as incremental cost-effectiveness-ratio (ICER). The economic impact of shifting from current to WHO target smoking prevalence levels was also analysed<sup>36</sup>.

**Early treatment** - The analysis suggests that early treatment to reduce conversion from CIS to MS is cost-effective from health care provider perspective across EU healthcare systems (ICER of EUR 3,000-41,000 per QALY). From a societal perspective it was always dominant, which means it was more effective and less costly.

**Lifestyle choices** - Consistent and significant annual QALY gains and savings are also demonstrated from smoking cessation based on decrease in disability measures (EDSS) and conversion to progressive MS (0.11 QALYs and EUR 2,500-16,400 per MS patient across country settings); and increase of vitamin D serum levels from < 20 to 20+ nmol/L on MS progression vs status quo (0.13 QALYs and EUR 435-6,210). Significant cost effectiveness of both lifestyle interventions is already evident when using conservative clinical effectiveness data. Such QALY gains and savings are more remarkable in patients with increased disability.

Early intervention and health lifestyle slow MS progression and indeed reduce the disease societal and health care costs, despite limitations of CIS economic models and evidence available from literature. We provide economic evidence to base appropriate public health interventions to reduce the MS burden in Europe.

## Stroke

### Improving the quality of stroke care

Webb A<sup>1</sup>, Fonseca AC<sup>2</sup>, Thijs V<sup>3</sup>, Berge E<sup>4</sup>, Frazekas F<sup>5</sup>, Norrving B<sup>6</sup>, Vanhooren G<sup>7</sup>

<sup>1</sup>University of Oxford, Oxford, United Kingdom; <sup>2</sup>Institute of Molecular Medicine, Universidade de Lisboa, Lisbon, Portugal; <sup>3</sup>Australia; <sup>4</sup>Florey Institute of Neuroscience and Mental Health, Melbourne; <sup>5</sup>University of Tromsø, Tromsø, Norway; <sup>6</sup>European Academy of Neurology (EAN); <sup>7</sup>Lund University, Sweden; <sup>7</sup>European Stroke Organization (ESO)

### CONTEXT

Stroke is a leading cause of disability and death among adults. It is the second cause of death worldwide and the first cause of acquired disability<sup>37</sup>. Despite improvements in care, around one third of the 1.3 million people who have a stroke in Europe each year will not survive. One third will make a good recovery, but one third will live with long-term disability<sup>38</sup>. Furthermore, stroke results in post stroke dementia, depression, epilepsy and falls that cause substantial morbidity and economical costs<sup>39</sup>. Strokes are more likely to occur with ageing<sup>39</sup> with 75% of strokes happening to people older than 65 years. However, 25% of strokes still occur in younger people of working age, resulting in more prolonged impairment, greater dependency and a significant loss of productivity.

In this study, we describe the key issues and unmet needs along the patient pathway. We propose recommendations on how to improve stroke care in the future through the delivery of evidence-based interventions within the stroke unit, and we evaluate the economic impact of a full implementation of stroke unit care (Box 5)<sup>40</sup>.

### CARE PATHWAY ANALYSIS RESULTS: BARRIERS TO OPTIMAL TREATMENT

Care for stroke patients begins before a stroke has happened with the identification of people at risk of stroke, modification of lifestyle patterns, and treatment of vascular risk factors in the primary care setting. It then focuses on optimal treatment of acute stroke in an acute stroke unit and on avoiding further vascular events (secondary prevention), ideally delivered through a comprehensive stroke service. The effect of acute treatment is dependent on the time from stroke onset. Every step of the patient trajectory from symptom onset to the start of treatment within the hospital should be optimized in order to save time and to offer all opportunities for reperfusion, i.e. thrombolysis and thrombectomy. A shorter delay from onset of symptoms to treatment with intravenous thrombolysis (IVT) can make the difference between being independent or dependent on help from others. During and after the acute phase, targeted rehabilitation is needed to reduce the remaining deficits to a minimum and to reintegrate

stroke victims into normal life. We have identified three areas representing significant gaps in implementation of effective interventions<sup>40</sup>:

**INADEQUATE TREATMENT OF ATRIAL FIBRILLATION (AF).** AF is an established risk factor for ischemic stroke, and the detection of AF in patients with ischemic stroke has therapeutic consequences. Patients with atrial fibrillation have an increased risk of ischemic stroke that is five times higher than the risk of ischemic stroke in patients without this arrhythmia<sup>41</sup>. Overall, AF is estimated to be responsible for approximately 15% of all strokes<sup>42,43</sup>, most of which could be avoided through improved detection and use of available drugs that can significantly decrease the risk of AF-related stroke. Although oral anticoagulation after ischemic stroke in patients with AF is recommended by the European Stroke Organization (ESO), many patients still do not receive such treatment. In the UK, only 53% of patients with atrial fibrillation identified at high risk are receiving anticoagulants<sup>44</sup>, with similarly low rates of prescription in other European countries, including Germany (55%), Poland (41%), and Greece (41%).

**LOW IMPLEMENTATION OF STROKE UNITS.** Stroke units are multi-disciplinary units devoted to care for patients with stroke, providing a wide range of proven interventions, from acute reperfusion therapies (thrombolysis, thrombectomy), to early rehabilitation and secondary prevention. Treatment in stroke units has been shown to reduce the risk of death and disability (ref. Peter Langhorne's review), and ESO strongly recommends the establishment of stroke units in all centres caring for stroke patients (ref. ESO guideline). Still, the implementation of stroke unit care and comprehensive stroke services is inadequate across Europe (ref. Burden of Stroke Report) due to cost barriers, lack of appropriately trained staff and limited provision of specialised facilities, despite strong evidence for its clinical and cost-effectiveness (see box).

**LOW ACCESS TO REHABILITATION.** Many stroke survivors experience functional deficits that make them dependent on others for their daily tasks. Rehabilitation aims to enable people with disabilities to regain physical, intellectual, psychological and/or social function [ref]. The early rehabilitation process from a stroke should be initiated in a stroke unit. However, it is rarely complete when it is time to leave hospital. Although it has been shown that continued rehabilitation after discharge during the first year after stroke reduces the risk of disability [ref], only very few clinical trials have been conducted in this field. Therefore, many of the recommendations for treatment in this field are weak, and investment in funding of research in this area is essential.

## CONCLUSIONS & RECOMMENDATIONS

Improve primary and secondary prevention of Stroke Population based initiatives are required to improve primary prevention of stroke, through control of hypertension and identification of individuals with asymptomatic AF, including screening programs for people at risk. After a stroke, patients should be carefully monitored to detect asymptomatic AF, for example with

long-term heart rate monitoring. Once AF is detected, patients should receive oral anticoagulant therapy, unless there are clear contraindications.

**Foster implementation of Stroke Units and Comprehensive Stroke Centres** Stroke units should be established in all centres caring for stroke patients through national policy initiatives, supported by a requirement for stroke unit certification through the ESO program. Strategic plans are also required to improve access to Comprehensive Stroke Centres that provide sophisticated facilities for reperfusion therapies, through development of facilities, clinical services and targeted training programs.

**Improve the access to timely and effective rehabilitation** Access to timely and individualized rehabilitation should be available to all stroke patients, through development of acute stroke units linked into stepped rehabilitation services matched to patient need, from community-based early supported discharge up to comprehensive inpatient rehabilitation units.

#### Box 5. Cost effectiveness analysis of full implementation of acute stroke treatments in the UK healthcare setting

To assess the impact of optimising acute stroke care in Europe, we studied the health-economic effects of full implementation of acute stroke treatments and early secondary prevention through establishing comprehensive stroke services, compared to a 'usual' care scenario where these interventions are not provided. We assessed the relative balance of benefits and costs over a predicted life-time of care needs 40, using the UK health-care setting as an example.

The analysis estimated that by providing all the recommended acute stroke interventions available in a Comprehensive Stroke Service, almost 1 less person is dead or dependent for every 10 patients treated, reducing overall mortality from 14.4% to 11.8%. Although implementing such interventions costs money, raising the cost per patient from £36,820 per patient to £41,071, the resulting benefits equate to a cost of £17,438 per year of healthy life, which is well below the acceptable threshold for a cost-effective healthcare intervention. This conservative analysis is comparable to previous cost-effectiveness analyses of stroke unit provision in the UK and elsewhere in Europe. Furthermore, real-life measurements of the cost-benefits of stroke service reorganisation in the UK suggest that the actual cost-effectiveness of such service changes may be even greater and potentially cost-saving. Overall, despite the logistical challenges and costs of implementation of comprehensive stroke services, such improvements in stroke care will significantly reduce the overall burden of death and disability in a cost-effective, and potentially cost-saving, way.



## NORMAL PRESSURE HYDROCEPHALUS (NPH)

### A treatable but often not treated disease

Tinelli M<sup>1</sup>, Guldemond N<sup>2</sup>, Kehler U<sup>3</sup>

<sup>1</sup>London School of Economics (LSE); <sup>2</sup>The Institute of Health Policy & Management (iBMG) Erasmus Univeristy;

<sup>3</sup>Asklepios Klinik Altona, Hamburg, Germany;

### CONTEXT

Normal pressure hydrocephalus (NPH) is a brain disorder, which affects mainly people above the age of 65. NPH prevalence is over 5% in the elderly<sup>45</sup>. Moreover, it is also estimated that 5% to 10% of patients with dementia, including Alzheimer's disease, are effected by NPH<sup>46,47</sup>. Given that NPH is an age-related disorder, the number of NPH cases is expected to grow as the population ages.

NPH is characterized by the accumulation of excess cerebrospinal fluid (CSF) in the brain's ventricles, which are fluid-filled chambers. As brain ventricles enlarge with excess CSF, they can damage nearby brain tissue, leading to difficulty walking, problems with thinking and reasoning (dementia), and loss of bladder control, which often leads to dependence in activities of daily living, a higher risk of falls and an earlier transition to nursing homes<sup>48,49</sup>.

The causes of NPH can be several and are poorly understood, but may be due to cerebral vessel disease. In most cases, the causes cannot be treated and no medication exists; however, NPH patients can be effectively treated with shunt surgery, which involves placing a tube into the brain to drain the excess fluid. The high success rate of this clinical intervention is diminished by delayed diagnosis and treatment. So far only a small proportion of NPH patients receives timely and adequate treatment, and a large proportion does not receive any form of treatment.

Despite the fact that NPH is a growing public health problem among the ageing population, there is a lack of population-based studies to map the economic impact of NPH across healthcare systems and the economic benefits of timely and adequate treatment. However, the sparse evidence available suggests that treating individuals older than 65 years of age can lower healthcare provider costs and be cost effective<sup>50,51</sup>.

This study aimed to identify unmet needs and key issues throughout the course of the disease that prevent NPH patients to receive adequate and timely treatment<sup>52</sup>. Furthermore, an assessment of the socio economic impact of an optimised scenario where the identified unmet needs (treatment gaps) were anticipated in contrast with the treatment as currently provided was carried out (Box 6)<sup>52</sup>.

## CARE PATHWAY ANALYSIS RESULTS: BARRIERS TO OPTIMAL TREATMENT

This section describes the unmet needs (treatment gaps) along the development of the disease, and, more specifically, diagnosis, treatment, recovery and follow-up.

**MIS- (OR DELAYS IN) DETECTION/DIAGNOSIS.** A major treatment gap exists in the early onset of the first NPH symptoms and the correct diagnosis. The initial symptoms are slight and difficult to detect. There is a lack of knowledge and expertise at both the primary and secondary care level: the referral of GP's and experience of medical specialists is often not sufficient, resulting in delayed or wrong diagnoses. The problem could be characterised as a wrong routing of the patient, resulting in an inefficient use of experience and techniques, which are available at specialised clinics and professionals. Consequently, many patients do not have access to appropriate NPH care.

**NO TIMELY TREATMENT.** Another treatment gap is the time to intervention. Numerous studies have demonstrated that a longer duration of NPH symptoms is associated with the lower likelihood of response to shunting. Without early diagnosis and appropriate treatment, NPH results in preventable walking problems, incontinence and dementia leading to a greater dependency on care and hospitalisation and an avoidable earlier death. Patients who receive treatment remain independent for much longer<sup>53-55</sup>.

**INADEQUATE TREATMENT FOLLOW UP.** A third treatment gap is the inadequate monitoring of the disease development over time and the related follow-up. Early detection of shunt insufficiency or shunt complication after intervention is needed in order to reduce the negative effects of complications. The same applies to NPH patients without shunt intervention to anticipate deterioration at the earliest moment possible.

**INFORMATION GAP.** A cross-cutting treatment gap is the access, sharing and use of information between formal and informal carers. Accordingly, the awareness of professionals across the healthcare spectrum (e.g. primary care and specialised care) of available diagnosis and treatment options, as well as specialised NPH teams and clinics, is too low. This information gap contributes to the aforementioned treatment gaps as well as that the necessary multidisciplinary collaboration and appropriate referrals is severely hindered.

The limited access, sharing and use of information also poses problems for the patient, their family and informal caregivers in the different disease stages. Finding relevant information at the early onset of the problems related to NPH reduces anxiety and uncertainty. Information is essential for self-management and patient/family education; for example, it is important to learn about the purpose, use and expected outcome of the shunt therapy, as well as which signs and symptoms to report if they experience worsening gait disturbance, incontinence and disorientation. Furthermore, communication and information sharing is a key aspect of peer support and shared decision-making<sup>56</sup>.

## CONCLUSIONS & RECOMMENDATIONS

To overcome the gaps in diagnosis and treatment of normal pressure hydrocephalus, we recommend to:

**Raise awareness** of normal pressure hydrocephalus through information and education of relevant healthcare professionals such as GPs, neurologist, radiologists, urologists and supporting disciplines.

**Provide adequate access to quality NPH care**, it is necessary that a sufficient number of specialised care teams are available in each European country and/or region, typically consisting of a neurosurgeon, neurologist, geriatrician, radiologist, and urologist as well as supporting disciplines such as a specialised nurse and physiotherapist. This team should maintain a good interaction with primary and social care professionals in which the GP and geriatrician have an important role. Finally, given the effectiveness of available treatment, timely shunt surgery should be promoted and adequately reimbursed to ensure all NPH patient have access to the most optimal quality of care (Box 1).

**Empower patient and informal caregivers such as family, friends and neighbours** through the facilitation of virtual care networks. This could be established by an easy accessible digital platform where relevant information can be exchanged between patients, formal and informal carers. Such a care network should also be connected with the GP and specialised NPH centres.

### Box 6. ECONOMIC EVALUATION: the cost effectiveness of addressing treatment gap in NPH patient population

In this economic evaluation, we assessed the socio economic impact of delivering timely and adequate NPH treatment. We calculated the cost effectiveness of delivering shunt surgery to NPH-prevalent patients 65 years old or older in Germany (about 34,000 patients—a very low estimation<sup>52</sup>). The model compared two alternatives, current care (25% of NPH patients receiving a shunt) vs. target care (90% of NPH patients receiving a shunt). The model looked at health care costs (diagnosis, shunt intervention and follow up care, i.e. visits, hospitalisation, nursing care) from the public health insurance perspective as well as effectiveness outcomes (in terms of lives saved and quality adjusted life years, QALYs). The periods considered included 5, 10, 15-year (lifetime) terms. Delivering shunt surgery was more costly and the economic costs increased at longer term for the increased longevity of the NPH patients and their access to long term care, whereas effectiveness data showed gain in QALYs and lives saved at all time points. Overall shunt surgery proved to be cost-effective within the NICE thresholds across time, within a range of 10,000 euros (5 years) to 35,000 euros (lifetime) per gained QALY.

## HEADACHE

### Effective and Cost-effective solutions to the burden of headaches: education and structured headache services in primary health care

Matilde L<sup>1</sup>, Steiner TJ<sup>2</sup>, Ruiz de la Torre E<sup>3</sup>, Paemeleire K<sup>4</sup>, Mitsikostas D<sup>4</sup>

<sup>1</sup>Fondazione IRCCS Istituto Neurologico Carlo Besta; <sup>2</sup>NTNU Norwegian University of Science and Technology;

<sup>3</sup>European Headache Alliance (EHA); <sup>4</sup>European Headache Federation

## CONTEXT

Headache is a symptom experienced, at some time, by nearly everybody. In some people, it is a recurrent and painful feature of one of the headache disorders, which are real and often lifelong neurobiological illnesses. There are more than 200 distinct headache disorders<sup>57</sup> but, from the perspectives of public health, health-care needs assessment and health policy, only three are important: migraine, tension-type headache (TTH) and medication-overuse headache (MOH). These three disorders affect men, women and children in every part of the world, including over half of Europe's adults<sup>58</sup>.

**Migraine** is a primary headache disorder<sup>57</sup>. Migraine almost certainly has a genetic basis, although environmental factors play a role in how it affects those who have it. Migraine usually starts at puberty and then recurs throughout life, with attacks on average once or twice a month but in some people much less and in others much more frequently. They last for hours, up to 2–3 days. Headache and nausea are the key features of attacks, but vomiting may also occur, and many people are bothered by even normal levels of light and sound. The headache is typically severe, one-sided and pulsating, and made worse by any physical activity. The visual disturbances of migraine (flashing lights and blind spots) are part of migraine aura, which, when it happens, usually precedes the headache. Although these visual symptoms are often thought of as an essential feature of migraine, in reality only one third of people with migraine experience them, and not in every attack.

**Tension-Type Headache (TTH)** is also a primary headache disorder and its mechanism is poorly understood although it may be stress-related, or associated with musculoskeletal problems in the neck<sup>57</sup>. It is highly variable, often beginning in the teenage years and most troublesome in the 30s. In most people, TTH also occurs in attack-like episodes, usually lasting a few hours but sometimes persisting for several days. Attacks can be infrequent or frequent, and in a few people headache is present on more days than not ("chronic TTH"), sometimes every day without relief. TTH is usually a mild or moderate headache. Lacking the specific features and associated symptoms of migraine, it is commonly described as pressure or tightness, like a band around the head, but sometimes spreading into or from the neck.

**Medication-overuse headache (MOH)**, a secondary headache disorder, is an avoidable condition usually caused by mistreatment of migraine or TTH<sup>57</sup>. MOH begins with episodic headache, in most cases migraine or TTH, treated in each attack with an analgesic or other medication. When headaches occur on 15 or more days per month for more than three months, they become chronic headaches, such as Chronic Migraine and Chronic TTH, and are often associated to medication overuse. Over time – months or longer – headache episodes and medication intake become more frequent. In the end-stage, which not all patients reach, headache is there all day, fluctuating with medication use repeated every few hours. MOH is oppressive and persistent, although often at its worst on waking.

Effective treatments exist for these disorders. For migraine, lifestyle modifications can greatly reduce frequency of attacks, while a range of medications, including simple analgesics, anti-emetics and specific anti-migraine drugs (triptans), can relieve or abort attacks. A number of prophylactic drugs, taken daily, can also reduce attack frequency. For TTH, simple analgesics are effective, although a prophylactic medication taken as a preventative is recommended when attacks are very frequent (more than twice a week), and in chronic TTH, so as not to risk the development of MOH. Treatment of MOH is first and foremost by withdrawal of the overused medication. Although success is usual, MOH is better avoided in the first place by public education.

The Global Burden of Disease Study 2010<sup>59</sup> established that TTH and migraine are the second and third most common diseases in the world, affecting an estimated 22% and 15% of adults respectively. Only dental caries is more common. MOH affects only 2-3% of adults (and some children)<sup>60</sup>, but is one of the headache disorders characterized by headache on more days than not. Migraine, TTH and MOH are prevalent in both sexes and in all age groups, but women between 20 and 50 years are those who have the highest prevalence<sup>57,58</sup>. Although effective treatments exist for these disorders, headache disorders are certainly underdiagnosed and under treated with substantial socio economic consequences.

Together these three disorders are the 3rd leading cause of disability in the world – top in women under 50 years<sup>61</sup>. Migraine alone is the 6th leading cause of disability (3rd in men and women under 50 years), responsible for almost 3% of all disability and more than half of all disability arising from neurological disorders<sup>59</sup>. MOH is the 18th highest cause of disability<sup>61</sup>. Headache disorders are a huge financial drain, because disability leads to lost productivity. Each million of the population in Europe loses an estimated 400,000 lost days from work or school every year to migraine alone<sup>62</sup>. The Eurolight Project on cost of headache disorders in Europe reported that published evidence indicates that migraine is a costly neurological diseases for European society<sup>62</sup>. The estimated cost of headache disorders in Europe is well in excess of €100 billion per year<sup>63</sup>.

For this reason, implementation of effective headache health care is likely to be cost-saving<sup>64</sup>. In this study, we reviewed the headache care pathway, identifying and describing the principal barriers preventing patients to receive timely and adequate treatment. We proposed a solution to overcome those barriers, the implementation of structured and based in primary care headache services, and we made evidence based socio economic evaluation of interventions in three European countries<sup>65</sup> (Box 7).

### CARE PATHWAY ANALYSIS RESULTS: BARRIERS TO OPTIMAL TREATMENT

**INADEQUATE HEALTH CARE SYSTEM.** Effective treatments exist for these disorders, but health-care systems that should provide them do not exist or fail to reach many who need it<sup>64,66</sup>. The roots of this failure mostly lie in education failure, at every level<sup>64</sup>, but also in limited accessibility to appropriate care. Where headache care is established, the focus is on specialist clinics, delivering high-end care at relatively high cost but with very limited capacity and swamped by patients whose needs are less but unmet elsewhere<sup>62</sup>.

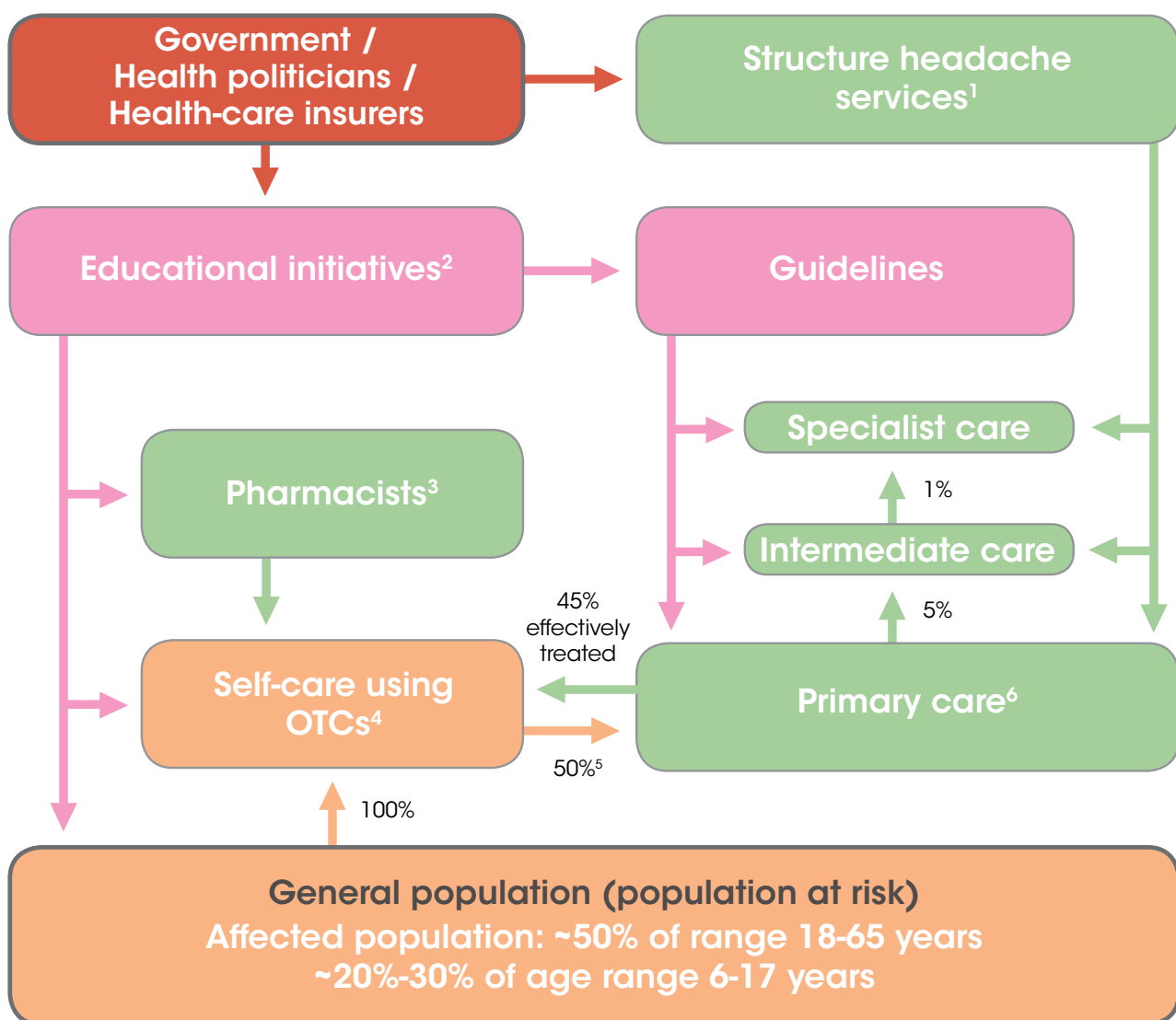
**LACK OF DISEASE RECOGNITION.** Headache disorders are consequently under-recognized in society, under-prioritized in health policy, under-diagnosed in the population and undertreated in health-care systems. People with headache fail to seek health care that is inadequate, and adhere poorly to it.

## CONCLUSIONS & POLICY RECOMMENDATIONS

The solution is implementation of structured headache services (Figure 1). They should be based in primary care to provide sufficient reach: headache care for most people requires neither specialist expertise nor investigations, and can and should be provided by primary-care physicians using the skills they have with basic additional training<sup>63,67</sup>. Specialist services at second and third levels should offer referral lines to cater for the relatively few complex headache disorders requiring tailored and multidisciplinary care. Supporting educational initiatives are needed: aimed at health-care providers to improve competence at their respective levels and at the public to promote self-care and effective use of headache services<sup>63,67</sup>.

Our specific recommendations (Figure 1) are:

1. Headache services should be based in primary care and supported by specialist care.
2. Educational support initiatives are needed<sup>63</sup>: aimed at health-care providers to improve competence at their respective levels and at the public to promote self-care and effective use of headache services<sup>67</sup>.
3. Pharmacists have a key role in advising on use of over-the-counter (OTC) and other drugs, discouraging overuse, and on use of headache services.
4. Within this system, everyone with headache should make best use of OTC drugs.
5. About 50% of people with headache need professional health care<sup>67</sup>.
6. Primary care effectively manages most of these people; specialist care is reserved for the few who need it because of high-frequency, chronicity, headache complicated by comorbidities, uncommon but severe primary headache or secondary headache disorders<sup>67</sup>.



**Figure 1.** Proposed recommendations: structured headache services, and patients' journey

## BOX 7. ECONOMIC EVALUATION OF STRUCTURED HEADACHE SERVICES

We modelled cost-effectiveness of structured headache services delivering treatments for each of the headache types, with efficacy known from randomized controlled trials. Three health-care systems – of Russia, Spain and Luxemburg – brought different experiences of health service delivery and financing into the model. Data sources were published evidence, including population-based surveys <sup>64,66,68</sup>, GBD surveys <sup>61,69</sup> and earlier estimations using the WHO-CHOICE model <sup>70</sup>. We made annual and 5-year cost estimates from health-care provider and societal perspectives (2017 figures, Euros). We expressed effectiveness as healthy life years (HLYs) gained, and cost-effectiveness as incremental cost-effectiveness ratios (ICERs) (cost to be invested/HLY gained). We applied WHO thresholds to establish cost-effectiveness: *ie*, interventions costing <3x gross domestic product (GDP) per capita per HLY are cost-effective, those costing < GDP per capita are highly cost-effective <sup>70</sup>. Scenarios for comparison were current care versus target, with the assumptions that implemented services with provider-training would achieve higher coverage and consumer-education would lead to better adherence, each, conservatively, by 50% of the gap between current and ideal. Economic output included direct costs (resources sunk into health-care provision) and indirect costs (lost work productivity). We performed sensitivity analyses with regard to how much lost productivity might be recovered to test robustness of the model.

In the 1-year time frame from the provider perspective, structured headache services are cost-effective across headache types – well below WHO thresholds<sup>70</sup>. Over 5 years they are even more cost effective. Results are consistent across health-care systems. From the societal perspective, structured headache services are not only cost-effective but also cost-saving, for all headache types and health-care systems, at 1 and 5 years. The higher the country's wage level, the greater the economic savings for society (Luxemburg > Spain > Russia).

Lost productivity has a major impact on economic estimates because predicted savings in work productivity greatly exceed the investments in health-care estimated to achieve these savings. In a conservative scenario, where we assume that remedying disability will recover only 20% of lost productivity, the intervention remains cost-effective across all models. For TTH, predicted savings from productivity gains are smaller than estimated investment costs in Russia and Spain, but the intervention is still cost-effective <sup>70</sup>. In Luxemburg it remains cost-saving.

Structured headache services supported by patient and provider education are effective and cost-effective solutions to headache and its long-term disability. From the health-care provider perspective, cost-effectiveness is least (ICERs greatest) for TTH because of its much lower disability weight compared with those for migraine and MOH <sup>60</sup>. In practice, structured headache services will not discriminate: they must manage all headache types; however, people with TTH are least likely to require them.



## EPILEPSY

### Cost savings and improved patient outcomes from best management of epilepsy

Marson AG<sup>1</sup>, Bolan A<sup>2</sup>, Mahon J<sup>2</sup>, Little A<sup>3</sup>, Dickson R<sup>2</sup>, Boon P<sup>4</sup>, Depondt C<sup>1</sup>, Martikainen J<sup>5</sup>, Ryvlin P<sup>4</sup>, Kälviäinen R<sup>4</sup>

<sup>1</sup>International League Against Epilepsy (ILAE); <sup>2</sup>University of Liverpool; <sup>3</sup>European Federation of Neurological Associations (EFNA); <sup>4</sup>European Academy of Neurology (EAN); <sup>5</sup>University of Eastern Finland

#### CONTEXT

Epilepsy is a chronic neurological disorder characterized by repeated seizures (> 24 h apart); a single seizure with a high probability of seizure recurrence, or diagnosis of an epilepsy syndrome. The incidence of epilepsy in developed countries is approximately 50 per 100,000 individuals per year, with the greatest rates for infants and the elderly. In Europe, epilepsy affects 6 million people (prevalence 8/1000) and the lifetime cumulative prevalence of epilepsy is 3%.

Despite the development of a new generation of antiepileptic drugs and surgical approaches to management, ~30% of patients are drug-refractory, with significant associated co-morbidities of depression, cognitive impairment and other neuropsychiatric diseases. The aetiology of these co-morbidities is multi-factorial: antiepileptic drugs, genetic factors, aetiology of epilepsy and seizures all contribute. Eighty per cent of people with epilepsy live in low- to medium-income countries, and epilepsy is responsible for 0.3 per cent of all deaths worldwide according to the Global Burden of Disease Study. The risk of sudden unexpected deaths in Epilepsy (SUDEP) has been estimated to be 24 times higher in young persons with epilepsy than the risk of sudden unexplained death in the general population of the same age. SUDEP incidence is estimated at 1 per 10,000 patient-years in newly diagnosed epilepsy and 2-10 cases of SUDEP per 1,000 patient-years in patients with refractory epilepsy. The most important risk factor of SUDEP is a history of generalized tonic-clonic seizures.

The epilepsy 'treatment gap', defined as the proportion of people with epilepsy who require treatment but do not receive it or receive inadequate treatment, has been proposed as a useful parameter to compare access to and quality of care for epilepsy patients across populations. The 'treatment gap' varies from 10-20% in developed countries to 75% in low-income countries. Stigma and discrimination related to epilepsy are also prevalent in Europe.

In this study, we assessed the epilepsy care pathway to identify the major unmet needs and reasons for treatment gaps (both those needing research and better evidence to inform treatment decisions and those needing better organization of services). We also performed an analysis to identify the economic and health benefits 'current' management vs. evidence-based 'best' management strategies (box 8)<sup>71</sup>.

## CARE PATHWAY ANALYSIS RESULTS: BARRIERS TO OPTIMAL TREATMENT

### INVESTIGATION AND MANAGEMENT FOLLOWING AN INITIAL UNPROVOKED SEIZURE.

Approximately 3% of the population will develop epilepsy, but 2 to 3 times as many patients will experience a single seizure or seizure-like event. A diagnosis of epilepsy has significant medical, social, and emotional consequences. Patients diagnosed with a possible first unprovoked seizure require assessment by a healthcare professional with appropriate specialist training and where appropriate electroencephalography and epilepsy protocol-specific magnetic resonance imaging of the brain, which includes thin-cut coronal slices, to determine aetiology, the likely risk of recurrence and the need for long-term treatment. Patients with a high risk of recurrence should be counselled about the likely risk of seizure recurrence with or without antiepileptic treatment. For those that choose treatment, an antiepileptic drug should be carefully selected taking into account comorbidities, adverse effect profile, and type of epilepsy is essential along with appropriate counselling. **Barriers:** *Scientific:* We cannot precisely predict who will have further seizures and we cannot prevent the development of epilepsy or the process of epileptogenesis. *Organizational:* Access to specialist services and assessment is variable even after a first tonic-clonic seizure. If the first symptoms are focal symptoms, the diagnosis may be delayed for years.

### TREATMENT OF PATIENTS WHO HAVE A SECOND (OR MORE) UNPROVOKED SEIZURE.

The choice of antiepileptic medication is primarily based on the presumed type of epilepsy. Antiepileptic medications can be divided into broad-spectrum and narrow-spectrum agents. Narrow-spectrum agents are typically effective in patients with focal onset seizures. However, some narrow-spectrum agents may worsen myoclonic and absence seizures in patients with idiopathic generalized epilepsies. Broad-spectrum agents improve seizures in patients with focal epilepsy and most generalized epilepsies. Use of a broad-spectrum agent is recommended for patients if there is insufficient evidence pointing to a focal onset. The choice of antiepileptic medication should account for the patient's comorbidities, other medication use, age, sex, and the cost of the medication one of the most important factors being teratogenic risk for women of childbearing age. In patients diagnosed with epilepsy after two or more unprovoked seizures, approximately 50% will become seizure-free after starting the first appropriately dosed antiepileptic medication. The likelihood of seizure freedom declines with increased number of antiepileptic medication regimens, with a further 13% becoming seizure-free after initiation of a second antiepileptic medication and 4% after initiation of a third antiepileptic medication. Thus, approximately two-thirds of people with epileptic seizures can be controlled with currently available antiepileptic drugs, leaving one-third with uncontrolled epilepsy. The temporal patterns of epilepsy leave a substantial number of patients following also a relapsing-remitting course.

**Barriers:** *Scientific:* The etiologies (structural, genetic, metabolic, infectious, immunological) of epilepsy and the specific epilepsy syndromes are extremely heterogenous and have an

important impact on seizure outcome. At present, we have few biomarkers in epilepsy. EEG helps differentiate between focal and generalized epilepsy syndromes, and MRI imaging identifies lesions associated with a poorer prognosis. However, for the great majority of people with epilepsy, we have no biomarkers that aid the choice of a specific drug for an individual. Indeed, none may exist for currently available treatments, and drug choices are made based on knowledge (often inadequate) of effect in broad populations. As a result, many patients undergo a period of trial and error in order to find the best treatment(s). Organizational: It is estimated that 70% of people could have their seizures fully controlled with appropriate AEDs. This would be achieved with early access to specialist assessment and comprehensive care including appropriate counselling. However, only 52% of people with epilepsy in the UK have their seizures fully controlled with AEDs. This indicates that currently available medical treatments are not used to their full potential.

### **TREATMENT OF PATIENTS WITH EPILEPSY THAT IS REFRACTORY TO MEDICAL TREATMENTS.**

Epilepsy can be treated in an affordable way with low-cost medication such as the traditional antiepileptic drugs. Whilst many of the new drugs have better tolerability profiles than standard treatments, none have been proven to be more effective. Better tolerated treatments can have an important influence on outcome due to better compliance, leading to better seizure control. The International League Against Epilepsy (ILAE) defines a refractory epilepsy patient as one who does not respond to two adequate medical treatments. Refractory epilepsies occur in approximately one-third of people diagnosed with epilepsy. For this group of patients, non-drug options include respective surgery, ketogenic diets and neuromodulation to improve seizure control and quality of life. Barriers: Scientific: We have no biomarkers to allow early identification of patients destined to be refractory and who would benefit from epilepsy surgery or neuromodulation. Organizational: There is substantial underutilization of the treatment options for refractory epilepsy. The mean delay between first seizures and epilepsy surgery is still nearly 20 years for the majority and it is estimated that only 40% of refractory patients get comprehensive diagnostic evaluation. As soon as patients are diagnosed as having refractory epilepsy, they should all be referred for comprehensive diagnostic evaluation to a tertiary epilepsy centre.

## **CONCLUSIONS & RECOMMENDATIONS**

The epilepsy treatment gap is a major issue in Europe<sup>72-81</sup>. It is determined by affordability, accessibility and availability of care and treatment. Closing the epilepsy treatment gap will require a multifaceted approach, including raising awareness of epilepsy and the effectiveness of treatments in the general population and among those working in health services; training healthcare professionals with skills to diagnose and manage epilepsy; and providing coordinated, networked and accessible services allowing management from first seizure through to complex epilepsy surgery, also taking into account comorbidities and other needs such as education and fertility.

**Specific policy recommendations are:**

- Raise public awareness (campaign) and awareness among health care professional (GPs, general physicians, emergency medicine)
- Provide specialist epilepsy training (neurologists, specialist nurses)
- Link emergency and GP services with epilepsy/seizure services to ensure rapid access to expertise following first seizures(s).
- Provide access to specialist expertise for refractory patients
- Provide timely access to epilepsy surgery services
- Provide counselling and peer-support in collaboration with patient organizations
- Invest in research

### Box 8. 'Best' management of epilepsy is cost-saving and improves patient outcomes

An economic model was constructed to explore the impact on the patient and healthcare provider transitioning from the 'current' management of people with epilepsy to what can be considered as the 'best' management. The model is only for people who have epilepsy. Benefits of correct diagnosis of other conditions through better management have not been considered. The drivers of the model are faster access to effective treatments resulting in remission or reduction in seizures. The model does not concern itself with actual choice of anti-epileptic drugs (AEDs). Specifically, 'best' management has been simplified in the model to be:

- Immediate referral to a specialist centre and commencement of AEDs for all patients having had two seizures.
- Choice of initial AED most likely to benefit patients in the opinion of specialists with rapid switching of treatments that are proving ineffective
- Offer of surgery for those where it is appropriate (or, vagal nerve stimulation where it is not) for all refractory patients after two years on AEDs or remain refractory after trying two drugs – whichever comes first

The conservative findings are that over a 25-year time horizon, 'best management' compared to 'current management' would result in:

- A 48.7% reduction in epilepsy related mortality (SUDEP or death from seizure) from 75.2 to 38.5 per 1,000 patients
- A 57.3% reduction in convulsive seizures from an average of 8.2 to 3.5 per patient
- A 1.05 QALY gain (discounted) per patient
- A saving of £4,565 (discounted) per patient

Initial results from the model suggest significant improvements in patient outcome and an associated reduction in costs could be achieved from a move to best management in the UK. The model is also constructed such that whilst the results currently are from a UK perspective it can be readily adapted to any setting.

Under a conservative set of assumptions and utilising the seizure experience of patients prior to joining the SANAD trial 82 and seizure reduction seen whilst on the trial, the results of our analysis suggest that the improvement in patient outcomes and reduction in healthcare costs from current to best management of epilepsy would be significant. Achieving best management would not be without cost. However, if NICE values a QALY at £20,000, best management would be considered to offer good value for money to the UK National Health Service (NHS) (due to the expected costs savings and QALY gains) provided that it costs less than an additional £25,500 per patient to achieve.

## ALZHEIMER'S DISEASE (AD)

### The potential of treating Alzheimer's disease before the onset of dementia

Sikkes SAM<sup>1</sup>, Handels R<sup>2,3</sup>, Vermunt L<sup>1</sup>, Scheltens P<sup>1</sup>, Visser PJ<sup>1,2</sup>

<sup>1</sup>VU University Medical Center Amsterdam; <sup>2</sup>Maastricht University; <sup>3</sup>Karolinska Institutet;

#### CONTEXT

In Europe, currently an estimated 10.5 million people have dementia, and this number is expected to increase to 18.66 million by 2050<sup>83</sup>. In approximately 70% of the people with dementia, Alzheimer's disease (AD) is the underlying cause. AD is a progressive neuro-degenerative disease characterized by a decline in memory, thinking, behavior and the ability to perform everyday activities. Ultimately, these impairments lead to a loss of independence, an increasing need for support by others and requires up to full-time care as the disease progresses.

AD dementia is associated with major health and social care costs of which the majority is related to long-term formal and informal care: both direct and indirect care costs increase with increasing severity of the disease. The total estimated cost of dementia in Europe in 2015 was US\$ 300 billion<sup>83</sup>. In addition, dementia is associated with a considerable disease impact, affecting the quality of life of both people with dementia and their caregivers.

Current treatments are symptomatic, and therefore do not change the underlying disease trajectory. Because of the lack of disease-modifying treatments that can delay the onset of disease, AD is one of the most challenging health and socio-economic problems society currently faces. Amyloid build-up ("Amyloid pathology") is one of the characteristics of AD, and recent research findings demonstrated that this can be detected up to 25 years before the onset of clinical dementia, providing the opportunity for interventions that may postpone the onset of dementia. AD develops along a continuum, with the early stages of disease termed preclinical (asymptomatic patients, but with the potential for patients to experience subjective cognitive decline (SCD)), followed by the development of mild cognitive impairment (MCI) and increasingly severe stages of AD dementia: mild, moderate and severe.

The Dementia case study of the Value of Treatment project analyzes the current AD care pathway and "patient journey" by identifying the patient and caregiver needs. The study has also developed a health-economic model that will provide an estimate of the potential value of such hypothetical treatment that slows down the progression to dementia in people with amyloid pathology who do not yet have dementia (Box 9)<sup>84</sup>.

## CARE PATHWAY ANALYSIS RESULTS: BARRIERS TO OPTIMAL TREATMENT

The current care pathway or “patient journey” in people with AD highlighted two important care needs and treatment gaps<sup>84</sup>.

**MISSED OR DELAYED DIAGNOSIS.** It has been estimated that around half of the people living with dementia in Europe have never been diagnosed and, for those diagnosed, it will most likely happen at a moderate stage<sup>85,86</sup>. Patients and caregivers often felt misunderstood by their surroundings, including family members, friends and the GP, and indicated difficulty gaining access to specialty care. They experienced the trajectory from first symptoms to a diagnosis made in specialty care as very long. Most common barriers to the diagnosis of AD are health system related and include lack of GP training and specialist doctors in the country/region, waiting lists, the absence of guidelines, etc. Thus, there is an urgency to understand and recognize early stage and at-risk AD stages to ensure a rapid diagnosis, which could then provide opportunities for interventions. Finally, patients and caregivers perceived the lack of awareness of dementia and the social stigmas attached to the disease as important obstacles to diagnosis<sup>87,88</sup>.

**NO ADEQUATE TREATMENT AND CARE.** Research into treatments of Alzheimer’s disease has suffered frequent setbacks, with no new approved drug treatment for AD for the past 10 years. Whilst symptomatic treatment is widely available, there is currently no disease modifying treatment that could cure the disease or slow disease progression. In addition, in several countries in Europe, the person with dementia is not routinely involved in treatment decisions. In addition, access to a professional in the community (i.e. support worker) who provides ongoing information and support to people with dementia varies.

## CONCLUSIONS & RECOMMENDATIONS

Treatment of AD is expected to be most effective and cost-effective (box 1) when started early in the disease process. Early diagnosis and treatment will be even more crucial once disease-modifying treatments become available. This is an overview of recommendations for overcoming barriers and promoting early detection and treatment as the first steps in improving clinical care and management of dementia:

- **Raise awareness and understanding** that AD starts long before the onset of dementia, which will provide new treatment opportunities for the prevention of dementia. Diagnosis before the onset of dementia should be accompanied by careful counselling and addressing possible stigma.

- **Improve access to diagnostic and specialist care services**, and support for people with (early) AD following diagnosis. This includes investments in healthcare infrastructure & training for professionals.
- **Support and promote dementia research** to increase understanding of AD, improve diagnostics and support the development of new promising therapies. This includes the identification of research (funding) priorities.

### Box 9. The potential health-economic impact of treating Alzheimer's disease before the onset of dementia

In the health-economic evaluation, we assessed the potential health-economic impact of a hypothetical (pharmacological) treatment that would delay the onset of AD dementia in persons diagnosed with preclinical or prodromal AD. We evaluated care costs and quality of life in a scenario of usual care and compared it to a scenario where the disease progression rate was reduced by 50%, using a Markov model.

In the hypothetical treatment, a smaller proportion of people would progress to advanced stages with mild, moderate or severe dementia. As mortality was lower in pre-dementia states, people were estimated to live longer. This resulted in an increase of quality adjusted life years (QALYs) of 1.75 per patient. Overall, the treatment scenario was estimated to reduce the total lifetime care costs compared to the usual care scenario by € 12,406 per person over 25 years (treatment costs excluded). These results were highly sensitive to assumptions of dementia-related mortality, where the costs savings were € 20,351 per person under the assumption of a flat mortality rate.



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## European Brain Council Brussels Office

Rue d'Egmont, 11  
BE-1000 Brussels  
Tel: + 32 (0)2 513 27 57  
[www.braincouncil.eu](http://www.braincouncil.eu)

[VoT@braincouncil.eu](mailto:VoT@braincouncil.eu)  
 [@EU\\_Brain](https://twitter.com/EU_Brain)  
[#ValueofTreatment](https://twitter.com/ValueofTreatment)



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