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# Structured headache services based in primary care and supported by education: Effective and cost-effective solutions to the burden of headache

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# Barriers to 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

## Background

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 as well as increased risk of sudden unexpected death.

## Methods

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 per cent in developed countries to 75 per cent 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 barriers to achieving optimal treatment (both those needing research and better evidence to inform treatment decisions and those needing better organization of services).

## Barriers to optimal treatment:

### Investigation and management following an initial unprovoked seizure:

- **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:**

- **Scientific:** 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 timely and appropriate AED treatment. This would be achieved with early access to specialist assessment and comprehensive care including appropriate counselling and partnership with the patient. 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:**

- **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

## **Recommendations**

- 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 peer-support in collaboration with patient organizations
- Invest in research



Juha Karjula, a 38 year-old kindergarten teacher, obtained his university Master's degree despite having refractory epilepsy. He was diagnosed with focal epilepsy as a high school student, after having his first tonic-clonic seizure. Despite of detailed investigations, the cause of his epilepsy has remained unknown. For years his seizures were not adequately controlled with different AEDs, which were used either as monotherapy or in combination therapy. Some AEDs also resulted in unbearable side-effects, such as speech problems. However, with comprehensive evaluation and with arduous successive treatment attempts, seizure control was achieved in 2011. At the moment Juha is using a combination of two AEDs. He is seizure-free and has no significant side-effects of his current treatment.

In his experience, it is important to have good communication between a person with epilepsy and their neurologist. If needed, a support person or a family member, someone who knows a patient's everyday life and wishes, could act as 'interpreter' between the doctor and the patient to ensure the patient is understood. In this way Juha had good interaction with his doctor and found a way for mutual understanding with his doctor about how he wants to be treated.

Text: Sari Tervonen, Photo: Hannu Miettinen IBE/Finland

## Conclusions

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. Service need to be well-coordinated, networked and accessible allowing management from first seizure through to complex epilepsy surgery, whilst also taking into account and managing co-morbidities.

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## Acknowledgements:

This work was supported by Livanova and UCB Biopharma SPRL. We would like to thank Peter Dedeken for the contribution to this work. A digital version of the poster and other supporting documents are available here:

<http://www.braincouncil.eu/activities/projects/the-value-of-treatment/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

## Background

Clinical guidelines have been published in the UK recommending that patients with epilepsy should be treated by specialists and rapidly offered alternative treatments to anti-epileptic drugs (AEDs) if they are not achieving remission by 2 years.<sup>1</sup>

The aim of this research was to assess how health outcomes for patients in the UK NHS, and the resource use associated with seizures and complications, would change if care were delivered in line with the NICE Guideline ('best management') instead of how patients with epilepsy are currently being managed ('current management'). Best management was simplified into the following key principles of care:

- Patients are referred to an epilepsy specialist after two seizures
- Specialists select an initial AED and monitor and adapt treatment as required
- Patients not in remission at 2 years are assessed for surgery and those eligible are offered surgery
- Patients ineligible for surgery are assessed for vagal nerve stimulation (VNS) and those eligible are offered VNS.

## Methods

A Markov model with a 25 year time horizon and one week cycle was constructed to explore the impact on the patient and healthcare provider (the NHS) from moving from current management of people with epilepsy to best management. The model pathway starts from second seizure (patient age 30), moves to management by a specialist (treatment with AEDs) and finally goes to surgery or provision of VNS. In each cycle there is a probability a patient has a seizure (non-convulsive, convulsive status epilepticus or refractory convulsive status epilepticus), or dies from SUDEP (sudden unexpected death in epilepsy) or from any cause (Figure 1).

Estimates of remission and seizure rates under best and current management with AEDs were derived from the SANAD (Standard And New Antiepileptic Drugs) trial data.<sup>2</sup> SANAD baseline data, other published sources and clinical assumption were used to determine remaining transition probabilities. Costs were incurred from the perspective of the NHS. Only costs associated with seizures and their complications were considered. Utility values were identified from the literature for neurological damage and for people with epilepsy that were not in remission.

In all cases, the model was constructed conservatively to provide a lower estimate of the benefits of best management. For example the costs of neurological damage from seizures were not considered in the base case.

## Results

Initial results from the model suggest that significant improvements in patient outcomes and an associated reduction in costs could be achieved with a move from current management to best management in the UK NHS. The model suggests that, over 25 years, best management would generate cost savings of £4,565 (discounted) or £6,033 (undiscounted) per patient from treating seizures and associated complications. There would also be a quality adjusted life year (QALY) gain per patient of 1.05 (discounted) or 1.62 (undiscounted). The cost and QALY savings over 5 year periods up to 25 years are shown in Figures 1 and 2 respectively.

The costs savings are generated from a reduction in convulsive seizures, which with best management are reduced from an average of 8.2 per patient to 3.5 per patient over 25 years. This in turn results in a 56.7% reduction in the costs (undiscounted) of treating convulsive seizures, such that costs fall from £10,605 to £4,589 per person over 25 years. With a 67.7% reduction in patients with neurological damage (from 25.5 to 8.3 per 1,000 patients), there would also be a significant reduction in the costs of treatment and potential ongoing care for this group; these additional costs have not been included in the modelling.

The QALY gains are generated from a 48.7% reduction in epilepsy related mortality (SUDEP or death from seizure) over 25 years (mortality falls from 75.2 to 38.5 per 1,000 patients), the reduction in patients with long-term neurological damage and from an increase in patients being seizure free and becoming seizure free earlier. By 10 years the model predicts that, with best management, 61.0% of patients will be alive and in remission. With current management only 33.0% will be alive and seizure free. With best management at 10 years, a further 11.6% will have had seizure reduction with VNS as opposed to only 0.2% with current management.

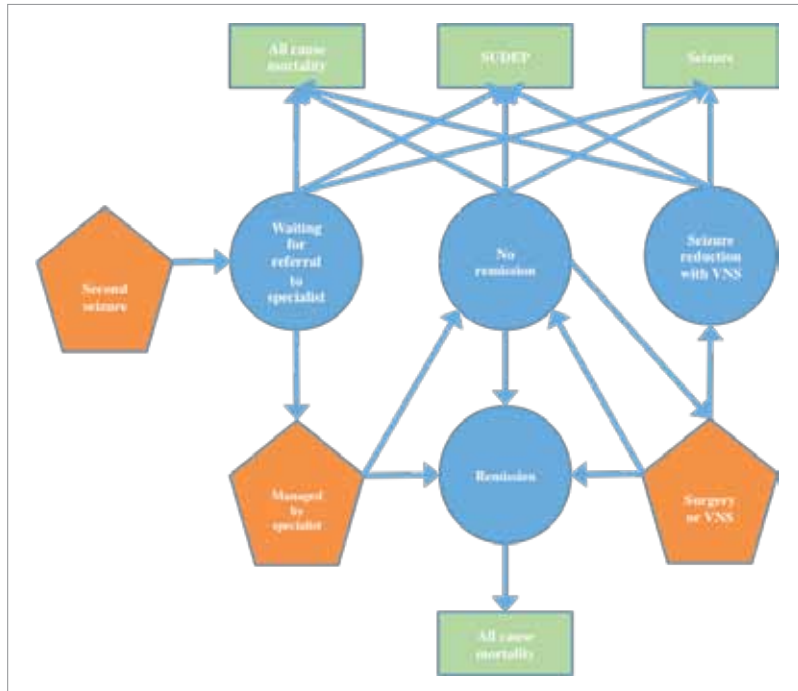


Figure 1: Simplification of model pathway

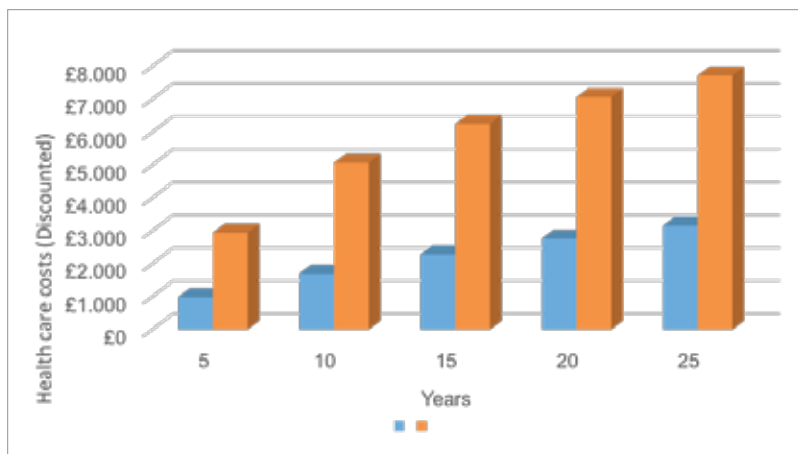


Figure 2: Healthcare costs per person over 25 years with best and current management

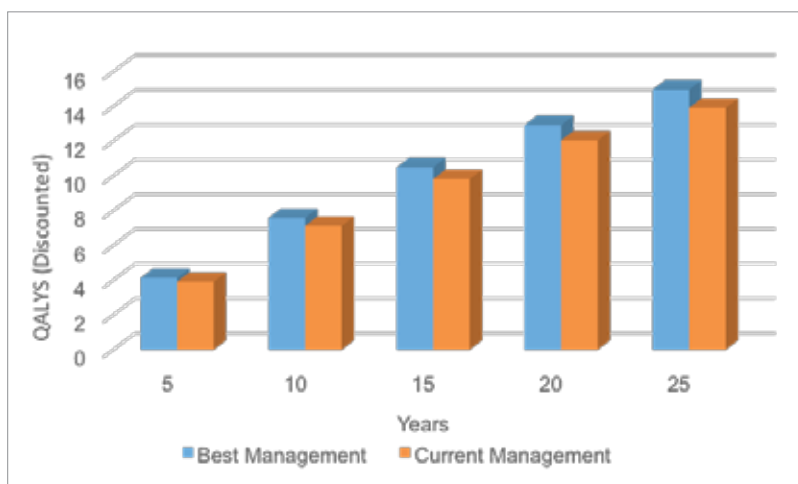


Figure 3: QALYs per person over 25 years with best and current management

## Conclusions

Under a conservative set of assumptions and utilising the seizure experience of patients prior to joining the SANAD trial 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 NHS (due to the expected costs savings and QALY gains) provided that it costs less than an additional £25,500 per patient to achieve.

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National Institute for Health and Care Excellence. 2016. Epilepsies: diagnosis and management (CG137). <https://www.nice.org.uk/guidance/cg137>; Marson AG et al. 2007. The SANAD study of effectiveness of valproate, lamotrigine, or topiramate for generalised and unclassifiable epilepsy: an unblinded randomised controlled trial. Lancet.

## Acknowledgements:

This work was supported by Livanova and UCB Biopharma SPRL. We would like to thank Peter Dedeken (UCB Biopharma SPRL) for the contribution to this work. A digital version of the poster and other supporting documents are available here:

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# Headache: The patient journey

Leonardi M<sup>1,3</sup>, Ruiz De La Torre E<sup>2</sup>, Steiner TJ<sup>3,6</sup>, Raggi A<sup>1</sup>, D'Amico D<sup>1</sup>, Grazi L<sup>1</sup>, Paemeleire K<sup>4</sup>,  
Guldemand N<sup>5</sup> and Mitsikostas M<sup>4</sup>

<sup>1</sup>Foundation IRCCS Neurological Institute Carlo Besta; <sup>2</sup>European Headache Alliance, <sup>3</sup>Lifting The Burden;

<sup>4</sup>European Headache Federation (EHF); <sup>5</sup>The Institute of Health Policy & Management (iBMG);

<sup>6</sup>NTNU Norwegian University of Science and Technology

## Headaches Background

Headache is a symptom experienced, at some time, by nearly everybody in Europe and worldwide. In some people, it is a recurrent and painful feature of one of the headache disorders: although more than 200 distinct headache disorders exist [1], **Migraine, Tension-Type Headache (TTH) and Medication-Overuse Headache (MOH)** are the most common, burdensome and relevant from a public health perspective. These three disorders affect men, women and children in every part of the world, including over half of Europe's adults [2]. The Global Burden of Disease Study 2010 [3] established that **TTH and migraine are the second and third most common diseases in the world, estimated to affect 22% and 15% of adults respectively, while MOH affects 2-3% of adults**. Headache disorders are a great burden for sufferers and 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 [4], and the estimated cost of headache disorders in Europe is well in excess of €100 billion per year [4]. Headache disorders are 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.

## Disease management and Treatment

Migraine, TTH and MOH are diagnosed solely on history. Headache diaries clarify the pattern of headaches and associated symptoms as well as medication use or overuse. Investigations, including neuroimaging, are indicated only when the history or examination suggest headache is secondary to another condition.

**Effective treatments exist for these disorders.** For migraine, lifestyle modifications can greatly reduce frequency of attacks, while a range of medications, including simple analgesics or triptans, can relieve or abort attacks. A number of prophylactic drugs, taken daily, can also reduce attack frequency. For TTH, simple analgesics are effective, and prophylaxis is recommended for high-frequency and chronic TTH, to reduce the risk of chronification. 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 a combination of public education and good management of the headache disorders that lead to MOH.

Non-pharmacological approaches to headache treatment are promising options, particularly for those cases where pharmacological therapies are not indicated. Examples of them include nutraceuticals and diets, behavioral therapies and non-invasive neurostimulation methods. They are well tolerated, can be combined with conventional drug therapies, and some of them are effective both for preventative and acute treatment.

## The Care pathway: Treatment Gaps and Unmet Needs

The “care pathway” for most European people with headache is a series of dead ends. Many who would benefit from professional care find it unavailable, fragmentary or difficult to access. Where headache services exist, they tend to be focused in specialist headache clinics, delivering high-end multidisciplinary care with very limited capacity. Such clinics are needed by the minority with complex disorders, but cannot serve this purpose when inundated by people who could be effectively treated in primary care – as most people needing headache care require neither specialist expertise nor investigations. Contrariwise, one in every three people receiving care for migraine in Russia and Spain, and one in every four in Luxemburg, do so from specialists. Good health care can greatly reduce the burden of headache, but it persists – principally because health-care systems that should provide this care do not exist or fail to reach many who need it. The roots of this failure mostly lie in education failure, at every level, but also in limited accessibility to appropriate care.

- **Lack of knowledge among health-care providers** is a problem seen in medical schools: worldwide, only four hours are committed to headache disorders in formal undergraduate medical training lasting 4-6 years.
- **Poor awareness of headache disorders exists similarly among the general public:** headache disorders are not perceived by the public as serious as they do not cause death and are not contagious. Consequently, headaches are often trivialized as “normal” and seen in those who complain of them as merely an excuse to avoid responsibility.
- **On a political level, many governments, even if aware of it, do not acknowledge the substantial burden of headache on society.** Health care for headache obviously comes at a cost: large numbers of people need treatments, together with advices on correct usage, and delivery of these requires organized health care.

When my kids were younger , I used to spend my nights out in the garage so they wouldn't hear me screaming in the night because of my headaches. They did though.

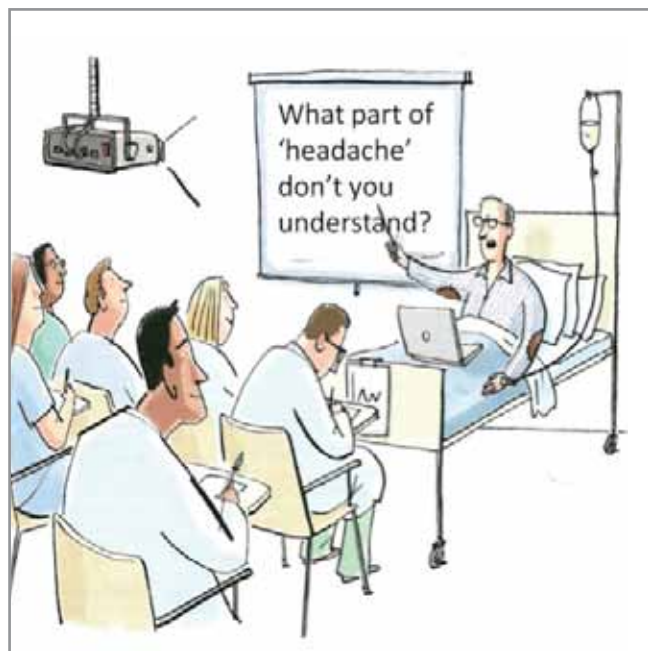
**Roberta, Italy, May 2017**

I was in the Migraine Clinic for four weeks. In hindsight, I am glad to have come here and not to go somewhere else. For the first time, I had the feeling of being taken seriously. It was clear to me from the beginning that I cannot expect miracles in the short time. But prevention has begun and the doctors treated me sympathetically.

**Flecki5, Germany, December 2016**

My wife suffers from a rare type of chronic migraine. Last week she was in the hospital for 3 days getting infusion treatment. Right after that she received Botox injections and she was still in a great deal of pain. She had a severe migraine episode for 3 weeks. She always has a migraine, it's just how well the pain can be managed. It's very hard watching her go through this.

**Luis, Spain, October 2016**



## Recommendations

**About 50% of people with headache need professional care and cannot rely on self-medication: headache services should be based in primary care to provide sufficient reach and have to be supported by specialist care.**

**Properly educated primary care professionals effectively manage most of headache sufferers; specialist care is reserved for the small proportion of the more complex situations such as high-frequency and chronic headaches or headaches complicated by comorbidities who need it: people that reach specialist care are those that fail in controlling headaches with primary care indications or that are at risk of developing MOH.** 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.

**Educational initiatives are needed:** aimed at health-care providers to improve competence at their respective levels, so to reduce the underdiagnosis of headache disorders, and at the public to promote self-care and effective use of headache services.

# Conclusions: the value of treating headache

**Implementation of good headache health care is likely to be cost-saving.** Headache care for most people can and should be provided by professionals such as primary-care physicians, using the skills they have with basic additional training. **The solution is implementation of headache services through education of professionals at primary care level:** structured, based in primary care to provide sufficient reach, and supported by educational initiatives that will enable to reduce the underdiagnosis of headache disorders. Structured headache services, at second or third level of care, should provide adequate diagnosis and treatments to the more complex situations such as high-frequency and chronic headaches or headaches complicated by comorbidities that require tailored multidisciplinary care.

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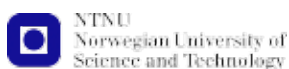
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<http://www.braincouncil.eu/activities/projects/the-value-of-treatment/Headache>





# Structured headache services based in primary care and supported by education:

## Effective and cost-effective solutions to the burden of headache

Steiner TJ<sup>1,6</sup>, Leonardi M<sup>1,2</sup>, Ruiz de la Torre E<sup>3</sup>, Paemeleire K<sup>4</sup>, Tinelli M<sup>5</sup> and Mitsikostas M<sup>4</sup>

<sup>1</sup>Lifting The Burden; <sup>2</sup>Foundation IRCCS Neurological Institute Carlo Besta; <sup>3</sup>European Headache Alliance (EHA); <sup>4</sup>European Headache Federation (EHF); <sup>5</sup>London School of Economics (LSE); <sup>6</sup>NTNU Norwegian University of Science and Technology

## Background

Headache disorders are disabling, often lifelong neurological illnesses. Migraine, tension-type headache (TTH) and medication-overuse headache (MOH) are of major public-health importance: collectively the 3rd highest cause of disability in populations worldwide, they result in much lost productivity and very high indirect costs (>€100 billion per year in EU) [1]. Nevertheless they are poorly treated, although effective treatments exist. The objectives of the economic analysis were to estimate cost/effectiveness of a proposed solution: structured headache services based in primary care and supported by educational initiatives (Figure 1).

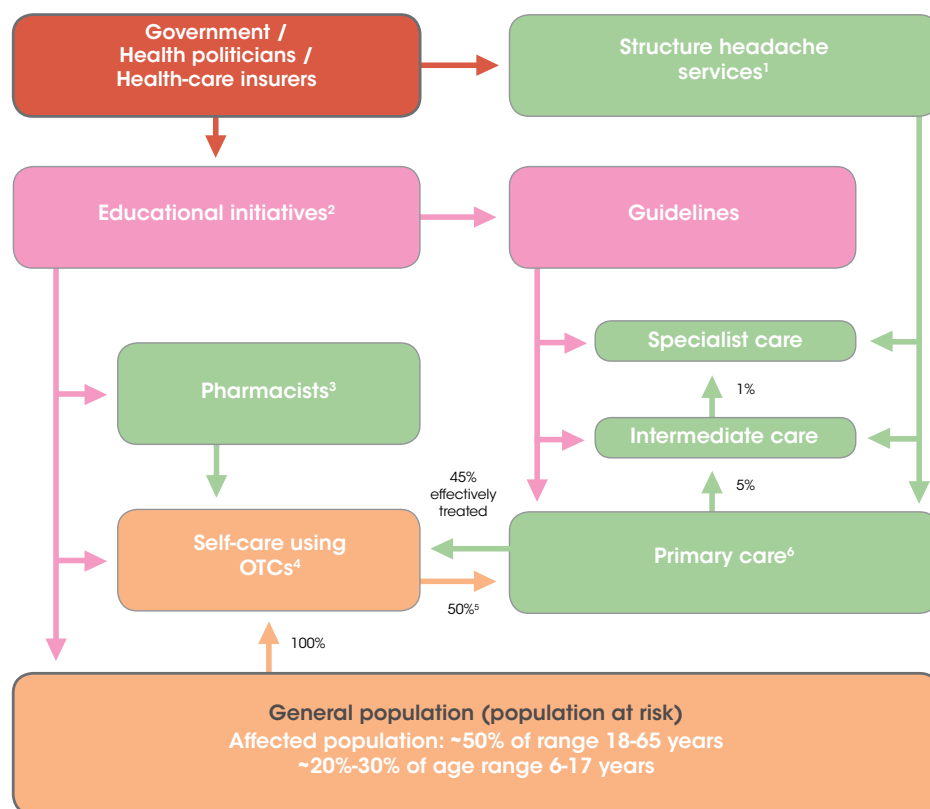


Figure 1: Proposed solution: structured headache services, and patients' journey

### Notes:

1. Structured headache services are based in primary care and supported by specialist care.
2. Educational initiatives are aimed at health-care providers to improve competence at their level, and at the public to promote self-care and effective use of both over-the-counter (OTC) drugs and headache services.

3. Pharmacists advise on use of OTC and other drugs, discouraging overuse, and on use of headache services.
4. Within these services, everyone with headache should make best use of OTC drugs.
5. About 50% of people with headache need professional health care.
6. Primary care provides effective management for most of these; specialist care is reserved for the small proportion who need it.

## Methods

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 [2,3], GBD surveys [4,5] and earlier estimations using the WHO-CHOICE model [6]. 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, cost-effectiveness as incremental cost-effectiveness ratios (ICERs) (cost to be invested/HLY gained). Scenarios for comparison were baseline (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 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.

## Results

In the 1-year time frame from the provider perspective, the intervention is cost-effective across headache types – well below WHO thresholds (ie, interventions costing  $<3x$  gross domestic product [GDP] per capita per HLY are cost-effective, those costing  $< GDP$  per capita are highly cost-effective) (Figure 2) [6]. Over 5 years the intervention is even more cost effective (Figure 3). Results are consistent across health-care systems. From the societal perspective the intervention is not only cost-effective but also cost-saving, for all headache types and health-care systems, at 1 and 5 years (Figure 4). The higher the country's wage level, the greater the economic savings for society (Luxembourg  $>$  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 (Figure 5). For TTH, predicted savings from productivity gains are smaller than estimated investment costs in Russia and Spain, but the intervention is still cost-effective [6]. In Luxemburg it remains cost-saving.

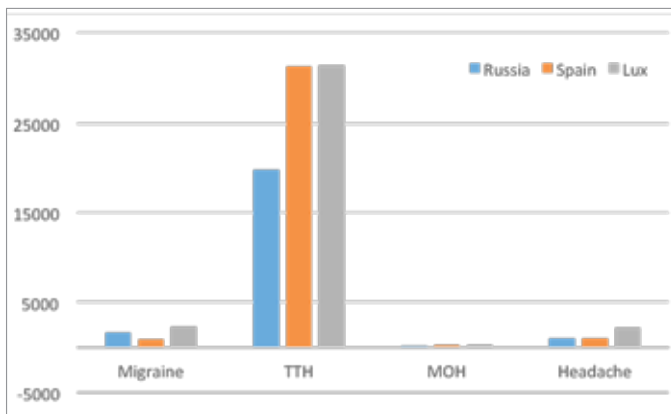


Figure 2: ICER (euros spent for each HLY gained) at one year (health-care perspective)

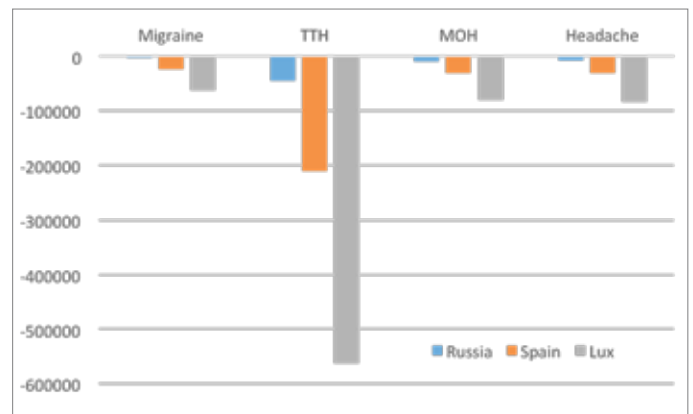


Figure 4: ICER at 5 years (societal perspective)

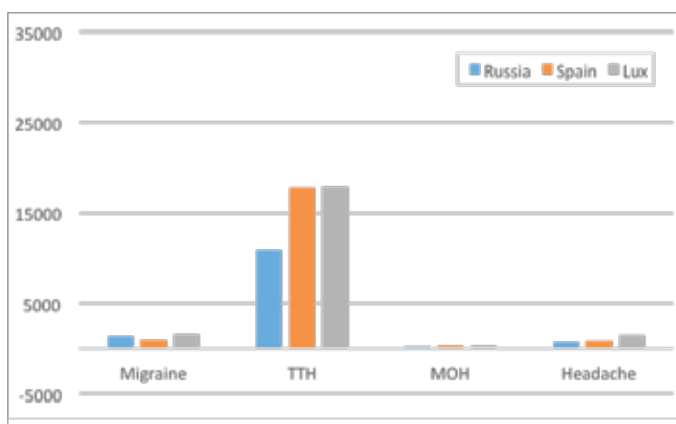


Figure 3: ICER at 5 years (health-care perspective)

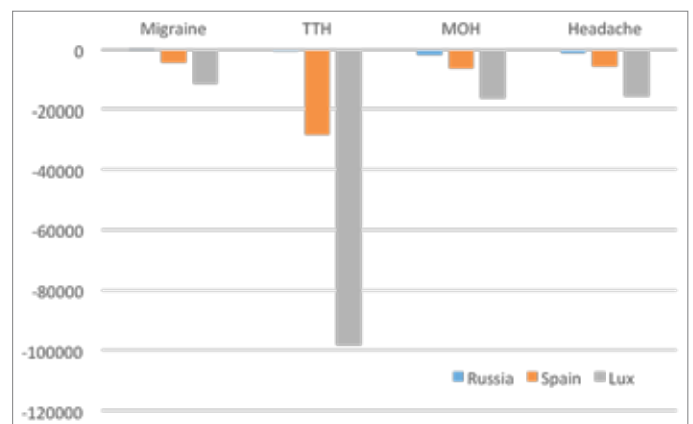


Figure 5: ICER at 5 years (societal perspective, conservative scenario: remedied disability recovers only 20% of lost productivity)

## Conclusions

Structured headache services supported by patient and provider education are effective and cost-effective solutions to headache and its long-term disability. Cost-effectiveness is least (ICERs greatest) for TTH because of its much lower disability weight compared with those for migraine and MOH [4]. In practice, structured headache services will not discriminate: they must manage all headache types; however, people with TTH are least likely to require them.

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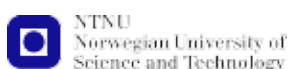
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<http://www.braincouncil.eu/activities/projects/the-value-of-treatment/Headache>



# Improving the quality of stroke care

Fonseca AC<sup>1</sup>, Webb A<sup>2</sup>, Randall G<sup>3</sup>, Thijs V<sup>4</sup>, Berge E<sup>5</sup>, Frazekas F<sup>6</sup>, Norrving B<sup>7</sup>, Vanhooren G<sup>8</sup>

<sup>1</sup>Universidade de Lisboa; <sup>2</sup>University of Oxford; <sup>3</sup>Stroke Alliance for Europe (SAFE);

<sup>4</sup>Florey Institute of Neuroscience and Mental Health, University of Melbourne; <sup>5</sup>University of Tromsø;

<sup>6</sup>European Academy of Neurology (EAN); <sup>7</sup>Lund University; <sup>8</sup>European Stroke Organization (ESO)

## Background

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. 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. Furthermore, stroke results in post stroke dementia, depression, epilepsy and falls that cause substantial morbidity and economical costs. Strokes are more likely to occur with ageing, 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.

## Methods

In this study we describe the key issues and unmet needs along the patient pathway, based on research methodology defined by the Rotterdam Institute of Health Policy and Management for the “patient journey” analysis. We gathered data from a literature review, stroke experts, patients’ associations and neurological scientific societies. We propose recommendations on how to improve stroke care in the future through the delivery of evidence-based interventions within the stroke unit.

## Treatment Gaps

**INADEQUATE TREATMENT OF ATRIAL FIBRILLATION (AF).** Patients with AF have an increased risk of ischemic stroke that is five times higher than the risk of patients without this arrhythmia. AF is estimated to be responsible for 15 % of all strokes. Most of these strokes could be avoided through improved detection and use of anticoagulants. Although anticoagulation in AF patients is recommend by the European Stroke Organization (ESO), low rates of prescription can still be found in several European countries, including UK (53%), Sweden (53%), Poland (41%), and Greece (41%).

**LOW IMPLEMENTATION OF STROKE UNITS** STROKE UNITS are multi-disciplinary units devoted to care of stroke patients. They provide a wide range of 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. ESO strongly recommends the establishment of stroke units. Still, the implementation of stroke units is inadequate across Europe due to cost barriers, lack of trained staff and limited provision of specialised facilities.

**LOW ACCESS TO REHABILITATION.** Many stroke survivors experience functional deficits that make them dependent for their daily tasks. Rehabilitation aims to enable people with disabilities to regain physical, intellectual, psychological and/or social function. The rehabilitation process from a stroke starts in a stroke unit and frequently needs to be continued after the patient is discharged from the hospital. It has been showed that continued rehabilitation after discharge during the first year after stroke reduces the risk of disability.

## 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. 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.

## Patient testimonies

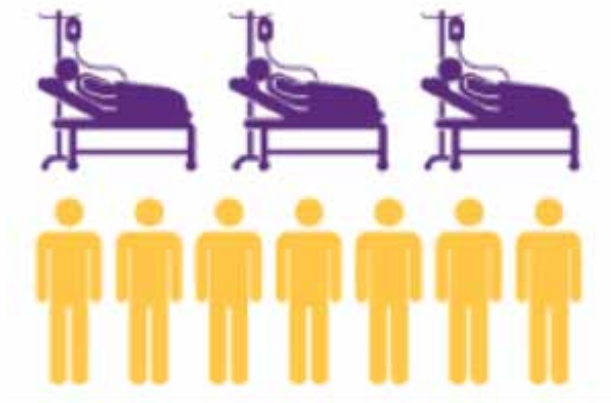
**Before** "I never had thought before about that disease; I had no way of knowing, nobody in the family had ever had a stroke. I thought everything was fine and I was relatively young. I was 47." (Female stroke survivor, Austria)

**During** "While I was having a shower I suddenly felt like something had exploded in my head. I was not able to speak any more and I felt like the right side of my body had disappeared." (Female stroke survivor, Netherlands)

"I was lucky enough to be in a Clinic which is across the street from the Emergency Centre. The full diagnostic was done in the first hour of the onset of symptoms. I received thrombolytic therapy and recovered completely, as if I never had a stroke" (Male stroke survivor, Serbia)

**Afterwards** "The worst thing about it was that I had no understanding about stroke at all. No one had told me "you may feel like this, you may feel like that". No one explained to my partner what it was going to be like moving forward, what the consequences might be, or not be" (Male stroke survivor, UK).

**Across Europe, it is estimated that only 30% of patients receive stroke unit care.**



## Conclusions

Stroke is a leading cause of morbidity and mortality in Europe. To reduce the burden of stroke, major treatments gaps need to be addressed such as inadequate treatment of atrial fibrillation, low implementation of stroke units and low access to rehabilitation. Resources should be directed to improve primary prevention and secondary prevention and to optimize the current existing treatments for acute stroke.

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## Acknowledgements:

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<http://www.braincouncil.eu/activities/projects/the-value-of-treatment/stroke>





# Cost effectiveness analysis of full implementation of acute stroke treatments in the UK setting

Webb A<sup>1</sup>, Thijs V<sup>2</sup>, Fonseca AC<sup>3</sup>, Randall G<sup>4</sup>, Berge E<sup>5</sup>, Frazekas F<sup>6</sup>, Norrving B<sup>7</sup>, Vanhooren G<sup>8</sup>

<sup>1</sup>University of Oxford; <sup>2</sup>Florey Institute of Neuroscience and Mental Health, University of Melbourne; <sup>3</sup>Universidade de Lisboa;

<sup>4</sup>Stroke Alliance for Europe (SAFE); <sup>5</sup>University of Tromsø; <sup>6</sup>European Academy of Neurology (EAN); <sup>7</sup>Lund University;

<sup>8</sup>European Stroke Organization (ESO)

## Background

Stroke is the second leading cause of death and dependency in Europe and costs the EU > €30 billion in direct healthcare costs, and considerably more in indirect costs, yet there is a large gap in translating evidence of significant reductions in death and dependency in randomised controlled trials of acute stroke treatments to the real world. Across Europe, only approximately 30% of patients have access to acute stroke unit care, and there is wide variation in access to intravenous thrombolysis (clot-busting drugs) and mechanical thrombectomy [1]. Optimal acute stroke treatment, initiation of secondary prevention and transition to appropriate rehabilitation depends on access to Comprehensive Stroke Services. Therefore, we assessed the cost-efficacy of full implementation of such acute stroke treatments to the maximum extent possible in the population, using the UK as a model, compared to available evidence in other European settings.

## Methods

The primary intervention assessed was the provision of Comprehensive Stroke Services through an acute stroke unit, providing optimal acute stroke care, secondary prevention and transition to rehabilitation in accordance with current guidelines and best practice. The expected summative effect and cost of interventions were estimated, and compared to the expected outcomes and costs from non-provision of these interventions. Clinical efficacy data was taken from available meta-analyses of randomised controlled trials for each intervention [2,3], with expected ideal rates of uptake estimated from published registry data and expert opinion. Costs of interventions, hospital costs and cost of resulting death and dependency were taken from extensive reports available for the UK [4]. A Markov model was used to calculate cost-effectiveness of full implementation of acute stroke treatment, expressed in Quality Adjusted Life-Years (QALYs), with a life-time horizon. The model outcomes were total costs, total QALYs, incremental costs, incremental QALYs and the incremental cost-effectiveness ratio (ICER). Sensitive analyses for variation in cost-effectiveness for variation in estimated costs and benefits were performed. Results were compared to published cost-effectiveness analyses in a systematic review.

## Results

### EFFECT OF INTERVENTION

Full implementation of acute ischemic stroke treatments to the maximum extent possible led to absolute reductions in death or dependency at six months after stroke of 97.5 patients per 1000 acute ischemic stroke patients treated (NNT=10.3). The rate of dependency in the intervention group was 25.9% versus 29.8% in the group in which none of the interventions was performed. Mortality rates were 11.8% versus 14.4%. The comparable estimated QALYs were 3.38 vs 3.14.

### MEDICAL RESOURCE CONSUMPTION

The average cost of intervention was £9,566 versus £6,640 in the standard of care group. The average length of stay was updated to UK average length of stays in 2015. The medical resource consumption per year after the first six months period was £1938 in the independent state and £5782 in the dependent state. Overall, taking the base case example, the total costs of care in the intervention group were £41,071.32, compared to £36,820.38 in the non-intervention group.

### COST-EFFECTIVENESS

The intervention was cost effective with an ICER of £17,437.82, (incremental change: QALY=0.2438; cost=£4,251) below the standard cost-effectiveness threshold of £30,000 or a conservative threshold of £20,000. This was highly robust in sensitivity analyses, being affected by increasing patient age, increasing cost of intervention and degree of disability at 6 months. However, the intervention was estimated to be cost-beneficial in 4.9% of sensitivity analyses, and only dominated by non-intervention in 24.8% of probabilistic sensitivity analyses, and was likely to be cost-effective despite using the most pessimistic input parameters.

### COMPARISON TO OTHER PUBLISHED REPORTS

In cost-effectiveness analyses of large UK stroke service reorganisations in the UK, systematic implementation of stroke unit care services was cost-effective with an ICER of £5500 per QALY [5], with subsequent initiation of hub-and-spoke acute stroke services in London resulting in an estimated cost-saving of £811 per patient, consistent with multiple European settings.

Intervention	Population applicable	NNT (mRS 3-6)	Number prevented
Acute stroke unit care	1000	18	56
Thrombolysis	250	40	10
Endovascular clot retrieval	100	5	20
Early aspirin	650	71	9
AF detection and treatment	1000	34	1.5
Carotid endarterectomy	100	142	0.7
<b>Total</b>	<b>1000</b>		<b>97.5</b>

Table1: Estimated benefits of acute stroke interventions and initiation of secondary prevention Strategies from published randomised controlled trials.

Acute Treatment Costs	Intervention Group	No intervention group
Hospitalization cost	4916.98	5354.05
Thrombolysis	537.91	0.00
Carotid endarterectomy	473.50	0.00
Clot retrieval	886.19	0.00
Stroke specialist	274.00	0.00
Occupational therapist	102.00	0.00
Physiotherapist	170.00	0.00
Speech and language therapist	68.00	0.00
Social worker	40.00	0.00
Early aspirin	2.03	0.00
Early anticoagulation	106.40	0.00
Late aspirin if no anticoagulation	37.63	0.00
Nursing home	525.64	525.64
Inpatient rehabilitation	1285.58	1285.58
Monitoring for AF	140.08	0.00
<b>Total Acute costs per patient</b>	<b>9565.94</b>	<b>6639.62</b>
<b>Incremental costs per patient</b>	<b>2926.31</b>	

Table 2: UK costs (2015) for provision of interventions associated with Comprehensive Stroke Services

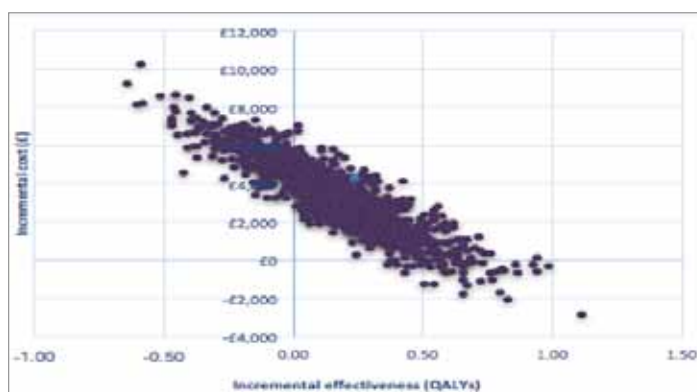


Table1: Estimated benefits of acute stroke interventions and initiation of secondary prevention Strategies from published randomised controlled trials.

## Conclusions

This analysis suggests that full implementation of stroke services would be a cost-effective treatment for acute ischemic stroke in the United Kingdom healthcare setting. This is consistent with reports from multiple European healthcare settings. The model compared ideal implementation of services compared to no service provision and is therefore readily translatable across Europe, dependent upon local costs of intervention.

Although provision of Comprehensive Stroke Services represents a significant logistical and financial challenge, the ultimate benefits are likely to be extensive, both in terms of cost and in terms of the total burden of death and disability due to stroke in the European population.

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This work was supported by BMS-Pfizer Alliance. We would like to thank Charles Faid (Pfizer Inc.) and Stephanie Roso (Pfizer Inc.) for their contribution to this work. A digital version of the poster and other supporting documents are available here:

<http://www.braincouncil.eu/activities/projects/the-value-of-treatment/stroke>



# Patient journey for people with Alzheimer's disease

Sikkes SAM<sup>1</sup>, Handels R<sup>2,3</sup>, Vermunt L<sup>1</sup>, Scheltens P<sup>3</sup>, Quoidbach V<sup>4</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; <sup>4</sup>European Brain Council (EBC)

## Background

Dementia is characterized by a decline in memory, thinking, behavior and the ability to perform everyday activities. Ultimately, dementia leads to a loss of independence and an increasing need for support by others. In Europe, currently an estimated 10.5 million people have dementia, and this number is expected to increase to 18.66 million in 2050 [1], which makes dementia one of the most challenging healthcare and socio-economic problems society currently faces. In 70% of the people with dementia, Alzheimer's disease (AD) is the underlying cause. In search of disease modifying treatments, research has increasingly focused on the pre-dementia stages of AD, which develop along a continuum from healthy asymptomatic, to the first symptoms such as memory complaints, to mild cognitive impairment (MCI) and subsequently to different stages of AD (mild, moderate, severe). It is yet unknown how an early diagnosis or such early treatments would affect patient and caregivers in clinical practice. We therefore aim to characterize the patient journey, by describing the patient and caregiver needs in the different AD disease stages and the potential effect of an hypothetical early intervention.

## Methods

We used three different sources for the patient journey. First, Alzheimer Europe described care pathways to diagnosis and post-diagnostic care and support for people with dementia in 2014, which incorporated information from 30 European countries [2]. Whilst this work was specifically for people who have already symptoms of dementia, many of the conclusions from this work are also relevant to the pre-dementia stages. Second, as part of the VoT project, we performed interviews with people experiencing cognitive decline and their caregivers at the VUmc Alzheimer Center, Amsterdam, the Netherlands in 2016. Our target population for the interviews consisted of people in the early stages of AD, along the entire disease spectrum. We interviewed six participants, consisting of a person with subjective cognitive decline (SCD) and his caregiver, a person with MCI, a person with AD (young-onset) and his caregiver and a caregiver of a person with AD (late-onset). Third, the patient journey was further discussed in the VoT workgroup (April 22nd, 2016). Based on the available evidence, we identified two important treatment gaps: diagnosis and treatment.

## Treatment gaps: diagnosis and treatment

**Diagnosis** is a critical stage for people with dementia and their families, as it may provide access to treatment and support. 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 late moderate stage [3,4]. In most European countries the general practitioner (GP) is the gateway to diagnosis, but the diagnosis is mostly made by specialists including neurologists, psychiatrists and geriatricians. The most common barriers to the diagnosis of dementia include the lack of specialists, the long waiting lists, the variable provision of and access to diagnostic services in the country, the lack of guidelines and of clear pathways before and after diagnosis. GP's training and expertise in recognizing and managing dementia may be another relevant factor contributing to missed or delayed diagnosis [5,6]. Finally, lack of awareness about dementia (among the public and GPs) and the social stigma attached to the disease were perceived as important obstacles to diagnosis. This was also recognized in the patient journey interviews (see Box 1). Regarding **treatment**, care and support needs of the individual with dementia are not systematically monitored, with most countries reporting an "on demand" approach. Also, the type of information and the time at which people with dementia and their families receive information greatly varies among countries. It is often reported that information provided by GPs depends on their own knowledge and attitudes and may therefore not be consistent. Similarly, whilst social workers and community nurses are also relevant providers of information and may facilitate access to relevant services, these professionals are often consulted only when care needs arise. This suggests that, too often, care and support systems are crisis driven rather than preventive and proactive (see Box 2). The results are summarized in Figure 1.

## Recommendations

Based on our inventory we have the following six policy recommendations:

1. Increase awareness and understanding of early and at risk stages of AD. This would include a broad recognition of these stages as part of the disease spectrum, the burden of (early) AD, addressing stigma and fear of the disease.
2. Timely and accurate diagnosis. There is an urgency to ensure a rapid diagnosis to reduce long periods of uncertainty in patients and caregivers.
3. Improve access to diagnostic services and care. This would include training for GPs to address the diagnostic gap.

## Box 1 Diagnosis - patient journey interviews

“people distance themselves and are not very understanding when you experience cognitive problems. I became very lonely” (individual with MCI)

“not knowing what’s wrong is very frustrating, a diagnosis should be made sooner” (individual with MCI)

“[the long trajectory of the diagnostic process was] a very difficult period of my life” (individual with AD)

‘...receiving the diagnosis actually helped in a way; I now know it’s not me [...], it’s the disease’. (individual with AD)

## Box 2 Treatment - patient journey interviews

Both patients and caregivers mention knowledge gaps as an important limitation in receiving adequate care from the GP

‘I had a separate conversation with the psychologist during the follow-up, which I thought was very worthwhile’ (caregiver of individual with SCD)

“[By going to the University hospital] I can meet other people with dementia, I can participate in and contribute to scientific research. There is this whole community of people with dementia that attend lectures for laymen’ (individual with AD)

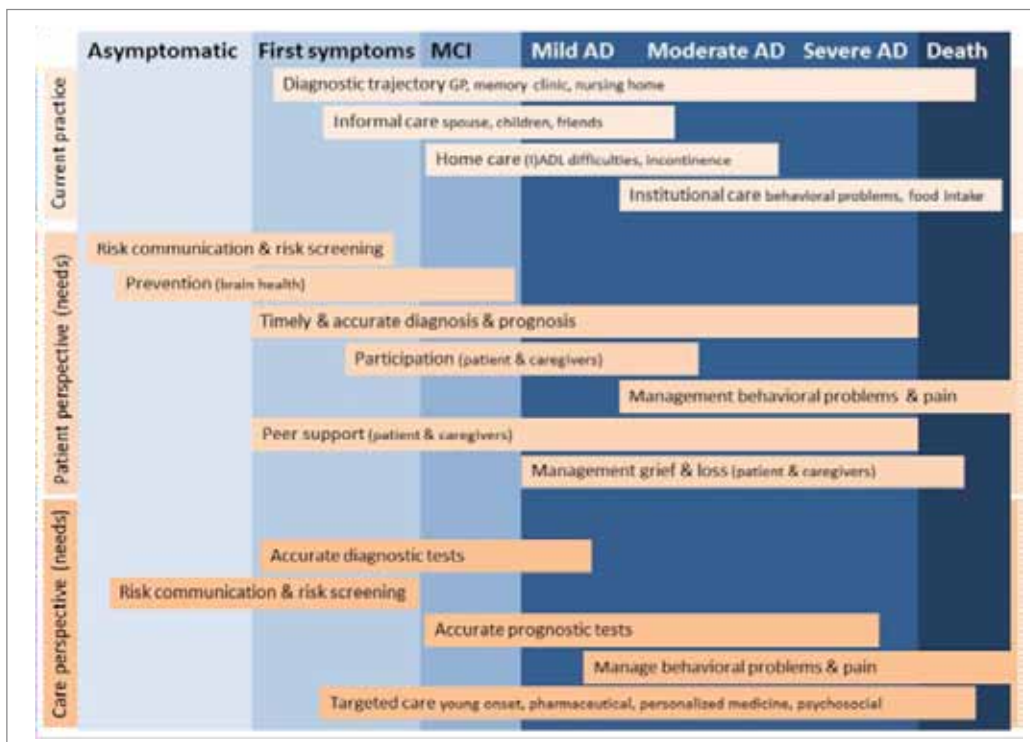


Figure 1: Patient journey treatment gaps and care needs along the continuum of AD

4. Ensure access to support for people with (early) AD following diagnosis. Navigating the care system is often perceived difficult, and should be improved.
5. Support the development of a comprehensive patient care pathway for the entire AD spectrum. This would need to include the patient and caregiver perspective.
6. Support and promote dementia research. This would lead to improved diagnostics and speed up the development of new promising therapies

## Conclusions

The patient journey for people with or at risk for AD is characterized by a long diagnostic process, which can be improved by increasing awareness, understanding and access to diagnostic services and care. Care and treatment is not provided systematically, and navigating the care system is difficult. We provided recommendations for improving diagnosis and treatment, that will affect the entire continuum of AD.

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## Acknowledgements:

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<http://www.braincouncil.eu/activities/projects/the-value-of-treatment/Dementia>



# Potential health-economic impact of treating Alzheimer's Disease (AD)

Handels R<sup>1,2</sup>, Sikkes SAM<sup>3</sup>, Vermunt L<sup>3</sup>, Scheltens P<sup>3</sup>, Knapp M<sup>4</sup>, Visser PJ<sup>1,3</sup>

<sup>1</sup>Maastricht University; <sup>2</sup>Karolinska Institutet; <sup>3</sup>VU University Medical Center Amsterdam; <sup>4</sup>London School of Economics (LSE)

## Background

In Europe, currently an estimated 10.5 million people have dementia, which is characterised by a decline in memory, thinking, behaviour and the ability to perform everyday activities. This not only affects persons' quality of life, it is also associated to large care-related costs. The largest costs are related to long-term care facilities and informal care. Developments in disease-modifying treatments have shifted towards early pre-dementia intervention in order to prevent a person from progression to dementia. Persons with subjective cognitive decline or mild cognitive impairment are among the target population potentially eligible for future treatment. Such treatments have the potential to reduce the dementia-related burden and associated care costs.

**The aim of this study** was to develop a health-economic model that assesses the potential value of disease-modifying treatment for people with amyloid pathology who have not yet developed AD dementia.

## Methods

We constructed a Markov model to simulate the disease progression, costs and quality-adjusted life years (QALY) of a virtual cohort over a 25-year period. The baseline simulation cohort reflected persons who visited a memory clinic and had normal cognition or a diagnosis of MCI, and were tested positive on amyloid beta. Costs in the health care sector (medical, home care, institutionalized care and informal care) were included to reflect a societal perspective.

A strategy in which a hypothetical disease-modifying treatment (DMT) was initiated to a virtual cohort of 10,000 persons with subjective cognitive decline (SCD) or mild cognitive impairment (MCI) with positive amyloid beta was compared to the control strategy reflecting care as usual. Transition probabilities between the pre-dementia states were estimated based on data from the DESCRIPA, ADNI and ADC studies, and from a previously developed model by Green et al. [1]. Costs were obtained from the ICTUS study [2].

We assumed a 50% reduction of the progression to dementia due to the DMT, no treatment costs, no side effects, state-dependent mortality and a 3.5% discount rate.

## Results

The results indicated that early identification and disease-modifying treatment of AD provides a window of opportunity to prevent progression to stages that affect activities of daily living when disease-modifying interventions are available in clinical practice.

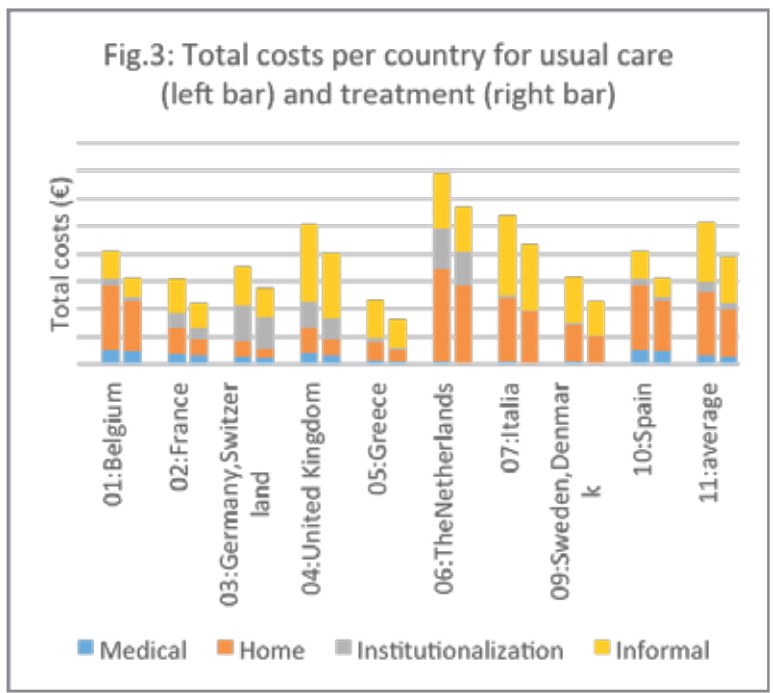
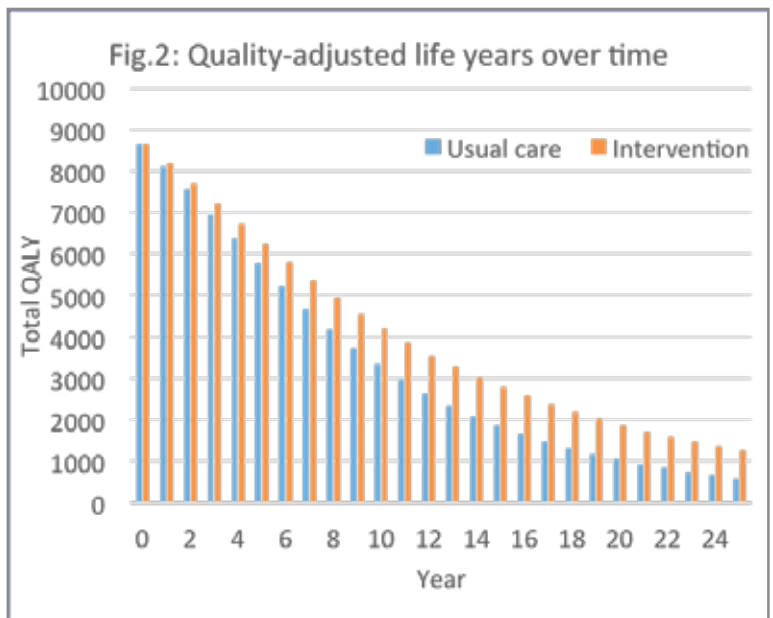
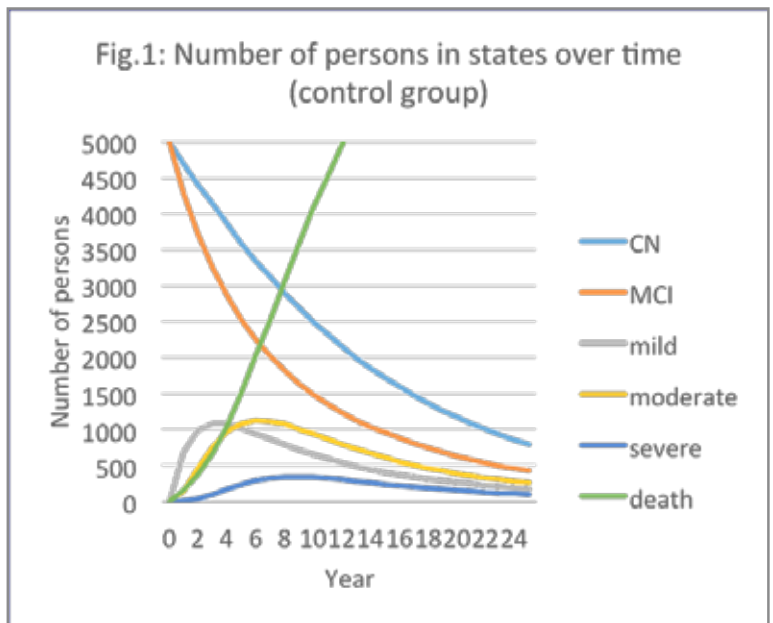
Reducing AD progression in pre-dementia by 50% was estimated to maintain persons longer with NC and MCI. This resulted in a smaller proportion of persons living with mild, moderate or severe dementia. Because mortality was lower in pre-dementia states, people were estimated to live longer (see figure 1 for the number of persons in states over time in usual care).

Reducing AD progression was estimated to increase the total of quality-adjusted life years (QALYs), both due the higher quality of life of living with less severe disease states as well as increased life years (see figure 2).

Slower progression in the treated cohort resulted in reduced care-related costs. The average total costs over the 25-year time horizon varied across European countries (Netherlands highest, Greece lowest), although the majority of the costs were attributed to home/day care, long-term institutional care and informal care (see figure 3).

However, results were dependent to our assumptions regarding mortality. Sensitivity analysis showed the outcomes were sensitive for assumptions on treatment effectiveness, mortality and treatment duration (see table 1). Assuming a flat mortality rate of 10% resulted in a larger cost savings of € 20,351 per person over lifetime versus 12,406 under the assumption of state-dependent mortality.

This study showed the importance of considering a societal perspective with regard to the possibility to finance treatment from savings in other care sectors as the savings in the medical sector reflected only a proportion of the total savings. However, a large reduction of the savings originated from the value that was placed on informal care, which might not fully reflect transferable resources to finance treatment.



## Conclusions

The simulation study showed the potential of early intervention with pharmacological treatment in persons with SCD and MCI with regard to improving QALYs and reducing care costs. The results were, however, sensitive to assumptions among which a state-specific or flat mortality rate.

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# Normal Pressure Hydrocephalus:

## A treatable but often not treated disease

Kehler U<sup>1</sup>, Kistner B, Guldemond N<sup>2</sup>

<sup>1</sup>Asklepios Klinik Altona, Hamburg, Germany; <sup>2</sup>The Institute of Health Policy & Management (iBMG) Erasmus University

## Background

Normal pressure hydrocephalus (NPH) is a brain disorder, which affects mainly people above the age of 65. NPH prevalence is over 5% in elderly [1]. Moreover, it is also estimated that 5% to 10% of patients with dementia, including Alzheimer's disease, are actually effected by NPH [2,3]. Given 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 and which often leads to dependence of help in daily activities, a higher risk of falls and an earlier transition to nursing homes [4,5].

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, a large proportion does not even get any.

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 [6,7].

This study aimed to identify unmet needs and key issues throughout the course of the disease, which prevent NPH patient to receive adequate and timely treatment.

## Methods

This study aiming at an inventory of patients' needs along the development of their disease for people with the condition 'Normal Pressure Hydrocephalus', in order to identify the key issues for improvement and formulate policy recommendations accordingly. The needs and key issues from a patient perspective during different disease stages has been collected through patient journey mapping, as part of a service design methodology. The service design methodology followed an iterative approach (various stakeholder consultations) to define

usual care and an optimised scenario which was further substantiated by a literature review. The relation between identified needs and issues and various care aspects were discussed: both from a work floor and a healthcare system perspective. Accordingly, possible solutions were suggested and discussed among the stakeholders for mutual agreement.

## The Care pathway: Treatment Gaps and Unmet Needs

**MIS- (OR DELAYS IN) DETECTION/DIAGNOSIS.** This 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.** 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 much longer independent [8–10].

**INADEQUATE TREATMENT 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.** 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 poses also problems for the patient, family and informal caregivers in the different disease stages. Finding relevant information at the early onset of the problems related to NPH reduce anxiety and uncertainty. Information is essential for self-management and patient/family education. Also communication and information sharing is a key aspect of peer support and shared decision-making [11].

## Recommendations

**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 OF 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 patients having access to the most optimal quality of care.

**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 centers.

“I was treated 10 years for Parkinson´s Disease before somebody told me I do have Normal pressure hydrocephalus.”

“My doctors told me, I have to live with my walking problems, there is no treatment. Then I read the article in the newspaper about Normal Pressure Hydrocephalus and I recognized myself. After getting treatment, I can participate at my social life again...”

“The radiologist told me this is brain atrophy. When I showed it to a NPH-specialist, he told me it is very likely NPH. After testing and treatment I got back to almost normal life.”

“Patients with NPH costs too much time in my office, it is not worthwhile for my budget to occupy with this disease.”

## Conclusions

Normal Pressure Hydrocephalus is a treatable but often not treated disease, resulting in unnecessary and avoidable disease burden for both the patient and his loved ones as well as for the healthcare system. The actions required for closing this treatment gap are straightforward but need the support from all stakeholders involved at a regional, national and European level: including the endorsement of governments and responsible authorities.

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## Acknowledgements:

We would like to thank you Giovanni Esposito and Vinciane Quidbach for their contribution to this work. A digital version of the poster and other supporting documents are available here:

<http://www.braincouncil.eu/activities/projects/the-value-of-treatment/NPH>



# The cost effectiveness of addressing treatment gap in Normal Pressure Hydrocephalus patient population

Tinelli M<sup>1</sup>, Kehler U<sup>2</sup>

<sup>1</sup>London School of Economics (LSE); <sup>2</sup>Asklepios Klinik Altona, Hamburg, Germany

## Background

Normal pressure hydrocephalus (NPH) is a treatable but underdiagnosed condition. The number of diagnosed patients will probably increase in the future which may challenge allocation of resources to secure long term benefits of the shunt surgery. Shunt surgery is successful in most patients and it is reported that more than 85% of operated patients improved their health related quality of life (HRQOL), almost to the same level as found in the normal population [1]. However, there is very limited evidence of the cost-effectiveness of treatment for iNPH [1-4] and no data are available on the socio economic impact of delivering timely and adequate NPH treatment in Europe.

## Methods

We calculated the cost effectiveness of delivering shunt surgery to NPH prevalent patients with 65 years old or more in Germany (about 34,000) patients. The model compared two alternatives, current care (25% of NPH patients receiving shunt [4]) vs. target care (90% of NPH patients receiving shunt). The model (see figure 1) looked at health care costs (diagnosis, shunt intervention and follow up care, i.e. visits, hospitalisation, nursing care) from the public health insurance perspective. Effectiveness outcomes were also considered (in terms of lives saved and quality adjusted life years, QALYs). Cost effectiveness is reported as cost to be invested/QALYs (quality-adjusted-life-years) gained (incremental cost effectiveness ratio [ICERs]). The modelling covered different timeline of treatment (5, 10, 15 years as lifetime). Epidemiological data [5-7] as well as survival [8], quality of life [9] and economic [10-11] data were sourced from the literature, and expert were asked their opinion when evidence was not available (e.g. shunt success rate, use of resources, unit costs for specialist visits).

## Results

Delivering shunt surgery was more costly and the economic costs increased at longer term for the increased longevity of the NPH patients and their prolonged access to long term care (figure 2). Effectiveness data showed gain in QALYs and lives saved at all time points. Overall shunt surgery proved to be cost-effective across time (5-10-15 years) in terms of both cost per life saved (27,900 -111,000 -247,000 Euros) and cost per QALY (10,200 - 22,000 - 35,100 Euros).

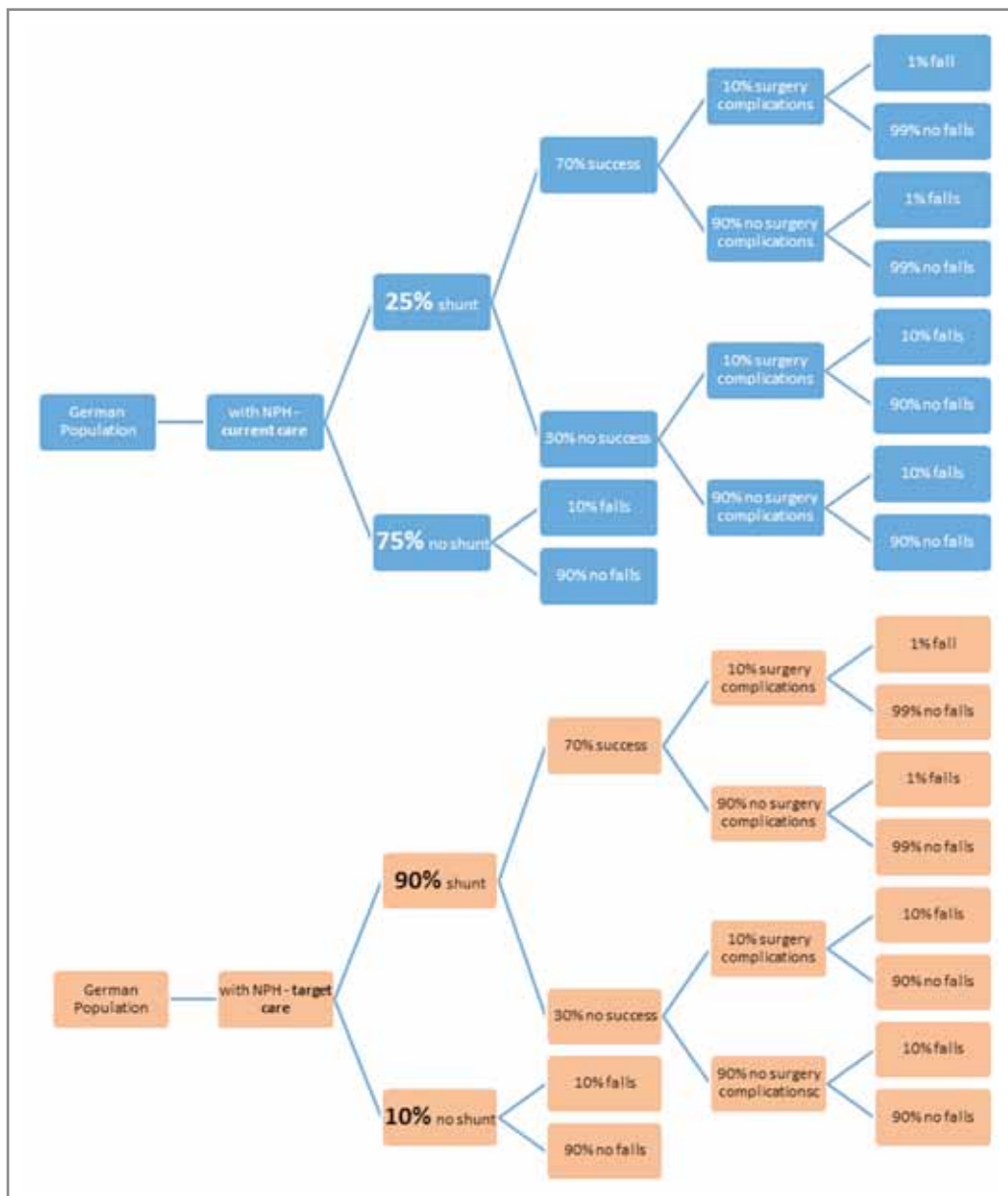


Figure 1: Decision tree

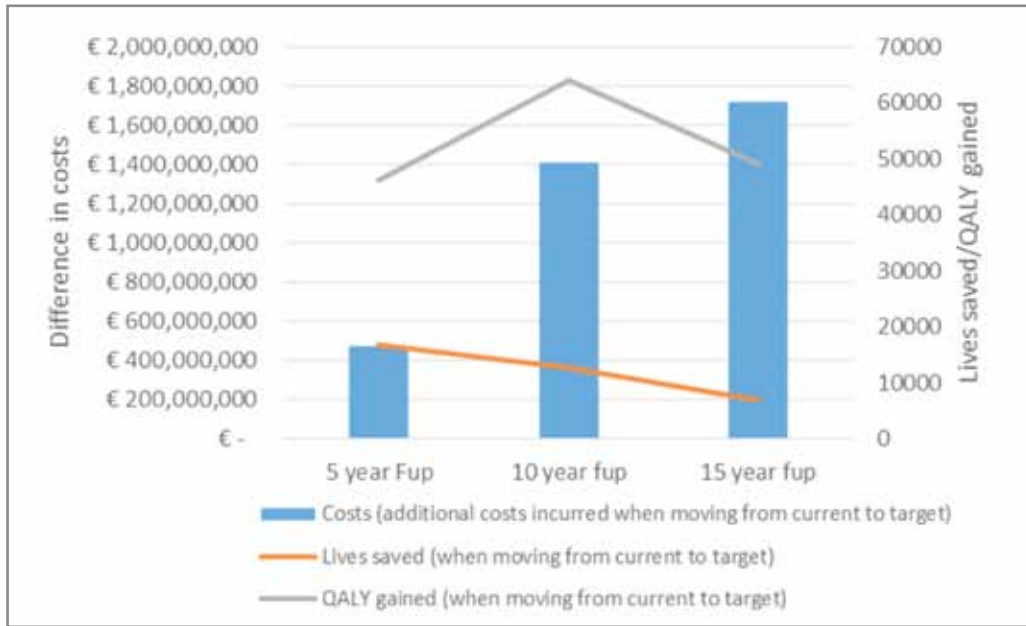


Figure 2: Difference in cost and effectiveness indicators when shifting to target NPH model of care

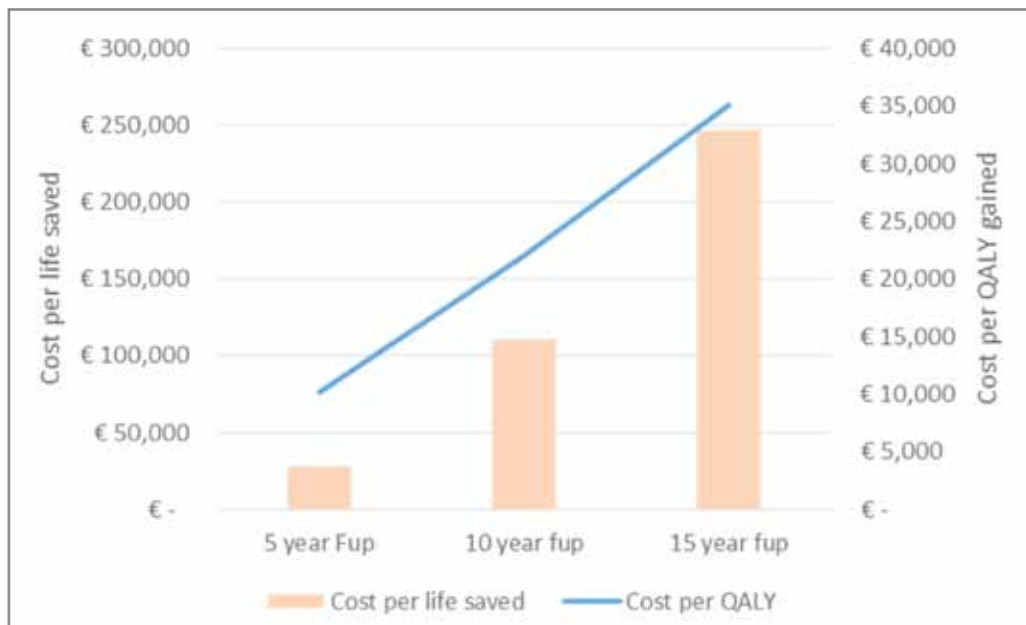


Figure 3: Difference in cost and effectiveness indicators when shifting to target NPH model of care

## Conclusions

From the preliminary result of the model, it can be concluded that shunt treatment in iNPH is cost-effective. The estimated average ICER of £10,000-35,000 Euros per gained QALY is below the UK National Institute for Health and Care Excellence (NICE) acceptance level of £20,000 for cost-effective interventions.

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# Parkinson's Disease Patient Journey

Ahmerkamp-Böhme J<sup>1</sup>, Petersen G<sup>2</sup>, Deuschl G<sup>3</sup>, Flanagan E<sup>3</sup>, Graham L<sup>5</sup>, Oertel W<sup>3</sup>,  
Guldemand N<sup>6</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); <sup>6</sup>The Institute of Health Policy & Management (iBMG).

## Background

Parkinson's Disease (PD) is a chronic progressive disorder of the central nervous system. Approximately 1.25 million people (mainly elderly) are affected in Europe and the figure is expected to double within the next twenty years. The diagnosis is mainly based on the following cardinal symptoms: rigidity, tremor, bradykinesia and impaired postural reflexes. Whereas the symptoms can easily be controlled in the first years, PD may lead to a considerable loss of quality of life, to care dependency and disability in the advanced stage. The financial burden for both, the patient (and his family) as well as the society, is enormous. Currently, about 12% of the European budget for neurological diseases is spent for PD which is the second most common neuronal disease after Alzheimer's disease.

## Methods

A multi-disciplinary team with patient representatives, clinical experts, health economic experts and industry partners worked together from May 2016 until June 2017 to evaluate diagnosis and treatment gaps of PD in Europe to identify best practices and solutions for better PD care models in Europe to prepare recommendations how to implement proposed solutions. A detailed patient journey matrix has been prepared to identify the current gaps of PD care – starting from prevention, screening/prodrom, early intervention, disease management, disability and rehabilitation, until end-stage management and palliative care. The most relevant issues have been identified by the team for further evaluation. Literature and research reports (like MyPD Journey research reports from EPDA<sup>2</sup> or what matters most? From Parkinson's UK<sup>2</sup>) have been used to identify best practices in Europe and to prepare recommendations for better PD care (Lit from NL and Israel). A sub-team has investigated the economic and quality of life impact of the identified treatment gaps on the patients and the society (see VoT PD poster economic evaluation).

## The Care pathway: Treatment Gaps and Unmet Needs

### 1. DELAYED OR INADEQUATE DIAGNOSIS

Although 50% of patients are diagnosed by a PD specialist, there is a high risk of a delayed or inadequate diagnosis. The range of PD symptoms is diverse and most symptoms are common to other diseases.

## 2. NO ADEQUATE TREATMENT

Adequate treatment of PD gets more and more difficult with the progression of the disease. Many aspects like age of a patient, change with individual symptoms, existing co-morbidities, potential of side effects of treatment have to be taken into consideration and require the knowledge of PD specialists. Currently, not every patient in Europe has access to PD specialists and new PD therapies (surgical techniques, pump therapies).

## 3. NON-ADHERENCE TO TREATMENT

PD patients frequently show poor adherence to prescribed therapies than they actually do. Better treatment adherence is important for patient's well-being and has a significant cost impact on the health care system.

# Recommendations

1. Better information and **active involvement of patients and caregivers** will help to identify the best possible treatment and will result in a better treatment-adherence.
2. **Improved communication and coordination** processes will help to establish integrated and multi-disciplinary care systems. Countries and regions that are leading in this respect might share their knowledge and their experiences.
3. Each patient should have **access to the best possible treatment and therapy** at each stage of the disease.
4. The **public needs to be better informed** about the complexity of PD and patient needs. Patients (especially the younger ones!) should not need to worry about stigmatization.
5. **More investment in research** including basic science, patient-oriented research and development of new treatment solutions is required. Currently, research allocations to brain disorders do not match with the socioeconomic impact of the disease as proposed by the European institutions.

## What matters to Patients and Caregivers?

### **Diagnosis**

"I was diagnosed 2 ½years ago, although I had it for five years. I went to 14 appointments with different neurologists and they all failed to recognise I had the disease [...]."

(Patient, Italy)

### **Treatment**

"They thought he may have a brain tumour. I have to say we were very unlucky with our neurologist. He sent us the diagnosis per fax...can you imagine? He did not even bother to call him in for a conversation."

(Carer, Germany)

### **Acceptance**

"He was sent home with a prescription and the Consultant told him they would make him feel better but we were not told about the side effects. First week was grand as it was a low dose, the second week was a nightmare cause of his blood pressure... One night I thought he was going to die in the bed on me. I can honestly say, in those initial years, he was over medicated."

(Carer, Ireland)

### **Coping**

"One thing which is difficult with Parkinson's is that it is so unpredictable. It varies so much from day to day, hour to hour so you just have to take every day as it comes."

(Carer, Ireland)

## Conclusions

Decision and policy makers are asked to act soon in order to face the financial and societal burden resulting from an increasing number of patients suffering from PD in Europe. A good balance is needed between cost effectiveness of PD diagnosis & treatment and the well-being of the individual. Due to the high complexity of the disease, better knowledge and well-coordinated care models are needed as already available in some countries in Europe. Support of politicians is requested to broadly implement available solutions and known best practices in all European member states.

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<http://www.braincouncil.eu/activities/projects/the-value-of-treatment/PD>





# The economic benefit of a timely, adequate, and adherent Parkinson's Disease treatment

Tinelli M<sup>1</sup>, Ahmerkamp-Böhme J<sup>2</sup>, Deuschl G<sup>3</sup>, Petersen G<sup>4</sup>, Oertel W<sup>3</sup>, Dodel R<sup>3</sup>

<sup>1</sup>London School of Economics (LSE); <sup>2</sup>Jung & Parkinson; <sup>3</sup>European Academy of Neurology (EAN); <sup>4</sup>Grünenthal

## Background

Parkinson's disease (PD) is a chronic progressive neurodegenerative disease affecting approximately 7 million people globally with devastating socioeconomic effects on individuals, their families and society. Total European costs of PD in 2010 alone accounted for €13.9 billion [1]. The global prevalence of PD is increasing over time and it is expected to double within the next 20 years (up to 2% in people over the age of 60 and 6% in people over 80 years [2]). The current investigation goes into more detail on major cost drivers based on the specific needs of the patients identified in the patients' journey. We have focused on three major topics: Lack of early/timely treatment; Lack of adequate treatment for advanced PD; and Lack of treatment adherence.

## Methods

**Lack of early/timely treatment.** The first economic analysis looked at the short term cost-effectiveness gains attached to treatment start at different stages in the patient journey (graded according to Hoehn and Yahr stages (H&Y) compared with no treatment. With a decision analytic modelling approach, we evaluated the impact of a hypothetical treatment (with fixed gain in effectiveness compared with no treatment as per published data of early PD interventions[3,4]) when given to patients at different health states (Hoehn and Yahr stages, H&Y). Annual cost estimates were reported for the societal perspective ([5] inflated to 2017 figures, Euros). Effectiveness was expressed in terms of Quality Adjusted Life-Years (QALYs) gains. Cost effectiveness was reported in terms of incremental cost effectiveness ratio (ICER). Published economic and QALY data for different H&Y stages [6] were used to create a matrix that enabled to attach annual societal costs [5] to different QALY values (health states; see figure 1). Sensitivity analyses were applied to test the robustness of the model according to variation in the QALY improvements (0.05-0.10-0.15 QALY) and intervention costs (zero up to 6 Euro daily). Two separate EU healthcare systems were considered, including Germany and UK.

**Lack of 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 analysis looked at direct costs (2017 figures, Euros) and QALYs comparing a current scenario where only a small proportion of eligible patients receive best treatment (2% on DBS+BMT) vs 88% on BMT vs 10% no treatment, with a target scenario where a larger number of patients receive best treatment (15% on DBS+BMT) vs 85% on BMT only (see figure 2).

Published economic evidence representing clinical progression and capturing treatment effect (QALY) and costs using Markov modeling techniques were used to provide long term (5 years) cost and QALY evidence for two different healthcare settings (Germany [7] and UK [8,9], discount rates 3% and 3.5% per annum respectively).

**Lack of treatment adherence.** A third set of analyses looked at the economic impact of: adherence to treatment (e.g. looking at the change in average patient healthcare costs according to level of adherence); and of a shift towards increased adherence to treatment in the PD patient community. With a decision analytic model (figure 4) we calculated the economic savings (2017 figures, Euros) when moving from status quo (current care) to a target scenario with improved adherence rates. Outcomes for the economic evaluation were healthcare costs (drug costs, A&E, hospitalisations, GP visits, day care and care home stay). A timeframe of 1.5 years was considered. Sensitivity analyses looked at grouping patients according to different definition of adherence (Duration of therapy, DOT, or medication possession ratio, MPR\*). Use of resources data were extracted from previous publications [10-12]. Unit costs for Germany and UK were sourced elsewhere ([13-16] and [17-18]). The perspective adopted was for the public health insurance (Germany) and NHS (UK).

*\*Duration of therapy (DOT) - it assesses the duration of time, or persistence that a patient is treated with APDs. DOT was measured as the number of days between the first and last filled prescription of all PDs and the days' supply of the last fill, date of death, or the end of 19 months or whichever came first. Medication possession ratio (MPR) - it assesses how regularly patients take APDs while in their possession. Calculated as the total days' supply from all APD classes (numerator) divided by the aggregate DOT of all drug classes (denominator).*

## Results

**Lack of early/timely treatment.** A short term modelling (one year time frame) suggests that the hypothetical PD treatment intervention is cost-effective regardless of the initial health state of the patient receiving the treatment (Germany cost savings between -1000 and -5400 Euros with 0.10 QALY gain; UK cost saving of -1800 and -7600 with 0.10 QALY gains, see Figure 2). When the treatment enables the patient to improve to a less severe H&Y stage (e.g. transitions from stage 2 to 1, from stage 3 to 2 or from stages 4/5 to 3; figure 2) it was found 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 stage 4/5 to 3) was more cost saving than from stage 3 to 2; e.g. -5400 Euros vs. -1030 Euros as economic impact of 0.10 QALY gain in Germany; -7600 Euros vs. -

6000 Euros as economic impact of 0.10 QALY gain in UK). Sensitivity analyses showed that the treatment remain cost-effective within the NICE thresholds (or cost-saving when shifting between H&Y stages) even the worst scenario (with the most costly intervention option). When doubling or tripling the treatment effectiveness from 0.05 to 0.10 or 0.05 to 0.15 the window of opportunity to move to a less severe H&Y stage increased proportionally. The findings were consistent across healthcare systems. If we extrapolate the results to model the economic impact of early/timely treatment on a longer period (5 years or more) we can anticipate that such practices would enable to decrease the related societal and health care costs across healthcare systems.

**Lack of adequate treatment for advanced PD.** 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; see table 1).

**Lack of treatment adherence.** Results showed that low level of adherence would correspond to an increase in annual patient costs (increase of 20-40% in Germany and 80-300% in UK depending on the definition of adherence used; see figure 5). More use of hospital and residential/nursing care home services were the main drivers of such increases. Meeting the target adherence to treatment rates would generate a cost saving of 239,000-576,000 euros (Germany) and 917,000-2,980,000 euros (UK) every 1000 patients treated adequately.

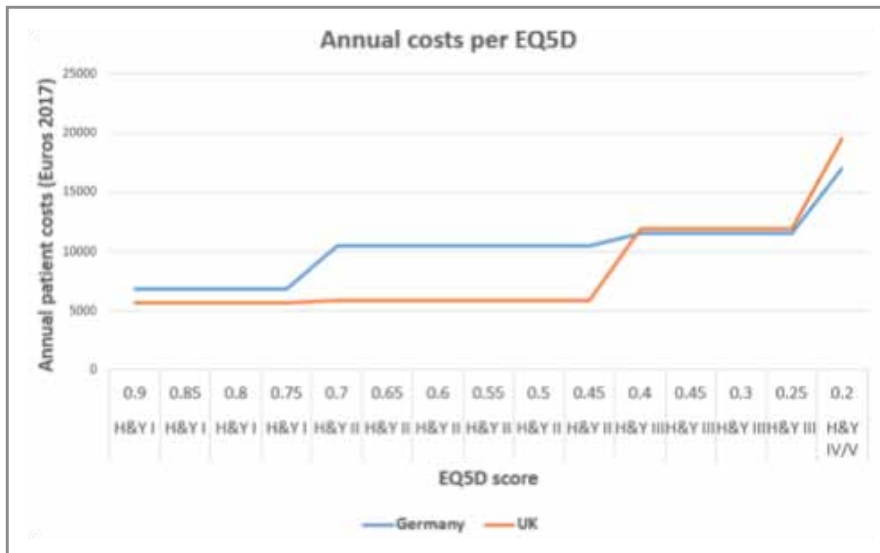


Figure 1: **Lack of early/timely treatment.** Annual costs according to EQ5D score/severity of the disease

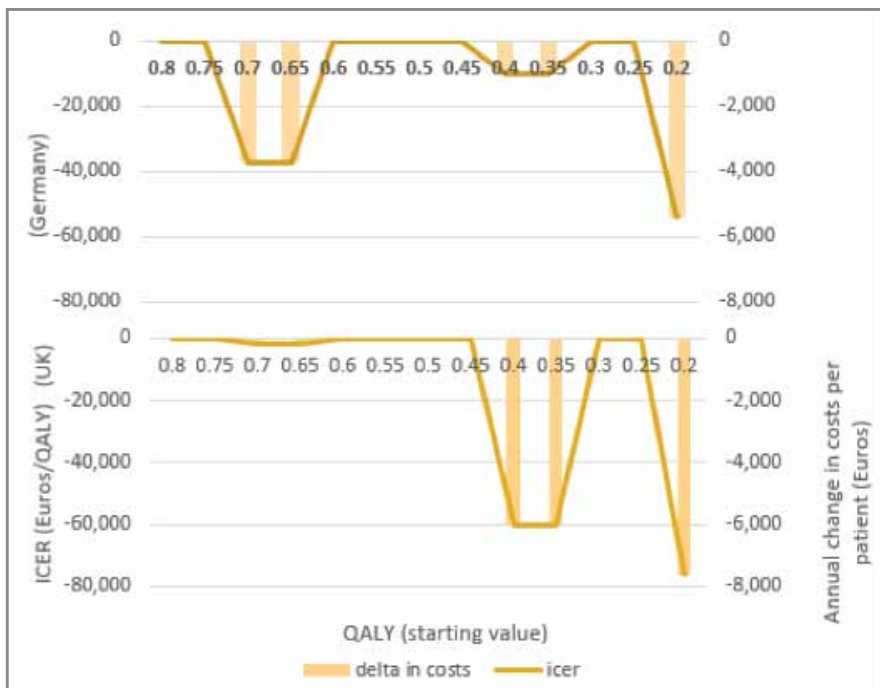


Figure 2: **Lack of early/timely treatment.** Economic impact of of a hypothetical treatment with fixed 0.10 QALY gain when given to patients at different health states (public providers' perspective)

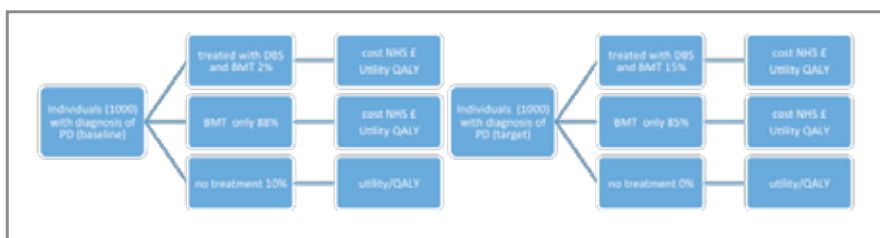


Figure 3: **Lack of adequate treatment for advanced PD.** Decision trees for the baseline and target scenarios

Country (source of data)	Scenarios	Cost per 1000 people (5 years; Euros, 2017)	QALY gain per 1000 people (5 years)	ICER
Germany (Dams[7])	Target	€ 38,041,643	3134	€ 14,836
	Baseline	€ 31,540,872	2696	
UK (Eggington[8])	Target	€ 64,369,795	1360	€ 32,681
	Baseline	€ 54,944,966	1072	
UK (McIntosh [9])	Target	€ 168,183,714	7145	€ 28,127
	Baseline	€ 138,680,392	6096	

Table 1: **Lack of adequate treatment for advanced PD.** Cost effectiveness of best treatment

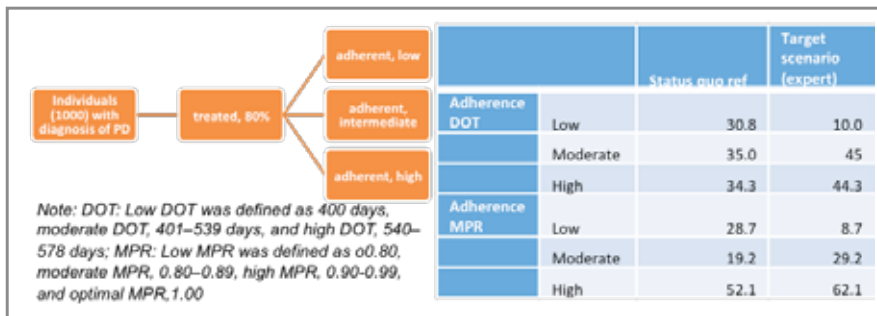


Figure 4: **Lack of treatment adherence.** Decision trees for the baseline and target scenarios

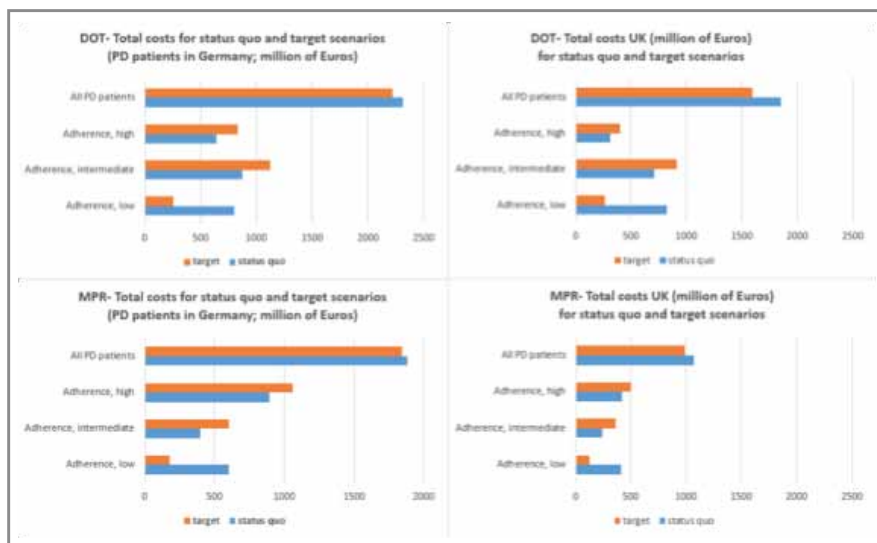


Figure 5: **Lack of treatment adherence.** Total costs for status quo and target scenarios (1000 patients, 2017 Euros, 1.5 years of treatment) (public providers' perspective)

# Conclusions

The economic analyses confirmed that timely, adequate, and adherent approach to Parkinson's disease treatment are paramount to: reducing the risk of disease progression; limiting the effects of PD on quality of life; and tackling the economic impact on service providers across healthcare systems.

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## Acknowledgements:

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<http://www.braincouncil.eu/activities/projects/the-value-of-treatment/PD>



# Restless Legs Syndrome:

Increase disease awareness to reduce patient suffering and reduce societal cost

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>, Guldemond N<sup>6</sup>, Trenkwalder C<sup>7</sup> and Oertel W<sup>8</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>The Institute of Health Policy &

Management (iBMG), Erasmus University; <sup>7</sup>Paracelsus Elena Klinik and Goettingen University; <sup>8</sup>European Academy of Neurology (EAN)

## Background

Restless Legs Syndrome (RLS) (or Willis/Ekbom Disease – WED) is a common neurological disease which is often unrecognized or misdiagnosed. 2.7% of the European population suffer from moderate to severe RLS: an uncontrollable urge to move the legs due to highly unpleasant pain-like sensations, leading to chronic sleep deprivation [1]. Wrong diagnoses and wrong treatments occur due to lack of knowledge and expertise at both the primary and secondary care levels, and as a consequence wrong routing of the patient. As a result RLS patients often have to wait many years before getting a correct diagnosis. Access to appropriate RLS care is not generally available across Europe. RLS cannot be cured, medicines are available and provide symptom suppression only. Side effects of the medicines of first choice have created new and serious problems. In this study the authors describe the patient's journey through the healthcare systems in three countries (DE, FR, IT) and describe the barriers to optimal treatment and the unmet needs of patients.

## Methods

The RLS care pathway was mapped in order to identify the unmet needs of patients as well as the underlying causal factors. Which are the barriers to optimal treatment? A case study including all possible aspects of the typical RLS patient was written, an extensive literature search on RLS and its treatment was done, a working group was formed. The group set out to identify the typical stages in the patient journey. Diagnostic delay, access to good care, the cost of non-treatment, sick leave, loss of income/job, proportion of drug resistant patients, awareness of RLS among medical professionals, (lack of) available medicines and – importantly – incorrect application and dosages, that cause adverse reactions thereof, possible prevention, screening/prodroma, early intervention, and overall disease management were all mapped. Based on the data thus gathered and the stories of three hypothetical patients, each in the three countries studied (DE, FR, IT), the cost differences between adequate and inadequate treatment could be calculated, and the burden of the lack of awareness and the resulting societal cost unveiled.

## Treatment Gaps & Unmet Needs

- There is a huge lack of awareness and knowledge of Restless Legs Syndrome. As a result patients are not taken seriously, wrong diagnoses are made and false treatments are given.

- The knowledge among in particular primary care physicians leaves much to be desired, referrals to specialists are often not done, resulting in delayed or false diagnoses and either no or wrong treatment
- Medicines for RLS do exist. Treatment of first choice to date are the dopamine agonists. Adverse reactions if applied incorrectly to these drugs in RLS patients are frequent, the most severe adverse reaction being the paradoxical phenomenon called augmentation
- Augmentation is a severe adverse reaction of the dopamine agonists in RLS. With high doses RLS symptoms become much worse and spread over the entire body during many hours per day.
- A significant aspect of augmentation is often a misinterpretation of this phenomenon: when symptoms get worse, the doctor will assume loss of efficacy and increase the dosage. This results in even more severe augmentation. More is not better in RLS treatment!
- Due to this a drug holiday is often advised, an almost impossible journey for the patient due to extreme withdrawal symptoms and no sleep for many days.
- The number of truly knowledgeable RLS specialists in Europe is very limited to non-existing in some countries
- Due to lack of awareness medicines are not reimbursed for RLS in many countries
- All available medicines were registered for other diseases in the first place; there is no systematic pharmacological research for RLS per se.

## Recommendations

Policies aiming to increase disease awareness and recognition among primary care physicians and specialists would allow patients to receive adequate treatment and alleviate their suffering. Thus:

- Include RLS disease in general medical education across all of Europe
- Improve access to information
- Increase research budgets
- Support patient organisations



"I went to see a different neurologist a few weeks back. He would not listen to me, and told me RLS is a muscle disorder, nothing to do with neurology...."

RLS patient, May 12, 2017

"I am so glad I found you, patient group, I have visited at least ten doctors in the past years and no one has been able to help me....What you describe is exactly what I have.."

Patient, 2017

"We want to have a second child. But my first pregnancy was an absolute awful nightmare, and I just cannot bear the thought of another long period with almost no sleep. Can you help??"

Patient, 2017

"Thank God I watched the TV programme. It let me know that it's not all in my mind and I am not alone. Listening to others made the world of difference to me, I have struggled for so many years...."

Patient, 2017



## Conclusions

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 correct 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. Equally important the search into the cause(s) of RLS and for new treatment strategies have to be intensified in order to reduce the suffering of people with RLS and to reduce the substantial societal costs.

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## Acknowledgements:

This study was generously supported with grants from Vifor Pharma, UCB Biopharma SPRL, The European RLS Study Group and the combined European RLS Patient organizations of Europe, the UK, France, Spain, Sweden and The Netherlands. A digital version of the poster and other supporting documents are available here: <http://www.braincouncil.eu/activities/projects/the-value-of-treatment/RLS>



# Socio economic impact of RLS & inadequate RLS treatment across different healthcare systems

Tinelli M<sup>1</sup>, Jaarsma J<sup>2</sup>, Dauvilliers Y<sup>3</sup>, Ferri R<sup>4</sup>, Rijsman R<sup>5</sup>, Sakkas GK<sup>6</sup>, Trenkwalder C<sup>7</sup> and Oertel W<sup>8</sup>

<sup>1</sup>London School of Economics (LSE); <sup>2</sup>European Alliance for Restless Legs Syndrome (EARLS); <sup>3</sup>Gui-de-Chauliac Hospital; <sup>4</sup>Oasi Research Institute (IRCCS); <sup>5</sup>Center for Sleep and Wake disorders, Haaglanden MC; <sup>6</sup>Plymouth Marjon University; <sup>7</sup>Paracelsus Elena Klinik and Goettingen University; <sup>8</sup>European Academy of Neurology (EAN)

## Background

Restless legs syndrome (RLS) is one of the most common neurological disorders. Adult prevalence of RLS in European population is about 2.7%, with women affected twice as often as men [1]. The key characteristics of RLS, including severe sleep disorders, restlessness in the evening and discomfort while at rest, have substantial impact on normal daily activities and lives of sufferers and their families. Given its high prevalence in the general population and how it affects their lives, it is necessary to evaluate the socio economic impact of RLS and the inadequate RLS treatment across different EU healthcare systems.

## Methods

**Socio economic impact of RLS.** The economic burden of RLS was estimated for the first time across EU settings using the framework adopted by the EBC in "The economic cost of brain disorders in Europe 2010" [2] in three separate healthcare systems, France, Germany and Italy, as examples of EU nations with different healthcare systems with regard to delivery of services, financing and coverage. Epidemiological and cost data were derived from the literature [1-4]. The estimates included health care costs as well as indirect costs to society, such as lost productivity due to reduced ability to work or to work at full capacity.

**Socio economic impact of inadequate RLS treatment.** RLS patients often receive no or a delayed 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 three hypothetical patients (see box below). A panel of experts from the three countries was consulted and asked to: create the three case studies, gather their personal opinion on the use of resources in the different scenarios as well as provide source of unit cost from their local country public tariff (when available) and their personal data. For each of the three scenarios two alternative were compared, including baseline scenario (ie. delayed diagnosis, insufficient response and augmentation) vs. their respective target adequate RLS treatment. Timeframe varied according to the personal life story described in the three case studies. Cost included those for the one person described in the case study and covered those incurred by the health care provider or society, pending on the individual cases. Discount rate of 3.5% was applied as appropriate.

## Box : Case studies

**Delayed diagnosis:** Catherine is a 67-year-old RLS patient who has had RLS all her life. She received the correct diagnosis only after years of suffering. Subsequently medication was given at a too high dosage, as a consequence of which her symptoms further worsened and augmentation eventually occurred. Because of her poor health condition, she had to receive 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. [Total period of time covered: from JANUARY 1960 up to NOVEMBER 2016]

**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 inpatient because of insufficient sleep quality. She presented a mild memory decline causing some difficulties in the activities of daily life. [Total period of time covered: from JANUARY 2005 up to NOVEMBER 2016]

**Augmentation:** Peter is a 67-year-old male who presents very severe RLS symptoms. He has consulted several neurologists, who treated him as inpatient. Because of his poor response to the treatment, the dose of his medications was steadily increased for several years. As a result of the high dose of the medicines, Peter was hospitalised with severe RLS symptoms and the diagnosis augmentation was made. [Total period of time covered: from November 2012 up to November 2016]

## Results

### Socio economic impact of RLS (Fig 1):

When considering the overall burden of brain disorders in the EU subsample given by the three countries, RLS is ranked the fifth largest economic disease burden (with mood disorders as first place, followed by dementia, Psychotic and Anxiety disorders).

### Socio economic impact of inadequate RLS treatment:

**Delayed diagnosis (Fig 2):** 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 (for details see Table 2). When health care and productivity costs incurred by the whole society are considered, adequate treatment provides cost savings at a level of 35,000-50,500 Euros per patient case.

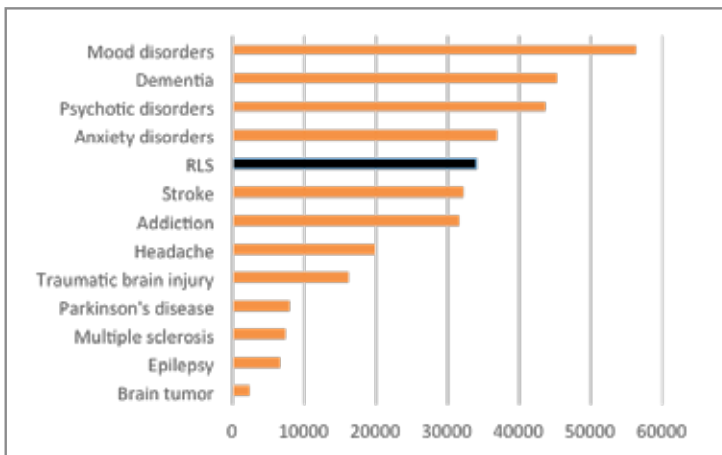


Figure 1:  
**Socio economic impact of RLS in France-Germany-Italy (pooled data). Ranking table with yearly total costs (€PPP million, 2016; pooled data)**

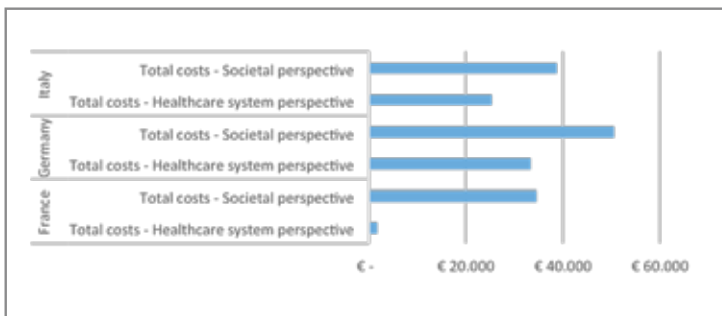


Figure 2:  
**Delayed diagnosis: Savings for Catherine case when shifting to target treatment (56 year-time frame)**

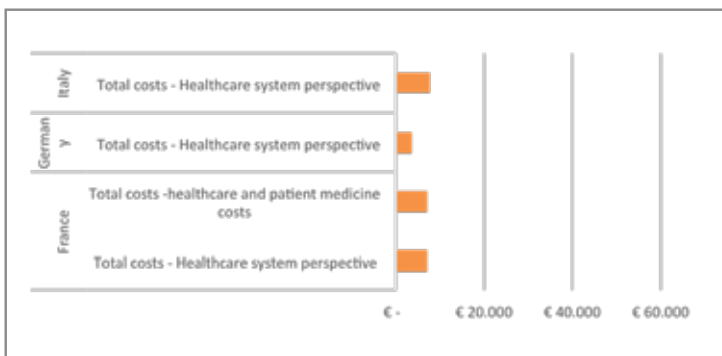


Figure 3:  
**Insufficient response: Savings for Camila case when shifting to target treatment (11 year-time frame)**

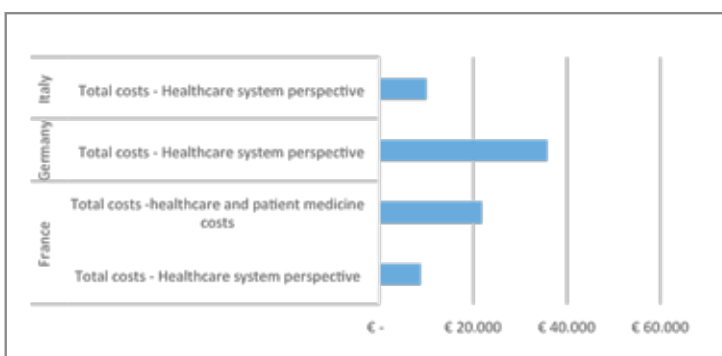


Figure 4:  
**Augmentation: Savings for Peter case when shifting to target treatment (4 year-time frame)**

**Notes:**

**Societal perspective** - Italy and Germany: healthcare costs (visits, hospital, tests), productivity loss and patient costs for medicines; France: healthcare costs (medicines, visits, hospital, tests), productivity loss.

**Healthcare perspective** - Italy and Germany: healthcare costs (visits, hospital, tests); France: healthcare costs (medicines, visits, hospital, tests).

**Insufficient response (Fig 3):** On an 11-year time horizon there is a cost saving of 3,600-7,800 euro per patient case.

**Augmentation (Fig 4):** 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 case in 4-year time horizon. The variation in estimates across the three countries may be attributable to differences in health delivery practices, coverages and care payment systems.

## Conclusions

Our analysis finds RLS to cause a significant personal and social burden and the economic benefit we can foresee when meeting adequate treatment is tangible and it is confirmed for the three case studies. When translating RLS costs (and the impact of RLS inadequate treatment) to the general population we foresee substantial economic impacts well beyond what may be anticipated from current epidemiological figures in the literature. Crucially epidemiological studies define RLS only according to three questions used in epidemiological surveys, but not along the need of treatment, and therefore these numbers should be considered a rough estimate of the overall RLS impact .

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[1] Allen RP et al. Prevalence and disease burden of primary restless legs syndrome: results of a general population survey in the United States. 2011. *Mov Disord.* 2011 Jan; [2] Gustavsson A et al. Cost of disorders of the brain in Europe 2010. *European Neuropsychopharmacology* ; [3] Dodel R, et al. Health economic burden of patients with restless legs syndrome in a German ambulatory setting. 2010. *Pharmacoeconomics*; [4] Salas R et al. The real burden of restless legs syndrome: clinical and economic outcomes. 2012. *Am J Manag Care*; [5] GDP per capita (2016) <http://www.tradingeconomics.com/>; [6] Cost effectiveness and strategic planning (WHO-CHOICE).

## Acknowledgements:

This study was generously supported with grants from Vifor Pharma, UCB Biopharma SPRL, The European RLS Study Group and the combined European RLS Patient organizations of Europe, the UK, France, Spain, Sweden and The Netherlands.

A digital version of the poster and other supporting documents are available here:

<http://www.braincouncil.eu/activities/projects/the-value-of-treatment/RLS>



# Schizophrenia: The Patient Journey

Mohr P<sup>1</sup>, Ieven A<sup>2</sup>, Arteel P<sup>3</sup>, Boyer P<sup>1</sup>, Galderisi S<sup>1</sup>, Karkkainen H<sup>3</sup>, Wasserman D<sup>1</sup>, Guldmond N<sup>4</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>The Institute of Health Policy & Management (iBMG), Erasmus University.

## Background

Schizophrenia is a severe mental disorder, which affects 0.8-1.5% of the population. It is a clinically heterogeneous illness with highly variable course, typically episodic. Frequent relapses contribute to neurobiological impairment, functional and social decline, and poor treatment response. Schizophrenia has a substantial impact on patients, their families, caregivers, and society in general. It is one of the top 25 leading causes of disability worldwide, affecting negatively all the aspect of a person's life. Schizophrenia can be effectively managed: in most cases recovery and social reintegration through adequate treatment and care is possible. However, currently more than 50% of people with schizophrenia do not receive appropriate, timely, and adequate treatment. The patient journey is a description of how patients experience a disease or condition from their first awareness of symptoms through all stages of the illness. It represents an alternative view on mental illness, based on person's individual experience, highlighting the fact that the daily life experience of patients is diverse. The patient journey aims to identify key issues in the care for schizophrenia patients that have to be improved.

## Methods

We analysed the care pathway of schizophrenia patients to identify major barriers preventing patients with schizophrenia from receiving timely and adequate treatment and we proposed recommendations on how to overcome them. The journey is based on inventory of needs and treatment opportunities using focus group sessions, expert interviews, consumers' input, and a literature review.

The focus was on three highly relevant patient pathways (Fig. 1):

- (1) Indicated prevention for individuals at risk of developing schizophrenia
- (2) Early intervention and reduction of the duration of untreated psychosis (DUP) for patients not yet diagnosed with schizophrenia
- (3) Relapse prevention for patients after first episode of schizophrenia, and patients with episodic course of the illness

## Treatment Gaps and Unmet Needs

Care pathway analysis identified the following barriers to optimal treatment:

**Health care services: missed or delayed detection/diagnosis:** The current systems do not provide appropriate prevention for patients at risk and early intervention services. Other contributing factors include lack of disease awareness among patients, families, and public; lack of information,

training and education among primary care providers; stigmatizing attitudes and beliefs about schizophrenia.

**Limited access to timely and adequate treatment:** The current model does not provide optimal management of schizophrenia due to the poor collaboration among health and social care professionals and lack of continuity of the antipsychotic treatment. Furthermore, there is a lack of cooperation between care providers and patients and their families, inadequate utilisation of pharmacological and psychosocial interventions, and proper patient monitoring.

**Non-adherence to treatment:** A major factor causing non-adherence, in addition to illness-related factors (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:** Social and vocational rehabilitation (employment services, money management counselling, cognitive remediation, social skills training) helps people with schizophrenia to improve overall functioning and social reintegration, to participate fully in their communities

**Low implementation of deinstitutionalization:** Deinstitutionalization has been demonstrated to be beneficial to the patients while not leading to severe adverse consequences. The objective is to bring people back to their own environments out of the inpatient setting and keep them out of hospitals by preventing relapse.

## Recommendations

### Main Recommendations

**Invest in research** to continue developing new treatments that can improve quality of life, functioning and reduce associated direct and indirect costs.

**Promote prevention and early intervention programmes**, which have beneficial socio economic impact.

**Raise awareness** of the public and medical professionals and fight stigma.

**Support patients and groups of caregivers** for information, expertise, sharing 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.



## Complementary Recommendations

**Support advocacy and peer group community** and empower them to voice their needs within the treatment alliance and in the discussions with healthcare professionals.

**Train healthcare professionals** and look into incentive systems to promote a timely diagnosis, referral, treatment and care.

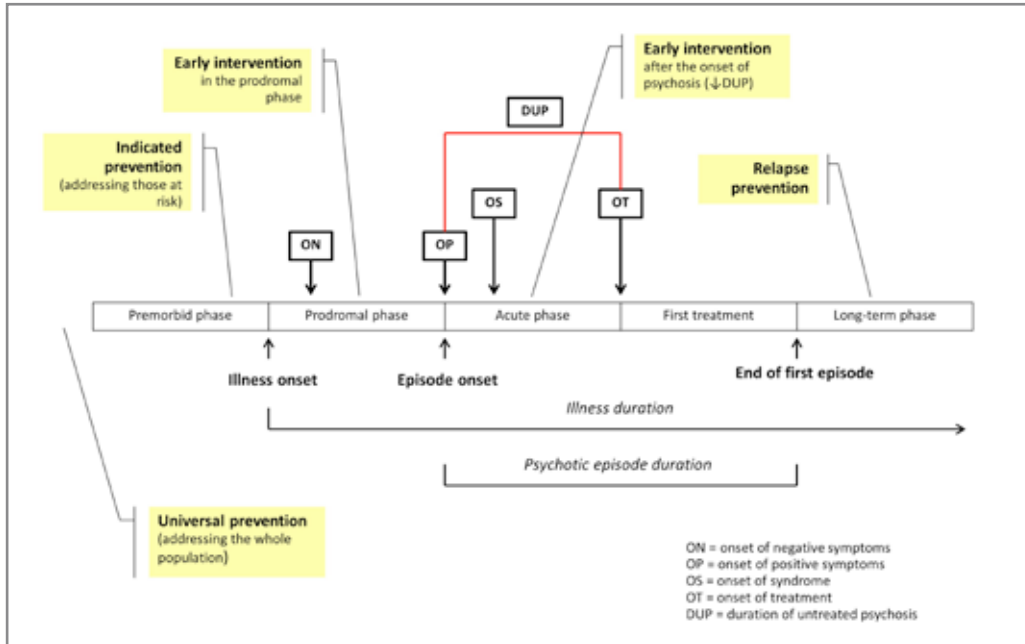


Figure 1: Intervention strategies early in the course of schizophrenia



## Conclusions

Most people with schizophrenia need a lifelong treatment; however, they can live their own life if they receive timely and proper treatment. In general, we found that the provision of early detection and early intervention programmes is of great importance for an effective management of the illness. 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.

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<http://www.braincouncil.eu/activities/projects/the-value-of-treatment/schizophrenia>



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

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

<sup>1</sup>National Institute of Mental Health; <sup>2</sup>London School of Economics (LSE); <sup>3</sup>GAMIAN Europe;

<sup>4</sup>European Psychiatric Association (EPA); <sup>5</sup>EUFAMI

## Background

Early intervention (EI) services were developed to provide support before and after the onset of psychosis. These services are currently well-incorporated in mental health policies of some countries, such as the United Kingdom (Garety et al., 2006; NICE, 2016) where they appear to be cost-effective in a longer period of time, especially because of the reduction of both, in-patient stay and lost productivity (Andrew et al., 2012; Hastrup et al., 2013; McCrone et al., 2010; Mihalopoulos et al., 2009; Valmaggia et al., 2009). In other countries of Central and Eastern Europe (see Czech Republic), these services are mostly unavailable and mental health care systems are predominantly hospital-based leading to excessively long hospitalizations, and unmet needs (Winkler et al., 2017, 2016b). Current mental health care reforms in the CR region are focused on deinstitutionalization as it has been demonstrated to improve the quality of life of people with severe mental illnesses while not leading to homelessness, criminality or suicides (Kunitoh, 2013; Winkler et al., 2016a). EI services could therefore be developed within these reforms and enable people with incipient psychosis to stay in the community rather than in the psychiatric hospitals. The objective of this economic analysis was to assess the socio-economic impact of EI programmes in two separate healthcare systems in Europe: UK where EI are already available, and Czech Republic, where EI not available yet, but they could be developed within the current mental health care reform.

## Methods

Decision trees were used to model the economic impact of adopting and/or scaling up EI services in two countries chosen to represent both old and new EU member states. All model structures and parameter choices were agreed with a panel of experts.

**In the United Kingdom (UK):** We assessed the economic value of providing EI before the onset of psychosis (individuals with prodromal symptoms) and after the onset of psychosis (individuals with first episode psychosis in secondary care) compared with usual care in the countries. EI model adopted here is based on Valmaggia et al (2009) and 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). Relevant epidemiological, probabilities and economic data were sourced from published literature (Nielsson et al 2008, Home Office, 2005, Vallmaggia et al. 2009) (Bond et al 2015; McCrone et al. 2009; <https://www.gov.uk/national-minimum-wage-rates> ONS 2016; Randall et al, 2016; Home Office, 2005; Blood et al, 2016). Short (1-2 years), medium (2-5 yrs) and long-term (>5 yrs) time frames were considered. Discount rate of 3.5 was applied as needed.

**In Czech Republic (CR):** The Czech economic model estimated the incremental value of adopting indicated prevention for people at high risk of psychosis and EI services for people with the first episode of psychosis (defined as those with first hospitalization for psychosis). Healthcare and employment costs were calculated for the annual costs of the programme. While appropriate probabilities were sourced from the literature, epidemiological and economic data were based on Czech registers and unit costs (*Unpublished, NIMH CZ; HIS, 2017; Fusar-Poli et al., 2012; van der Gaag et al., 2013; Vallmaggia et al. 2009; Randall et al. (2015b); Craig et al., 2004; Park et al., 2016; NHS, 2016; Garety et al., 2006; Power et al., 2007; Nordentoft et al., 2008; Petersen et al., 2005*).

## Results

**In UK: EI programme** (assuming about 15,800 people in UK have prodromal symptoms): 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 39m Euros extra cost).

**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 (20m - 32m Euros saving respectively).**

**In UK: EI programme:** EI was less costly (and more effective) than usual care in terms of:

- Employment costs (and probability of being employed). In the **short term** (2 years) it can generate a potential cost-savings of 50,372 Euros
- Crime costs (and number of homicide prevented). In the short term at two years after treatment, it can generate the potential cost-savings of 187,605 Euros.
- Housing costs (and probabilities of spending at least 1 day in supported housing). In the **medium term** (5 years) it can generate cost-savings of 133,000 Euros.

The findings were still robust in a series of sensitivity analyses looking at variations in the probabilities of being employed in standard care and costs of accused crime events.

**In CR, (Indicated prevention and EI programmes):** The economic model demonstrated that costs associated with care as usual for people with the first episode of psychosis were about **46 million Euro each year** (knowing - based on national registers - that there are were about 5,500 people with psychotic disorders hospitalized for the first time at an outpatient psychiatrist in CZ (2015)).

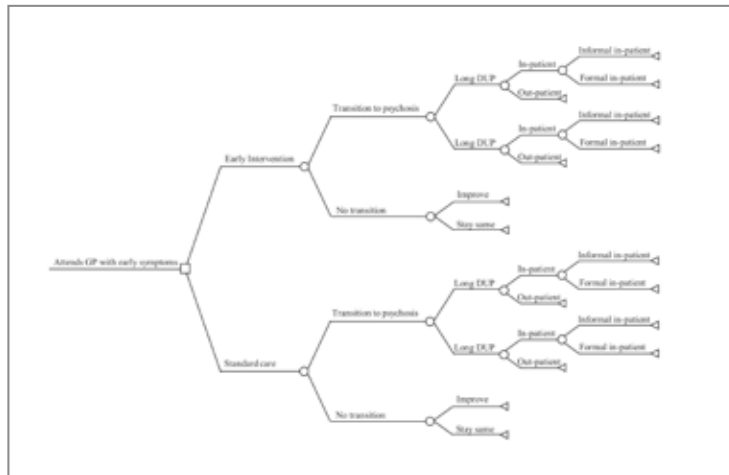


Figure 1: UK - EI model

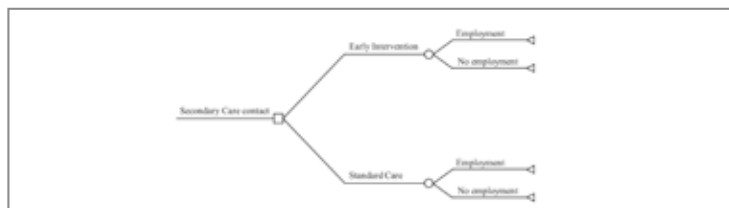


Figure 2: UK - EI model for employment

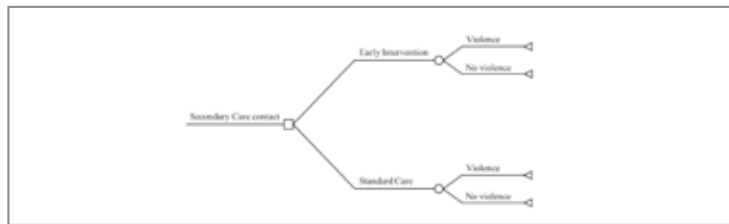


Figure 3: UK - EI model for crime

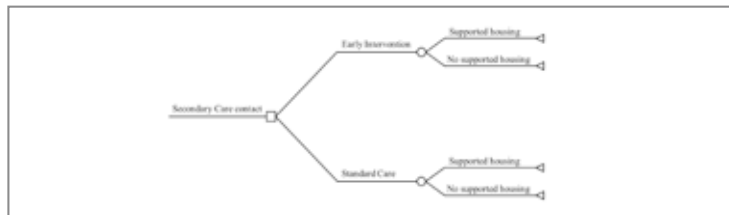


Figure 4: UK - EI model for housing

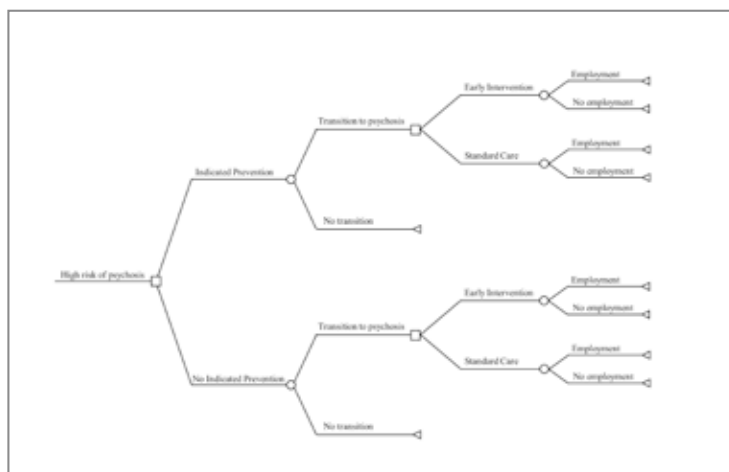


Figure 5: CR - Indicated prevention & EI model

>It is estimated that these costs could be reduced by 25 % if only Indicated prevention services were adopted (policy change 1), 33 % if only Indicated prevention services were adopted (policy change 2) and 40 % if both, Indicated prevention and EI services, were adopted (policy change 3) in the country. This means an annual cost savings of about 2,000-2,800-3,300 Euro per patient when introducing policy changes 1-2-3 respectively.

These estimates are very conservative in terms of that only health care costs and costs associated with reduced work productivity, and do not include costs associated with other sectors, e.g. social care, informal care, criminal justice, housing arrangements.

## Conclusions

Overall, the UK economic analyses showed early detection and early intervention services for people with early psychosis had the potential for cost-savings from a societal perspective. Our results suggest that adopting Indicated prevention and EI services in the Czech Republic would be highly cost saving due to decrease in hospitalizations and better employment outcomes of people with psychoses. Uncertainty was tested in multiple sensitivity analyses which demonstrated robustness of the results across settings.

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<http://www.braincouncil.eu/activities/projects/the-value-of-treatment/schizophrenia>



# Averting multiple sclerosis long-term societal and healthcare costs

## Early intervention and lifestyle choices as key to success

Pugliatti M<sup>1,6</sup>, Moroni M<sup>1</sup>, Antonovici A<sup>2</sup>, Hausmann B<sup>2</sup>, Hellwig K<sup>3</sup>, Quoidbach V<sup>4</sup>, Sorensen PS<sup>5,6</sup>

<sup>1</sup>University of Ferrara; <sup>2</sup>European Multiple Sclerosis Platform (EMSP); <sup>3</sup>St. Josef Hospital; <sup>4</sup>European Brain Council (EBC),

<sup>5</sup>University of Copenhagen; <sup>6</sup>European Academy of Neurology (EAN)

## Background

Multiple sclerosis (MS) is a chronic, inflammatory demyelinating and degenerative disease of the central nervous system (CNS) with typical onset between age 20-40 years. Over 2 million people have MS worldwide, with 770.000 people in Europe affected. MS is the commonest cause of non-traumatic neurological disability in young adults [1]. MS imposes a high burden on society, in terms of production losses as well as on families, with a very high need for informal care. All types of costs increase with increasing disease severity. MS is an acquired immune-mediated inflammatory and degenerative disease due to an abnormal immune response to environmental triggers in people who are genetically predisposed. The actual cause is unknown [2]. The MS course is unpredictable, with some people minimally affected and others rapidly accumulating disability. To date, there is no cure for MS, but a number of disease modifying treatments (DMTs). Early diagnosis and treatment may delay, or even prevent, the previously inevitable disability [3]. The course of MS implies different stages, from the clinical onset and clinically isolated syndrome (CIS), to later stages of life featuring severe cognitive decline and physical disability. Also economic and patient related outcomes, vary across these stages of the disease. We therefore aimed to define the MS 'patient journeys' capturing the main unmet needs on the different life domains.

## Methods

In order to perform a 'MS patient journeys' analysis, scientific and lay literature was scrutinized for the disease relevant clinical features, disease course, prognostic factors, available DMTs, guidelines for the management of a person with MS, and implications for his/her quality of life and social functioning. Also the economic burden of the different stages of the disease was considered. The 'MS patient's voice' was listened to, through the wealth of material from the European MS Platform and its initiatives. In particular, semistructured interviews were conducted by EMSP with two MS patients advocates each representing a separate journey.

## Treatment Gaps

In Europe patients with MS face three significant treatment gaps in their care pathway: (1) **poor access to treatment** (first treatment, switch therapy); (2) non- or reduced adherence specific to the DMTs; and (3) **poor treatment of fatigue**. Recent economic crisis has exacerbated the **unequal access to medicines**. The increasingly cost of DMTs and shrinking of public health budgets

jeopardies access to essential medicines. In 2014, considerable variations were detected in the access to DMTs for people with RR MS: 13% in Poland, 21% in UK and other Eastern Europe countries and 69% in Germany to give examples. Difference in access can be explained by healthcare infrastructure, number of neurologists, access to a neurologist, restrictive reimbursement and price of medicines and affordability as well as lack of awareness in the value of treatment [4]. Nearly half of the currently available DMTs involve self-injection, and all cause adverse events of varying degrees of severity. **This affect treatment adherence in patients with MS** (eg., forgetting the medication, injection anxiety, perceived lack of efficacy, coping with adverse events). **Fatigue** is reported in ca 96% of patients [5]. As an 'invisible' symptom of MS, fatigue can sometimes be confused with depression or just not "trying hard enough". Fatigue is a major cause of stopping working or reducing working hours. People with MS are missing out on an estimated 18 years of their working lives. While some of the symptomatic treatments are fairly good, treatment of fatigue needs to be urgently addressed.

## Recommendations

**Patient Journey 1:** In this stage of the disease the **MS patient's needs** concerns (1) **diagnosis:** an early diagnosis through lab and instrumental examinations, (2) **therapy:** treatment of the acute phase; (3) **information and psychological support:** communication of diagnosis. **The diagnosis** of MS is based on spatial and temporal dissemination criteria which are searched for by means of clinical, lab and instrumental (neuroimaging) tests. Avoiding misdiagnosis or delaying MS diagnosis becomes crucial to ensure a correct and comprehensive management of the person with MS. The Centre for Diagnosis and Treatment of MS ('MS Centre'), including Day Hospital and Day Service, or even hospitalization represents the adequate **health care setting**, wherein the patient care pathway, incl., treatment choices and monitoring, should be coordinated. **The communication of the diagnosis** – a very delicate phase – should involve the patient and his/her direct relatives, the neurologist and when possible – also a psychological support. This communication must be correct and comprehensive, adequate to the patient's level of bio-psycho-social specificity, extended in time. **Information** in this phase is in general a priority for most patients. **Patient Journey 2:** Some health care needs are in common with Patient Journey 1 (DMTs continuation, symptomatic treatment, their monitoring, multidisciplinary approach at the MS Centre), but **rehabilitation and palliative care** may feature this stage. This person would need **documentation to start insurance procedures for disability**, adequate working conditions (changes), prescription for aids/devices, home and means of transportation adjustment. He or she **should be managed at home**, hence



the need of home care integrated with the territory primary level health care. Health care should pivot on the **General Practitioner (GP)**, on the **rehabilitation specialist**, and on the **nursing staff** (eg., a case manager), social services and residential structure to integrate health care (including palliative care) or admit the person.

### **The experience of a young patient with RRMS**

"I started treatment (DMT) immediately after diagnosis...The most common symptoms for me are walking and gait difficulties, leg's spasticity, bladder problems, balance problems and fatigue... I think that the most important thing receiving an MS diagnosis is to take your time to understand what's happening; then you have to learn to live with MS and all that it can mean.... Sure it affects many aspects. At first it is a shock. I think that nobody can accept a chronic disease but you can learn to live with it in the best way you can".

### **The experience of a patient with progressive MS**

"There was no DMD at the time I was diagnosed... I now manage my progressive condition with DMD medication, rehabilitation, physical training plan to maintain the undamaged part of my body, I also take nutrition and vitamin supplement as needed... My conclusions, in agreement with my neurologist, and seconded by several other researchers/neurologists is to continue what has been a very positive treatment experience. A multidisciplinary health team including psychosocial assistance with good communication is essential..."

## **Conclusions**

MS imposes a high burden on patients and society, due to production losses, and a very high need for informal care. All types of costs increase with increasing severity of the disease. MS incidence is increasing, particularly among women. Lifestyle factors (eg., cigarette smoking, vitamin D insufficiency) have been consistently found in association to increased risk for MS onset in the general population and disease worsening. To date, there is no cure for MS, yet MS has become a treatable disease. Early diagnosis and start of DMTs may delay, or prevent, the previously inevitable disability. Once the diagnosis is confirmed, a coordinated multidisciplinary approach is needed, with MS nurses and MS psychologists, and physiotherapists for rehabilitation [6]. Two MS 'patient journeys' are defined, based on specific

needs, challenges and preferences: (1) the person with a new diagnosis of CIS fearing to develop defined MS, or with new MS diagnosis of MS, relapsing-remitting phase, fearing prognostic uncertainty towards worsening and disability accumulation; (2) the person with progressive MS experiencing accumulating disability, limitations in work and social life, dependence from others in daily activities; reduced response to most treatments (EDSS 4 to 9.5). Treating MS nowadays should aim to preserve brain and cognitive reserve through the early use of DMTs and by adopting a 'brain-healthy' lifestyle, which implies considering patients' values and preferences. Patients with MS face three main unmet needs, ie, gaps in access to treatment, DMT-specific non-adherence, treatment of fatigue. In addition, we need a more holistic approach to care. Awareness-raising on the fluctuating nature and often invisible symptoms of the disease together with small adaptations can help keep people in work.

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## Early intervention and lifestyle choices as key to success

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<sup>1</sup>London School of Economics; <sup>2</sup>University of Ferrara; <sup>3</sup>European Multiple Sclerosis Platform (EMSP); <sup>4</sup>St.Josef Hospital; <sup>5</sup>University of Copenhagen; <sup>6</sup>European Academy of Neurology (EAN)

\*Tinelli M and Pugliatti M have contributed equally to the work.

## Background

Multiple sclerosis (MS) is a progressive neuro-inflammatory and -degenerative disease typically affecting young adults in the prime of life, causing irreversible physical and mental disability. It is the leading cause of non-traumatic disability in young adults in many developed countries [1]. The burden of MS to society include direct (medical and non-medical) and indirect costs. In Europe, such burden amounts to €15.5 billion, and €37,000/case/year [2,3]: higher for other long-term conditions such as asthma, chronic obstructive pulmonary disease and diabetes [4]. MS societal costs increase significantly with disability: from €23,000 for mild MS to €77,000 for severe MS [3], as well as indirect costs (productivity losses for sick leave, incapacity to work and early retirement), and also informal care costs largely falling outside of the health and social care systems, borne by PwMS and families. Modifiable lifestyle factors seem to modulate the risk of MS in the population, as well as its worsening [1]. We aimed to analyse the economic gain of MS early treatment on the long-term societal costs, as well as the potential role of reducing the prevalence of two common modifiable lifestyle factors (ie., cigarette smoking habit, low vitamin D serum levels) to avert MS worsening based on identified clinical outcomes.

## Methods

Efficacy data on early treatment reducing conversion from CIS to MS, and on increased risk of MS progression or disability from exposure to cigarette smoking and low vitamin D serum levels were taken from meta-analyses or systematic reviews [5-7].

**Early treatment** - Published data on the cost-effectiveness of CIS early treatment to conversion to MS were updated to 2017 figures and used to compare the economic evidence across different healthcare systems (Italy, Spain, Sweden [8-10]). Cost estimates were reported for both societal and healthcare provider perspectives (Euros). Effectiveness was expressed as Quality Adjusted Life-Years (QALYs) gains. Cost-effectiveness was reported as incremental cost-effectiveness ratio (ICER).

**Lifestyle risk factors** - Decision analytical tree modeling was developed and applied to assess the economic impact of:

- **Smoking cessation** [11] vs ever smokers (decrease in mean EDSS score % [5] and conversion from RRMS to SPMS [6]; model 1);
- **Increase of vitamin D (25(OH)D) serum level** on MS progression [2] vs status quo [11] (model 2).

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 [12] inflated to 2017 figures (Euros), and effectiveness in terms of QALY figures [13]. Sensitivity analyses were applied to test the robustness of the models according a range of effectiveness' levels [5,6]. Smoking analyses included additional model (model 3) to evaluate the economic impact of shifting from current [11] to target smoking prevalence levels as proposed by WHO [14].

## Results

**Early treatment** - 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 (table 1).

**Lifestyle risk factors** - Consistent and significant annual QALY gains and savings have been shown from smoking cessation (0.11 QALYs and EUR 2,500-16,400 per case across country settings; figure 1) and increase of vitamin D serum levels (0.13 QALYs and EUR 435-6,210; figure 2). 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. When considering the prevalence-based model (smoking only) the shift from current to WHO target smoking levels brings savings and QALY gains (cost-effective and cost saving approaches as per NICE; table 2).

Country	Time horizon (years)	Groups	NHS costs pp (euro)	Societal costs pp (euro)	QALY	ICER
Spain	50	CIS	371,452	654,772.75	15.42	NHS 41,162 SOCIETY - 13,566
		CDMS	340,992	664,811.74	14.68	
Italy	25	CIS	199,247	258,367.89	7.84	NHS 2,994 SOCIETY - 18,775
		CDMS	198,379	264,939.15	7.49	
Sweden	40	CIS	N/A	821,013.52	13.79	N/A SOCIETY - 54,157
		CDMS		849,716.63	13.26	

Table 1: **Early treatment to reduce conversion of CIS to CDMS**  
(Clinically Definite Multiple Sclerosis): cost effectiveness analysis; pp=per person

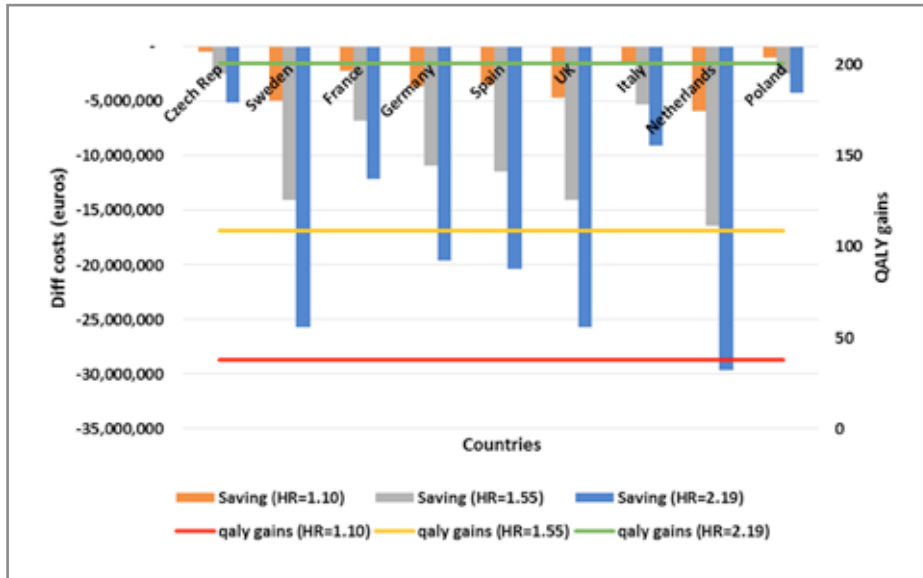


Figure 1: **Smoking cessation:** difference in costs (negative sign = saving) and QALY gains according to different adjusted estimate of risk (HR, Hazard Ratio) when considering a pop. of 1000 MS no smokers (compared with 1000 MS smokers)

Country	Outcome indicator (measure of risk)	Diff cost per 1000 MS patients	QALY gained per 1000 MS patient	ICER
Italy	progression EDSS score (HR=1.55)	- 607,459	19.43	- 31,260
	progression EDSS score (HR=1.10)	13,716	7.87	1,744
	conversion from RR to SP (RR= 1.88)	- 375,221.58	17.18	- 21,839
Sweden	conversion from RR to SP (RR=1.47)	- 200,402	9.18	- 21,839
	progression EDSS score (HR=1.55)	- 1,489,370	15.85	- 93,945
	progression EDSS score (HR=1.10)	- 275,054	6.42	- 42,860
	conversion from RR to SP (RR= 1.88)	- 433,383	19.84	- 21,839
	conversion from RR to SP (RR=1.47)	- 231,466	10.60	- 21,839

Table 2: **Smoking cessation: shift from current to WHO target smoking levels**



Figure 2: **Increase of vitamin D serum levels:** difference in costs (if negative sign = saving) and QALY gains according to different adjusted estimate of risk (SDM, Standardised Mean Difference) when considering a pop. of 1000 MS increase of vitamin D serum levels (from <20 mmol/l to 20+ mmol/l), compared with 1000 MS no increase of vitamin D serum levels.

## Conclusions

Early treatment and a brain healthier lifestyle slow MS progression and indeed reduce the disease societal and healthcare costs. To the best of our knowledge, our work provide first economic evidence to base appropriate public health interventions to reduce the MS burden in Europe, also by means of controlling modifiable lifestyle factors in disease worsening. Further research is needed to overcome methodological limitations (eg., CIS economic models and evidence from available from the literature).

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# NOTES


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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)  
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