

3.4 Brain Disorders

3.4.1 Summary

In 2004, brain disorders accounted for a third of the entire disease burden, with a cost in Europe alone of more than €135 bn in direct healthcare costs. Current treatments for brain disorders are largely symptomatic, and do not respond fully to patient needs. There is an obvious need for disease-modifying therapies, and to increase efficacy and tolerability of the symptomatic treatments that are currently available. The following proposals are suggested as areas where there is a clear need for further research, and where a public–private partnership can have a significant impact:

- The identification and validation of pre-symptomatic and surrogate markers for disease progression. Approaches should include genomic, proteomic, and metabonomic profiling in human pathology samples and animal tissues; functional and structural brain imaging; correlation of clinical with experimental data and bioinformatics approaches, and establishing European standards and networks for the validation of biomarkers;
- The development of model systems that translate to human pathology and are predictive of clinical efficacy. Human material should be used where possible, and better correlation between clinically relevant and experimental endpoints is needed;
- A better understanding of disease mechanisms at a systems level, using human models of psychopathology and determination of drug effects and dosing along with quantitative behavioural and neuroimaging measures;
- Co-ordinating European stroke networks and developing post-injury treatments, with basic research on functional recovery and determination of validated outcome measures for such treatments.

3.4.2 Introduction

The terminology 'Brain and brain-related diseases' used in this document encompasses all fields concerned with the nervous system (central and peripheral including the senses and motor systems) on all levels (from molecules to behaviour), including diseases of the nervous system. Brain disorders account for around 35% of the disease burden in Europe³⁹. There are an estimated 127 million Europeans living with a brain disorder out of a population of 466 million, and the total annual costs to European society in 2004 were estimated at €368 bn (€135 bn in direct medical costs, of which €13 bn were directly attributable to drug costs)⁴⁰. Psychiatric disorders, excluding dementia, accounted for 62% of all costs, with the remainder accounted for by neurological disorders. The global market for CNS medicines for the 12 months to March 2004 was \$59.6 bn, and it is the second-fastest growing therapeutic area⁴¹. The cost of bringing a new drug to market today is estimated to be greater than \$900 mn, and the chances of bringing a Phase I candidate to market in CNS is considerably lower (by up to three-fold) than other disease areas⁴². Based on incidence costs, burden and an analysis on unmet needs in Europe, the priorities for brain disorders are set out in Figure 25 below.

Neurology	Cases (M)	/	Costs €bn
Dementia	4.89	/	55.2
Stroke/Trauma	1.83	/	23.8
Migraine	40.78	/	27.0
Epilepsy	2.69	/	15.5

³⁹ Olesen J. and Leonardi M., The Burden of brain diseases in Europe. *Eur. J. Neurol* (2003) 10: 471-477.

⁴⁰ Andlin-Sobocki P., Jonsson B., Witche H-U., Olesen J., Costs of disorders of the brain in Europe. *Eur. J. Neurol.* (2005) 12: supp 1. *In Press.*

⁴¹ IMS Health Retail Drug Monitor March 2004

⁴² Kola and Landis, J., *Nature Reviews Drug Discovery*, (2004) 3, 711-715

Neurology	Cases (M)	/	Costs €bn
Multiple Sclerosis	0.379	/	8.7
Parkinson's	1.158	/	10.7

Psychiatry	Cases (M)	/	Costs €bn
Anxiety	41.41	/	41.4
Affective Disorders	20.87	/	105.6
Addiction	9.194	/	57.2
Psychotic Disorders	3.69	/	35.2

Figure 25 : Brain Diseases Costs and Incidence

3.4.3 Present Status of the Disease Area

For **Dementia**, some patients receive moderate symptomatic relief with acetyl cholinesterase inhibitors (AchEI) or NMDA receptor inhibitors (memantine). There is a clear need for disease-modifying agents that could slow or stop the progression of Alzheimer's disease, and for more effective symptomatic treatments, including medicines with improved efficacy on behavioural symptoms, both cognitive and non-cognitive, in all dementias. There is a clear need for diagnostic tools for patient selection, and for improved surrogates to approved efficacy end-points. Because of the complex pathophysiology, it is likely that multiple therapies will be required to manage symptoms and control disease in individual patients.

In **Stroke/Trauma**, tissue plasminogen activator (TPA) is the only registered treatment for acute stroke, and it can only be initiated within three hours of the onset of symptoms, and after a CT scan to exclude haemorrhage. This represents around 3% of stroke patients, with a clear benefit being seen in just 10–15% of treated patients. There is a clear need for treatments that could reduce acute damage or improve recovery post-stroke and trauma, and for improved clinical access to early diagnosis and treatment.

Multiple sclerosis is currently treated with interferons (alpha and beta), Copaxone and Mitoxantrone, which have numerous side-effects and are considered to be of marginal benefit. The greatest unmet needs are for treatments that halt the progression of the disease.

In **Epilepsy**, several medicines have existed for many years that control seizures in around two-thirds of patients, but none are disease-modifying and many have serious side-effects. Several new antiepileptic drugs (AEDs) have better efficacy and/or better tolerance, but there are still no disease-modifying treatments.

In patients with **Parkinson's**, levo-dopa and dopamine agonists have been used as symptomatic treatments for more than 30 years, but there are still no disease-modifying therapies, and patients become tolerant to existing symptomatic treatments. As a result, the greatest unmet need is for disease modifying treatments.

The mainstays of treatment in Europe for **affective and bipolar disorders** are SSRIs, with a smaller percentage of patients receiving tricyclics or SNRIs. The next five to 10 years will see an increasingly crowded and genericised market. There is a need for improved response and remission rates, reduced mood-switching in bipolar patients, and a decreased propensity for causing sexual dysfunction. This may be achieved by new classes of drugs that are now in development, and by more personalised prescribing, informed by pharmacogenomics.

The mainstay of **schizophrenia** treatment is atypical antipsychotics such as risperidone, olanzapine, quetiapine and clozapine. The continuing long-term side-effect burden, such as weight gain, metabolic problems and lethargy, and efficacy limitations contribute to compliance problems. New mechanistic approaches are clearly needed, as all present therapies are targeted at dopamine D2 receptors to some degree. The level of unmet need is high for positive, negative and cognitive symptoms.

Acute treatment is necessary for all attacks of **migraine**. The triptans are effective and well-tolerated, but few patients achieve complete relief from pain, and many have recurrences. About 10–20% of patients who have frequent attacks need prophylactic drug treatment. The only available drugs are those with another primary indication, they are generally not very effective and have many side-effects. The greatest unmet needs are for an effective migraine-specific prophylactic medication, and for a more effective acute treatment that has no cardiovascular side-effects.

3.4.4 Bottlenecks

Four key priority areas have been identified by our expert group where there is a clear need for further research, and where a public–private partnership can have a significant impact, these are:

- The identification and validation of pre-symptomatic and surrogate markers for disease progression;
- The development of model systems that translate to human pathology and are predictive of clinical efficacy;
- A better understanding of disease mechanisms at systems level, leading to better target selection;
- Application and intervention networks for stroke, and development of post-injury treatments.

3.4.4.1 Identification and Validation of Pre-symptomatic and Surrogate Markers for Disease Progression

Brain disease addressed	Dementia, stroke, Parkinson's, MS
Scientific approach	<ul style="list-style-type: none"> • Genomic, proteomic, and metabonomic (including lipidomic) profiling in human pathology samples and animal tissues; • Functional and structural brain imaging, focus on detection of responders vs. non responders to therapeutic intervention; • Correlation of clinical with experimental data and bioinformatics approaches; • Profiling of responders to specific treatments.
How it addresses the bottlenecks	Definition of pre-symptomatic cases for treatment = increased efficacy, development of surrogate markers = increased efficacy reduced drug attrition.
Key players, networks and organisations	AddNeuroMed group (FP6), industry, SMEs, academic groups, FENS (Federation of European Neuroscience Societies), clinicians, HUGO (Human Genome Organisation), HUPO (Human Proteome Organisation), EMBO (European Molecular Biology Organisation), regulators, European Federation of Neurological Societies (EFNS).
Existing infrastructure and infrastructure needs	Tissue banks, sample and bioinformatics standardisation, specialist imaging centres with standardised protocols and transferable data management systems.
Feasibility	Feasible, but as yet unvalidated (high risk).
Resource allocation	Based on the AddNeuroMed network for Alzheimer's disease (€15m), we can estimate at least €60 mn over five years if it is extended to four other brain disorders.
Metrics of success	Discovery of pre-symptomatic markers for dementia and Parkinson's, diagnostic markers for acute brain injury (in particular stroke), predictive and surrogate markers of functional recovery in acute brain injuries.

3.4.4.2 Development of model systems that translate to human pathology and are predictive of clinical efficacy

Brain disease addressed	All
Scientific approach	<ul style="list-style-type: none"> • Use of human tissue wherever possible, development of better animal models incorporating human receptors and disease mechanisms; • Generation of complex <i>in vitro</i> models that predict efficacy and aligning these with current discovery platforms; • Generation of target validation technologies using conditional knock-outs/knock-ins in vertebrates, extension of target validation systems to simple model organisms (for example zebra fish)

	<p>or drosophila) to express mechanisms relevant to humans;</p> <ul style="list-style-type: none"> • Chemical genetics probes, functional genomics (for example RNAi), pathway modelling, and also modelling of clinically relevant end-points in animal models, for example behavioural measures for stroke; • Integration with a relevant biomarker strategy such as that described above in model systems; • Integration of pharmacogenomic approaches into animal or <i>in vitro</i> models; • Identification of key parameters to select responders to specific therapeutic approaches.
How it addresses the bottlenecks	Better efficacy of pre-clinical candidates, and less attrition as a result of non-human translation. Better target validation technologies will result in less failure because of a lack of human efficacy. Bringing risk forward by integrating biology into the discovery process earlier will reduce failures caused by a lack of appropriate efficacy.
Key players, networks and organisations	Academia: particularly groups working on modelling disease systems. Clinicians: a better dialogue between basic and clinical scientists is needed to identify relevant model end points. Industry, SMEs such as contract research organisations. <i>In vitro</i> specialist organisations such as ECVAM (European Centre for Validation of Alternative Methods) and IVTIP (In-Vitro Technology Industrial Platform group). FENS (Federation of European Neuroscience Societies).
Existing infrastructure and infrastructure needs	
Feasibility	Feasible but as yet unvalidated (high risk).
Resource allocation	Six key areas and 10 diseases @ €2 mn = €120 mn over five years.
Metrics of success	Models that would be validated in the clinic and predict clinical efficacy.

3.4.4.3 Better Understanding Disease Mechanisms (at Systems Level) for Improved Target Selection

Brain disease addressed	Psychiatric disorders, dementia
Scientific approach	Use of human models of psychopathology, for example in anxiety/depression, fear potentiated startle (analogous with animal screening models) or emotional processing (human-specific): determine drug effects and dosing using quantitative behavioural and neuroimaging measures. Define contribution of polymorphism at key receptor genes to model's properties. Better mechanistic understanding of mechanisms of cognitive decline in dementia.
How it addresses the bottlenecks	Extend validity of animal screening models to predict efficacy. Fail candidate drugs early in development on basis of functional tests in healthy volunteers or relevant patients. Potential to identify responders via pharmacogenomics of modelled response. Rank performance of NCEs in human models to fast-track promising candidate medicines to patients.
Key players, networks and organisations	Academia (neuroscientists, psychologists, clinical scientists, neurologists, psychiatrists), industry, patients organisations, SME.
Existing infrastructure and infrastructure needs	
Feasibility	Very high – but requires pre-competitive development of standard profiles of sensitivity for human tests.

Resource allocation	Core support for network of 10 academic centres per disease area with three major disease areas: €2 mn each (total €60 mn) over five years. Support for a co-ordinating SME: €30 mn over five years.
Metrics of success	Investment in specific projects by the pharmaceutical industry: early Phase I discrimination of multiple candidate medicines leading to go or no-go development decisions.

3.4.4.4 Co-ordination of Clinical Intervention Networks and Research Programmes for Stroke and Development of Post-injury Therapies

Brain disease addressed	Stroke/Trauma
Scientific approach	<ul style="list-style-type: none"> • Standardisation (by comparison) of methods in European rapid intervention networks for acute treatment of stroke patients. Alignment with national efforts to produce a European standard; • Basic research into post-injury neurobiology including plasticity and neuroregeneration in brain and spinal cord; • Basic research into post-injury neurobiology including plasticity and neuroregeneration in brain and spinal cord; • Basic research in rehabilitation approaches and the scientific basis for efficacy.
How it addresses the bottlenecks	Will allow acute intervention therapies to be improved and reduce attrition. Development of novel approaches based on post-injury plasticity and neuroregeneration will create new therapeutic fields. Development and definition of outcome measures will allow assessment of treatments and thus reduce attrition of post injury therapies.
Key players, networks and organisations	Clinical networks (e.g. European Brain Injury Consortium and European Brain Council), academia, rehabilitation professionals and stroke networks, patient groups (e.g. EFNA), industry associations device industry, SMEs, European stem cell networks.
Existing infrastructure and infrastructure needs	
Feasibility	For intervention centres is high; for post-injury treatments is unknown.
Resource allocation	Co-ordination of European acute centres will be achieved through specific support actions (€1.25 mn). Research into restorative therapies would require €20 mn for academic groups and around €20 mn for SME participation in the projects. It is estimated that this would support about five strategic research projects (STREPS) over five years.
Metrics of success	Novel treatments for brain-injured patients and validated measures for post-injury recovery. More stroke patients assessed \leq 3 hours.

3.4.5 Resources

The total resources required to implement the current priorities has been estimated at €311.25 mn for a period of five years. This is based on the following assumptions: two to three large integrated projects for the identification of pre-symptomatic and surrogate markers; four or five integrated projects and up to 10 focused strategic projects (STREPS) on the development of more predictive disease models; three integrated projects to develop a better understanding of diseases at systems level in psychiatric disorders, including dementia; one specific support action for co-ordinating stroke networks; and five STREPS focused on research into the mechanism of post-injury recovery following acute brain injuries. As many of these proposals are in outline format, the costs represent a best guess by the participant group. These figures will be updated as the proposals are developed and approved.

Activities	Costs (€mn)
Identification and validation of presymptomatic and surrogate markers for disease progression	12.0
Development of model systems that translate to human pathology and are predictive of clinical efficacy	24.0
Better Understanding Disease Mechanisms (at Systems Level) for Improved Target Selection	18.0
Co-ordination of Clinical Intervention Networks and Research Programmes for Stroke and Development of Post-injury Therapies	8.25
TOTAL BRAIN (€mn per year)	62.3

3.4.6 List of Contributors

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